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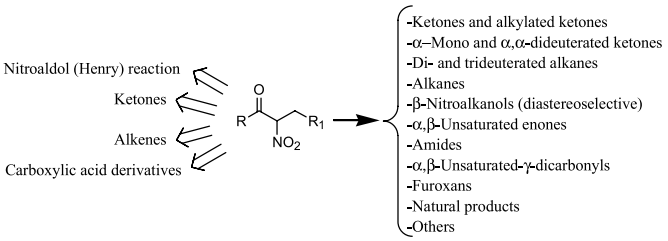
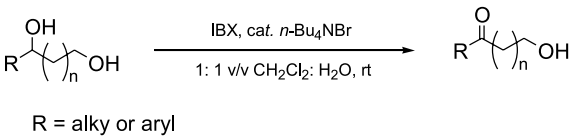
Contents

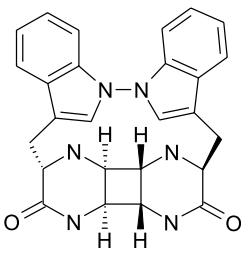
REPORT

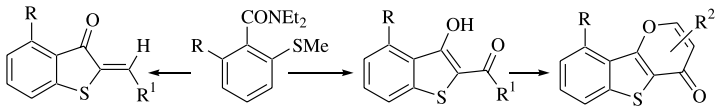


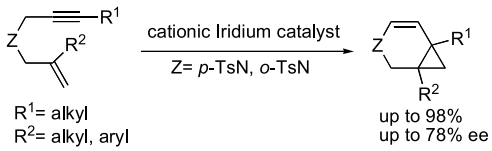
ARTICLES

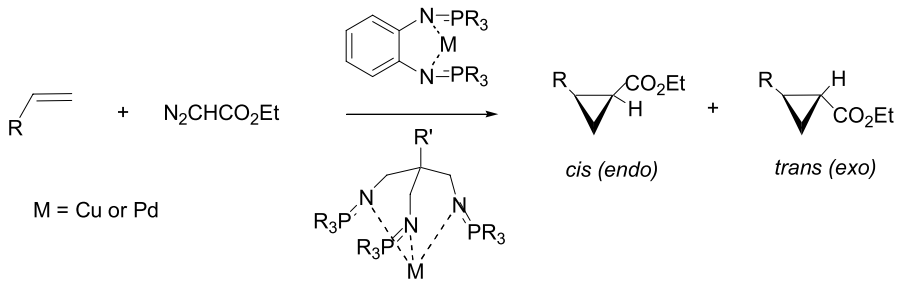


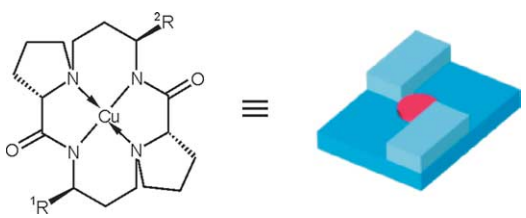
Schischkiniin, a unique indole alkaloid with anti-cancer and anti-oxidant properties, together with four known lignans and three flavonoids have been isolated from the seeds of *C. schischkinii*.



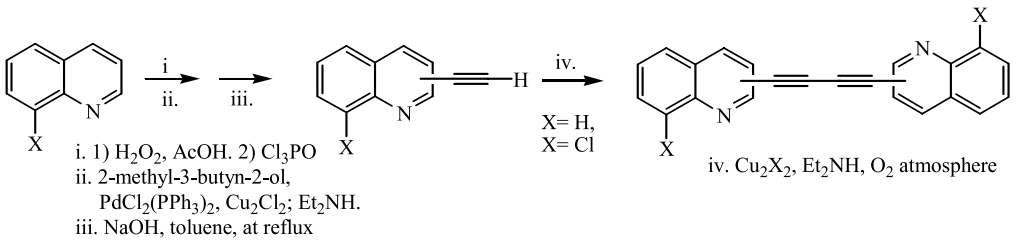


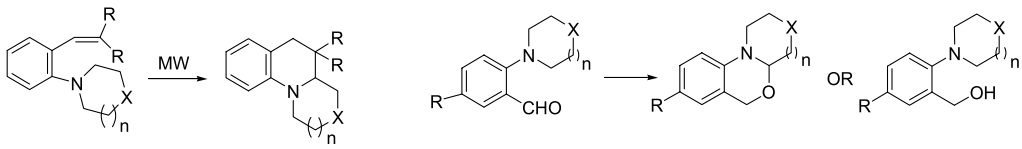


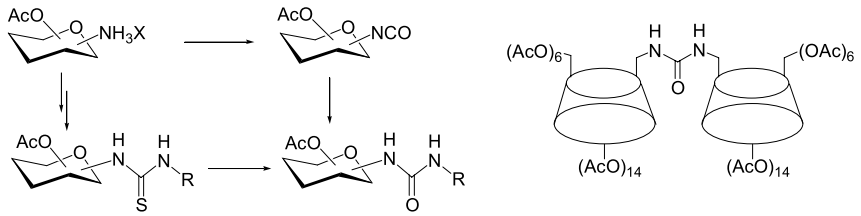


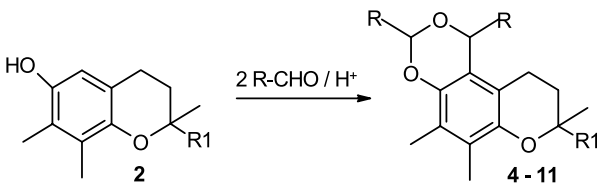


New chiral dioxocyclam derivatives were synthesized starting from α-amino acids. This class of ligands form transition metal complexes with uncommon topology.

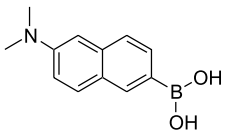




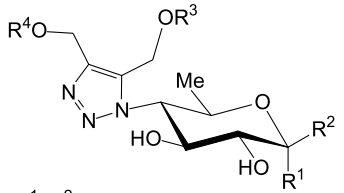




Condensation of γ-tocopherol with 2 equiv of aldehydes in a facile one-pot reaction provided 1,3,8-trioxa-phenanthrenes as precursors for the thermal in situ generation of *ortho*-quinone methide intermediates.

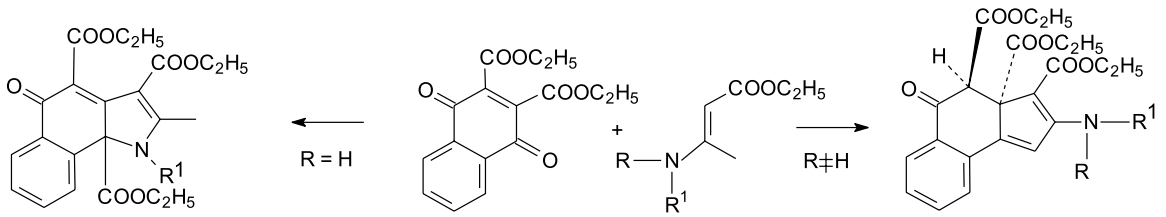


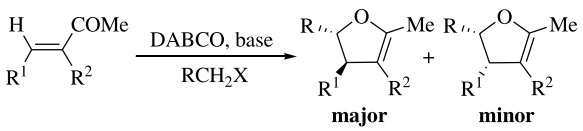
6-DMANBA (**1**)



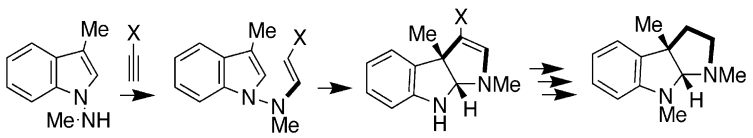
R^1, R^2 = H, OMe, glycosyl residue
R^3, R^4 = H, maltosyl residue

The synthesis of new glycosylated triazoles and their inhibiting effects for a panel of glycosidases are reported.

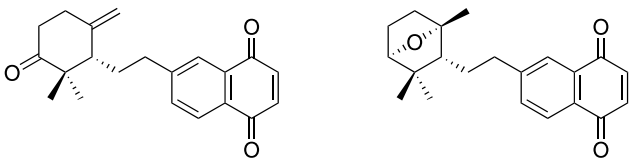


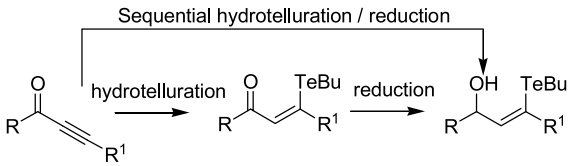


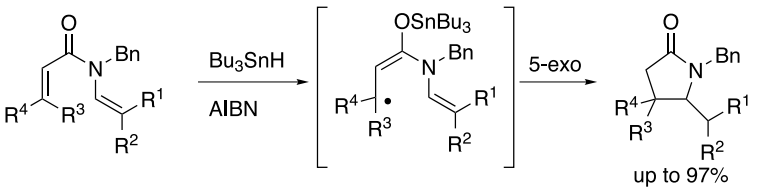
major **minor**



S-Alkyl thiocarbamates (*S*-alkyl *O*-alkyl carbonothioates) were synthesized in good to excellent yields by solvent-assisted thiocarboxylation of amines (alcohols) with carbon monoxide and sulfur under mild conditions (1 atm, 20 °C) in DMSO or DMF.







OTHER CONTENTS

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Acyclic α-nitro ketones: a versatile class of α-functionalized ketones in organic synthesis

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Contents

Keywords: α-Nitro ketones; Acyclic; Organic synthesis.
Abbreviations: AIBN, azobisisobutyronitrile; ALA-5, δ-aminolevulinic acid; CIMP, 2-chloro-5-iodomethylpyridine; DBU, 1,8-diazobicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DHRGC, dynamic high-resolution gas chromatography; DMAP, 4-dimethylaminopyridine; HMPA, hexamethylphosphoramide; HMPT, hexamethylphosphoric triamide; LDA, lithium diisopropylamide; LR, Lawesson reagent; PCC, pyridinium chlorochromate; TBDMS, *tert*-butyldimethylsilyl; THF, tetrahydrofuran; THP, tetrahydropyranyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMSCN, trimethylsilyl cyanide; TNM, tetranitromethane.
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1. Introduction

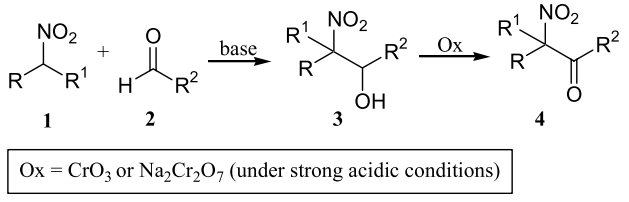
α-Nitro ketones are an emerging class of molecules in organic synthesis, due to the presence on two adjacent positions of the carbonyl group and the carbon–nitro group moiety, that offers a new reactivity pattern, peculiar to α-nitro ketones. However, α-nitro cycloalkanones and acyclic α-nitro ketones have unlike reactivities and are utilized differently. The ring cleavage, promoted by external[1] or internal nucleophiles (zip reactions),[2] represents the main behaviour of cyclic α-nitro ketones, and these retro-Claisen condensations have already been exhaustively reviewed,[1,2] while this report is mainly devoted to provide a comprehensive coverage of the synthesis, reactivity and possible transformations of acyclic α-nitro ketones,[3] as well as their utilization in several interesting synthetic applications. Some common reactivities of both cyclic and acyclic α-nitro ketones will be also reported.

2. Synthesis of acyclic α-nitro ketones

Acyclic α-nitro ketones can be mainly obtained by the following sources: (i) formation of a new carbon–carbon bond by reaction of the nitro–carbanion, derived by basic treatment of the corresponding nitroalkane, with aldehydes (nitroaldol reaction) or with carboxylic acid derivatives; (ii) from ketones (or their enol derivatives); (iii) from orthoformate derivatives and (iv) from alkenes.

2.1. From the nitroaldol (Henry) reaction

The synthesis of the title compounds was firstly carried out in two steps: (i) basic nitroaldol reaction of a nitroalkane **1** with an aldehyde **2**, and (ii) treatment of the obtained nitroalkanol **3** with chromium trioxide[4] or sodium dichromate[4b,5] (Scheme 1) in strong acid.

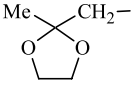


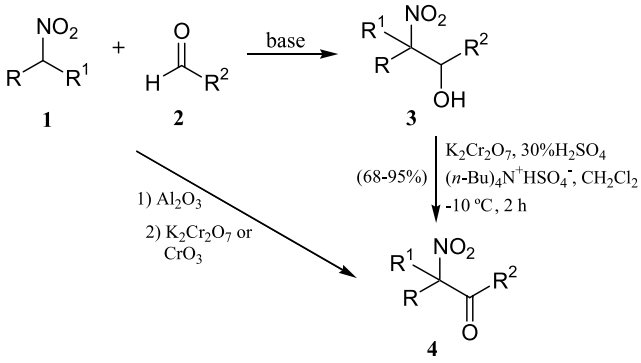
Scheme 1.

However, these severe conditions frequently produced low yields, and acid-labile functionalities present in the molecule did not survive. These drawbacks were later solved by the application of a milder oxidative procedure, using pyridinium chlorochromate (PCC)[6] (**3** to **4**), that proceeded (61–87% yield) smoothly, even in the presence of acid-labile groups (Table 1).

A further improved oxidative method was then developed by the application of the phase-transfer technique,[7] that was carried out by the addition of potassium dichromate or potassium chromate and 30% sulphuric acid to a solution of the nitroalkanols **3** and tetra-*n*-butylammonium hydrogen sulfate, in dichloromethane and at −10 °C (Scheme 2).

Table 1. Representative examples of the synthesis of α-nitro ketones by oxidation with PCC

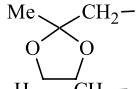
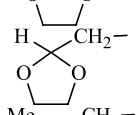
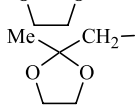
Entry	R	R_1	R_2	Yield of **4** from **3** (%)
1	H	Me	*c*-C_6H_{11}	83
2	H	Et	*i*-Pr	87
3	H	Et	$Ph(CH_2)_2$	86
4	H	$MeO_2C(CH_2)_2$	Me	65
5	H	$THPOCH_2$	*i*-Pr	61
6	H		Me	78



Scheme 2.

Under these conditions, many functionalities (esters, acetals, ketals, ethers and carbon–carbon double bonds) are retained and good yields (68–95%) of the α-nitro ketones are obtained (Table 2).

Table 2. Representative examples of the synthesis of α-nitro ketones by oxidation with potassium dichromate

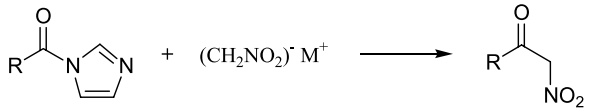
Entry	R	R^1	R^2	Yield of **4** from **1**+**2** (%)	Yield of **4** from **3** (%)
1	Me	Me	$CH_2{=}CH(CH_2)_2$		77
2	H	Me	$CH_2{=}CH(CH_2)_2$	72	84
3	H	Me	$Ph(CH_2)_2$	80	93
4	H		$Ph(CH_2)_2$		71
5	H		*n*-C_6H_{13}	72	82
6	H		*n*-C_6H_{13}		95

Furthermore, the solvent-free nitroaldol reaction on alumina, followed by in situ oxidation of the formed nitroalkanols, proceeded in a one-pot synthesis of α-nitro ketones (Scheme 2, **1**+**2** to **4**).[7,8]

2.2. From carboxylic acid derivatives

The synthesis of α-nitro ketones by C-acylation of nitroalkanes has been carried out, in the past, with limited success and, in fact, the pioneering applications of this process, using either acyl halides, anhydrides, or activated

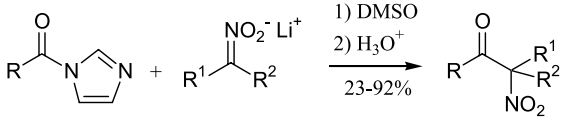
esters have proved to be of little synthetic value for the preparation of α-nitro ketones.[9] Seebach then published[10] the synthesis of the title compounds by the reaction of a doubly metalated complex $[R\text{-}C{=}NO_2]^{2-}2Li^+$, generated at 90 °C, with acid chlorides or esters. Next, the preparation of α-nitro ketones via a direct acylation or sodium of potassium methanenitronate with the appropriate *N*-acylimidazole was reported[11] (Scheme 3).



M = Na, K
R = Ph, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *m*-$NO_2C_6H_4$
3,5-$(MeO)_2C_6H_3$, 3,4-$Me_2C_6H_3$, $Ph(CH_2)_2$, Me

Scheme 3.

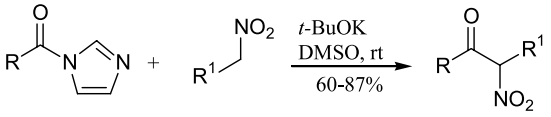
A more complete procedure[12] was based on the acylation of a dimethylsulfoxide solution of the lithium salt of the nitroalkane (previously prepared and stored in dry form) with acylimidazoles (Scheme 4).



R = Me, Ph, MeO, EtO, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$;
R^1 = Me, $CH_2CH(OCH_2)_2$; R^2 = H, Me

Scheme 4.

Then, other authors[13] developed a method by, which it is possible to overcome the tedious and time consuming use of the dry form of the lithium nitronate; in fact, the potassium salt, prepared in situ (Scheme 5) by treatment of the nitroalkane with potassium *t*-butoxide in dimethylsulfoxide, is reactive enough to allow the formation of α-nitro ketones, in good yields, by reaction with acylimidazoles (Table 3).

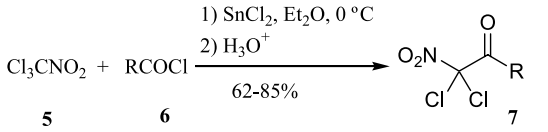


Scheme 5.

Table 3. Representative examples of the synthesis of α-nitro ketones from acylimidazoles

Entry	R	R^1	Yield of α-nitro ketones (%)
1	*n*-C_6H_{13}	Me	71
2	Me	Bn	87
3	*p*-ClC_6H_4	Me	68
4	*n*-C_6H_{13}	$MeCO(CH_2)_2$	62
5	*n*-C_6H_{13}	$MeO_2(CH_2)_2$	68

An interesting procedure for the preparation of dichloronitro ketones was reported by Demir et al.[14] starting from acyl chlorides. Thus, trichloronitromethane **5** adds to acyl chlorides **6** in the presence of tin(II) chloride yield to the

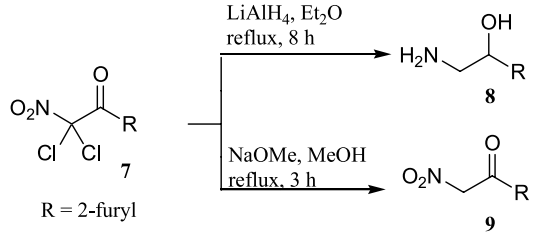


R = Me, CH_2Cl, Et, *i*-Pr, 2-thiophenil, Ph, 2,4-dichlorophenyl, 4-*n*-pentyloxyphenyl, 2-furyl.

Scheme 6.

dichloronitro ketones **7**, via a substitution reaction (Scheme 6).

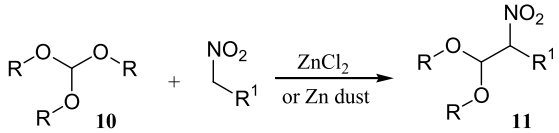
Finally, reduction and/or dechlorination of **7** gives the amino alcohols **8** and nitro ketones **9**, respectively, in good yields (Scheme 7).



Scheme 7.

2.3. From ketones or alkyl orthoformates

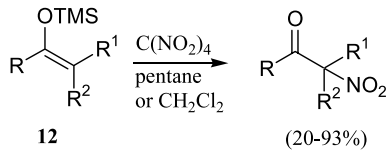
α-Nitro ketones can be prepared from a series of carbonyl derivatives and, in this context, originally, arylnitro ketones have been obtained from ketones with a poor-yielding method[15] (15–45%). Later, Rene and Royer[16] proposed a new method to obtain nitroacetaldehyde dialkylacetals **11**, by the reaction of alkyl orthoformates **10** with an excess of nitroalkanes, in the presence of zinc chloride (Scheme 8).



R = Me, Et, *n*-Pr; R^1 = H, Me

Scheme 8.

A very efficient procedure was then discovered using tetranitromethane (TNM) as a mild nitrating agent[17] of cyclic and acyclic silyl enol ethers **12** (Scheme 9).[18] In fact, highly coloured (red) solutions of various enol silyl ethers



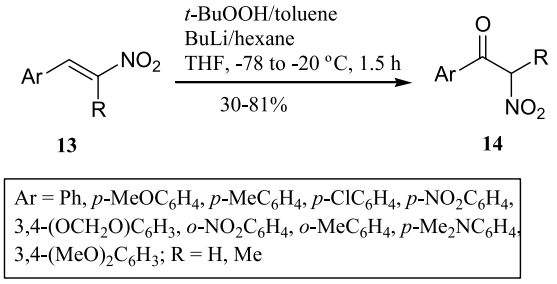
R = Aryl, *n*-Pr, *t*-Bu; R^1 = H; R^2 = H, Me, Et, *n*-Bu, Bn or R^1-R^2= cycloalkyl

Scheme 9.

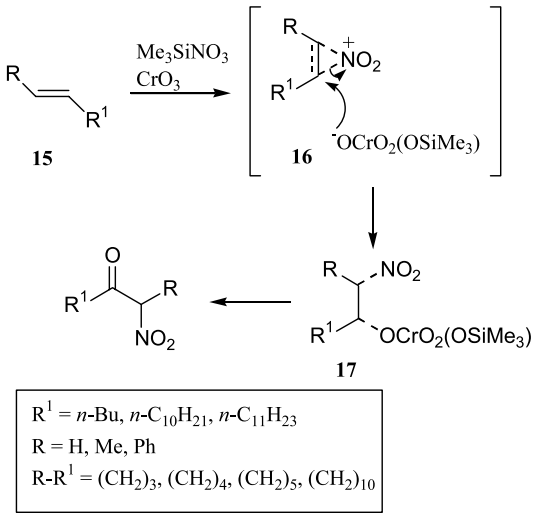
and TNM were readily bleached to afford good yields of the title compounds in the dark at room temperature or below.

2.4. From alkenes

Treatment of substituted β-nitrostyrenes **13** with *tert*-butyl hydroperoxide and butyllithium gives the α-nitro acetophenones **14** in satisfactory to good yields (Scheme 10);[19] the oxidation works well with a variety of nitrostyrenes.



Scheme 10.



Scheme 11.

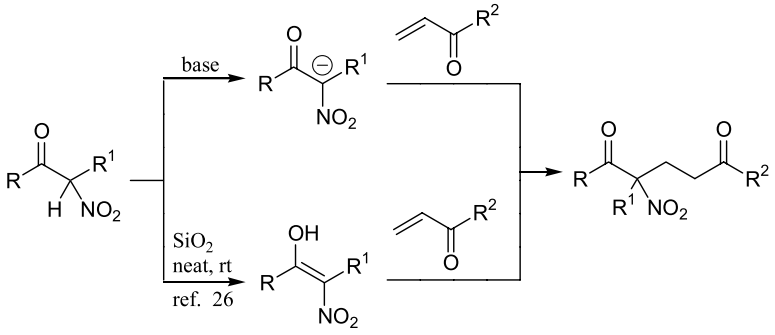
The combination of trimethylsilyl nitrate (prepared in situ from silver nitrate and chlorotrimethylsilane[20]) and chromium trioxide readily converts the olefins **15** into the corresponding, cyclic and acyclic, α-nitro ketones (Scheme 11),[21] in good yields. The authors presumed that a species such as $O_2N–O–CrO_2–(OSiMe_3)$ is generated in situ and acts as a source of $^{+}NO_2$ and $^{-}OCrO_2–(OSiMe_3)$ and eventually reacts with the olefins to yield the α-nitro ketones. The intermediate **16** is attacked by the species $^{-}OCrO_2–(OSiMe_3)$ to give another intermediate **17**, followed by cleavage of the O–Cr bond, with concomitant oxidation, to yield the α-nitro ketones.

3. Reactivity of acyclic α-nitro ketones

α-Nitro ketones have been demonstrated to be very useful intermediates in organic synthesis and, in recent years, their utility in the preparation of a variety of important units has been explored. The peculiar chemical behaviour of these molecules is due to the presence, in two vicinal positions, of highly versatile functionalities such as the carbonyl group and the nitro group. Moreover, the α-nitro ketones containing an α-hydrogen atom are very acidic molecules[22–24] with pK_a values close to carboxylic acids. In aqueous solution, they are characterized by a relatively high enol content and by the possible presence of the α-ketonitronic *aci* form at equilibrium. The kinetics of the reversible enantiomeric interconversion of the α-nitro ketones have been studied by dynamic high-resolution gas chromatography (DHRGC),[25] and the obtained results show the dramatic effect of an α-nitro substituent on the rate of enolization of simple ketones. The fairly acidic proton α to the nitro group can be easily removed under mild conditions, thus permitting the C–C bond formation and, in this context, the Michael addition of α-nitro ketones to α,β-unsaturated carbonyl derivatives is of great interest. This reaction is usually performed under basic conditions,[2] but the easy enolization of the α-hydrogenated α-nitro ketones (both cyclic and acyclic) offers the opportunity to perform the conjugate addition also under solid acidic catalysis (SiO_2, Scheme 12),[26] giving good yields of the formed 2-nitro-1,5-dicarbonyl derivatives (Table 4).

3.1. Denitration of α-nitro ketones

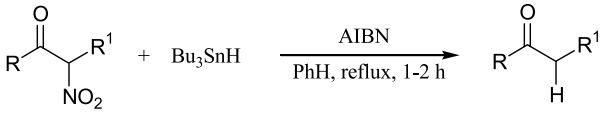
The upsurge in the utilization of the α-nitro ketones is strongly connected with the discovery of new methods, which lead to the displacement of the nitro group by a hydrogen. The first report recognised that tin hydrides are excellent reagents for the denitrohydrogenation reaction of nitro derivatives.[27] This procedure selectively replaces the nitro group with a hydrogen on secondary and tertiary α-nitro ketones, while it fails with the primary ones. The



Scheme 12.

Table 4. Representative examples of the Michael addition of α-nitro ketones to conjugated enones

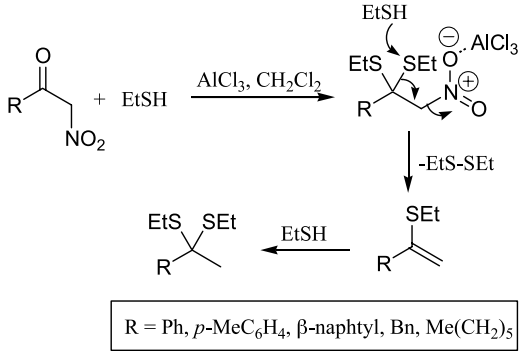
Entry	R	R^1	R^2	Yield of 2-nitro-1,5 dicarbonyls (%)
1	Ph	H	Me	87
2	*c*-C_6H_{11}	*n*-Bu	Me	86
3	$Me(CH_2)_2CH(Me)$	Me	Me	88
4	$Ph(CH_2)_2$	Et	Et	76
5	Ph	H	*n*-Pr	86



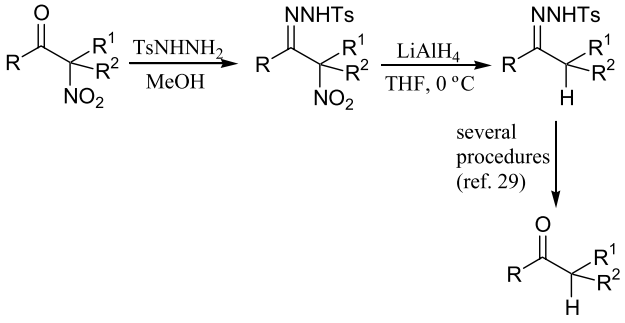
Scheme 13.

Table 5. Representative examples of denitration of α-nitro ketones with Bu_3SnH/AIBN

Entry	R	R^1	Yield of denitrated ketones (%)
1	*p*-CNC_6H_4	Me	77
2	*n*-C_6H_{13}	$MeCO(CH_2)_2$	84
3	*n*-C_6H_{13}	$MeO_2C(CH_2)_2$	80
4	Me	$MeO_2C(CH_2)_4$	90



Scheme 14.



Scheme 15.

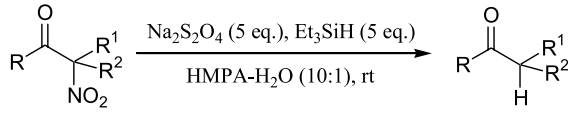
reaction proceeds (Scheme 13) via free-radical chain processes, in refluxing benzene and in the presence of a catalytic amount of azobisisobutyronitrile (AIBN), and Ono and co-workers have reported[13a] a series of useful applications (Table 5).

Replacement of the nitro group by hydrogen in primary α-nitro ketones has been realized on treatment with ethanethiol in the presence of aluminium chlororide.[28] A possible mechanism involves an ionic process according to Scheme 14.

Later, we developed an easy and efficient procedure for the hydrodenitration of α-nitro ketones by treatment of their tosylhydrazones with lithium aluminium hydride, in dry THF, at 0 °C.[29a] This method (Scheme 15) gave high yields of the denitrated products and proved to be very efficient for secondary and tertiary nitro derivatives.

The obtained tosylhydrazones are, in general, crystalline derivatives, so that it is possible to purify the products by simple crystallization. On the other hand, tosylhydrazones may be easily cleaved[29b] to afford good yields of the corresponding denitrated ketones (Table 6).

The nitro group can also be replaced by hydrogen on treatment with a soft reducing agent such as sodium dithionite. Therefore, the denitration of various α-nitro ketones was carried out with the $Na_2S_2O_4$–Et_3SiH system in hexamethylphosphoramide (HMPA)–H_2O (Scheme 16).[30]



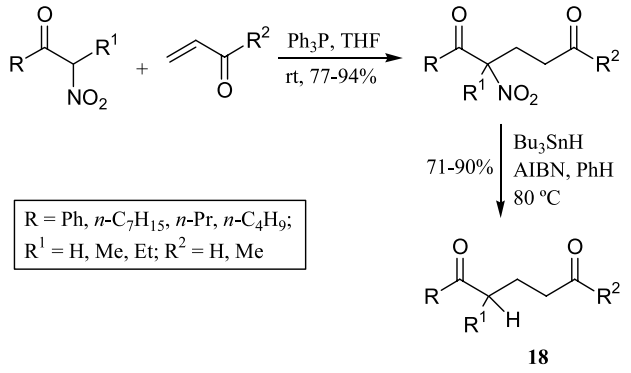
Scheme 16.

Thus, the easy availability of α-nitro ketones from a variety of precursors, combined with the possibility to replace the nitro group by a hydrogen, make these compounds the key building blocks for the synthesis of several important targets.[13,31–39] In fact, the sequence,[31] Michael addition of α-nitro ketones to methyl vinyl ketone or acrylaldehyde, and denitration with Bu_3SnH, affords the 1,5-dicarbonyl compounds **18**, an important class of compounds, especially as intermediates for the preparation of cyclohexenones, in good yields (Scheme 17).

The reaction of α-nitro ketones with 37%-formaldehyde, in the presence of a catalytic amount of Ph_3P, is an elegant

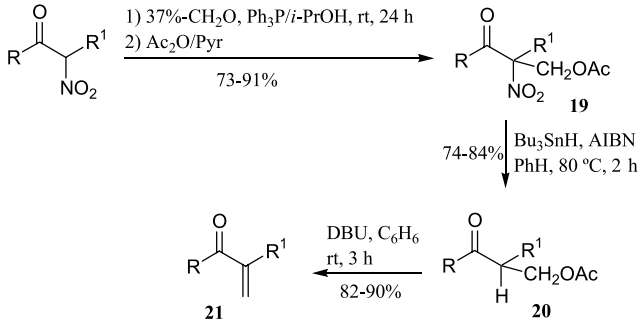
Table 6. Representative examples of denitration of α-nitro ketones with $LiAlH_4$, via their tosylhydrazones

Entry	R	R^1	R^2	Yield of α-nitro ketone tosylhydrazones (%)	Yield of denitrated tosylhydrazones (%)
1	*n*-Pr	Me	H	89	81
2	*i*-Pr	Et	H	85	86
3	*c*-C_6H_{11}	Me	H	81	87
4	$Ph(CH_2)_2$	Me	Me	65	94



Scheme 17.

procedure for the regioselective synthesis of α-methylene carbonyl compounds.[32] As shown in Scheme 18, a mixture of α-nitro ketone, 37%-CH_2O and Ph_3P/*i*-PrOH gives the hydroxymethylated compounds, which were acetylated with acetic anhydride in pyridine, yielding the compounds **19**. Subsequent treatment of **19** with Bu_3SnH/AIBN resulted in clean denitration to give **20**, which were converted into α-methylene ketones **21** on treatment with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), in benzene, and in good yields (Table 7).



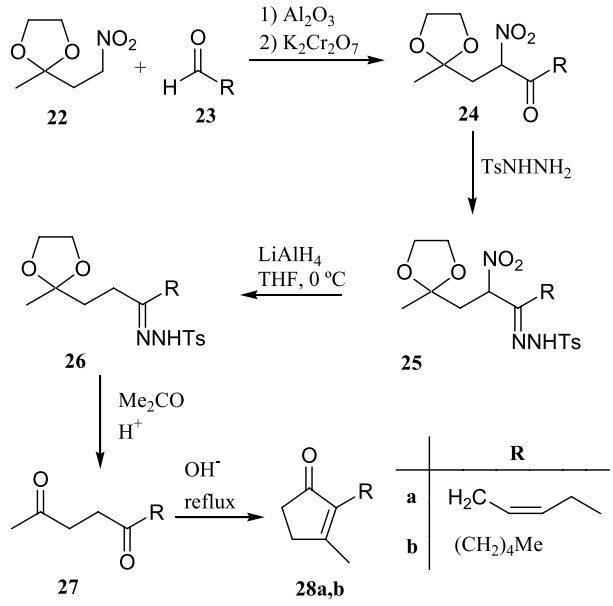
Scheme 18.

Table 7. Representative examples of the synthesis of α-methylene ketones **21**

Entry	R	R^1	Yield of **21** from **20** (%)
1	*n*-Pr	Et	90
2	*i*-Pr	Et	82
3	n-C_5H_{11}	Me	85
4	n-C_6H_{13}	Me	85

In Scheme 19, (*Z*)-jasmone **28a** and dihydrojasmone **28b** have been prepared[34] starting from the nitro ketal **22**. The nitroaldol reaction of **22** with the appropriate aldehydes **23** is the chain-lengthening reaction, followed by the in situ oxidation and denitration, via the *p*-toluenesulfonylhydrazones **25** and **26** of the corresponding α-nitro ketones **24**. Removal of the protecting groups yielded the 1,4-diketones **27**, which were cyclized to **28** with alkali.

The synthesis of (*Z*)-5-undecen-2-one **34**, the principal volatile component of the pedal gland exudates of the bontebox *Damaliscus dorcas dorcas*, has been carried out[35] via denitration of the α-nitro ketone **31**. This procedure

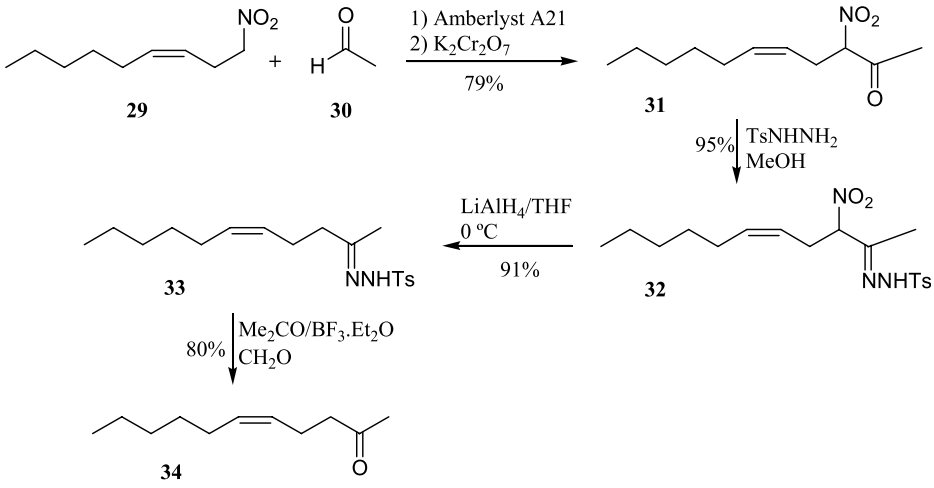


Scheme 19.

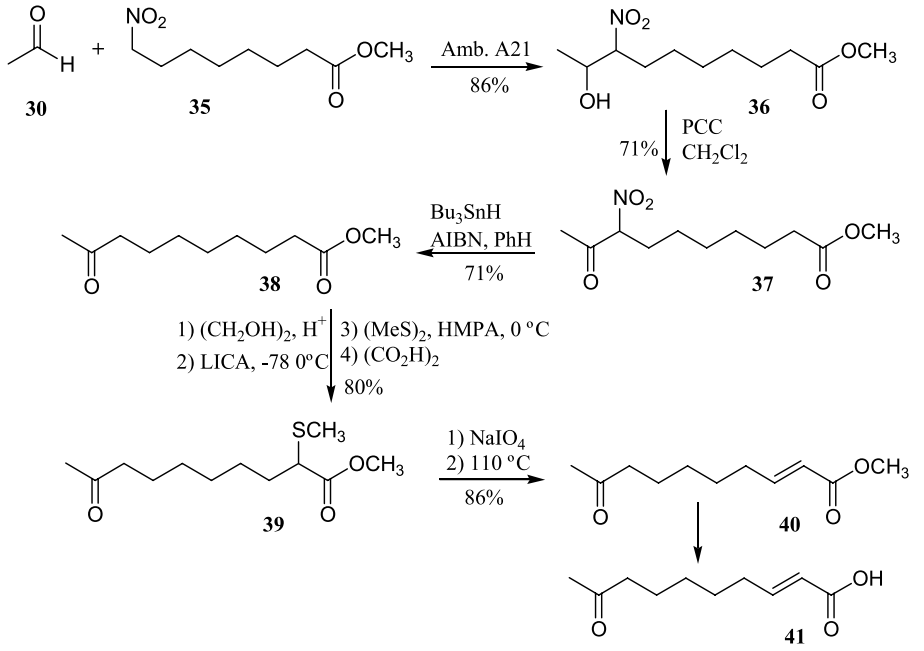
(Scheme 20) starts from (*Z*)-1-nitro-3-nonene **29** as the (*Z*)-3-nonen-1-yl-anion synthon. The nitroaldol reaction of **29** with acetaldehyde **30** (catalysed by Amberlyst A21), followed by in situ potassium dichromate oxidation, under phase-transfer catalysis, afforded the nitro ketone **31**. Reaction of **31** with $TsNHNH_2$ gave the corresponding hydrazone **32** in high yield (95%). Treatment of compound **32** with $LiAlH_4$, in THF at 0 °C, produced the denitrated hydrazone **33**. Subsequent deprotection of **33**, performed in acetone/water with a catalytic amount of boron trifluoride etherate, furnished (*Z*)-5-undecen-2-one **34**, having achemical purity of 98% by GLC, in 54% overall yield from **29**.

Methyl 8-nitrooctanoate **35** is a useful starting material[36] for the synthesis of 9-oxo-(*E*)-2-decenoic acid **41**, an important sex attractant of the queen bee, also implicated as a pheromone of termites (Scheme 21). Thus, the reaction of **35** with acetaldehyde **30**, in the presence of Amberlyst A21, gave the nitroalkanol **36**. Subsequent oxidation with pyridinium chlorochromate in dichloromethane furnished the α-nitro ketone **37**, which, by reaction with Bu_3SnH and a catalytic amount of AIBN in refluxing benzene, was denitrated to **38** (46% overall yield). The keto ester **38** then be converted into the α,β-unsaturated methyl ester **40**, via sulfenylation/dehydrosulfenylation reactions giving **39**.

(*Z*)-Heneicos-6-en-11-one **47**, a (*Z*)-δ,ε-alkenone isolated in 1975, is the sex pheromone of the Douglas Fir Tussock moth (*Orgyia pseudotsugata*). Douglas Fir Tussock moth is a severe defoliator of fir forest and, consequently, there has been considerable interest in the synthesis of this pheromone. In Scheme 22 is reported[37] its convenient preparation, via denitration of the nitro ketone **44**. Thus, nitroaldol reaction of the nitroalkene **42** with undecanal **43** on Amberlyst A21, and in the absence of solvent, followed by oxidation of the resulting nitroalcohol with potassium dichromate under a phase-transfer catalyst, yielded **44** (70%), and then conversion of **44** into the corresponding tosylhydrazone **45** was performed in 90% yield. Finally, denitration of **45** with $LiAlH_4$ in THF at 0 °C to **46**, followed



Scheme 20.



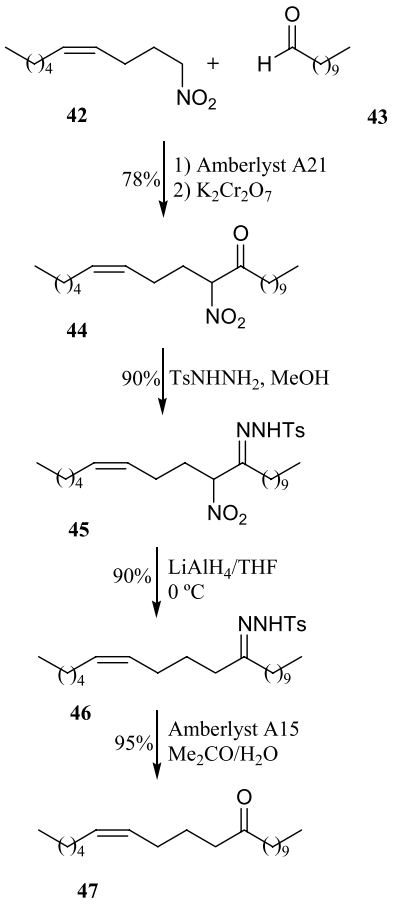
Scheme 21.

by regeneration of carbonyl group, carried out in acetone–water with the catalyst, Amberlyst A15, gave the pheromone **47** in 60% overall yield and with high isomeric purity (>99% by ^{13}C NMR).

The asymmetric synthesis of spiroketals can also be obtained from the denitration of α-nitro ketone and, in fact,[39] as depicted in Scheme 23, the TBDMS-protected nitro alcohol (*S*)-**49**, obtained from **48**, was acetylated by acetylimidazole under the catalysis of DBU in THF, giving (*S*)-**50** in 62% yield. The next step was to eliminate the nitro group from **50**. Thus, the reaction of (*S*)-**50** with Bu_3SnH/AIBN gave the TBDMS-protected (*S*)-6-hydroxy-2-heptanone **51** in 92% yield. The ω-hydroxybutylation of the methyl group of the compound **51** was accomplished by generating the enolate with LDA and reaction with 4-chloro-1-(tetrahydropyranyloxy)butane, in the presence of NaI. Deprotection of the obtained **52** with 6 M HCl in methanol produced (via **53**) (*2S,6R*)-(−)-2-methyl-1,7-dioxaspiro[5.6]dodecane **54**, a pheromone for *Andrena haemorrhoa*, in 46% yield (the optical purity of the product has been measured to be 97%).

3.2. Conversion of α-nitro ketones into α-phenylthio ketones

The nitro group on α-nitro ketones, due to its activation by the carbonyl, can be replaced by a phenylthio group in the reaction with benzenethiol or its potassium salt.[40] This reaction (Scheme 24) proceeds by an electron–transfer mechanism and is applicable to the general synthesis of α-phenylthio ketones **55**, from primary and secondary nitro derivatives. In a typical procedure, a mixture of nitro ketone, benzenethiol and AIBN, in hexamethylphosphoric

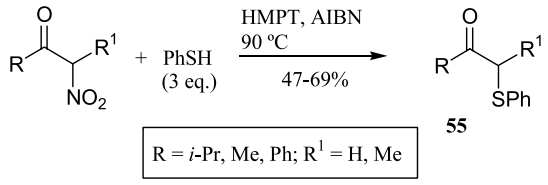


Scheme 22.

triamide (HMPT), afforded the thio-substituted product in satisfactory yields at 90 °C for 1 h.

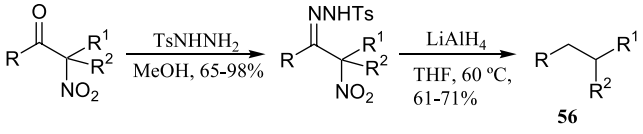
3.3. Tandem denitration–deoxygenation of α-nitro ketones

The importance of α-nitro ketones in organic synthesis has been increased by the discovery of efficient procedures to effect the substitution of the nitro group with hydrogen.



Scheme 24.

However, an increased utilization of these compounds resulted in the discovery of new procedures for the removal of both the nitro and the carbonyl groups. In this context, the first tandem denitration–deoxygenation process was realized on the basis of the indirect method to effect the denitrohydrogenation of α-nitro ketones[28] and on the Caglioti reaction[41] for the carbonyl to methylene conversion, via tosylhydrazones. Thus, the conversion of α-nitro ketones into the corresponding tosylhydrazones, followed by reduction[42] of the latter with lithium aluminium hydride in tetrahydrofuran (THF) at 60 °C (Scheme 25), provides the corresponding alkanes **56** in good to high yields (Table 8).

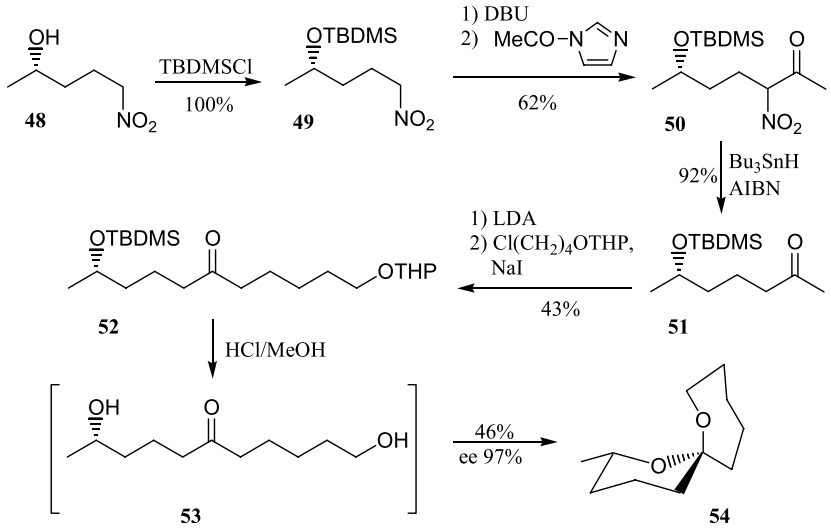


Scheme 25.

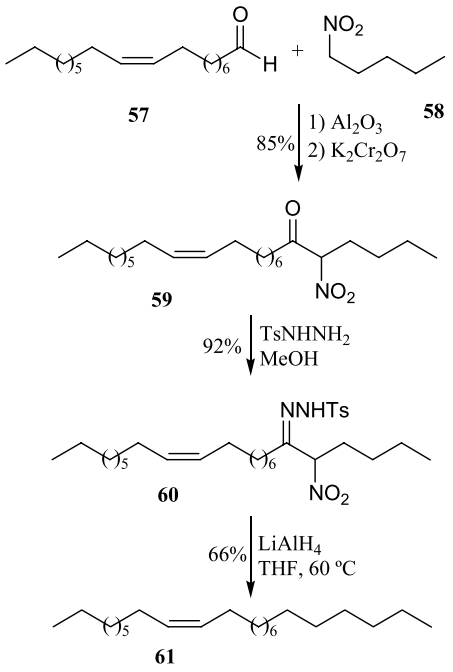
Table 8. Representative examples of the preparation of alkanes from α-nitro ketones

Entry	R	R^1	R^2	Yield of alkanes (%)
1	$Ph(CH_2)_2$	*n*-C_8H_{17}	H	61
2	*n*-$C_{11}H_{23}$	*n*-C_6H_{11}	H	68
3	$Ph(CH_2)_2$	Me	Me	67
4	$Ph(CH_2)_2$	Me	H	70

The preparation of (*Z*)-9-tricosene **61**, a sex pheromone component of the mature female housefly (*Musca domestica*), has been reported[42] as an application of the above procedure (Scheme 26).



Scheme 23.



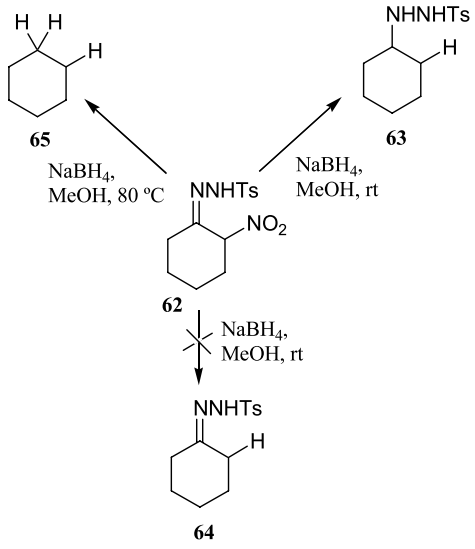
Scheme 26.

Thus, nitroaldol reaction of oleic aldehyde **57** with 1-nitropentane **58** on basic alumina in the absence of any solvent, followed by in situ oxidation of the resulting nitro alcohol with potassium dichromate in the presence of tetra-*n*-butylammonium hydrogen sulfate, as a phase-transfer catalyst, afforded the nitro ketone **59** in 85% yield. The conversion of the compound **59** into the corresponding (*p*-tolylsulfonyl)hydrazone **60** was performed in 92% yield, after recrystallization. Reduction of the compound **60** with lithium aluminium hydride at 60 °C produced the target pheromone component **61** in 66% yield.

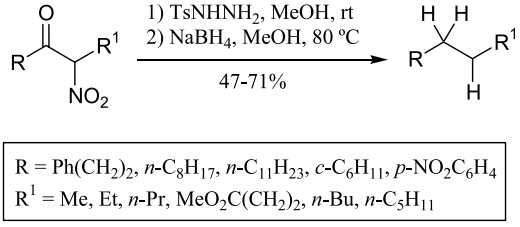
A novel procedure for the simultaneous denitration–deoxygenation of 2-nitro ketones reported by $TsNHNH_2$–$NaBH_4$.[43] The idea started with the observation that the reduction of 2-nitrocyclohexanone tosylhydrazone **62** (Scheme 27) with $NaBH_4$, at room temperature, gave the *N*-cyclohexyl-*N*′-tosylhydrazine **63**, instead of the expected[28] cyclohexanone tosylhydrazone **64**, whereas, if the temperature was raised to 80 °C, cyclohexane **65** was obtained in 60% yield.

These results prompted the authors to develop a new, chemoselective, one-pot procedure for the simultaneous denitration–deoxygenation of 2-nitro ketones, firstly by their conversion into the corresponding tosylhydrazones (Scheme 28) in methanol at room temperature, followed by the addition of $NaBH_4$ and refluxing at 80 °C. Thus, the desired alkanes were readily obtained in satisfactory to good yields. Under these conditions, other functionalities such as esters and nitro-aromatic groups, were preserved.

A very useful application of the latter procedure is the two-steps synthesis of 2-methylheptadecane **68**,[44] the sex attractant pheromone of at least nine species of the *Artidae* family, and a flavour component in several mango varieties, and in black soya beans, in blue-green algae, etc. The



Scheme 27.



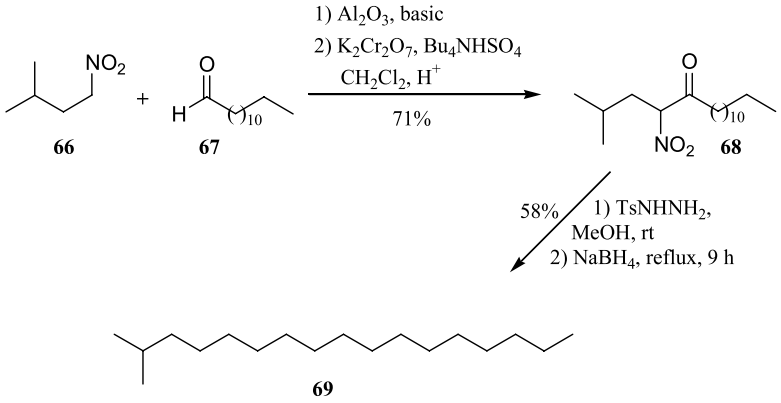
Scheme 28.

preparation (Scheme 29) has been achieved starting from 1-nitro-3-methylbutane **66**. Nitroaldol reaction of tridecanal **67** with **66** on basic alumina, followed by in situ oxidation of the obtained nitroalkanol, gave the nitro ketone **68** in 71% yield. The tandem denitration–deoxygenation of **68** to **69** was performed by converting **68** into the corresponding tosylhydrazone and subsequent in situ reduction with $NaBH_4$ at 80 °C. 2-Methylheptadecane **69** was readily produced in 41% overall yield.

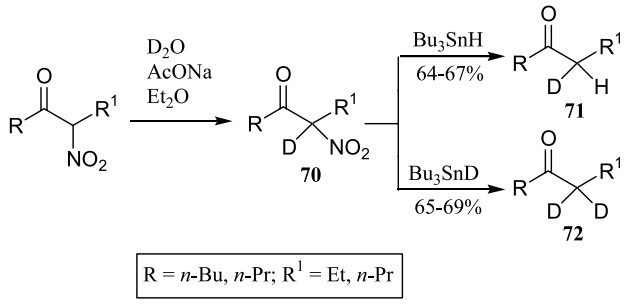
3.4. α-Nitro ketones as precursors of deuterated molecules

Based on the above reported procedures[13,28] for the denitrohydrogenation of α-nitro ketones, two new methods for the highly regiospecific C-α deuteration of alkyl ketones have been developed. α-Deuterated ketones are usually obtained from the enol derivatives of the corresponding ketones, but with poor regiospecificity. Firstly, Ono et al. published[45] the regioselective α-mono- or α,α-di-deuteration of some carbonyl compounds from α-nitro ketones by H–D exchange of the α-hydrogen. As shown in Scheme 30, α-nitro ketones are treated with D_2O–AcONa in diethyl ether to result in a clean H–D exchange giving **70**. Treatment of **70** with Bu_3SnX (X=H, D) produced **71** or **72**, respectively, in good yields.

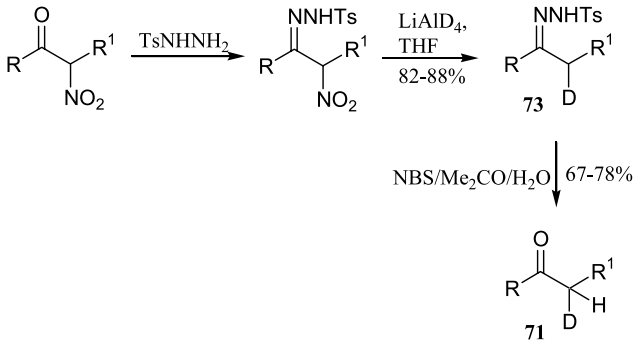
The conversion of the α-nitro ketones into **71** can also be performed by an indirect procedure[46] through conversion into their tosylhydrazones (Scheme 31) and treatment of the latter with lithium aluminium deuteride in tetrahydrofuran



Scheme 29.



Scheme 30.



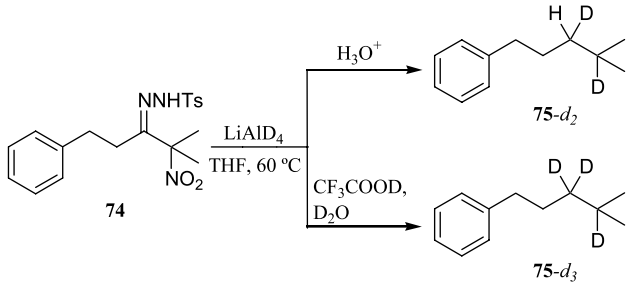
Scheme 31.

at 0–10 °C to give the α-deuterio tosylhydrazone **73** in good yield; regeneration of the carbonyl group, from **73** to **71**, can be performed, without loss of deuterium, with *N*-bromosuccinimide (Table 9). Although this procedure is indirect, it compares favourably with the known methods in terms of simplicity performance, toxicity, and efficiency.

Table 9. Representative examples of α-deuterated ketones prepared

Entry	R	R^1	Yield of **73** (%)	Yield of **71** (%)
1	Ph	Me	88	82
2	*c*-C_6H_{11}	Me	90	88
3	$Ph(CH_2)_2$	Me	81	85

In addition to the above procedures to afford α-deuterated ketones, α-nitro ketones are also prone to give, via their tosylhydrazones, di- or tri-deuterated alkanes. In fact, when (Scheme 32) the α-nitro ketone tosylhydrazone **74** was

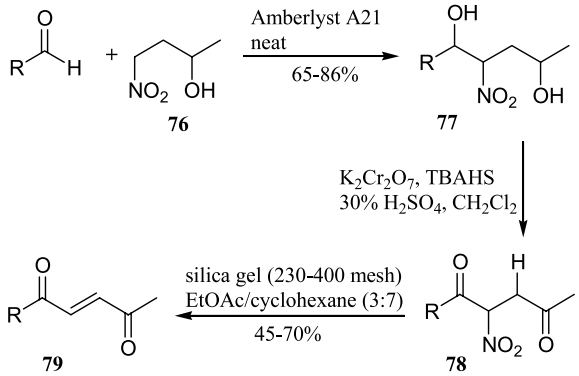


Scheme 32.

reduced[42] with lithium aluminium deuteride at 60 °C for 10 h, quenching with 2 N aqueous HCl gave the compound **75**d_2 (≥98% isotopically pure di-deuterated alkane) in 55% yield, while treating the reaction mixture with trifluoroacetic acid-*d*/D_2O (1/9) produced the compound **75**d_3 (≥98% isotopically pure tri-deuterated alkane) in 52% yield.

3.5. α-Nitro ketones as precursors of (*E*)-α,β-unsaturated-γ-dicarbonyl compounds

(*E*)-Enediones are valuable intermediates for the synthesis of important molecules such as prostaglandins, rethrolones, perfumes, pheromones, macrocycles, and other natural products.[47] Thus, it is evident that the preparation of conjugated enediones is a very important goal, and α-nitro ketones have been demonstrated to be very convenient building blocks for their synthesis. In fact, the nitroaldol reaction (Scheme 33) between an aldehyde and the γ-nitro



Scheme 33.

alcohol **76**, in the presence of Amberlyst A21 and in the absence of any solvent, gave the nitro diols **77** in good yields. Potassium dichromate oxidation of **77** under phase-transfer conditions afforded the crude α-nitro ketones **78**. Vigorous stirring (20 h) of **78** in a mixture of cyclohexane/EtOAc (7:3) and silica gel (0.040–0.063 mm) and subsequent flash chromatography effected the elimination of nitrous acid and afforded α,β-unsaturated-γ-dicarbonyl derivatives **79** exclusively as the (*E*)-isomers in 45–70% yields from **77** (Table 10).[47]

Table 10. Representative examples of the synthesis of enediones **79**

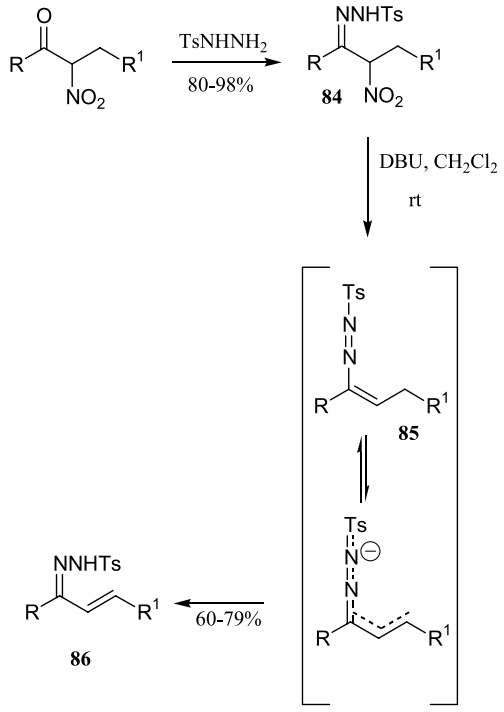
Entry	R	Yield of **77** (%)	Yield of **79** (%)
1	n-$C_{10}H_{21}$	86	58
2	c-C_6H_{11}	78	58
3	$Ph(CH_2)_2$	80	70
4	z $Me(CH_2)_7CH{=}CH(CH_2)_7$	70	58
5	$Me(CH_2)_4CH(NO_2)(CH_2)_2$	82	65

As an application of this strategy, a convenient synthesis (Scheme 34) of (*E*)-non-3-ene-2,5-dione **83**, the main component isolated from the volatile compounds derived from the cephalic secretion of workers of *Trigona tataira*, has been reported.[48] The preparation started with the nitroaldol reaction of pentanal **80** with *rac*-**76**, the resulting β-nitro alcohol *rac*-**81** was then oxidized to the α-nitro ketone **82**, which afforded the target enedione **83** via elimination of nitrous acid assisted by Et_3N (69.7% overall yield).

3.6. α-Nitro ketones as precursors of (*E*)-α,β-unsaturated enones

The discovery that the replacement of the nitro group by hydrogen in nitro ketones can be performed through their tosyl hydrazones (Scheme 35)[28] has been the driving force for the development of a new application of α-nitro ketones as precursors of α,β-unsaturated enones.

As reported in Scheme 35, treatment of α-nitro ketone tosylhydrazones, easily obtained from the corresponding ketones, with DBU (1.5 mol), in dichloromethane at room temperature gives, after a short time (15 min), the α,β-unsaturated ketone tosylhydrazones **86**.[49] The formation of **86** takes place by a 1,4-elimination of nitrous acid from **84**, affording the 1-tosylazoalkenes **85**, which, under basic conditions (DBU), tautomerize to the more stable enone tosylhydrazones **86**.

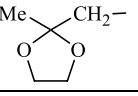


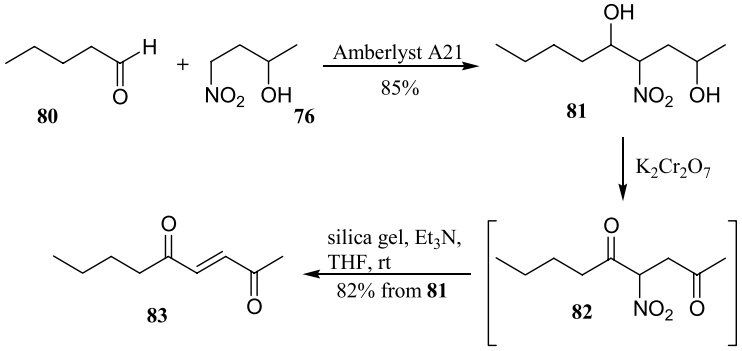
Scheme 35.

The azo-diazo conversion of **85** to **86** can be related to the electron-withdrawing power of the tosyl group, which, through the conjugated double-bond system, strongly polarizes the allylic hydrogen of alkene.

Satisfactory to high yields of isolated products were observed both in the conversion of the α-nitro ketones into **84**, as well as in the formation of **86** (Table 11).

Table 11. Representative examples of the synthesis of α,β-unsaturated compounds **86**

Entry	R	R^1	Yield of **86** (%)
1	$Ph(CH_2)_2$	H	60
2	z $MeCH_2CH{=}CH(CH_2)_2$	H	70
3	$Ph(CH_2)_2$		74

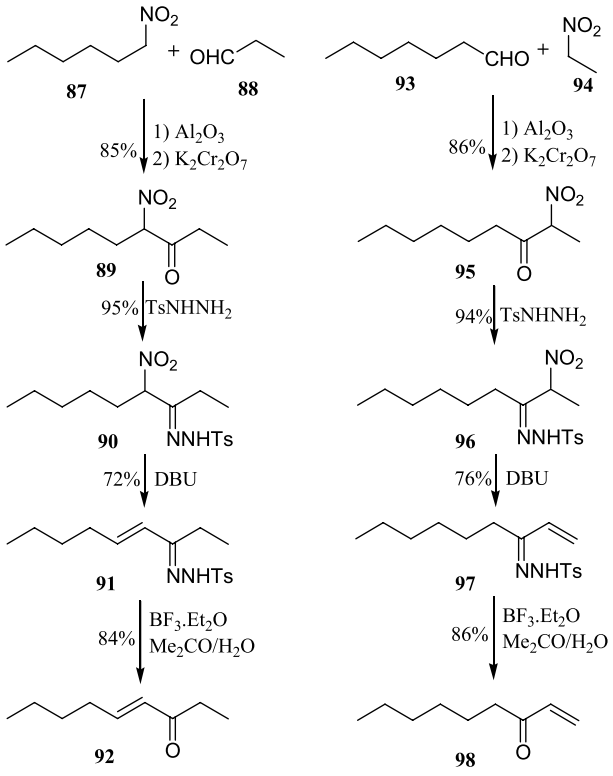


Scheme 34.

Tosylhydrazones are, in general, crystalline and it is possible to obtain the pure compounds easily by recrystallization. Moreover, the tosylhydrazones **86** may be readily cleaved to give the corresponding enones by a multitude of procedures,[29] so that the method represents a new α,β-unsaturated ketone synthesis, from α-nitro ketones.

Since it is possible to prepare nitro ketones with the nitro group in either the α- (**89**) or α′-position (**95**) from the appropriate starting material, the above procedure offers a regioselective approach for the synthesis of α,β-unsaturated carbonyl compounds (Scheme 36). In fact, a solvent-free nitroaldol reaction (**87** with **88** or **93** with **94**) on basic alumina and in situ oxidation, under phase-transfer conditions, with potassium dichromate affords, in one-pot and in 85 and 86% yields, **89** and **95**, respectively. Following the procedure reported in Scheme 35, **89** and **95** were the transformed into the corresponding tosylhydrazones **90** and **96** in good yields (95 and 94%), then converted into **91** and **97** (72 and 76% yields), which, after regeneration of the ketones with acetone/water/boron trifluoride etherate, give (*E*)-4-nonen-3-one **92** and 1-nonen-3-one **98** in **84** and 86% yields [overall yields 9% (**92**) and 53% (**98**) in four steps].

By this method, even if the formation of both *Z*- and *E*-isomers is plausible, exclusively the latter is obtained.



Scheme 36.

3.7. Stereoselective synthesis of β-nitro alcohols from α-nitro ketones

β-Nitro alcohols are an important class of compounds frequently used as key intermediates in the construction of numerous natural products and other useful biologically active compounds.[50] For these reasons, the stereoselective synthesis of β-nitro alcohols represents an attractive area of research. Although the nitroaldol (Henry) reaction has a remarkable ability to yield the latter compounds, the levels of the stereoselectivity are usually low, because the basicity needed for the Henry reaction produces the epimerisation of the formed nitroalkanols. In this context, an alternative way for an asymmetric synthesis of β-nitro alcohols is the stereoselective reduction of the corresponding α-nitro ketones.

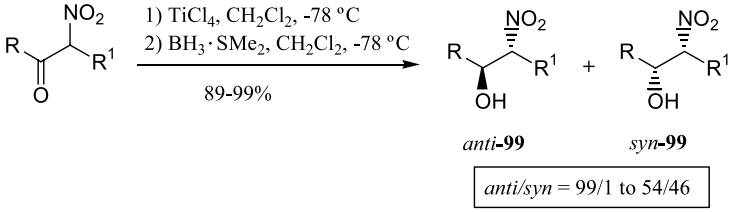
Thus, the first $TiCl_4$-mediated diastereoselective reduction of α-nitro ketones to *anti*-β-nitro alcohols **99** has been recently developed (Scheme 37).[50]

These studies have revealed that the reduction of α-nitro ketones at low temperature (−78 °C) with borane-dimethyl sulfide (BH_3 SMe_2) in the presence of $TiCl_4$ provides good to excellent *anti* selectivity (Table 12).

The sense of the stereocontrol may be predicted by invoking the cyclic Cram chelate model[51] for hydride delivery to the carbonyl moiety. This is clearly due to the chelation by the titanium atom, which creates a bridge between the oxygen atoms of the C=O and NO_2 groups. In the resulting six-membered cyclic intermediate, the most populated conformation A, respect to B, is preferentially attacked by the incoming hydride ion at the less-hindered side opposite R^1 (Scheme 38). It is obvious that every increase in bulkiness of R^1, shifting the conformational equilibrium towards the A conformation, increases the *anti*/*syn* ratio.

Later, Crich et al. reported[52] the asymmetric synthesis of highly substituted β-nitro alcohols from α,α-disubstituted-α-nitro ketones, by their reduction under (*S*)-oxazaborolidine catalysis **100**, in the presence of borane-dimethyl sulfide, resulting in the enantio-enriched nitro alcohols (Scheme 39).

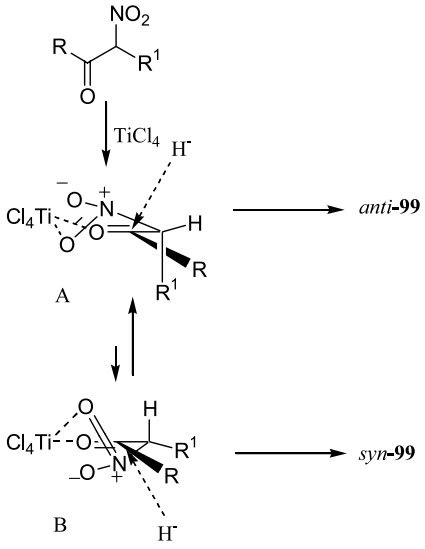
Inspection of the obtained results reveals that high enantioselectivities are obtained, provided that the smaller substituent on the ketone is a primary alkyl group, that is, when the size difference between the two substituents is maximized (Table 13).



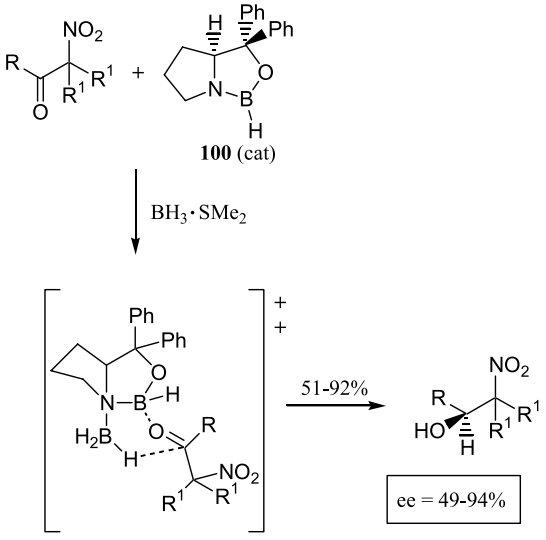
Scheme 37.

Table 12. Representative examples of the stereoselective synthesis of β-nitroalkanols **99**

Entry	R	R^1	Yield of **99** (%)	*anti*/*syn*
1	Ph	*n*-C_5H_{11}	95	>99/1
2	*o*-$NO_2C_6H_4$	Me	96	91/9
3	*n*-C_8H_{17}	*i*-Bu	90	75/25
4	Ph	Me	93	91/9
5	*i*-Pr	*n*-Pr	89	56/44



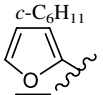
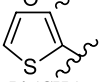
Scheme 38.

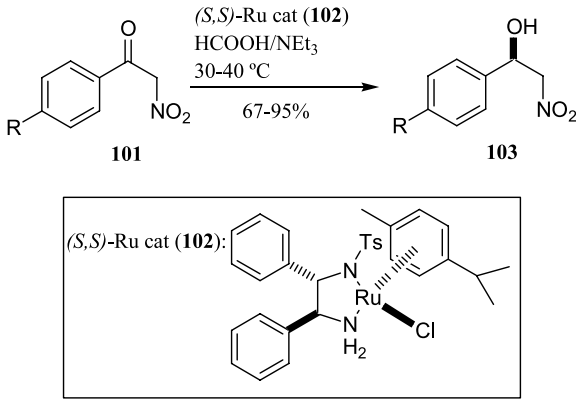


Scheme 39.

2-Nitro acetophenone derivatives **101** can be effectively reduced[53] with a mixture of HCOOH/NEt_3 containing a chiral Ru(II) catalyst, RuCl[(*S*,*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine](η⁶-*p*-cymene) **102**, giving the corresponding optically active alcohols **103** (Scheme 40). The Ru catalyst **102** effects asymmetric transfer hydrogenation with HCOOH as a hydrogen source with excellent *R* enantioselectivity (ee 95–96%). Then, the

Table 13. Representative examples of the preparation of enantio-enriched β-nitroalkanols by reduction of α-nitro ketones with (*S*)-oxazaborolidine **100**

Entry	R	R^1	Yield of β-nitroalkanols (%)	ee (%)
1	Me	Me	71	93
2	*c*-C_6H_{11}	Me	92	60
3		Me	81	74
4		Me	51	49
5	$Ph(CH_2)_2$	*c*-C_5H_9	76	94



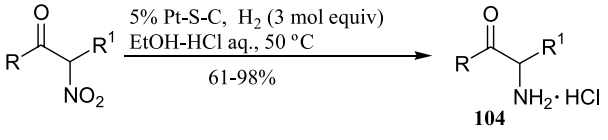
Scheme 40.

obtained nitroalkanols **103** can be converted into optically active amino alcohols with excellent ees.

3.8. Synthesis of α-amino ketones from α-nitro ketones

Chemoselective conversion (Scheme 41) of α-nitro ketones into α-amino ketone hydrochlorides **104**,[54], which are known to be valuable precursors into the asymmetric synthesis of β-amino alcohols and into the synthesis of symmetric and asymmetric pyrazines,[54] can be accomplished with 5% Pt sulfide on carbon as catalyst, in good yields (Table 14).

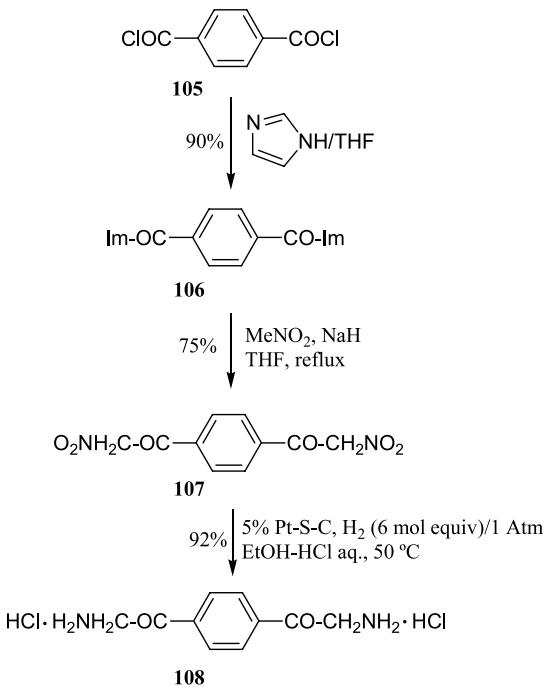
Deactivation of the sulfur-containing catalyst (5% Pt–S–C) is essential in order to suppress the formation of further



Scheme 41.

Table 14. Representative examples of the synthesis of α-amino ketones **104**

Entry	R	R^1	Yield of **104** (%)
1	*p*-ClC_6H_4	H	85
2	Ph	H	98
3	2-Naphthyl	H	85
4	Me	Me	85



Scheme 42.

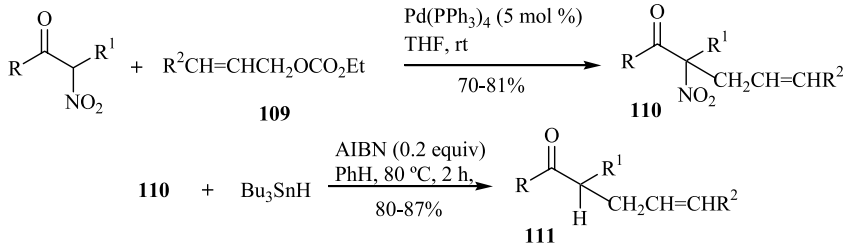
juxtaposition on two adjacent positions offers many opportunities for alkylation. In fact, depending on the reaction conditions, the alkylation of the title compounds can be performed on the α- or α′-position, or on the carbon bearing the carbonyl group.

In Scheme 12, an example of α-alkylation of α-nitro ketones by their addition to electron-poor alkenes[26] has been already described.

However, α-allylation of α-nitro ketones can be easily performed[55] by palladium(0) catalysis, by stirring a mixture of the title compounds, allylic carbonates **109**, and $Pd(PPh_3)_4$ (5 mol%) in tetrahydrofuran (Scheme 43), resulting in the allylated products **110**, in good yields (Table 15).

Since the allylated α-nitro ketones **110** can be further denitrated to **111**, with Bu_3SnH,[13] the procedure shown in Scheme 43 constitutes a new method for the regioselective α-allylation of ketones.

During studies on the reactions of conjugated azoalkenes **112** with β-nitro carbonyl derivatives,[56] α-nitro ketones have been demonstrated to be useful nucleophiles for the synthesis of α,β-unsaturated hydrazones **114** (Scheme 44).



Scheme 43.

Table 15. Representative examples of the synthesis of allylated derivatives **110** and **111**

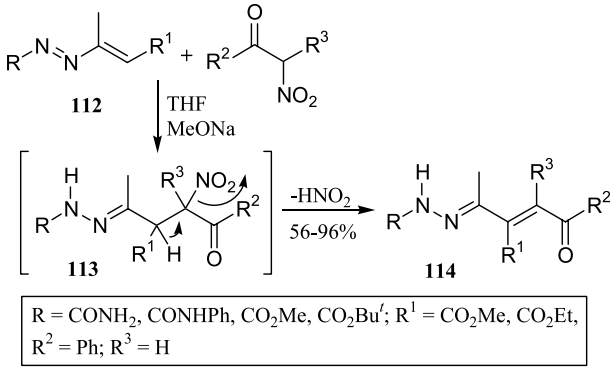
Entry	R	R^1	R^2	Yield of **110** (%)	Yield of **111** (%)
1	*n*-Bu	Et	Ph	70	85
2	*n*-Pr	*n*-Pr	Ph	72	83
3	*n*-Pr	*n*-Pr	H	81	80
4	*n*-C_6H_{13}	Me	Ph	75	80

reduced derivatives such as β-nitro alcohols or nitroalkanes (due to further reduction of the β-nitro alcohol).

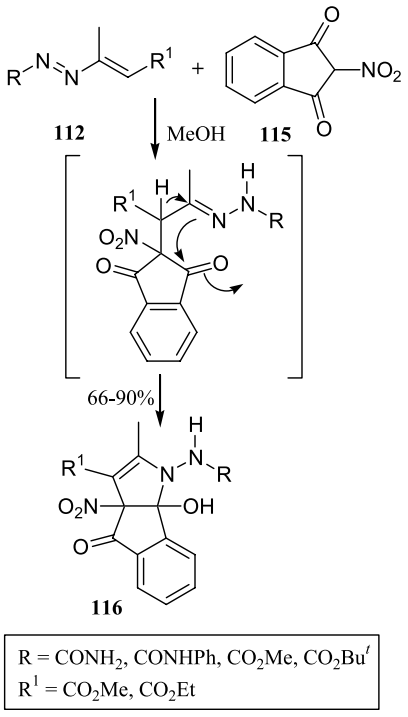
Taking advantage of this chemoselective methodology, the synthesis of terephthaloylbis(methylamine) dihydrochloride **108**, a compound, which is a useful building block for the preparation of aromatic oligomers, has been achieved starting from terephthaloyl chloride **105**, as depicted in Scheme 42. Terephthaloyldiimidazole **106**, prepared by Staab's method,[9b] was transformed into terephthaloylbis(nitromethane) **107** (75% yield), which, by subsequent hydrogenation with 5% Pt–S–C, gave **108** in 92% yield.

3.9. Alkylation of α-nitro ketones

Given the well-known chemical differences between the carbonyl group and the carbon–nitro moiety, their



Scheme 44.



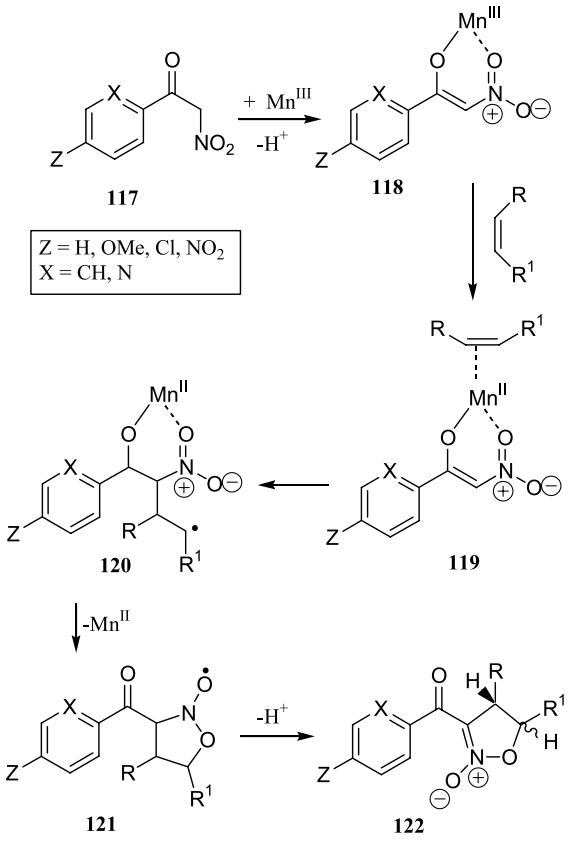
Scheme 45.

The formation of **114** proceeds in one pot, following two different steps (Michael addition of the nitro ketone to **112** and base-catalysed elimination of nitrous acid from **113**) favoured by the simultaneous behaviour of the nitro group as a strong electron-withdrawing group and a good leaving group.

In the reaction of **112** with 2-nitro-1,3-indanedione **115**, in methanol, the formation of three fused rings **116** (Scheme 45), containing at the same time powerful functional groups (nitro, hydroxy, carbonyl and aminocarbonyl) suitable for further interesting transformations, has been achieved.

α′-Aryl α-nitro ketones **117** have been alkylated in the α-position by oxidative free-radical additions to alkenes, mediated by electrochemically regenerable manganese(III) acetate,[57] affording the isoxazoline *N*-oxides **122**.

Scheme 46 shows the most likely reaction mechanism for the formation of **122**; the complex **118** is formed during the

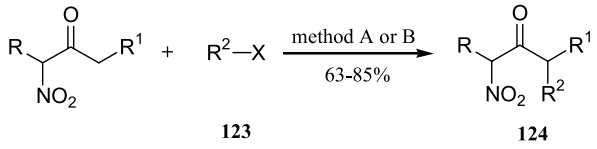


Scheme 46.

first step, and then the unsaturated acceptor compound is complexed to the Mn^{III} to form an Mn^{III}-**117**-alkene complex **119**. The secondary alkyl radical **120** is formed directly from the complex **119**, while the formation of the isoxazoline *N*-oxides **122** from the radical adduct **120** can be explained by assuming that the formation of a nitroxyl radical **121** takes place.

α-Nitro ketones can be additionally alkylated at the α^1 position, with an alkyl halide **123**, through a doubly deprotonated form (Scheme 47), giving the R^2-alkylated α-nitro ketones **124** (Table 16).[58]

Double deprotonation was initially carried out at −70 °C using LDA/HMPA (5:1) as the solvent, and the alkylation process was realized at 0 °C (method A). However, this



method A: 1) LDA (15 mmol), THF/heptane, -35 °C, HMPA (4 mmol), 15 min. 2) α-nitro ketone (5 mmol), R^2-X (10 mmol), -70 to 0 °C, 60 min. 3) AcOH.
method B: 1) LDA (15 mmol), THF, -35 °C, TMEDA (15 mmol), 15 min. 2) HMPA (4 mmol), α-nitro ketone (5 mmol), -70 °C, 30 min. 3) R^2-X (10 mmol), -50 °C, 3-5 h. 4) AcOH, -50 °C.

Scheme 47.

Table 16. Representative examples of the α^1-alkylation of α-nitro ketones

Entry	R	R^1	R^2X	Yield of **124** (%)	Method
1	Et	H	$PhCH_2Br$	66	A
2	Me	Et	*z* $Me_3CH{=}CHCH_2Br$	67	A
				80	B
3	Me	Et	MeI	85	B
4	Et	Me	$Me(CH_2)_3I$	68	A

procedure did not give fully satisfying yields and, in order to enhance the nucleophilicity of the dianion, an LDA solution of one equivalent of TMEDA, a well-known lithium-chelating agent, was added. This procedure (method B) involves carrying out the alkylation step at −50 °C with a considerable increase in the yield of the process (75–85%).

The method works well with both acyclic and cyclic α-nitro ketones, and the latter are isolated as a mixture of diastereomers in, which the *cis* form strongly predominates.

A representative application of this approach would be the synthesis of (+)-muscone **129**, carried out from α-nitrocyclopentadecanone **125** (Scheme 48).[59] The preparation starts with the key step concerning the Cα′-alkylation of **125** (with methyl iodide), to give the α′-methyl nitro ketone **126**, then, following a reported procedure[60] for the conversion of cyclic α-nitro ketones into the corresponding conjugate nitro alkenes, **126** is converted into the nitro olefin **128** (via the nitro alcohol **127**) that is prone to furnish the 3-methylpentadecanone [(±)-muscone] **129** (70% yield, 40% overall yield based on **125**) by reaction with sodium hypophosphite and Raney-Ni.

Previously, the utility of the title compounds as precursors of β-nitroalkanols has been demonstrated (Schemes 37–40), and, moreover, α-nitro ketones can additionally be employed as electrophilic species for their transformation into tertiary β-nitro alcohols. This conversion can be efficiently obtained from the reaction of cyclic and acyclic α-nitro ketones with 2 equiv of an organomagnesium or organolithium reagent.[61] Unexpectedly, Grignard reagents do not deprotonate the α acidic proton of the nitro ketone, but, instead, strongly coordinate with the carbonyl and the nitro oxygen. A second equivalent of reagent is thus necessary to carry out the addition. Grignard reagents are unable to attack monoanion a (Fig. 1), while organolithium compounds are stronger nucleophiles than organomagnesium reagents and can attack the deprotonated substrates.

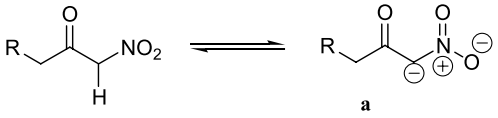
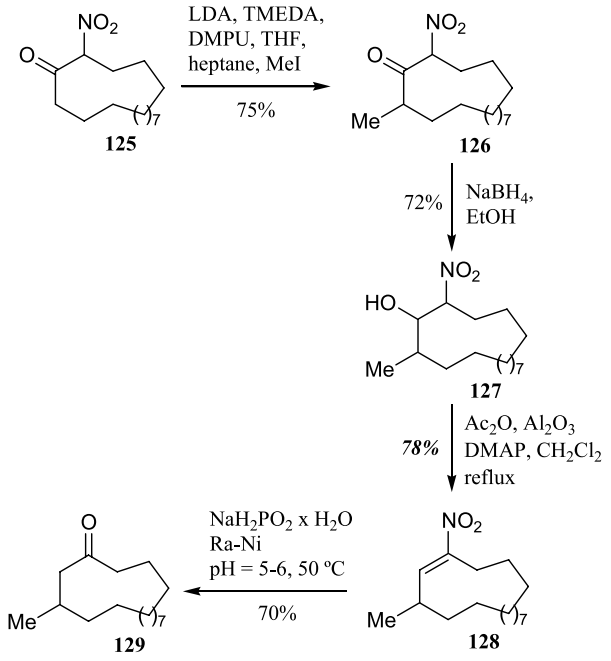
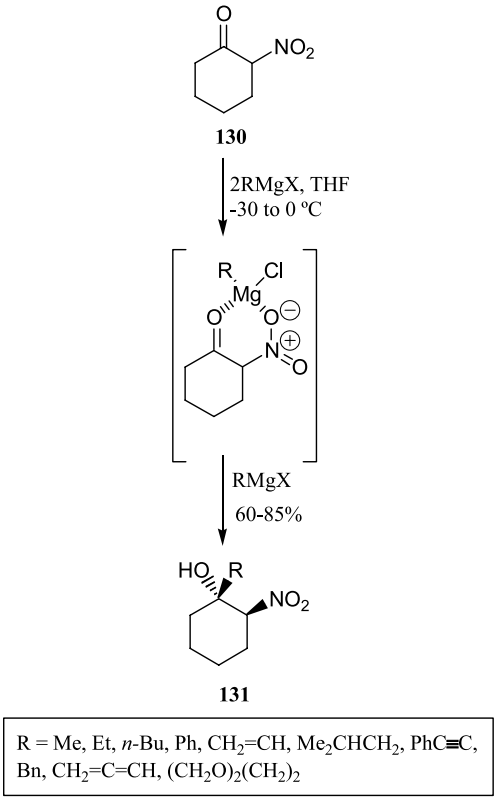


Figure 1.

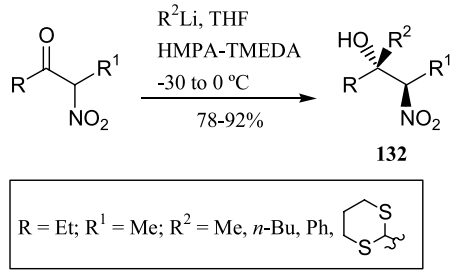
The diastereoselectivity of the reactions depends on the reagent used. Grignard reagents produce almost exclusively *trans* nitroalkanols **131** with the α-nitrocyclohexaanone **130**, whereas organolithium derivatives show little or no selectivity (Scheme 49).



Scheme 48.



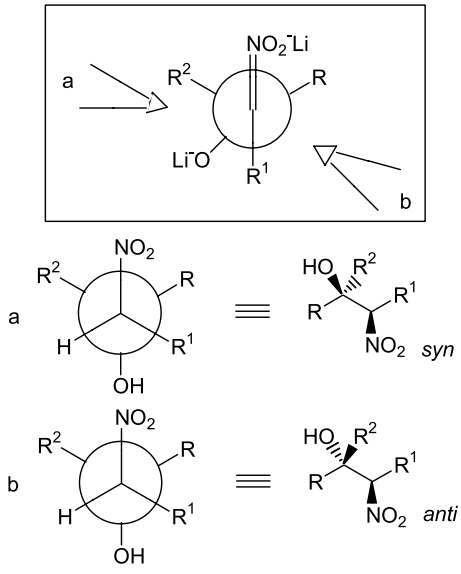
Scheme 49.



Scheme 50.

Conversely (Scheme 50), lithium reagents show excellent stereoselectivity with open-chain substrates and afford the *anti* diasteromers **132**.

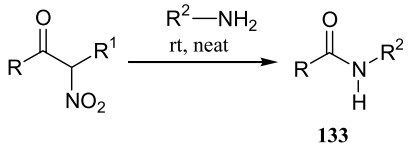
A possible explanation of these stereochemical outcomes is the participation of the conformation for the nitronate anion. In that conformation, the negatively charged oxygens are forced to assume the *anti* position because of the electronic repulsion (Scheme 51).



Scheme 51.

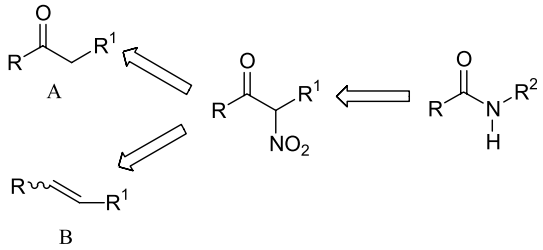
3.10. Conversion of α-nitro ketones into amides

The reaction of linear α-nitro ketones with primary amines allows the formation of amides **133** through the cleavage of the carbon–carbon bond between the carbonyl group and the carbon–nitro moiety, promoted by the nucleophilic effect of the amine (Scheme 52).[62] The reaction is performed at room temperature, without any catalyst and/or solvent, and gives good yields of the amides **133** (Table 17).



Scheme 52.

This cleavage of a C(1)–C(2) bond by the action of nucleophiles is a very useful transformation for cyclic α-nitro ketones,[1] while it is much less common for the acyclic ketones. Thus, the substitution shown in Scheme 52 is a surprising result, but is of great importance, because the title compounds can be easily prepared from ketones[15–18] A or alkenes[19,21] B, and the methodology can therefore be regarded as a formal way to convert alkenes or ketones into amides (Scheme 53).



Scheme 53.

The method has been tested with a very large series of both nitro ketones and primary amines showing, in general, good efficiency. However, the reaction times (usually 4–15 h) and the yields (31–100%) seem to be dependent upon the bulk of the alkyl group (R^2). Moreover, when the amine is aromatic (R^2 = Ar), the efficacy of the reaction, due to the reduced nucleophilicity of the amine, decreases.

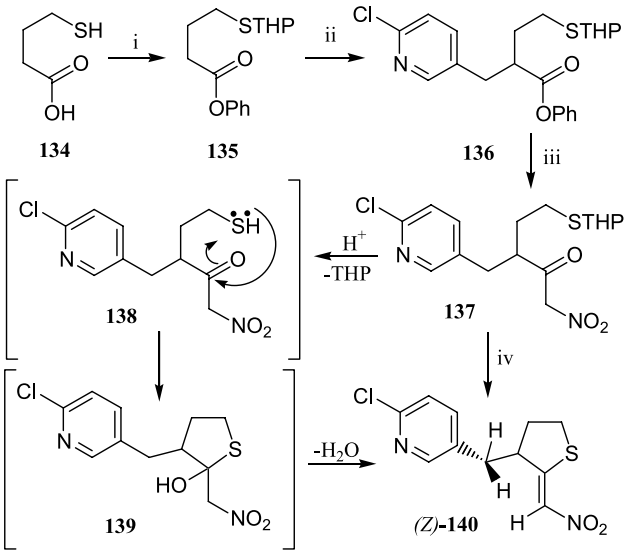
3.11. α-Nitro ketones as electrophiles and as nucleophiles

Neonicotinoids, represented by imidacloprid, are the only major new class of insecticides introduced in the past three decades. The nitroguanidine/nitromethylene moiety is an important structural requirement of these neonicotinoid insecticides. Three nitromethylene analogues of imidacloprid have been synthesized in order to probe the *Drosophila* neonicotinoid–nicotinic acetylcholine receptor interaction. Specifically, 3-(6-chloropyridin-3-yl)methyl-2-nitromethylene-tetrahydrothiophene **140** and -tetrahydrofuran **148** have been synthesized through novel approaches using α-nitro ketones as electrophiles and as nucleophiles, respectively.[63]

The synthesis of **140** starts with the double protection of 4-mercaptobutyric acid **134** (Scheme 54) to give **135**. Then, the 6-chloropyridin-3-ylmethylene moiety is introduced by

Table 17. Representative examples of the conversion of α-nitro ketones into amides

Entry	R	R^1	R^2	Reaction time (h)	Yield of **133** (%)
1	$Ph(CH_2)_2$	Et	*i*-Pr	15	quant.
2	Ph	Me	Bn	5	quant.
3	Ph	H	Bn	6	quant.
4	Ph	Et	Ph	168	75
5	*n*-Bu	*i*-Pr	*n*-Bu	15	quant.



(i) (a) dihydropyran, pyridinium *p*-toluensulfonate, CH_2Cl_2, rt, overnight, (b) DCC, DMAP, PhOH, CH_2Cl_2, rt, overnight, overall 53%; (ii) LDA, CIMP, HMPA, THF, -78 °C to rt, overnight, 62%; (iii) $MeNO_2$, $KOBu^t$, DMSO, <20 °C, overnight, 79%; (iv) 37% HCl, rt, 30 min, 86%.

Scheme 54.

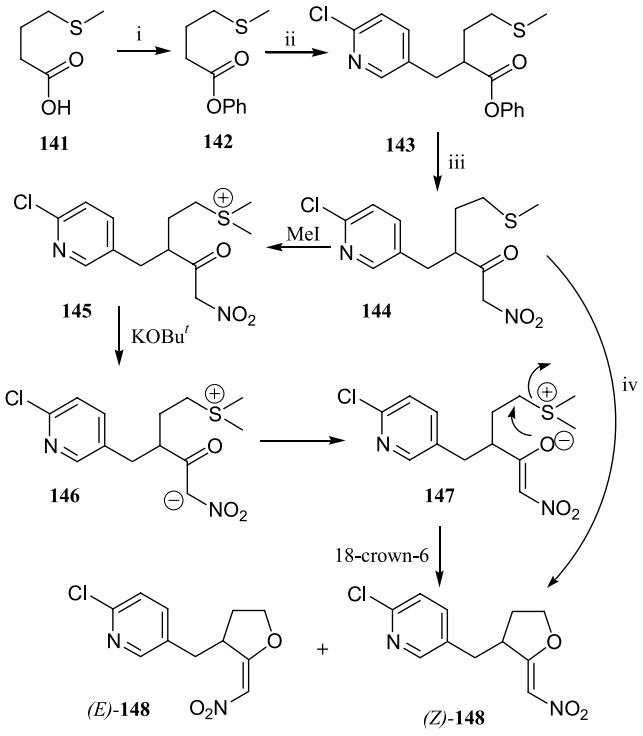
deprotonation of **135** with LDA, followed by reaction with 2-chloro-5-iodomethylpyridine (CIMP). The resulting phenyl ester **136** is converted into the α-nitro ketone **137** in excellent yield by reaction with the anion generated by treatment of nitromethane with potassium *tert*-butoxide. The next step is devoted to removing the THP protecting group from **137** to provide a free thiol for intramolecular attack (**138**) at the carbonyl site to form the hemimercaptal **139**. Thus, the α-nitro ketone **137** is treated with concentrated HCl (37%), leading to the target compound (*Z*)-**140**.

The tetrahydrofuran derivative **148** is prepared starting (Scheme 55) from 4-methylsulfanylbutyric acid **141** that is converted into the phenyl ester **142**. The latter, by reaction with CIMP, gives, through the compounds **143**–**146**, **147** that is further transformed into the α-nitro ketone **144** by reaction with nitromethane. Compound **144** is treated with iodomethane and potassium *tert*-butoxide successively to finish the cyclization in one pot. The major product is the desired (*Z*)-**148**, with lesser amounts of (*E*)-**148**. The final one-pot cyclization includes three consecutive reactions: methylation at the sulfur atom, generation of the enol anion of the α-nitro ketone **147**, and intramolecular attack of the enol anion at C5.

Thus, in Scheme 54, the α-nitro ketone **137** serves as an electrophile, while the α-nitro ketone **144** (Scheme 55) serves as a nucleophile.

3.12. α-Nitro ketones as precursors of furoxans

Furoxans were found to play an important pharmacological role, as they are able to increase the cytosolic level of cGMP in human platelets, to activate the rat liver soluble guanylate cyclase and to release NO when treated with thiol

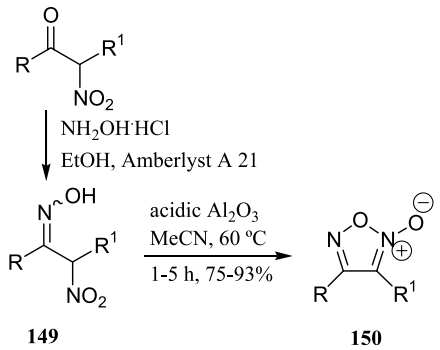


(i) DCC, PhOH, DMAP, CH_2Cl_2, rt, overnight, 91%; (ii) LDA, CIMP, HMPA, THF, -78 °C to rt, overnight, 75%; (iii) $MeNO_2$, $KOBu^t$, DMSO, <20 °C, overnight, 87%; (iv) MeI, MeOH, rt, overnight; then $KOBu^t$, 18-crown-6, DMF, rt, 2 h, 27% for *(Z)*-**148** and 21% for *(E)*-**148**.

Scheme 55.

compounds under physiological conditions resulting in a potent vasodilatant effect. Recently, we have demonstrated that these molecules can be conveniently obtained from α-nitro ketones and, although one example has been previously reported[64] treating benzoylnitromethane with $TeCl_4/Et_3N$ at −78 °C, our procedure[65] represents the first general method for the synthesis of furoxans **150** from α-nitro ketoximes **149** (easily obtainable from the corresponding α-nitro ketones[66]) using acidic alumina as catalyst (Scheme 56).

The reaction is carried out by adding a solution of **149**, in acetonitrile, to a suspension of acidic alumina (Brockmann I) in acetonitrile at 60 °C. The reaction takes from 1 to 5 h and, after simple work up, affords furoxan derivatives in



Scheme 56.

Table 18. Representative examples of the conversion of α-nitro ketones to furoxans

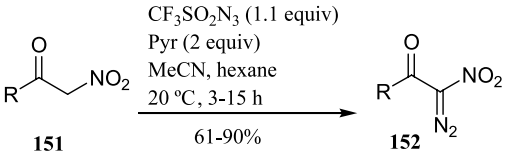
Entry	R	R_1	Yield of **150** (%)
1	Et	Me	91
2	$Ph(CH_2)_2$	Et	83
3	*i*-Pr	*n*-Pr	85

good yield (Table 18) from both cyclic and acyclic α-nitro ketoximes.

3.13. α-Nitro-α-diazocarbonyl derivatives from α-nitro ketones

The importance of α-diazocarbonyl reagents has been recognized for a number of year and, in fact, these reagents are ideal precursors for several transition metal-catalyzed processes including cyclopropanation and X-H insertion reactions (X=C, O, N, S, P, etc.). In this context, α-nitro-α-diazocarbonyl derivatives are particularly useful and, recently,[67] in addition to the conventional methodologies for their preparation, an improved procedure for their synthesis from α-nitro ketones has been reported.

As shown in Scheme 57, a hexane solution of trifluoromethanesulfonyl (triflyl) azide reacts smoothly with primary nitro ketones **151** (R=alkyl or aryl) or nitroacetates (R=Alk–O–), in acetonitrile, upon addition of pyridine to generate the α-nitro-α-diazocarbonyl derivatives **152** in satisfactory to good yields (61–90%). The yields obtained from α-nitro ketones are generally lower than those obtained from α-nitro acetates.

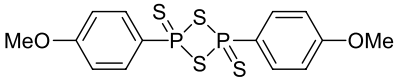


Scheme 57.

3.14. Acylthioamides from α-nitro ketones

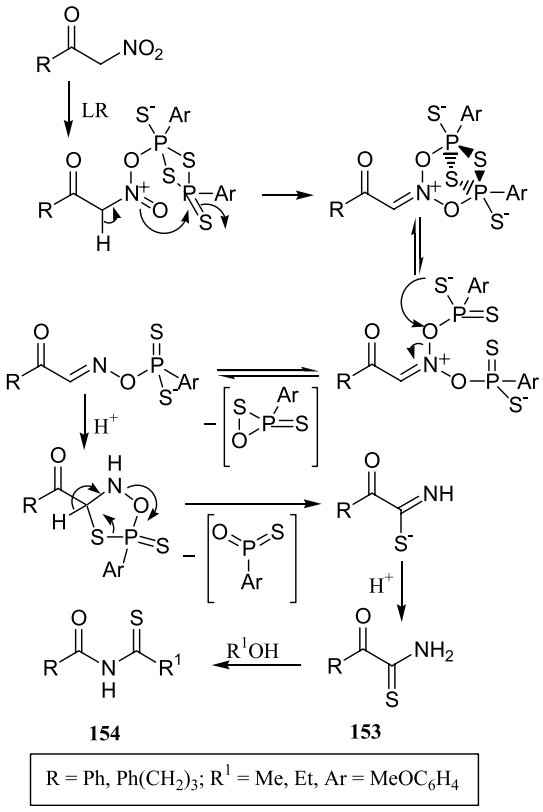
Primary α-nitro ketones react with 2,4-bis(4-methoxyphenyl)-1,3-dithiadiphosphetane 2,4-disulfide, Lawesson's reagent (LR; Fig. 2), allowing access to the acylthioamides **153**.[68]

Thus, aryl and alkyl ketones react in hot toluene, to provide the acylthioamides **153**, following the sequence shown in Scheme 58. Subsequent treatment with alcohols (R^1OH) converted **153** into the acylthiourethanes **154**.



Lawesson's reagent (LR)

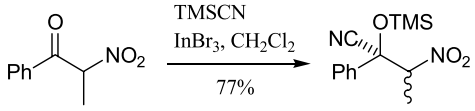
Figure 2.



Scheme 58.

4. Other reactions

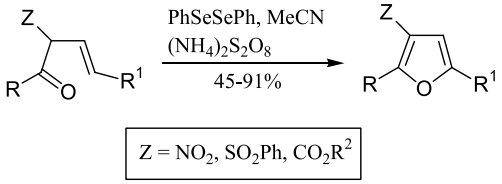
The catalytic addition of trimethylsilyl cyanide (TMSCN) to a large variety of hetero-substituted ketones, including α-nitro ketones, promoted by anhydrous $InBr_3$, produces the cyanation of the carbonyl group in good yields (Scheme 59).[69]



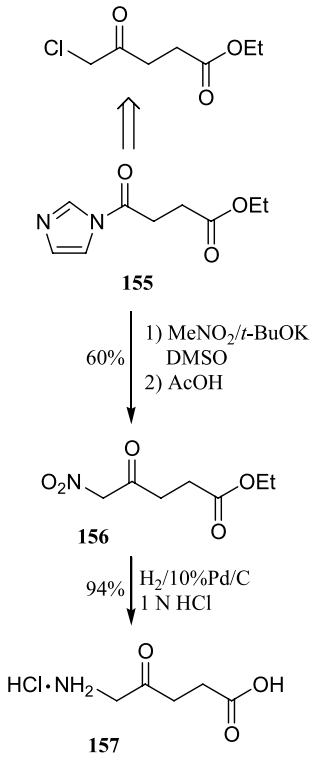
Scheme 59.

β,γ-Unsaturated ketones, containing an electron-withdrawing group in the α-position, react with diphenyl diselenide and ammomiun persulfate, in acetonitrile, to afford the substituted furans in moderate to good yields (Scheme 60).[70]

δ-Aminolevulinic acid (5-ALA), involved in heme biosynthesis, has been synthesized using an α-nitro ketone as the



Scheme 60.



Scheme 61.

chloro-1-propyne,[73] or with aromatic aldehydes and cyanothioacetamide.[74]

5. Conclusions

We have demonstrated that acyclic α-nitro ketones are a highly versatile class of α-hetero-substituted ketones, easily obtained from alkenes, ketones or by the nitroaldol (Henry) reaction or from activated carboxylic acids. The title compounds offer the possibility to be employed in many important transformations and, for this reason, several targets can be obtained by their use as the key building blocks. Thus, because α-nitro ketones provide a wide range of synthetic opportunities, we believe that this report will be of great utility for chemists working in the field of organic synthesis.

Acknowledgements

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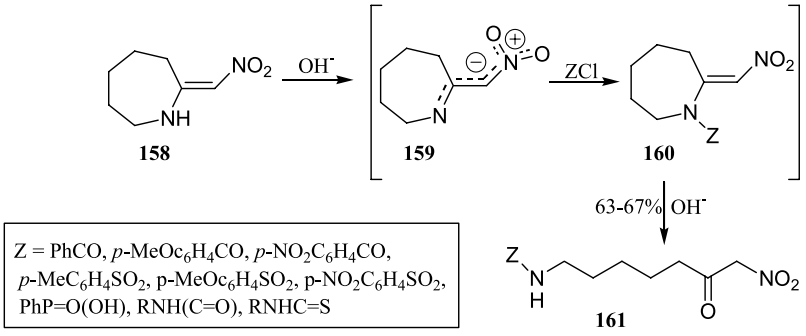

Scheme 62.

immediate precursor.[71] The synthesis (Scheme 61) starts from the imidazolyl derivative **155** that is converted into the corresponding α-nitro ketone **156** by a procedure described earlier.[13] The latter undergoes facile reduction and concomitant hydrolysis under aqueous acidic catalytic hydrogenation conditions to give the desired 5-ALA·HCl **157** in 94% yield.

6-Aminocaproic acid blocks the action of plasminogen activators and, in order to prepare some analogs of this acid, some α-nitro ketone derivatives **161** have recently[72] been synthesized (Scheme 62) from the nitroenamine **158** that, by basic treatment, converts into the *N*-substituted-1-nitro-2-heptanones **158**, through the intermediates **159** and **160**.

Other possible reactivities of the title compounds have been tested by reacting α-nitro ketones with 1-trimethylsilyl-3-

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Biographical sketch

Roberto Ballini obtained his Laurea degree in Chemistry from the University of Camerino-Italy. After an experience at the ENI-ANIC (Petrolchemical Industry) in Ravenna, he began his academic career at the University of Camerino as Research Fellowship. Then, he became Assistent Professor in Organic Chemistry, then was promoted to Associate Professor (Organic Chemistry), and then full Professor of Organic Chemistry in 2000. His research interests include a large area of the chemistry of aliphatic nitro compounds, with particular interest in the chemistry of functionalised nitro derivatives, including the generation of both carbon–carbon single bond and carbon–carbon double bond, the cleavage of carbon–carbon bond, the conversion of the nitro derivatives into other functionalities and the use of nitroalkanes as the key building blocks in the synthesis of important targets, such as natural products, featured of enhanced biological activity. Other special fields of extensive interest concern also (i) different aspects of the heterogeneous catalysis applied to fine chemicals and pharmaceuticals production; (ii) the exploitation of solvent-free and multicomponent reactions and (iii) the use of aqueous medium in the organic reactions.

Giovanna Bosica was born in Atri, Italy, in 1967. She is a researcher at the Department of Chemical Sciences of the University of Camerino, Faculty of Sciences and Technologies, since 1999. She received her Laurea in Chemistry *cum laude* in 1993 from the University of Camerino and, four years later, from the same institution her doctoral degree in Chemical Sciences working under the supervision of Prof. R. Ballini. She spent a research period from April to September 1995 in the laboratories of Prof. B. Zwanenburg (Department of Organic Chemistry, University of Nijmegen, the Netherlands) as an Erasmus Fellow. Her research interests concern the use of nitrocompounds in new synthetic methodologies, synthesis of heterocycle compounds and biologically active natural products, heterogeneous catalysis and green chemistry.

Dennis Fiorini was born in1975; she studied Chemistry at the University of Camerino (Italy) and in 1999 she developed part of her thesis work in the laboratory of Professor Zwanenburg in Nijmegen (Netherlands). She received her degree in Chemistry in 2000. During the same year she started her research on the chemical reactivity of nitro compounds and worked under the supervision of Prof. Roberto Ballini. In 2002 she began her Ph.D. studies and received the degree in 2005. Her research interests concern the study of the ability of nitroalkanes to form single and double carbon–carbon bonds and their application in the synthesis of natural target products having biological activity. Some aspects of her recent research deal with heterogeneous catalysis, solventless reactions and other procedures related to green chemistry.

Alessandro Palmieri was born in Jesi, Italy, in 1978. He began his studies in Chemistry in 1997 at the University of Camerino-Italy, where he received his Laurea degree *cum laude* in 2002 under the guidance of Professor Enrico Marcantoni. After a scholarship in laboratory of Professor Roberto Ballini on the synthesis of natural products with important biological activities, in March of 2004 he started the Ph.D. studies. His research interests include natural product synthesis and the application of aliphatic nitrocompounds in the formation of new C–C and C═C bond.

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IBX/*n*-Bu_4NBr/CH_2Cl_2–H_2O: a new mild system for selective oxidation of secondary alcohols

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Abstract—A new alternative system for the chemoselective oxidation of secondary hydroxyl group to ketone with IBX/*n*-Bu_4NBr in CH_2Cl_2–H_2O has been developed. Under the reaction conditions, the secondary hydroxyl group was highly chemoselectively oxidized to the corresponding ketone, in moderate to good yields at rt, in the presence of primary hydroxyl group within the same molecule.

1. Introduction

The oxidation of alcohols to carbonyl compounds is a fundamental reaction in organic chemistry and several methods covering a wide variety of reagents have been developed for this important synthetic transformation.[1] Desired experimental conditions include high yields, mild conditions, high chemoselectivity, readily available non-toxic reagent, and compatibility with functional groups present in the substrates. In the synthesis of naturally occurring compounds, one usually faces the manipulation of compounds containing several types of hydroxyl functional groups, and it is necessary to selectively oxidize a single hydroxyl group (primary or secondary alcohol) within the same molecules. Thus, selective transformation of hydroxyl group has been a challenging target for synthetic chemists since it offers an alternative to synthesis via selective protection and deprotection. Many oxidizing reagents are known to promote selective oxidation of secondary alcohols in the presence of primary alcohols, including halogen-based oxidants, for example, *N*-bromoacetamide,[2] *N*-chloro/bromosuccinimide,[3] Cl_2/pyridine,[4] Br_2/HMPA/$NaHCO_3$,[5] $(Bu_3Sn)_2O/Br_2$,[6] $NOCl/CH_3CO_2H$,[7] $NaBrO_3/NaHSO_3$,[8] and $Ce(SO_4)_2/NaBrO_3$.[9] The other important oxidizing agents are peroxides/metal system,[10] dimethyldioxiranes,[11] DMSO-based reagents,[12] and Oppenauer oxidation variations.[13] Despite these readily available procedures, development of a better selective oxidation system is still desirable.

As part of our ongoing efforts in the development of newer applications of hypervalent iodine (V) compounds, we wish to report a new application of 2-iodoxybenzoic acid (IBX) with catalytic amount of tetrabutylammonium bromide (*n*-Bu_4NBr) for selective oxidation of secondary hydroxyl group. Chemoselective oxidation of sulfides to sulfoxides in the presence of an alcohol functional group using IBX/tetraethylammonium bromide (Et_4NBr) has been documented in the literature.[14] To our knowledge, there is no previous study that was directed toward selective oxidation of secondary hydroxyl group in the presence of primary hydroxyl within the same molecule using IBX as an oxidizing reagent.

2. Results and discussion

To begin with, a monofunctional alcohol, benzyl alcohol, was chosen as a substrate for investigating reaction conditions. Thus, it was subjected to the oxidation by IBX in the presence of a collection of phase transfer catalysts, that is *n*-Bu_4NBr, Et_4NCl, Et_4NBr, Et_4NI, $BnMe_3NBr$, and $BnEt_3NCl$ (Table 1). It should be noted that the type of halide anion of the catalyst has considerable effect on the oxidation reaction (Table 1, entries 2–4). The tetraethylammonium bromide (Et_4NBr) catalyzed the reaction more effectively than the corresponding iodide and chloride, respectively. The *n*-Bu_4NBr gave the best conversion of 89% (Table 1, entry 1). Tetrabutylammonium bromide was therefore, chosen as a catalyst of choice for further investigating optimum reaction conditions (Table 2).

From the results as shown in Table 2, for the oxidation using IBX alone in dichloromethane, moderate conversion of

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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
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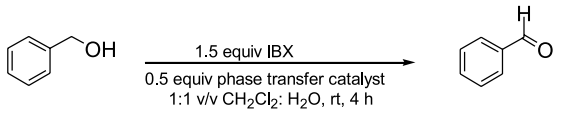
Table 1. Phase transfer catalyst optimization



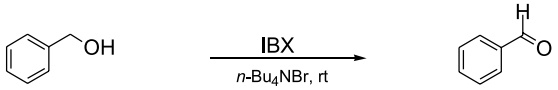
Entry	Phase transfer catalyst	Conversion (%)[a]
1	*n*-Bu_4NBr	89
2	Et_4NCl	22
3	Et_4NBr	62
4	Et_4NI	37
5	$BnMe_3NBr$	18
6	$BnEt_3NCl$	30

[a] Conversion (%) was calculated from ^1H NMR (300 MHz) integration.

mechanisms previously reported for the phase transfer catalyzed IBX oxidation of sulfides to sulfoxides.[14]

Comparative studies of our method (Method A) with those reported in the literature for IBX oxidation of alcohols (Methods B[15] and C[16]) were conducted. The selectivity and efficiency of our method are clearly demonstrated as shown in Table 4. A control experiment was also carried out with the 2,2,4-trimethyl-1,3-pentanediol substrate using the conditions described in Table 4 (Method A) without the *n*-Bu_4NBr. The oxidation gave all the possible products, that is the corresponding hydroxyketone (31%), hydroxyaldehyde (4%), dicarbonyl (2%), and recovered starting material (37%). The results seem to suggest that the origin of

Table 2. Optimization of reaction conditions



Entry	H_2O:CH_2Cl_2 (v/v)	IBX (equiv)	*n*-Bu_4NBr (equiv)	Time (h)	Conversion (%)[a]
1	0:100	1.5	—	4	45
2	1:1	1.5	—	7	31
3	0:100	1.5	0.5	2	88
4	1:3	1.5	0.5	4	92
5	1:1	1.5	0.5	4	89
6	1:1	1.5	0.1	4	70
7	1:1	1.5	1.0	4	60

[a] Conversion (%) was calculated from ^1H NMR (300 MHz) integration.

benzyl alcohol to benzaldehyde was obtained (Table 2, entry 1). A similar result was obtained when water was used as a co-solvent, even with prolonged reaction time (Table 2, entry 2). Reaction in the presence of 0.5 equiv of *n*-Bu_4NBr proceeded with shorter reaction time and provided better conversion (Table 2, entries 3–5). The v/v ratio of CH_2Cl_2:H_2O employed can be as low as 1:1. When either a lesser or stoichiometric amount of *n*-Bu_4NBr was employed, lower conversions were obtained (Table 2, entries 6–7). Therefore, the 1:1 v/v of H_2O:CH_2Cl_2 solvent system will be used in the standard conditions.

According to Tables 1 and 2, even though the oxidation reaction of monofunctional alcohols proceeded efficiently with as few as 1.5 equiv of IBX, an increased reaction rate was observed with excess oxidant. For the oxidation of diols, it was found that the use of 3 equiv of IBX afforded the best results; very small amounts of dicarbonyls or lactones were obtained. Based on this observation, 3 equiv of IBX were selected to examine the chemoselective oxidation of a variety of diols. The results are summarized in Table 3.

The observed transformations were chemoselective when both the primary and the secondary hydroxyl functional groups were present within the same molecules (Table 3). The ketones with the primary alcohol untouched were obtained in moderate to good yields. The dicarbonyl compounds as well as some lactones in cases leading to five- or six-membered ring lactones were also formed as minor products. The exact mechanism of selective oxidation is still unclear, but we propose that it should follow those chemoselectivity of IBX oxidation of diols under a bi-phasic solvent system in our study stems from the choice of solvent. The role of the bromide anion was believed to follow the previously suggested mechanism for Et_4NBr catalyzed IBX oxidation of sulfides to sulfoxides by causing a polarization of the I=O bond and leading to a reaction rate acceleration.[14]

3. Conclusion

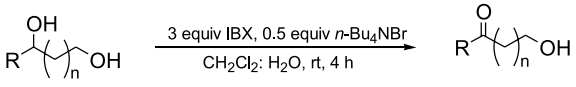
In conclusion, a selective and efficient new alternative method has been developed for the oxidation of secondary hydroxyl groups to ketones, in moderate to good yields, in the presence of primary hydroxyl groups within the same molecule. The reaction conditions do not involve moisture sensitive and environmentally unfriendly agents. We anticipate that this protocol will, to some extent, be of broad interest and use to the chemistry community.

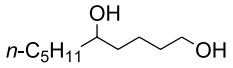
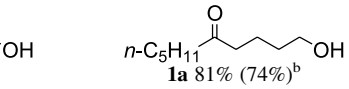
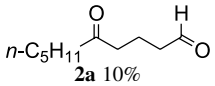
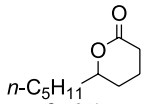
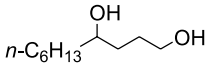
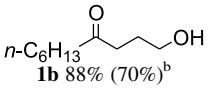
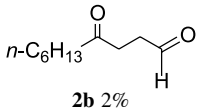
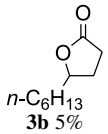
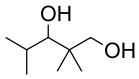
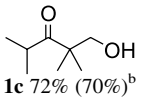
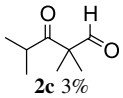
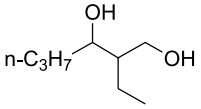
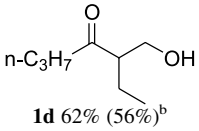
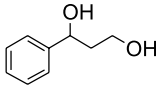
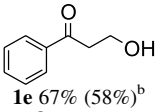
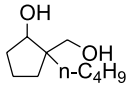
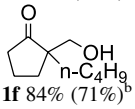
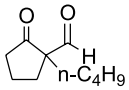
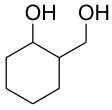
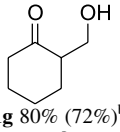
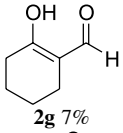
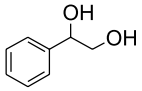
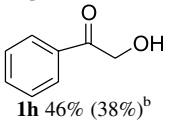
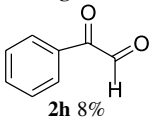
4. Experimental

4.1. General

Melting points (uncorrected) were determined on an Electrothermal 9100 Apparatus. Reagents were obtained from commercial sources and used as received. Column chromatography was performed using silica gel 60 (70–230 mesh). Analytical TLC was performed with silica gel 60 PF_{254} aluminium sheet with 0.2 mm layer of silica gel. ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR

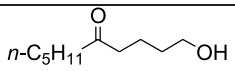
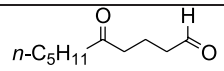
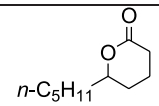
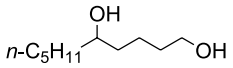
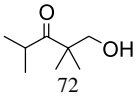
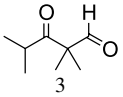
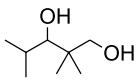
Table 3. Selective oxidation of secondary hydroxyls using IBX/*n*-Bu_4NBr in 1:1 v/v of H_2O:CH_2Cl_2



Entry	Substrate	Product (% yield)[a]		
1		 **1a** 81% (74%)[b]	 **2a** 10%	 **3a** 3%
2		 **1b** 88% (70%)[b]	 **2b** 2%	 **3b** 5%
3		 **1c** 72% (70%)[b]	 **2c** 3%	
4		 **1d** 62% (56%)[b]		
5		 **1e** 67% (58%)[b]		
6		 **1f** 84% (71%)[b]	 **2f** 8%	
7		 **1g** 80% (72%)[b]	 **2g** 7%	
8		 **1h** 46% (38%)[b]	 **2h** 8%	

[a] GC yields.
[b] Yields (%) given in parentheses are isolated yields after purification by column chromatography.

Table 4. Comparison of the oxidation of diols by IBX under other conditions

Substrate	Method[a]	Product (% yield)[b]		
				
	**A**[c]	81	10	3
	B	[d]	83	16
	C	[d]	76	23
				
	**A**[e]	72	3	
	B	[d]	77	
	C	[d]	86	

[a] Method **A**: 3 equiv IBX, 0.5 equiv *n*-Bu_4NBr, CH_2Cl_2:H_2O (1:1), rt, 4 h; Method **B**: 3 equiv IBX, DMSO, rt, 4 h; Method **C**: 3 equiv IBX, EtOAc, 80 °C, 4 h.
[b] GC yields.
[c] Starting material was recovered (6%).
[d] Not detected by GC.
[e] Starting material was recovered (21%).

spectra were recorded at 75 MHz with residual non-deuterated solvent peak as an internal standard. IR spectra were recorded on a GX FT-IR system (Perkin Elmer) spectrometer. Elemental analyses were determined on a Perkin Elmer Elemental Analyzer 2400 CHN. High resolution mass spectra were obtained on a Micromass model VQ-TOF2 mass spectrometer.

4.2. General procedure for the oxidation

To a stirred suspension of IBX (3.0 equiv) in H_2O:CH_2Cl_2 (v/v=1:1, 0.25 M based on starting alcohol) was added *n*-Bu_4NBr (0.5 equiv) followed by the addition of alcohol (1.0 equiv) in one portion. The mixture was stirred at rt for 4 h. The residual solids were filtered off and washed thoroughly with diethyl ether. The combined filtrate was washed successively with 8% sodium thiosulfate (15 mL), water (2×15 mL) and brine (1×15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated (aspirator). The crude product was subsequently examined by gas chromatography for determining product conversion. Purification of the crude product by column chromatography (SiO_2) provided the isolated yield of the ketone.

4.2.1. Preparation of 1-hydroxy-5-decanone (1a). According to the general procedure, oxidation of 1,5-decanediol (174 mg, 1 mmol) gave 1-hydroxy-5-decanone, after column chromatography on silica gel (18×1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 127 mg (isolated yield; 74%) as colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate, R_f=0.17. IR (neat, cm^{-1}) 3423, O–H; 1712, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 3.57 (2H, br s) 2.55–2.10 (4H, m) 1.70–1.10 (11H, m) 0.82 (3H, t, J=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 211.6, 62.1, 42.7, 42.1, 32.0, 31.3, 23.5, 22.4, 19.6, 13.8. Molecular ion (M+H) calcd for $C_{10}H_{21}O_2$: 173.1542; found (ESI-TOF) m/e=173.1536, error=3 ppm.

4.2.2. Preparation of 1-hydroxy-4-decanone (1b). According to the general procedure, oxidation of 1,4-decanediol (174 mg, 1 mmol) gave 1-hydroxy-4-decanone, after column chromatography on silica gel (18×1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 120 mg (isolated yield; 70%) as colorless liquid:[17] analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate, R_f=0.16. IR (neat, cm^{-1}) 3422, O–H; 1707, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 3.64 (2H, t, J=6.1 Hz) 2.55–2.30 (4H, m) 2.00–1.66 (2H, m) 1.65–1.44 (2H, m) 1.40–1.17 (7H, m) 0.88 (3H, t, J=6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 212.1, 62.1, 42.9, 39.4, 31.5, 28.8, 26.4, 23.8, 22.4, 14.0.

4.2.3. Preparation of 1-hydroxy-2,2,4-trimethyl-3-pentanone (1c). According to the general procedure, oxidation of 2,2,4-trimethyl-1,3-pentanediol (146 mg, 1 mmol) gave 1-hydroxy-2,2,4-trimethyl-3-pentanone, after column chromatography on silica gel (18×1.5 cm, 8:2 *n*-hexane/diethyl ether as eluent), 101 mg (isolated yield; 70%) as colorless liquid:[12a] analytical TLC on silica gel, 8:2 *n*-hexane/diethyl ether, R_f=0.12. IR (neat, cm^{-1}) 3479, O–H; 1699, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 3.56 (2H, s) 3.18–3.02 (1H, m) 2.85 (1H, br d, J=7.4 Hz) 1.18 (6H, s) 1.06 (6H, d, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 221.5, 69.3, 49.6, 34.5, 21.0, 19.8.

4.2.4. Preparation of 3-hydroxymethyl-4-heptanone (1d). According to the general procedure, oxidation of 2-ethyl-1,3-hexanediol (185 mg, 1.27 mmol) gave 3-hydroxymethyl-4-heptanone, after column chromatography on silica gel (18×1.5 cm, 7:3 *n*-hexane/diethyl ether as eluent), 103 mg (isolated yield; 56%) as colorless liquid:[10c] analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether, R_f=0.05. IR (neat, cm^{-1}) 3422, O–H; 1705, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 3.80 (1H, dd, ABX, J=11.0, 7.4 Hz) 3.70 (1H, dd, ABX, J=11.0, 4.1 Hz) 2.70–2.57 (1H, m) 2.48 (2H, t, J=7.3 Hz) 2.14 (1H, br s) 1.75–1.39 (4H, m) 0.93 (3H, t, J=7.5 Hz) 0.92 (3H, t, J=7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 215.1, 62.4, 54.9, 44.8, 21.2, 16.8, 13.7, 11.8.

4.2.5. Preparation of 3-hydroxy-1-phenyl-1-propanone (1e). According to the general procedure, oxidation of 3-hydroxy-1-phenyl-1-propanol (152 mg, 1 mmol) gave 3-hydroxy-1-phenyl-1-propanone, after column chromatography on silica gel (18×1.5 cm, 8.5:1.5 *n*-hexane/ethyl acetate as eluent), 86.9 mg (isolated yield; 58%) as a colorless liquid:[18] analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate, R_f=0.29. IR (neat, cm^{-1}) 3412, O–H; 1681, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.97 (2H, d, J=7.3 Hz) 7.59 (1H, t, J=7.4 Hz) 7.48 (2H, t, J=7.5 Hz) 4.05 (2H, t, J=5.4 Hz) 3.24 (2H, t, J=5.4 Hz) 2.85 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 200.4, 136.6, 133.4, 128.6, 128.0, 58.0, 40.3.

4.2.6. Preparation of 2-butyl-2-hydroxymethylcyclopentanone (1f). According to the general procedure, oxidation of 2-butyl-2-hydroxymethylcyclopentanol (221 mg, 1.28 mmol) gave 2-butyl-2-hydroxymethylcyclopentanone, after column chromatography on silica gel (18×1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 156 mg (isolated yield; 71%) as a pale yellow liquid: analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate, R_f=0.32. IR (neat, cm^{-1}) 3448, O–H; 1731, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 3.62 (1H, d, J=11.0 Hz) 3.47 (1H, d, J=11.0 Hz) 2.36 (1H, br s) 2.31–2.17 (2H, m) 2.01–1.80 (4H, m) 1.55–1.01 (6H, m) 0.88 (3H, t, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 224.7, 65.7, 53.4, 38.8, 32.2, 30.5, 26.2, 23.2, 19.1, 13.8. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.29; H, 10.45.

4.2.7. Preparation of 2-hydroxymethylcyclohexanone (1g). According to the general procedure, oxidation of 2-hydroxymethylcyclohexanol (130 mg, 1 mmol) gave 2-hydroxymethylcyclohexanone, after column chromatography on silica gel (18×1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 91.8 mg (isolated yield; 72%) as a colorless liquid:[19] analytical TLC on silica gel, 6:4 *n*-hexane/ethyl acetate, R_f=0.25. IR (neat, cm^{-1}) 3421, O–H; 1702, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 3.81–3.68 (1H, m) 3.68–3.54 (1H, m) 2.79 (1H, br s) 2.61–1.36 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 214.6, 62.5, 52.1, 42.1, 30.0, 27.4, 24.6.

4.2.8. Preparation of 2-hydroxy-1-phenylethanone (1h). According to the general procedure, oxidation of 1-phenyl-

1,2-ethanediol (138 mg, 1 mmol) gave 2-hydroxy-1-phenyl-ethanone, after column chromatography on silica gel (18× 1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 52.4 mg (isolated yield; 38%) as a white solid:[20] mp 84.6–85.2 °C (Aldrich chemicals 86–89 °C); analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate, R_f=0.31. IR (neat, cm^{-1}) 3428, O–H; 1682, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.93 (2H, d, J=7.6 Hz) 7.63 (1H, t, J=7.4 Hz) 7.51 (2H, t, J=7.7 Hz) 4.89 (2H, s) 2.98 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 198.4, 134.3, 133.4, 128.9, 127.7, 65.4.

4.3. Characterization data for dicarbonyl compounds 2

4.3.1. 5-Oxodecanal (2a). Colorless liquid:[21] analytical TLC on silica gel, 6:4 *n*-hexane/ethyl acetate, R_f=0.52. IR (neat, cm^{-1}) 1709, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 9.75 (1H, s) 2.55–2.43 (4H, m) 2.39 (2H, t, J=7.4 Hz) 1.97–1.80 (2H, m) 1.65–1.47 (2H, m) 1.40–1.16 (4H, m) 0.89 (3H, t, J=6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 210.3, 201.8, 42.8, 42.6, 41.1, 31.2, 23.3, 22.2, 15.8, 13.7.

4.3.2. 4-Oxodecanal (2b). Colorless liquid:[22] analytical TLC on silica gel, 6:4 *n*-hexane/ethyl acetate, R_f=0.47. IR (neat, cm^{-1}) 1712, C=O. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 9.80 (1H, s) 2.80–2.67 (4H, m) 2.47 (2H, t, J=7.5 Hz) 1.65–1.50 (2H, m) 1.40–1.18 (6H, m) 0.88 (3H, t, J=6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 208.8, 200.4, 42.6, 37.3, 34.5, 31.4, 28.7, 23.7, 22.3, 13.9.

4.3.3. 2,2,4-Trimethyl-3-oxopentanal (2c). Colorless liquid:[23] analytical TLC on silica gel, 8:2 *n*-hexane/diethyl ether, R_f=0.45. IR (neat, cm^{-1}) 1736, 1702, C=O; 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 9.64 (1H, s) 3.03–2.97 (1H, m) 1.35 (6H, s) 1.06 (6H, d, J=6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 213.5, 200.9, 60.7, 36.5, 19.2, 19.0.

4.3.4. 1-Butyl-2-oxocyclopentanecarbaldehyde (2f). Colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether, R_f=0.55. IR (neat, cm^{-1}) 1745, 1713, C=O; 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 9.41 (1H, s) 2.66–1.07 (12H, m) 0.90 (3H, t, J=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 215.3, 199.0, 67.5, 38.6, 32.7, 27.7, 26.6, 22.9, 19.2, 13.7. Molecular ion (M+H) calcd for $C_{10}H_{17}O_2$: 169.1229; found (ESI-TOF) m/e=169.1223, error=3 ppm.

4.3.5. 2-Hydroxy-1-cyclohexenecarbaldehyde (2g). Orange liquid;[24] analytical TLC on silica gel, 8:2 *n*-hexane/ethyl acetate, R_f=0.48. IR (neat, cm^{-1}) 3421, O–H; 1715, C=O; 1603, C=C. 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 14.40 (1H, br s) 8.64 (1H, s) 2.47–2.25 (4H, m) 1.80–1.59 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 187.5, 184.9, 108.8, 31.2, 23.1, 22.5, 21.2.

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Isolation, structure elucidation and bioactivity of schischkiniin, a unique indole alkaloid from the seeds of *Centaurea schischkinii*

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Abstract—Reversed-phase HPLC analysis of the methanol extract of the seeds of *Centaurea schischkinii* afforded a novel indole alkaloid, named schischkiniin (**1**), together with four lignans, arctiin (**2**), matairesinoside (**3**), matairesinol (**4**), and arctigenin (**5**), and three flavonoids, astragalin (**6**), afzelin (**7**) and apigenin (**8**). While the structure of schiskiniin (**1**) was established unequivocally by UV, HRFABMS and a series of 1D and 2D NMR analyses, all known compounds were readily identified by comparison of their spectroscopic data with literature data. The free radical scavenging properties of these compounds were assessed using the DPPH assay, and their general toxicity and cytotoxicity were evaluated, respectively, by brine shrimp lethality and MTT cytotoxicity assays with CaCo-2 colon cancer cell lines. Arctigenin (**5**) exhibited promising in vitro anticancer activity ($IC_{50}=7$ μM) while with schischkiniin (**1**) the activity was of moderate level ($IC_{50}=76$ μM).

1. Introduction

Centaurea schischkinii Tzvelev (family: Asteraceae *alt*. Compositae), an erect perennial, is an endemic species distributed in the East Anatolian regions of Turkey.[1] To our knowledge, no report on the isolation of any plant secondary metabolites from *C. schischkinii* or any pharmacological properties of this plant is available to date. However, many species of the genus *Centaurea* have long been used in traditional medicine to cure various ailments, for example, diabetes, diarrhoea, rheumatism, malaria, hypertension etc., and a variety of secondary metabolites have been reported from different species of this genus.[2] As part of our on-going phytochemical investigation on the species of the genus *Centaurea*,[3–16] we now report on the isolation, structure elucidation and bioactivity of a series of compounds, including a novel indole alkaloid, named schischkiniin (**1**), four lignans, arctiin (**2**), matairesinoside (**3**), matairesinol (**4**), and arctigenin (**5**), and three flavonoids, astragalin (**6**), afzelin (**7**) and apigenin (**8**) from the seeds of *C. schichskinii*.

2. Results and discussion

Reversed-phase preparative HPLC analysis of the methanol extract of the seeds of *C. schischkinii* led to the isolation of a novel indole alkaloid, named schischkiniin (**1**), four lignans, arctiin (**2**), matairesinoside (**3**), matairesinol (**4**), and arctigenin (**5**), and three flavonoids, astragalin (**6**), afzelin (**7**), and apigenin (**8**). The spectroscopic data of the known lignans (**2–5**) and flavonoids (**6–8**) were in good agreement with literature data.[17–23] The structure of schischkiniin (**1**) was established unequivocally by UV, HRFABMS and a series of 1D and 2D NMR analyses.

Compound **1** was obtained as a gum and the molecular formula was determined as $C_{26}H_{24}N_6O_2$ from its HRMS spectrum where the $[M+Na]^+$ ion was observed at *m/z* 475.1857 ($C_{26}H_{24}N_6O_2Na$ requires *m/z* 475.1858). The compound showed positive colour reaction with Dragendorff's reagent. The UV absorption maxima at 220 and

Keywords: *Centaurea schischkinii*; Asteraceae; Afzelin; Apigenin; Arctigenin; Arctiin; Astragalin; Matairesinol; Matairesinoside; Schischkiniin; DPPH assay; Cytotoxiciy; MTT assay; Colon cancer.
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Table 1. ^{1}H (coupling constant J in Hz in parentheses) and ^{13}C NMR data, and ^{1}H–^{13}C long-range (^{2}J and ^{3}J) correlation observed in HMBC spectra of **1**

Position	δ_H in ppm	δ_C in ppm	HMBC correlation	
	1	**1**	^{2}J	^{3}J
2	7.15s	123.9	C-3	C-3a, C-7a, C-8
3	—	108.4	—	—
3a	—	127.3	—	—
4	7.65d (8.2)	118.1	C-3a	C-3, C-6, C-7a
5	7.01dd (8.2, 8.2)	118.9	—	C-3a, C-7
6	7.08dd (8.2, 8.2)	121.5	C-7	C-4, C-7a
7	7.32d (8.2)	111.2	—	C-3a, C-5
7a	—	137.2	—	—
8	3.47dd (4.4, 15.2), 3.10dd (9.2, 15.2)	27.3	C-3, C-9	C-2, C-3a, C-10
9	3.82[a]	55.5	C-8	C-12, C-3
10	—	174.0	—	—
12	3.86[a]	55.4	C-13, C-12′	C-10, C-13′
13	3.84[a]	55.5	C-12, C-13′	C-9, C-12′

[a] Overlapped peaks, assigned with the help of ^{1}H–^{13}C HSQC correlation.

280 nm indicated that this compound might be an indole alkaloid.[2] In the ^{1}H NMR spectrum of **1** (Table 1), a singlet at δ 7.15 and the signals at δ 7.65, 7.08, 7.32 and 7.01, were typical of a 3-substituted indole skeleton, and could be assigned to H-2, H-4, H-5, H-6 and H-7.[2] In the ^{13}C NMR spectrum (Table 1) all signals required for a 3-substituted indole skeleton were also present. In addition to the signals attributable to the 3-substituted indole skeleton, the ^{1}H and ^{13}C NMR spectra also showed signals for a methylene (δ_H 3.47 and 3.10, δ_C 27.3), three methines (δ_H 3.80–3.86, δ_C 55.5, 55.4 and 55.5) and an amide carbonyl (δ_C 174.0). All these signals formed the part structure **1a**. Taking the molecular formula and molecular mass into account, it was clear that the ^{1}H and ^{13}C NMR signals actually displayed signals for just one of the two identical parts of the molecule. Therefore, the molecule must be composed of two of these part structures **1a**. When combining two **1a** structures, only structure **1** could satisfy the molecular formula and molecular mass of this molecule. Further evidence to support the structure of **1** was obtained from a series of ^{1}H–^{13}C long-range couplings observed in its HMBC spectrum (Table 1). In the HMBC spectrum, H-12 showed ^{2}J correlation to C-13 and C-12′, and ^{3}J to C-10 and C-13′. Similarly, H-13 displayed ^{2}J correlation to C-12 and C-13′, and ^{3}J to C-9 and C-12′. Owing to overlapped ^{1}H NMR signals for H-9, H-12 and H-13, ^{1}H–^{1}H NOESY was not successful to establish the relative stereochemistry at C-9 (and C-9′), C-12 (and C-12′) and C-13 (and C-13′). Although it is difficult to completely determine the relative stereochemistry of this unique molecule, the use of biogenetic speculation in tandem with molecular mechanics may give an insight into the stereochemistry of schischkiniin (**1**). Simple diketopiperazines such as the Trp-Gly diketopiperazine (**9**) are common natural products (Fig. 1). On this occasion we are assuming that the naturally occurring L-Trp has been incorporated into **9**. The next steps would involve the reduction and dehydration of the Gly residue, resulting in the formation of **10**, followed or preceded by the dimerisation at the Trp indole *N* to give the dimer **11**. This dimer would then undergo a photochemically allowed 2+2 cycloaddition to give 4 possible products. Schischkiniin (**1**) is a symmetrical structure as is evident from the degeneracy of the resonances in the NMR spectra. For this reason two possible asymmetric structures can be ruled out leaving only possibilities **1b** and **1c**. Molecular mechanics calculations[24,25] to determine the global energy minima of these possible structures suggest that **1c** has the lowest total energy function 986.93 kcal/mol (Fig. 2). Although it is possible that a natural product is enzymetically biosynthesised in a high-energy conformation, in this case a photochemically driven cycloaddition reaction will result in the lowest energy product. We therefore, speculate that the relative stereochemistry of schischkiniin is as shown in **1c**. If we assume that the origin of the Trp residue is L-Trp then we may also predict the absolute stereochemistry as shown. Thus, this novel indole alkaloid was identified as schischkiniin (**1**), which is a tryptophan-derived alkaloid. In addition to the indole skeleton, compound **1** also possesses a distinct macrocyclic polyamine ($n=14$) structure.

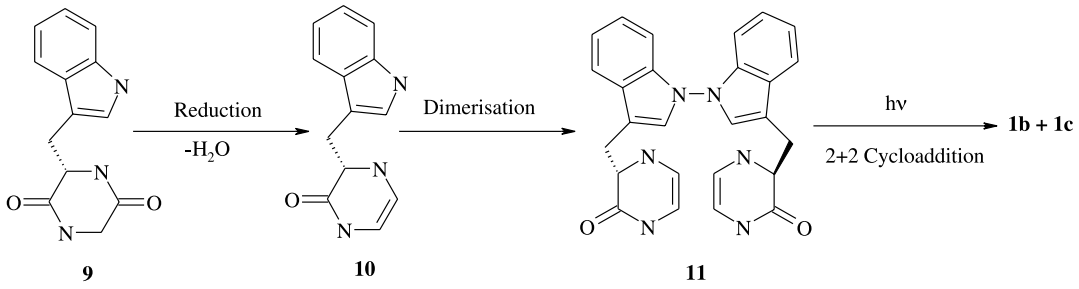
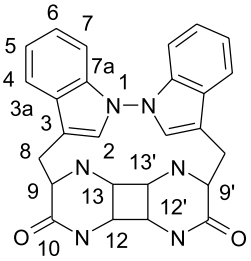
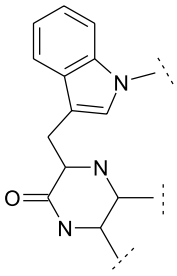


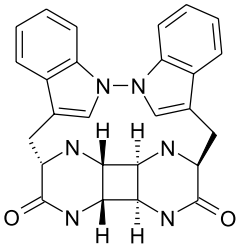
Figure 1. Proposed biogenetic pathway for the formation of schischkiniin (**1**) from a simple diketopiperazine **9**. The reduction/dehydration and dimerisation steps may be reversed.



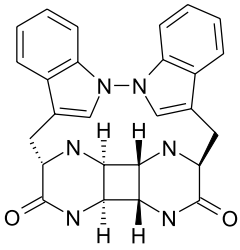
1



1a



1b



1c

The DPPH assay[26] is an easy and straightforward method for determining the free radical scavenging property of a compound. DPPH is a molecule containing a stable free radical. In the presence of an antioxidant, which can donate an electron to DPPH, the purple colour, which is typical of the free DPPH radical, decays, and the change in absorbance at 517 nm is monitored spectrophotometrically. All compounds (**1**–**8**) showed low to moderate levels of free radical scavenging activity ($IC_{50}=16.0\times10^{-2}$–$2.02\times10^{-3}$ mg/mL) (Table 2). Among four structurally related lignans **2**–**5**, matairesinol (**4**) showed the most prominent antioxidant property, which could be attributed to the presence of the highest number of phenolic hydroxyl groups (four –OH) in the molecule. Despite not having any phenolic hydroxyl group in the molecule, compound **1** still showed significant antioxidant activity ($IC_{50}=3.8\times10^{-3}$ mg/mL) (Table 1).

The brine shrimp lethality assay, which has been proven to be an effective and rapid assay method to screen compounds for potential general toxicity and cytotoxic activity[27] was used to determine the general toxicity of compounds **1**–**8**. The LD_{50} of these compounds were in between 1.4×10^{-1} and 2.0×10^{-3} mg/mL (Table 2). Arctigenin (**5**) was found to be the most toxic of all test compounds towards brine shrimp ($LD_{50}=2.0\times10^{-3}$ mg/mL) and displayed toxicity comparable to that of the positive control podophyllotoxin ($LD_{50}=2.79\times10^{-3}$ mg/mL), a well known cytotoxic lignan. The novel alkaloid (**1**) also showed significant general toxicity in this assay ($LD_{50}=7.2\times10^{-3}$ mg/mL).

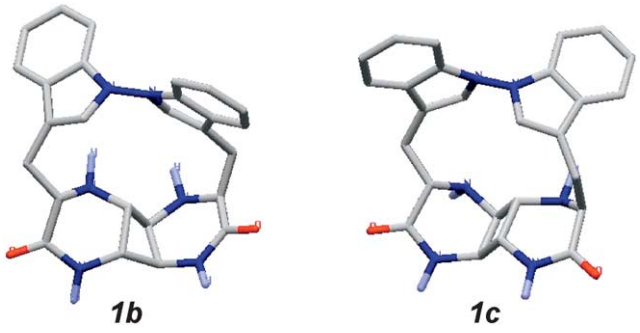


Figure 2. Global energy minima for structures **1b** and **1c** (heavy atoms and polar hydrogens only shown). The global minimum for **1b** was found 15 times ($E_{tot}=1022.68$ kcal/mol) and the global minimum for **1c** was found 37 times ($E_{tot}=986.93$ kcal/mol).

The in vitro cytotoxicities (IC_{50} μM) of all the compounds isolated and characterised in this work were determined by the MTT assay against colon cell lines, CaCo-2 (Table 1).[29] The novel indole alkaloid schischkiniin (**1**) exhibited moderate in vitro anticancer activity with an IC_{50} of 76 μM. The flavanoids astragalin (**6**), afzelin (**7**) and apigenin (**8**) showed low cytotoxicities with IC_{50} values 302, 316 and 133.1 μM, respectively. Similarly all isolated lignans demonstrated low levels of activity, for example, arctiin (**2**, $IC_{50}=220$ μM), matairesinoside (**3**, $IC_{50}=288$ μM), matairesinol (**4**, $IC_{50}=124$ μM), with the exception of arctigenin (**5**), which gave an IC_{50} value 7 μM, and therefore, can be considered to be an active compound against colon cancer cells in vitro. In the lignans and flavanoids described above, the presence of a sugar moiety in the molecule tends to reduce significantly the anticancer activity of these compounds. It can be assumed that the presence of a sugar group could prevent the effective transport of these compounds through the cell membrane, hence their reduced biological activities.

The degree of general toxicity displayed by the test compounds in the brine shrimp lethality assay corresponded well with the cytotoxic potentials of these compounds observed in the MTT assay using colon cancer cell line.

Table 2. Antioxidant (DPPH assay) and cytotoxic (MTT assay) activities, and brine shrimp toxicity (brine shrimp lethality assay) of compounds **1–8**

Compounds	Antioxidant activity IC_{50} (mg/mL)	Cytotoxicity IC_{50} (μM)	Brine shrimp toxicity LD_{50} (mg/mL)
1	3.8×10^{-3}	76	7.2×10^{-3}
2	16.0×10^{-2}	220	9.8×10^{-2}
3	2.19×10^{-3}	288	1.65×10^{-2}
4	2.02×10^{-3}	124	5.5×10^{-3}
5	1.88×10^{-2}	7	2.0×10^{-3}
6	8.0×10^{-2}	315	1.4×10^{-1}
7	11.6×10^{-2}	427	8×10^{-1}
8	1.44×10^{-2}	133	9.3×10^{-3}
Quercetin	2.88×10^{-5}	—	—
Podophyllotoxin	—	6×10^{-2}	2.79×10^{-3}

3. Experimental

3.1. General procedures

UV spectra were obtained in MeOH using a Hewlett-Packard 8453 UV–vis spectrometer. MS analyses were performed on a Quattro II triple quadrupole instrument. NMR spectra were recorded in CD_3OD on a Varian Unity INOVA 400 MHz NMR spectrometer 400 (400 MHz for ^1H and 100 MHz for ^{13}C) using the residual solvent peaks as internal standard. HPLC separation was performed using a Dionex prep-HPLC system coupled with Gynkotek GINA50 autosampler and Dionex UVD340S Photo-Diode-Array detector. A Luna C_{18} preparative (10 μM, 250 mm×21.2 mm) and/or a Luna C_{18} semi-preparative HPLC column (5 μM, 250 mm×10 mm) were used. Sep-Pak Vac 35 cc (10 g) C_{18} cartridge (Waters) was used for pre-HPLC fractions. HMBC spectra were optimised for a long range J_{H-C} of 9 Hz and the NOESY experiment was carried out with a mixing time of 0.8 s.

3.2. Plant material

The seeds of *C. schischkinii* were collected from East Anatolia, Turkey (B7 Erzincan, 30.5 km from Erzincan to Gumushane, 2024 m, 39°53′29″ N 39°21′6″ E), during September–October 2002. The voucher specimens, 10 VII.2002 and PH800001, have been maintained, respectively, in the herbarium of the Plant Ecology Laboratory, Science Faculty, Anadolu University, Turkey, and of the Plant and Soil Science Department, University of Aberdeen, Scotland (ABD).

3.3. Extraction and isolation of compounds

Ground seeds of *C. schischkinii* (80 g) were Soxhlet-extracted, successively, with *n*-hexane, dichloromethane and methanol (MeOH) (1 L each). The MeOH extract was fractionated by solid phase extraction method using a Sep-Pak C_{18} (10 g) cartridge eluting with a step gradient: 40, 60, 80 and 100% MeOH in water (200 mL each). Preparative-HPLC (eluted with a linear gradient-water: MeOH=65:25–30:70 over 50 min followed by 70% MeOH for 10 min, 15 mL/min, monitored by photo-diode-array detector) of the Sep-Pak fraction, which was eluted with 40% MeOH, afforded **1**, (7.5 mg; t_R=8.1 min), lignans **2** (59.2 mg; t_R=24.4 min), **3** (518.6 mg; t_R=28.5 min) and **4** (29.9 mg, t_R=33.4 min) and flavonoids **6** (11.7 mg, t_R=32.2 min) and **7** (11.5 mg, t_R=36.1 min). Compound **1** was further purified by semiprep HPLC (eluted with a linear gradient- water:acetronitrile (ACN)=10:90–60:40 over 50 min followed by 40% ACN for 10 min, 2 mL/min, monitored by photo-diode-array detector). Similar HPLC purification of the 60% Sep-Pak fraction resulted in the isolation of **6** (13.7 mg) and **8** (27.3 mg).

3.3.1. Schischkiniin (1). Gum; 7.5 mg; UV (MeOH) λ_{max} 220, 280 nm; HRFABMS: $C_{26}H_{24}N_6O_2Na$ $[M+Na]^+$ requires *m/z* 475.1858 (found 475.1857); ^1H and ^{13}C NMR (Table 1).

3.4. Free radical scavenging activity: DPPH assay

2,2-Diphenyl-1-picrylhydrazyl (DPPH), molecular formula $C_{18}H_{12}N_5O_6$, was obtained from Fluka Chemie AG, Bucks. Quercetin was obtained from Avocado Research Chemicals Ltd, Shore road, Heysham, Lancs. The method used by Takao et al.[26] was adopted with appropriate modifications.[10,11] DPPH (4 mg) was dissolved in MeOH (50 mL) to obtain a concentration of 80 μg/mL.

3.4.1. Qualitative assay. Test compounds (**1–8**) were applied on a TLC plate and sprayed with DPPH solution using an atomiser. It was allowed to develop for 30 min. The colour change (purple on white) was noted.

3.4.2. Quantitative assay. Test compounds (**1–8**) were dissolved in MeOH to obtain a concentration of 0.5 mg/mL each. Dilutions were made to obtain concentrations of 5×10^{-2}, 5×10^{-3}, 5×10^{-4}, 5×10^{-5}, 5×10^{-6}, 5×10^{-7}, 5×10^{-8}, 5×10^{-9}, 5×10^{-10} mg/mL. Diluted solutions (1 mL each) were mixed with DPPH (1 mL) and allowed to stand for 30 min for any reaction to occur. The UV absorbance was recorded at 517 nm. The experiment was performed in triplicate and the average absorption was noted for each concentration. The same procedure was followed for the positive control, quercetin, a well known natural antioxidant.

3.5. Brine shrimp lethality assay

Shrimp eggs were purchased from The Pet Shop, Kittybrewster Shopping Complex, Aberdeen, UK. The bioassay was conducted following the procedure described by Meyer et al.[27] The eggs were hatched in a conical flask containing 300 mL artificial seawater. The flasks were well

aerated with the aid of an air pump, and kept in a water bath at 29–30 °C. A bright light source was left on and the nauplii hatched within 48 h. The compounds **1**–**8** were dissolved in 20% aq DMSO to obtain a concentration of 1 mg/mL. These were serially diluted two-times, and seven different concentrations were obtained. A solution of each concentration (1 mL) was transferred into clean sterile universal vials with pipette, and aerated sea-water (9 mL) was added. About 10 nauplii were transferred into each vial with pipette. A check count was performed and the number alive after 24 h was noted. LD_{50}s were determined using the Probit analysis method.[28]

3.6. MTT cytotoxicity assay

CaCo-2 cells were maintained in Earle's minimum essential medium (Sigma), supplemented with 10% (v/v) foetal calf serum (Labtech Int.), 2 mM L-glutamine (Sigma), 1% (v/v) non-essential amino acids (Sigma), 100 IU/mL penicillin and 100 μg/mL streptomycine (Sigma). Exponentially growing cells were plated at 2×10^4 cells cm^{-2} into 96-well plates and incubated for 72 h before the addition of drugs. Stock solution of compounds were initially in DMSO or H_2O and further diluted with fresh complete medium.

The growth-inhibitory effects of the compounds (**1**–**8**) were measured using standard tetrazolium MTT assay.[29] After 72 h of incubation at 37 °C, the medium was removed, and 100 μL of MTT reagent (1 mg/mL) in serum free medium was added to each well. The plates were incubated at 37 °C for 4 h. At the end of the incubation period, the medium was removed and pure DMSO (200 μL) was added to each well. The metabolised MTT product dissolved in DMSO was quantified by reading the absorbance at 560 nm on a micro plate reader (Dynex Technologies, USA). The IC_{50} values were calculated from the equation of the logarithmic line determined by fitting the best line (Microsoft Excel) to the curve formed from the data. The IC_{50} value was obtained from the equation $y=50$ (50% value).

3.7. Modelling conditions

Minimisations (2000 steps) were carried out using MacroModel version 6.5[24] using the Merck Molecular Force Field. The generalised Born solvent accessible area continuum solvent model[25] was used to simulate H_2O solvent, due to the unavailability of parameters for MeOH. The minimisations were followed by 1000 steps of Monte Carlo conformational searching to give the global energy minima shown in the figures. The global energy minima were found 15 times for **1b** (1022.68 kcal/mol) and 37 times for **1c** (986.93 kcal/mol).

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Application of directed metalation in synthesis. Part 8: Interesting example of chemoselectivity in the synthesis of thioaurones and hydroxy ketones and a novel anionic *ortho*-Fries rearrangement used as a tool in the synthesis of thienopyranones and thiafluorenones☆

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Dedicated to Professor N. B. Chapman on his 90th birthday

Abstract—Chemoselective synthesis of thioaurones or 3-hydroxy benzo[*b*]thiophen-2-aryl ketones, 1-hydroxy naphtho[2,1-*b*]thiophen-2-aryl ketones and chalcones from *N*,*N*-diethyl-*ortho*-methyl sulfanyl aryl amides were described. (Benzo[*b*]thiophen-2-yl) alkylates and (naphtho[2,1-*b*]thiophen-2-yl) alkylates undergo a novel anionic *ortho*-Fries rearrangement leading to (3-hydroxy benzo[*b*]thiophen-2-yl) and (1-hydroxy naphtho[2,1-*b*]thiophen-2-yl) alkyl ketones. The hydroxy ketones were used as intermediates in the synthesis of wide range of benzothienopyranones and thiafluorenones.

1. Introduction

We have earlier demonstrated[2–6] the usefulness of directed metalation[7] in providing regiocontrolled access to contiguously substituted thiophene and benzene, which are key intermediates in the synthesis of condensed heterocycles incorporating a fused thiophene ring. In continuation of this work, we have reported[1] in a recent communication, two novel high-yielding syntheses of 3-hydroxybenzo[*b*]thiophenes carrying acyl function in the 2-position termed as hydroxy ketones **1**. Either thioaurones (also known as hemithioindigo) **2** or hydroxy ketones **1a–e** and **1h–r**, including several chalcones can be chemoselectively synthesized via the same one-pot reaction involving a common thioindoxyl **3**[2,3] intermediate, while 3-hydroxybenzo[*b*]thiophene **1f–g** and **1s–t** carrying an alkyl carbonyl substituent in the 2-position were obtained through a novel intramolecular anionic rearrangement.

The interesting and unprecedented switch of chemoselectivity observed during the formation of hydroxy ketones **1a–e** and **1h–r** and the novel anionic *ortho*-Fries rearrangement observed during the formation of hydroxy alkyl ketones **1f–g** and **1s–t** lead to products that are intermediates[1] in the synthesis of benzothieno[3,2-*b*]-pyranones. The latter are important synthetic targets because of the interesting biological activities shown by members of this class of compounds.[8–10] Thioaurones have a wide range of applications.[11] They are employed in dyes, cosmetics, aqueous jet-printing ink and as photochromic materials.[12] It was therefore, necessary to examine the scope of these reactions by examining a wider range of substrates.

2. Results and discussion

A consequence of the development of expedient synthesis of thioindoxyls **3**[2,3] from readily available *N*,*N*-diethyl aryl carboxamides **4a–d**[2,3,7] was the easy accessibility of

☆ Part 7: see Ref. 1.

Keywords: Directed metalation; Chemoselectivity; Thioaurones; Chalcone; Anionic *ortho*-Fries rearrangement; Benzothienopyranone.
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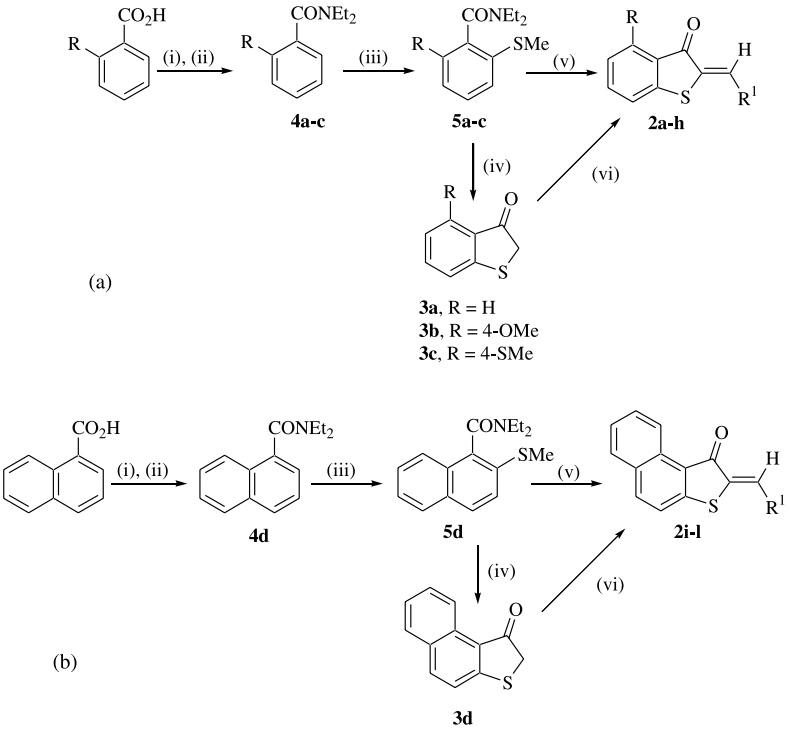


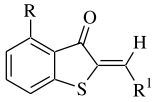
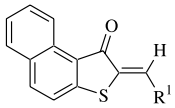
Scheme 1. Reagents and conditions: (i) $SOCl_2$/benzene/reflux; (ii) *N*,*N*-diethyl amine/benzene/rt; (iii) *s*-BuLi/TMEDA/THF/$(SCH_3)_2$/−78 °C to rt; (iv) LDA (1.5 equiv)/THF/−78 °C to rt; (v) LDA (2.5 equiv)/THF/R^1CHO (1.1 equiv)/−10 to 0 °C; (vi) LDA (1.5 equiv)/THF/R^1CHO (1.1 equiv)/−10 to 0 °C.

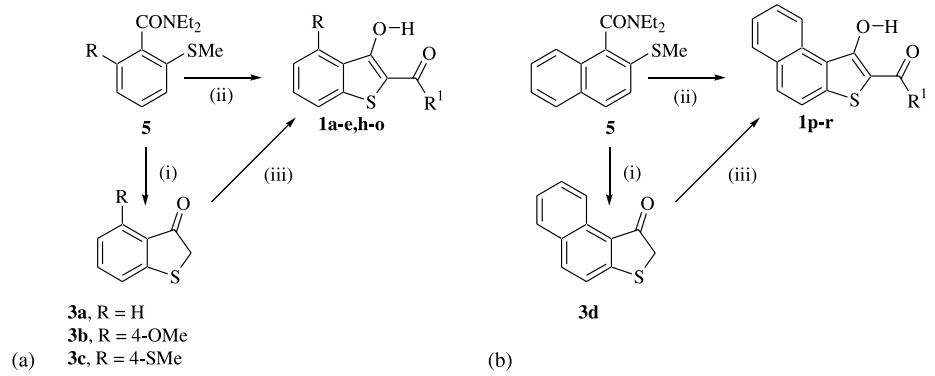
thioaurones **2** in a one-pot reaction in high yields. In comparison to the one-pot synthesis of thioaurones reported by Cabbidu,[13] the one-pot synthesis developed in our laboratory (Scheme 1a and b) allows a wider variation of substituents in the final products. The starting amide **4a**–**d** were converted into its *ortho*-methyl sulfanyl derivative **5a**–**d** via standard protocol of directed *ortho*-lithiation and quenching with dimethyldisulfide. The resulting methyl-sulfanyl derivatives **5a**–**d**[2,3,7] were treated with LDA at 0 °C and after stirring for 1 h at that temperature, a solution of the aryl aldehyde or cinnamaldehyde (1.2 equiv) in tetra-hydrofuran was added while the temperature of the reaction mixture was maintained at 0 °C. Acidic work up after stirring for further 2 h at that temperature afforded a red crystalline material, and the crude reaction product was purified by column chromatography over silica gel to afford the thioaurones **2** in good to excellent yields (Table 1). In common with the observation of Cabbidu,[13] we found that attempted one-pot synthesis of thioaurones using alkyl aldehydes were accompanied by the formation of intractable materials, presumably resulting out of polymeric self-condensation of the aldehydes.

The crude thioaurones were occasionally accompanied by trace amounts of another compound, which could be separated by careful column chromatography over silica gel. Existence of intramolecular hydrogen bonding between hydroxyl and carbonyl functions present in these compounds, was evident from the peaks at 3440–3425 cm^{-1} and at 1590 cm^{-1} in their IR spectra. Additional corroboration for the presence of hydrogen bonding was provided by the ^1H NMR spectra, which displayed signals due to hydrogen bonded OH as a slightly broad one proton singlet at around 13.5 ppm. From analytical and spectroscopic data these compounds were assigned as the (3-hydroxybenzo[*b*] thiophen-2-yl) (**1a**–**e** and **1h**–**o**) and (1-hydroxy naphtho[2,1-*b*]thiophen-2-yl) (**1p**–**r**) aryl ketone structures (Scheme 2a and b).

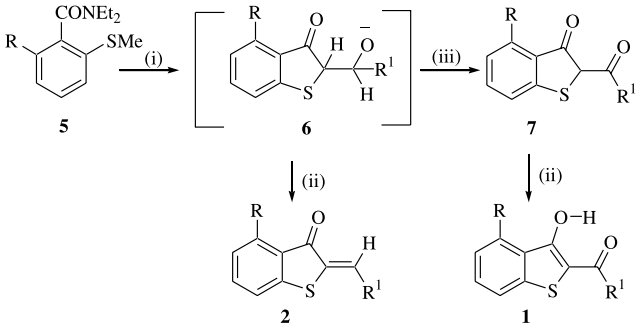
Exclusive formation of the hydroxy aryl ketones was assured when the aryl aldehyde was used in excess followed by stirring the reaction mixture at room temperature for several hours. The plausible reaction mechanism (Scheme 3) requires the formation of thioindoxyl **3** as the common intermediate for both the thioaurones and the hydroxy ketones. The ionic intermediate **6** is formed by sequential deprotonation at the 2-position of **3** and subsequent attack

Table 1. Thioaurones or hemi-thioindigo

Entry	Compound	R	R^1	Yield (%)
				
2a		H	*p*-ClC_6H_4	79
2b		H	CH=CHPh	75
2c		OMe	Ph	76
2d		OMe	CH=CHPh	80
2e		SMe	Ph	78
2f		SMe	*p*-ClC_6H_4	80
2g		SMe	2-thienyl	92
2h		SMe	CH=CHPh	78
				
2i			Ph	82
2j			*p*-ClC_6H_4	93
2k			2-thienyl	88
2l			CH=CHPh	79



Scheme 2. Reagents and conditions: (i) LDA (1.5 equiv)/THF/−78 °C to rt; (ii) LDA (2.5 equiv)/THF/R^1CHO (2.2 equiv)/−10 °C to rt; (iii) LDA (1.5 equiv)/THF/R^1CHO (2.2 equiv)/−10 °C to rt.

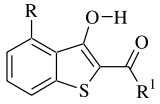
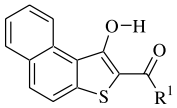


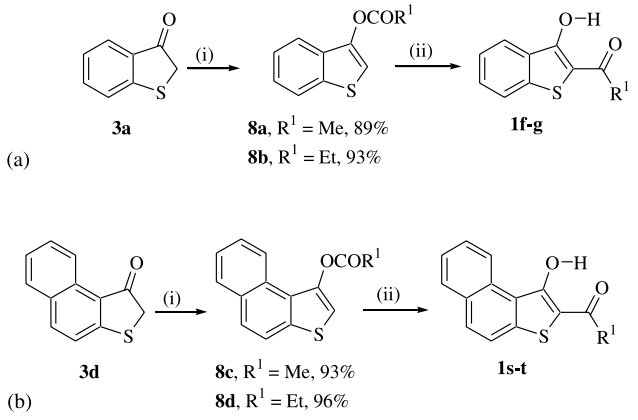
Scheme 3. Reagents and conditions: (i) LDA (2.5 equiv)/THF/R^1CHO (1.1 equiv)/−10 to 0 °C; (ii) aq HCl; (iii) R^1CHO (1.1 equiv)/−10 °C to rt.

by the incipient carbanion on the carbonyl carbon of the aryl aldehyde. Acidic work up, after keeping the reaction mixture at 0 °C for 1 h, results in dehydration affording the thioaurones **2**. When the reaction mixture was stirred at room temperature in the presence of excess aryl aldehyde for 5–6 h, it has sufficient time to undergo Cannizzaro type hydride transfer resulting in the formation of the 1,3-dicarbonyl compound **7**, which subsequently enolises to the hydroxy ketone **1a–e** and **1h–r** (Table 2). The transfer of hydride to the aldehyde during the formation of the hydroxy ketone is clearly evident from the exclusive formation of the latter when excess aldehyde is used. It was however, difficult to isolate the alcohol that should form concomitantly with the hydride transfer. The proposed mode of hydride transfer was inferred from GC analysis of the crude reaction product obtained for the synthesis of the compound **1a** (R=H) from *o*-methylsulfanyl benzamide and benzaldehyde. GC analysis of the crude reaction product contained a peak with the same retention time as that of benzyl alcohol whose gas chromatogram was run separately. Benzyl alcohol was then added to the crude reaction product and the GC of the mixture was run separately. The GC trace did not show any additional peaks and an increase of the height of the peaks, which was earlier surmised as that of benzyl alcohol, was observed. Occurrence of the Cannizzaro-type hydride transfer was thus, confirmed and an interesting switch of chemoselectivity is thus, observed between elimination product **2** and the 1,3-dicarbonyl compound **7** depending upon the reaction conditions.

An aromatic compound carrying hydroxyl and acyl substituents on two contiguous carbons can act as key intermediates for annulating a pyranone ring on to the existing core (vide infra). While hydroxy ketones **1a–e** and **1h–r** can now be easily obtained from **5a–d**, it was not possible to synthesize alkyl hydroxy ketones **1f–g** and **1s–t** in the same way because of the polymerisation of the starting aldehydes under the reaction condition as stated above. We could however, synthesize the latter via a novel anionic *ortho*-Fries rearrangement. Anionic *ortho*-Fries rearrangement[14] under directed metalation condition, as originally reported by Snieckus[14] consists of directed lithiation at the *ortho*-position of an *O*-carbamate substituent followed by intramolecular rearrangement in the absence electrophile quench. We report here, similar rearrangement undergone by an *ortho*-deprotonated alkyl carboxylate species **8a–d** (Scheme 4a and b). Alkyl carboxylates have no directing power in directed metalation

Table 2. Hydroxy ketones

Entry	Compound	R	R^1	Yield (%)
				
1a		H	Ph	93
1b		H	*p*-ClC_6H_4	89
1c		H	2-thienyl	93
1d		H	*p*-$OMeC_6H_4$	91
1e		H	CH=CHPh	95
1f		H	Me	67
1g		H	Et	73
1h		OMe	Ph	91
1i		OMe	*p*-ClC_6H_4	93
1j		OMe	2-thienyl	90
1k		OMe	CH=CHPh	89
1l		SMe	Ph	91
1m		SMe	*p*-ClC_6H_4	93
1n		SMe	2-thienyl	90
1o		SMe	CH=CHPh	88
				
1p			Ph	90
1q			*p*-ClC_6H_4	93
1r			CH=CHPh	85
1s			Me	55
1t			Et	63



Scheme 4. Reagents and conditions: (i) NaH/THF/R^1COCl/rt; (ii) LDA/THF/−80 °C to rt.

reactions since nucleophilic substitution reaction occurs in the presence of alkyl lithium. However, for our purpose, we could take advantage of the acidic nature of the proton in the α-position to the ring sulfur atom in benzo[*b*]thiophene, allowing smooth deprotonation at that position, with LDA. Treatment of thioindoxyl **3a**[2,3] and **3d**[3] with acetyl and propionyl chloride in THF in the presence of oil-free sodium hydride afforded **8a**, **8b**,[1] **8c** and **8d** in excellent yields. When the compounds **8a–d** were treated with LDA in THF at −80 °C, deprotonation indeed took place in the position α to the ring sulfur atom, as expected. Usual acidic work up after keeping the reaction mixture at room temperature for 6 h afforded the rearranged products **1f–g** and **1s–t** in very good yields (Table 2). A trace amount of **3a** and **3d** were also formed, which were separated by column chromatography over silica gel.

Several of the hydroxy ketones obtained by the above two routes served as key intermediates in the annulation of a γ-pyranone ring onto the benzo[*b*]thiophene or naphtho[2,1-*b*]thiophene core. Bubbling dry HCl gas into a dry ethanolic solution of **1e**, **1k**, **1o** and **1r** afforded dihydropyranones **9a**,[1] **9b**, **9c** and dihydrothiafluorenone **9d**, respectively, (Scheme 5a and b) in excellent yields.

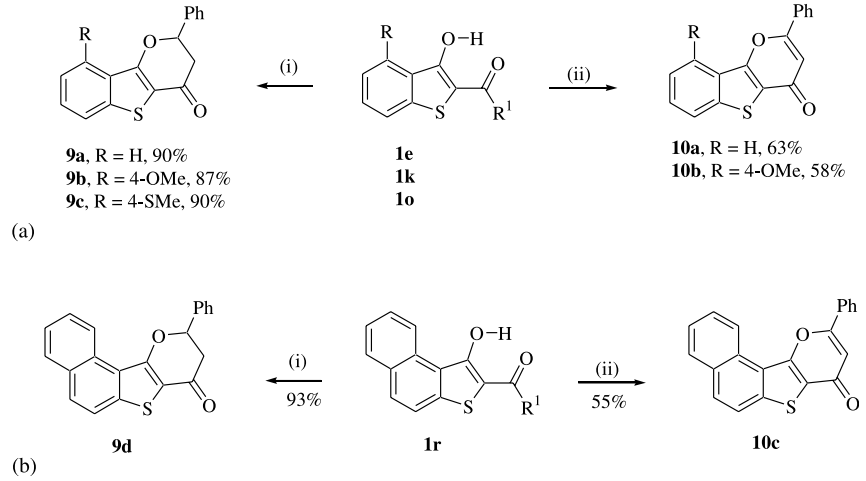
The usefulness of the chemoselective synthesis of chalcones **1e**, **1k** and **1r** is amply demonstrated in the expedient synthesis of pyranones **10a–b** and fluorenone **10c** (Scheme 5a and b), respectively. Previously, Mustafa synthesized this class of compounds from **1f**[17] by first converting them into chalcones through reaction with aryl aldehydes followed by treatment with seleniumdioxide.[15,16] We could obtain the chalcones in one step from **5** and cinnamaldehyde, which were then converted into pyranone derivatives **10a–c** by usual treatment with seleniumdioxide in dry isoamyl alcohol.

Treatment of **1f** and **1g** with oil-free sodium hydride (2.5 equiv) in dry THF was followed by addition of ethyl formate and stirring for 10 h at room temperature. Addition of water and acidification with 2 N HCl after most of the solvent was evaporated, afforded the crude cyclised product **11a–b**, which were purified by column chromatography over silica gel. We found that 2-hydroxy-3-methyl-2,3-dihydro benzo[4,5]thieno[3,2-*b*]pyran-4-one (**11b**) remains as 1:1 mixture of diasteromers. The hydroxy compounds **11a** and **11b** were dehydrated with *p*-toluenesulfonic acid in benzene to afford **12a** and **12b**, respectively, in 90 and 95% yields (Scheme 6).

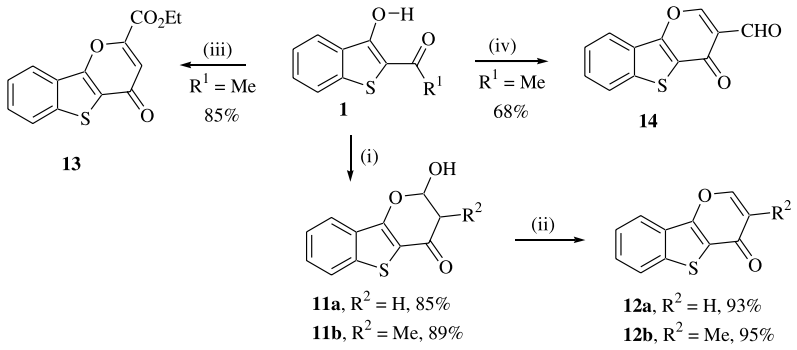
The hydroxy ketone **1f** was also used as an intermediate in the synthesis of ethyl benzo[4,5]thieno[3,2-*b*]pyran-4-one-2-carboxylate[8] (**13**) and benzo[4,5]thieno[3,2-*b*]pyran-4-one-3-carboxaldehyde (**14**) in very good yields. Compound **13** was obtained in 85% yield when **1f** was treated with oil free sodium hydride in THF followed by diethyl oxalate while treatment of **1f** with dimethyl formamide and phosphorus oxychloride afforded **14** in 68% yield (Scheme 6).

3. Conclusion

The one-pot reaction of *N*,*N*-diethyl-*ortho*-methylsulfanyl aryl amides with aryl aldehydes in the presence of LDA associated with an interesting switch of chemoselectivity is yet another example of usefulness of directed metalation as a methodology in synthetic aromatic and heteroaromatic chemistry. While one of the alternative products, thioaurones have a multitude of applications, the other



Scheme 5. Reagents and conditions: (i) Dry ethanol/dry HCl (g); (ii) SeO_2/dry isoamyl alcohol/reflux.



Scheme 6. Reagents and conditions: (i) NaH/THF/HCO_2Et; (ii) PTSA/benzene/reflux; (iii) NaH/THF/$(CO_2Et)_2$; (iv) DMF/$POCl_3$.

alternative products 3-hydroxy-2-ketoaryl benzo[*b*]thiophenes and 1-hydroxy-2-ketoaryl naphtho[2,1-*b*]thiophenes are important synthetic intermediates. A novel anionic *ortho*-Fries rearrangement described in this paper, has led to 3-hydroxy-2-ketoalkyl benzo[*b*]thiophenes, which are used as intermediates in the synthesis of benzothienopyranones having different types of substitution in γ-pyranone ring.

4. Experimental

4.1. General

Melting points (uncorrected) were recorded in open capillaries on a hot stage apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in deuteriochloroform on a Bruker DPX-300 spectrometer. Chemical shifts (δ) are expressed in ppm using tetramethylsilane as internal standard. IR spectra were recorded on FTIR-8300 and SHIMADZU spectrometers, for solids in KBr discs and for liquids by placing a thin layer of the sample between two KBr discs. Commercially available solvents were purified by distillation. Diethyl ether and tetrahydrofuran were kept overnight over potassium hydroxide and subsequently purified further by the benzophenone ketyl method. Dinethyl sulfate was washed with water and kept over anhydrous potassium carbonate before use. Both *n*- and *s*-butyl lithium were prepared by slow addition of the appropriate halide to the freshly prepared dispersion of lithium in *n*-hexane (for *n*-butyl lithium) or cyclohexane (for *s*-butyl lithium) under sonication. Petroleum ether has boiling point 60–80 °C. Silica gel (60–120 mesh) was used for column chromatography.

4.1.1. General synthesis of thioaurones taking 2-(4-chlorobenzylidene)benzo[*b*]thiophen-3-one (2a) as representative. To a well stirred solution of LDA (5 mmol) in THF (15 mL), **5a** (0.45 g, 2.4 mmol) in THF (5 mL) was added by syringe while the temperature of the reaction mixture was kept between −10 and 0 °C. After stirring for 1 h, 4-chlorobenzaldehyde (0.34 g, 2.4 mmol) in THF (5 mL) was added to the reaction mixture at the same temperature. After stirring for 2 h at 0 °C, water (25 mL) was added to the reaction mixture and the pH was maintained between 4 and 5 by addition of 2 N HCl. After extraction with chloroform the organic layer was washed with water and dried (Na_2SO_4). The crude red solid residue left after evaporation of the solvent was purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/15)], yellow solid, yield 0.43 g, 79%, mp 162–165 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1678, 1580 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.95 (1H, d, J=7.7 Hz), 7.89 (1H, s), 7.64–7.56 (3H, m), 7.51–7.43 (3H, m), 7.33 (1H, d, J=7.7 Hz); ^{13}C (75 MHz, $CDCl_3$) δ_C: 188.8, 146.1, 136.5, 135.8, 133.3, 133.1, 132.4, 132.4, 131.1, 130.6, 129.2, 129.2, 127.5, 126.1, 124.3. Anal. Calcd for $C_{15}H_9ClOS$: C, 66.05; 3.33%. Found C, 66.28; 3.41%.

4.1.2. 2-(3-Phenylallylidene)benzo[*b*]thiophen-3-one (2b). Prepared from **5a** (0.45 g, 2 mmol) in THF (5 mL), LDA (5 mmol) in THF (15 mL) and cinnamaldehyde (0.32 g, 2.4 mmol) in THF (5 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/13)], red solid, yield 0.39 g, 75%, mp 138–140 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1662, 1579, 1559 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.69 (1H, d, J=11 Hz), 7.58 (1H, d, J=7.9 Hz), 7.55–7.25 (8H, m), 7.13–6.99 (2H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 188.3, 145.6, 143.9, 136.3, 135.4, 133.3, 132.0, 130.0, 129.3, 129.3, 128.2, 127.9, 127.9, 127.1, 125.7, 124.6, 124.3. Anal. Calcd for $C_{17}H_{12}OS$: C, 77.24; 4.58%. Found C, 77.11; 4.49%.

4.1.3. 2-Benzylidene-4-methoxybenzo[*b*]thiophen-3-one (2c). Prepared in the same way from **5b** (0.25 g, 1 mmol) in THF (5 mL). LDA (2.2 mmol) in THF (10 mL) and benzaldehyde (0.13 g, 1 mmol) in THF (3 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/15), yellow solid, yield 0.25 g, 76%, mp 160–161 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1680, 1576 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.88 (1H, s), 7.71–7.68 (2H, m), 7.53–7.38 (4H, m), 7.07 (1H, d, J=7.7 Hz), 6.76 (1H, d, J=8.2 Hz) 4.01 (3H, s); ^{13}C (75 MHz, $CDCl_3$) δ_C: 187.1, 161.2, 148.7, 136.9, 134.8, 132.6, 131.2, 131.2, 130.6, 130.1, 129.3, 129.3, 118.9, 116.3, 108.3, 56.3. MS: (*m*/*z*) 267 (M^+-1), 268 (M^+), 269 (M^++1). Anal. Calcd for $C_{16}H_{12}O_2S$: C, 71.62; 4.51%. Found C, 71.75; 4.62%.

4.1.4. 4-Methoxy-2-(3-phenylallylidene) benzo[*b*]thiophen-3-one (2d). Prepared in the same way from **5b** (0.25 g, 1 mmol) in THF (5 mL), LDA (2.2 mmol) in THF (10 mL) and cinnamaldehyde (0.13 g, 1 mmol). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/13)] to afford thioaurone **2d** as reddish crystalline

material, yield 0.25 g, 80%, mp 180–182 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1664, 1585, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.60–7.43 (4H, m), 7.40–7.29 (3H, m), 7.09–6.90 (3H, m), 6.71 (1H, d, $J=8.2$ Hz), 3.97 (3H, s, OCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 186.4, 160.9, 147.7, 142.9, 136.6, 136.5, 133.3, 132.0, 129.7, 129.2, 129.1, 128.0, 127.8, 124.6, 116.4, 107.9, 96.4, 56.2. Anal. Calcd for $C_{18}H_{14}O_2S$: C, 73.44; 4.79%. Found C, 73.53; 4.85%.

4.1.5. 2-Benzylidene-4-methylsulfanyl benzo[*b*]thiophen-3-one (2e). Prepared in the same way from **5c** (0.27 g, 1 mmol), in THF (5 mL), LDA (2.5 mmol) in THF (10 mL) and benzaldehyde (0.13 g, 1.2 mmol) in THF (3 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/9)], red solid, yield 0.22 g, 78%, mp 173–175 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1673, 1577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.87 (1H, s), 7.68–7.65 (2H, m), 7.48–7.38 (4H, m), 7.19 (1H, d, $J=7.6$ Hz), 7.03 (1H, d, $J=7.6$ Hz), 2.49 (3H, s, SCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 187.3, 160.7, 147.1, 145.4, 134.4, 132.8, 131.7, 131.7, 131.1, 128.2, 128.2, 125.6, 124.3, 119.9, 118.7, 13.9. Anal. Calcd for $C_{16}H_{12}OS_2$: C, 67.57; 4.25%. Found C, 67.56; 4.36%.

4.1.6. 2-(4-Chlorobenzylidene)-4-methylsulfanyl benzo-[*b*]thiophen-3-one (2f). Prepared from **5c** (0.27 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (10 mL) and 4-chlorobenzaldehyde (0.17 g, 1.2 mmol) in THF (3 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/15)] gave yellow solid, yield 0.25 g, 80%, mp 213–215 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1655, 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.81 (1H, s), 7.62–7.59 (2H, m), 7.49–7.42 (3H, m), 7.21 (1H, d, $J=7.7$ Hz), 7.06 (1H, d, $J=7.7$ Hz), 2.54 (3H, s, SCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 188.7, 160.1, 147.1, 145.4, 134.4, 132.8, 131.8, 131.8, 131.1, 129.2, 129.2, 125.6, 124.5, 119.9, 118.7, 13.8. Anal. Calcd for $C_{16}H_{11}ClOS_2$: C, 60.27; 3.48%. Found C, 60.39; 3.53%.

4.1.7. 4-Methylsulfanyl-2-(thiophen-2-yl)methylene benzo[*b*]thiophen-3-one (2g). Prepared from **5c** (0.27 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (10 m) and thiophen-2-carboxaldehyde (6.13 g, 1 mmol) in THF (3 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/14)] gave yellow solid, yield 0.26 g, 92%, mp 166–168 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1666, 1581, 1554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.05 (1H, s), 7.63 (1H, d, $J=4.9$ Hz), 7.48–7.42 (2H, m), 7.24–7.16 (2H, m), 7.04 (1H, d, $J=7.9$ Hz), 2.5 (3H, s, SCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 188.1, 159.7, 145.5, 139.6, 134.6, 133.5, 132.7, 131.6, 130.7, 128.9, 125.6, 120.3, 119.3 14.2. Anal. Calcd for $C_{14}H_{10}OS_3$: C, 57.90; 3.47%. Found C, 57.78; 3.52%.

4.1.8. 4-Methylsulfanyl-2-(3-phenylallylidene)benzo[*b*] thiophen-3-one (2h). Prepared from **5c** (0.54 g, 2 mmol), LDA (5 mmol) in THF (15 mL) and cinnamaldehyde (0.3 g, 2.5 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/12)] gave red solid, yield 0.48 g, 78%, mp 210–212 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1655, 1574, 1554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.62–7.52 (3H, m), 7.47–7.35 (4H, m), 7.19–6.97 (4H, m), 2.50 (3H, s, SCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 187.9, 160.0, 146.9, 145.3, 143.3, 136.4, 132.8, 132.5, 129.8, 129.2, 129.2, 128.2, 127.8, 127.8, 124.6, 120.0, 119.2, 14.2. Anal. Calcd for $C_{18}H_{14}OS_2$: C, 60.27; 3.48%. Found C, 60.39; 3.53%.

4.1.9. 2-Benzylidene naphtho[2,1-*b*]thiophen-1-one (2i). Prepared in the same way from **5d** (0.27 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (10 mL) and benzaldehyde (0.13 g, 1.2 mmol) in THF (3 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/14)], yellow solid, yield 0.24 g, 82%, mp 186–188 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1678, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 9.37 (1H, d, $J=8.5$ Hz), 8.02–7.98 (2H, m), 7.86 (1H, d, $J=8.1$ Hz), 7.75–7.67 (3H, m), 7.55–7.40 (5H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 189.3, 150.5, 144.7, 136.6, 134.7, 134.4, 132.1, 131.7, 131.1, 131.1, 130.5, 130.0, 129.4, 129.4, 129.0, 128.8, 126.7, 123.5, 121.9. Anal. Calcd for $C_{19}H_{12}OS$: C, 79.14; 4.19%. Found C, 79.26; 4.11%.

4.1.10. 2-(4-Chlorobenzylidene)naphtho[2,1-*b*]thiophen-1-one (2j). Prepared from **5d** (0.27 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (10 mL) and 4-chlorobenzadehyde (0.17 g, 1.2 mmol) in THF (3 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/14)] gave yellow solid, yield 0.3 g, 93%, mp 216–218 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1680, 1569 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 9.35 (1H, d, $J=8.4$ Hz), 8.03 (1H, d, $J=8.6$ Hz), 7.95 (1H, s), 7.87 (1H, d, $J=8.2$ Hz), 7.74–7.65 (3H, m), 7.56–7.44 (4H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 189.2, 150.1, 136.8, 136.5, 133.2, 132.8, 132.4, 132.1, 132.1, 131.7, 131.6, 130.2, 129.7, 129.7, 128.9, 126.8, 123.7, 123.5, 121.9. Anal. Calcd for $C_{19}H_{11}ClOS$: C, 70.69; 3.43%. Found C, 70.82; 3.52%.

4.1.11. 2-Thiophen-2-ylmethylene naphtho[2,1-*b*]thiophen-1-one (2k). Prepared from **5d** (0.27 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (10 mL) and thiophen-2-carboxaldehyde (0.13 g, 1.2 mmol) in THF (3 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/14)], yield 0.26 g, 88%, mp 180–182 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1677, 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 9.37 (1H, d, $J=8.5$ Hz), 8.20 (1H, s), 8.02 (1H, d, $J=8.6$ Hz), 7.87 (1H, d, $J=8.1$ Hz), 7.73–7.64 (2H, m), 7.57–7.51 (3H, m), 7.21–7.19 (1H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 189.3, 149.6, 139.6, 136.5, 134.2, 132.7, 132.1, 131.9, 130.0, 128.9, 128.8, 126.8, 126.7, 124.8, 123.5, 123.5, 122.0. Anal. Calcd for $C_{17}H_{10}OS_2$: C, 69.36; H, 3.42%. Found C, 69.48; H, 3.27%.

4.1.12. 2-(3-Phenyallylidene)naphtho[2,1-*b*]thiophen-1-one (2l). Prepared from **5d** (0.55 g, 2 mmol) in THF (7 mL), LDA (5 mmol) in THF (15 mL) and cinnamaldehyde (0.31 g, 2.4 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/12)] gave red solid, yield 0.5 g, 79%, mp 243–245 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1666, 1579, 1553 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 9.37 (1H, d, $J=8.5$ Hz), 8.02 (1H, d, $J=8.6$ Hz), 7.87 (1H,

d, $J=8.1$ Hz), 7.78–7.67 (2H, m), 7.58–7.50 (4H, m), 7.43–7.26 (3H, m), 7.18–7.05 (2H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 189.2, 149.6, 144.4, 136.8, 134.4, 132.4, 132.2, 130.5, 130.4, 129.7, 129.7, 129.6, 129.5, 129.2, 128.4, 128.4, 127.0, 125.5, 125.1, 124.0, 122.5. Anal. Calcd for $C_{21}H_{14}OS$: C,80.22; 4.49%. Found C, 80.35; H, 4.55%.

4.1.13. General synthesis of hydroxy ketones taking (4-chlorophenyl) (3-hydroxy benzo[*b*]thiophen-2-yl) methanone (1b) as representative. To a well-stirred solution of LDA (2.5 mmol) in THF (15 mL) kept at −10 °C, **5a** (0.22 g, 1 mmol) in THF (4 mL) was added by syringe. The reaction mixture was stirred at that temperature for 1 h followed by addition of *p*-chlorobenzaldehyde (0.34 g, 2.4 mmol) in THF (5 mL). The reaction mixture was then allowed to attain room temperature and stirred at that temperature for 6 h. Work up consisted of addition of water (25 mL) to the reaction mixture, maintenance of pH at 4–5 by dropwise addition of HCl (2 N) followed by extraction with chloroform (3×20 mL). The organic layer was washed with water (3×25 mL) and dried (Na_2SO_4). Removal of solvent and purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/17)] gave yellow solid, yield 0.27 g, 89%, mp 136–138 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3446, 1589 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 13.30 (1H, s, O*H*), 8.00–7.84 (3H, m), 7.68 (1H, d, $J=8.1$ Hz), 7.60–7.29, (4H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 190.2, 165.5, 140.5, 138.9, 136.3, 130.3, 130.0, 129.7, 129.7, 128.9, 128.9, 127.3, 124.7, 123.9, 122.8. MS: (M^+) 288.6. Anal. Calcd for $C_{15}H_9ClO_2S$: C, 62.39; H, 3.14%. Found C, 62.47; H, 3.23%.

4.1.14. (3-Hydroxybenzo[*b*]thiophen-2-yl) (thiophen-2-yl) methanone (1c). Prepared in the same way from **5a** (0.23 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL) and thiophen-2-carboxaldehyde (0.23 g, 2.4 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/17)] gave yellow solid, yield 0.23 g, 93%, mp 118 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3442, 1571 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 13.36 (1H, s, O*H*), 8.07 (1H, d, $J=3.8$ Hz), 7.98 (1H, d, $J=8.1$ Hz), 7.70–7.67 (2H, m), 7.52–7.47 (1H, m), 7.38–7.33 (1H, m), 7.18–7.15, (1H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 185.6, 164.8, 144.2, 139.5, 134.2, 130.8, 130.5, 128.9, 128.9, 128.8, 128.8, 127.5, 124.7, 123.7, 123.2, 122.3, 111.6. MS: (M^+) 260, ($M^+ +1$) 261. Anal. Calcd for $C_{13}H_8O_2S_2$: C, 59.98; H, 3.10%. Found C, 59.82; H, 3.23%.

4.1.15. (4-Methoxyphenyl) (3-hydroxy benzo[*b*]thiophen-2-yl) methanone (1d). Prepared in the same way from **5a** (0.223 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL) and *p*-methoxybenzaldehyde (0.34 g, 2.5 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/16)] gave yellow solid, yield 0.24 g, 91%, mp 106 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3446, 1589 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 13.71 (1H, s, O*H*), 8.13–8.06 (3H, m), 7.76 (1H, d, $J=8.1$ Hz), 7.58–7.53, (1H, m), 7.46–2.41 (1H, m), 7.05–7.01 (2H, m), 3.92 (3H, s, OCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 190.2, 165.2, 163.3, 140.3, 130.8, 130.8, 130.6, 130.3, 129.9, 124.6, 123.8, 122.8, 113.9, 113.9, 109.1, 55.5. Anal. Calcd for $C_{16}H_{12}O_3S$: C, 67.59; H, 4.25%. Found C, 67.43; H, 4.38%.

4.1.16. 1-(3-Hydroxy benzo[*b*]thiophen-2-yl)-3-phenyl propenone (1e). Prepared in the same way from **5a** (0.45 g, 2 mmol) in THF (5 mL), LDA (5 mmol) in THF (15 mL) and cinamaldehyde (0.53 g, 4 mmol) in THF (5 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/16)], red solid, yield 0.53 g, 95%, mp 139–141 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3420, 1576 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 13.21 (1H, s, O*H*), 8.05 (1H, d, $J=7.8$ Hz), 7.97 (1H, d, $J=15.3$ Hz), 7.79 (1H, d, $J=8.1$ Hz), 7.69–7.66 (2H, m), 7.59–7.27, (5H, m), 7.09 (1H, d, $J=15.3$ Hz); ^{13}C (75 MHz, $CDCl_3$) δ_C: 185.6, 164.8, 144.2, 139.5, 134.2, 130.8, 130.5, 128.9, 128.9, 128.8, 128.8, 127.5, 124.7, 123.7, 123.2, 122.3, 111.6. MS: (M^+) 280, ($M^+ +1$) 281. Anal. Calcd for $C_{17}H_{12}O_2S$: C, 72.83; H, 4.31%. Found C, 72.95; H, 4.43%.

4.1.17. General synthesis of aryl alkyl ketones taking 1-(3-hydroxy benzo[*b*]thiophen-2-yl) propan-1-one (1g) as representative. To a well stirred solution of LDA (2.5 mmol) in THF (10 mL) kept at −80 °C a solution of **8b** (0.41 g, 2 mmol) in THF (5 mL) was added by syringe and after stirring for 30 min at that temperature the reaction mixture was allowed to reach room temperature. After stirring for another 6 h, 2 N HCl was added to the reaction mixture followed by extraction with chloroform (3× 25 mL). The organic layer was washed with brine and dried (Na_2SO_4). The residue left after removal of solvent was purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/20)], amorphous solid, yield 0.30 g, 73%, mp 72 °C. IR (KBr) ν_{max}: 3500, 1626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 12.28 (1H, s, O*H*), 7.99–7.96 (1H, m), 7.78–7.71 (1H, m), 7.55–7.49 (1H, m), 7.43–7.37 (1H, m), 2.84 (2H, q, $J=7.2$ Hz, COCH_2CH$_3$), 1.30 (3H, t, $J=7.2$ Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCL_3$) δ_C: 200.0, 161.4, 138.8, 129.7, 124.7, 123.7, 123.2, 120.4, 110.9, 34.1, 8.1. Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89%. Found: C, 64.16; H, 4.97%.

4.1.18. (3-Hydroxy-4-methoxy benzo[*b*]thiophen-2-yl) phenyl methanone (1h). Prepared according to the general synthesis of hydroxy ketone **1b** from **5b** (0.22 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL) and benzaldehyde (0.25 g, 2.4 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/18)] gave yellow solid, yield 0.26 g, 91%, mp 138 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3421, 1589 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 14.27 (1H, s, O*H*), 8.03–8.00 (2H, m), 7.62–7.44 (4H, m), 7.29 (1H, d, $J=8.0$ Hz), 6.79 (1H, d, $J=8.0$ Hz), 4.04 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 191.1, 167.6, 169.0, 138.6, 132.8, 131.9, 129.0, 129.0, 128.7, 128.7, 124.6, 122.5, 120.2, 115.5, 105.5, 56.3. MS (EI): (M^+) 284, ($M^+ +1$) 285. Anal. Calcd for $C_{16}H_{10}O_3S$: C, 67.59; H, 4.25%. Found: C, 67.73; H, 4.33%.

4.1.19. (4-Chlorophenyl) (3-hydroxy-4-methoxybenzo[*b*] thiophen-2-yl)methanone (1i). Prepared in the same way from **5b** (0.25 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL) and *p*-chlorobenzaldehyde (0.28 g, 2 mmol) in THF (5 mL). Purification by column

chromatography [eluent: ethyl acetate–petroleum ether (1/17)] gave yellow solid, yield 0.29 g, 93%, mp 158 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3435, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 13.94 (1H, s, O*H*), 7.74.7.71 (2H, m), 7.68 7.28.7.26, (3H, m), 7.04 (1H, d, $J=8.1$ Hz), 6.55 (1H, d, $J=8.1$ Hz), 3.80 (3H, s, OCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 189.5, 167.9, 159.0, 143.5, 139.2, 136.8, 132.1, 130.1, 130.1, 129.3, 129.3, 120.1, 115.5, 108.4, 105.6, 56.3. MS: (M^+) 318, ($M^+ +1$) 319, ($M^+ +2$) 320. Anal. Calcd for $C_{16}H_{11}ClO_2S$: C, 62.39; H, 3.14%. Found C, 62.47; H, 3.23%.

4.1.20. (3-Hydroxy-4-methoxy benzo[*b*]thiophen-2-yl) (thiophen-2-yl)methanone (1j). Prepared in the same way from **5b** (0.25 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL) and thiophen-2-aldehyde (0.23 g, 2.2 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/18)] gave yellow solid, yield 0.26 g, 90%, mp 174–176 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3469, 1593, 1574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 14.28 (1H, s, O*H*), 8.08–8.07(1H, m), 7.73 (1H, dd, $J=0.9$, 4.9 Hz), 7.49–7.44 (1H, m), 7.31–7.20 (2H, m), 6.78 (1H, d, $J=$ 7.8 Hz), 4.02 (3H, s, OCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 181.8, 168.0, 158.9, 143.2, 142.9, 134.2, 132.7, 132.0, 128.8, 120.1, 115.6, 107.3, 105.7, 65.3. MS: ($M^+ -1$) 289, (M^+) 290, ($M^+ +1$) 291. Anal. Calcd for $C_{14}H_{10}O_3S_2$: C, 57.91; H, 3.47%. Found C, 57.78; H, 3.58%.

4.1.21. 1-(3-Hydroxy-4-methoxybenzo[*b*]thiophen-2-yl)-3-phenyl propenone (1k). Prepared from **5b** (0.51 g, 2 mmol) in THF (5 mL), LDA (5 mmol)in THF (15 mL) and cinnamaldehyde (0.54 g, 4.4 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/16)] gave red solid, yield 0.54 g, 89%, mp 164–166 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3421, 1633, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 13.86 (1H, s, O*H*), 7.94 (1H, d, $J=$ 15.5 Hz), 7.66–7.63 (2H, m), 7.49–7.41 (3H, m), 7.32–7.26 (2H, m), 7.06 (1H, d, $J=15.3$ Hz), 6.79 (1H, d, $J=8.0$ Hz), 4.03 (3H, s, OCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 184.5, 158.9, 144.0, 142.6, 134.9, 131.9, 131.1, 129.7, 129.0, 129.0, 128.9, 128.9, 128.8, 128.7, 120.7, 116.0, 105.6, 56.3. MS: (M^+) 310, ($M^+ +1$) 311, ($M^+ +2$) 312. Anal. Calcd for $C_{18}H_{14}O_3S$: C, 69.66; H, 4.55%. Found C, 69.80; H, 4.63%.

4.1.22. (3-Hydroxy-4-methylsulfanylbenzo[*b*]thiophen-2-yl)phenyl methanone (1l). Prepared from **5c** (0.27 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/17)] gave yellow solid, yield 0.27 g, 91%, mp 144 °C (ethyl acetate–petroleum ether. IR (KBr) ν_{max}: 3440, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 14.62 (1H, s, O*H*), 8.03–8.00 (2H, m), 7.59–7.50 (3H, m), 7.43–7.41 (2H, m), 7.07–7.03 (1H, m), 2.55 (3H, s, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 189.3, 169.6, 142.8, 140.4, 137.7, 132.5, 130.3, 128.7, 128.7, 128.3, 128.3, 126.3, 119.2, 118.5, 108.7, 14.7. Anal. Calcd for $C_{16}H_{12}O_2S_2$: C, 63.97; H, 4.03%. Found: C, 63.85; H, 4.11%.

4.1.23. (4-Chlorophenyl) (3-hydroxy-4-methylsulfanyl benzo[*b*]thiophen-2-yl) methanone (1m). Prepared from **5c** (0.27 g, 1 mmol) in THF (5 mmol), LDA (2.5 mmol) in THF (15 mL) and 4-chlorobenzaldehyde (0.30 g, 2.5 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/17)] gave yellow solid, yield 0.32 g, 93%, mp 211 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3433, 1583 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 14.54 (1H, s, O*H*), 7.99–7.95 (2H, m), 7.55–7.40, (4H, m), 7.09–7.07 (1H, m), 2.57 (3H, s, SCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 187.9, 169.9, 142.7, 140.6, 138.9, 136.0, 130.5, 129.8, 129.8, 129.2, 129.2, 129.0, 119.3, 118.5, 110.2, 14.7. Anal. Calcd for $C_{16}H_{11}ClO_2S_2$: C, 57.39; H, 3.31%. Found C, 57.48; H, 3.38%.

4.1.24. (3-Hydroxy-4-methylsulfanyl benzo[*b*]thiophen-2-yl) (thiophen-2-yl) methanone (1n). Prepared from **5c** (0.27 g, 1 mmol) in THF (5 mL), DA (2.5 mmol) in THF (5 mL) and thiophene-2-carboxaldehyde (0.28 g, 2.2 mmol) in THF (5 mL). Purification by column chromatography (eluent: ethyl acetate–petroleum ether (1/17)] gave red solid, yield 0.27 g, 90%, mp 182 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3423, 1556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 14.28 (1H, s, O*H*), 8.09 (1H, d, $J=3.3$ Hz), 7.74 (1H, d, $J=4.8$ Hz), 7.45–7.41 (2H, m), 7.26–7.22 (1H, m), 7.09–7.06 (1H, m), 2.56 (3H, s, SCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 180.4, 169.2, 142.0, 140.1, 133.7, 132.3, 130.2, 129.8, 128.3, 123.6, 119.2, 118.5, 105.2, 14.6. Anal. Calcd for $C_{14}H_{10}O_2S_3$: C, 54.87; H, 3.29%. Found C, 54.99; H, 3.37%.

4.1.25. 1-(3-Hydroxy-4-methylsulfanyl benzo[*b*]thiophen-2-yl)-3-phenyl propenone (1o). Prepared from **5c** (0.54 g, 2 mmol) in THF (5 mL), LDA (5 mmol) in THF (15 mL) and cinamaldehyde (0.66 g, 5 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/16)] gave red solid, yield 0.54 g, 88%, mp 183 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3421, 1613, 1578 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 14.51 (1H, s, O*H*), 7.82 (1H, d, $J=15.4$ Hz), 7.56–7.52 (2H, m), 7.43–7.32 (5H, m), 6.98–6.96 (1H, m), 6.87 (1H, d, $J=15.4$ Hz), 2.57 (3H, s, SCH_3); ^{13}C (75 MHz, $CDCl_3$) δ_C: 181.9, 171.6, 143.8, 142.5, 140.9, 134.8, 131.1, 130.9, 129.3, 129.3, 128.9, 128.9, 127.8, 122.1, 119.6, 119.3, 111.2, 15.0. Anal. Calcd for $C_{18}H_{14}O_2S_2$: C, 66.23; H, 4.32%. Found C, 66.35; H, 4.38%.

4.1.26. (1-Hydroxy naphtho[2,1-*b*]thiophen-2-yl) phenyl methanone (1p). Prepared from **5d** (0.27 g, 1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL) and benzaldehyde (0.25 g, 2.5 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/16)] gave yellow solid, yellow 0.27 g, 90%, mp 142 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3444, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 14.14 (1H, s, O*H*), 9.16 (1H, d, $J=8.1$ Hz), 8.06–8.03 (2H, m), 7.91–7.84 (2H, m), 7.69–7.54 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 191.5, 167.6, 141.6, 138.4, 132.5, 131.4, 131.2, 130.3, 128.7, 128.7, 128.5, 128.4, 128.4, 127.8, 126.1, 124.4, 124.1, 120.6, 110.0. Anal. Calcd for $C_{19}H_{12}O_2S$: C, 74.98; H, 3.97%. Found: C, 74.86; H, 3.89%.

4.1.27. (4-Chlorophenyl) (1-hydroxy naphtho[2,1-*b*]thiophen-2-yl) methanone (1q). Prepared from **5d** (0.27 g,

1 mmol) in THF (5 mL), LDA (2.5 mmol) in THF (15 mL) and *p*-chlorobenzaldehyde (0.35 g, 2.5 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/17)] gave yellow solid, yield 0.31 g, 93%, mp 213 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3433, 1583 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 14.07 (1H, s, O*H*), 9.18 (1H, d, $J=8.4$ Hz), 8.02–7.90 (4H, m), 7.74–7.50, (5H, m); ^{13}C (75 MHz, $CDCl_3$) δ_C: 191.5, 167.9, 141.6, 139.6, 138.9, 136.7, 131.7, 131.2, 130.3, 130.3, 129.8, 129.8, 129.0, 128.5, 127.9, 126.3, 124.4, 120.6, 110.3. Anal. Calcd for $C_{19}H_{11}ClO_2S$: C, 67.35; H, 3.37%. Found C, 67.48; H, 3.33%.

4.1.28. 1-(1-Hydroxy naphtho[2,1-*b*]thiophen-2-yl)-3-phenyl propenone (1r). Prepared from **5d** (0.55 g, 2 mmol) in THF (5 mL), LDA (5 mmol) in THF (15 mL) and cinamaldehyde (0.66 g, 5 mmol) in THF (5 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/15)] gave red solid, yield 0.56 g, 85%, mp 171 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3425, 1630, 1578 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 13.80 (1H, s, O*H*), 9.11 (1H, d, $J=8.3$ Hz), 7.94–7.68 (3H, m), 7.66–7.52 (5H, m), 7.42–7.23 (3H, m), 7.07 (1H, d, $J=15.4$ Hz); ^{13}C (75 MHz, $CDCl_3$) δ_C: 185.6, 166.9, 143.9, 140.2, 134.4, 131.3, 131.2, 130.9, 130.2, 129.0, 129.0, 128.7, 128.7, 128.3, 127.8, 126.2, 124.6, 124.4, 122.5, 120.9, 112.3. Anal. Calcd for $C_{21}H_{14}O_2S$: C, 76.34; H, 4.27%. Found C, 76.49; H, 4.33%.

4.1.29. 1-(1-Hydroxy naphtho[2,1-*b*]thiophen-2-yl) ethan-1-one (1s). Prepared according to the general synthesis of aryl alkyl ketone from **8c** (0.24 g, 1 mmol) in THF (5 mL) and LDA (1.5 mmol) in THF (10 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/20)], amorphous solid, yield 0.13 g, 55%, mp 67 °C. IR (KBr) ν_{max}: 3470, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 13.6 (1H, s, O*H*), 8.97 (1H, d, $J=$ 8.0 Hz), 7.87–7.84 (2H, m), 7.63–7.51 (3H, m), 2.47 (3H, s, COCH_3); ^{13}C NMR (75 MHz, $CDCL_3$) δ_C: 199.3, 164.5, 139.4, 131.7, 131.3, 130.5, 128.9, 127.7, 126.6, 126.4, 124.8, 121.1, 111.3, 18.8. Anal. Calcd for $C_{14}H_{10}O_2S$: C, 69.40; H, 4.16%. Found: C, 69.23; H, 4.28%.

4.1.30. 1-(1-Hydroxynaphtho[2,1-*b*]thiophen-2-yl) propan-1-one (1t). Prepared in the same way from **8d** (0.26 g, 1 mmol) in THF (5 mL), LDA (1.5 mmol) in THF (10 mL). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/20)], solid material, yield 0.16 g, 63%, mp 88 °C. IR (KBr) ν_{max}: 3483, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 13.0 (1H, s, O*H*), 9.10 (1H, d, $J=$ 8.4 Hz), 7.93–7.86 (2H, m), 7.70–7.55 (3H, m), 2.89–2.81 (2H, m, COCH_2CH$_3$), 1.39–1.29 (3H, m, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCL_3$) δ_C: 199.9, 164.6, 139.5, 131.5, 131.2, 130.6, 128.7, 127.9, 126.5, 126.4, 124.7, 121.2, 111.6, 34.3, 8.7. Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72%. Found: C, 70.45; H, 4.83%.

4.1.31. General synthesis of alkanoic acid aryl ester taking (benzo[*b*]thiophen-3-yl) acetate as example (8a). A solution of **3a** (0.60 g, 4 mmol) in THF (10 mL) was added dropwise to a magnetically stirred suspension of oil free sodium hydride (0.30 g, 6 mmol) in THF (10 mL). After stirring the reaction mixture for 1 h, acetyl chloride (0.5 g, 7 mmol) was added to it and stirring was continued for 10 h at room temperature followed by removal of solvent under reduced pressure. The residue left was decomposed with water and extracted with diethyl ether (15×3 mL). The organic layer was washed with water and dried (Na_2SO_4). The residue left after removal of solvent was purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/20)] to afford clear liquid, yield 0.71 g, 89%. IR (Neat) ν_{max}: 1764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.83–7.80 (1H, m), 7.74–7.71 (1H, m), 7.44–7.39 (3H, m), 2.40 (3H, s COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 168.3, 140.7, 136.9, 132.1, 125.2, 124.3, 122.9, 120.4, 111.9, 21.0. Anal. Calcd for $C_{10}H_8O_2S$: C, 62.68; H, 4.19%. Found: C, 62.60; H, 4.26%.

4.1.32. (Naphtho[2,1-*b*]thiophen-1-yl) acetate (8c). Prepared in the same way from **3d** (2 g, 10 mmol) in THF (15 mL), sodium hydride (0.6 g, 15 mmol) in THF (25 mL) and acetyl chloride (1.2 g, 15 mmol). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/20)], clear liquid, yield 2.2 g, 93%. IR (Neat) ν_{max}: 1779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.62 (1H, d, $J=8.2$ Hz), 7.85–7.80 (1H, m), 7.78–7.59 (2H, m), 7.56–7.38 (3H, m), 2.37 (3H, s COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 168.6, 143.6, 135.9, 132.0, 129.1, 129.0, 126.9, 126.5, 126.4, 125.8, 123.4, 121.3, 112.3, 22.0. Anal. Calcd for $C_{14}H_{10}O_2S$: C, 69.40; H, 4.26%. Found: C, 69.53; H, 4.33%.

4.1.33. (Naphtho[2,1-*b*]thiophen-1-yl) propionate (8d). Prepared in the same way from **3d** (2 g, 10 mmol) in THF (15 mL), sodium hydride (0.6 g, 15 mmol) in THF (25 mL) and propionylchloride (1.5 g, 15 mmol). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/20)], clear liquid, yield 2.3 g, 96%. IR (Neat) ν_{max}: 1764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.84 (1H, d, $J=8.2$ Hz), 7.98 (1H, d, $J=7.6$ Hz), 7.80–7.57 (5H, m), 2.89 (2H, s COCH_2), 1.47 (3H, s CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 171.4, 143.0, 135.2, 131.3, 128.4, 128.3, 126.1, 125.7, 125.1, 122.8, 120.6, 111.5, 27.9, 8.4. Anal. Calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72%. Found: C, 70.33; H, 4.81%.

4.1.34. General synthesis of dihydropyranones from chalcones taking 9-methoxy-2-phenyl-2,3-dihydrobenzo[4,5]thieno[3,2-*b*]pyran-4-one (9b) as representative. Dry HCl gas was bubbled through a solution of **1k** (0.31 g, 1 mmol) in ethanol (20 mL) for 4 h. After removal of most of the ethanol under reduced pressure, the reaction mixture was diluted with chloroform, the organic layer was washed with water and dried (Na_2SO_4). Residue left after removal of solvent was purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/4)], white solid, yield 0.26 g, 87%, mp 182 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.56–7.54 (2H, m), 7.48–7.37 (4H, m), 7.35–7.32 (1H, m), 6.77 (1H, d, $J=8.1$ Hz), 5.82 (1H, d, $J=$ 12.0 Hz, OC*H*CH$_2$), 3.94 (3H, s, OCH_3) 3.10–2.99 (2H, m, COCH_2CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 186.5, 167.7, 161.9, 158.1, 143.4, 138.6, 131.0, 129.1, 128.9, 128.9, 126.3, 120.4, 116.3, 114.4, 105.6, 82.7, 56.2, 43.7. Anal. Calcd for $C_{18}H_{14}O_3S$: C, 69.66; H, 4.55%. Found: C, 69.59; H, 4.48%.

4.1.35. 9-Methylsulfanyl-2-phenyl-2,3-dihydrobenzo[4,5]thieno[3,2-*b*]pyran-4-one (9c). Prepared from **1o** (0.16 g, 0.5 mmol) in ethanol (20 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/4)] gave solid material, yield 0.14 g, 90%, mp 170–172 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 7.56–7.46 (2H, m), 7.42–7.28 (5H, m), 6.98 (1H, d, $J=7.5$ Hz), 5.77 (1H, dd, $J=3.7$, 13.0 Hz, OC*H*CH_2), 3.07–2.84 (2H, m, COCH_2CH), 2.45 (3H, s, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 185.9, 161.6, 142.1, 138.6, 137.8, 129.1, 128.6, 128.6, 128.4, 126.1, 125.7, 119.2, 119.1, 114.7, 82.7, 43.4, 14.5. Anal. Calcd for $C_{18}H_{14}O_2S_2$: C, 66.23; H, 4.32%. Found: C, 66.13; H, 4.27%.

4.1.36. 10-Phenyl-9,10-dihydro-11-oxa-7-thiabenzo[*c*]fluoren-8-one (9d). Prepared from **1r** (0.33 g, 1 mmol) in ethanol (20 mL). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/4)] gave solid material, yield 0.30 g, 93%, mp 158 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.81 (1H, d, $J=7.6$ Hz), 7.87–7.79 (2H, m), 7.70 (1H, d, $J=8.8$ Hz), 7.56–7.39 (7H, m), 5.58 (1H, dd, $J=3$, 13.5 Hz, OC*H*CH_2), 3.21–2.87 (2H, m, COCH_2CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 186.3, 162.1, 141.3, 138.5, 132.3, 130.4, 129.5, 128.9, 128.8, 128.8, 128.4, 127.5, 126.1, 126.1, 125.9, 123.8, 121.2, 117.7, 114.3, 83.1, 43.8. Anal. Calcd for $C_{21}H_{14}O_2S$: C, 76.34; H, 4.27%. Found: C, 76.11; H, 4.38%.

4.1.37. General synthesis of pyranones from chalcones taking 2-phenylbenzo[4,5]thieno[3,2-*b*]pyran-4-one (10a) as representative. Selenium dioxide (0.23 g, 2.2 mmol) and **1e** (0.28 g, 1 mmol) were heated under reflux in dry isoamyl alcohol (3 mL) for 15 h. The reaction mixture was filtered when hot. Most of the solvent of filtrate was removed under reduced pressure and the solid precipitate, which separated was filtered and washed with 1:1 mixture of ethyl acetate and petroleum ether and crystallized from ethyl acetate. Yield 0.17 g, 63%, mp 178 °C. IR (KBr) ν_{max}: 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.18 (1H, d, $J=7.5$ Hz), 7.96–7.90 (3H, m), 7.62–7.52 (5H, m), 6.95 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 187.5, 174.9, 163.1, 153.7, 139.2, 131.5, 131.3, 129.2, 129.0, 129.0, 126.2, 126.1, 125.3, 124.8, 123.9, 121.9, 109.0. MS: $(M^+ +1)$ 278.07. Anal. Calcd for $C_{17}H_{10}O_2S$: C, 73.31; H, 3.62%. Found: C, 73.53; H, 3.39%.

4.1.38. 9-Methoxy-2-phenylbenzo[4,5]thieno[3,2-*b*]pyran-4-one (10b). Prepared in the same way from **1k** (0.31 g, 1 mmol) and selenium dioxide (0.23 g, 2.2 mmol). Red solid, yield 0.18 g, 58%, mp 203 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1628 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.00–7.91 (2H, m), 7.55–7.52 (3H, m), 7.49–7.42 (2H, m), 6.99 (1H, s), 6.88 (1H, d, $J=6.9$ Hz), 4.10 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 189.5, 177.3, 174.6, 156.6, 140.9, 139.3, 131.3, 131.1, 130.0, 128.9, 128.9, 125.8, 125.8, 123.4, 115.7, 107.7, 105.6, 55.8. MS: $(M^+ +1)$ 309.05. Anal. Calcd for $C_{18}H_{12}O_3S$: C, 70.11; H, 3.92%. Found: C, 69.93; H, 4.03%.

4.1.39. 10-Phenyl-11-oxa-7-thiabenzo[*c*]fluoren-8-one (10c). Prepared from **1r** (0.33 g, 1 mmol) and selenium dioxide (0.23 g, 2.2 mmol). Red solid, yield 0.18 g, 55%, mp 225 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.96 (1H, d, $J=8.1$ Hz), 8.00–7.95 (3H, m), 7.92 (1H, d, $J=8.7$ Hz), 7.83(1H, d, $J=8.7$ Hz), 7.76–7.71 (1H, m), 7.66–7.58 (4H, m), 6.95 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 188.3, 174.5, 163.6, 155.4, 139.1, 131.6, 13.4, 131.2, 129.9, 129.2, 129.2, 128.8, 128.5, 127.8, 126.2, 126.2, 126.1, 123.4, 123.2, 121.0, 108.8. MS: $(M^+ +1)$ 329.14. Anal. Calcd for $C_{21}H_{12}O_2S$: C, 76.81; H, 3.68%. Found: C, 76.73; H, 3.59%.

4.1.40. 2-Hydroxy-2,3-dihydro benzo[4,5]thieno[3,2-*b*]pyran-4-one (11a). To a well stirred suspension of oil-free sodiumhydride (0.12 g, 2.5 mmol) in THF (10 mL) a solution of **1f** (0.2 g, 1 mmol) in THF (5 mL) was added under external cooling. After 15 min ethyl formate (0.1 g, 2 mmol) was added to the reaction mixture, which was stirred at room temperature for another 10 h. Residue left after removal of most of the solvent under reduced pressure was decomposed with water, acidified with dilute HCl, extracted with chloroform and dried (Na_2SO_4). Purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/5)], white solid, yield 0.18 g, 85%, mp 117 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3280, 1727 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ_H: 7.97–7.87 (2H, m), 7.62–7.57 (1H, m), 7.51–7.46 (1H, m), 6.19–6.17 (1H, m, OC*H*OH), 3.12–3.05 (2H, m, COCH_2); ^{13}C NMR (75 MHz, acetone-d_6) δ_C: 196.3, 155.7, 141.5, 138.4, 131.7, 129.7, 125.8, 123.2, 122.7, 102.7, 44.7. Anal. Calcd for $C_{11}H_8O_3S$: C, 59.99; H, 3.66%. Found: C, 79.76; H, 3.75%.

4.1.41. 2-Hydroxy-3-methyl-2,3-dihydro benzo[4,5]thieno[3,2-*b*]pyran-4-one (11b). Prepared in the same way from **1g** (0.21 g, 1 mmol) in THF (5 mL), sodium hydride (0.12 g, 2.5 mmol) in THF (10 mL) and ethyl formate (0.1 g, 2 mmol). Purification by column chromatography [eluent: ethyl acetate–petroleum ether (1/5)], white solid (obtained as a 1:1 diasteromeric mixture), yield 0.20 g, 89%, mp 140–150 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 3265, 1632 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ_H: 7.94–7.83 (2H, m), 7.59–7.52 (1H, m), 7.48–7.44 (1H, m), 6.07–6.06 (1/2H, d, OC*H*OH), 5.76–5.73 (1/2H, d, OC*H*OH), 3.17–3.13 (1/2H, m, COC*H*), 2.84–2.77 (1/2H, m, COC*H*), 1.27–1.22 (3H, m, CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ_C: 205.4, 129.3, 129.0, 124.9, 124.8, 123.8, 123.8, 122.7, 122.5, 103.2, 101.2, 47.3, 45.9, 11.0, 8.6. Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30%. Found: C, 61.65; H, 4.43%.

4.1.42. Benzo[4,5]thieno[3,2-*b*]pyran-4-one (12a). In a round bottom flask fitted with Dean-stark water separator **11a** (0.22 g, 1 mmol) and catalytic amount of *p*-toluene sulphonic acid was heated under reflux in benzene (10 mL) for 3 h. Residue left after removal of most of the solvent was followed by extraction with diethyl ether, washed with water and dried (Na_2SO_4). Residue left after removal of solvent was purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/5)] to afford colorless solid, yield 0.18 g, 93%, mp 167 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1633, 1622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.06–7.78 (4H, m), 7.68–7.35 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 198.7, 161.3,

153.3, 140.7, 138.7, 136.4, 132.6, 129.5, 125.2, 122.6, 122.2. Anal. Calcd $C_{11}H_6O_2S$: C, 65.33; H, 2.99%. Found: C, 65.45; H, 3.13%.

4.1.43. Benzo[4,5]thieno[3,2-*b*]pyran-4-one-3-carboxaldehyde (14). To an externally cooled and stirred mixture of **1f** (0.4 g, 2 mmol) in DMF (3 mL), phosphoryl chloride (1 mL) was added. The reaction mixture was allowed to reach room temperature and after stirring at that temperature for 13 h, was poured into crushed ice and extracted with chloroform. The organic phase was washed with water and dried (Na_2SO_4). Residue left after removal of solvent was purified by column chromatography [eluent: ethyl acetate–petroleum ether (1/4)] gave white solid, yield 0.32 g, 68%, mp 133 °C (ethyl acetate–petroleum ether). IR (KBr) ν_{max}: 1675, 1648 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ_H: 9.73 (1H, s, C*H*O), 8.23–7.58 (4H, m), 7.13 (1H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ_C: 200.3, 184.3, 165.5, 143.9, 136.2, 130.5, 128.3, 124.2, 124.1, 122.9, 121.7, 103.7. Anal. Calcd for $C_{12}H_6SO_3$: C, 62.10; H, 2.63%. Found: C, 62.48; H, 2.33%.

Acknowledgements

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Iridium-catalyzed enantioselective cycloisomerization of nitrogen-bridged 1,6-enynes to 3-azabicylo[4.1.0]heptenes

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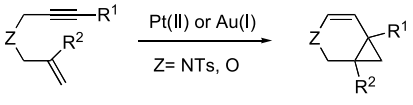
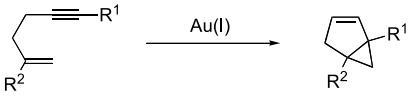
Abstract—A cationic iridium complex catalyzes a cycloisomerization of nitrogen-bridged 1,6-enynes to give 3-azabicyclo[4.1.0]heptenes in good to high yield. When an iridium-chiral diphosphine complex is used, the reaction proceeds enantiomerically to give chiral cyclopropanes fused by a six-membered ring system.

1. Introduction

Transition metal-catalyzed cycloisomerization of unsaturated systems provides an atom-economical protocol for the construction of cyclic compounds.[1] Especially, 1,*n*-enynes have been comprehensively investigated as the most common unsaturated motif,[2] and various types of cycloisomerizations have been reported according to the choice of enynes and transition metal catalysts including Pd,[3] Ru,[4] Rh,[5,6] Ti,[7] and Ir complexes.[8] Since Blum reported $PtCl_4$ catalyzed cycloisomerization of allyl propargyl ethers into 3-oxabicyclo[4.1.0]heptenes,[9] this type of transformation has been comprehensively studied from both a synthetic and mechanistic point of view:[10,11] $PtCl_2$ was found to be an efficient catalyst, and various 1,6-enynes bridged by nitrogen and oxygen were transformed into 3-aza- and 3-oxabicyclo[4.1.0]heptene skeletons, respectively (Eq. 1). Au(I) salt is another choice of catalyst,[12] and 1,5-enynes possessing no heteroatom on their tethers were also submitted to the present cycloisomerization (Eq. 2).[13]



(1)



(2)

This manuscript discloses a cationic iridium complex-catalyzed cycloisomerization of 1,6-enynes bridged by nitrogen, which gave 3-azabicyclo[4.1.0]heptenyl derivatives. Moreover, we achieved the first example of an enantioselective version of the present cycloisomerization by iridium-chiral diphosphine complexes and obtained optically active cyclopropanes fused by a six-membered ring system.

Iridium complex-catalyzed cycloisomerizations of 1,6-enynes, having carbon chains on their tethers, have already been reported, where cyclic 1,3-dienes[8a,c] or 1,4-dienes[8b] were obtained. The present results show a different pattern of transformation owing to the choice of enynes and iridium complexes.

2. Results and discussion

We have already reported iridium complex-catalyzed carbonylative couplings.[14] During our study, we examined Pauson–Khand-type reaction of enyne **1a** for the synthesis of a cyclopentenone having a quaternary carbon. No carbonylative product could be detected, however, bicyclic compound **2a** was obtained in good yield (Eq. 3). No iridium complex-catalyzed cycloisomerization along with cyclopropane ring formation has been reported; therefore, we have further investigated the reaction conditions.

Keywords: Iridium; Enynes; Cycloisomerization; Enantioselective; Cyclopropanes.
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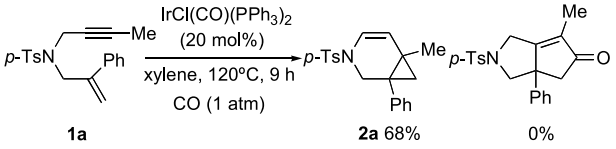
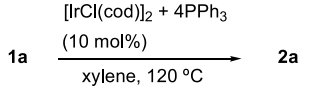


(3)

We used an in situ-prepared Ir–triphenylphosphine complex (Table 1). Under an atmosphere of argon, enyne **1a** was consumed but bicyclic product **2a** could not be detected (entry 1). Under an atmosphere of carbon monoxide, product **2a** was obtained in moderate yield, but enyne **1a** was not completely consumed within 24 h (entry 2). When the catalyst was prepared under CO, then the reaction was done under Ar, the reaction proceeded more smoothly to give cycloadduct **2a** in higher yield. These results imply that CO is important as a π-acceptor ligand of the catalyst.[15]

We next examined cationic iridium complexes, which were prepared from Vaska's complex and silver salts (Table 2).

Table 1. The effect of atmosphere on the cycloisomerization of **1a**

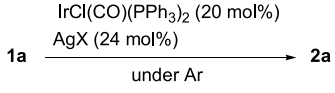


Entry	Atmosphere	Time (h)	Yield (%)
1	Ar	3	—
2	CO	24	41
3	CO then Ar	12	60

By addition of AgOTf to Vaska's complex in 1,2-dimethoxyethane (DME), the reaction proceeded at 60 °C to give product **2a** in very high yield (entry 1). Other ethereal solvents of higher boiling points (1,4-dioxane and dibutyl ether) accelerated the reaction but gave lower yields (entries 2, 3). Halogenated solvents (1,2-dichloroethane and chlorobenzene) also gave good results, but the yield did not exceed that of DME (entries 4, 5). As a result of the screening of the silver salts, the reaction proceeded more efficiently when SbF_6 was used as a counter anion of the catalyst (entries 1, 6, 7).

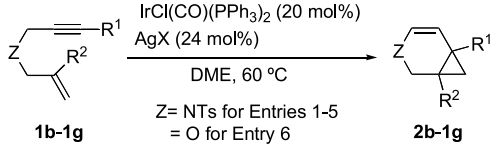
Various 1,6-enynes were submitted to the reaction using cationic iridium catalysts, which were in situ prepared from Vaska's complex and AgOTf or $AgSbF_6$ (Table 3). *n*-Butyl-substituted enyne **1b** was also transformed into the corresponding cycloadduct **2b** in refluxed DME (entry 1). Various aryl groups could be tolerable as a substituent on the alkene moiety of enynes (entries 2–4). Enyne **1f**, possessing methyl groups on its alkyne terminus and alkene, were a good substrate, and bicyclic product **2f** was obtained in almost quantitative yield by the addition of $AgSbF_6$ (entry 5). Oxygen-bridged enyne **1g** was also completely consumed under the same reaction conditions, but cyclopropane product **2g** could only be obtained in low yield from a complex mixture (entry 6). Nitrogen-bridged enyne **1h**, possessing a phenyl group on its alkyne terminus, and carbon-bridged enyne **1i** did not react even in refluxed DME.

Table 2. Effect of solvents and counter anions of cationic iridium complex on the cycloisomerization of **1a**



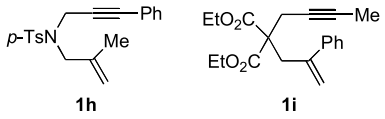
Entry	X	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	OTf	DME	60	24	94
2	OTf	Dioxane	100	3	74
3	OTf	Bu_2O	120	1	41
4	OTf	DCE	60	24	68
5	OTf	PhCl	100	3	89
6	SbF_6	DME	60	2	84
7	BF_4	DME	60	24	72

Table 3. Cationic iridium complex-catalyzed cycloisomerization of various enynes



Entry	R^1	R^2	1	AgOTf		$AgSbF_6$	
				Time (h)	Yield (%)	Time (h)	Yield (%)
1[a]	*n*-Bu	Ph	**1b**	20	55	1	84
2	Me	4-ClPh	**1c**	24	71	1.5	84
3	Me	4-MeOPh	**1d**	4	66	0.5	76
4	Me	2-Naphthyl	**1e**	8	60	0.5	72
5	Me	Me	**1f**	2	80	1	98
6	Me	Ph	**1g**	24	25	0.5	24

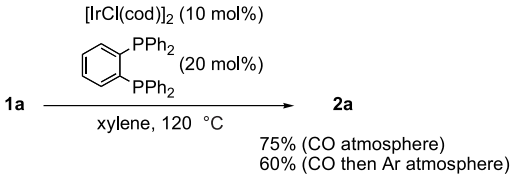
[a] In refluxed DME.



1h **1i**

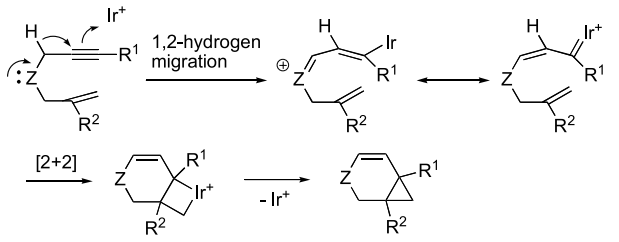
As in the Pt(II) salt-catalyzed reaction, the heteroatoms on the tether of the enynes are crucial in an iridium complex-catalyzed reaction. A mechanism via the carbene complex, which is stabilized by donor heteroatoms, could be possible (Scheme 1).[10c]

We further investigated an enantioselective version of the present cycloisomerization for the synthesis of chiral cyclopropanes. As a result of a preliminary experiment using an achiral bidentate ligand, 1,2-bis(diphenylphosphino)benzene was found to be best. Unlike the reaction using triphenylphosphine as a ligand, here a CO atmosphere throughout the reaction gave a better yield than an Ar atmosphere after complexation under a CO atmosphere (Eq. 4 and Table 1).[15]



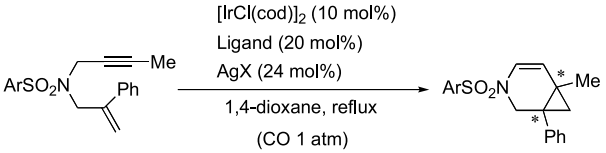
(4)

Actually, enantioselective cycloisomerization was examined by cationic chiral iridium complexes, which were prepared from $[IrCl(cod)]_2$, a chiral diphosphine and a silver salt (Table 4). The reaction enantiomerically proceeded by BINAP ligand to give chiral cycloadduct **2a** in moderate ee of 52% (entry 1).[16] A substituent of nitrogen on the enyne apparently affects the enantioselectivity, and higher ee was achieved by *o*-TsN-bridged enyne **1j**, and TolBINAP was a better chiral ligand than BINAP in each case (entries 1–6). $AgBF_4$ gave almost the same results as AgOTf (entry 7). It took a longer reaction time, however,



Scheme 1. Proposed mechanism of cycloisomerization of heteroatom-bridged enynes.

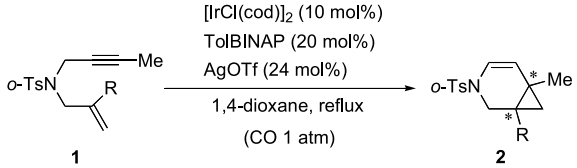
Table 4. Optimization of enantioselective cycloisomerization of enynes by a chiral cationic iridium complex



Entry	Ar	X	Ligand	Time (h)	Yield (%)	ee (%)
1	*p*-Tolyl	OTf	BINAP	3	87	52
2	*p*-Tolyl	OTf	TolBINAP	2	92	66
3	*o*-Tolyl	OTf	BINAP	10	59	64
4	*o*-Tolyl	OTf	TolBINAP	2	79	75
5	Mesityl	OTf	BINAP	3	59	57
6	Mesityl	OTf	TolBINAP	2	70	64
7	*o*-Tolyl	BF_4	TolBINAP	6	82	74
8	*o*-Tolyl	SbF_6	TolBINAP	7	34	55
9[a]	*o*-Tolyl	OTf	TolBINAP	4	71	73
10[b]	*o*-Tolyl	OTf	TolBINAP	9	70	78

[a] $[IrCl(cod)]_2$ (5 mol%), TolBINAP (10 mol%), AgOTf (12 mol%).
[b] $[IrCl(cod)]_2$ (2 mol%), TolBINAP (4 mol%), AgOTf (5 mol%).

Table 5. Enantioselective cycloisomerization of nitrogen-bridged enynes by the chiral cationic iridium complex



Entry	R	**1**	Time (h)	Yield (%)	ee (%)
1	4-ClPh	**1l**	7	71	74
2	4-MeOPh	**1m**	5	69	44
3	2-Naphthyl	**1n**	9	71	35
4[a]	2-Naphthyl	**1e**	3	57	64

[a] *p*-TsN-bridged enynes **1e** was used.

decrease of the amounts of catalyst could be possible without loss of enantioselectivity (entries 9, 10).

Under the best reaction conditions (Table 4, entry 4), we examined an enantioselective cycloisomerization of several enynes (Table 5). Enyne **1l**, possessing 4-chlorophenyl on the alkene, gave the same enantioselectivity as the phenyl group, however, enyne **1m** gave moderate ee (entries 1,2). In the case of the naphthyl group, *p*-TsN-bridged enyne **1e** gave better ee than *o*-TsN-bridged enyne **1n** (entries 3, 4).

3. Conclusion

In summary, we have developed a cationic iridium complex-catalyzed cycloisomerization of nitrogen-bridged 1,6-enynes for the synthesis of a 3-azabicyclo[4.1.0] heptenyl skeleton. Enantioselective transformation was also realized by a cationic iridium–chiral phosphine complex. The enynes are limited to nitrogen-bridged ones, and the enantioselectivity is not sufficiently high, however, the present results open a new protocol for an iridium complex-catalyzed cycloisomerization and an enantioselective transformation.

4. Experimental

4.1. General

Optical rotation was measured using Jasco DIP-370 polarimeter. IR spectra were recorded with Horiba FT210 spectrophotometer. NMR spectra were measured with JASCO DIP-1000 or Varian VXR-300S spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ was used as solvent. Mass spectra were measured with JEOL JMS-SX102A and elemental analyses with Perkin Elmer PE2400II. Dehydrated xylene, 1,2-dimethoxyethane, and 1,4-dioxane are commercially available and they were dried over molecular sieves 4 Å and degassed by argon or carbon monoxide bubbling before use. All reactions were examined using an argon or CO balloon.

4.2. Typical experimental procedure for cycloisomerization of enynes (Table 3)

Under an atmosphere of argon, $IrCl(CO)(PPh_3)_2$ (15.6 mg, 0.02 mmol) and AgOTf (6.2 mg, 0.024 mmol) or $AgSbF_6$ (8.2 mg, 0.024 mmol) was placed in a flask under an argon atmosphere. 1,2-Dimethoxyethane (1.5 mL) was added, then the resulting mixture was stirred at 60 °C for 0.5–24 h. The solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give cycloadduct **2**.

4.2.1. *N*-(2-Phenylprop-2-en-1-yl)-*N*-(*p*-tosyl)but-2-yn-1-amine (1a). White solid. Mp 120 °C; IR ($CHCl_3$) 2932, 2304, 2222, 903, 756 cm^{-1}; ^1H NMR $\delta=1.51$ (t, $J=2.4$ Hz, 3H), 2.43 (s, 3H), 3.92 (d, $J=2.4$ Hz, 2H), 4.22 (s, 2H), 5.32 (s, 1H), 5.55 (s, 1H), 7.28–7.36 (m, 5H), 7.49–7.53 (m, 2H), 7.74 (d, $J=8.4$ Hz, 2H). ^{13}C NMR $\delta=3.3$, 7.0, 21.6, 36.1, 50.5, 71.3, 81.9, 116.8, 126.3, 128.0, 128.3, 129.1, 135.6, 137.7, 141.4, 143.1. Anal. Calcd for $C_{20}H_{21}NO_2S$; C, 70.77; H, 6.24; N, 4.13. Found: C, 70.70; H, 6.34; N, 4.16.

4.2.2. *N*-(2-Phenylprop-2-en-1-yl)-*N*-(*p*-tosyl)hept-2-yn-1-amine (1b). Pale yellow oil; IR (neat) 2932, 2322, 901, 756 cm^{-1}; ^1H NMR $\delta=0.82$–0.86 (m, 3H), 1.18–1.25 (m, 4H), 1.85–1.89 (m, 2H), 2.43 (s, 3H), 3.96 (s, 2H), 4.23 (s, 2H), 5.32 (s, 1H), 5.55 (s, 1H), 7.24–7.37 (m, 5H), 7.51–7.54 (m, 2H), 7.74 (d, $J=7.5$ Hz, 2H). ^{13}C NMR $\delta=13.6$, 18.2, 21.6, 21.9, 30.5, 36.2, 49.9, 72.0, 86.6, 116.8, 126.3, 127.9, 128.0, 128.3, 129.2, 135.7, 137.7, 141.4, 143.1; HRMS for M+1 found *m/e* 382.1839, calcd for $C_{23}H_{28}NO_2S$: 382.1841.

4.2.3. *N*-[2-(4-Chlorophenyl)prop-2-en-1-yl]-*N*-(*p*-tosyl)but-2-yn-1-amine (1c). White solid. Mp 108–109 °C; IR ($CHCl_3$) 2922, 2302, 2224, 901, 762 cm^{-1}; ^1H NMR $\delta=$ 1.50 (t, $J=2.4$ Hz, 3H), 2.44 (s, 3H), 3.89 (q, $J=2.4$ Hz, 2H), 4.18 (s, 2H), 5.32 (s, 1H), 5.54 (s, 1H), 7.28–7.31 (m, 4H), 7.43–7.48 (m, 2H), 7.71–7.76 (m, 2H). ^{13}C NMR $\delta=$ 3.3, 21.6, 36.1, 50.0, 71.0, 82.0, 117.4, 127.6, 127.9, 128.4, 129.1, 133.8, 135.4, 136.0, 140.3, 143.3. Anal. Calcd for $C_{20}H_{20}ClNO_2S$; C, 64.25; H, 5.39; N, 3.75. Found: C, 64.29; H, 5.35; N, 3.66.

4.2.4. *N*-[2-(4-Methoxyphenyl)prop-2-en-1-yl]-*N*-(*p*-tosyl)but-2-yn-1-amine (1d). White solid. Mp 91–92 °C; IR ($CHCl_3$) 2922, 903, 758 cm^{-1}; ^1H NMR $\delta=1.49$ (t, $J=$ 2.3 Hz, 3H), 2.43 (s, 3H), 3.80 (s, 3H), 3.90 (q, $J=2.3$ Hz, 2H), 4.18 (s, 2H), 5.21 (s, 1H), 5.47 (s, 1H), 6.85–6.88 (m, 2H), 7.28–7.31 (m, 2H), 7.47–7.50 (m, 2H), 7.73–7.76 (m, 2H). ^{13}C NMR $\delta=3.3$, 21.6, 36.0, 50.1, 55.3, 71.2, 81.8, 113.6, 115.2, 127.5, 128.0, 129.0, 130.0, 135.6, 140.5, 143.1, 159.3. Anal. Calcd for $C_{21}H_{23}NO_3S$; C, 68.27; H, 6.27; N, 3.79. Found: C, 67.92; H, 6.24; N, 3.60; HRMS for M+1 found *m/e* 370.1489, calcd for $C_{21}H_{24}NO_3S$: 370.1477.

4.2.5. *N*-[2-(2-Naphthyl)prop-2-en-1-yl]-*N*-(*p*-tosyl)but-2-yn-1-amine (1e). White solid. Mp 124–125 °C; IR ($CHCl_3$) 3024, 903, 756 cm^{-1}; ^1H NMR $\delta=1.53$ (t, $J=$ 2.4 Hz, 3H), 2.43 (s, 3H), 3.95 (q, $J=2.4$ Hz, 2H), 4.33 (s, 2H), 5.42 (s, 1H), 5.69 (s, 1H), 7.26–7.99 (m, 11H). ^{13}C NMR $\delta=3.4$, 21.6, 36.2, 50.1, 71.4, 81.9, 99.9, 117.3, 124.3, 125.5, 126.1, 127.4, 127.8, 128.0, 128.4, 129.1, 132.9, 133.2, 134.9, 135.7, 141.3, 143.1; HRMS for M+1 found *m/e* 390.1530, calcd for $C_{24}H_{24}NO_2S$: 390.1528.

4.2.6. *N*-(2-Methylprop-2-en-1-yl)-*N*-(*p*-tosyl)but-2-yn-1-amine (1f). White solid. Mp 40–41 °C; IR ($CHCl_3$) 2932, 2308, 1342, 1334, 1160, 917 cm^{-1}; ^1H NMR $\delta=1.50$ (t, $J=2.4$ Hz, 3H), 1.76 (s, 3H), 2.42 (s, 3H), 3.69 (s, 2H), 3.97 (q, $J=2.4$ Hz, 2H), 4.94 (s, 1H), 4.95 (s, 1H), 7.28 (dd, $J=$ 0.6, 8.7 Hz, 2H), 7.72–7.75 (m, 2H). ^{13}C NMR $\delta=3.3$, 19.8, 21.6, 36.1, 52.4, 71.5, 81.5, 115.0, 127.8, 129.0, 136.1, 139.4, 143.0. Anal. Calcd for $C_{15}H_{19}NO_2S$; C, 64.95; H, 6.90; N, 5.05. Found: C, 65.18; H, 7.09; N, 5.07.

4.2.7. But-2-yn-1-yl 2-phenylprop-2-en-1-yl ether (1g). Colorless oil; IR (neat) 3022, 2402, 1216, 756 cm^{-1}; ^1H NMR $\delta=1.87$ (t, $J=2.4$ Hz, 3H), 4.15 (q, $J=2.4$ Hz, 2H), 4.45 (s, 2H), 5.36 (s, 1H), 5.55 (s, 1H), 7.24–7.49 (m, 5H). ^{13}C NMR $\delta=3.8$, 57.6, 71.2, 75.0, 82.6, 114.9, 125.9, 127.7,

128.2, 138.5, 143.5; HRMS for M+1 found *m/e* 187.1121, calcd for $C_{13}H_{15}O$: 187.1123.

4.2.8. 6-Methyl-1-phenyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2a). White solid. Mp 120–121 °C; IR ($CHCl_3$) 3026, 1647, 1166, 762 cm^{-1}; ^1H NMR δ=0.85 (s, 3H), 0.96 (dd, J=1.2, 4.7 Hz, 1H), 1.20 (d, J=4.7 Hz, 1H), 2.43 (s, 3H), 2.97 (d, J=11.5 Hz, 1H), 3.96 (d, J=11.5 Hz, 1H), 5.35 (d, J=8.1 Hz, 1H), 6.36 (dd, J=1.2, 8.1 Hz, 1H), 7.18–7.31 (m, 7H), 7.63 (d, J=8.1 Hz, 2H). ^{13}C NMR δ=19.2, 21.2, 22.0, 24.5, 40.0, 48.4, 118.2, 121.1, 127.3, 127.4, 128.7, 130.0, 135.1, 139.1, 143.9. Anal. Calcd for $C_{20}H_{21}NO_2S$; C, 70.77; H, 6.24; N, 4.13. Found: C, 70.57; H, 6.41; N, 4.01.

4.2.9. 6-Butyl-1-phenyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2b). Pale yellow oil; IR (neat) 2932, 1216, 977, 756 cm^{-1}; ^1H NMR δ=0.60–0.67 (m, 1H), 0.75 (t, J=7.2 Hz, 3H), 0.99–1.37 (m, 7H), 2.43 (s, 3H), 3.02 (d, J=11.3 Hz, 1H), 3.92 (d, J=11.3 Hz, 1H), 5.45 (d, J=8.1 Hz, 1H), 6.39 (d, J=8.1 Hz, 1H), 7.19–7.26 (m, 5H), 7.30 (d, J=8.7 Hz, 2H), 7.63 (d, J=8.4 Hz, 2H). ^{13}C NMR δ=14.1, 21.7, 22.6, 22.8, 23.7, 29.1, 33.7, 40.4, 48.3, 116.0, 121.1, 127.0, 127.1, 128.3, 129.6, 129.7, 134.9, 138.8, 143.6; HRMS for M found *m/e* 381.1753, calcd for $C_{23}H_{27}NO_2S$: 381.1762.

4.2.10. 1-(4-Chlorophenyl)-6-methyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2c). White solid. Mp 42–43 °C; IR ($CHCl_3$) 3030, 2930, 1644, 1164, 752 cm^{-1}; ^1H NMR δ=0.77 (s, 3H), 0.86 (dd, J=1.1, 4.5 Hz, 1H), 1.14 (d, J=4.5 Hz, 1H), 2.36 (s, 3H), 2.85 (d, J=11.3 Hz, 1H), 3.85 (d, J=11.3 Hz, 1H), 5.26 (d, J=7.8 Hz, 1H), 6.29 (dd, J=1.1, 7.8 Hz, 1H), 7.05–7.25 (m, 6H), 7.55 (d, J=8.4 Hz, 2H). ^{13}C NMR δ=19.0, 20.9, 21.7, 24.2, 39.0, 48.0, 117.6, 121.0, 126.9, 128.6, 129.7, 131.0, 132.9, 134.7, 137.4, 143.7; HRMS for M found *m/e* 373.0928, calcd for $C_{20}H_{20}ClNO_2S$: 373.0903.

4.2.11. 1-(4-Methoxyphenyl)-6-methyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2d). White solid. Mp 39–40 °C; IR ($CHCl_3$) 3030, 2956, 1164, 756 cm^{-1}; ^1H NMR δ=0.85 (s, 3H), 0.91 (d, J=4.5 Hz, 1H), 1.18 (d, J=4.5 Hz, 1H), 2.42 (s, 3H), 2.92 (d, J=11.7 Hz, 1H), 3.78 (s, 3H), 3.93 (d, J=11.7 Hz, 1H), 5.33 (d, J=8.1 Hz, 1H), 6.34 (d, J=8.1 Hz, 1H), 6.80–6.83 (m, 2H), 7.10–7.13 (m, 2H), 7.30 (d, J=7.8 Hz, 2H), 7.63 (d, J=8.1 Hz, 2H). ^{13}C NMR δ=18.9, 20.9, 21.6, 24.3, 39.0, 48.1, 55.3, 113.8, 118.0, 120.6, 126.9, 129.7, 130.7, 130.9, 134.8, 143.5, 158.5; HRMS for M+1 found *m/e* 370.1465, calcd for $C_{21}H_{24}NO_3S$: 370.1477.

4.2.12. 6-Methyl-1-(2-naphthyl)-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2e). Colorless oil; IR (neat) 3022, 1216, 756 cm^{-1}; ^1H NMR δ=0.89 (s, 3H), 1.11 (dd, J=1.1, 4.7 Hz, 1H), 1.30 (d, J=4.7 Hz, 1H), 2.43 (s, 3H), 3.08 (d, J=11.4 Hz, 1H), 4.00 (d, J=11.4 Hz, 1H), 5.39 (d, J=8.1 Hz, 1H), 6.41 (dd, J=1.1, 8.1 Hz, 1H), 7.29–7.78 (m, 11H). ^{13}C NMR δ=19.1, 20.9, 21.7, 24.4, 39.8, 48.0, 117.8, 120.8, 125.8, 126.1, 127.0, 127.5, 127.6, 128.0, 128.5, 129.7, 132.4, 133.3, 134.7, 136.4, 143.6; HRMS for M+1 found *m/e* 390.1533, calcd for $C_{24}H_{24}NO_2S$: 390.1528.

4.2.13. 1,6-Dimethyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2f). Spectral data were accorded with those in literature.[10b]

4.2.14. 6-Methyl-1-phenyl-3-oxabicyclo[4.1.0]hept-4-ene (2g). Colorless oil; IR (neat) 3012, 1647, 936, 756 cm^{-1}; ^1H NMR δ=0.90 (s, 3H), 1.10 (d, J=4.5 Hz, 1H), 1.48 (d, J=4.5 Hz, 1H), 3.79 (d, J=10.2 Hz, 1H), 4.07 (d, J=10.2 Hz, 1H), 5.21 (d, J=5.7 Hz, 1H), 6.20 (d, J=5.7 Hz, 1H), 7.22–7.32 (m, 5H). ^{13}C NMR δ=18.0, 20.8, 24.0, 38.2, 68.6, 112.5, 126.8, 128.3, 129.8, 138.5, 141.0; HRMS for M+1 found *m/e* 187.1159, calcd for $C_{13}H_{15}O$: 187.1123.

4.3. Typical experimental procedure for enantioselective cycloisomerization of enynes (Table 5)

Under an atmosphere of carbon monoxide, TolBINAP (13.6 mg, 0.02 mmol) and $[Ir(cod)Cl]_2$ (6.7 mg, 0.01mmol) were stirred in 1,4-dioxane (0.5 mL) at room temperature. After the addition of a 1,4-dioxane solution (1.0 mL) of enyne **1** (0.10 mmol) and AgOTf (6.2 mg, 0.024 mmol), the reaction mixture was stirred under reflux for 2–7 h. The solvent was removed under reduced pressure, and the crude products were purified by thin-layer chromatography to give chiral cycloadduct **2**. Enantiomeric excess was determined by HPLC analysis using a chiral column.

4.3.1. *N*-(2-Phenylprop-2-en-1-yl)-*N*-(*o*-tosyl)but-2-yn-1-amine (1j). White solid. Mp 101–102 °C; IR ($CHCl_3$) 3202, 756 cm^{-1}; ^1H NMR δ=1.72 (t, J=2.4 Hz, 3H), 2.37 (s, 3H), 3.94 (q, J=2.4 Hz, 2H), 4.28 (s, 2H), 5.36 (d, J=0.9 Hz, 1H), 5.47 (d, J=0.9 Hz, 1H), 7.14–7.25 (m, 6H), 7.29–7.34 (m, 1H), 7.45 (dt, J_d=1.2 Hz, J_t=7.5 Hz, 1H), 7.98 (dd, J=1.4, 8.0 Hz, 1H). ^{13}C NMR δ=3.6, 20.4, 35.4, 50.0, 72.2, 81.5, 117.3, 125.8, 126.1, 127.8, 128.2, 130.1, 132.5, 132.6, 137.0, 138.0, 138.4, 142.0. Anal. Calcd for $C_{20}H_{21}NO_2S$; C, 70.77; H, 6.24; N, 4.13. Found: C, 70.74; H, 6.25; N, 4.07.

4.3.2. *N*-Mesityl-*N*-(2-phenylprop-2-en-1-yl)but-2-yn-1-amine (1k). White solid. Mp 118–119 °C; IR ($CHCl_3$) 2922, 2302, 2222, 754, 665 cm^{-1}; ^1H NMR δ=1.82 (t, J=2.4 Hz, 3H), 2.32 (s, 3H), 2.42 (s, 6H), 3.89 (q, J=2.4 Hz, 2H), 4.19 (s, 2H), 5.38 (s, 1H), 5.43 (s, 1H), 6.88–6.96 (m, 4H), 7.06–7.13 (m, 2H), 7.17–7.23 (m, 1H). ^{13}C NMR δ=3.7, 21.1, 22.8, 34.7, 49.7, 72.8, 81.1, 117.8, 126.0, 127.6, 128.0, 131.8, 132.1, 138.1, 140.6, 142.2, 142.4. Anal. Calcd for $C_{22}H_{25}NO_2S$; C, 71.90; H, 6.86; N, 3.81. Found: C, 71.94; H, 6.80; N, 3.74.

4.3.3. *N*-[2-(4-Chlorophenyl)prop-2-en-1-yl]-*N*-(*o*-tosyl)but-2-yn-1-amine (1l). White solid. Mp 67–69 °C; IR ($CHCl_3$) 2924, 2304, 2226, 1328, 903, 748 cm^{-1}; ^1H NMR δ=1.69 (t, J=2.4 Hz, 3H), 2.41 (s, 3H), 3.92 (q, J=2.4 Hz, 2H), 4.25 (s, 2H), 5.37 (s, 1H), 5.46 (s, 1H), 7.10–7.24 (m, 5H), 7.31 (m, 1H), 7.45 (dt, J_d=1.5 Hz, J_t=7.5 Hz, 1H), 7.96 (dd, J=1.5, 8.0 Hz, 1H). ^{13}C NMR δ=3.9, 20.9, 35.8, 50.3, 72.2, 82.0, 118.3, 126.2, 127.8, 128.6, 130.4, 132.8, 133.0, 134.0, 136.7, 137.2, 138.5, 141.2. Anal. Calcd for $C_{20}H_{20}ClNO_2S$; C, 64.25; H, 5.39; N, 3.75. Found: C, 64.12; H, 5.55; N, 3.76.

4.3.4. *N*-[2-(4-Methoxyphenyl)prop-2-en-1-yl]-*N*-(*o*-tosyl)but-2-yn-1-amine (1m). Colorless oil; IR (neat) 2922, 2260, 2226, 1325, 909, 758 cm^{-1}; ^1H NMR δ= 1.69 (t, J=2.4 Hz, 3H), 2.42 (s, 3H), 3.79 (s, 3H), 3.93 (q, J=2.4 Hz, 2H), 4.25 (s, 2H), 5.26 (d, J=0.9 Hz, 1H), 5.40 (d, J=0.9 Hz, 1H), 6.71–7.17 (m, 4H), 7.22–7.34 (m, 2H), 7.44 (dt, J_d=1.5 Hz, J_t=7.5 Hz, 1H), 7.97 (dd, J=1.5, 8.0 Hz, 1H). ^{13}C NMR δ=3.5, 20.6, 35.3, 50.1, 55.3, 72.1, 80.5, 81.4, 113.5, 115.8, 125.8, 127.3, 130.1, 130.3, 132.4, 132.6, 138.3, 141.1, 159.2; HRMS for M+1 found *m/e* 370.1482, calcd for $C_{21}H_{24}NO_3S$: 370.1477.

4.3.5. *N*-[2-(2-Naphthyl)prop-2-en-1-yl]-*N*-(*o*-tosyl)but-2-yn-1-amine (1n). Colorless oil; IR (neat) 2922, 2300, 2226, 1328, 897, 756 cm^{-1}; ^1H NMR δ=1.72 (t, J= 2.4 Hz, 3H), 2.32 (s, 3H), 3.97 (q, J=2.4 Hz, 2H), 4.39 (s, 2H), 5.46 (s, 1H), 5.61 (s, 1H), 7.09–7.79 (m, 10H), 8.00 (dd, J=1.5, 8.1 Hz, 1H). ^{13}C NMR δ=3.6, 20.4, 35.4, 50.1, 72.2, 81.5, 117.9, 124.2, 125.1, 125.8, 126.0, 127.3, 127.8, 128.2, 130.1, 132.5, 132.6, 132.8, 132.9, 135.3, 136.9, 138.2, 141.8; HRMS for M+1 found *m/e* 390.1539, calcd for $C_{24}H_{24}NO_2S$: 390.1528.

4.3.6. 6-Methyl-1-phenyl-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2a). $[\alpha]_D^{24}$ −72.54 (*c* 0.85, $CHCl_3$, 52% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 19 min for major isomer and 22 min for minor isomer).

4.3.7. 6-Methyl-1-phenyl-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2j). White solid. Mp 156–157 °C; IR ($CHCl_3$) 3028, 1649, 1162, 762 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 1.02 (d, J=4.5 Hz, 1H), 1.19 (d, J=4.5 Hz, 1H), 2.60 (s, 3H), 3.18 (d, J=12.2 Hz, 1H), 3.80 (d, J=12.2 Hz, 1H), 5.39 (d, J=7.8 Hz, 1H), 6.46 (d, J=7.8 Hz, 1H), 7.19–7.47 (m, 8H), 7.87 (d, J=8.1 Hz, 1H). ^{13}C NMR δ=19.1, 20.9, 21.0, 24.5, 40.0, 47.8, 117.4, 120.7, 126.2, 127.1, 128.4, 129.6, 129.9, 132.7, 132.9, 136.5, 137.4, 138.7; HRMS for M+1 found *m/e* 340.1347, calcd for $C_{20}H_{22}NO_2S$: 340.1371. $[\alpha]_D^{19}$ −206.16 (*c* 1.42, $CHCl_3$, 75% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 7 min for major isomer and 9 min for minor isomer).

4.3.8. 3-Mesityl-6-methyl-1-phenyl-3-azabicyclo[4.1.0]hept-4-ene (2k). Pale yellow oil; IR (neat) 2928, 1160, 758 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 1.05 (d, J=4.6 Hz, 1H), 1.27 (d, J=4.6 Hz, 1H), 2.30 (s, 3H), 2.57 (s, 6H), 3.19 (d, J=11.7 Hz, 1H), 3.62 (d, J=11.7 Hz, 1H), 5.36 (d, J= 7.8 Hz, 1H), 6.44 (d, J=7.8 Hz, 1H), 6.94 (s, 2H), 7.21–7.32 (m, 5H). ^{13}C NMR δ=19.3, 21.0, 23.1, 24.6, 39.8, 47.3, 116.5, 120.5, 127.0, 128.1, 128.4, 129.6, 131.9, 132.0, 138.9, 139.9, 142.6; HRMS for M+1 found *m/e* 368.1661, calcd for $C_{22}H_{26}NO_2S$: 368.1684. $[\alpha]_D^{27}$ −64.73 (*c* 0.23, $CHCl_3$, 57% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 5 min for major isomer and 6 min for minor isomer).

4.3.9. 1-(4-Chlorophenyl)-6-methyl-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2l). Colorless oil; IR (neat) 3030, 2930, 1352, 1166, 750 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 0.98 (d, J=4.8 Hz, 1H), 1.20 (d, J=4.8 Hz, 1H), 2.60 (s, 3H), 3.13 (d, J=11.7 Hz, 1H), 3.78 (d, J=11.7 Hz, 1H), 5.37 (d, J=7.8 Hz, 1H), 6.46 (d, J=7.8 Hz, 1H), 7.13–7.49 (m, 7H), 7.88 (d, J=8.1 Hz, 1H). ^{13}C NMR δ=19.0, 20.7, 20.8, 24.5, 39.2, 47.6, 117.1, 120.9, 126.3, 128.7, 129.9, 131.1, 131.3, 132.8, 133.1, 136.5, 137.3, 137.5; HRMS for M found *m/e* 373.0913, calcd for $C_{20}H_{20}ClNO_2S$: 373.0903. $[\alpha]_D^{20}$ −103.89 (*c* 0.36, $CHCl_3$, 74% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 8 min for major isomer and 14 min for minor isomer).

4.3.10. 1-(4-Methoxyphenyl)-6-methyl-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2m). White solid. Mp 41–42 °C; IR (neat) 2924, 1518, 1164, 756 cm^{-1}; ^1H NMR δ=0.88 (s, 3H), 0.96 (dd, J=1.1, 4.5 Hz, 1H), 1.16 (d, J=4.5 Hz, 1H), 2.60 (s, 3H), 3.12 (d, J=11.7 Hz, 1H), 3.77 (d, J=11.7 Hz, 1H), 3.77 (s, 3H), 5.37 (d, J=8.1 Hz, 1H), 6.43 (dd, J=1.1, 8.1 Hz, 1H), 6.80–7.47 (m, 7H), 7.87 (d, J=8.1 Hz, 1H). ^{13}C NMR δ=19.1, 20.8, 20.9, 24.6, 39.4, 47.8, 55.3, 113.8, 117.5, 120.5, 126.2, 129.9, 130.7, 130.8, 132.7, 132.8, 136.5, 137.4, 158.5; HRMS for M found *m/e* 369.1406, calcd for $C_{21}H_{23}NO_3S$: 369.1399. $[\alpha]_D^{19}$ −85.59 (*c* 0.21, $CHCl_3$, 44% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AD: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 9 min for major isomer and 8 min for minor isomer).

4.3.11. 6-Methyl-1-(2-naphthyl)-3-(*o*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2n). White solid. Mp 45–46 °C; IR ($CHCl_3$) 3024, 2930, 1642, 1342, 1164, 754 cm^{-1}; ^1H NMR δ=0.91 (s, 3H), 1.16 (dd, J=1.2, 4.8 Hz, 1H), 1.28 (d, J=4.8 Hz, 1H), 2.62 (s, 3H), 3.28 (d, J=12.0 Hz, 1H), 3.84 (d, J=12.0 Hz, 1H), 5.42 (d, J=7.8 Hz, 1H) 6.50 (dd, J=1.2, 8.1 Hz, 1H), 7.26–7.80 (m, 10H), 7.88 (d, J= 7.8 Hz, 1H). ^{13}C NMR δ=19.3, 20.9, 20.9, 24.7, 40.0, 47.7, 50.7, 117.2, 120.7, 125.8, 126.1, 126.2, 127.5, 127.6, 128.0, 128.5, 129.9, 132.4, 132.7, 132.9, 133.3, 136.3, 137.4; HRMS for M found *m/e* 389.1462, calcd for $C_{24}H_{23}NO_2S$: 389.1449. $[\alpha]_D^{20}$ −147.54 (*c* 1.04, $CHCl_3$, 35% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AS: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 11 min for major isomer and 14 min for minor isomer).

4.3.12. 6-Methyl-1-(2-naphthyl)-3-(*p*-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (2e). $[\alpha]_D^{26}$ −94.65 (*c* 0.53, $CHCl_3$, 64% ee). Enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel AD-H: (eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 23 min for major isomer and 15 min for minor isomer).

Acknowledgements

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16. Almost no asymmetric induction was observed by MeDUPHOS and CHIRAPHOS ($<2\%$ ee).

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Olefin cyclopropanation catalyzed by new diiminophosphorane and triiminophosphorane complexes of copper and palladium

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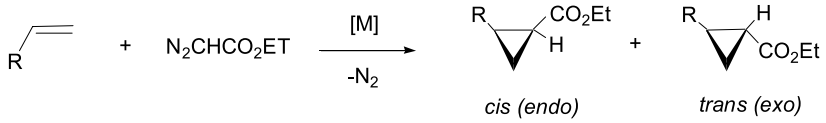
Abstract—Chelating diiminophosphorane and tripodal iminophosphorane copper and palladium complexes are found to efficiently catalyze the cyclopropanation of activated monosubstituted olefins with ethyl diazoacetate. Cycloolefins, and linear α-olefins are somewhat less reactive. The diastereoselectivities of the reactions are moderate and no major differences were seen when comparing the bidentate chelating ligand to the tripodal ligands.

1. Introduction

Organic chemists have always been fascinated by cyclopropanes because the smallest cycloalkane is present as a basic structural element in a great variety of natural and synthetic components of notable interest.[1,2] Cyclopropanes, besides their utility as such, can also be used as synthons in the molecular construction. They are versatile intermediates and can be converted into a variety of useful products by cleavage of the strained three-membered ring. This has led to the development of many methods for cyclopropanation reactions, including the Simmons–Smith reaction[3,4] and the now quite popular transition metal-catalyzed reactions of diazo compounds with olefins (Scheme 1).[2,5]

Control of the stereochemistry of this reaction is an important objective in organic synthesis and to date, the need for cheap, readily available, and highly diastereoselective cyclopropanation catalysts remains, however, largely unmet and the trans to cis (or *syn* to *anti*) selectivities remain usually modest with most Cu-based catalysts. This results from the fact that the stereocontrol of the intermolecular cyclopropanation reaction is most often controlled by the particular olefin-diazocompound combination, more bulky ester groups favoring the formation of the trans product. Recent developments have highlighted the use of nitrogen ligands in homogeneous catalysis, including enantioselective cyclopropanation catalyzed by transition metals.[6,7] This resulted in the emergence of copper complexes containing a large variety of ligands[8] that include inter alia Schiff bases,[9,10] oxazolines,[11,12] semicorrin,[13] and tris(pyrazolyl)[14,15] ligands for the cyclopropanation reaction.

The present article reports the first results of a work aimed at assessing the potential utility of a series of transition metal complexes based on chelating diiminophosphorane ligands and on triiminophosphorane ligands (their tripodal analogues) as catalysts for the cyclopropanation of olefins with ethyl diazoacetate (EDA) as the carbene source (Scheme 1). Iminophosphoranes are predominantly two electron σ-donors with only minor π-acceptor properties. They feature a short P–N bond and act as neutral monodentate ligands via the lone pair at the nitrogen centre. Further, iminophosphoranes where the carbon backbone bridges the two or three nitrogen atoms (such as those reported in this study) are expected to be sterically demanding ligands since their bulky phosphino substituents



Scheme 1.

Keywords: Cyclopropanation; Alkenes; Diazoester; Iminophosphorane; Tripodal ligand.
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are close to the metal centre. The triiminophosphorane ligands utilized in this work constitute a new family of tripodal ligands, the synthesis of which will be reported elsewhere (Scheme 2).[26]

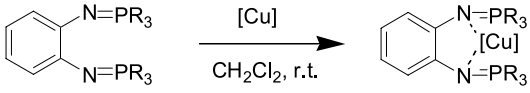
Scheme 2.

The iminophosphorane ligand being quite flexible, the symmetry induced by the ligand seems to strongly depend on the coordination sphere of the metal.[16] The diiminophosphorane ligands formally form 16 electron complexes with Cu(I)- and Pd(II) whereas tripodal iminophosphoranes are expected to form 18 electron complexes provided ligation to all three nitrogen atoms takes place. Because these ligands can act in different coordination modes, the different occupancy of the metal coordination sphere might thus, bring about different geometry and have an influence on the catalytic behavior of the metal complexes. Indeed, if complexes of four-coordinate copper are most often tetrahedral, they can also be square-planar whereas six-coordinate copper complexes are octahedrally disposed. The coordination chemistry of iminophosphoranes and of imino-aza-P(V) ligands has recently been reviewed.[17] To date, however, there is only one report in the literature on the use of diiminophosphorane ligands in olefin cyclopropanation.[16]

2. Results and discussion

2.1. Diiminophosphorane complexes of Cu and Pd

The diiminophosphorane ligands **1–4** were prepared as previously reported by reacting a dibromotriarylphosphorane (Ar_3PBr_2, prepared in situ) with *o*-phenylenediamine in the presence of triethylamine.[16] The corresponding air stable metallic complexes **5–8** were formed by reacting the four different ligands **1–4** with the appropriate metallic salt, respectively, CuOTf, $Cu(OTf)_2$ (OTf= trifluoromethanesulfonate anion) or $PdCl_2$ in dichloromethane (Scheme 3).



1 (R = phenyl)
2 (R = cyclopentyl)
3 (R = cyclohexyl)
4 (R = diphenylcyclohexyl)

5 (R = phenyl)
6 (R = cyclopentyl)
7 (R = cyclohexyl)
8 (R = diphenylcyclohexyl)

Scheme 3.

Screening cyclopropanation experiments with the complexes were performed under typical reaction conditions as already reported,[18] using a syringe pump for diazoester addition (EDA) and with styrene or cyclooctene as model substrates for activated and non-activated olefins, respectively. In order to minimize carbene coupling, a large excess of styrene has been used; the molar ratio Cu:EDA:styrene being 1:100:1000 and its addition occurs very slowly by means of a drip. The tests have been realized at two different temperatures, 60 °C and rt and the reaction products (*cis* and *trans* cyclopropanes, diethyl maleate, and fumarate) identified by comparison with authentic samples and quantified by VPC. Table 1 summarizes the results obtained with styrene.

It follows that, as usual, various parameters that include the catalyst structure, the substrate and the reaction temperature affect to some extent the rates and the yields of the reactions, as well as their diastereoselectivities (cis/trans or *exo*/*endo* ratio).

As a rule, the cyclopropanation reactions take place with

Table 1. Styrene cyclopropanation with $Ph(N{=}PR_3)_2$–Cu and Pd catalysts

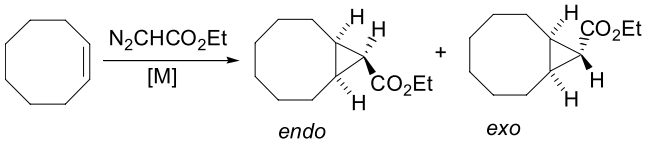
T (°C)	Ligand PR_3[a]	Metal	Cyclopropanation[b]		Dimerisation	
			Yield (%)	cis/trans	Yield (%)	Maleate/fumarate
60 °C	PCp_3	Cu(II)	99	0.65	0.5	0.94
		Cu(I)	95	0.63	5	1.49
		Pd(II)	93	0.50	7	0.15
	Ph_2Cy	Cu(II)	95	0.61	5	1.30
		Cu(I)	98	0.66	2	1.22
	PPh_3	Cu(II)	96	0.54	4	0.72
		Cu(I)	99	0.45	0.5	0.27
		Pd(II)	98	0.55	2	0.45
	PCy_3	Cu(II)	98	0.70	2	0.63
		Cu(I)	87	0.73	12	0.71
rt[c]	PCp_3	Cu(II)	79	0.92	18	1.01
		Pd(II)	82	0.46	18	0.13
	Ph_2Cy	Cu(II)	90	0.31	7	1.29
	PPh_3	Cu(II)	89	0.42	9	3.89
		Pd(II)	74	0.62	25	0.67
	PCy_3	Cu(II)	90	0.62	8	1.07
		Cu(I)	88	0.85	12	1.72

[a] Abbreviations: Cp, cyclopentyl; Cy, cyclohexyl.
[b] Experimental conditions: Cu complex, 0.01 mmol; styrene, 2 mL; ethyl diazoacetate (EDA), 1 mmol diluted by the olefin up to 1 mL; addition time, 3 h. Yields based on EDA.
[c] rt, room temperature.

high yields (>95%) at 60 °C, whatever the initial oxidation state of copper. There is a general agreement that EDA reduces Cu(II) to Cu(I) species and that in both cases, the active form of copper is the +1 oxidation state.[8,19] Only a small amount of carbene dimers (ethyl maleate and ethyl fumarate) is formed as by-products. On the whole, the alteration of the phosphine part of the ligand does not much influence the cyclopropanation yields, although it does affect the diastereoselectivity of the reaction. This is mostly noticeable with the copper(I) catalysts for which the ratio cis/trans varies from 0.45 to 0.73 at 60 °C (i.e., about a 30–40% fraction of *cis* isomers), depending on the selected phosphine. Such values come within the range of results obtained with the vast majority of Cu-based catalysts reported up to now.[9] Even if the stereoselectivity of the cycloaddition remains modest, there seems to exist a direct relationship between the steric bulk of the phosphine and the relative amount of *cis* cyclopropane synthesized, which increases following the series $PPh_3 < PPh_2Cy \approx PCp_3 < PCy_3$. No such trend is seen for carbene dimers.

The reactions also take place at rt with the copper and palladium complexes though the reaction time for diazoester decomposition needs then to be lengthened, and it takes around 20 h for the reaction to be complete instead of 3 h at 60 °C. The yields remain very good, although slightly lower than those obtained at higher temperature.

The same copper- and palladium-based catalysts have been applied to the cyclopropanation of cyclooctene, a non activated olefin (Scheme 4). The results of the cyclopropanation reactions at two different temperatures are reported in Table 2.



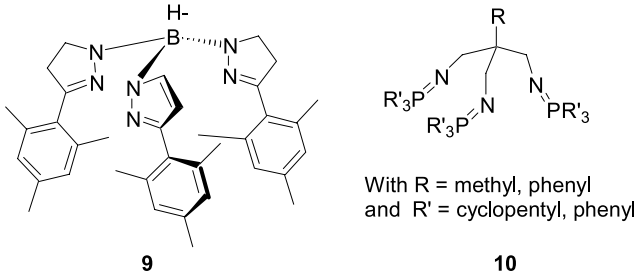
Scheme 4.

At 60 °C, good cyclopropanation yields are obtained with both metal complexes, though slightly inferior to those observed with styrene. With both metals, the *exo*-cyclopropane is preferentially formed, especially with Pd-based catalysts, the copper(II) complexes forming relatively more *endo*-isomer. Here also all metal complexes remain active for EDA decomposition at rt, although the duration of the reaction time needs again to be considerably increased. The cyclopropanation yields fall from 90% for a reaction performed at 60 °C to 60% at rt with the less efficient Cu-based system. The simultaneous increase of maleate and fumarate formation that is observed is concomitant with a fall of the cyclopropanation yields. Moreover, the issue of the cyclopropanation reaction in term of selectivity is similar to that obtained at higher temperature.

It appears from these preliminary results that the structural features of the ligand used in the cyclooctene or styrene cyclopropanation reactions do not modify the outcome of the reactions to a large extent, neither in terms of stereoselectivity nor of yield. On the other hand, replacing copper for palladium, mostly brings about some modification of the ratio of the isomers formed. In this context, the diiminophosphoranes complexes of palladium even if they are slightly more selective than the corresponding copper triflate based complexes, are also slightly less efficient cyclopropanation catalysts, especially with cyclooctene.

2.2. Triiminophosphorane complexes of Cu and Pd

Recent advances in olefin cyclopropanation catalyzed by metal complexes have highlighted the interest of tridentate ligands for obtaining highly active and selective catalysts. It is the case namely for complexes based on pyridine-bisoxazoline (pybox) and on homoscorpionate ligands (pyrazolylborates, Tp, see Scheme 5), some of which are capable of inducing large enantiomeric excesses in the conversion of alkenes into cyclopropanes while also favoring cis-isomer formation.[15,20,21] The necessity of being able to promote reactions of highly enantioselective and *cis*-selective cyclopropanation is illustrated inter alia by the recent synthesis of a powerful inhibitor of the inverse transcriptase (HIV-1).[22]



Scheme 5.

Table 2. Cyclooctene cyclopropanation with $Ph(N{=}PR_3)_2$–Cu and –Pd catalysts

T (°C)	Ligand[a]	Metal	Cyclopropanation		Dimerisation		Time (h)
			Yield (%)	*endo*/*exo*	Yield (%)	Maleate/fumarate	
60 °C	$Ph(N{=}PCp_3)_2$	Cu(II)	92	0.41	7	1.36	5
		Pd(II)	83	0.16	17	0.38	5
	$Ph(N{=}PPh_3)_2$	Cu(II)	89	0.50	10	1.41	4
		Pd(II)	89	0.19	11	0.94	48
rt[b]	$Ph(N{=}PCp_3)_2$	Cu(II)	73	0.39	27	1.46	22
		Pd(II)	68	0.20	32	0.38	22
	$Ph(N{=}PPh_3)_2$	Cu(II)	60	0.47	39	1.60	22

[a] Experimental conditions: complex, 0.01 mmol; cyclooctene, 2 mL; ethyl diazoacetate, 1 mmol diluted by the olefin up to 1 mL; addition time, 3 h.
[b] rt, room temperature.

Table 3. Styrene cyclopropanation with tripodal ligand-based catalysts

T (°C)	Ligand[a]	Metal	Cyclopropanation[b]		Dimerisation	
			Yield (%)	cis/trans	Yield (%)	Maleate/fumarate
60	CH_3–C–(CH_2NPPh_3)$_3$	Cu(II)	97	0.57	3	1.33
		Pd(II)	81	0.56	19	0.59
	CH_3–C–(CH_2NPCp_3)$_3$	Cu(II)	88	0.47	12	1.95
	Ph–C–(CH_2NPPh_3)$_3$	Cu(II)	97	0.54	3	1.40
		Pd(II)	86	0.52	14	0.73
	Ph–C–(CH_2NPCp_3)$_3$	Cu(II)	93	0.50	7	1.32
rt[c]	CH_3–C–(CH_2NPPh_3)$_3$	Cu(II)	84	0.60	15	1.76
	CH_3–C–(CH_2NPCp_3)$_3$	Cu(II)	86	0.12	12	0.90

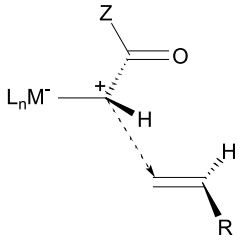
[a] Abbreviations: Cp, cyclopentyl; Cy, cyclohexyl.
[b] Experimental conditions: complex, 0.01 mmol; styrene, 2 mL; ethyl diazoacetate, 1 mmol diluted by the olefin up to 1 mL; addition time, 3 h.
[c] rt, room temperature.

There are some coordinating similarities between the pyrazolyborate **1** ligands shown in Scheme 5 and the triiminophosphoranes **2**. Each of these ligands looks like a hand formed by three 'fingers' relatively independent from each other, although one might expect a somewhat greater flexibility for the triiminophosphoranes. Each 'fingers' contains a sp^2 nitrogen atom that will coordinate to the transition metal through its lone electron pair. The proposed tridentate chelation is based on their spectroscopic data as no suitable crystals of any complexes have been obtained so far.

Pérez and co-workers,[14,15,20,23,24] and Penoni and co-workers[25] have demonstrated the potential of copper complexes bearing homoscorpionate (Tp) ligands in carbene reactions. Hence, this justifies the interest of exploring the catalytic activity of the new triimino-phosphorane ligand system in olefin cyclopropanation. The triiminophosphorane ligands were prepared as reported and the corresponding metallic complexes were formed by reaction of the ligand with the appropriate metallic salt in a dichloromethane solution.[22] Screening cyclopropanation experiments were performed under the same reaction conditions as reported for the diiminophosphorane complexes[18] and an overview of the activity/selectivity pattern of Cu- and Pd-complexes ligated to such tripodal ligands is reported hereafter.

The results for styrene cyclopropanation at two different temperatures are summarized in Table 3. It comes out that these triiminophosphorane-based complexes present a good catalytic activity, the yields vary from 81 and 99% and the secondary products (ethyl maleate and ethyl fumarate) are formed in low amounts when the reactions are performed with copper at 60 °C. The yields obtained with the Pd-based complexes are somewhat lower and from that on, an increased formation of carbene dimers can be observed. No significant influence of the substituent (methyl or phenyl group) at the sp^3 carbon bearing the three functionalized tethers is seen.

The diastereoselectivity of the reaction at 60 °C is not exceptional and does not vary much from one ligand to the other. In the whole, the cis- and trans-cyclopropanes are formed in an average ratio 35:65 whatever the ligand utilized. The ligand structure seems thus, to have relatively little influence on the outcome of the cyclopropanation reaction even if the stereoselectivity of the reactions can be significantly different to that observed with the corresponding bis-iminophosphorane complexes. This concurs with what has already been reported by Pérez and co-workers,[15,20] and according to these authors, the catalyst structure has little influence on the stereoselectivity of the reaction. This fact has been rationalized assuming that the high reactivity of the metal–carbene complex results from a transition state (A) (Scheme 6) in which the olefin remains always at a relatively important distance from the metal centre, which prevents it from being significantly affected by the steric bulk of the ligand. For that reason, the steric influences are not decisive in the induction of the diastereoselectivity.



Scheme 6.

At rt, the results are slightly less satisfactory regarding the yield of the cyclopropanation. On the other hand, in the case of the CH_3–C–(CH_2NPCp_3)$_3$ ligand, the copper complex tends to form predominantly the trans-isomer in a more significant way than at higher temperature. Furthermore, the stereoselectivity is opposite to that, which is observed with the corresponding bis-Cp-iminophosphorane (cis/trans ratios = 0.12 vs 0.92, see Table 1).

In order to study the influence of the substrate and of the stereo-electronic effects in these cyclopropanation reactions, differently substituted styrene derivatives and some aliphatic or aromatic olefins have been tested with the metal complex [CH_3–C–(CH_2NPCp_3)$_3$Cu(OTf)$_2$]. The results are reported in Table 4.

As a whole, the yields of the cyclopropanation reaction of the styrene derivatives are good to excellent (entries 1–7), with the exception of 4-*t*-butylstyrene and to a lesser extent of 4-methylstyrene. It should be noted that 4-methoxy as well as 4-chloro, and 4-trifluoromethylstyrenes give high yields of cyclopropanation products. Electron-rich and electron-depleted styrenes are thus, suitable targets for the carbene (or carbenoid) species formed in situ. The

Table 4. Cyclopropanation of various olefins with EDA and CH_3–C–$(CH_2NPCp_3)_3Cu(OTf)_2$

Entry	Substrate	Cyclopropanation[a]		Dimerisation (%)
		Yield (%)	cis/trans ratio	
1	Styrene	88	0.54	12
2	4-Chlorostyrene	93	0.45	7
3	4-Methoxystyrene	98	0.50	2
4	4-*t*-Butylstyrene	62	0.47	16
5	4-Methylstyrene	78	0.49	21
6	α-Methylstyrene	89	0.80	10
7	4-Trifluoromethylstyrene	91	0.49	9
8	1-Octene	52	0.51	48
9	Cyclooctene	77	0.65	23
10	1-Decene	68	0.61	32
11	Diethyl fumarate	2	—	nd[b]
12	Phenylacetylene	21	—	79

[a] Experimental conditions: complex, 0.005 mmol; olefin, 1 mL; ethyl diazoacetate, 1 mmol diluted by the olefin up to 1 mL; addition time, 3 h; temperature, 60 °C.
[b] nd, not determined.

copper-catalyzed reactions of ethyl diazoacetate with linear alkenes or cycloalkenes are more difficult but proceed in relatively good yields, although as expected, the activated alkenes (styrenes) are always more reactive than the non-activated ones (1-octene, cyclooctene, 1-decene).

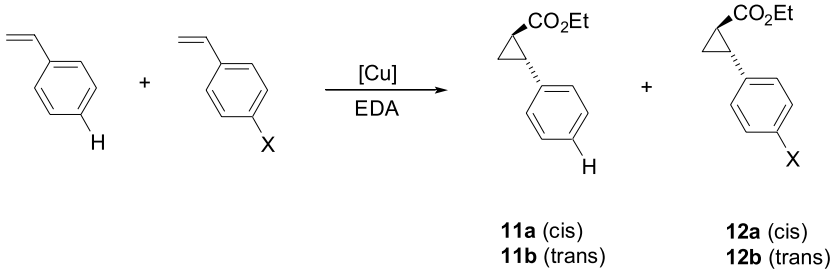
Globally, all the diasteroselectivities of the cyclopropanations obtained with the different olefins remain more or less in the same range of cis/trans ratio but for α-methylstyrene where it reaches the value of 0.8. This styrene derivative is known to give frequently ratio of isomeric cyclopropanes close to 1.

Despite the fact that the steric requirements for di- and triiminophosphorane complexes are quite different, the resulting stereoselectivities remain relatively close (although sometimes significantly different, however), and are difficult to rationalize. We have then performed competition experiments with *para*-substituted styrenes to obtain some further informations on the electronic effects of these ligands in the cyclopropanation reaction.

Four different complexes have been employed as the precatalyst in the competitive cyclopropanation of an equimolar mixture of two styrenes, the non-substituted $C_6H_5CH{=}CH_2$ and a *para*-substituted styrene of general formula $XC_6H_4CH{=}CH_2$ (Scheme 7). The ratio of the resulting cyclopropanes **11a**,**b**:**12a**,**b** were determined by gas chromatography. The results are summarized in Table 5.

In all cases, the cyclopropanation reaction favors the electron rich derivatives, whatever the kind of copper complex used (bearing a di- or a triiminophosphorane type ligand), that is, the *p*-methoxy- and *p*-*tert*butylstyrenes, whereas the electron-withdrawing groups such as Cl and CF_3 clearly disfavor the cycloaddition. This confirms the electrophilic character of carbenes (carbenoids) formed during the cyclopropanation reaction and is consistent with the observation that the carbene addition on electron poor olefins such as diethyl maleate or diethyl fumarate is only poorly effective, as depicted in Table 4.

Furthermore, the complexes ligated to cyclopentyl-triiminophosphoranes always appear to be more selective than their bis-iminophosphorane counterparts, the reverse



Scheme 7.

Table 5. Competition experiments[a] with *para*-substituted styrenes

Catalyst	Ratio of products [(**12a**+**12b**)/(**11a**+**11b**)]			
	p-OMe/H	*p*-*t*Bu/H	*p*-Cl/H	*p*-CF_3/H
Ph-1,2-$(N{=}PPh_3)_2Cu(OTf)_2$	1.66	1.67	0.72	0.32
Ph-1,2-$(N{=}PCp_3)_2Cu(OTf)_2$	1.63	1.54	0.79	0.49
CH_3–$C(CH_2N{=}PCp_3)_3Cu(OTf)_2$	2.07	1.86	0.84	0.52
Ph-1,2-$(N{=}PPh_3)_3Cu(OTf)_2$	1.38	1.46	0.83	0.21

[a] Experimental conditions: complex, 0.005 mmol; olefin, 1 mL of an equimolar mixture; ethyl diazoacetate, 1 mmol diluted by the equimolar mixture of olefins up to 1 mL; addition time, 3 h; temperature, 60 °C.

trend being observed with the phenyl-substituted ligands. On the other hand, the phenyl-bisiminophosphoranes show the reverse trend and select preferentially the electron-rich olefins when compared to their triiminophosphorane analogs. This constitutes a further indication that the metal complexes of bis- and triiminophosphoranes yield different active species in situ.

In conclusion, the present investigations have shown that the Cu- and Pd- di- and triiminophosphoranes are good to excellent catalysts for olefin cyclopropanation. However, despite the bulkiness of the iminophosphoranes used in this study, the stereoselectivities of the cyclopropanation reactions remains modest.

3. Experimental

3.1. General procedure for the cyclopropanation experiments

Cyclopropanation reactions were performed in small 10 mL two necked flasks fitted by a three way stopcock and by a septum. In this flask, 1×10^{-5} mol of the copper complex are introduced. The flask is then placed under inert atmosphere by three consecutives vacuum–argon cycles. To the catalyst, 2 mL of the dried, distillated, and degassed olefin are then added. The flask is heated to 60 °C in an oil bath (excepted for the reactions carried out at rt). In a 1 mL seringe, 0.125 g of the diazocompound are weighted and diluted up to 1 mL with the olefin. The diazoester is slowly added to the alkene solution via a syringe pump, the duration of the addition is 3 h at 60 °C. The kinetics of ethyl diazoacetate decomposition is followed by volumetry through N_2 evolution. To this end, the reaction flask is connected via the three way stopcock to a water column through a metallic canula. At the end of the reaction, the reaction mixture is analyzed by gas chromatography and the reaction products identified and quantified by comparison with authentic samples.

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Structure-driven design and synthesis of chiral dioxocyclam derivatives

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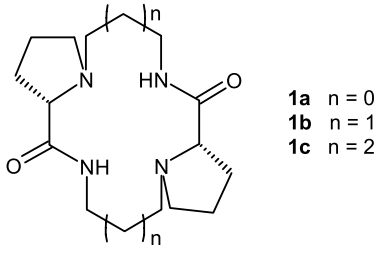
Abstract—Based on an analysis of previously reported structures and a potential geometry fit with substrates, a new family of chiral dioxocyclam derivatives have been designed. The synthesis of those ligands was accomplished starting from L-proline and α-D-amino acids (converted to β-amino acids) with a key step of macrocyclization reaction of amino esters. All ligands were converted into neutral copper(II) complexes (amide groups underwent deprotonation of upon treatment of ligands with copper(II) acetate). The complexes exhibit the desired shape of their active surfaces, as proved by X-ray analysis.

1. Introduction

Macrocyclic ligands, with nitrogen atoms as the electron pair donors, are known to exhibit an exceptionally high affinity for transition metal cations.[1] They are the subject of wide interest owing to their application in processes, such as ion sequestration,[2] catalysis[3] and for biomedical uses.[4,5] Cyclam derivatives, that belong to the mentioned group of compounds, not only form stable complexes with various transition cations,[6] but their complexes have been shown to catalyze organic reactions such as alkene epoxidation,[3,7,8] epoxide carboxylation,[9] electrochemical annulation,[10] and oxidation of hydrocarbons.[11] Despite the fact that in most of these reactions new stereogenic centres could be formed, the exploration of asymmetric catalysis has been so far limited.[12]

In this context, we were interested in the synthesis of a novel class of enantiomerically pure cyclam derivatives and its 12-membered and 16-membered analogues (Scheme 1).[13] Knowing that efficient asymmetric catalysis involves steric and electrostatic interaction between ligand, cation and substrates, and that this interaction depend on ligand structure, we decided to apply previously described methodology for the synthesis of a new class of chiral dioxocyclam derivatives and their complexes with Ni^{2+} and Cu^{2+} ions. Additionally, we would like to report herein on the design and structural study of the new compounds.



Scheme 1.

2. Results and discussion

2.1. Ligand design

In the preceding papers, we have presented an attractive and efficient synthetic route to optically pure dioxocyclam **1b**,[13] which upon deprotonation forms stable neutral complexes with Ni^{2+} and Cu^{2+}. X-ray analysis of **Ni·1b**[13] and **Cu·1b** (Fig. 1) shows that both complexes exhibit very similar tetrahedrally distorted square-planar geometry. Two pyrrolidine rings in **Ni·1b** and **Cu·1b** complexes are located at the same side of the macrocyclic ligand plane, which may result in inaccessibility of the metal cation from this side. Although the other side of the ligand, which is important for the possible interaction of the metal centre with a guest molecule, is approximately flat, it possesses a rectangular depression, which is parallel to the macrocycle plane and it

Keywords: Cyclams; Amino acids; Amides; X-ray diffraction; Macrocyclic ligands; Transition metal complexes.
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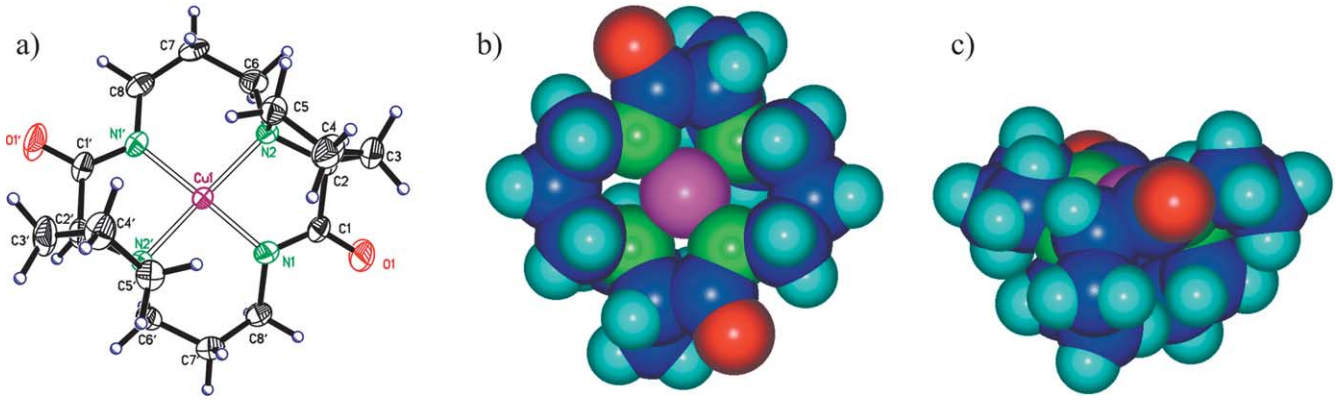


Figure 1. X-ray crystal structure of **Cu·1b**: (a) ORTEP presentation; (b) space filling view from the top; (c) space filling view from the side.

is surrounded by the hydrogens of the propylene bridges. The amide oxygens are located in the opposite vertices of this rectangular area. Both complexes have very similar structure, and in our opinion, this is a strong argument in favour of the thesis that the availability of the coordinated central atom should be similar for all complexes of the transition metals with a doubly-deprotonated tetradentate ligand of type **1b**. The geometry of such complexes can be symbolically illustrated as the model solid **C1** (Fig. 2).

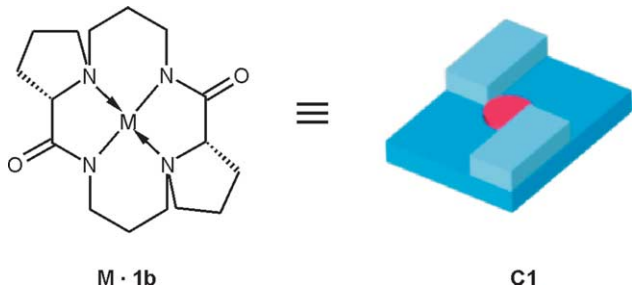


Figure 2. A schematic representation of **Cu·1b** geometry.

The features of the model complex **C1** can be summarised as follows: 1°—the geometry of the binding sites of the ligand is flat; 2°—the metal cation, which is coordinated inside the macrocycle gap, can be accessible for the substrate molecule only from one side, the other side of the macrocycle is completely inaccessible; 3°—the access to the metal cation being in the centre of the rectangle is limited by two groups located in the vertices of the rectangle. The above characterises the resulting molecule, with a C_2 axis as a symmetry element, which is perpendicular to the macrocycle plane and goes through the centre of the macrocycle gap or a cation therein.

The examples of previously prepared chiral catalytically active tetraazamacrocyclic derivatives are presented in Figure 3. Their geometry can be represented as the model **C2**. Analysis of those structures leads to the conclusion that their common feature is the presence of the C_2 axis positioned in the macrocycle plane.[14] Each of these systems have ternary stereogenic centres as the source of chirality. Thus, only one group, which modifies the close neighbourhood of the macrocycle gap, falls to each side of such a macrocycle.

Comparison of the models **C1** and **C2** reveals that complexes of **1b** provide a completely new topology. Moreover, it can be assumed that ligands of type **C2** offer too much flexibility to the interaction with a possible guest molecule (the substrate), and therefore, enantiotopic or enantiofacial discrimination will be less efficient (Fig. 4).

Thus, we found the geometry of type **C1** appealing and decided to extend our studies to more elaborate systems. We noticed that the depressions on **Ni·1b** and **Cu·1b** molecular surfaces are quite shallow, and thus we decided to prepare ligands that would have deeper cavities. The only reasonable site for modification of the model system **1b** is the less-crowded side of the macrocycle, which enables the access to the central metal cation, and therefore, is responsible for the chiral recognition of molecules. To achieve better similarity of the complex to the model solid **C1**, we resolved to insert an additional substituent into two opposite vertices of the above-mentioned rectangular

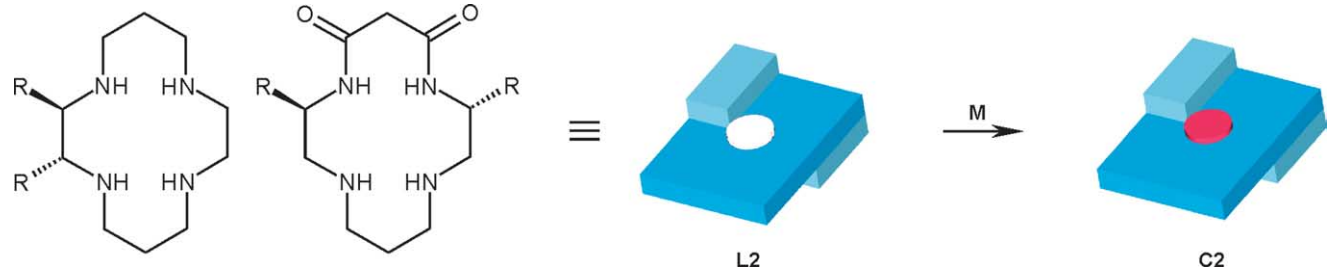


Figure 3. A schematic representation of the geometry of known chiral cyclam complexes.

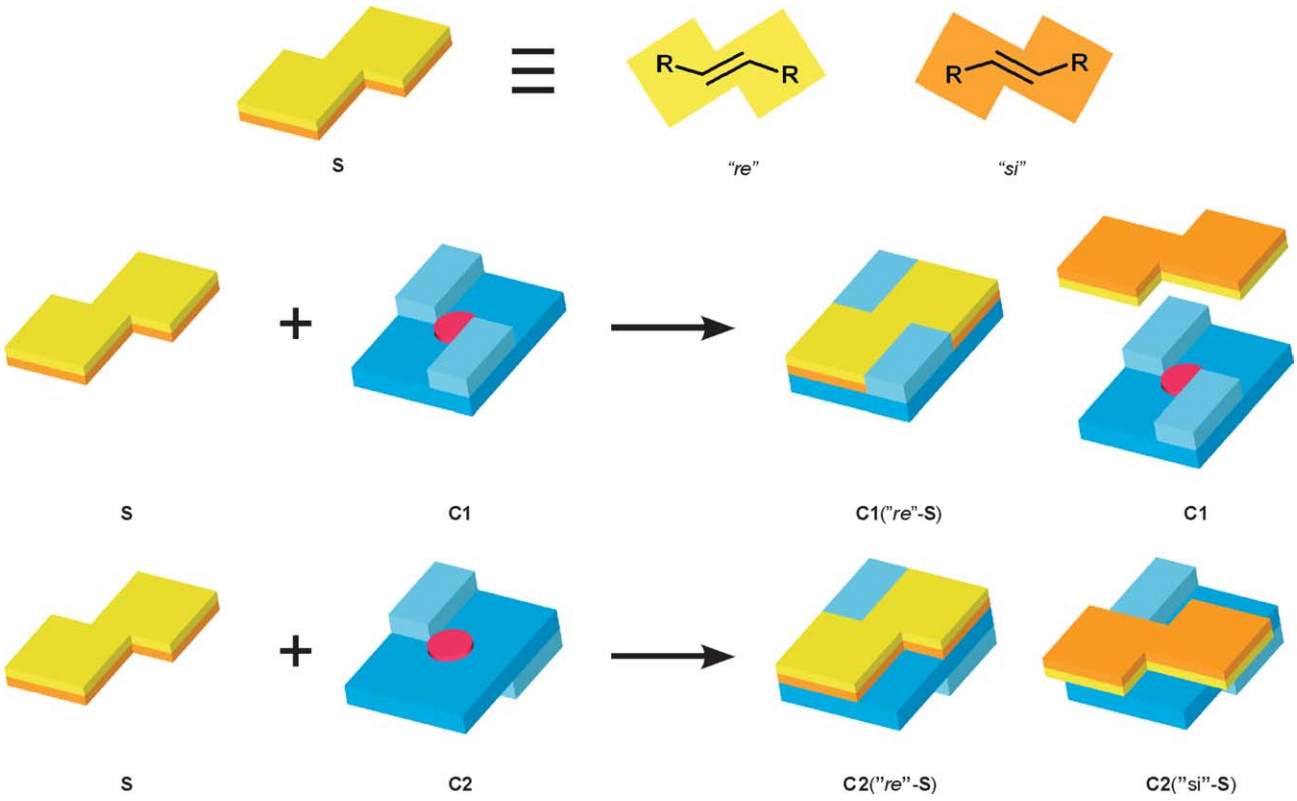


Figure 4. A schematic representation of the enantiofacial discrimination of the (*E*)-disubstituted olefins (S) by the molecules of shape **C1** and lack of such discrimination by the molecules of shape **C2**.

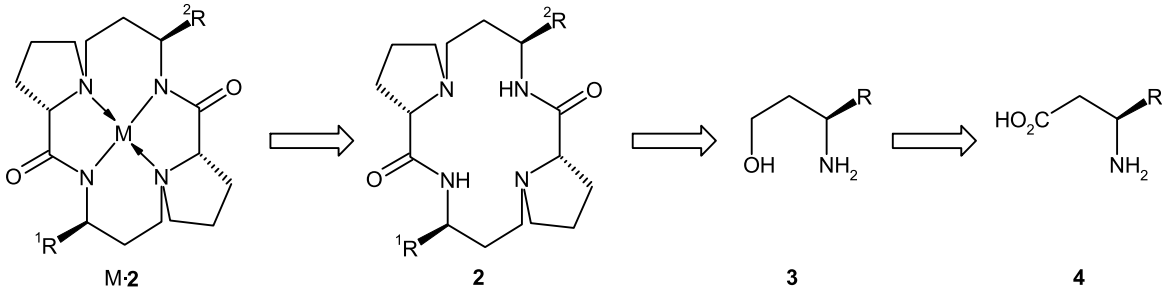
depression. The change from hydrogens to R groups leads to the ligands of type **2** (Scheme 2).

2.2. Preparation of ligands

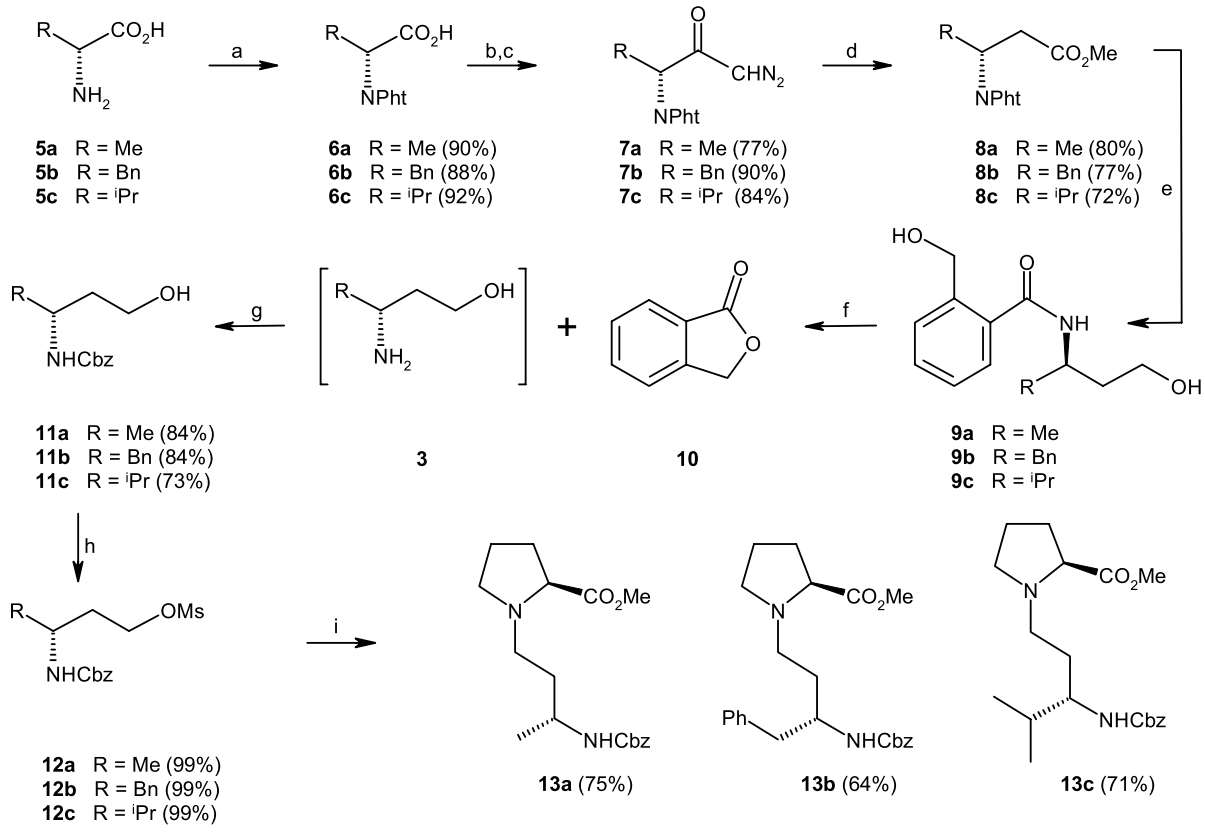
The retrosynthetic analysis indicates that precursors for modified ligands of type **2** are chiral 1,3-aminoalcohols **3**, which are closely related to D-β-amino acids (**4**) (Scheme 2). Therefore, it was necessary to synthesise the D-β-amino acids indicated by the retrosynthetic analysis, then to convert them into the intermediates **3** in order to prepare the ligands **2** using the already developed synthetic pathway.

Several methods for the preparation of the enantiomerically pure β-amino acids are known.[14c,15] Among them, the most practical one seemed to us the Arndt–Eistert synthesis (homologation of the easily available α-amino acids). We employed this method to prepare aminoalcohols **3**, and consequently ligands **2**, where R is methyl, benzyl and isopropyl, using three amino acids, viz, D-alanine (**5a**), D-phenylalanine (**5b**), and D-valine (**5c**), respectively. In the first step, the amino groups of the amino acids **5a–c** were protected by treating with the phthalic anhydride to afford the *N*-phthaloyl derivatives **6a–c** (Scheme 3). The *N*-protected acids **6a–c** were then converted into the corresponding acid chlorides, which reacted with an excess of diazomethane to give the respective diazoketones **7a–c** The key transformation, that is, the Wolff rearrangement was carried out by treating the methanolic solution of the diazoketone (**7a–c**) with a catalytic amount of silver benzoate, which resulted in formation of the rearranged methyl esters **8a–c** in good yields.

The *N*-phthaloyl protection was cleaved by the method of Ganem and co-workers.[16] The five-membered phthalimide ring was reductively opened by treatment with lithium borohydride to form the benzyl hydroxy function, and, simultaneously, the ester group was transformed to the hydroxymethyl group. The diols **9a–c**, under mild acidic



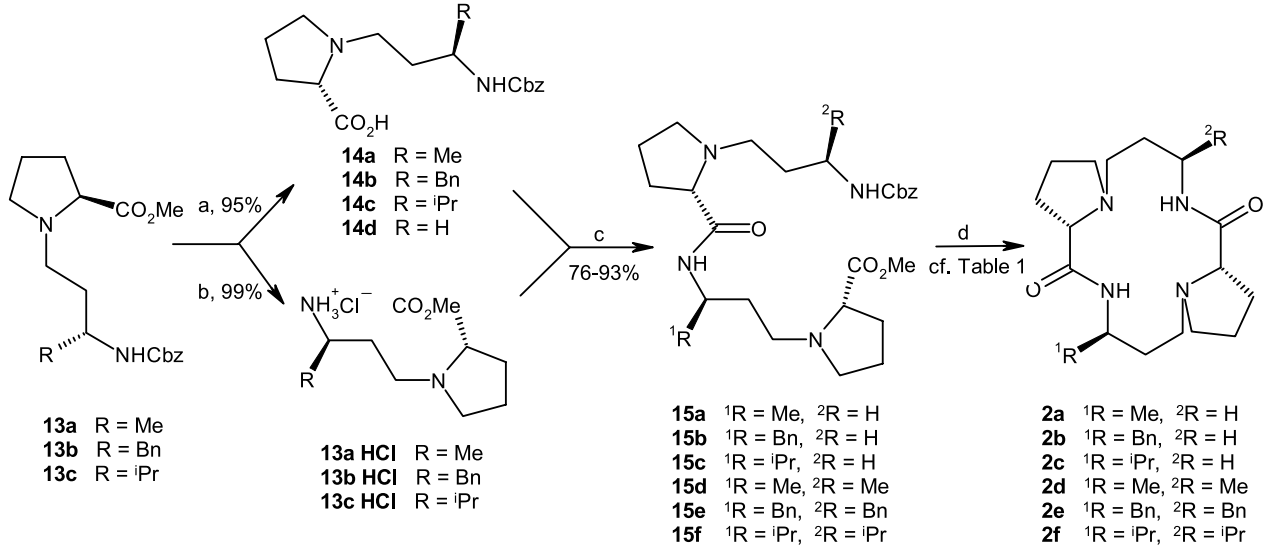
Scheme 2. The retrosynthetic analysis.



Scheme 3. Reaction conditions: (a) phthalic anhydride, Et_3N, toluene, reflux; (b) $SOCl_2$, cat. DMF; (c) CH_2N_2, Et_2O, toluene, 0 °C; (d) cat. $PhCO_2Ag$, Et_3N, MeOH, reflux; (e) $LiBH_4$, THF/H_2O; (f) AcOH, 80 °C; (g) CbzCl, CH_2Cl_2/aq NaOH; (h) Ms_2O, Et_3N, CH_2Cl_2; (i) L-Proline methyl ester, Et_3N, MeCN, reflux.

conditions, underwent lactonization, to give the lactone **10** and the elimination products, which were the desired amino alcohols of type **3**, the amino groups thereof were protected by treatment with benzyl chloroformate to yield the *N*-protected aminoalcohols **11a–c**. In each case, the overall yields for three last steps were high (~85%). The synthesis of *N*-Cbz-blocked aminoalcohols **11a–c** from the *N*-phthaloyl substrates (Scheme 3) only seemingly requires more effort than the synthesis starting from analogous *N*-Cbz-protected amino acids. The attempts to perform such a reaction sequence on the *N*-Cbz-protected substrates failed at the stage of formation of diazoketones. The esterification of alcohols **11a–c** with mesyl anhydride gave quantitatively *N*-blocked mesylates **12a–c**, which were then used for *N*-alkylation of L-proline methyl ester. This gave the chiral building blocks **13a–c**.

Hydrolysis of **13a–c** gives acids **14a–c**, that were subjected



Scheme 4. Reaction conditions: (a) aq NaOH/MeOH; (b) H_2/Pd-C, HCl/MeOH; (c) ^{t}BuOCOCl, Et_3N, CH_2Cl_2, −20 °C→0°; (d) H_2/Pd-C, MeOH; then MeOH, base, at rt or at 10 kbar, 50 °C, see Table 1.

Table 1. Effect of the reaction conditions on the yield of macrocyclisation of amino esters **15a–f**

Entry	Product	Conditions	Yield%
1	**2a**	NaOH, MeOH, rt, 1 day	75
2	**2b**	NaOH, MeOH, rt, 1 day	82
3	**2c**	NaOH, MeOH, rt, 1 day	77
4	**2d**	$NaOCH_3$, MeOH, rt, 30 days	15
5	**2d**	DBU, MeOH, 10 kbar, 50 °C, 3 days	24
6	**2d**	Et_3N, MeOH, 10 kbar, 50 °C, 3 days	36
7	**2d**	Et_3N, MeOH, 10 kbar, 50 °C, 7 days	40
8	**2e**	Et_3N, MeOH, 10 kbar, 50 °C, 7 days	5
9	**2f**	Et_3N, MeOH, 10 kbar, 50 °C, 7 days	2

to condensation with amino ester hydrochlorides **13a–c·HCl** to give corresponding pseudo-peptides **15d–e** (Scheme 4). In order to prepare monosubstituted compounds **15a–c**, the aminoester hydrochlorides **13a–c·HCl** were condensed with acid **14d** obtained from 3-aminopropanol in a similar way.[13b]

N-Cbz-protected amino esters **15a–c** are immediate precursors of the monosubstituted ligands **2** (R^1=H; R^2=Me, Bn or ^{i}Pr), while the compounds **15d–f** are the precursors of the disubstituted ligands **2** (R^1=R^2=Me, Bn or ^{i}Pr). The macrocyclisation of the α,ω-diester precursors to compounds of type **2** was attempted in the presence of sodium hydroxide in methanol, because these conditions proved to be most universal in the case of preparation of analogous compounds of type **2**. The singly-modified amino esters **15a–c**, underwent intramolecular amidation in the presence of methanolic NaOH, to afford the desired monosubstituted macrocycles **2a–c** (Scheme 4) in very good yields (75–82%, Table 1).

The disubstituted amino esters **15d–f** gave no macrocyclic products at all under the same conditions. The only products identified by ESI-MS were the salts of corresponding carboxylic acids. These results suggested that hydrolysis of the methyl ester group caused by hydroxyl anions is much faster than the desired intramolecular aminolysis. Therefore, the use of sodium methoxide appeared to be a possible way for overcoming this problem. This idea was tested using the disubstituted amino ester **15d** to give the macrocyclic diamide **2d** in 15% yield.

The more successful attempt to increase the reactivity of the amine/methyl ester system was the high-pressure reaction in the presence of a base (triethylamine or DBU). The yield for macrocyclic diamide **2d** improved (24–40%), but the other two diamides (**2e** and **2f**) formed in low yields (5 and 2%, respectively), which still allowed for their isolation and characterisation (Table 1).

The comparison of highly reactive monosubstituted amino esters **15a–c** with their disubstituted analogues **15d–f**, which react very reluctantly, leads to the conclusion that this is probably due to different character of the reacting amino groups. Although, in all cases, the ester carbonyl group is attacked by the primary amino group, this amino group is linked to a primary carbon atom in the case of highly reactive substrates (**15a–c**). In the case of amino esters **15d–f**, however, the primary amino group is linked to a secondary carbon atom.

2.3. Structural studies

Two compounds of type **2**, that is, the dimethyl derivative

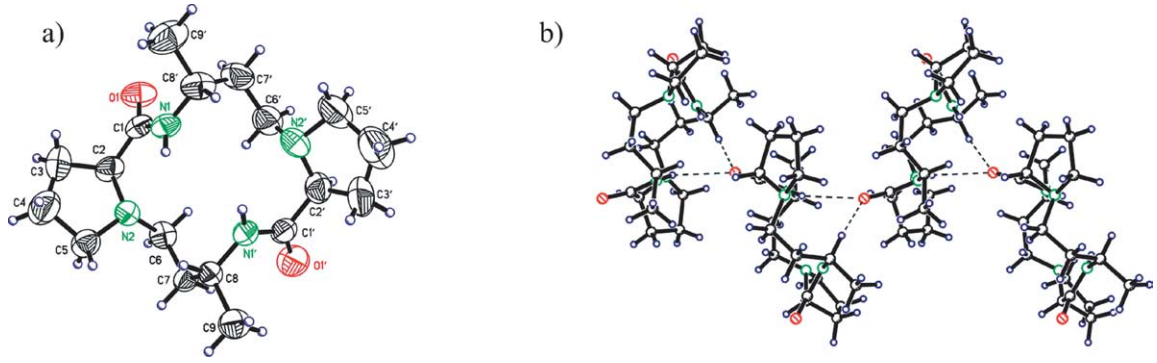


Figure 5. X-ray crystal structure of **2d**: (a) ORTEP presentation; (b) packing pattern.

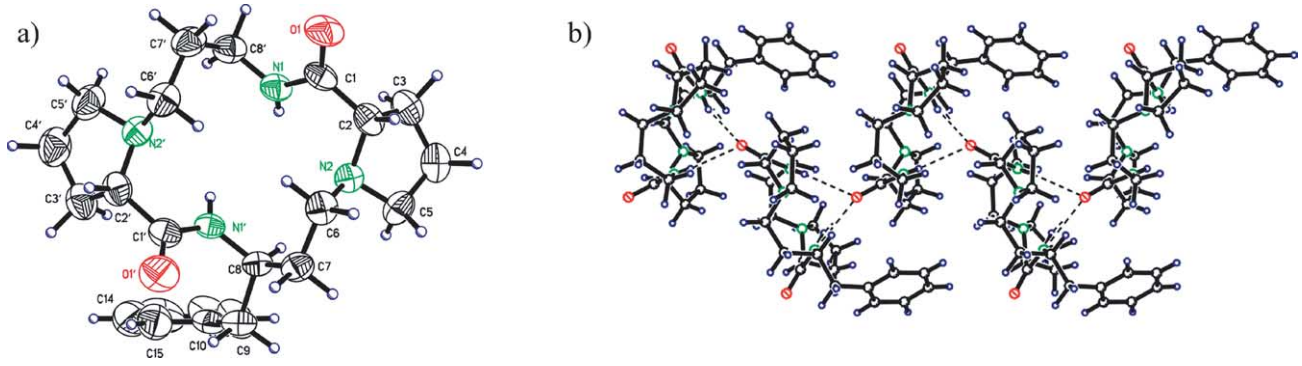


Figure 6. X-ray crystal structure of **2b**: (a) ORTEP presentation; (b) packing pattern.

2d and the monobenzyl derivative **2b**, gave monocrystals suitable for the X-ray diffraction analysis. The structures of these ligands along with their packing modes in the solid state are shown in Figures 5 and 6. The conformations of the macrocyclic rings in both structures are very similar. The proline rings are almost co-planar with the main planes of the macroring. Carbonyl oxygen atoms are positioned perpendicularly to the macroring plane and point to the same side of the macrocycle, slightly outside of the macrocycle centre. The amide hydrogen atoms are thus directed to the opposite side. It is worth mentioning that amide hydrogen atoms are in the close proximity of proline amine lone pairs (distances $H_{amide}\cdots N_{proline}$ in all cases are less than 2.4 Å) forming intramolecular five-membered hydrogen bonded rings. Additionally both amide hydrogen atoms form convergent hydrogen bonds with the carbonyl oxygen of the neighbouring molecule.

All ligands of type **2** form stable complexes with copper cations, in an analogous way to the parent ligand **1b**. The complexes of the mono- and dimethyl derivatives **Cu·2a** and **Cu·2d** gave monocrystals suitable for the X-ray structure determination. Their structures (Figs. 7 and 8) are similar to that of the parent complex **Cu·1b** (Fig. 1). Upon complexation, ligands underwent deprotonation losing amide hydrogen atoms and formed neutral complexes. The geometry of the metal centre is square-planar tetrahedrally distorted. Comparison of all structures reported thus far shows that the tetrahedral twist, defined as the rms deviation from the least-square plane passing through four nitrogen atoms, is slightly larger for all copper complexes (±0.35 Å for **Cu·1b**, ±0.33 Å for **Cu·2a**, ±0.39 Å for **Cu·2d**) than for the **Ni·1b** complex (±0.28 Å). The presence of one or two methyl groups, which are perpendicular to the macrocycle plane makes the crucial depressions on the surface much deeper, which is in agreement with our ligand design.

Preliminary experiments revealed that copper complexes with ligands of type **2** can act as catalysts in cyclopropanation of olefins. The reaction between methylstyrene and ethyldiazoacetete in the presence of **Cu·2b** led to the formation of *trans*-isomer of ethyl 2-methyl-3-phenylcyclopropanecarboxylate with 30% ee, however, no asymmetric induction was observed for the *cis*-isomer.

3. Conclusions

Most of the previously reproted chiral cyclams possesses C_2 symmetry axis that is parallel to the macrocyclic plane. In this paper, we have designed and synthesised a new class of chiral dioxocyclams having a C_2 symmetry axis that is perpendicular to the main plane of the macrocycle. The synthesis was accomplished using L-proline ester and amino alcohols as the starting materials. Such oxocyclams form neutral complexes with copper ions undergoing simultaneous deprotonation of amide groups. Since such complexes exhibit one potentially catalytically active surface that is approximately flat, we have also designed and synthesised the modified ligands in order to accomplish higher asymmetry of the complex surfaces. X-ray structure analyses confirmed the designed topology. Preparation of this family of compound proved the efficiency and

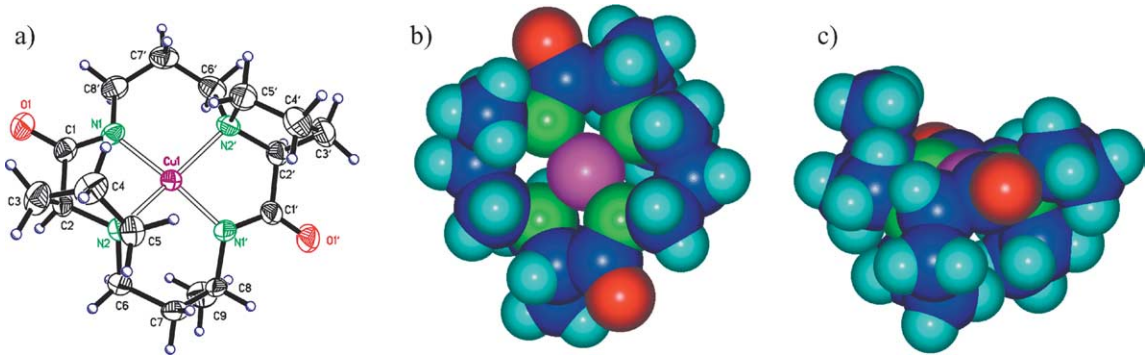


Figure 7. X-ray crystal structure of **Cu·2a**: (a) ORTEP presentation; (b) space filling view from the top; (c) space filling view from the side.

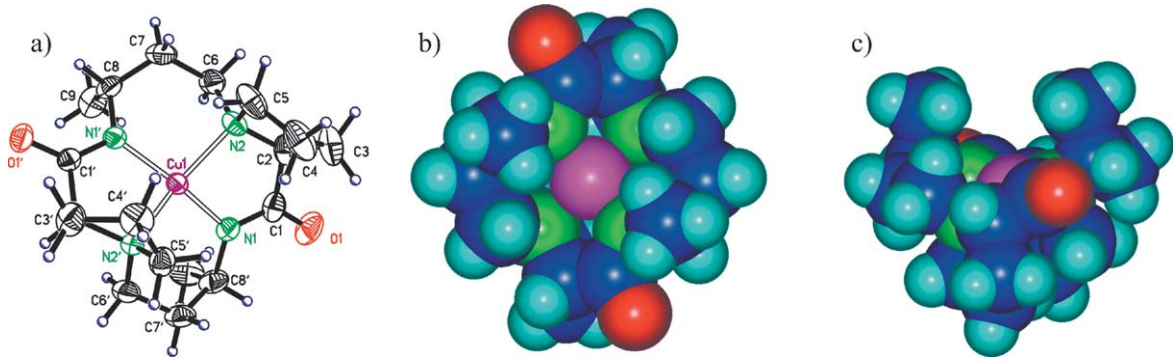


Figure 8. X-ray crystal structure of **Cu·2d**: (a) ORTEP presentation; (b) space filling view from the top; (c) space filling view from the side.

generality of our synthetic pathway that leads to the chiral analogues of cyclam.

4. Experimental

4.1. General remarks

Crystallographic data (excluding structure factors) for the structures discussed in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 273756-273760. 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]. Summary of the crystallographic data and details concerning synthesis of *N*-protected amino alcohols **11a–c** are provided in the Supplementary material. If not stated otherwise, all reagents were obtained from commercial sources and used as received. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh), the thin-layer chromatography was carried out using Merck Kieselgel F_{254} plates.

4.2. General procedure for Cbz-protected aminoalcohol mesylation

Cbz-protected aminoalcohol (19.1 mmol) and triethylamine (1.1 equiv, 3.0 mL) was dissolved in dry dichloromethane (100 mL) and placed in cooling bath. Methanesulfonyl anhydride (1.1 equiv, 3.76 g) was added in a few portions with vigorous stirring to prevent local overheating. Reaction was completed right after the last portion of anhydride had been added (TLC). The mixture was transferred into a separator and washed with 0.5 M HCl aq (50 mL), satd $NaHCO_3$ aq (50 mL), and dried over anhydrous magnesium sulfate. Solvents were removed under reduced pressure and the solid residue was crystallized from CH_2Cl_2/hexane furnishing chromatographically pure mesylate (quant. yield) as colourless crystals.

4.2.1. (*R*)-1-Mesyloxy-*N*-(benzyloxycarbonyl)-3-aminobutane (12a). Prepared from alcohol **11a**. Colourless crystals; mp 67–70 °C; $[\alpha]_D^{20}$ −13.8 (*c* 0.54 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C, TMS): δ=7.38–7.29 (m, 5H; arom.), 5.09 (br s, 2H; CH_2Ph), 4.64 (br s, 1H; N*H*), 4.37 (t, 2*H*, *J*=6.3 Hz; CH_2O), 3.96–3.84 (m, 1H; C*H*N), 2.97 (s, 3H; SO_2CH_3), 1.98–1.79 (m, 2H; CH_2), 1.22 (d, *J*=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C, TMS): δ=155.8, 136.4, 128.6, 128.2, 128.1, 67.0, 66.7, 44.3, 37.3, 36.4, 21.2; IR (KBr): ν=3338, 2971, 1680, 1539, 1457, 1349, 1259, 1161, 1091, 1034, 991, 965, 824, 758, 698, 527 cm^{-1}; MS (ESI HR, MeOH): calcd for $[C_{13}H_{19}NO_5SNa]^+$ 324.0876; found 324.0868; elemental analysis (%) calcd for $C_{13}H_{19}NO_5S$: C 51.8, H 6.31, N 4.65; found: C 51.6, H 6.56, N 4.52.

4.2.2. (*S*)-1-Mesyloxy-*N*-(benzyloxycarbonyl)-3-amino-4-phenylbutane (12b). Prepared from alcohol **11b**. Colourless crystals; mp 93–95 °C; $[\alpha]_D^{20}$ −8.2 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C, TMS): δ=7.37–7.13 (m, 10H; arom.), 5.06 (d_{AB}, 2H, J_{AB}=12.2 Hz, δ_{AB}=16.8 Hz; OCH_2Ph), 4.68 (d, 1H, *J*=7.5 Hz; N*H*), 4.29–4.21 (m, 2H; CH_2O), 4.08–3.99 (m, 1H; C*H*N), 2.92 (s, 3H; SO_2CH_3), 2.87–2.78 (m, 2H; CH_2Ph), 2.07–1.98 (m, 1H; C*H*H), 1.84–1.75 (m, 1H; CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C, TMS): δ=155.9, 137.0, 136.4, 129.3, 128.6, 128.5, 128.2, 128.0, 126.8, 67.1, 66.7, 49.3, 41.2, 37.2, 33.7; IR (KBr): ν=3345, 3033, 2957, 1687, 1533, 1453, 1348, 1261, 1161, 1070, 1022, 988, 829, 750, 697, 527 cm^{-1}; MS (ESI HR, MeOH): calcd for $[C_{19}H_{23}NO_5SNa]^+$ 400.1189; found 400.1203; elemental analysis (%) calcd for $C_{19}H_{23}NO_5S$: C 60.48, H 6.10, N 3.71; found: C 60.54, H 6.34, N 3.57.

4.2.3. (*S*)-1-Mesyloxy-*N*-(benzyloxycarbonyl)-3-amino-4-methylpentane (12c). Prepared from alcohol **11c**. Colourless wax; mp 45–46 °C; $[\alpha]_D^{20}$ −20.6 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C, TMS): δ=7.38–7.29 (m, 5H; arom.), 5.09 (d_{AB}, 2H, J_{AB}=12.2 Hz, δ_{AB}=22.1 Hz; CH_2Ph), 4.61 (br d, 1H, *J*=9.8 Hz; N*H*), 4.31–4.20 (m, 2H; CH_2OH), 3.70–3.63 (m, 1H; C*H*N), 2.94 (s, 3H; SO_2CH_3), 2.04–1.96 (m, 1H; C*H*), 1.82–1.66 (m, 2H; CH_2), 0.93 (d, *J*=6.8 Hz; CH_3), 0.90 (d, *J*=6.8 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C, TMS): δ=156.4, 136.5, 128.6, 128.2, 128.1, 67.5, 66.8, 53.1, 38.4, 37.1, 32.3, 19.0, 17.6; IR (KBr): ν=3356, 3035, 2957, 2876, 1694, 1529, 1468, 1354, 1245, 1169, 1055, 974, 911, 811, 738, 697, 645, 526, 457 cm^{-1}; MS (ESI HR, MeOH): calcd for $[C_{15}H_{23}NO_5SNa]^+$ 352.1189; found 352.1195; elemental analysis (%) calcd for $C_{15}H_{23}NO_5S$: C 54.71, H 6.99, N 4.26; found: C 54.48, H 7.25, N 4.09.

4.3. General procedure for L-proline methyl ester alkylation

A solution of L-proline methyl ester (19.3 mmol, 2.50 g), freshly prepared from its hydrochloride, mesylate (19.3 mmol) and triethylamine (1.0 equiv, 2.7 mL) in acetonitrile (10 mL) was kept at room temperature overnight and then stirred at 50 °C until all the mesylate was consumed (TLC). Solvents were evaporated under reduced pressure and the dry residue was partitioned between ethyl acetate (0.20 L) and water (25 mL). Organic layer was additionally washed with water (25 mL), brine and dried over anhydrous sodium sulfate. Chromatographic purification of the crude mixture on silica gel in ethyl acetate–hexane (7/3) afforded pure Cbz-protected aminoester as colourless oil.

4.3.1. (2*S*,9*R*)-2,6-Cyclo-6-aza-9-(benzyloxycarbonylamino)decanoic acid methyl ester (13a). Prepared from mesylate **12a** in 75% yield; $[\alpha]_D^{20}$ −42.8 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.37–7.26 (m, 5H; C_6H_5), 5.87 (br s, 1H; N*H*), 5.09 (d_{AB}, 2H, J_{AB}=12.3 Hz, δ_{AB}=22.2 Hz; CH_2Ph), 3.90–3.77 (m, 1H; C*H*CH$_3$), 3.70 (s, 3H; OCH_3), 3.19–3.11 (m, 2H; C*H*CO$_2$, NC*H*H), 2.91–2.83 (m, 1H; NCH*H*), 2.46–2.39 (m, 1H; NC*H*H), 2.29–2.23 (m, 1H; NCH*H*), 2.15–2.05 (m, 1H; C*H*H), 1.95–1.69 (m, 4H; 2×CH_2), 1.57–1.49 (m, 1H; CH*H*), 1.17 (d, 3H, *J*=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 156.0, 137.1, 128.5, 127.8, 66.2, 66.1, 53.1, 51.8, 51.2, 46.2, 34.1, 29.3, 23.3, 20.3; IR ($CHCl_3$): ν=3439, 3321, 2955, 2817, 1714, 1512, 1454, 1344 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{18}H_{27}N_2O_4$ [M+H$^+$]: 335.1965; found: 335.1955.

4.3.2. (2*S*,9*R*)-2,6-Cyclo-6-aza-9-(benzyloxycarbonylamino)-10-fenylodecanoic acid methyl ester (13b). Prepared from mesylate **12b** in 64% yield; $[\alpha]_D^{20}$ −29.1 (*c* 0.80 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.36–7.15 (m, 10H; 2×C_6H_5), 6.01 (d, 1H, *J*=7.8 Hz; N*H*), 5.08 (d_{AB}, 2H, J_{AB}=12.7 Hz, δ_{AB}=21.0 Hz; OCH_2Ph), 3.98 (br s, 1H; C*H*CH_2Ph), 3.70 (s, 3H; OCH_3), 3.16–3.09 (m, 2H; C*H*CO_2, NC*H*H), 2.99–2.88 (m, 2H; C*H*HPh, NC*H*H), 2.79–2.72 (dd, 1H, J_1=7.8 Hz, J_2=13.4 Hz; C*H*HPh), 2.44–2.39 (m, 1H; NCH*H*), 2.24–2.18 (m, 1H; NCH*H*), 2.13–2.05 (m, 1H; C*H*H), 1.95–1.70 (m, 4H; CH_2, 2× C*H*H), 1.51–1.43 (m, 1H; CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 156.0, 138.4, 137.1, 129.4, 128.4, 128.3, 127.8, 128.7, 126.2, 66.2, 66.1, 53.2, 51.8, 51.7, 51.4, 40.3, 30.8, 29.4, 23.3; IR ($CHCl_3$): ν=3445, 3318, 2954, 2814, 1714, 1511, 1454, 1338 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{24}H_{30}N_2O_4Na$ [M+Na^+]: 433.2098; found: 433.2121.

4.3.3. (2*S*,9*S*)-2,6-Cyclo-6-aza-9-(benzyloxycarbonylamino)-10-metyloundecanoic acid methyl ester (13c). Prepared from mesylate **12c** in 71% yield; $[\alpha]_D^{20}$ −37.1 (*c* 0.85 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ= 7.36–7.28 (m, 5H; C_6H_5), 5.38 (d, 1H, *J*=9.3 Hz; N*H*), 5.09 (d_{AB}, 2H, J_{AB}=12.3 Hz, δ_{AB}=30.6 Hz; CH_2Ph), 3.70 (s, 3H; OCH_3), 3.52–3.44 (m, 1H; NHC*H*), 3.18–3.11 (m, 2H; C*H*CO, NC*H*H), 2.79 (dt, 1H, J_1=8.0 Hz, J_2=12.0 Hz; NC*H*H), 2.49–2.41 (m, 1H; NCH*H*), 2.32–2.23 (m, 1H; NCH*H*), 2.15–2.04 (m, 1H; C*H*H), 1.95–1.69 (m, 5H; CH_2, C*H*H, CH*H*, C*H*), 1.58–1.48 (m, 1H; CH*H*), 0.90 (d, 3H, *J*=7.9 Hz; CH_3), 0.88 (d, 3H, *J*=7.1 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 156.5, 137.0, 128.4, 127.9, 127.8, 66.3, 66.1, 55.7, 53.4, 52.0, 51.8, 31.6, 30.4, 29.4, 23.3, 19.1, 18.4; IR ($CHCl_3$): ν=3441, 3331, 2963, 2816, 1719, 1513, 1456 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{20}H_{31}N_2O_4$ [M+H^+]: 363.2278; found 363.2297; elemental analysis calcd (%): C 66.30, H 8.29, N 7.73; found: C 66.09, H 8.36, N 7.62.

4.4. General procedure for amide bond formation

A mixture of *N*-benzyloxycarbonyl aminoester (3.69 mmol) and water (50 mL) was emulsified by vigorous stirring while heated in reflux, until saponification was complete (TLC) and the reaction mixture turned into a clear solution. Water was evaporated under reduced pressure. Residual traces of water were removed as water–dichloromethane azeotrope by dissolving crude product in dichloromethane followed by evaporation at atmospheric pressure, repeated three times. Crude *N*-benzyloxycarbonyl amino acid was used without further purification. Amino acid (3.69 mmol) and triethylamine (4 equiv, 2.0 mL) were dissolved in dry dichloromethane (37 mL). The solution was cooled to −20 °C under argon and *iso*-butylchloroformate (1 equiv, 0.49 mL) was added dropwise. The reaction mixture was stirred for 1 h at −20 °C, and then at 0 °C for additional 1 h. A solution of aminoester hydrochloride (3.32 mmol), prepared parallel by hydrogenolysis of *N*-benzyloxycarbonyl aminoester (3.32 mmol) in methanolic solution of hydrogen chloride (3.5 mmol) over 5% Pd-C; was added in dry CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to warm up and was kept at room temperature overnight. Solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate (0.17 L), washed with water (2× 50 mL), brine (30 mL) and dried over anhydrous magnesium sulfate. Purification by column chromatography afforded pure amide as a colourless oil.

4.4.1. (2*S*,9*R*,12*S*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-19-(benzyloxycarbonylamino)-9-metylo-11-oksononadecanoic acid methyl ester (15a). Prepared from acid **14d** and amine **13a** in yield 93%; $[\alpha]_D^{20}$ −67.6 (*c* 0.80 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.57 (d, 1H, *J*= 8.7 Hz; N*H*), 7.37–7.28 (m, 5H; C_6H_5), 5.08 (br s, 2H; CH_2Ph), 4.92 (br s, 1H; N*H*), 4.13–4.03 (m, 1H; C*H*CH_3), 3.68 (s, 3H; OCH_3), 3.32–3.12 (m, 4H), 3.11 (dd, 1H, J_1= 6.0 Hz, J_2=8.8 Hz; C*H*CO), 2.95 (dd, 1H, J_1=5.3 Hz, J_2= 9.8 Hz; C*H*CO_2), 2.84 (dt, 1H, J_1=8.0 Hz, J_2=12.1 Hz), 2.67–2.55 (m, 1H), 2.47–2.32 (m, 2H), 2.30–2.21 (m, 2H), 2.20–2.04 (m, 2H), 1.93–1.53 (m, 10H), 1.13 (d, 3H, *J*= 6.6 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ= 174.7, 173.9, 156.4, 136.6, 128.5, 128.4, 128.0, 68.1, 66.5, 66.2, 53.9, 53.4, 53.2, 51.8, 51.5, 43.2, 39.2, 34.6, 30.6, 29.3, 29.2, 24.0, 23.1, 20.3; IR ($CHCl_3$): ν=3680, 3452, 3326, 2974, 2815, 1720, 1655, 1517, 1455 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{26}H_{41}N_4O_5$ [M+H^+]: 489.3071; found 489.3120.

4.4.2. (2*S*,9*R*,12*S*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-9-benzylo-19-(benzyloxycarbonylamino)-11-oksononadecanoic acid methyl ester (15b, 76%). Prepared from acid **14d** and amine **13b** in 76% yield; $[\alpha]_D^{20}$ −58.6 (*c* 0.84 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): 7.61 (d, 1H, *J*=8.8 Hz; CON*H*), 7.38–7.17 (m, 10H; 2×C_6H_5), 5.11 (d_{AB}, 2H, J_{AB}=12.1 Hz, δ_{AB}=18.4 Hz; OCH_2Ph), 5.03 (br s, 1H; CO_2N*H*), 4.38–4.30 (m, 1H; C*H*CH_2Ph), 3.72 (s, 3H; OCH_3), 3.24–3.05 (m, 5H; CH_2NH, 2×NC*H*H, C*H*CO), 2.95–2.85 (m, 4H; CH_2Ph, NC*H*H, C*H*CO_2), 2.52–2.43 (m, 1H; NC*H*H), 2.42–2.36 (m, 1H; NCH*H*), 2.34–2.21 (m, 3H; 3×NCH*H*), 2.20–2.07 (m, 2H; C*H*H), 1.96–1.50 (m, 10H; 4×CH_2, 2×CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 174.1, 156.4, 138.4, 136.6, 129.2, 128.5, 128.3, 128.2, 128.0, 126.2, 68.1, 66.6, 66.2, 53.9, 53.5, 53.2, 51.8, 51.7, 48.1, 40.2, 39.2, 32.1, 30.6, 29.3, 29.1, 24.0, 23.1; IR ($CHCl_3$): ν=3452, 3321, 2954, 2816, 1719, 1656, 1515, 1456 cm^{-1}; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{32}H_{45}N_4O_5$ [M+H^+]: 565.3384; found 565.3412; elemental analysis calcd (%): C 68.08, H 7.80, N 9.93; found: C 67.82, H 8.02, N 9.66.

4.4.3. (2*S*,9*S*,12*S*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-19-(benzyloxycarbonylamino)-11-okso-9-(2′-propylo) nonadecanoic acid methyl ester (15c). Prepared from acid **14d** and amine **13c** in 88% yield; $[\alpha]_D^{20}$ −67.7 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.37–7.29 (m, 5H; C_6H_5), 5.12–5.05 (m, 3H; N*H*, CH_2Ph), 4.99 (br s, 1H; N*H*), 3.79–3.72 (m, 1H; NHC*H*), 3.70 (s, 3H; OCH_3), 3.31–3.14 (m, 4H; NHCH_2, 2×NC*H*H), 3.10 (dd, 1H, J_1= 5.8 Hz, J_2=8.8 Hz; C*H*CO), 3.01 (dd, 1H, J_1=5.1 Hz, J_2= 9.7 Hz; C*H*CO), 2.76–2.65 (m, 2H; 2×NC*H*H), 2.43–2.33 (m, 2H; 2×NCH*H*), 2.31–2.23 (m, 2H; 2×NCH*H*), 2.21–2.05 (m, 2H; 2×C*H*H), 1.96–1.65 (m, 10H; 2×CH*H*, 3× CH_2, C*H*H, C*H*), 1.59–1.50 (m, 1H; CH*H*), 0.87 (s, 3H; CH_3), 0.86 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.8, 174.1, 156.4, 136.6, 128.5, 128.1, 128.0, 68.4, 66.6, 66.2, 53.9, 53.7, 53.5, 52.3, 52.2, 51.8, 39.3,

31.7, 31.1, 30.6, 29.6, 29.4, 24.1, 23.2, 19.2, 18.4; IR ($CHCl_3$): ν=3454, 3330, 2963, 2816, 1722, 1657, 1516, 1456 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{28}H_{45}N_4O_5$ [M+H$^+$] 517.3384; found: 517.3406.

4.4.4. (2*S*,9*R*,12*S*,19*R*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-19-(benzyloxycarbonylamino)-9-metylo-11-okso-icosanoic acid methyl ester (15d). Prepared from acid **14a** and amine **13a** in 87% yield; $[\alpha]_D^{20}$ −64.9 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.64 (d, 1H, *J*=8.1 Hz; N*H*), 7.37–7.29 (m, 5H; C_6H_5), 5.07 (br s, 2H; CH_2Ph), 4.92 (br s, 1H; N*H*), 4.11–4.04 (m, 1H; C*H*CH_3), 3.76–3.65 (m, 4H; C*H*CH_3, OCH_3), 3.21–3.16 (m, 1H), 3.13–3.07 (m, 2H), 2.99–2.92 (m, 1H), 2.89–2.81 (m, 1H), 2.64–2.54 (m, 1H), 2.53–2.46 (m, 1H), 2.38–2.22 (m, 3H), 2.20–2.06 (m, 2H), 1.92–1.54 (m, 10H), 1.16 (d, 3H, *J*=6.5 Hz; CH_3), 1.12 (d, 3H, *J*=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.6, 174.2, 155.8, 136.6, 128.5, 128.0, 67.7, 66.4, 66.3, 54.4, 53.4, 52.9, 51.8, 51.5, 45.7, 43.2, 36.2, 34.4, 30.8, 29.4, 24.1, 23.0, 21.5, 20.1; IR ($CHCl_3$): ν=3439, 3323, 2974, 2815, 1718, 1655, 1514, 1455 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{27}H_{43}N_4O_5$ [M+H$^+$] 503.3228; found: 503.3236; elemental analysis calcd (%): C 64.54, H 8.37, N 11.16; found: C 64.24, H 8.48, N 11.17.

4.4.5. (2*S*,9*R*,12*S*,19*R*)-2,6-Cyclo-12,16-cyclo-6,10,16-triaza-9-benzylo-19-benzyloxycarbonyl-amino)-20-phenylo-11-oksoicosanoic acid methyl ester (15e). Prepared form acid **14b** and amine **13b** in 75% yield; $[\alpha]_D^{20}$ −49.1 (*c* 0.85 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): 7.64 (d, 1H, *J*=9.7 Hz; CON*H*), 7.35–7.11 (m, 15H; 3×C_6H_5), 5.04 (d_{AB}, 2H, J_{AB}=12.3 Hz, δ_{AB}=30.5 Hz; OCH_2Ph), 4.84 (d, 1H, *J*=8.4 Hz; CO_2N*H*), 4.28–4.21 (m, 1H; C*H*CH_2Ph), 3.88–3.81 (m, 1H; C*H*CH_2Ph), 3.66 (s, 3H; OCH_3), 3.17–3.11 (m, 1H; NC*H*H), 3.06 (dd, 1H, J_1=6.1 Hz, J_2=8.5 Hz; C*H*CO_2), 3.02–2.97 (m, 1H; NC*H*H), 2.92 (dd, 1H, J_1=4.2 Hz, J_2=9.7 Hz; C*H*CO), 2.86–2.70 (m, 5H; 2×CH_2Ph, NC*H*H), 2.57–2.48 (m, 1H; NC*H*H), 2.47–2.40 (m, 1H; NCH*H*), 2.37–2.31 (m, 1H; NCH*H*), 2.34–2.17 (m, 2H; 2×NCH*H*), 2.14–2.03 (m, 2H; 2×C*H*H), 1.91–1.47 (m, 10H; 4×CH_2, 2×C*H*H); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.7, 174.3, 155.9, 138.5, 137.7, 136.6, 129.4, 129.2, 128.5, 128.4, 128.3, 128.1, 128.0, 126.5, 126.3, 67.6, 66.5, 66.3, 54.3, 53.5, 52.9, 51.8, 51.7, 50.9, 48.5, 41.6, 40.4, 33.2, 31.6, 30.8, 29.4, 24.2, 23.1; IR ($CHCl_3$): ν=3434, 3322, 2956, 2816, 1736, 1720, 1656, 1512, 1456, 1404, 1347 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{39}H_{51}N_4O_5$ [M+H$^+$] 655.3854; found: 655.3860.

4.4.6. (2*S*,9*S*,12*S*,19*S*)-2,6-Cyclo-12,16-cyclo–6,10,16-triaza-19-(benzyloxycarbonylamino)-20-metylo-11-okso-9-(2′-propylo)henicosanoic acid methyl ester (15f). Prepared from acid **14c** and amine **13c** in 93% yield; mp 64–66 °C; $[\alpha]_D^{20}$ −69.3 (*c* 0.70 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=7.41 (d, 1H, *J*=10.1 Hz; N*H*), 7.37–7.29 (m, 5H; C_6H_5), 5.08 (br s, 2H; CH_2Ph), 4.68 (d, 1H, *J*=9.7 Hz; N*H*), 3.77–3.71 (m, 1H; NHC*H*), 3.70 (s, 3H; OCH_3), 3.52–3.46 (m, 1H; NHC*H*), 3.20–3.15 (m, 1H; NC*H*H), 3.15–3.09 (m, 2H; NC*H*H, C*H*CO), 3.04 (dd, 1H, J_1=4.5 Hz, J_2=10.1 Hz; C*H*CO), 2.74–2.67 (m, 1H; NC*H*H), 2.65 (dt, 1H, J_1=5.6 Hz, J_2=11.5 Hz; NC*H*H), 2.52 (dt, 1H, J_1=4.4 Hz, J_2=11.5 Hz; NCH*H*), 2.41–2.33 (m, 1H; NCH*H*), 2.33–2.26 (m, 2H; 2×NCH*H*), 2.19–2.05 (m, 2H; 2×C*H*H), 1.94–1.51 (m, 12H; 2×CH*H*, 4×CH_2, 2×C*H*), 0.91–0.85 (m, 12H, 4×CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.8, 174.4, 156.3, 136.6, 128.5, 128.1, 128.0, 67.8, 66.6, 66.2, 54.9, 54.4, 53.9, 53.5, 52.4, 52.2, 51.8, 32.2, 32.1, 31.9, 31.2, 30.8, 29.5, 24.3, 23.2, 19.2, 18.9, 18.3, 17.6; IR (KBr): ν=3276, 2960, 2811, 1741, 1724, 1636, 1523, 1455 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{31}H_{51}N_4O_5$ [M+H$^+$] 559.3854; found: 559.3858; elemental analysis calcd (%): C 66.55, H 8.96, N 10.04; found: C 66.56, H 9.05, N 9.98.

4.5. Macrocyclization procedures

N-Cbz-protected aminoesters **15a–f** were subjected to catalytic hydrogenation (H_2 over Pd-C in methanol) prior to cyclization reactions. The aminoester (1.90 mmol), obtained from **15a–f**, was dissolved in 0.5 M NaOH solution in methanol (0.20 L), and allowed to stand at room temperature for 1 day. The reaction mixture was neutralized with aq HCl and evaporated to dryness. The solid residue was dissolved in water (20 mL) and extracted with $CHCl_3$ (4×20 mL). The combined chloroform extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by column chromatographic (CH_2Cl_2/methanol=19:1) followed by a recrystallization. Details of other macrocyclization procedures were described in our previous work.[13b]

4.5.1. (4*R*,7*S*,17*S*)-1,5,11,15-Tetraaza-4-methyltricyclo[15.3.0.0.^{7,11}]icosan-6,16-dion (2a) Recrystallization from CH_2Cl_2/hexane yielded **2a** as colourless crystals; mp 140–141 °C; $[\alpha]_D^{20}$ −53.4 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.45 (br s, 1H; N*H*), 8.36 (br s, 1H; N*H*), 4.09–4.01 (m, 1H; C*H*CH_3), 3.74–3.67 (m, 1H), 3.31–3.24 (m, 2H), 3.14–3.03 (m, 2H), 3.00 (dd, 1H, J_1=9.8 Hz, J_2=5.4 Hz; C*H*CO), 2.91 (dd, 1H, J_1=9.3 Hz, J_2=5.8 Hz; C*H*CO), 2.86–2.80 (m, 1H), 2.55 (dt, 1H, J_1=12.4 Hz, J_2=3.5 Hz), (ddd, 1H, J_1=12.8 Hz, J_2=5.0 Hz, J_3=2.3 Hz), 2.28–2.17 (m, 4H), 1.93–1.71 (m, 9H), 1.58 (ddt, 1H, J_1=15.2 Hz, J_2=5.0 Hz, J_3=1.6 Hz), 1.20 (d, 3H, *J*=6.6 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.8, 173.9, 70.5, 70.0, 56.3, 53.6, 53.4, 52.0, 44.9, 40.4, 31.2, 30.6, 30.5, 25.2, 24.2, 23.8, 19.2; IR ($CHCl_3$): ν=3678, 3325, 2822, 1654, 1530, 1471 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{17}H_{30}N_4O_2Na$ [M+Na$^+$] 345.2261; found: 345.2283.

4.5.2. (4*R*,7*S*,17*S*)-1,5,11,15-Tetraaza-4-benzylotricyclo[15.3.0.0.^{7,11}]icosan-6,16-dion (2b) Recrystallization from CH_2Cl_2/ether yielded **2b** as colourless crystals; mp 184–188 °C; $[\alpha]_D^{20}$ −71.5 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.13 (br s, 1H; N*H*), 8.08 (br s, 1H; N*H*), 7.30–7.18 (m, 5H; C_6H_5), 4.01–3.93 (m, 1H; NHC*H*), 3.55–3.47 (m, 1H; NHC*H*H), 3.26–3.16 (m, 4H; NHCH*H*, 2×NC*H*H, C*H*HPh), 3.07–2.97 (m, 2H; C*H*CO, NC*H*H), 2.91 (dd, 1H, J_1=6.3 Hz, J_2=9.6 Hz; C*H*CO), 2.82 (dt, 1H, J_1=2.5 Hz, J_2=12.3 Hz; NC*H*H), 2.67 (dd, 1H, J_1=8.6 Hz, J_2=13.3 Hz; CH*H*Ph), 2.46 (dt, 1H, J_1=3.2 Hz, J_2=12.5 Hz; NCH*H*), 2.40–2.34 (m, 1H; NCH*H*), 2.26–2.15 (m, 4H; 2×NCH*H*, 2×CHC*H*H), 1.89–1.63 (m, 10H; 2×CHCH*H*, 4×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$,

30 °C): δ=174.7, 174.1, 138.8, 129.3, 128.4, 126.3, 70.2, 69.6, 54.9, 53.4, 53.1, 52.2, 51.3, 39.2, 39.0, 30.5, 30.4, 28.0, 25.3, 24.1, 23.8; IR ($CHCl_3$): ν=3323, 2821, 1658, 1528, 1443 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{23}H_{35}N_4O_2$ [M+H$^+$] 399.2755; found: 399.2764; elemental analysis calcd (%) C 69.35, H 8.54, N: 14.07; found: C 69.33, H 8.51, N 13.87.

4.5.3. (4*R*,7*S*,17*S*)-1,5,11,15-Tetraaza-4-(2′-propylo)tricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2c) Recrystallization from CH_2Cl_2/hexane yielded **2c** as colourless crystals; mp 185–187 °C; $[\alpha]_D^{20}$ −76.4 (*c* 0.50 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.13 (br s, 1H; N*H*), 8.94 (br s, 1H; N*H*), 3.59–3.48 (m, 2H; NHC*H*H, NHC*H*), 3.31–3.16 (m, 3H; NHCH*H*, 2×NC*H*H), 3.03 (dd, 1H, J_1=4.6 Hz, J_2=10.2 Hz; C*H*CO), 2.97–2.84 (m, 3H; 2×NC*H*H, C*H*CO), 2.53–2.42 (m, 2H; 2×NCH*H*), 2.29–2.15 (m, 4H; 2×NCH*H*, 2×CHC*H*H), 2.06–1.98 (m, 1H; $(CH_3)_2$C*H*), 1.91–1.69 (m, 10H; 2×CHCH*H*, 4×CH_2), 0.93 (d, 3H, J=6.8 Hz; CH_3), 0.88 (d, 3H, J=6.7 Hz; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=175.3, 173.4, 70.2, 69.3, 55.2, 55.0, 54.0, 53.2, 52.9, 39.5, 30.8, 30.7, 30.3, 27.1, 25.3, 24.5, 23.7, 20.1, 19.2; IR (KBr): ν=3364, 3304, 2961, 2813, 2772, 1673, 1648, 1539, 1513, 1435 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{19}H_{35}N_4O_2$ [M+H$^+$] 351.2755; found: 351.2781; elemental analysis calcd (%): C 65.14, H 9.71, N 16.00; found: C 64.90, H 9.87, N 15.83.

4.5.4. (4*R*,7*S*,14*R*,17*S*)-1,5,11,15-Tetraaza-4,14-dimethyltricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2d) Recrystallization from CH_2Cl_2/ether/hexane yielded **2d** as colourless crystals; mp decomposition at 222 °C; $[\alpha]_D^{20}$ −83.8 (*c* 0.25 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.72 (br s, 2H; 2×N*H*), 4.16–4.08 (m, 2H; 2×C*H*CH_3), 3.32–3.27 (m, 2H), 3.11 (dt, 2H, J_1=12.6 Hz, J_2=1.3 Hz), 2.96 (dd, 2H, J_1=5.8 Hz, J_2=9.6 Hz), 2.41 (ddd, 2H, J_1=12.8 Hz, J_2=5.2 Hz, J_3=1.9 Hz), 2.29–2.18 (m, 4H), 1.99–1.69 (m, 8H), 1.51–1.45 (m, 2H), 1.22 (d, 6H, J=6.6 Hz; 2×CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.0, 70.5, 53.6, 51.9, 44.9, 31.0, 30.8, 24.0, 19.3; IR (KBr): ν=3437, 3298, 2962, 2771, 1647, 1545, 1444 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{18}H_{33}N_4O_2$ [M+H$^+$] 337.2598; found: 337.2608.

4.5.5. (4*R*,7*S*,14*R*,17*S*)-1,5,11,15-Tetraaza-4,14-dibenzylotricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2e) $[\alpha]_D^{20}$ −35.3 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ= 8.52 (br s, 2H; 2×N*H*), 4.30–4.18 (m, 10H; 2×C_6H_5), 4.01 (br s, 2H; 2×NHC*H*), 3.35 (dd, 2H, J_1=5.5 Hz, J_2= 13.2 Hz; 2×C*H*HPh), 3.21 (t, 2H, J=7.7 Hz; 2×NC*H*H), 3.16–3.07 (m, 2H; 2×NC*H*H), 2.98 (dd, 2H, J_1=6.0 Hz, J_2=9.5 Hz, 2×C*H*CO), 2.68 (dd, 2H, J_1=9.7 Hz, J_2= 13.2 Hz; 2×CH*H*Ph), 2.37 (dt, 2H, J_1=3.3 Hz, J_2= 12.7 Hz; 2×NCH*H*), 2.29–2.21 (m, 2H; 2×CHC*H*H), 2.21–2.14 (m, 2H; 2×NCH*H*), 1.90–1.76 (m, 4H; 2× CHCH*H*, 2×C*H*H), 1.76–1.66 (m, 6H; 2×CH*H*, 2×CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=174.3, 138.8, 129.3, 128.5, 126.3, 70.3, 53.2, 51.9, 51.4, 39.0, 30.6, 27.1, 23.9; IR ($CHCl_3$): ν=3288, 3066, 1674, 1541, 1455 cm^{-1}; MS (HR ESI, MeOH): *m/z* calcd for $C_{30}H_{41}N_4O_2$ [M+H$^+$]: 489.3224; found: 489.3231.

4.5.6. (4*S*,7*S*,14*S*,17*S*)-1,5,11,15-Tetraaza-4,14-bis-(2′-propylo)tricyclo[15.3.0.0.[7,11]]icosan-6,16-dion (2f) ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=8.08 (br s, 2H; 2× N*H*), 3.44–3.29 (m, 2H; 2×C*H*CO), 3.23–3.18 (m, 2H; 2× NC*H*H), 3.05–2.93 (m, 4H; 2×NHC*H*, 2×NC*H*H), 2.45–2.36 (m, 2H; 2×NCH*H*), 2.26–2.16 (m, 4H; 2×NCH*H*, 2×CHC*H*H), 2.10–1.96 (m, 4H; 2×C*H*H, 2×$(CH_3)_2$C*H*), 1.90–1.61 (m, 8H; 2×CHCH*H*, 2×CH*H*, 2×CH_2), 0.96 (d, 6H, J=6.7 Hz; 2×CH_3), 0.91 (d, 6H, J=6.7 Hz; 2× CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=173.9, 69.8, 55.3, 53.3, 52.4, 31.0, 30.5, 27.6, 24.1, 20.6, 19.9; MS (HR ESI, MeOH): *m/z* calcd for $C_{22}H_{40}N_4O_2Na$ [M+Na$^+$]: 415.3043; found: 415.3050.

4.6. Preparation of complexes

Equimolar amount of diamide **2a–d** or **1b** and $Ni(OAc)_2$ or $Cu(OAc)_2$ were dissolved in methanol. The formed bright green solution is stirred at boiling temperature for about 5 min. During the heating colour of solution is changing from green to dark red or violet and acetic acid is evaporating. Solvents were evaporated and prepared complexes were crystallized from methanol/ether.

4.6.1. Complex Ni·1b. Mp 247 °C; $[\alpha]_D^{20}$ −294 (*c* 0.047 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ=4.79–4.73 (m, 2H; 2×NC*H*H), 3.30–3.23 (m, 4H; 2×NCH*H*, 2× C*H*CO), 2.99 (dt, 2H, J_1=14.1 Hz, J_2=4.0 Hz; 2× NC*H*H), 2.78–2.70 (m, 2H; 2×NC*H*H), 2.28–2.21 (m, 2H; 2×NCH*H*), 2.19–2.21 (m, 2H; 2×NCH*H*), 2.07–1.95 (m, 4H; 2×CHCH_2), 1.93–1.82 (m, 4H; 2×CH_2), 1.64–1.57 (m, 2H; 2×C*H*H), 1.49–1.39 (m, 2H; 2×CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 30 °C): δ=178.6, 74.4, 57.3, 55.7, 40.4, 26.5, 24.8, 21.2; IR (KBr): ν=3442, 3382, 2937, 2848, 1573, 1420 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$=570 (80), 480 (180), 210 (15,200), 240 nm (15,600 L cm^{-1} mol^{-1}); MS (HR LSIMS): *m/z* calcd for $C_{16}H_{27}N_4O_2Ni$ [M+H$^+$]: 364.1409; found: 364.1383.

4.6.2. Complex Cu·1b. Mp 215–217 °C; $[\alpha]_D^{20}$ +920 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3452, 2929, 2854, 1576, 1448, 1407 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$=493 (530), 269 (8400), 213 (32,000 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd for $C_{16}H_{26}N_4O_2CuNa$ [M+Na$^+$]: 392.1244; found 392.1236.

4.6.3. Complex Cu·2a. Mp 228–230 °C; $[\alpha]_D^{20}$ +308 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3432, 2962, 2887, 1576, 1444, 1405, 1333, 1300 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$= 497 (300), 270 (3600), 215 (15,000 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd for $C_{17}H_{28}N_4O_2NaCu$ [M+ Na$^+$]: 406.1400; found 406.1428.

4.6.4. Complex Cu·2b. Mp 90 °C; $[\alpha]_D^{20}$ +838 (*c* 0.14 in $CHCl_3$); IR ($CHCl_3$): ν=3667, 3363, 2979, 2858, 1582, 1453, 1404 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$=493 (300), 268 (3800), 212 (20,000 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd for $C_{23}H_{33}N_4O_2Cu$ [M+H$^+$]: 460.1894; found: 460.1894.

4.6.5. Complex Cu·2c. Mp 198–200 °C; $[\alpha]_D^{20}$ +480 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3482, 3393, 2953, 2860, 1586, 1571, 1450, 1397 cm^{-1}; UV/vis (EtOH): $\lambda_{max}(\varepsilon)$= 504 (350), 301 (3800), 270 (4200), 214 nm (18,500 L cm^{-1} mol^{-1}); MS (HR ESI, MeOH): *m/z* calcd

for: $C_{19}H_{32}N_4O_2NaCu$ $[M+Na^+]$ 434.1713; found: 434.1735.

4.6.6. Complex Cu·2d. Mp decomposition at 260 °C; $[\alpha]_D^{20}$ +590 (*c* 0.10 in $CHCl_3$); IR (KBr): ν=3453, 2960, 2926, 2861, 1578, 1439, 1401 cm^{-1}; UV/vis (EtOH): λ_{max}=500, 272, 215 nm; MS (HR ESI, MeOH): *m*/*z* calcd for $C_{18}H_{31}N_4O_2Cu$ $[M+H^+]$: 398.1738; found: 398.1756.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.049. Supplementary data available: synthesis of compounds **6** to **11**, and crystallographic details.

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Synthesis of *n*-chloroquinolines and *n*-ethynylquinolines (*n* = 2, 4, 8): homo and heterocoupling reactions

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Abstract—The *n*-(ethynyl)quinolines were satisfactorily prepared by heterocoupling reaction between the appropriate *n*-chloroquinoline and 2-methyl-3-butyn-2-ol, catalyzed by palladium, followed by treatment with a catalytic amount of powdered sodium hydroxide in toluene. The *n*-(ethynyl)quinolines were transformed in the corresponding conjugate 1,4-bis[*n*′-(quinolyl)]buta-1,3-diynes by oxidative dimerization, catalyzed by cuprous chloride, with excellent yields. Moreover, the heterocoupling between *n*′-haloquinoline and *n*′-(ethynyl)quinoline (*n*′, 2′ or 3′), catalyzed by palladium, gives 2′,2′-bis(quinoline) or 1,2-di(3′-quinolyl)ethyne, respectively. The same coupling reaction with zerovalent nickel complexes, gives a mixture of 1,2,4- and 1,3,5-tri(*n*′-quinolyl)benzene.

1. Introduction

Earlier, some chloroquinolines had been synthesized as antimalarial precursors,[1] and more recently it has been reported that the 4-aminoquinoline nucleus in chloroquine and related antimalarials having the 7-chloro group act by complexing ferriprotoporphyrin IX.[2] However, quinolines have not been used for the preparation of molecular organic compounds,[3] although some quinoline derivatives are good candidates to form part of new materials with conductive and optical properties.

The use of molecular organic materials as conductors and in nonlinear optics is of considerable interest since such materials have inherent synthetic flexibility, which permits the design of specific molecular properties.[4] In this way, the solid state polymerization of 1,3-diynes to form crystalline conjugated polydiynes has attracted much attention,[5] although many of them are inactive in the solid state, they do undergo liquid crystal polymerization.[6]

Here we describe an efficient synthesis of the 2-, 3-, and 4-quinolylacetylene units (**11**–**14**), the oxidative dimerization to 1,4-bis(*n*-quinolyl)buta-1,3-diyne (**4a**–**c**), their structural thermal analysis and their catalysed coupling reactions. The acetylene derivatives (**11**–**14**) were also obtained for the synthesis of π-conjugated polyenes and furthermore, serve for the synthesis of nanostructures containing those useful units.[7] Poly(vinylquinolines) and their fluorescence properties have been previously reported.[8]

2. Results and discussion

Conjugated ethynyl derivatives having a heterocyclic ring such as pyridine has been reported,[7] and we are now interested in the synthesis and structural analysis of conjugated ethynylquinolines as starting units to prepare molecular networks.

2.1. *n*-(Ethynyl)quinolines

The conjugated *n*-(ethynyl)quinolines (**11**–**14**) (*n* = 2, 3, 4) were satisfactory obtained by cross-coupling reaction between the appropriate *n*-chloroquinoline (compounds **1**, **2**, **6**) and 2-methyl-3-butyn-2-ol catalysed by the palladium–copper system (Sonogashira method).[9a] A modification on the hydrolysis treatment of the crude reaction products was employed,[10] which consists in the incorporation of a small amount of potassium cyanide to a saturated ammonium chloride aqueous solution that permits the pure isolation of the corresponding 2-methyl-4-(*n*′-quinolyl)-3-butyn-2-ol in good to practically quantitative yield. The potassium cyanide avoids the quinoline–palladium complexes separation. The cross-coupling reaction with 3-chloroquinoline fails while 3-bromoquinoline was used with excellent results.[10] However, 2-chloroquinoline was recently used in carbonylation reactions catalysed by palladium.[11]

Keywords: Chloroquinolines; Ethynylquinolines; 1,3-Butadiynes; Homocoupling; Heterocoupling.
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Finally, the *n*-ethynylquinolines were obtained by treatment of the corresponding 2-methyl-4-(*n'*-quinolyl)-3-butyn-2-ol with catalytic amounts of powdered sodium hydroxide (10–15% mol), in toluene at the reflux temperature, in good to excellent yields (**11**–**13**), in short reaction times (half to 4 h), (Scheme 1). The purification of the *n*-ethynylquinolines was carried out by silica gel column chromatography (**11**, **14**) or by sublimation in a cold-finger surface, giving a microcrystalline white solid (**12**, **13**). We have also used the purification by sublimation in the preparation of the ethynylpyridines.[10]

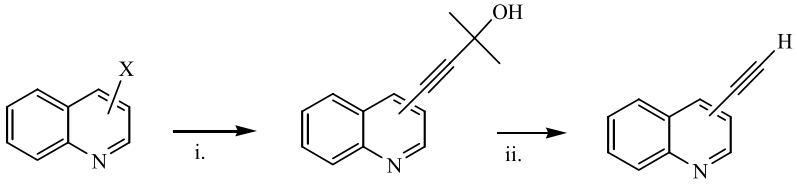
2.2. *n*-Chloroquinolines

The starting 2-chloro (**1**) and 4-chloro (**2**) quinolines were prepared by reaction of anhydrous quinoline-*N*-oxide,[3] with phosphoryl trichloride,[12] yielding a mixture of both isomers, which were isolated by chromatography as yellow solids (47 and 32%, respectively), (Scheme 2).

The 2,8-dichloroquinoline (**6**) was obtained by reaction of anhydrous 8-chloroquinoline-*N*-oxide with phosphoryl trichloride, as the unique product, in moderate yield (52%), while 4,8-dichloroquinoline was detected only as traces in the crude product. Hence, the high regiospecificity of the reaction was due to the serious sterical hindrance of the chloro atom in position 8, although the reaction can be interpreted through an oxyphosphorane adduct anion in a rapid concerted mechanism, Scheme 2.

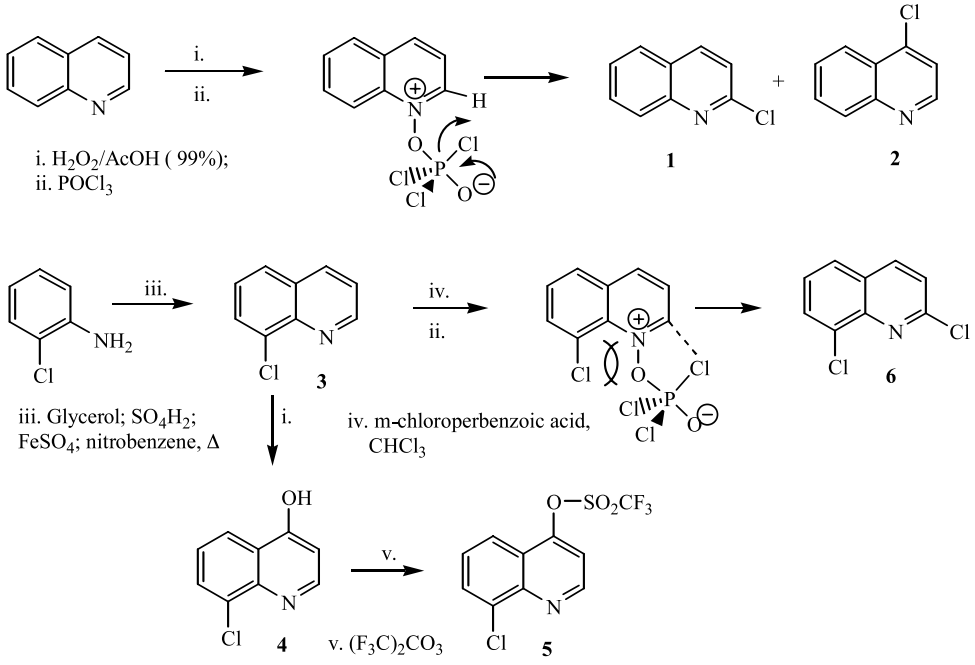
The starting 8-chloroquinoline (**3**) was prepared by the Skraup synthesis between *o*-chloroaniline and 1,2,3-trihydroxypropane catalysed by sulfuric acid, in good yield (78%).[13] The structure of **3** was confirmed by ^{1}H NMR spectrum, which shows unequivocally the H-2 and H-4 protons at 8.97 and 8.09 ppm with *ortho* and *meta* coupling constants (J=4.3, 1.6 Hz and J=8.6, 1.6 Hz, respectively).

A remarkable fact takes place in the preparation of 8-chloroquinoline-*N*-oxide under the same conditions used for the preparation of quinoline-*N*-oxide. 8-chloro-4-hydroxyquinoline (**4**) was obtained in good yield (62%) as the unique transformation product, which mechanism probably proceeds by *N*-protonation followed by water



X= 2-Cl **1**	**7**	n,2		92%	**11**	n,2		91%
X= 3-Br	**8**	n,3		97%	**12**	n,3		95%
X= 4-Cl **2**;	**9**	n,4		86%	**13**	n,4		86%
X= 2-Cl,8-Cl **6**	**10**	n,2	8-Cl	91%	**14**	n,2	8-Cl	65%

Scheme 1.



Scheme 2.

addition, (Scheme 2). The 4-hydroxyquinoline was treated with triflic anhydride yielding the triflate derivative (mp 108–110 °C), which confirms the 4-hydroxyquinoline structure (Scheme 2).

The 8-chloroquinoline-*N*-oxide was obtained by reaction of 8-chloroquinoline with *m*-chloroperbenzoic acid in chloroform with low yield (32%) but, the untransformed starting quinoline was completely recovered.

2.3. 1,4-Di(*n*-quinolyl)-1,3-butadiynes

To increase the π-extended conjugation of the *n*-ethynylquinolines carried out was the catalytic oxidative dimerization to the 1,4-di(*n*-quinolyl)-1,3-butadiynes. Recognized earlier was the oxidative coupling dimerization of the terminal acetylenes in the presence of cupric salts in pyridine, giving symmetric conjugate 1,3-diynes in good yields (Eglinton reaction).[14] A modified method using catalytic amounts of cuprous and ammonium salts in the presence of an oxidizing agent, also provides good yields (Glaser reaction) because of the triple bond oxidative specificity.[14]

Recently, been proposed is a mechanism for the reaction, which takes into account the Cu(I)/O_2 interaction and the easy redox interconversion Cu(I)/Cu(III),[15] as intermediates in the homocoupling reaction.

2.4. 1,4-Di(*n′*-quinolyl)-1,3-butadiyne (15–18)

The oxidative dimerization of *n*-ethynylquinolines (**11**–**14**) under the Glaser conditions, in the presence of catalytic amounts of cuprous chloride, pyridine as the base was carried out at 40 °C, under oxygen atmosphere, giving 1,4-di(*n′*-quinolyl)-1,3-butadiyne (**15**–**18**), which were isolated as microcrystalline white powder, in good to excellent yield, (Scheme 3).

The 1,3-butadiynes **15**–**17** are photosensitive to the sunlight and decompose, with the darkness of the samples, near to the melting point, which were determined by differential scanner calorimetry (DSC).[16]

2.5. 1,4-Di(3′-quinolyl)-1,3-butadiyne (16)

Oxidative dimerization of compound **12** affords 1,4-di(3′-quinolyl)-1,3-butadiyne (**16**) (80%). Crystals of **16** were photosensitive to the sunlight and under exposure turn to insoluble deep-blue crystals. A crystalline powder sample of compound **16**, after sunlight exposure for 2 days, was analysed by mass spectrometry, using the MALDI-TOF technique.

Thus, a mixture of topooligomers were detected by complete volatilization of the sample, in the following distribution: 1,3-diyne monomer **16**, 42.4%; 1,3-diyne dimer 31.4%; 1,3-diyne trimer 22.7%; 1,3-diyne tetramer 3.2%; 1,3-diyne pentamer 0.3%; and 1,3-diyne hexamer in traces.

2.6. 1,4-Di(4′-quinolyl)-1,3-butadiyne (17)

Oxidative coupling of compound **13** affords 1,4-di(4′-quinolyl)-1,3-butadiyne (**17**) in practically quantitative yield (97%). The diyne **17** shows a clear melting point at 215–216 °C.

2.7. 1,4-Di[2′-(8′-chloroquinolyl)]-1,3-butadiyne (18)

The oxidative dimerization of compound **14** affords 1,4-di[2′-(8′-chloroquinolyl)]-1,3-butadiyne (**18**) (30%), (Scheme 3), but all of the untransformed starting product was recovered. The presence of the 8′-chloro atoms in the 1,3-butadiyne **18** produce a clear melting point at 212–214 °C and stability under sunlight exposure.

2.8. Structural analysis of the 1,4-di(*n′*-quinolyl)-1,3-butadiynes 15–18

The 1,3-butadiynes **15**–**18** in the ^{1}H NMR spectrum show the characteristic pyridine proton signals as doublets. Thus, H-3, H-4 and H-2, H-4 appears for compound **15** at 7.57 and 8.16 ppm (J=8.6 Hz); compound **16** at 9.00 and 8.37 ppm (J=1.9 Hz); compound **17** at 8.81 and 7.61 ppm (J=3.9 Hz); and compound **18** at 7.46 and 8.30 ppm (J=8.6 Hz), respectively.

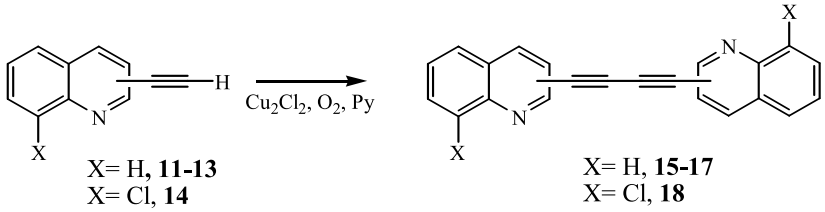
The mass spectrum of the 1,3-butadiynes **15**–**18** show the molecular as the base peak at 304 (372 for **18**) and the double charge M^{+2} molecular peak at 152 (186 for **18**) that is the following more significant in the spectrum and was characteristic of the 1,4-diaryl-1,3-butadiynes.[10]

2.9. Coupling reaction between *n*-haloquinolines and *n*-ethynylquinolines

The coupling between a *n*-haloquinoline and a *n*-ethynylquinoline catalyzed by palladium can give the 1,2-di(*n′*-quinolyl)ethynes, which can be used as starting compounds for the catalytic cyclotrimerization analysis to obtain the hexa-(*n*-quinolyl)benzene derivatives.

2.10. Coupling reaction between 2-chloroquinoline and 2-ethynylquinoline

The coupling between 2-chloroquinoline (**1**) and 2-ethynylquinoline (**11**) in presence of dichloro bis(triphenylphosphine)



Scheme 3.

palladium/cuprous iodide catalyst system, in diethylamine yields the homocoupled of **1** to 2,2′-bis(quinoline) **19** as the unique product, (Scheme 4).

However, the reaction between 2-chloroquinoline (**1**) and 2-ethynylquinoline (**11**), with dichloro bis(triphenylphosphine) nickel–zinc catalyst system, affords the cyclotrimerization of the acetylene **11**, giving a mixture of 1,3,5- (**20**) and 1,2,4-tris(2′-quinolyl)benzene (**21**) (43%) (64:36 molar ratio, respectively, by ^{1}H NMR), (Scheme 4).

2.11. Coupling reaction between 3-bromoquinoline and 3-ethynylquinoline (12)

The coupling between 3-bromoquinoline and 3-ethynylquinoline (**12**), catalyzed by the palladium–copper system, gives the heterocoupled 1,2-di(3′-quinolyl)ethyne (**22**) in good yield (70%), (Scheme 5). Compound **22** was a stable white crystalline solid, which shows fluorescence radiation emission in dichloromethane with two maxima at 354 and 371 (quantum yield Φ, 18%, referred to a solution of 2-aminopiridine).

Compound **22** was employed for the cyclotrimerization with several homogeneous catalyst systems, such as $Cl_2Pd(Ph_3P)_2$–$SiMe_3Cl$,[17] $V(acac)_3$–$AlEt_3$,[18] $Cl_2Ni(Ph_3P)_2$–Zn[19] and also with transfer phase agents, but in all the cases compound **22** was recovered untransformed, (Scheme 5).

However, the same coupling reaction between 3-bromoquinoline and acetylene **12** was also carried out with zerovalent nickel complexes[20–22] but only a mixture of 1,2,4-/1,3,5-tris(3′-quinolyl)benzene was obtained in good yield (80%).

3. Conclusions

2-Chloro, 4-chloro and 2,8-dichloroquinoline were especifically obtained by treatment of the corresponding dehydrated *N*-oxide with phosphoryl chloride in good yield. The ethynylquinolines can be efficiently obtained by heterocoupling with 2-methyl-3-butyn-2-ol catalyzed by palladium, followed of propanone elimination. In this way, 2-ethynyl-8-chloroquinoline was specifically isolated. The *n*-(ethynyl)quinolines can be transformed in the corresponding conjugate 1,4-bis[*n*′-(quinolyl)]buta-1,3-diynes in the presence of cuprous chloride catalyst, with excellent yields.

The heterocoupling between 2-chloroquinoline and 2-(ethynyl)quinoline, catalyzed by palladium, affords 2,2-bis(quinoline). However, the heterocoupling between 3-bromoquinoline and 3-(ethynyl)quinoline, catalyzed by palladium, affords to 1,2-di(3′-quinolyl)ethyne.

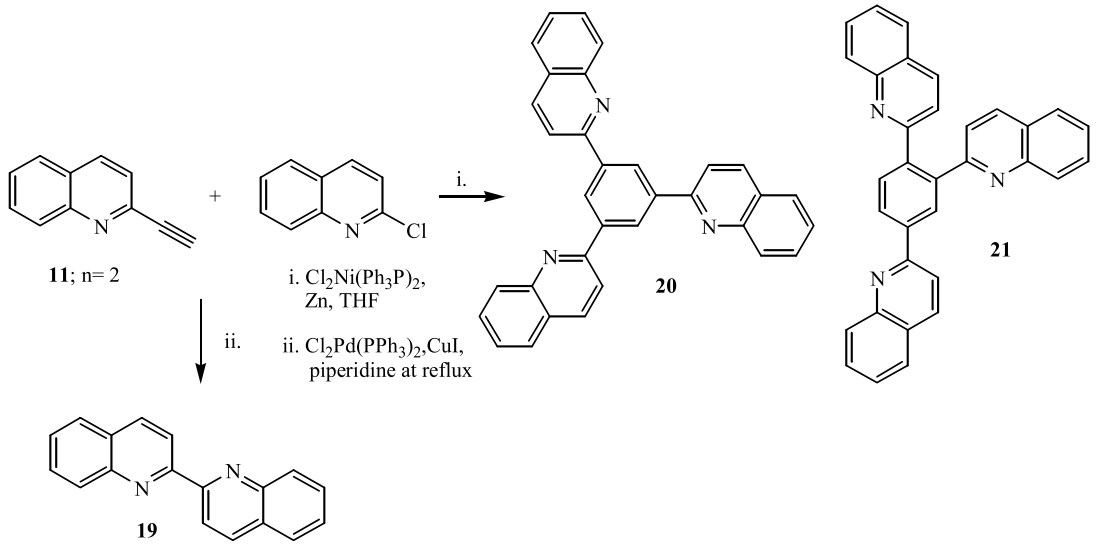
The coupling reaction between 2-chloroquinoline and 2-ethynylquinoline (or 3-bromoquinoline and 3-ethynylquinoline) with zerovalent nickel complexes, gives only a mixture of 1,2,4- and 1,3,5-tris(2′-quinolyl)benzene (or 1,2,4- and 1,3,5-tris(3′-quinolyl)benzene).

4. Experimental

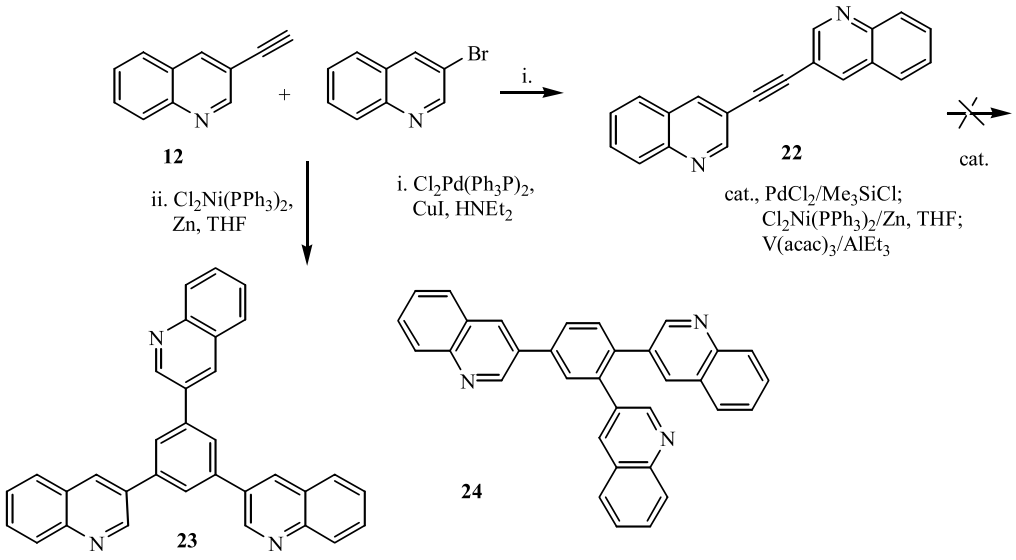
4.1. General methods

Melting points were determined using a Buchi or Reichert stage microscope and are uncorrected, the differential scanning calorimetric measures (DSC) were recorded using a Perkin–Elmer apparatus. IR spectra were recorded using a Bruker Vector 22 spectrophotometer, and the wave numbers are given in cm^{-1}. The ^{1}H NMR spectra were recorded using a Bruker Aspect spectrometer (200 or 300 MHz). Chemical shifts are given in δ with TMS as internal reference and constants coupling *J* are given in Hz. Mass spectra were recorded using a VG AutoSpec spectrometer and the MALDI-TOF spectra were recorded using a Bruker Reflex III spectrometer. UV–vis spectra were recorded using a Hewlett Packard 8453 spectrometer, frequency are given in nm and ε en L mol^{-1} cm^{-1}.Yields are given after chromatography column or solvent extraction.

4.1.1. 2-Chloroquinoline (1) and 4-chloroquinoline (2). A solution of anhydrous quinoline *N*-oxide (7.52 g, 0.052 mol)



Scheme 4.



Scheme 5.

in phosphoryl trichloride (43.8 mL, 0.465 mol) was prepared by slow addition at 0 °C. The mixture was refluxed for 3 h and then poured on ice, neutralized with aqueous ammonium hydroxide and extracted with dichloromethane. The extracts were dried on sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/dichloromethane, 1:5), giving 2-chloroquinoline (**1**) (3.98 g, 47%) as a yellow solid, mp 36–38 °C and 4-chloroquinoline (**2**) (2.71 g, 32%) as a yellow solid, mp 33–34 °C.[12]

2-Chloroquinoline (**1**). ν_{max}(KBr)/cm^{-1} 3055 (ArC–H st), 1616, 1585, 1562, 1496, 1462 and 1420 (C=C and C=N st conj.), 1135 and 1094 (ArC–H (ip), 815, 778 and 742 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 7.38 (d, 1H, $J_{3-4}=8.3$ Hz, H-3), 7.56 (ddd, 1H, $J_{5-6}=8.1$ Hz, $J_{6-7}=7.0$ Hz, $J_{6-8}=1.2$ Hz, H-6), 7.72 (ddd, 1H, $J_{7-8}=8.3$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.4$ Hz, H-7), 7.80 (dd, 1H, $J_{5-6}=8.1$ Hz, $J_{5-7}=1.4$ Hz, H-5), 8.01 (dd, 1H, $J_{7-8}=8.3$ Hz, $J_{6-8}=1.2$ Hz, H-8) and 8.08 (d, 1H, $J_{3-4}=8.3$ Hz, H-4); δ_C (50 MHz, $CDCl_3$) 122.1 (C-3), 126.6 (C-4a), 126.7 (C-6), 127.3 (C-5), 128.3 (C-7), 130.3 (C-8), 138.6 (C-4), 147.6 (C-8a) and 150.3 (C-2); $\lambda_{max}(CH_2Cl_2)$/nm 233, 273, 304 and 318. C_9H_6NCl (163.60). Anal. Calcd C 66.07, H 3.70, N 8.56, Cl 21.67; found: C 65.93, H 3.61, N 8.43.

4-Chloroquinoline (**2**). δ_H (200 MHz, $CDCl_3$) 7.47 (d, 1H, $J_{2-3}=4.3$ Hz, H-3), 7.62 (ddd, 1H, $J_{5-6}=8.3$ Hz, $J_{6-7}=7.0$ Hz, $J_{6-8}=1.7$ Hz, H-6), 7.75 (ddd, 1H, $J_{7-8}=8.3$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.3$ Hz, H-7), 8.12 (dd, 1H, $J_{5-6}=8.3$ Hz, $J_{5-7}=1.3$ Hz, H-5), 8.20 (dd, 1H, $J_{7-8}=8.3$ Hz, $J_{6-8}=1.7$ Hz, H-8) and 8.77 (d, 1H, $J_{2-3}=4.3$ Hz, H-2); δ_C (50 MHz, $CDCl_3$) 121.1 (C-3), 124.0 (C-6), 126.4 (C-4a), 127.5 (C-5), 129.7 (C-7), 130.2 (C-8), 142.5 (C-4), 149.0 (C-8a) and 149.7 (C-2); $\lambda_{max}(CH_2Cl_2)$/nm 230, 281, 304 and 316. C_9H_6NCl (163.60). Anal. Calcd C 66.07, H 3.70, N 8.56, Cl 21.67; found: C 66.23, H 3.49, N 8.64.

4.1.2. 8-Chloroquinoline (3). Following the Skraup reaction, to a solution of *o*-chloroaniline hydrochloride (20 g, 122 mmol), and glycerol (17.8 mL, 244 mmol) in nitrobenzene (12.6 mL), was added $FeSO_4 \cdot 7H_2O$ (2.0 g, 7.2 mmol) and SO_4H_2 (33 mL, 98%). The mixture was stirred for 5 h at 80 °C and after neutralized with NaOH (12 N) and extracted with dichloromethane. The organic layer was washed (2×50 mL) with hydrochloric acid (10%). The extracts were dried with sodium sulfate, filtered and the solvent removed under reduced pressure yielding a brown oil, which was distilled at reduced pressure yielding 8-chloroquinoline as a colorless oil, 15.51 g (bp 175 °C at 30 mm Hg, 78%,[11b]). Purification can also be carried out by silica gel column chromatography (dichloromethane/hexane 4:1 ($R_f=0.19$).

ν_{max}(film)/cm^{-1}: 1593, 1490, 1459, 1380, 1304, 1209, 1062, 980, 823, 784; δ_H (200 MHz, $CDCl_3$): 9.07 (1H, dd, $J_1=4.3$ Hz, $J_2=1.61$ Hz, H-2), 8.21 (1H, dd, $J_1=8.6$ Hz, $J_2=1.61$ Hz, H-4), 7.86 (1H, dd, $J_1=7.53$ Hz, $J_2=1.08$ Hz, H-7), 7.77 (1H, dd, $J_1=8.06$ Hz, $J_2=1.08$ Hz, H-5), 7.48 (1H, dd, $J_1=8.06$ Hz, $J_2=7.53$ Hz, H-6); 7.43 (1H, dd, $J_1=8.6$ Hz, $J_2=4.3$ Hz, H-3); *m/z* 163/5 (M^+, 100); 136/8 (9); 128 (30); 127 (13); 101 (13); 75 (13); 74 (9); 68 (11); 51 (9); 50 (12); 44 (51). C_9H_6NCl (163.60). Anal. Calcd C 66.07, H 3.70, N 8.56, Cl 21.67; found C 65.87, H 3.44, N 8.62.

4.1.3. 4-Hydroxy-8-chloroquinoline (4). To a solution of 8-chloroquinoline (**3**) (6.42 g, 39.24 mmol) and acetic acid (99%, 9.42 g, 157 mmol), under argon atmosphere was added hydrogen peroxide (30%, 12 mL, 118 mmol), and warmed at 60 °C for 20 h. Then the solvent was evaporated under reduced pressure, neutralized with concentrated sodium carbonate and extracted with dichloromethane. The resulting extract was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash silica gel column cromatography (dichloromethane/hexane, 10:1) to give **4**, 4.37 g (62%) as a yellow solid, mp 225 °C (dec); ν_{max}(KBr)/cm^{-1} 3600–3000 (OH and N–H st), 1689 (C=O st), 1616, 1586, 1504, and 1467 (C=C and C=N st conj.), 995 and 964 (ArC–H (ip), 757 and 670 (ArC–H (oop); δ_H (200 MHz, MeOD), 8.57 (d, 1H, $J_{2-3}=2.7$ Hz, H-2), 7.47 (d, 1H, $J_{2-3}=2.7$ Hz, H-3), 7.37 (t, 1H, $J_{5-6,6-7}=8.1$ Hz, H-6), 7.55 (dd,

1H, J_{6-7}=8.1 Hz, J_{5-7}=1.2 Hz, H-7), 7.62 (dd, 1H, J_{5-6}= 8.1 Hz, J_{5-7}=1.2 Hz, H-5); δ_C (50 MHz, MeOD) 118.3 (C-3), 126.8 (C-5 and C-7), 127.8 (C-6), 132.9 (C-4a), 133.3 (C-8), 138.9 (C-8a), 146.5 (C-2) and 155.6 (C-4); *m/z* 179 (M^+, 100), 151 (7), 124 (7), 116 (11) and 89 (23).

C_9H_6NClO (179.60). Anal. Calcd C 60.19, H 3.37, N 7.80; found: C 59.89, H 3.44, N 7.55.

4.1.4. 8-Chloro-4-trifluoromethylsulfonyloxyquinoline (5). To a solution of 4-hydroxy-8-chloroquinoline (**4**) (200 mg, 1.11 mmol) in dry dichloromethane (15 mL), under argon atmosphere, at 0 °C were added 4-dimethylaminopyridine (28 mg, 0.22 mmol), 2,6-lutidine (0.19 mL, 1.55 mmol) and triflic anhydride (0.23 mL, 1.33 mmol). The mixture was stirred at 0 °C for 2 h and 1 h at room temperature and then was treated with water. The organic layer was dried with sodium sulfate, filtered and solvent removed at reduced pressure, to yield a residual solid, which was purified by silica gel column chromatography (dichloromethane), giving 8-chloro-4-trifluoromethilsulfonyloxyquinoline (**5**) (280 mg, 81%) as a white solid, mp 108–110 °C.

ν (KBr): 1616, 1586, 1504 and 1467 (C=C, C=N), 1348 (S=O), 1245, 1140, 995, 964, 750 (C–F); δ_H (200 MHz, MeOD), 8.91 (d, 1H, J_{2-3}=2.7 Hz, H-2), 8.10 (d, 1H, J_{2-3}= 2.7 Hz, H-3), 7.88 (dd, 1H, J_{5-6}=8.1 Hz, J_{5-7}=1.1 Hz, H-5), 7.77 (dd, 1H, J_{6-7}=8.1 Hz, J_{5-7}=1.1 Hz, H-7), 7.54 (t, 1H, $J_{5-6,6-7}$=8.1 Hz, H-6); δ_C (50 MHz, MeOD), 144.1 (C-2), 143.1 (CF_3), 133.9 (C-8a), 130.8 (C-7), 129.0 (C-4), 128.4 (C-5), 127.3 (C-6), 127.0 (C-3), 121.8 (C-8), 115.4 (C-4a); *m/z*, 311 (M^+, 47), 178 (10), 150 (100), 123 (32), 88 (10).

$C_{11}H_8ClF_3NO_3S$ (326.69). Anal. Calcd C 40.44, H 2.47, N 4.29; found: C 40.59, H 2.44, N 4.13.

4.1.5. 8-Chloroquinoline-*N*-oxide. To a solution of 8-chloroquinoline (**3**) (6.37 g, 38.93 mmol) in chloroform (10 mL), under argon atmosphere at 0 °C, was slowly added *m*-chloroperbenzoic acid (11 g, assay 57–90%). The mixture was stirred at 40 °C during 5 days and then the solvent was removed under reduced pressure, giving a brown residual oil, which was purified by silica gel flash column cromatography (dichloromethane/tetrahydrofuran, 2:1). The 8-chloroquinoline *N*-oxide (2.22 g, 32%) was isolated as a white solid, mp 103–105 °C.

ν_{max}(KBr)/cm^{-1}: 1654, 1592, 1558 and 1467 (C=C and C=N st conj.), 952 (ArC–H (ip), 790 and 743 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 7.29 (dd, 1H, J_{3-4}=8.6 Hz, J_{2-3}=6.3 Hz, H-3), 7.47 (t, 1H, $J_{5-6,6-7}$=7.8 Hz, H-6), 7.69 (d, 1H, J_{5-6}=7.8 Hz, H-5), 7.73 (d, 1H, J_{6-7}=7.8 Hz, H-7), 7.75 (dd, 1H, J_{3-4}=8.6 Hz, J_{2-4}=1.6 Hz, H-4) and 8.51 (dd, 1H, J_{2-3}=6.3 Hz, J_{2-4}=1.6 Hz, H-2).

C_9H_6ONCl (179.60). Anal. Calcd C 60.19, H 3.37, N 7.80; found: C 59.87, H 3.66, N 7.85.

4.1.6. 2,8-Dichloroquinoline (6). A solution of 8-chloroquinoline-*N*-oxide (365 mg, 2.03 mmol) and phosphoryl trichloride (1.82 mL, 18.29 mmol) at 0 °C, was heated to reflux temperature for 3 h and then poured onto ice, neutralized with a saturated aqueous ammonium chloride solution and extracted with dichloromethane. The extracts were dried with sodium sulfate, filtered and solvent removed, giving a brown solid, which was purified by flash silica gel column cromatography (hexane/dichloromethane, 2:1). Then, solvent was removed and 2,8-dichloroquinoline was isolated (208 mg, 52%) as a white solid, mp 104–105 °C; δ_H (200 MHz, $CDCl_3$) 7.46 (d, 1H, J_{3-4}=8.6 Hz, H-3), 7.49 (dd, 1H, J_{5-6}=8.3 Hz, J_{6-7}= 7.5 Hz, H-6), 7.75 (dd, 1H, J_{5-6}=8.3 Hz, J_{5-7}=1.5 Hz, H-5), 7.85 (dd, 1H, J_{6-7}=7.5 Hz, J_{5-7}=1.5 Hz, H-7) and 8.13 (d, 1H, J_{3-4}=8.6 Hz, H-4); δ_C (50 MHz, $CDCl_3$) 123.4 (C-3), 126.5 (C-6), 126.9 (C-5), 128.1 (C-4a), 130.6 (C-7), 132.6 (C-8), 139.2 (C-4), 144.2 (C-8a) and 151.7 (C-2); *m/z* 197 (M^+, 100), 162 (85), 126 (26), 99 (20) and 75 (15); $\lambda_{max}(CH_2Cl_2)$/nm 239, 289, 307 and 321.

$C_9H_5NCl_2$ (198.05). Anal. Calcd C 54.58, H 2.54, N 7.07; found: C 54.38, H 2.82, N 7.15.

4.1.7. 2-Methyl-4-(2′-quinolyl)-but-3-yn-2-ol (7). General method. To a solution of 2-chloroquinoline (**1**) (3.3 g, 20.17 mmol) and 2-methylbut-3-yn-2-ol (2.19 mL, 22.19 mmol) in freshly distilled diethylamine (10 mL), under argon atmosphere, were added dichloro bis(triphenylphosphine) palladium (141.6 mg, 0.2 mmol) and cuprous iodide (7.68 mg, 0.04 mmol). The mixture was stirred for 30 min at 40 °C and after, the excess of diethylamine was removed under reduced pressure. The residual solid was washed with an aqueous solution of ammonium chloride and potassium cyanide and finally extracted with dichloromethane. The extract was dried with sodium sulfate, filtered and the solvent evaporated to afford a yellow solid that was purified by flash silica gel column chromatography (hexane/ethylacetate, 2:1). The 2-methyl-4-(2′-quinolyl)-but-3-yn-2-ol (**7**) (3.93 g, 92%) was isolated as a yellow solid, mp 103–104 °C. ν_{max}(film)/cm^{-1} 3340 (O–H st), 2220 (C≡C st), 1610, 1587, 1545, 1495, 1455 and 1422 (C=C and C=N st conj.), 1380 and 1360 (CH_3 δ si), 829 and 753 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 1.68 (s, 6H, 2×CH_3), 3.22 (s, 1H, OH), 7.44 (d, 1H, J_{3-4}=8.2 Hz, H-3), 7.52 (ddd, 1H, J_{5-6}=7.8 Hz, J_{6-7}=6.8 Hz, J_{6-8}=1.0 Hz, H-6), 7.68 (ddd, 1H, J_{7-8}=8.8 Hz, J_{6-7}=6.8 Hz, J_{5-7}=1.3 Hz, H-7), 7.72 (dd, 1H, J_{5-6}=7.8 Hz, J_{5-7}=1.3 Hz, H-5), 8.06 (d, 1H, J_{3-4}=8.2 Hz, H-4) and 8.11 (dd, 1H, J_{7-8}=8.8 Hz, J_{6-8}= 1.0 Hz, H-8); δ_C (50 MHz, $CDCl_3$) 31.2 (2×CH_3), 65.4 (C–OH), 82.5 (Ar*C*≡C), 94.6 (ArC≡*C*), 124.2 (C-3), 127.1 (C-6), 127.4 (C-5), 129.2 (C-7), 130.0 (C-8), 136.1 (C-4), 143.2 (C-8a) and 148.0 (C-2).

$C_{14}H_{13}ON$ (211.26). Anal. Calcd C 79.59, H 6.20, N 6.63; found: C 79.38, H 6.34, N 6.52.

4.1.8. 2-Methyl-4-(3′-quinolyl)-but-3-yn-2-ol (8). Following the preparation of **7**, a mixture of 3-bromoquinoline (5.06 g, 24.3 mmol), 2-methylbut-3-yn-2-ol (2.25 mL, 26.7 mmol) in freshly distilled diethylamine (15 mL), under argon atmosphere was added, dichloro bis(triphenylphosphine) palladium(II) (174 mg, 0.25 mmol) and cuprous iodide (10.0 mg, 0.05 mmol). The mixture was stirred at 40 °C for 1 h, giving 2-methyl-4-(3′-quinolyl)-but-3-yn-2-ol (**8**) (4.98 g, 97%) as colourless crystals, mp 112–113 °C.[9b] δ_H (200 MHz, $CDCl_3$) 1.70 (s, 6H, 2×CH_3),

3.50 (s, 1H, OH), 7.54 (ddd, 1H, $J_{5-6}=8.1$ Hz, $J_{6-7}=7.0$ Hz, $J_{6-8}=1.1$ Hz, H-6), 7.70 (ddd, 1H, $J_{7-8}=8.1$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.6$ Hz, H-7), 7.75 (dd, 1H, $J_{5-6}=8.1$ Hz, $J_{5-7}=1.6$ Hz, H-5), 8.10 (dd, 1H, $J_{7-8}=8.1$ Hz, $J_{6-8}=1.1$ Hz, H-8) and 8.20 (d, 1H, $J_{2-4}=2.1$ Hz, H-4) and 9.04 (d, 1H, $J_{2-4}=2.1$ Hz, H-2).

$C_{14}H_{13}ON$ (211.26). Anal. Calcd C 79.59, H 6.20, N 6.63; found: C 79.38, H 6.34, N 6.52.

4.1.9. 2-Methyl-4-(4′-quinolyl)-but-3-yn-2-ol (9). Following the preparation of **7**, a mixture of 4-chloroquinoline (**2**) (2.0 g, 12.22 mmol), 2-methylbut-3-yn-2-ol (1.33 mL, 13.45 mmol) in freshly distilled diethylamine (7 mL), was added dichloro bis(triphenylphosphine) palladium (86 mg, 0.12 mmol, 0.9%) and cuprous iodide (4.7 mg, 0.02 mmol, 0.15%). The mixture was stirred for 2 days at the reflux temperature, giving (**9**) (2.19 g, 86%) as a yellow solid, mp 100–102 °C. δ_H (200 MHz, $CDCl_3$) 1.71 (s, 6H, $2\times CH_3$), 3.54 (s, 1H, OH), 7.13 (d, 1H, $J_{2-3}=4.7$ Hz, H-3), 7.31 (ddd, 1H, $J_{5-6}=8.6$ Hz, $J_{6-7}=7.0$ Hz, $J_{6-8}=1.1$ Hz, H-6), 7.50 (ddd, 1H, $J_{7-8}=8.6$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.6$ Hz, H-7), 8.00 (dd, 1H, $J_{5-6}=8.6$ Hz, $J_{5-7}=1.6$ Hz, H-5), 8.06 (dd, 1H, $J_{7-8}=8.6$ Hz, $J_{6-8}=1.1$ Hz, H-8) and 8.66 (d, 1H, $J_{2-3}=4.7$ Hz, H-2). $C_{14}H_{13}ON$ (211.26). Anal. Calcd C 79.59, H 6.20, N 6.63; found: C 79.63, H 6.10, N 6.33.

4.1.10. 2-Methyl-4-[-2′-(8′-chloroquinolyl)]-but-3-yn-2-ol (10). Following the preparation of **7**, a mixture of 2,8-dichloroquinoline (**6**) (367 g, 1.85 mmol), 2-methylbut-3-yn-2-ol (0.2 mL, 2.02 mmol) in freshly distilled diethylamine (2 mL) were added dichloro bis(triphenylphosphine) palladium (37 mg, 0.05 mmol) and cuprous iodide (2 mg, 0.01 mmol). The mixture was stirred for 1 h at 40 °C, giving 2-methyl-4-[2′-(8′-quinolyl)]-but-3-yn-2-ol (**10**) (415 mg, 91%) as a yellow solid, mp 78–80 °C. δ_H (200 MHz, $CDCl_3$) 1.67 (s, 6H, $2\times CH_3$), 3.22 (s, 1H, OH), 7.44 (dd, 1H, $J_{5-6}=8.6$ Hz, $J_{6-7}=7.8$ Hz, H-6), 7.54 (d, 1H, $J_{3-4}=8.6$ Hz, H-3), 7.70 (dd, 1H, $J_{5-6}=8.6$ Hz, $J_{5-7}=1.6$ Hz, H-5), 7.83 (dd, 1H, $J_{6-7}=7.8$ Hz, $J_{5-7}=1.6$ Hz, H-7) and 8.11 (d, 1H, $J_{3-4}=8.6$ Hz, H-4); δ_C (50 MHz, $CDCl_3$) 31.2 ($2\times CH_3$), 64.9 (C–OH), 83.9 (Ar*C*≡C), 96.8 (ArC≡*C*),125.1 (C-3), 126.6 (C-6), 126.9 (C-5), 128.3 (C-4a), 130.2 (C-7), 132.4 (C-8), 136.8 (C-4), 143.9 (C-8a) and 153.3 (C-2); *m/z* 245 (M^+, 50), 230 (100), 202 (75), 188 (78) and 162 (28). $C_{14}H_{12}ONCl$ (245.70). Anal. Calcd C 68.44, H 4.92, N 5.70; found: C 68.70, H 4.74, N 5.76.

4.1.11. 2-Ethynylquinoline (11). General method. To a solution of 2-methyl-4-(2′-quinolyl)-but-3-yn-2-ol (**7**) (379 mg, 1.79 mmol) in dry toluene (2 mL), under argon atmosphere, was introduced powder of sodium hydroxide (10 mg, 0.25 mmol) and refluxed for 1 h. Then, the reaction mixture was filtered and the solvent was removed giving a brown oil, which was purified by flash silica gel column chromatography (hexane/ethylacetate, 3:1). The 2-ethynylquinoline (**11**) (168 mg, 61%) was isolated as a yellow solid, mp 46–47 °C. ν_{max}(KBr)/cm^{-1} 3172 (≡C–H st), 2103 (C≡C st), 1616, 1593, 1552, 1500, 1457 and 1422 (C=C and C=N st conj.), 833 and 758 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 3.25 (s, 1H, C≡CH), 7.53 (d, 1H, $J_{3-4}=8.1$ Hz, H-3), 7.54 (ddd, 1H, $J_{5-6}=8.1$ Hz, $J_{6-7}=7.0$ Hz, $J_{6-8}=1.6$ Hz, H-6), 7.72 (ddd, 1H, $J_{7-8}=8.6$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.6$ Hz, H-7), 7.77 (dd, 1H, $J_{5-6}=8.1$ Hz, $J_{5-7}=1.6$ Hz, H-5), 8.10 (dd, 1H, $J_{7-8}=8.6$ Hz, $J_{6-8}=1.6$ Hz, H-8) and 8.12 (d, 1H, $J_{3-4}=8.1$ Hz, H-4); δ_C (50 MHz, $CDCl_3$) 77.5 (ArC≡*C*–H), 83.3 (Ar*C*≡C–H), 124.0 (C-3), 127.3 (C-4a, C-5 and C-6), 129.2 (C-7), 130.0 (C-8), 136.1 (C-4), 142.3 (C-8a) and 147.9 (C-2); *m/z* 153 (M^+, 100), 126 (30) and 76 (19); $\lambda_{max}(CH_2Cl_2)$/nm 240, 285, 316 and 330.

$C_{11}H_7N$ (153.18). Anal. Calcd C 86.25, H 4.61, N 9.14; found: C 86.36, H 4.65, N 9.27.

4.1.12. 3-Ethynylquinoline (12). Following the preparation of **11**, 2-methyl-4-(3′-quinolyl)but-3-yn-2-ol (**8**) (4.5 g, 21.3 mmol) in dry toluene (15 mL) and powder of sodium hydroxide (0.1 g, 2.5 mmol) at reflux temperature for 4 h, gave an orange solid, which was purified by sublimation on a cool-finger surface (40 Torr) at 50 °C. The 3-ethynylquinoline (**12**) was isolated as colourless crystals, 2.84 g, 87%, mp 78–79 °C.[9b] ν_{max}(KBr)/cm^{-1} 3165 (≡C–H st), 2095 (C≡C st), 1620, 1600, 1560, and 1490 (C=C and C=N st conj.), 790 and 750 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 3.28 (s, 1H, C≡CH), 7.58 (br dd, 1H, $J_{5-6}=7.8$ Hz, $J_{6-7}=7.0$ Hz, H-6), 7.73 (ddd, 1H, $J_{7-8}=8.6$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.6$ Hz, H-7), 7.79 (dd, 1H, $J_{5-6}=7.8$ Hz, $J_{5-7}=1.6$ Hz, H-5), 8.10 (br d, 1H, $J_{7-8}=8.6$ Hz, H-8), 8.29 (d, 1H, $J_{2-4}=2.3$ Hz, H-4), and 8.95 (d, 1H, $J_{2-4}=2.3$ Hz, H-2); $\lambda_{max}(CH_2Cl_2)$/nm 239 (ε, 30,054), 282 (ε, 7717), 316 (ε, 3579), and 330 (ε, 3659 L mol^{-1} cm^{-1}).

$C_{11}H_7N$ (153.18). Anal. Calcd C 86.25, H 4.61, N 9.14; found: C 86.12, H 4.39, N 8.93.

4.1.13. 4-Ethynylquinoline (13). Following the preparation of **11**, 2-methyl-4-(4′-quinolyl)but-3-yn-2-ol (**9**) (190 mg, 0.9 mmol) in dry toluene (2 mL), and powder of sodium hydroxide (4 mg, 0.1 mmol) at reflux temperature for 30 min, gave 4-ethynylquinoline (**13**) as a white solid, mp 96–97 °C (103 mg, 75%). ν_{max}(KBr)/cm^{-1} 3187 (≡C–H st), 2088 (C≡C st), 1579, 1560, 1503, 1464 and 1420 (C=C and C=N st conj.), 851, 811 and 803 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 3.67 (s, 1H, C≡CH), 7.53 (d, 1H, $J_{2-3}=4.5$ Hz, H-3), 7.60 (ddd, 1H, $J_{5-6}=8.3$ Hz, $J_{6-7}=6.7$ Hz, $J_{6-8}=1.6$ Hz, H-6), 7.74 (ddd, 1H, $J_{7-8}=8.6$ Hz, $J_{6-7}=6.7$ Hz, $J_{5-7}=1.6$ Hz, H-7), 8.11 (dd, 1H, $J_{5-6}=8.3$ Hz, $J_{5-7}=1.6$ Hz, H-5), 8.27 (dd, 1H, $J_{7-8}=8.6$ Hz, $J_{6-8}=1.6$ Hz, H-8) and 8.87 (d, 1H, $J_{2-3}=4.5$ Hz, H-2); $\lambda_{max}(CH_2Cl_2)$/nm 302, 311 and 325.

$C_{11}H_7N$ (153.18). Anal. Calcd C 86.25, H 4.61, N 9.14; found: C 86.41, H 4.39, N 9.15.

4.1.14. 8-Chloro-2-ethynylquinoline (14). Following the preparation of **11**, 2-methyl-4-[2′(8-chloroquinolyl)]but-3-yn-2-ol (**10**) (414 mg, 1.68 mmol) in dry toluene (10 mL) and powder of sodium hydroxide (7 mg, 0.17 mmol) at reflux temperature for 1 h, gave 8-chloro-2-ethynylquinoline (**14**) as an orange solid, mp 92–95 °C (202 mg, 65%).

ν_{max}(KBr)/cm^{-1} 3199 (≡C–H st), 2098 (C≡C st), 1609, 1593, 1542, 1500, 1491 and 1422 (C=C and C=N st conj.), 834, 760 and 670 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 3.29 (s, 1H, C≡CH), 7.47 (dd, 1H, $J_{5-6}=8.1$ Hz, $J_{6-7}=7.0$ Hz,

H-6), 7.60 (d, 1H, $J_{3-4}=8.5$ Hz, H-3), 7.72 (dd, 1H, $J_{5-6}=8.1$ Hz, $J_{5-7}=1.2$ Hz, H-5), 7.85 (dd, 1H, $J_{6-7}=7.3$ Hz, $J_{5-7}=1.2$ Hz, H-7) and 8.15 (d, 1H, $J_{3-4}=8.5$ Hz, H-4); δ_C (50 MHz, $CDCl_3$) 78.7 (ArC≡*C*–H), 83.3 (Ar*C*≡C–H), 125.1 (C-3), 126.6 (C-6), 127.2 (C-5), 128.6 (C-4a), 130.2 (C-7), 133.4 (C-8), 136.6 (C-4), 143.1 (C-8a) and 144.4 (C-2); *m/z* 187 (M^+, 100), 152 (28), 125 (10) and 84 (17); $\lambda_{max}(CH_2Cl_2)$/nm 219, 251, 308 and 334.

$C_{11}H_6NCl$ (187.62). Anal. Calcd C 70.42, H 3.22, N 7.47; found: C 70.33, H 3.03, N 7.16.

4.1.15. 1,4-Di(2′-quinolyl)-1,3-butadiyne (15). General method. A solution of cuprous chloride (10 mg, 0.1 mmol) and 2-ethynylquinoline (**11**) (85 mg, 0.55 mmol) in freshly distilled pyridine (30 mL), under oxygen atmosphere at 40 °C, was stirred for 150 min. Then, the solvent was removed at reduced atmosphere giving a brown solid, which was washed with an aqueous ammonium chloride solution and extracted with dichloromethane. The joining extracts were dried with anhydrous sodium sulfate, filtered and the solvent was evaporated affording a brown solid that was crystalized from acetonitrile/hexane (1:1). The 1,4-di(2′-quinolyl)-1,3-butadiyne (**15**) was isolated as a white solid (76 mg, 89%), mp 210 °C (dec). ν_{max}(KBr)/cm^{-1} 1616, 1589, 1550, 1496, 1456 and 1422 (C=C and C=N st conj.), 1111 (ArC–H (ip), 823, 785, 768 and 740 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 7.57 (d, 2H, $J_{3-4}=8.6$ Hz, H-3 and H-3′), 7.60 (m, 2H, H-6 and H-6′), 7.74 (m, 2H, H-7 and H-7′), 7.80 (m, 2H, H-5 and H-5′), 8.07 (m, 2H, H-8 and H-8′) and 8.16 (d, 2H, $J_{3-4}=8.6$ Hz, H-4 and H-4′); *m/z* 304 (M^+, 100), 152 (14), 128 (6) and 76 (7); $\lambda_{max}(CH_2Cl_2)$/nm 223 (ε, 84,170), 256 (ε, 146,670), 335 (ε, 80,580), 344 (ε, 77,010) and 360 (ε, 94,390 L mol^{-1} cm^{-1}).

$C_{22}H_{12}N_2$ (304.35). Anal. Calcd C 86.82, H 3.97, N 9.20; found: C 86.65, H 3.52, N 9.35.

4.1.16. 1,4-Di(3′-quinolyl)-1,3-butadiyne (16). Following the preparation of **15**, cuprous chloride (20 mg, 0.2 mmol) and 3-ethynylquinoline (**12**) (200 mg, 1.3 mmol) in pyridine (30 mL) at 60 °C, was stirred for 6 h affording 1,4-di(3′-quinolyl)-1,3-butadiyne (**16**) as a white solid, 160 mg, 80%, mp 233.7 °C (DSC). Compound **16** is photosensitive in the solid state and turns to a dark-blue solid by sunlight exposure. ν_{max}(KBr)/cm^{-1} 1610, 1598, 1550, 1490, 1461 and 1422 (C=C and C=N st conj.), 860, 790, 760 and 750 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$): 7.60 (br dd, 2H, $J_{5-6}=7.6$ Hz, H-6 and H-6′), 7.77 (ddd, 2H, $J_{7-8}=8.2$ Hz, $J_{6-7}=7.2$ Hz, $J_{5-7}=1.4$ Hz, H-7 and H-7′), 7.82 (dd, 2H, $J_{5-6}=7.6$ Hz, $J_{5-7}=1.4$ Hz, H-5 and H-5′), 8.12 (br d, 2H, $J_{7-8}=8.2$ Hz, H-8 and H-8′), 8.37 (d, 2H, $J_{2-4}=1.9$ Hz, H-4 and H-4′) and 9.00 (d, 2H, $J_{2-4}=1.9$ Hz, H-2 and H-2′); *m/z* 304 (M^+, 100), 152 (14), 124 (11); $\lambda_{max}(CH_2Cl_2)$/nm 221 (ε, 61,260), 254 (ε, 81,940), 316 (ε, 39,160), 335 (ε, 53,300) and 360 (ε, 56,220 L mol^{-1} cm^{-1}).

$C_{22}H_{12}N_2$ (304.35). Anal. Calcd C 86.82, H 3.97, N 9.20; found: C 86.60, H 4.05, N 9.11.

4.1.17. 1,4-Di(4′-quinolyl)-1,3-butadiyne (17). Following the preparation of **15**, cuprous chloride (5.4 mg, 0.054 mmol) and 4-ethynylquinoline (**13**) (82.4 mg, 0.54 mmol) in pyridine (4 mL), at 40 °C was stirred for 30 min, giving 1,4-di(4′-quinolyl)-1,3-butadiyne (**17**) as a white solid (79 mg, 97%), mp 215–216 °C; ν_{max}(KBr)/cm^{-1} 1573, 1503, 1460 and 1417 (C=C and C=N st conj.), 1077 and 1021 (ArC–H (ip), 851, 802 and 757 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 7.61 (d, 2H, $J_{2-3}=3.9$ Hz, H-3 and H-3′), 7.64 (ddd, 2H, $J_{5-6}=8.1$ Hz, $J_{6-7}=7.0$ Hz, $J_{6-8}=1.6$ Hz, H-6 and H-6′), 7.75 (ddd, 2H, $J_{7-8}=8.6$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.6$ Hz, H-7 and H-7′), 8.06 (dd, 2H, $J_{5-6}=8.1$ Hz, $J_{5-7}=1.6$ Hz, H-5 and H-5′), 8.27 (dd, 2H, $J_{7-8}=8.6$ Hz, $J_{6-8}=1.6$ Hz, H-8 and H-8′) and 8.81 (d, 2H, $J_{2-3}=3.9$ Hz, H-2 and H-2′); *m/z* 304 (M^+, 100), 275 (23), 249 (9), 152 (23) and 124 (12); $\lambda_{max}(CH_2Cl_2)$/nm 228, 271, 334, 345 and 371.

$C_{22}H_{12}N_2$ (304.35). Anal. Calcd C 86.82, H 3.97, N 9.20; found: C 86.59, H 3.87, N 8.94.

4.1.18. 1,4-Di[2′-(8′-chloroquinolyl)-1,3-butadiyne (18). Following the preparation of **15**, cuprous chloride (5 mg, 0.051 mmol) and 8-chloro-2-ethynylquinoline (**14**) (70 mg, 0.373 mmol) in pyridine (6 mL), The mixture was stirred at 40 °C for 4 h 30 min, affording 1,4-di[2′-(8′-chloroquinolyl)-1,3-butadiyne (**18**) as a yellow solid, mp 212–214 °C, (42.06 mg, 30%). ν_{max}(KBr)/cm^{-1} 1598, 1552, 1525, 1498, 1455 and 1426 (C=C and C=N st conj.), 1089 and 1032 (ArC–H (ip), 839, 793 and 758 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$); 7.46 (d, 2H, $J_{3-4}=8.6$ Hz, H-3 and H-3′), 7.79 (dd, 2H, $J_{5-6}=8.1$ Hz, $J_{6-7}=7.5$ Hz, H-6 and H-6′), 7.87 (dd, 2H, $J_{6-7}=7.5$ Hz, $J_{5-7}=1.6$ Hz, H-7 and H-7′), 8.15 (dd, 2H, $J_{5-6}=8.1$ Hz, $J_{5-7}=1.6$ Hz, H-5 and H-5′), and 8.30 (d, 2H, $J_{3-4}=8.6$ Hz, H-4 and H-4′); *m/z* 372 (M^+, 100), 337 (14), 302 (8), 210 (17), 186 (14), 168 (9), 163 (37), 151 (7), 127 (7) and 75 (5); λ_{max} (CH_2Cl_2)/nm 240, 269, 305, 344 and 365.

$C_{22}H_{10}N_2Cl_2$ (373.24). Anal. Calcd C 70.79, H 2.70, N 7.51; found: C 70.87, H 2.94, N 7.33.

4.1.19. Coupling reaction between 2′-chloroquinoline 11 and 2′-quinolylacetylene. (a) *$Cl_2Pd(Ph_3P)_2$–Cu_2I_2.* To a solution of 2-chloroquinoline (**1**) (278 mg, 1.7 mmol) and 2-ethynylquinoline (**11**) (200 mg, 1.3 mmol) in freshly distilled piperidine (15 mL), under argon atmosphere were successively added dichloro bis(triphenylphosphine) palladium (70 mg, 0.1 mmol) and cuprous iodide (10 mg, 0.05 mmol). The mixture was stirred for 3 days at reflux temperature, monitoring by TLC. Then, the piperidine was removed under reduced pressure and the residual solid was washed with an aqueous solution of ammonium chloride and potassium cyanide and extracted with dichloromethane. The joining extracts were dried on sodium sulfate, filtered and solvent evaporated under reduced pressure, giving a dark oil, which was purified by silica gel column cromatography (dichloromethane/acetonitrile, 10:1). The starting 2-ethynylquinoline (**11**) was isolated and also an orange solid (132 mg, 61%) mp 192–194 °C, that was identified as 2,2′-bis(quinoline) (**19**),[12b] δ_H (200 MHz, $CDCl_3$) 7.59 (ddd, 2H, $J_{5-6}=8.1$ Hz, $J_{6-7}=7.0$ Hz, $J_{6-8}=1.3$ Hz H-6 and H6′), 7.77 (ddd, 2H, $J_{7-8}=8.6$ Hz, $J_{6-7}=7.0$ Hz, $J_{5-7}=1.6$ Hz, H-7 and H-7′), 7.89 (dd, 2H, $J_{5-6}=8.1$ Hz, $J_{5-7}=1.6$ Hz, H-5 and H-5′), 8.25 (dd, 2H, $J_{7-8}=8.6$ Hz, $J_{6-8}=1.3$ Hz H-8 and H-8′), 8.34 (d, 2H, $J_{3-4}=8.6$ Hz, H-3 and H-3′), and

8.86 (d, 2H, J_{2-3}=8.6 Hz, H-4 and H-4′); *m/z* (%): 256 (M^+, 100), 128 (30) and 101 (13). $C_{18}H_{12}N_2$ (256.30). Anal. Calcd C 84.35, H 4.72, N 10.93; found: C 84.08, H 4.55, N 10.67.

(b) *$Cl_2Ni(PPh_3)_2$–Zn*. A suspension of dichloro bis(triphenylphosphine) nickel (0.4 g, 0.61 mmol) and triphenylphosphine (0.321 g, 1.22 mmol) and zinc powder (40 mg, 0.61 mmol) in dry THF (7 mL), was stirred at room temperature for 30 min. Then, a solution of 2-chloroquinoline (**1**) (100 mg, 0.61 mmol) and 2-ethynylquinoline (**11**) (118 mg, 0.76 mmol) in dry THF (8 mL), was added. The mixture was stirred at room temperature, under argon atmosphere, for 48 h and then filtered and the solvent removed under reduced pressure, giving a residual solid, which was washed with an aqueous solution of ammonium chloride and extracted with dichloromethane. The extract was dried with sodium sulfate, filtered and solvent evaporated under reduced pressure, giving a red solid, which was purified by flash silica gel column cromatography (hexane/ethyl acetate, 2:1). The starting 2-chloroquinoline (**2**) and a red oil that was identified as the mixture of 1,3,5- (**20**) and 1,2,4-tris(2′-quinolyl)benzene (**21**) (36:64, respectively) (50 mg, 43%). Isolation of the cyclotrimers was not possible and both were analyzed themselves; ν_{max}(KBr)/cm^{-1} 1644, 1618, 1596, 1558, 1503, 1461 and 1425 (C=C and C=N st conj.), 1096 and 1024 (ArC–H (ip), 865, 802 and 700 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 7.06 (d, J=7.5 Hz, H-3), 7.15 (d, J=8.1 Hz, H-3′), 7.54 (m, H-6 and H-6′), 7.73 (m, H-7, H-7′, H-5 and H-5′), 8.15 (m, H-4, H-4′, H-8, H-8 and H-c), 8.49 (dd, J=8.1 Hz, J=1.6 Hz, H-b), 8.71 (d, J=1.6 Hz, H-a) and 8.94 (s, H-a′); by GC/MS separation, 1,3,5-tris(2′-quinolyl)benzene (**20**) *m/z* 459 (M^+, 89%), 458 (100), 329 (6), 229 (25) and 128 (14); 1,2,4-tris(2′-quinolyl)benzene (**21**) *m/z* 459 (M^+, 41), 458 (49), 229 (14) and 128 (100). $C_{33}H_{21}N_3$ (459.54). Anal. Calcd C 86.25, H 4.61, N 9.14; found: C 86.26, H 4.44, N 8.87.

4.1.20. Coupling reaction between 3-bromoquinoline and 12: 1,2-di(3′-quinolyl)ethyne (22). To a solution of 3-bromoquinoline (0.62 g, 3 mmol) and 3-ethynylquinoline (**12**) (0.35 g, 2.29 mmol) in freshly distilled diethylamine (10 mL), under argon atmosphere, were introduced dichloro bis(triphenylphosphine) palladium (50 mg, 0.02 mmol, 3%) and cuprous iodide (8 mg, 0.04 mmol). The mixture was stirred for 6 days at reflux temperature and then the excess of diethylamine was removed at reduced pressure. The residual solid was washed with an aqueous solution of ammonium chloride and potassium cyanide and extracted with dichloromethane. The joining extracts were dried with sodium sulfate, filtered and the solvent evaporated to give a dark solid that was purified by flash silica gel column cromatography (dichloromethane/acetonitrile, 6:1). The 1,2-di(3′-quinolyl)ethyne (**22**) was isolated as a white solid, mp 164–169 °C (0.45 g, 70%); ν_{max}(KBr)/cm^{-1} 1616, 1599, 1564, 1487, 1466 and 1422 (C=C and C=N st conj.), 907, 787, 749 and 736 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) 7.60 (ddd, 2H, J_{5-6}=8.1 Hz, J_{6-7}=7.0 Hz, J_{6-8}=1.6 Hz, H-6 and H-6′), 7.76 (ddd, 2H, J_{7-8}=8.6 Hz, J_{6-7}=7.0 Hz, J_{5-7}=1.6 Hz, H-7 and H-7′), 7.84 (dd, 2H, J_{5-6}=8.1 Hz, J_{5-7}=1.6 Hz, H-5 and H-5′), 8.13 (dd, 2H, J_{7-8}=8.6, J_{6-8}=1.6 Hz, H-8 and H-8′), 8.39 (d, 2H, J_{2-4}=2.1 Hz, H-4 and H-4′) and 9.06 (d, 2H, J_{2-4}=2.1 Hz, H-2 and H-2′); δ_C (50 MHz, $CDCl_3$) 89.7 (Ar–C(C–Ar), 116.7 (C-3 and C-3′), 127.0 (C-4a and C-4a′), 127.3 (C-6 and C-6′), 127.6 (C-5 and C-5′), 129.3 (C-7 and C-7′), 130.3 (C-8 and C-8′), 138.5 (C-4 and C-4′), 146.9 (C-8a and C-8a′) and 151.8 (C-2 and C-2′); *m/z* 280 (M+, 100), 251 (9), 140 (11), 126 (9) and 100 (6); λ_{max}(CH_2Cl_2)/nm 227, 251, 267, 320, 334 and 347; UV–vis. λ_{max}(CH_2Cl_2)/nm 347 (46,100). Fluorescence λ (CH_2Cl_2), 354 and 371 (quantum yield Φ, 18%, referred to 2-aminopiridine in CH_2Cl_2).

$C_{20}H_{12}N_2$ (280.32). Anal. Calcd C 85.69, H 4.31, N 9.99; found: C 85.52, H 4.27, N 9.78.

4.1.21. 3′-Quinolylacetylene (12): cyclotrimerization to 1,3,5-tris(3′-quinolyl)benzene (23) and 1,2,4-tris(3′-quinolyl)benzene (24). *$Cl_2Ni(PPh_3)_2$–Zn*. A solution of dichloro bis(triphenylphosphine) nickel (0.22 g, 0.335 mmol), triphenylphosphine (0.161 g, 0.61 mmol) and zinc powder (20 mg, 0.31 mmol) in dry THF (4 mL), was stirred for 30 min at room temperature. Then, a solution of 3-ethynylquinoline (**12**) (60 mg, 0.38 mmol) in dry THF (4 mL), was added. The mixture was stirred at room temperature, under argon atmosphere, for 24 h, and finally, was filtered and the solvent removed under reduced pressure yielding a residual solid, which was washed with an aqueous solution of ammonium chloride and extracted with dichloromethane. The extract was dried with sodium sulfate, filtered and the solvent evaporated under reduced pressure, giving a red oil, which was purified by silica gel flash cromatography using hexane/ethyl acetate (2:1) as eluent. The red oil was isolated and identified as a mixture (40:60) of 1,3,5-tris (**23**) and 1,2,4-tris(3′-quinolyl)benzene (**24**) (69 mg, 80%). The separation of both cyclotrimers was not possible and both were analyzed themselves; ν_{max}(KBr)/cm^{-1}: 1644, 1618, 1596, 1558, 1503, 1461 and 1425 (C=C and C=N st conj.), 1096 and 1024 (ArC–H (ip), 865, 802 and 700 (ArC–H (oop); δ_H (200 MHz, $CDCl_3$) of the mixture: 1,2,4-tris(3′-quinolyl)benzene; 9.31 (d, J=2.3 Hz, H-2), 8.67 (d, J=8.0 Hz, H-8), 8.46 (d, J=2.3 Hz, H-4), 7.45–7.85 (m, H-5, H-6, H-7); 1,3,5-tris(3′-quinolyl)benzene; 9.34 (d, J=2.3 Hz, H-2), 8.50 (d, J=2.3 Hz, H-4), 8.67 (d, J=8.0 Hz, H-8), 7.95 s (s, H-2, H-4, H-6); *m/z* of the mixture; 459 (M^+, 100), 431 (8), 230 (24). $C_{33}H_{21}N_3$ (459.54). Anal. Calcd C 86.25, H 4.61, N 9.14; found: C 86.03, H 4.36, N 8.77. DSC analysis of the mixture **23** and **24** shows two endothermic peaks at 202 and 209 °C in 40:60 molar ratio.

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An efficient microwave-assisted solvent-free synthesis of pyrido-fused ring systems applying the *tert*-amino effect

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Abstract—Significant improvements in the synthesis of pyrido-fused heterocycles were observed when performing the reaction under solvent-free conditions, applying the *tert*-amino effect as the key ring closure methodology. An unexpected cyclization of *ortho*-(1′-azacycloalkyl)benzaldehydes has been studied in water and on solid support.

1. Introduction

Microwave(MW)-assisted solvent-free reactions have received much attention due to their enhanced reaction rates as well as higher yields and purities. These methods are regarded as environmentally benign and easy-to-perform, paving the way to the development of 'Green Chemistry' protocols.[1] Such kind of transformations can be conveniently and rapidly carried out in open vials, without having the problem of boiling solvents and excessive pressure build-up. In addition to their practical interest, MW-assisted solvent-free reactions, performed neat or on a non-absorbing support, are highly suitable to study the possible occurrence of special non-thermal MW effects,[2–4] as the absorption of the radiation is limited to the reactive species and not masked by any absorption of the solvent (essentially important when polar solvents are concerned). Recently, we reinvestigated the application of the *tert*-amino effect for the synthesis of pyridopyridazines and quinolines using MW irradiation.[5] Significant rate enhancements and yields, higher than those obtained under conventional heating conditions (Δ), were observed. However, in most cases, high boiling solvents were used, hampering the isolation of the final compounds. In this communication, we wish to report our recent study on the solvent-free synthesis of pharmacologically interesting pyrido-fused ring systems under both MW irradiation and conventional heating conditions. We also wish to report our preliminary results on the cyclization of *ortho*-[1′-azacycloalkyl]benzaldehydes in water in the presence of a base or in dry media, using Al_2O_3–KF as basic solid support.

2. Results and discussion

A strict comparison between reactions under MW irradiation and conventional heating conditions has been made, using a dedicated monomode MW reactor Discover (CEM) and a pre-heated oil bath under the same set of conditions. The bulk temperature of all reactions mixtures was measured by infrared detection (for closed vessel reactions, magnetical stirring, when using solvents) or by a fiber optic temperature sensor (for open vessel reactions, mechanical stirring, solvent-free conditions). The temperature profiles (ramp and hold time) appeared to be nearly identical under both MW and conventional heating conditions, avoiding thus any effect of thermal inertia. Temperature/power profile is given in one typical example (Fig. 1).

Two series of starting materials **1a–c**, and **3a–c**, synthesized according to the procedures described earlier,[6–8] were heated neat above their melting points under both conventional heating and MW irradiation conditions[9]

Keywords: Microwave; *tert*-Amino effect; Pyrido-fused; Solvent free.
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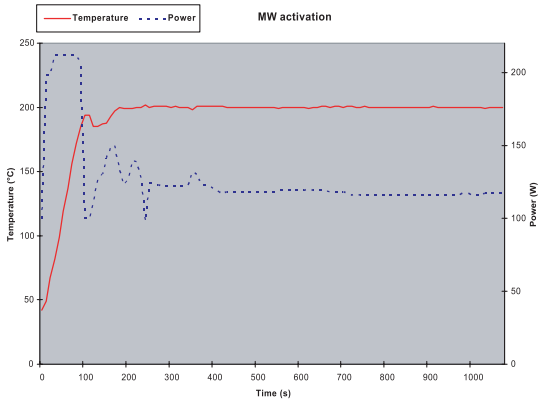
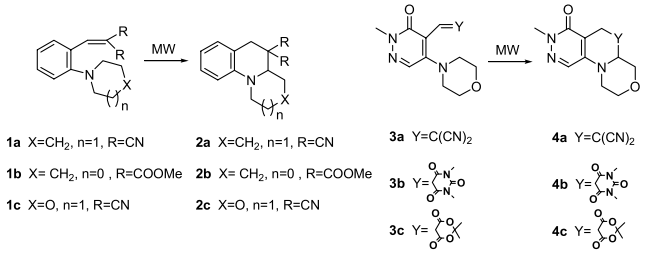


Figure 1. Temperature/power profile for the microwave-assisted solvent-free cyclization of **3a** in sealed vessel; temperature control using feedback from IR thermography (200 °C ceiling temperature, 200 W maximum power, 2 min ramp time, 18 min hold time).



Scheme 1. Solid-phase synthesis of pyrido-fused heterocycles.

(Scheme 1). In comparison with the reactions in solution,[7,8] the solvent-free procedure furnishes a remarkable improvement in yields and purities of the obtained products (Table 1). Thus, solvent-free cyclization of the *ortho*-vinyl-*tert*-aniline **1a** provided the fused product **2a** in 99% yield under both MW and conventional heating conditions, whereas in solution the isolated yields never exceeded 80%. Analogous results were obtained for the compound **1b**. Using the solvent-free procedure, the dinitrile derivative **3a** underwent ring closure in 18 min under MW irradiation (Fig. 1) and in 20 min under conventional heating conditions to afford the desired product **4a** in 75 and 78% yield, respectively. It should be noted that the best yield for the corresponding reaction in solution was 35% (DMSO, 150 °C, 44 h). However, when the reaction time was increased to 20 min, the yield of MW-assisted experiment dropped to 67% and turned out to be lower than the one obtained under oil bath conditions (78%) due to partial decomposition of the compounds. The dimethylbarbituric acid derivative **3b** has been cyclized under both MW-assisted and conventional solvent-free conditions at 210 °C within 1 min to afford the expected spirocyclic system **4b** in almost quantitative yield, compared to only 63% under the best conditions in *n*-butanol under MW irradiation.[5]

On the contrary, conventional heating or MW irradiation of the Meldrum's acid derivative **3c** at its melting point resulted in decomposition of the starting material, which can probably be explained by an easy decarboxylation of **3c** at this elevated temperature. The above-mentioned problem could be partially avoided by performing the reaction at 175 °C on neutral alumina, providing the spirocyclic product **4c** in 31% yield under conventional heating conditions and in 55% yield for the MW-assisted reaction, next to decomposition. The isolated yields appeared to be lower than the ones reported for the reactions in solution, but we could perform the cyclization in a substantially shorter time (7 min vs 5 h or 30 min) following this safe and

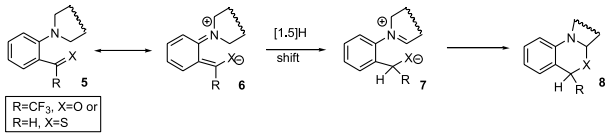
Table 1. Synthesis of pyrido-fused systems

Compound; mp (°C)	Solution-phase reactions[a]				Solvent-free reactions[b]		
	Method of activation	Solvent	Temp (°C)/ time[c]	Yield of **2** or **4** (%)	Method of activation	Temp (°C)/ time (min)	Yield of **2** or **4** (%)
1a (122)	Δ	*n*-BuOH	117/2 h	78	Δ	150/5	99
	MW	*n*-BuOH	200/3 min	80	MW	150/5	99
1b (88)	Δ	*n*-BuOH	117/22 h	67	Δ	170/17	87
	MW	*n*-BuOH	220/15 min	73	MW	170/17	86
1c (133–138 decomp.)	Δ	*n*-BuOH	117/ 35 h	84	Δ	180/22	94
					Δ	180/5	<2
	MW	*n*-BuOH	220/30 min	96	MW	180/22	94
					MW	180/5	58[d]
3a (180)	Δ	DMSO	150/44 h	35	Δ	200/18	57[e]
					Δ	200/20	78
	MW	DMSO	210/42 min	29	MW	200/18	75
					MW	200/20	67
3b (209)	Δ	xylene[f]	138/2 h	45	Δ	210/1	97
	MW	*n*-BuOH	230/5 min	63	MW	210/1	96
3c (216)	Δ	DMF	100/5 h	79	Δ	216/1	0[g]
					Δ[h]	175/ 7	31
	MW	DME	200/30 min	73	MW	216/1	0[g]
					MW[h]	175/7	55

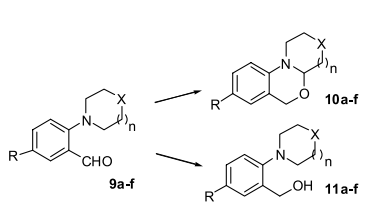
[a] Results reported in the literature.[5,7,8]
[b] All reactions were carried out in open vessels on a 0.5 mmol scale, for MW-assisted experiments at a maximum power level of 300 W for **1a–c**, **3b–c** and at 200 W for **3a**.
[c] Hold time for MW-assisted experiments.
[d] Ratio **1c**:**2c**=1:1.7 determined by GC and ^{1}H NMR.
[e] Ratio **3a**:**4a**=1:9 determined by GC and ^{1}H NMR.
[f] Performed with a catalytic amount of aluminum trichloride.
[g] Only decomposition of the starting material was observed.
[h] Performed on neutral alumina.

environmentally friendly protocol. For all solvent-free conversions, except for the dinitrile derivative **3a**, the yields as well as the time needed to reach completion appeared to be more or less the same under both conventional heating and MW irradiation conditions. When the morpholine derivative **1c** was heated neat at 180 °C for 22 min, the fused compound **2c** was formed in 94% yield in both MW and oil bath experiments. However, when the same reactions were checked after 5 min, practically no conversion of starting material **1c** was observed under conventional heating conditions, whereas MW irradiation seemed to be superior, providing the cyclized product **2c** in 58% yield.

In the course of our investigations of the '*tert*-amino effect' under MW irradiation we reported the formation of benz-1,3-oxazines[10] by ring closure of benzaldehydes bearing a *N*,*N*-dialkylamino group in the *ortho*-position.[5] The preparation of such benz-1,3-oxazines, starting from *ortho*-acyl-*N*,*N*-dialkylanilines[11] or 1-(1-pyrrolidinyl)-benzenes substituted with a thiocarbonyl group in the *ortho*-position,[12] has already been described in the literature. However, because of the better stabilization of the negative charge in the resonance form **6** (Scheme 2), in order to allow the intramolecular [1.5] hydrogen shift, a strongly electron-withdrawing group adjacent to the carbonyl moiety (R = CF_3) or a thiocarbonyl group (X = S) were reported to be crucial for this reaction to take place.[11a,12]



Scheme 2. Proposed mechanism for the cyclization of **5**.[11a,12]



Aldehyde	R	n	X
9a	H	0	CH_2
9b	MeO	0	CH_2
9c	H	1	CH_2
9d	MeO	1	CH_2
9e	H	1	O
9f	MeO	1	O

Scheme 3. Cyclization of benzaldehyde derivatives **9a**–**f**.

Here, we report our further investigations concerning the formation of benz-1,3-oxazines under microwave irradiation. First we examined the activity of aldehyde **9a** toward cyclization (Scheme 3). According to our previously reported procedure,[5] an aqueous suspension of **9a** was irradiated at 200 °C for 60 min in the presence of K_2CO_3 (1 equiv) to give benzoxazine **10a** in 41% yield together with 28% of recovered starting material (Table 2, entry 1) (caution: irradiation of the reaction mixture at a ceiling temperature above 200 °C, resulted in a rapid increase of pressure). Irradiation of an aqueous suspension of aldehyde **9a** at a lower temperature or for a shorter time, resulted in lower yields of benzoxazine **10a**. Moreover, performing the reaction applying the same set of parameters, but under conventional heating, did not result in any conversion of starting material (entry 2). Without the addition of base the reaction did not proceed neither in polar solvents (*n*-butanol or water, entries 4 and 5), nor when aldehyde **9a** was heated neat at a ceiling temperature of 200 °C (entry 6). Surprisingly, irradiation of a solution of **9a** in *n*-butanol in the presence of 1 equiv of K_2CO_3 resulted in formation of alcohol **11a**, together with unreacted starting material (entry 3). This could point to the occurrence of a competitive Cannizzaro reaction, although we were unable to detect the corresponding carboxylic acid. Lewis acid catalysis with $AlCl_3$ or TFA seemed to be ineffective (entries 7 and 8). Surprisingly the benz-1,3-oxazine **10a** was obtained in 17% yield when silica was used as a solid support (entry 9). In order to gain insight in the reaction mechanism, the irradiation of a suspension of aldehyde **9a** in D_2O in the presence of K_2CO_3 (1 equiv) was carried out under the same

Table 2. Cyclization of 2-(pyrrolidin-1-yl)benzaldehyde **9a**

Entry	Activation mode	Conditions[a]	Product (yield, %)
1	MW	H_2O, K_2CO_3 (1 equiv), 90 W, 200 °C, 60 min	**10a** (41%) **9a** (28%)
2	Δ	H_2O, K_2CO_3 (1 equiv), 200 °C, 60 min	—[b]
3	MW	*n*-BuOH, K_2CO_3 (1 equiv), 300 W, 200 °C, 60 min	**11a**[c]
4	MW	*n*-BuOH, 300 W, 250 °C, 60 min	—[b]
5	MW	H_2O, 300 W, 194 °C[d], 60 min	—[b]
6	MW	Neat, 300 W, 200 °C, 60 min	—[b]
7	MW	Toluene, $AlCl_3$ (cat), 300 W, 200 °C, 30 min	—[b]
8	MW	H_2O, TFA (1 equiv), 150 W, 200 °C, 30 min	—[e]
9	MW	Silica[f] 100 W, 200 °C, 60 min	**10a** (17%)
10	MW	D_2O, K_2CO_3 (1 equiv), 90 W, 200 °C, 60 min	**10a**(41%)[g]
11	MW	Al_2O_3–KF (3:1)[h], 100 W, 200 °C, 60 min	**10a**(42%)
12	Δ	Al_2O_3–KF (3:1)[h], 200 °C, 60 min	**10a** (28%)
13	MW	Al_2O_3[i], 100 W, 200 °C, 60 min	—[e]

[a] All reactions were performed on a 1 mmol scale in closed vessels with pressure control all along the reaction.
[b] No reaction, only starting material was recovered.
[c] Determined by CI-MS, not isolated.
[d] This is the maximum temperature that the system could reach.
[e] Complex mixture.
[f] 0.3 g of silica gel/mmol of starting material.
[g] No D insertion was observed.
[h] 0.4 g of Al_2O_3–KF/mmol of starting material.
[i] 0.3 g of Al_2O_3/mmol of starting material.

conditions as for entry 1 (entry 10). No incorporation of deuterium in the obtained benz-1,3-oxazine **10a** was observed, supporting the concept of a concerted cyclization mechanism (Scheme 2).[11a]

In order to develop a solvent free protocol, on the way to 'Green Chemistry', we decided to investigate the application of a basic solid support. Alumina/KF, introduced by Clark and Ando[13] seemed to be interesting for this purpose. This support differs from other oxide-type solid base catalysts due to so-called 'half-naked' and thus active fluorine anions, making it especially effective in promoting various base-catalyzed reactions.[14]

To get a proper dispersion of aldehyde **9a** on the support, the compound was dissolved in 0.5 mL of dichloromethane, which was subsequently evaporated from the alumina/KF suspension, under reduced pressure. The resulting solid was heated at 200 °C for 60 min under either MW-assisted or conventional conditions (entries 11 and 12) to provide benz-1,3-oxazine **10a** in 42 and 28% yield, respectively.

It should be noted that the use of basic alumina without KF (entry 13) resulted in the formation of a complex mixture containing only traces of the desired compound. To evaluate the scope and limitations of this method, a set of *ortho*-[1′-azacycloalkyl]benzaldehydes[6] was submitted to the optimized reaction conditions. Aqueous suspensions of aldehydes **9b–f** were irradiated at 200 ° C for 60 min in the presence of K_2CO_3 (1 equiv) or aldehydes **9b–f** were dispersed on an Al_2O_3–KF (3:1) mixture and irradiated at 200 °C for 60 min. Unfortunately only in the case of **9b** acceptable yields were obtained (Table 3). Switching from a five-membered pyrolidine substituent to a six-membered piperidine or morpholine moiety seems to have a deleterious effect on the outcome of this ring closure. Remarkably, an attempt to cyclize aldehydes **9e**,**f** in aqueous media resulted in the formation of the alcohols **11e**,**f**, without any trace of the desired compounds, whereas irradiation of **9e**,**f** on Al_2O_3–KF, afforded the benzoxazines **10e**,**f**.

3. Conclusion

A new operationally simple, safe and environmentally benign solvent-free procedure is described for the synthesis of different pyridopyridazines and quinolines, applying the *tert*-amino effect under both MW and conventional heating conditions. The isolated yields of the solvent-free reactions appeared to be significantly higher than the ones obtained in the corresponding reactions in solution. We also investigated the cyclization of *ortho*-(1′-azacycloalkyl) benzaldehydes to benz-1,3-oxazines in water in the presence of base or in dry media using Al_2O_3–KF as a basic solid-support under both conventional and MW-assisted conditions. The ring size of the *tert*-amino substituent seems to play an important role for the outcome of this reaction.

4. Experimental

4.1. General

Melting points were determined using a Reichert-Jung Thermovar apparatus or an Electrothermal 9200 digital melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM 250 or Bruker Avance 300 instrument, using $CDCl_3$ as solvent. The ^{1}H and ^{13}C chemical shifts are determined in ppm relative to tetramethylsilane, or using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150–250 °C as required. For thin-layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70–230 mesh silicagel (E.M. Merck)) were used. Crude products were analyzed by gas chromatography (GC 9000 Series Fisions), which was fitted with a non-polar capillary column and a Turbochrom data system developed by Perkin Elmer Co. Semiempirical (PM3) calculations were carried out by using Spartan program package (Spartan SGI Version 5.1.1., Wavefunction Inc. 1998) on silicon graphics (INDY R 4400). All chemicals were purchased from the commercial sources (across) and used without further purification. Aluminum oxide (basic, particle size 0.05–0.15 mm) was purchased from Fluka. Compounds **1a–c**, **3a–c** and **9a–f** were prepared according to the published procedures.[6–8] Compounds **2a–c** and **4a–c** have melting points and spectral data identical with the published values.[7,8] Compound **11e** is available from commercial sources (CAS N 465514-33-4).

4.2. Microwave irradiation experiments

A monomode CEM-Discover MW reactor (CEM Corporation PO Box 200 Matthews, NC 28106) was used in the standard configuration as delivered, including proprietary software.[15] All experiments were carried out in MW process vials (10 mL) with control of the temperature by infrared detection or fiber optic temperature sensor for open vessel experiments (as was the case for the reactions performed under conventional heating conditions). After completion of the reaction, the vial was cooled to 50 °C via air jet cooling.

Table 3. Cyclization of *ortho*-(1′-azacycloalkyl)benzaldehydes **9b–f** (Scheme 3)[a]

Entry	Aldehyde	R	*n*	X	Products (yield, %)	
					In water[b]	On Al_2O_3–KF[c]
1	**9b**	MeO	0	CH_2	**10b** (51) **9b** (11)	**10b** (52) **9b** (5)
2	**9c**	H	1	CH_2	**10c** (14) **9c** (30)	**10c** (9) **9c** (19)
3	**9d**	MeO	1	CH_2	**10d** (14) **9d** (27)	**10d** (9) **9d** (17)
4	**9e**	H	1	O	**11e** (10) **9e** (69)	**10e** (6) **9e** (17)
5	**9f**	MeO	1	O	**11f** (16) **9f** (50)	**10f** (6) **9f** (10)

[a] All reactions were performed on a 1 mmol scale; according to TLC-analysis, besides decomposition, no other compounds were formed than the one indicated.
[b] H_2O, K_2CO_3(1 equiv), 90 W, 200 °C, 60 min.
[c] Al_2O_3/KF (3:1), 0.4 g/mmol of starting material, 100 W, 200 °C, 60 min.

4.3. Solvent-free cyclization of 3c on aluminum oxide

Neutral alumina (0.8 g) was added to a solution of **3c** (0.17 g, 0.5 mmol) in dichloromethane (1 mL) and the solvent was evaporated under reduced pressure. The resulting yellowish powder was transferred to a vial and heated in an oil bath at 175 °C for 7 min or irradiated at 175 °C for 7 min (hold time) at 300 W maximum power. The vial was cooled to room temperature, the crude mixture was transferred to the top of a column filled with silica gel and purified using dichloromethane–ethylacetate (1:9) as eluent to give an analytically pure sample of **4c** in 55% yield.

4.4. Typical procedures for MW-assisted cyclizations of *ortho*-(1′-azacyclo-alkyl)benzaldehydes

(A). *In water*. A suspension of aldehyde **9a–f** (1 mmol) and K_2CO_3 (1 mmol) in water (3 mL) was irradiated in closed vessels with pressure control at 200 °C for 60 min (hold time) at 90 W maximum power. The reaction mixture was extracted with dichloromethane (10 mL×3). The combined organic layers were dried over Mg_2SO_4, filtered and evaporated. The residue was subjected to column chromatography on silica gel (eluent: dichloromethane–hexanes 1:1) for compounds **10a–c** or dichloromethane for compounds **10d–f**, **11e**,**f** to afford benzoxazines **10a–f** and alcohols **11e**,**f** as oils.

(B). *On alumina*. A solution of aldehyde **9a–f** (1 mmol) in dichloromethane (0.5 mL) was added to a mixture of Al_2O_3–KF (0.4 g, 3:1 w/w) and the solvent was evaporated under reduced pressure. The resulting yellowish powder was irradiated at 200 °C for 60 min at 100 W power, cooled to room temperature, applied on the top of a column with silica gel and purified as indicated under (A).

4.4.1. 1,2,3,3a-Tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine (10a). ^{1}H NMR ($CDCl_3$): δ 7.16 (t, 1H, J=7.3 Hz), 6.93 (d, 1H, J=7.3 Hz), 6.75 (t, 1H, J=7.3 Hz), 6.71 (d, 1H, J=8 Hz), 4.96 (d, 1H, J=14.6 Hz), 4.95 (m, 1H), 4.77 (d, 1H, J=14.6 Hz), 3.62 (m, 1H), 3.27 (m, 1H), 2.35 (m, 1H), 2.01 (m, 3H). ^{13}C NMR ($CDCl_3$): 143.6, 128.1, 125.1, 122.0, 118.3, 115.6, 89.9, 68.6, 50.1, 32.8, 23.0. DEPT ($CDCl_3$): 128.1, 125.1, 118.3, 115.6, 89.9, −68.6, −50.1, −32.8, −23.0. MS (CI): *m*/*z* (%)=176 (100) [MH^+]. HR-MS (EI): $C_{11}H_{13}ON$ calcd 175.09971, found 175.09869.

4.4.2. 7-Methoxy-1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine (10b). ^{1}H NMR ($CDCl_3$): δ 6.76 (d, 2H, J=1.5 Hz), 6.52 (s, 1H), 4.90 (d, 1H, J=14.6 Hz), 4.87 (m, 1H), 4.73 (d, 1H, J=14.6 Hz), 3.76 (s, 3H), 3.59 (m, 1H), 3.17 (m, 1H), 2.33 (m, 1H), 1.99 (m, 3H). ^{13}C NMR ($CDCl_3$): 153.4, 133.7, 124.3, 119.1, 114.1, 110.4, 90.1, 68.2, 56.1, 51.9, 32.9, 23.2. DEPT ($CDCl_3$): 119.1, 114.1, 110.4, 90.1, −68.2, 56.1, −51.9, −32.9, −23.2. MS (CI): *m*/*z* (%)=206 (100) [MH^+]. HR-MS (EI): $C_{12}H_{15}O_2N$ calcd 205.11028, found 205.10572.

4.4.3. 2,3,4,4a-Tetrahydro-1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazine (10c). ^{1}H NMR ($CDCl_3$): δ 7.17 (t, 1H, J=7.3 Hz), 6.93 (d, 2H, J=8 Hz), 6.85 (t, 1H, J=7.3 Hz), 5.02 (d, 1H, J=14.6 Hz), 4.85 (d, 1H, J=14.6 Hz), 4.32 (dd, 1H, ^3J=8, 3.7 Hz), 3.69 (m, 1H), 2.72 (m, 1H), 2.03 (m, 1H), 1.75 (m, 4H), 1.50 (m, 1H). ^{13}C NMR ($CDCl_3$): 146.0, 127.8, 125.0, 124.2, 120.1, 115.7, 86.5, 67.9, 47.3, 31.8, 25.6, 21.8. DEPT ($CDCl_3$): 127.8, 125.0, 120.1, 115.7, 86.5, −67.9, −47.3, −31.8, −25.6, −21.8. MS (CI): *m*/*z* (%)=190 (100) [MH^+]. HR-MS (EI): $C_{12}H_{15}ON$ calcd 189.11536, found 189.11484.

4.4.4. 8-Methoxy-2,3,4,4a-tetrahydro-1*H*,6*H*-pyrido-[1,2-*a*][3,1]benzoxazine (10d). ^{1}H NMR ($CDCl_3$): δ 6.90 (d, 1H, J=8.8 Hz), 6.76 (dd, 1H, ^3J=8.8 Hz, ^4J=2.9 Hz), 6.50 (d, 1H, J=2.9 Hz), 4.99 (d, 1H, J=14.6 Hz), 4.84 (d, 1H, J=14.6 Hz), 4.31 (q, 1H, J=2.9 Hz), 3.76 (s, 3H), 3.45 (m, 1H), 2.78 (m, 1H), 1.97 (m, 1H), 1.76 (m, 4H), 1.51 (m, 1H). ^{13}C NMR ($CDCl_3$): 154.4, 140.5, 126.5, 119.4, 113.7, 110.0, 86.3, 67.9, 55.9, 48.9, 31.4, 25.7, 20.9. DEPT ($CDCl_3$): 119.4, 113.7, 110.0, 86.3, −67.9, 55.9, −48.9, −31.4, −25.7, −20.9. MS (CI): *m*/*z* (%)=220 (100) [MH^+]. HR-MS (EI): $C_{13}H_{17}O_2N$ calcd 219.12593, found 219.12549.

4.4.5. 1,2,4,4a-Tetrahydro-6*H*-[1,4]oxazino[4,3-*a*][3,1]-benzoxazine (10e). ^{1}H NMR ($CDCl_3$): δ 7.20 (t, 1H, J=7.3 Hz), 6.89 (m, 3H), 5.05 (d, 1H, J=14.6 Hz), 4.90 (d, 1H, J=14.6 Hz), 4.37 (dd, 1H, ^3J=7, 3.6 Hz), 3.99 (m, 2H), 3.66 (m, 2H), 3.18 (t, 1H, J=5.1 Hz), 2.96 (m, 1H). MS (CI): *m*/*z* (%)=192 (100) [MH^+]. HR-MS (EI): $C_{11}H_{13}O_2$ calcd 191.09463, found 191.09509.

4.4.6. 8-Methoxy-1,2,4,4a-tetrahydro-6*H*-[1,4]oxazino-[4,3-*a*][3,1]benzoxazine (10f). ^{1}H NMR ($CDCl_3$): δ 6.87 (d, 1H, J=8.8 Hz), 6.76 (dd, 1H, ^3J=8.8 Hz, ^4J=2.9 Hz), 6.53 (d, 1H, J=2.9 Hz), 5.02 (d, 1H, J=14.6 Hz), 4.90 (d, 1H, J=14.6 Hz), 4.29 (q, 1H, J=2.9 Hz), 3.91 (m, 4H), 3.77 (s, 3H), 3.42 (m, 1H), 2.93 (m, 1H). ^{13}C NMR ($CDCl_3$): 155.0, 139.6, 126.5, 119.6, 113.9, 110.1, 82.9, 69.4, 67.7, 67.3, 55.9, 48.1. DEPT ($CDCl_3$): 119.6, 113.9, 110.1, 82.9, −69.4, −67.7, −67.3, 55.9, −48.1. MS (CI): *m*/*z* (%)=222 (100) [MH^+].

4.4.7. (2-Morpholinophenyl)methanol (11e). ^{1}H NMR ($CDCl_3$): δ 7.23 (m, 4H), 4.98 (br s, 1H), 4.83 (s, 2H), 3.89 (t, 4H, J=4.4 Hz), 3.01 (t, 4H, J=4.4 Hz). ^{13}C NMR ($CDCl_3$): 150.9, 136.0, 129.2, 128.9, 125.5, 121.1, 67.9, 64.8, 53.2. DEPT ($CDCl_3$): 129.2, 128.9, 125.5, 121.1, −67.9, −64.8, −53.2. MS (CI): *m*/*z* (%)=194 (26) [MH^+], 176 (31) [$MH^+ - H_2O$].

4.4.8. (5-Methoxy-2-morpholinophenyl)methanol (11f). ^{1}H NMR ($CDCl_3$): δ 7.17 (d, 1H, J=8.1 Hz), 6.82 (dd, 1H, ^3J=8.1 Hz, ^4J=2.9 Hz), 6.75 (d, 1H, J=2.9 Hz), 4.78 (s, 2H), 3.86 (t, 4H, J=4.4 Hz), 3.80 (s, 3H), 2.94 (t, 4H, J=4.4 Hz). ^{13}C NMR ($CDCl_3$): 157.4, 143.9, 137.6, 122.6, 114.3, 113.6, 67.9, 65.1, 55.8, 53.6. DEPT ($CDCl_3$): 122.6, 114.3, 113.6, −67.9, −65.1, 55.8, −53.6. MS (CI): *m*/*z* (%)=224 (62) [MH^+], 206 (31) [$MH^+ - H_2O$], 194 (6) [$MH^+ - Me_2O$]. HR-MS (EI): $C_{12}H_{17}O_3N$ calcd 223.12084, found 223.12110.

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New synthetic approaches to sugar ureas. Access to ureido-β-cyclodextrins

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Abstract—An efficient method for the preparation of urea-bridged cyclodextrins using triphosgene in the isocyanation step in an aqueous two-phase system is reported. Per-*O*-acetylated glycopyranosylamines and 2-amino-2-deoxy-α and β-D-glucose were also transformed into the corresponding isocyanates using either an aqueous two-phase or an anhydrous dichloromethane medium, and converted in situ into ureas. An alternative method for the preparation of sugar-derived ureas consisting of desulfurization of sugar thioureas with mercury oxide is also presented.

1. Introduction

Urea functionality is a structural feature present in many biologically active compounds, such as anti-mycobacterial[1] and anti-trypanosomal[2] agents, plant and insect growth regulators,[3,4] and as antagonists of natural receptors.[5,6] Several ureido derivatives have also proved to be anti-tumor agents,[7–9] and to inhibit HIV protease[10–15] and glycine transporter GlyT-2.[16]

In the carbohydrate field, pseudooligosaccharides incorporating a urea bridge have been found in glycocinnamoyl spermidine antibiotics.[17] Synthetic *N*-nitrosoureas derived from aminosugars have shown to be useful as antitumorals[18] and naturally-occuring streptozotocin,[19] a *N*-nitrosourea derived from 2-amino-2-deoxy-D-glucose, is widely used to induce diabetes mellitus in experimental animals.[20] Furthermore, some ureido glycuronate derivatives have shown to be α-glucosidase inhibitors[21] and *N*-acyl-*N*′-β-D-glucopyranosyl ureas exhibit strong inhibition against glycogen phosphorylase,[22] and so they could act as antidiabetic agents.[23]

Cyclodextrins are cyclic oligosaccharides that possess practical applications in medicinal[24] and supramolecular chemistry.[25] For instance, they are able to form complexes, improving solubilization and bioavailability of lipophilic drugs,[26,27] and they have also been used in the design of artificial enzymes[28,29] and for separation of enantiomers.[30] Much effort has been devoted to the preparation of cyclodextrin dimers[31] in order to improve the binding properties of the parent structure.[28] For this purpose, many different linkages have been introduced[32] in the preparation of dimers, among which we can find the urea tether.[33]

Sugar ureas have often been obtained by reaction of glycosylamines or amino sugars with alkyl or aryl isocyanates[34,35] in anhydrous solvents. The synthesis of fully *O*-protected sugar isocyanates has also been reported by Jochims[36] by reaction of *O*-protected amino sugars and toxic phosgene in anhydrous toluene.

To avoid handling hazardous phosgene, other methods to afford sugar ureas have been developed. These methods involve the use of aryl carbamates derived from amino sugars,[37] the use of phosphinimines[38] or carbodiimides[39] as intermediates, or the oxidation of glycosyl isocyanides with pyridine *N*-oxide proposed by Ichikawa et al.[40] By the last procedure, Prosperi et al. have described the synthesis of nonsymmetrical urea-linked disaccharides in which two glycopyranoside units are bound at the 1→2, 1→4, and 1→6 positions.[41]

Recently, we have communicated[42] our preliminary results on the one-pot two-phase preparation of sugar-derived ureas, including cyclodextrin derivatives. Ureas were obtained starting from sugar amines and glycopyranosylamines by using triphosgene[43] in the isocyanation step. Herein we report the full details of this procedure and our results of a different approach to access sugar ureas, based

Keywords: Cyclodextrin; Triphosgene; Sugar isocyanates; Ureas; Mercury oxide; Two-phase system.
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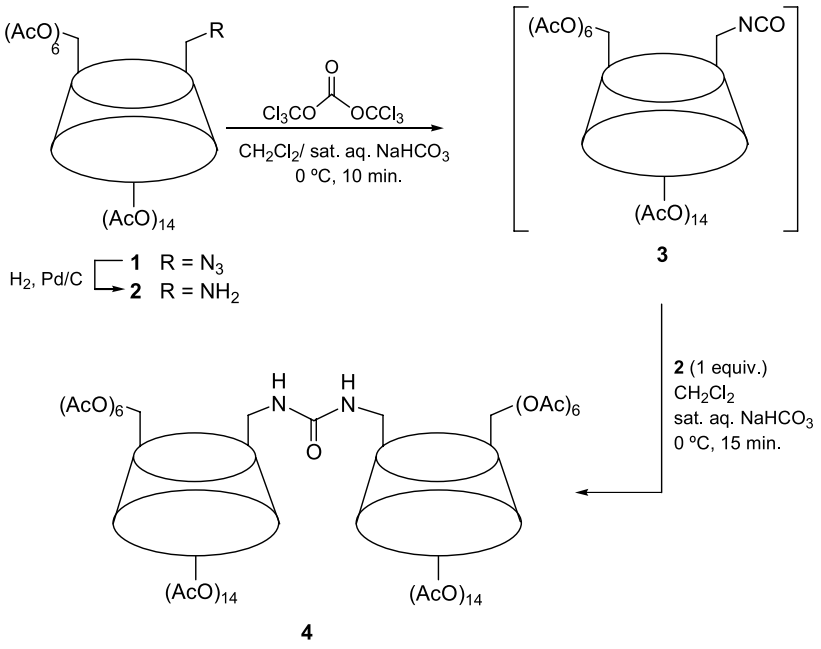


Scheme 1.

on desulfurization of sugar thioureas through non-isolated carbodiimides. Fischer's per-*O*-acetylated β-D-glucopyranosyl isocyanate **20**,[44] which we use without isolation in the synthesis of β-D-glucopyranosyl ureas, has been recently prepared as a crystalline form from the *O*-protected β-D-glucopyranosylamine with triphosgene under Schotten-Baumann conditions.[45]

2. Results and discussion

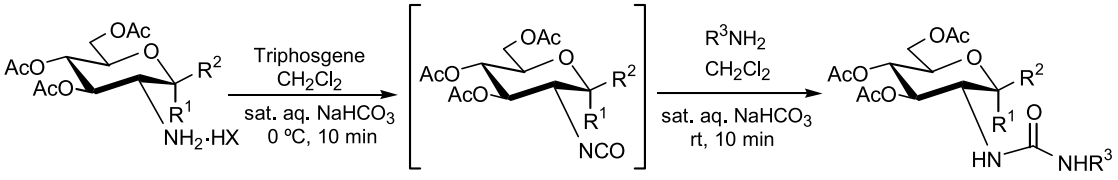
We have carried out the synthesis of β-cyclodextrin dimer **4** starting from per-*O*-acetylated 6^A-azido-6^A-deoxy-β-cyclodextrin **1**,[46] which was prepared in three steps from β-cyclodextrin: monotosylation with 1-(*p*-toluenesulfonyl)-imidazole,[47] acetylation and displacement of the tosyloxy group with sodium azide (Scheme 1).

Compound **1** was hydrogenated in the presence of palladium over charcoal to afford monoamino derivative **2**, which was used without further purification for the isocyanation step; thus, crude **2** was dissolved in a vigorously stirred 1:1 CH_2Cl_2–saturated aqueous $NaHCO_3$ mixture at 0 °C, to which solid triphosgene was added. After 15 min of stirring at 0 °C, another equivalent of monoamino **2** was added to afford β-cyclodextrin dimer **4** in a 49% yield for the three steps (hydrogenation, isocyanation of the amine and coupling with the same amine). The overall yield for the preparation of **4** is comparable to a recently described procedure[48] involving a polymer-bound triphenylphosphine, carbon dioxide and azide **1**.

The same method was applied to the preparation of per-*O*-acetylated 6-monodeoxy-6-mono[3-(β-D-glucopyranos-2-yl)ureido]-β-cyclodextrin **15** starting from readily available hydrochloride **6**[49] (Scheme 2). Treatment of compound **6** with triphosgene under the conditions described above led to isocyanate **8** which was used in situ for coupling with amine **2** to give β-cyclodextrin-derived urea **15** in a 46% yield, calculated from azide **1**.

Similarly, 2-ureido-α and β-D-glucopyranoses **9**, **10**, **12** and **13** and urea-linked symmetrical pseudo-disaccharides **11** and **14** were obtained (Scheme 2) in good yields (63–86%) starting from 2-amino-2-deoxy-D-glucopyranose hydrohalides of α- and β-configurations **5**[50] and **6**, and using alkyl and arylamines or the same hydrohalide for the coupling reaction with the non-isolated isocyanates **7** and **8** (Table 1, Method A).

Isocyanates **7** and **8** were obtained as syrups in quantitative yields by extraction with dichloromethane after the isocyanation step. NMR spectra of crude **7** and **8** showed no impurities; however, column chromatography of these



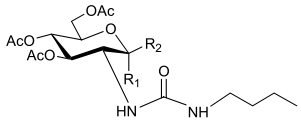
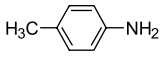
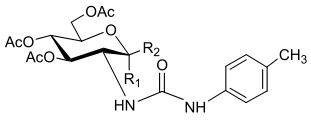
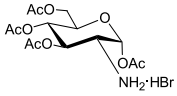
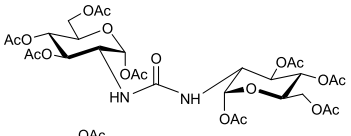
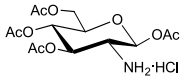
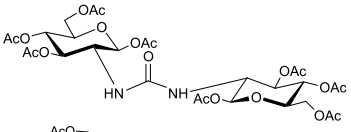
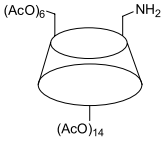
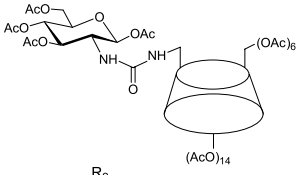
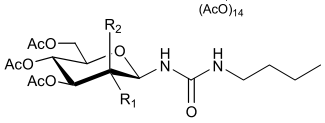
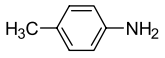
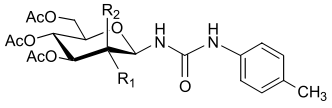
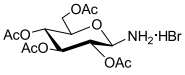
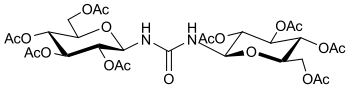
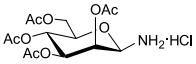
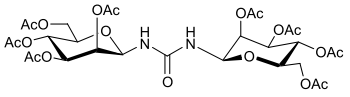
5 R^1=OAc, R^2=H, X=Br
6 R^1=H, R^2=OAc, X=Cl

7 R^1=OAc, R^2=H
8 R^1=H, R^2=OAc

9-11 R^1=OAc, R^2=H
12-15 R^1=H, R^2=OAc

Scheme 2.

Table 1. Synthesis of ureas **9–15** and **22–27**

Entry	Amines	Products	Ureas	Method	
				A[a]	B[b]
1	$CH_3(CH_2)_3NH_2$		**9** **12**	73[c] 86	58[c] —
2			**10** **13**	63 86	66 —
3			**11**	82	62
4			**14**	78	—
5			**15**	46	—
6	$CH_3(CH_2)_3NH_2$		**22** **25**	63 71	65 —
7			**23** **26**	66 58	64 —
8			**24**	99	54
9			**27**	69	—

[a] Biphasic CH_2Cl_2/water reaction conditions.
[b] Monophasic anhydrous CH_2Cl_2 reaction conditions.
[c] Isolated yields.

isocyanates led to extensive decomposition. Resonances at 125.9 and 126.7 ppm, for compounds **7** and **8** in ^{13}C NMR (Table 2), together with strong IR absorbtions at 2261 and 2253 cm^{-1}, respectively, confirm the presence of a –NCO moiety. These data are in agreement to those found for Fischer's isocyanate **20**,[44] studied spectroscopically by Ichikawa.[45]

Following the same one-pot biphasic procedure we have also carried out the preparation of per-*O*-acetylated glycopyranosyl ureas of D-*gluco* and D-*manno* configuration (Scheme 3). Crystalline hydrobromide **18**[51] was prepared from compound **16** after removal of the enamino group by oxidation with bromine in moist dichloromethane. Compound **18** was treated subsequently with triphosgene and with several amines in the biphasic medium to afford ureas **22–24**, via the non-isolated isocyanate **20**, in a 63–99% yield calculated from **18** (Table 1, Method A).

As hydrohalide **19**[52,53] could not be obtained as a crystalline product, the enamino group of compound **17** was removed by adding aliquots of a saturated solution of Cl_2 in moist CH_2Cl_2 at 0 °C over a 2 h period, until disappearance of the starting material by TLC. After solvent removal, crude hydrohalide **19** was directly used for the next two steps (isocyanation and coupling of isocyanate **21** with amines) to afford mannopyranosyl ureas **25–27** (Scheme 3) in a 58–71% overall yield for the three steps (Table 1, Method A). By-products formed in chlorolysis of enamine-derived **17** did not interfere with the following two steps. ^1H and ^{13}C NMR spectra of crude isocyanates **20**[45] and the hitherto unknown **21** (Table 2), obtained after the

Table 2. Selected data for isocyanates **7**, **8** and **21**

Compound	^{1}H and ^{13}C NMR data[a] (δ, ppm; J, Hz)						
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
7	6.25	3.80	5.39	5.07	4.08	4.29	4.04
8	5.59	3.78	5.14	5.01	3.83	4.29	4.07
21	4.77	5.39	5.05	5.22	3.71	4.23	4.17
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
7	3.6	10.4	9.7	9.9	3.9	2.3	12.3
8	8.6	10.2	9.4	9.7	4.6	2.1	12.6
21	1.2	3.2	10.0	10.0	5.0	2.5	12.5
	C-1	C-2	C-3	C-4	C-5	C-6	NCO
7	89.9	55.6	71.9	67.3	69.8	61.3	125.9
8	92.4	56.8	73.3	67.5	72.9	61.3	126.7
21	81.7	69.4	70.8	65.2	74.5	62.3	129.6

[a] In $CDCl_3$.

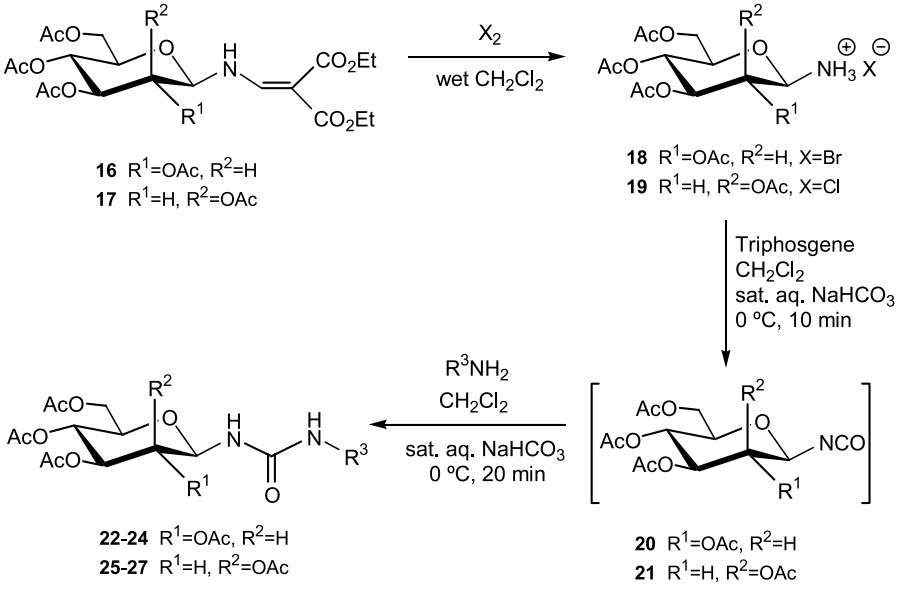
isocyanation step, showed these isocyanates to be the main products.

For the preparation of ureas **9**–**11**, and **22**–**24**, we also carried out the two steps (isocyanation and coupling with amines) in an anhydrous monophasic system. Thus, hydrohalides **5** and **18** were dissolved in dry dichloromethane containing 4 Å molecular sieves and diisopropylethylamine, and to the corresponding solutions at rt was dropwise added a solution of triphosgene in dry dichloromethane to give isocyanates **7** and **20**, respectively. These isocyanates were converted in situ into ureas **9**–**11** and **22**–**24** by addition of the corresponding amines in a 54–66% yield (Table 1, Method B). However, this procedure proved to be sensitive to moisture, and the use of molecular sieves proved to be essential for the yield of the reaction. Furthermore, the yields obtained by using anhydrous dichloromethane were in some examples lower than those obtained by the biphasic procedure (Table 1, Method A), despite moisture sensitivity associated to triphosgene and isocyanates.[54,55]

Finally, we have considered a third procedure for obtaining sugar ureas from the corresponding thioureas. They have been more extensively studied than the ureas counterparts due to easier preparation of sugar isothiocyanates[56] as compared to sugar isocyanates. This third procedure is based on the desulfurization of sugar thioureas by treatment with yellow mercury (II) oxide; these results contrast with the desulfurization of *O*-unprotected glucopyanosyl thioureas to afford trans-fused bicyclic isoureas.[57]

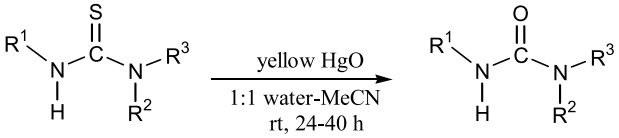
Treatment of thioureas **28**–**30** in aqueous acetonitrile with mercury oxide at rt for 1 h led to the corresponding carbodiimides, detected by TLC as a faster-moving compound; carbodiimides reacted slowly (24 h) at rt with water to give ureas **10**, **23** and **24** in a 67–74% yield (Table 3). For *N*,*N*-diethyl thiourea **31**, no carbodiimide was detected by TLC and a slower transformation (40 h) of thiourea into urea **32** took place in a 72% yield.

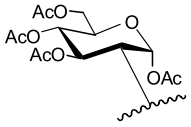
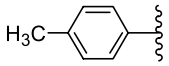
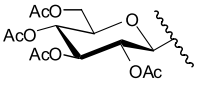
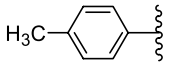
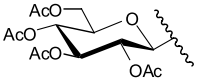
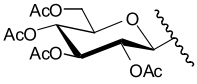
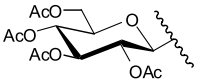
Per-*O*-acetylated thiourea **29** was prepared starting from thiourea **33**, easily available in a one-pot fashion from β-D-glucopyranosylamine.[57] Conventional acetylation of **33** at rt led regiospecifically to the new penta acetyl derivative **34** in



Scheme 3.

Table 3. Synthesis of ureas by desulfurization of thioureas **28–31**

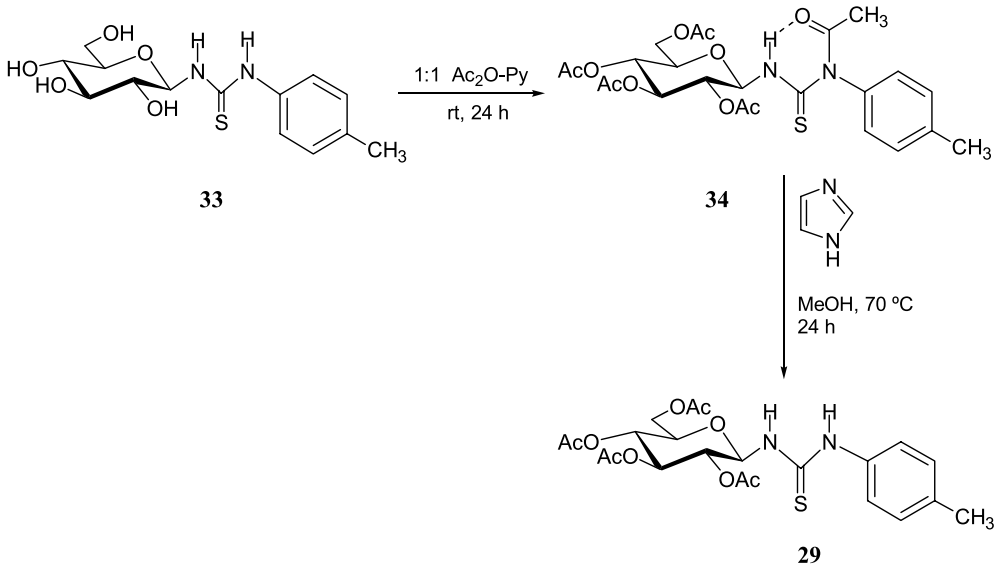


Entry	Thiourea	R^1	R^2	R^3	Urea	Yield (%)
1	**28**		H		**10**	67
2	**29**		H		**23**	74
3	**30**		H		**24**	68
4	**31**		CH_3CH_2–	CH_3CH_2–	**32**	72

a 73% yield (Scheme 4); probably due to steric hindrance no acetylation took place on the nitrogen attached to the sugar moiety. The strong deshielding exhibited by the NH proton in ^{1}H NMR of **34** (12.01 ppm) indicated the presence of an intramolecular hydrogen bonding with the carbonyl group of the vicinal *N*-acetyl moiety. Li et al. have recently reported[58] the use of imidazole as a mild base for the selective anomeric *O*-deacetylation of carbohydrates; using the same procedure we have carried out the selective *N*-deacetylation of **34** to give tetra-*O*-acetylated **29** in a 86% yield (Scheme 4).

Tetra-*O*-acetyl thioureas **28**, **31** and known **30**[51] were prepared by coupling reaction of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocianato-α-D-glucopyranose[59] and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylisothiocyanate[51] with the corresponding amines in EtOAc at rt.

In conclusion, we report a practical one-pot two-step synthesis in an aqueous two-phase system of urea-tethered cyclodextrin dimer **4** and of 6-monodeoxy-6-mono(*N*′-glucopyranos-2-ylureido)-β-cyclodextrin **15** through non-isolated sugar isocyanates. This procedure was also successfully applied to the preparation of other symmetrical and unsymmetrical *N*,*N*′-disubstituted sugar ureas including pseudodisaccharides with a (1→1) or (2→2) urea linkage. An anhydrous monophasic system was also used for the two-step synthesis, although the yields were generally lower. We also report the desulfurization of *O*-protected sugar thioureas with yellow mercury (II) oxide in aqueous



33 **34** **29**

Scheme 4.

acetonitrile as an alternative pathway for the preparation of sugar ureas.

3. Experimental

3.1. General procedures

Melting points were recorded on an Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter, and IR spectra (KBr disks) were obtained with an FT-IR Bomem MB-120 spectrophotometer. ^{1}H (300 and 500 MHz) and ^{13}C (75.5 and 125.7 MHz) NMR spectra were recorded on Bruker AMX-300 and AMX-500 spectrometers. The assignments of ^{1}H and ^{13}C signals were confirmed by homonuclear COSY and heteronuclear 2D correlated spectra, respectively. Mass spectra (EI, CI and FAB) were recorded on Kratos MS80-RFA and Micromass AutoSpec-Q mass spectrometers with a resolution of 1000 or 60,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (6–7 keV), using thioglycerol as matrix and NaI as salt. MALDI spectra were recorded with a TOFSPEC spectrometer. TLC was performed on aluminium pre-coated sheets (E. Merck Silica Gel 60 F_{254}); spots were visualized by UV light, by charring with 10% H_2SO_4 in EtOH. Column chromatography was performed using E. Merck Silica Gel 60 (40–63 μm).

3.2. *N*,*N*′-Bis[icosa-*O*-acetyl-6^{A}-deoxy-β-cyclodextrin-6^{A}-yl]urea (4)

A solution of 6^{A}-azido-6^{A}-deoxy-β-cyclodextrin **1** (260 mg, 0.13 mmol) in methanol (10 mL) was hydrogenated at atmospheric pressure by stirring with 10% Pd(C) catalyst for 2.5 h at rt. After filtration of the mixture through a Celite pad, the filtrate was concentrated to dryness to afford the crude amine **2** and divided into two equal portions. One portion was dissolved in an 1:1 CH_2Cl_2–saturated aqueous $NaHCO_3$ mixture (12 mL), cooled to 0 °C in an ice bath and treated with triphosgene (6.5 mg, 0.022 mmol). After 15 min of vigorous stirring the other portion of amine **2** was added and the stirring was maintained at rt for 15 min. Conventional work-up and column chromatography ($CH_2Cl_2 \rightarrow$40:1 CH_2Cl_2–MeOH) afforded cyclodextrin dimer **4** (127 mg, 49%) as a white amorphous powder, mp 172–178 °C; $[\alpha]_D^{26}$ +117 (*c* 1.1, CH_2Cl_2); lit.[33] $[\alpha]_D^{25}$ +121 (*c* 1.0, $CHCl_3$); IR ν_{max} 3300, 1748, 1541, 1433, 1371, 1233, 1042 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32–5.25 (m, 7H, H-3$^{A–G}$), 5.17 (d, 1H, $J_{1,2}$=3.5 Hz, H-1^{A}), 5.14–5.11 (m, 1H, NH), 5.10–5.05 (m, 6H, H-1$^{B–G}$), 4.87–4.71 (m, 7H, H-2$^{A–G}$), 4.58–4.49 (m, 6H, H-6a$^{B–G}$), 4.31–4.23 (m, 6H, H-6b$^{B–G}$), 4.18–4.11 (m, 6H, H-5$^{B–G}$), 3.98–3.94 (m, 1H, H-5^{A}), 3.88–3.82 (m, 1H, H-6a^{A}), 3.76–3.64 (m, 7H, H-4$^{A–G}$), 3.46–3.41 (m, 1H, H-6b^{A}), 2.14–2.03 (20 s, 60H, 20Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.6–170.3, 169.6–169.3 (CH_3CO), 158.2 (CO urea), 96.9–96.7 (C-1), 77.8–76.5 (C-4$^{A–G}$), 71.2–69.4 (C-2$^{A–G}$, C-3$^{A–G}$, C-5$^{A–G}$), 62.9–62.4 (C-6$^{B–G}$), 40.4 (C-6^{A}), 20.8–20.6 (CH_3CO); MALDITOF-MS *m*/*z* 3980 $[M+H]^+$. Anal. Calcd for $C_{165}H_{220}N_2O_{109}$ $4H_2O$: C, 48.96; H, 5.68; N, 0.96, found: C, 48.72; H, 5.35; N, 0.89.

3.3. General methods for the synthesis of ureas 9–15, 22–27 and 32.

Method A. To a vigorously stirred solution of the hydrohalides **5**, **6** or **18** (0.6 mmol) in an 1:1 mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ (12 mL) at 0 °C in an ice bath was added triphosgene (0.22 mmol); after 10 min of stirring, butylamine, *p*-toluidine, or the hydrohalides **5**, **6** or **18** (0.66 mmol) were added. For the preparation of D-glucosamine derived ureas **9–14** the coupling with the amines was performed at rt for 10 min; for the preparation of glycopyranosyl ureas **22–24** the coupling of the isocyanate with the amines was carried out at 0 °C for 20 min. Conventional work-up and column chromatography afforded ureas **9–14** and **22–24**. For the preparation of **15**, this procedure was carried out starting from hydrochloride **6** (0.13 mmol). Azide **1** (260 mg, 0.13 mmol) was hydrogenated as described in Section 3.2 to give amino cyclodextrin derivative **2**, which was added to the crude isocyanate **8** and the coupling reaction took place at rt for 15 min.

In the case of ureas **25–27**, to a solution of enamine **17** (0.6 mmol) in wet CH_2Cl_2 (10 mL) at 0 °C were added small portions of a saturated solution of Cl_2 in CH_2Cl_2 until disappearance of the starting material by TLC. Then the mixture was concentrated to dryness and the residue containing hydrochloride **19** was treated as described above to give ureas **25–27**.

Method B. To a stirred mixture of hydrohalides **5** or **18** (0.6 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 1.8 mmol) in CH_2Cl_2 (6 mL) containing 4 Å molecular sieves under Ar at rt was dropwise added a solution of triphosgene (0.2 mmol) in dry CH_2Cl_2 (3 mL) over 30 min. After a further 10 min of stirring a solution of butylamine or *p*-toluidine (0.6 mmol) in dry CH_2Cl_2 (3 mL) was added in one portion. In the case of adding the hydrohalides **5** or **18** (0.6 mmol), their solutions in CH_2Cl_2 (3 mL) had an extra portion of DIEA (1.2 mmol). The reaction mixture was stirred at rt for 10 min. Conventional work-up and column chromatography afforded ureas **9–11** and **22–24**.

Method C. To a solution of thioureas **28–31** (0.44 mmol) in 1:1 water–acetonitrile (20 mL) was added yellow mercury (II) oxide (572 mg, 2.64 mmol). The mixture was stirred at rt in the darkness for 24–40 h and then it was filtered through a Celite pad. The filtrate was concentrated to dryness and purified by column chromatography.

3.3.1. *N*-Butyl-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)urea (9). *Method A*. Column chromatography ($CH_2Cl_2 \rightarrow$40:1 CH_2Cl_2–MeOH) gave **9**: 196 mg, 73% as a syrup.

Method B. Column chromatography gave **9**: 150 mg, 58%. R_f=0.33 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{25}$ +62 (*c* 0.5, CH_2Cl_2); IR ν_{max} 3322, 2920, 1750, 1642, 1561, 1370, 1221, 1125, 1007 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (d, 1H, $J_{2,NH}$=9.2 Hz, NH′), 6.16 (d, 1H, $J_{1,2}$=3.5 Hz, H-1), 5.19–5.17 (m, 2H, H-3, H-4), 4.43 (t, 1H, J_{NH,CH_2}=5.5 Hz, NH), 4.31 (m, 1H, H-2), 4.22 (dd, 1H, $J_{5,6a}$=4.2 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.03 (dd, 1H, $J_{5,6b}$=2.2 Hz, H-6b),

3.95 (m, 1H, H-5), 3.08 (m, 2H, $CH_2\alpha$), 2.14, 2.06, 2.02, 2.01 (4s, 12H, 4Ac), 1.40 (m, 2H, $CH_2\beta$), 1.29 (m, 2H, $CH_2\gamma$), 0.88 (t, 3H, $J=7.4$ Hz, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.8, 170.7, 169.1, 168.6 (4 CO), 156.7 (CO urea), 91.5 (C-1), 71.2 (C-3), 69.7 (C-5), 67.6 (C-4), 61.7 (C-6), 52.0 (C-2), 40.3 ($CH_2\alpha$), 32.1 ($CH_2\beta$), 20.9, 20.8, 20.7, 20.5 (4 *C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); FAB-MS *m/z* 469 ([M+Na]$^+$, 100%), 915 ([2M+Na]$^+$, 10%); EI-MS *m/z* 446 ([M]$^+$, 1%); HREI-MS *m/z* calcd for [M]$^+$$C_{19}H_{30}N_2O_{10}$: 446.1900, found: 446.1897.

3.3.2. *N*-(*p*-Methylphenyl)-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)urea (10). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **10** as a white solid: 182 mg, 63%.

Method B. Column chromatography gave **10**: 191 mg, 66%.

Method C. The mixture was stirred for 24 h and purified by column chromatography to give **10**: 128 mg, 67%; mp 184–188 °C; R_f 0.30 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{23}$ +103 (*c* 1.2, CH_2Cl_2); IR ν_{max} 3345, 1753, 1659, 1603, 1533, 1514, 1370, 1223, 1132, 926 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (m, 4H, Ar–H), 6.97 (s, 1H, NH), 6.23 (d, 1H, $J_{1,2}=$ 3.4 Hz, H-1), 5.19 (m, 2H, H-3, H-4), 4.41 (t, 1H, $J_{2,NH}=$ 8.1 Hz, NH′), 4.24 (m, 1H, H-2), 4.24 (dd, 1H, $J_{5,6a}=$ 4.0 Hz, $J_{6a,6b}=$12.4 Hz, H-6a), 4.05 (dd, 1H, $J_{5,6b}=$2.2 Hz, H-6b), 3.97 (m, 1H, H-5), 2.29 (s, 3H, CH_3), 2.08, 2.07, 2.03, 2.01 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.5, 170.8, 169.1, 168.7 (4CO), 155.2 (CO urea), 135.1, 134.3, 129.8, 121.7 (Ar), 91.2 (C-1), 70.9 (C-3), 69.7 (C-5), 67.6 (C-4), 61.6 (C-6), 51.7 (C-2), 20.7, 20.7, 20.7, 20.5 (*C*H_3Ar, 4Ac); FAB-MS *m/z* 503 ([M+Na]$^+$, 100%); HREI-MS *m/z* calcd for [M]$^+$$C_{22}H_{28}N_2O_{10}$: 480.1744, found: 480.1740.

3.3.3. *N*,*N*′-Bis(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)urea (11). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **11** as a white solid: 177 mg, 82%.

Method B. Column chromatography gave **11**: 134 mg, 62%; mp 193–194 °C; R_f 0.12 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{18}$ +115° (*c* 1.0, CH_2Cl_2); IR ν_{max} 3366, 2963, 1753, 1562, 1373, 1227, 1040, 926 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, 1H, $J_{1,2}=$3.6 Hz, H-1), 5.16 (t, 1H, $J_{3,4}=$10.0 Hz, $J_{4,5}=$9.8 Hz, H-4), 5.09 (t, 1H, $J_{2,3}=$10.5 Hz, H-3), 4.66 (d, 1H, $J_{2,NH}=$9.4 Hz, NH), 4.28 (ddd, 1H, H-2), 4.20 (dd, 1H, $J_{5,6a}=$4.1 Hz, $J_{6a,6b}=$12.5 Hz, H-6a), 4.02 (dd, 1H, $J_{5,6b}=$ 2.1 Hz, H-6b), 3.94 (ddd, 1H, H-5), 2.14, 2.06, 2.00 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.0, 170.7, 169.0, 168.6 (4CO), 155.5 (CO urea), 91.2 (C-1), 70.9 (C-3), 69.7 (C-5), 67.5 (C-4), 61.6 (C-6), 51.9 (C-2), 20.8, 20.7, 20.6, 20.5 (4Ac); FAB-MS *m/z* 743 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+H]$^+$$C_{29}H_{41}N_2O_{19}$: 721.2303, found: 721.2296. Anal. Calcd for $C_{29}H_{40}N_2O$: C, 48.33; H, 5.59; N, 3.89, found: C, 48.13; H, 5.54; N, 3.96.

3.3.4. *N*-Butyl-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)urea (12). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **12** as a syrup: 230 mg, 86%. R_f 0.33 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{23}$ +33 (*c* 0.8, CH_2Cl_2); IR ν_{max} 3356, 2926, 2870, 1769, 1665, 1582, 1370, 1044, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (d, 1H, $J_{1,2}=$8.5 Hz, H-1), 5.14–5.10 (m, 2H, H-3, H-4), 4.57 (d, 1H, $J_{2,NH}=$9.5 Hz, NH′), 4.55 (t, 1H, $J_{NH,CH_2}=$5.5 Hz, NH), 4.27 (dd, 1H, $J_{5,6a}=$5.0 Hz, $J_{6a,6b}=$ 12.5 Hz, H-6a), 4.12 (dd, 1H, $J_{5,6b}=$2.0 Hz, H-6b), 4.08 (m, 1H, H-2), 3.81 (m, 1H, H-5), 3.12 (m, 2H, $CH_2\alpha$), 2.12, 2.09, 2.05, 2.03 (4s, 12H, 4Ac), 1.43 (m, 2H, $CH_2\beta$), 1.31 (m, 2H, $CH_2\gamma$), 0.90 (t, 3H, $J=$7.1 Hz, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.3, 170.7, 169.6, 169.3 (4CO), 157.0 (CO urea), 93.3 (C-1), 73.1, 72.9 (C-3, C-5), 67.9 (C-4), 61.8 (C-6), 54.2 (C-2), 40.2 ($CH_2\alpha$), 32.2 ($CH_2\beta$), 20.9, 20.7, 20.6, (4 *C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); FAB-MS *m/z* 469 ([M+Na]$^+$, 92%), 915 ([2M+Na]$^+$, 10%); HRCI-MS *m/z* calcd for [M+H]$^+$$C_{19}H_{31}N_2O_{10}$: 447.1978, found: 447.1981.

3.3.5. *N*-(*p*-Methylphenyl)-*N*′-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)urea (13). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **13**: 248 mg, 86% as a white solid; mp 184–186 °C; $[\alpha]_D^{18}$ +32 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3304, 2918, 1748, 1636, 1570, 1454, 1377, 1084, 1040, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–7.00 (m, 5H, Ar–H, NH), 5.78 (d, 1H, $J_{1,2}=$8.7 Hz, H-1), 5.27 (t, 1H, $J_{2,3}=$9.0 Hz, $J_{3,4}=$ 9.5 Hz, H-3), 5.25 (d, 1H, NH′), 5.10 (t, 1H, $J_{4,5}=$9.6 Hz, H-4), 4.25 (dd, 1H, $J_{5,6a}=$4.6 Hz, $J_{6a,6b}=$12.3 Hz, H-6a), 4.10 (dd, 1H, $J_{5,6b}=$1.5 Hz, H-6b), 4.05 (m, 1H, H-2), 3.82 (m, 1H, H-5), 2.27 (s, 3H, Me), 2.08, 2.06, 2.02 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2, 170.7, 169.5, 169.4 (4CO), 155.4 (CO urea), 135.4, 133.9, 129.8, 121.4 (Ar), 92.8 (C-1), 72.7 (C-3), 72.6 (C-5), 68.1 (C-4), 61.8 (C-6), 54.0 (C-2), 20.9, 20.8, 20.6 (*C*H_3Ar, 4Ac); FAB-MS *m/z* 480 ([M]$^+$, 22%), 503 ([M+Na]$^+$, 60%), 983 ([2M+Na]$^+$, 11%); HRFAB-MS *m/z* calcd for [M]$^+$$C_{22}H_{28}N_2O_{10}$: 480.1744, found: 480.1739. Anal. Calcd for $C_{22}H_{28}N_2O_{10}$: C, 55.00; H, 5.87; N, 5.83, found: C, 55.09; H, 5.90; N, 5.93.

3.3.6. *N*,*N*′-Bis(1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranos-2-yl)urea (14). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **14** as a white solid: 169 mg, 78%. R_f 0.18 (40:1 CH_2Cl_2–MeOH); mp 218–220 °C; $[\alpha]_D^{22}$ +25 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3331, 2940, 1750, 1659, 1599, 1433, 1371, 1227, 1040, 907 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, 1H, $J_{1,2}=$8.7 Hz, H-1), 5.22 (d, 1H, $J_{2,NH}=$8.9 Hz, NH), 5.18 (t, 1H, $J_{2,3}=$ 8.7 Hz, $J_{3,4}=$9.5 Hz, H-3), 5.10 (t, 1H, $J_{4,5}=$9.5 Hz, H-4), 4.26 (dd, 1H, $J_{5,6a}=$5.0 Hz, $J_{6a,6b}=$12.4 Hz, H-6a), 4.10 (q, 1H, H-2), 4.10 (dd, 1H, $J_{5,6b}=$1.5 Hz, H-6b), 3.83 (ddd, 1H, H-5), 2.08, 2.06. 2.03 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.3, 170.6, 169.7, 169.4 (4CO), 156.2 (CO urea), 93.3 (C-1), 72.7 (C-3), 72.6 (C-5), 68.1 (C-4), 61.9 (C-6), 54.2 (C-2), 20.8, 20.7, 20.6 (4Ac); FAB-MS *m/z* 743 ([M+Na]$^+$, 100%); HRFAB-MS *m/z* calcd for [M+H]$^+$$C_{29}H_{41}N_2O_{19}$: 721.2303, found: 721.2286. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$: C, 48.33; H, 5.59; N, 3.89, found: C, 48.37; H, 5.58; N, 3.93.

3.3.7. Icosa-*O*-acetyl-6^A-deoxy-6^A-[3-(1′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranos-2′-yl)ureido)]-β-cyclodextrin (15). *Method A*. Column chromatography ($CH_2Cl_2\rightarrow$40:1 CH_2Cl_2–MeOH) gave **15**: 140 mg, 46%, as a white solid; mp 146–152 °C; R_f 0.31 (40:1 CH_2Cl_2–MeOH, 2 elutions); $[\alpha]_D^{26}$ +101 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3295, 1746, 1520,

1456, 1366, 1221 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (d, 1H, $J_{1,2}=8.9$ Hz, H-1′), 5.35–5.21 (m, 8H, H-3^{A-G}, H-3′), 5.14 (d, 1H, $J_{1,2}=3.5$ Hz, H-1), 5.15–5.12 (m, 1H, NH), 5.10 (t, 1H, $J_{3',4'}=10.0$ Hz, H-4′), 5.09–5.06 (m, 5H, H-1^{B-F}), 4.98 (d, 1H, $J_{1,2}=3.0$ Hz, H-1), 4.94–4.91 (m, 1H, N*H*–CH_2), 4.89 (dd, 1H, $J_{1,2}=4.5$ Hz, $J_{2,3}=8.5$ Hz, H-2), 4.84 (dd, 1H, $J_{1,2}=4.0$ Hz, $J_{2,3}=9.7$ Hz, H-2), 4.81 (dd, 1H, $J_{1,2}=3.5$ Hz, $J_{2,3}=10.0$ Hz, H-2), 4.80 (dd, 1H, $J_{1,2}=$ 3.5 Hz, $J_{2,3}=9.5$ Hz, H-2), 4.77 (dd, 1H, $J_{1,2}=4.1$ Hz, $J_{2,3}=9.5$ Hz, H-2), 4.75 (dd, 1H, $J_{1,2}=3.6$ Hz, $J_{2,3}=$ 9.5 Hz, H-2), 4.67 (dd, 1H, $J_{1,2}=3.5$ Hz, $J_{2,3}=10.0$ Hz, H-2), 4.65–4.47 (m, 6H, H-$6a^{B-G}$), 4.33–4.22 (m, 7H, H-$6b^{B-G}$, H-6a′), 4.18–4.07 (m, 8H, H-5^{B-G}, H-2′, H-6b′), 4.01–3.97 (m, 1H, H-5^{A}), 3.94–3.89 (m, 1H, H-5′), 3.76–3.59 (m, 8H, H-4^{A-G}, H-$6a^{A}$), 3.47–3.42 (m, 1H, H-$6b^{A}$), 2.16–1.99 (24s, 72H, 24Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.5, 170.9–170.3, 169.6–169.3 (24CO), 157.7 (CO urea), 97.4, 97.0, 96.9, 96.9, 96.8, 96.5, 96.5 (C-1^{A-G}), 92.8 (C-1′), 78.4 (C-4^{A}), 77.2–76.1 (C-4^{B-G}), 72.8 (C-5′), 72.4 (C-3′), 71.5–69.0 (C-2^{A-G}, C-3^{A-G}, C-5^{A-G}), 68.1 (C-4′), 63.0, 62.8, 62.8, 62.5, 62.4, 62.2 (C-6^{B-G}), 61.8 (C-6′), 54.0 (C-2′), 40.9 (C-6^{A}), 20.9–20.6 (24Ac); FAB-MS *m/z* 2370 ($[M+Na]^+$, 29%). Anal. Calcd for $C_{97}H_{130}N_2O_{64}$ $2H_2O$: C, 48.87; H, 5.67; N, 1.18, found: C, 48.50; H, 5.24; N, 1.31.

3.3.8. *N*-Butyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (22). *Method A*. Column chromatography (hexane→1:1 hexane–EtOAc) yielded **22** as a syrup: 169 mg, 63%.

Method B. Column chromatography yielded **22**: 174 mg, 65%. R_f 0.24 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{22}$ 0 (*c* 0.7, CH_2Cl_2); IR ν_{max} 3329, 2957, 1753, 1657, 1562, 1433, 1368, 1227, 1101, 1036, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.28 (m, 2H, $J_{1,NH'}=9.3$ Hz, $J_{2,3}=9.5$ Hz, $J_{3,4}=$ 9.5 Hz, NH′, H-3), 5.14 (t, 1H, $J_{1,2}=9.4$ Hz, H-1), 5.04 (t, 1H, $J_{4,5}=9.7$ Hz, H-4), 4.87 (t, 1H, H-2), 4.62 (t, 1H, $J_{NH,CH_2}=6.5$ Hz, NH), 4.30 (dd, 1H, $J_{5,6a}=4.3$ Hz, $J_{6a,6b}=$ 12.5 Hz, H-6a), 4.06 (dd, 1H, $J_{5,6b}=1.8$ Hz, H-6b), 3.79 (ddd, 1H, H-5), 2.05, 2.03, 2.00, 1.99 (4s, 12H, 4Ac), 3.12 (q, 2H, $CH_2\alpha$), 1.43 (m, 2H, $CH_2\beta$), 1.29 (m, 2H, $CH_2\gamma$), 0.89 (t, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2, 170.7, 169.9, 169.6 (4 CO), 156.2 (CO urea), 80.2 (C-1), 73.1 (C-5), 72.9 (C-3), 70.6 (C-2), 68.3 (C-4), 61.8 (C-6), 40.2 ($CH_2\alpha$), 32.0 ($CH_2\beta$), 20.7, 20.6 (4 *C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); FAB-MS *m/z* 447 ($[M+H]^+$, 40%), 469 ($[M+Na]^+$, 100%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{19}H_{31}N_2O_{10}$: 447.1979, found: 447.1971.

3.3.9. *N*-(*p*-Methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (23). *Method A*. Column chromatography (hexane→1:1 hexane–EtOAc) yielded **23** as a white solid, 190 mg, 66%.

Method B. Column yielded **23**, 184 mg, 64%.

Method C. The mixture was stirred for 24 h and purified by column chromatography (hexane→1:1 hexane–EtOAc) to give **23**: 143 mg, 74%. R_f 0.22 (40:1 CH_2Cl_2–MeOH); mp 93–96 °C; $[\alpha]_D^{18}$ −17 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3189, 1746, 1645, 1575, 1393, 1092, 1034, 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14–7.06 (m, 4H, Ar–H), 6.87 (s, 1H, NH), 5.74 (d, 1H, $J_{1,NH'}=9.3$ Hz, NH′), 5.29 (t, 1H, $J_{2,3}=9.6$ Hz, $J_{3,4}=9.5$ Hz, H-3), 5.21 (t, 1H, $J_{1,2}=9.4$ Hz, H-1), 5.03 (t, 1H, $J_{4,5}=10.0$ Hz, H-4), 4.89 (t, 1H, H-2), 4.29 (dd, 1H, $J_{5,6a}=4.5$ Hz, $J_{6a,6b}=12.5$ Hz, H-6a), 4.05 (dd, 1H, $J_{5,6b}=1.9$ Hz, H-6b), 3.79 (ddd, 1H, H-5), 2.28 (s, 3H, Me), 2.05, 2.02, 2.01, 1.99 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.0, 170.7, 169.9, 169.6 (4CO), 154.4 (CO urea), 134.8, 129.8, 121.5 (Ar), 80.0 (C-1), 73.3 (C-5), 72.9 (C-3), 70.4 (C-2), 68.3 (C-4), 61.8 (C-6), 20.8, 20.7, 20.6 (*C*H_3Ar, 4*C*H_3CO); FAB-MS *m/z* 481 ($[M+H]^+$, 80%), 503 ($[M+Na]^+$, 45%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{22}H_{29}N_2O_{10}$: 481.1822, found: 481.1813. Anal. Calcd for $C_{22}H_{28}N_2O_{10}$ H_2O: C, 53.01; H, 6.07; N, 5.62, found: C, 53.33; H, 5.78; N, 5.37.

3.3.10. *N*,*N*′-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (24). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) yielded **24** as a white solid: 214 mg, 99%.

Method B. Column chromatography yielded **24**: 117 mg, 54%.

Method C. The mixture was stirred for 24 h and purified by column chromatography to give **24**: 197 mg, 68%. R_f 0.19 (40:1 CH_2Cl_2–MeOH); mp: 152–155 °C. $[\alpha]_D^{18}$ −5 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3362, 1750, 1543, 1435, 1370, 1229, 1036, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (d, 1H, $J_{1,NH}=9.1$ Hz, NH), 5.28 (t, 1H, $J_{1,2}=9.4$ Hz, $J_{2,3}=$ 9.5 Hz, H-2), 5.02 (m, 2H, $J_{3,4}=9.5$ Hz, $J_{4,5}=10.0$ Hz, H-1, H-4), 4.85 (t, 1H, H-3), 4.29 (dd, 1H, $J_{5,6a}=4.5$ Hz, $J_{6a,6b}=$ 12.5 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}=2.0$ Hz, H-6b), 3.81 (ddd, 1H, H-5), 2.05, 2.04, 2.01, 1.99 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 170.6, 169.9, 169.6 (4CO), 155.3 (CO urea), 80.0 (C-1), 73.2 (C-5), 72.8 (C-2), 70.5 (C-3), 68.2 (C-4), 61.7 (C-6), 20.7, 20.6 (4*C*H_3CO); CI-MS *m/z* 721 ($[M+H]^+$, 9%); HRCI-MS *m/z* calcd for $[M+H]^+C_{29}H_{41}N_2O_{19}$: 721.2303, found: 721.2290. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$ H_2O: C, 47.16; H, 5.73; N, 3.79, found: C, 47.10; H, 5.74; N, 3.55.

3.3.11. *N*-Butyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)urea (25). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) yielded **25** as a syrup: 190 mg, 71%. R_f 0.22 (1:1 hexane–EtOAc); $[\alpha]_D^{21}$ −19 (*c* 0.8, CH_2Cl_2); IR ν_{max} 3314, 2932, 1748, 1663, 1370, 1225, 1053, 964 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (dd, 1H, $J_{1,2}=1.2$ Hz, $J_{1,NH'}=9.6$ Hz, H-1), 5.35 (dd, 1H, $J_{2,3}=$ 3.3 Hz, H-2), 5.26 (d, 1H, NH′), 5.20 (t, 1H, $J_{3,4}=10.0$ Hz, $J_{4,5}=9.8$ Hz, H-4), 5.08 (dd, 1H, H-3), 4.60 (t, 1H, $J_{NH,CH_2}=$ 6.6 Hz, NH), 4.30 (dd, 1H, $J_{5,6a}=5.0$ Hz, $J_{6a,6b}=12.4$ Hz, H-6a), 4.06 (dd, 1H, $J_{5,6b}=2.3$ Hz, H-6b), 3.75 (ddd, 1H, H-5), 3.15 (q, 2H, $J=6.6$ Hz, $CH_2\alpha$), 2.18, 2.06, 2.02, 1.95 (4s, 12H, 4Ac), 1.44 (m, 2H, $CH_2\beta$), 1.30 (m, 2H, $CH_2\gamma$), 0.89 (t, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 170.4, 169.8, 169.7 (4CO), 155.9 (CO urea), 77.9 (C-1), 73.7 (C-5), 71.8 (C-3), 70.5 (C-2), 65.3 (C-4), 62.3 (C-6), 40.2 ($CH_2\alpha$), 30.0 ($CH_2\beta$), 20.9, 20.8, 20.7, 20.5 (4*C*H_3CO), 19.9 ($CH_2\gamma$), 13.7 (CH_3); CI-MS *m/z* 447 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+C_{19}H_{31}N_2O_{10}$: 447.1979, found: 447.1980.

3.3.12. *N*-(*p*-Methylphenyl)-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)urea (26). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) gave **26** as a white solid: 167 mg, 58%. R_f 0.25 (1:1 hexane–EtOAc); mp 80–88 °C; $[\alpha]_D^{18}$ −21 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3291, 2922, 1767, 1555, 1096, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (m, 4H, Ar–H), 6.89 (s, 1H, NH), 5.92 (d, 1H, $J_{1,NH'}$=9.5 Hz, NH′), 5.45 (dd, 1H, $J_{1,2}$=0.9 Hz, H-1), 5.39 (d, 1H, $J_{2,3}$=3.1 Hz, H-2), 5.17 (t, 1H, $J_{3,4}$=10.0 Hz, $J_{4,5}$=9.9 Hz, H-4), 5.08 (dd, 1H, H-3), 4.25 (dd, 1H, $J_{5,6a}$=5.0 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.01 (dd, 1H, $J_{5,6b}$=2.0 Hz, H6b), 3.75 (ddd, 1H, H-5), 2.27 (s, 3H, Me), 2.08, 2.01, 1.95 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7, 170.2, 169.8, 169.7 (4CO), 154.3 (CO urea), 134.7, 129.8, 122.0 (Ar), 77.6 (C-1), 73.8 (C-5), 71.6 (C-3), 70.3 (C-2), 64.3 (C-4), 62.3 (C-6), 20.8, 20.7, 20.6, 20.4 (*C*H_3Ar, 4*C*H_3CO); FAB-MS *m/z* 481 ($[M+H]^+$, 28%), 503 ($[M+Na]^+$, 100%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{22}H_{29}N_2O_{10}$: 481.1822, found: 481.1814.

3.3.13. *N,N′*-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-manopyranosyl)urea (27). *Method A*. Column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) gave **27** as a white solid: 149 mg, 69%. R_f 0.12 (1:1 hexane–EtOAc); mp 154–156 °C (from EtOH); $[\alpha]_D^{25}$ −24 (*c* 0.3, CH_2Cl_2); IR ν_{max} 3352, 2917, 1746, 1647, 1537, 1370, 1227, 1092, 1051, 874 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45 (dd, 1H, $J_{1,2}$=0.9 Hz, H-1), 5.45 (d, 1H, $J_{1,NH}$=9.6 Hz, NH), 5.37 (dd, 1H, $J_{2,3}$=3.3 Hz, H-2), 5.20 (t, 1H, $J_{3,4}$=10.0 Hz, $J_{4,5}$=10.0 Hz, H-4), 5.11 (dd, 1H, H-3), 4.29 (dd, 1H, $J_{5,6a}$=5.2 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.05 (dd, 1H, $J_{5,6b}$=2.0 Hz, H-6b), 3.77 (ddd, 1H, H-5), 2.21, 2.09, 2.04, 1.97 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.8, 170.2, 169.8, 169.7 (4CO), 153.8 (CO urea), 77.4 (C-1), 73.8 (C-5), 71.6 (C-3), 70.3 (C-2), 65.1 (C-4), 62.2 (C-6), 20.9, 20.8, 20.7, 20.5 (4*C*H_3CO); FAB-MS *m/z* 721 ($[M+H]^+$, 36%), 743 ($[M+Na]^+$, 100%); HRFAB-MS *m/z* calcd for $[M+H]^+C_{29}H_{41}N_2O_{19}$: 721.2304, found: 721.2294. Anal. Calcd for $C_{29}H_{40}N_2O_{19}$ H_2O: C, 47.16; H, 5.73; N, 3.79, found: C, 47.26; H, 5.61; N, 3.83.

3.3.14. *N,N*-Diethyl-*N′*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)urea (32). *Method C*. The mixture was stirred for 40 h and purified by column chromatography (CH_2Cl_2→40:1 CH_2Cl_2–MeOH) to give **32**, as an amorphous solid: 94 mg, 72%; mp 39–42 °C; $[\alpha]_D^{20}$ +19 (*c* 0.9, CH_2Cl_2); IR ν_{max} 3320, 2936, 1753, 1379, 1225, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (d, 1H, $J_{1,NH}$=9.3 Hz, NH′), 5.31 (t, 1H, $J_{2,3}$=9.5 Hz, $J_{3,4}$=9.4 Hz, H-3), 5.20 (t, 1H, $J_{1,2}$=9.3 Hz, H-1), 5.06 (t, 1H, $J_{4,5}$=9.6 Hz, H-4), 4.93 (t, 1H, H-2), 4.33 (dd, 1H, $J_{5,6a}$=4.0 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}$=2.2 Hz, H-6b), 3.80 (ddd, 1H, H-5), 3.18 (m, 4H, 2CH_2), 2.07, 2.03, 2.01, 2.0 (4s, 12H, 4Ac), 1.11 (t, 6H, $J_{H,H}$=7.2 Hz, 2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.4, 170.7, 169.98, 169.7 (4CO), 155.4 (CO urea), 80.8 (C-1), 73.2 (C-5), 73.0 (C-3), 70.8 (C-2), 68.5 (C-4), 61.8 (C-6), 41.3 (2*C*H_2), 20.8, 20.8, 20.7, 20.6 (4*C*H_3CO); 13.7 (2*C*H_3); CI-MS *m/z* 447 ($[M+H]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+C_{19}H_{31}N_2O_{10}$: 447.1979, found: 447.1955.

3.4. Method for the preparation of isocyanates 7 and 8

To a vigorously stirred solution of the hydrohalides **5** or **6** (0.6 mmol) in a 1:1 mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ (12 mL) at 0 °C was added triphosgene (0.22 mmol) in a single portion. After 10 min of stirring, the organic layer was separated, dried ($MgSO_4$), filtered and concentrated to dryness to give pure **7** or **8**.

3.4.1. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-isocyanato-α-D-glucopyranose (7). Yield: 224 mg, quantitative, as a syrup. R_f 0.32 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +126 (*c* 1.3, CH_2Cl_2); IR ν_{max} 2963, 2261, 1765, 1371, 1217, 1026, 936 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 and δ 2.22, 2.11, 2.07, 2.04 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) Table 2 and δ 170.5, 170.2, 169.4, 168.6 (4CO), 20.8, 20.6, 20.5 (4*C*H_3CO). Anal. Calcd for $C_{15}H_{19}NO_{10}\cdot 1/3H_2O$: C, 47.50; H, 5.23; N, 3.69, found: C, 47.55; H, 5.30; N, 3.69.

3.4.2. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-isocyanato-β-D-glucopyranose (8). Yield: 224 mg, quantitative, as a syrup. R_f 0.21 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{25}$ +32 (*c* 1.0, CH_2Cl_2); IR ν_{max} 2959, 2253, 1765, 1371, 1215, 1090, 872 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) Table 2 and δ 2.18, 2.09, 2.07, 2.02 (4s, 12H, 4Ac); ^{13}C NMR (125.7 MHz, $CDCl_3$) Table 2 and δ 170.5, 169.8, 169.5, 168.6 (4CO), 20.7, 20.6, 20.5 (4*C*H_3CO). Anal. Calcd for $C_{15}H_{19}NO_{10}$: C, 48.26; H, 5.13; N, 3.75, found: C, 48.17; H, 5.20; N, 3.79.

3.5. *N*-(*p*-Methylphenyl)-*N′*-(1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranos-2-yl)thiourea (28)

A mixture of hydrobromide **18** (250 mg, 0.58 mmol), thiophosgene (0.07 mL, 0.88 mmol) and calcium carbonate (176 mg, 1.76 mmol) in 1:1 water–CH_2Cl_2 (20 mL) was vigorously stirred at rt for 2 h. Then the mixture was filtered off and the organic layer containing known 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato-α-D-glucopyranose[59] was separated and concentrated to dryness. To a solution of crude isothiocyanate in EtOAc (10 mL) was added *p*-toluidine (62 mg, 0.58 mmol). The solution was kept at rt for 5 h and then it was concentrated to dryness and the residue was purified by column chromatography (CH_2Cl_2→ 80:1 CH_2Cl_2–MeOH) to give **28** as a white solid: 295 mg (93%). R_f 0.5 (40:1 CH_2Cl_2–MeOH); mp 140–142 °C; $[\alpha]_D^{25}$ +96 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3332, 1750, 1532, 1370, 1223, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H, NH), 7.24–6.99 (m, 4H, Ar–H), 6.31 (d, 1H, $J_{1,2}$=6.3 Hz, H-1), 5.80 (d, 1H, $J_{2,NH}$=8.3 Hz, NH′), 5.21 (m, 1H, H-4), 5.16 (m, 1H, H-3), 5.13 (m, 1H, H-2), 4.23 (dd, 1H, $J_{5,6a}$=4.1 Hz, $J_{6a,6b}$=12.5 Hz, H-6a), 4.03 (dd, 1H, $J_{5,6b}$=2.3 Hz, H-6b), 3.91 (ddd, 1H, $J_{4,5}$=9.5 Hz, H-5), 2.37 (s, 3H, CH_3), 2.08, 2.07, 2.00 1.94 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.6 (CS), 171.5, 170.8, 169.1, 168.3 (4CO), 138.6, 132.7, 130.9, 126.2 (Ar), 90.5 (C-1), 70.9 (C-3), 69.9 (C-5), 67.5 (C-4), 61.6 (C-6), 56.3 (C-2), 21.2 (*C*H_3Ar), 20.9, 20.8, 20.7, 20.6 (4*C*H_3CO); CI-MS *m/z* 497 ($[M+H]^+$, 35%); HRCI-MS *m/z* calcd for $[M+H]^+C_{22}H_{29}N_2O_9S$: 497.1594, found: 497.1570.

3.6. *N*-(*p*-Methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (29)

To a solution of *N*-acetyl-*N*-(*p*-methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea **34** (22 mg, 0.04 mmol) in MeOH (10 mL) was added imidazole (2.8 mg, 0.04 mmol). The solution was heated at 40 °C for 24 h and then it was concentrated to dryness and the residue was purified by column chromatography ($CH_2Cl_2 \rightarrow$80:1 CH_2Cl_2–MeOH) to give **29** as a syrup: 18 mg (86%). $[\alpha]_D^{23}$ −11 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3329, 1751, 1535, 1370, 1229, 1040, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H, NH), 7.25–7.03 (m, 4H, Ar–H), 6.52 (d, 1H, $J_{1,NH}$=8.7 Hz, NH′), 5.82 (t, 1H, $J_{1,2}$=9.0 Hz, H-1), 5.33 (t, 1H, $J_{2,3}$=9.3 Hz, $J_{3,4}$=9.6 Hz, H-3), 5.01 (t, 1H, $J_{4,5}$=9.9 Hz, H-4), 4.88 (t, 1H, H-2), 4.30 (dd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=12.3 Hz, H-6a), 4.08 (dd, 1H, $J_{5,6b}$=2.0 Hz, H-6b), 3.84 (ddd, 1H, H-5), 2.37 (s, 3H, Me), 2.06, 2.05, 2.01, 1.98 (4s, 12H, 4Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.3 (CS), 170.7, 170.6, 169.8, 169.5 (4CO), 138.3, 132.3, 130.7, 125.6 (Ar), 83.2 (C-1), 73.6 (C-5), 72.7 (C-3), 70.5 (C-2), 68.2 (C-4), 61.6 (C-6), 21.1 (CH_3Ar), 20.7, 20.6, 20.5, 20.5 (4CH_3CO); FAB-MS *m*/*z* 497 ($[M+H]^+$, 100%); HRFAB-MS *m*/*z* calcd for $[M+H]^+C_{22}H_{29}N_2O_9S$: 497.1594, found: 497.1625. Anal. Calcd for $C_{22}H_{28}N_2O_9S$: C, 53.22; H, 5.68; N, 5.64; S, 6.46, found: C, 53.35; H, 5.73; N, 5.55; S, 6.07.

3.7. *N*,*N*-Diethyl-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (31)

A mixture of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl hydrobromide **18** (400 mg, 0.94 mmol), thiophosgene (0.104 mL, 1.36 mmol) and calcium carbonate (280 mg, 2.8 mmol) in 1:1 water–CH_2Cl_2 (20 mL) was vigorously stirred at rt for 2 h. Then the mixture was filtered off and the organic layer, containing known 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylisothiocyanate[51] was separated and concentrated to dryness. Crude isothiocyanate was dissolved in EtOAc (5 mL) and to the solution was added *N*,*N*-diethylamine (0.100 mL, 0.94 mmol). The solution was kept at rt for 1 h and then it was concentrated to dryness and the residue was purified by column chromatography ($CH_2Cl_2 \rightarrow$80:1 CH_2Cl_2–MeOH) to give **31** as a white solid: 299 mg (69%); mp. 140–142 °C; R_f 0.54 (40:1 CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +14 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3378, 1750, 1362, 1225, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, 1H, $J_{1,NH}$=8.2 Hz, NH), 5.84 (t, 1H, $J_{1,2}$=9.6 Hz, H-1), 5.37 (t, 1H, $J_{2,3}$=9.6 Hz, $J_{3,4}$=9.7 Hz, H-3), 5.07 (t, 1H, $J_{4,5}$=10.1 Hz, H-4), 5.01 (t, 1H, H-2), 4.33 (dd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.11 (dd, 1H, $J_{5,6b}$=2.1 Hz, H-6b), 3.86 (ddd, 1H, H-5), 3.61 (m, 4H, 2CH_2), 2.07, 2.05, 2.02, 2.02 (4s, 12H, 4Ac), 1.20 (t, 6H, $J_{H,H}$=7.2 Hz, 2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.1 (CS), 172.1, 170.7, 169.8, 169.7 (4CO), 83.8 (C-1), 73.3 (C-5), 72.9 (C-3), 71.2 (C-2), 68.7 (C-4), 61.8 (C-6), 45.6 (2CH_2), 20.8, 20.7, 20.7, 20.7 (4CH_3CO), 12.4 (2CH_3); CI-MS *m*/*z* 463 ($[M+H]^+$, 68%); HRCI-MS *m*/*z* calcd for $[M+H]^+C_{19}H_{31}N_2O_9S$: 463.1750, found: 463.1769.

3.8. *N*-Acetyl-*N*-(*p*-methylphenyl)-*N*′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (34)

To a solution of *N*-(β-D-glucopyranosyl)-*N*′-(*p*-methylphenyl) thiourea **33**[42] (2.22 g, 6.76 mmol) in pyridine (15 mL) at 0 °C was added acetic anhydride (15 mL). The solution was kept at rt for 24 h and then it was co-concentrated with toluene and ethanol to dryness and the residue was crystallized from ethanol to give **34**: 2.66 g, 73%. Mp 140–144 °C; $[\alpha]_D^{25}$ +15 (*c* 1.0, CH_2Cl_2); IR ν_{max} 3318, 2922, 1753, 1682, 1370, 1225, 1044, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.01 (d, 1H, $J_{1,NH'}$=8.8 Hz, NH′), 7.26–7.05 (m, 4H, Ar–H), 5.79 (dd, 1H, $J_{1,2}$=9.3 Hz, H-1), 5.34 (t, 1H, $J_{2,3}$=9.3 Hz, $J_{3,4}$=9.3 Hz, H-3), 5.21 (t, 1H, H-2), 5.11 (t, 1H, $J_{4,5}$=10.0 Hz, H-4), 4.28 (dd, 1H, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.12 (dd, 1H, $J_{5,6b}$=2.1 Hz, H-6b), 3.82 (ddd, 1H, H-5), 2.39 (s, 3H, Me), 2.08, 2.07, 2.02, 1.92 (4s, 15H, 5Ac); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 186.8 (CS), 175.1, 170.8, 170.1, 169.6 (5CO), 139.6, 139.3, 130.3, 129.2 (Ar), 83.4 (C-1), 73.8 (C-5), 73.2 (C-3), 70.5 (C-2), 68.4 (C-4), 61.7 (C-6), 28.0 (NAc), 21.4 (CH_3Ar), 20.9, 20.7, 20.7, 20.7 (4CH_3CO); FAB-MS *m*/*z* 561 ($[M+Na]^+$, 28%); HRFAB-MS *m*/*z* calcd for $[M+H]^+C_{24}H_{31}N_2O_{10}S$: 539.1699, found: 539.1676. Anal. Calcd for $C_{24}H_{30}N_2O_{10}S$: C, 53.52; H, 5.61; N, 5.20; S, 5.95, found: C, 53.76; H, 5.77; N, 4.95; S, 5.43.

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Novel tocopheryl compounds XX. 1,3,8-Trioxaphenanthrenes derived from γ-tocopherol

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Abstract—Condensation of γ-tocopherol with aldehydes provides 2,4-disubstituted 1,3,8-trioxaphenanthrenes in a simple one-pot reaction. The reaction proceeded under acid catalysis according to a two-step alkylation–acetalisation mechanism in yields between 58 and 81%. The title compounds are precursors for the thermal generation of *ortho*-quinone methides, which can be in situ reduced to give antioxidants of the 5a-substituted α-tocopherol-type. The products were analytically characterized by NMR and HRMS.

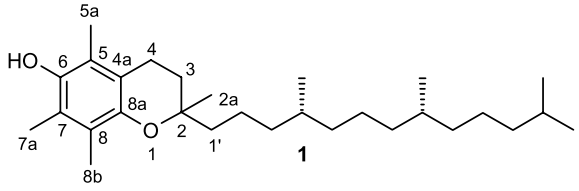
1. Introduction

Tocopherols, often collectively named as vitamin E, are located in the cell membrane and lipophilic cell compartments where they fulfill their role as antioxidants counteracting the negative effect of free radicals, mostly reactive oxygen species.[1] As natural antioxidants, tocopherols have been used in countless medications, health-care and cosmetic products. Due to their high antioxidative efficiency and full physiological compatibility, α-tocopherol-type antioxidants are increasingly used as stabilizers in all types of materials, which get in close contact with food or living systems, such as food containers, packaging foils, or kitchen plastic.

In particular esters of α-tocopherol (**1**) are used in the food industry as stabilizers in plastic packaging to prevent diffusion of potentially toxic artificial antioxidants into the food. However, there are some major drawbacks with regard to problems with phase-separation and demixing of the oily tocopherol stabilizers during extrusion, pressing, or melt processing. In addition, their thermostability is rather low and the action time is thus rather short, as the esters are readily cleaved releasing the phenol as the actually active antioxidant. Thus, the tocopherols are sometimes consumed even before they are needed in such antioxidatively 'demanding' process steps as of melting, thermal shaping, or extrusion. These difficulties explain why the search for optimized, tocopherol-based antioxidants continues.

In a current project aimed at developing tocopherol-based stabilizers for thermal processing of plastics, we were interested in tocopherol derivatives that thermally generate an *ortho*-quinone methide (*o*QM) intermediate, which in a subsequent reaction would be converted into the corresponding phenol (tocopherol) by reducing additives. *o*QM generation must be based on the *o*-hydroxy benzyl structure inherent in α-tocopherol-type antioxidants. Due to the low stability of *o*-hydroxy benzyl alcohols, ethers, halides, ammonium salts and thioethers, which very easily eliminate the benzylic substituent even upon slight thermal stress, we had to turn to more stable, cyclic derivatives of *o*-hydroxy benzyl alcohol, such as dioxaborins[2] developed by Lau and Dufresne or benzo-dioxins developed by Rosenau et al.[3,4] In addition, the synthesis should offer possibilities for modifying the chroman skeleton and for linking to polymeric supports.

In this work, we wish to communicate synthesis and analytical characterization of tocopherol-derived trioxaphenanthrenes, which are promising in meeting most of the above requirements.



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Keywords: Tocopherol; Vitamin E; Antioxidants; *ortho*-Quinone methide.
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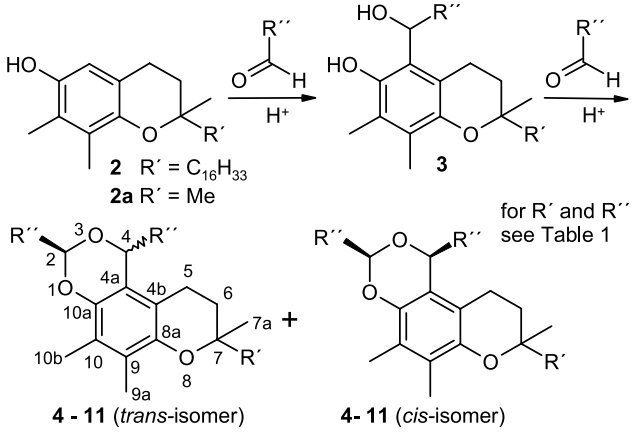
2. Results and discussion

2,4-Disubstituated phenanthrene derivatives **4–11** were formed by condensation of γ-tocopherol (**2**) with various aldehydes proceeding according to a two-step mechanism.[3] In the first step, γ-tocopherol (**2**) undergoes Friedel–Crafts-type electrophilic substitution at the only available aromatic ring position by the aldehyde, forming an *o*-hydroxybenzyl intermediate **3**. In the second step, intermediate **3** immediately binds excess aldehyde in a cyclic acetal structure (Scheme 1) to give tocopherol-based 1,3,8-trioxaphenanthrenes. Intermediate **3** was not detected in any case. Using the tocopherol in excess relative to the aldehyde produced the phenanthrene products along with non-reacted **2**. Under optimized reaction conditions, the condensation of **2** with aldehydes was conducted at rt in glacial acetic acid during 2 h, catalyzed by concd HCl. Increasing the reaction temperature caused a significant drop in yield, while a lowering slowed down the reaction time considerably before freezing the solvent. The use of other catalysts, such as ethereal HCl or Lewis acids (BF_3 etherate, $ZnCl_2$) proved to be rather ineffective in agreement with earlier studies. Increasing the aldehyde concentration to more than the stoichiometrically required 2 equiv did not improve yield. Also prolonged reaction times beyond 2 h were ineffective in this respect. Condensation of γ-tocopherol with ketones was unsuccessful at our hands so far, as was synthesis of 2,4-unsymmetrically substituted products by using binary aldehyde mixtures, due to problems with product separation. According to the optimized procedure, several 1,3,8-trioxaphenanthrene derivatives (**4–11**) were synthesized (Scheme 1 and Table 1).

According to the above mechanism, all 1,3,8-trioxaphenatrenes were obtained as a mixture of two diastereomers, distinguished by the two substituents in position 2 and 4 having either *cis*- or *trans*-arrangements. The *cis*/*trans*-ratio is determined by the steric conditions in the second reaction step: the *trans*-configuration is generally favoured in the case of sterically crowded substituents, whereas rather small substituents, such as methyl and ethyl, cause no discernible *cis*/*trans* discrimination. In the product mixture the *cis*/*trans* ratio can easily be determined by NMR: only the *cis*-isomers exhibit a long-range W-coupling of the H-2 and H-4 protons, the ^4J coupling constant being 0.4 Hz independent



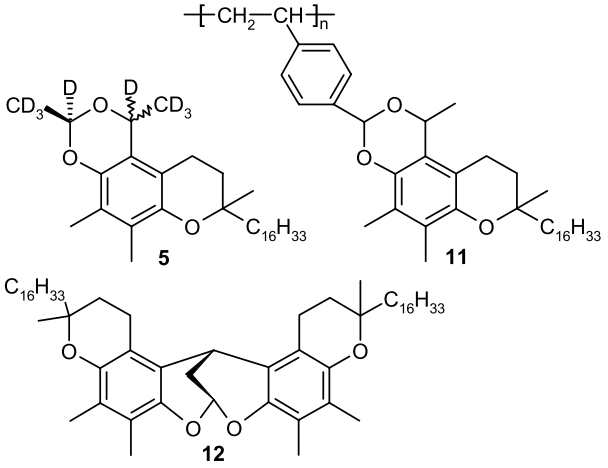
Scheme 1. Reaction of γ-tocopherol **2** or its model **2a** (R′=Me) with 2 equiv of aldehydes R″–CHO.

Table 1. Synthesis of trioxaphenathrenes **4–11**: isolated yields and *cis*/*trans* ratios

Compound	R′[a]	R″[a]	*cis*/*trans*[b]	Yield (%)
4	$C_{16}H_{33}$	Me	1:1	81[c]
5	$C_{16}H_{33}$	CD_3	1:1	77[c]
6	$C_{16}H_{33}$	Et	1:1	79[c]
7	$C_{16}H_{33}$	Prop	1:1.5	73[c]
8	$C_{16}H_{33}$	*i*-Prop	1:8.1	73[c]
9	$C_{16}H_{33}$	Phenyl	1:3.9	58[c]
10	CH_3	Phenyl	1:5	60[c]
11	$C_{16}H_{33}$	Polystyrol resin	n.d.	100[d]

[a] See also Scheme 1.
[b] Determined from the integrals in the ^{1}H NMR spectra.
[c] Isolated yields (mixture of diastereomers) rel. to γ-tocopherol (**2**).
[d] Isolated yield rel. to polymer-bound CHO, determined by FTIR.

of the substituents R″. A further interesting feature is the appearance of the 5-methylene group, that is the $^4CH_2$ in the 'former' tocopherol moiety, as broad multiplet at about 2.30–2.65 ppm, which is different from the appearance as sharp pseudo-triplet in almost all other tocopherol derivatives.



Using acetaldehyde-d_4 compound **5** carrying a trideuteromethyl group and a deuterium in each of the positions 2 and 4 was obtained. Polymer-bound phenanthrene **11** was obtained by transacetalization of **4** with *p*-anchored benzaldehyde moieties in CHO-modified merrifield resin containing 2.5–3.0 mmol/g aldehyde groups. The possibility to use transacetalization as a general method to modify the substituent in position 2 of the title compounds is currently being investigated. Condensation of **2** with malonodialdehyde, bis-protected as 1,1,3,3-tetramethoxypropane, afforded compound **12**, structurally resembling the recently described 'Siamese twin' tocopherol model compound.[5] The optimized synthesis of 'γ-twin' **12** used TFA as the solvent without catalyst.

In summary, the synthesized trioxaphenanthrenes seem to be good candidates with respect to the concept presented in the introduction. They generate intermediate *ortho*-quinone methides at temperatures above 150 °C, but are completely stable below. The thermal *ortho*-quinone methide generation with immediate reduction offered the possibility to produce the antioxidatively very efficient tocopherol only when it is most needed-during high thermal stress upon

processing. In antioxidatively less demanding processing stages, the phenolic OH group remains protected, thus leaving the antioxidative action to less costly stabilizers. Upon further thermal shaping the tocopherol is re-liberated and again becomes active. In addition, the phenanthrenes offer several further advantages: the tocopherol can be modified by substituents decreasing phase separation problems during melt processing, or binding the tocopherol moiety to solid supports or polymers by stable covalent bonds. Finally, the aldehyde bound in the phenanthrenes as acetal, which is released upon *ortho*-quinone methide generation, can be tuned in a way that the aldehyde itself can act as the reductant towards this intermediate. This is a subject of further development in our lab. Tests of the antioxidative effectiveness under melt processing conditions are currently carried out and will be reported elsewhere.

3. Experimental

All chemicals were commercially available. The merryfield resin used was obtained from Aldrich, Germany (particle size 200–400 mesh, 1% DVB cross-linked, 2.5–3.0 mmol/g (benz)aldehyde groups). Thin-layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Flash column chromatography was performed on silica gel G60 (40–63 μm). ^{1}H NMR spectra were recorded at 300.13 MHz, ^{13}C NMR spectra at 75.47 MHz with $CDCl_3$ as the solvents and TMS as the internal standard. Data are given in ppm. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra. Resonances of the isoprenoid side chain of tocopherols are not influenced by modifications of the chroman ring, and are therefore not listed; 'd.i.' denotes peaks with double intensity.

Atom numbering, given as superscript numbers before the respective carbon atom, was done according to the IUPAC recommendation for phenanthrenes as shown in Scheme 1, and thus does not correspond to the traditional numbering in tocopherols. All new compounds exhibited satisfactory HRMS analysis data.

3.1. General procedure for the preparation of 1,3,8-trioxa-phenanthrenes

To a solution of γ-tocopherol (**2**) in glacial acetic acid (2 mL) and concd H_2SO_4 (3 drops), 2 equiv of aldehyde were added through a syringe or a dropping funnel while stirring at rt. After stirring for 2 h, the reaction mixture was poured into ice-water. The aqueous phase was extracted repeatedly with *n*-hexane. The combined organic phases were washed sequentially with water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc/*n*-hexane, v/v=1:20) to give the *cis*/*trans*-mixture. Separation of *cis*/*trans*-isomers was achieved the same way with an EtOAc/hexane (v/v=1:50) eluant.

3.1.1. 2,4,7,9,10-Pentamethyl-7-(4,8,12-trimethyltridecyl)-4,5,6,7-tetrahydro-1,3,8-trioxaphenanthrene (4). Compound **4** was prepared as a yellow oil (0.19 g, 81%, *cis*/*trans*=1:1) according to the general procedure employing γ-tocopherol (0.20 g, 0.48 mmol) and acetaldehyde (0.04 g, 0.96 mmol). ^{1}H NMR: δ 1.20 and 1.21 (2×s, 3H, $^{7a}CH_3$), 1.48 (dd, 3H, ^{3}J=6.3 Hz, *cis*-$^{4}CH_3$), 1.52 (2×d, 6H, ^{3}J=5.1 Hz, *trans*-$^{4}CH_3$, *trans*-$^{2}CH_3$), 1.55 (d, 3H, ^{3}J=6.8 Hz, *cis*-$^{2}CH_3$), 1.61–1.90 (m, 2H, $^{6}CH_2$), 2.09 and 2.11 (2×s, 2×3H, $^{9a}CH_3$, $^{10b}CH_3$), 2.35–2.71 (m, 2H, $^{5}CH_2$), 4.95 (m, 2H, *cis*-^{2}CH, *trans*-^{4}CH), 5.14 (dq, 1H, ^{3}J=6.3 Hz, ^{4}J=0.4 Hz, *cis*-^{4}CH), 5.31 (q, 1H, ^{3}J=5.1 Hz, *trans*-^{2}CH). ^{13}C NMR: δ 11.4 and 11.7 ($^{9a}CH_3$, $^{10b}CH_3$), 19.7 ($^{5}CH_2$), 21.1 (^{4}CH–*C*H$_3$), 22.8 ($^{7a}CH_3$), 28.0 (^{2}CH–*C*H$_3$), 32.7 ($^{6}CH_2$), 68.6 (*trans*-^{4}CH), 70.5 (*cis*-^{4}CH), 74.7 (^{7}C), 89.5 (*trans*-^{2}CH), 95.2 (*cis*-^{2}CH), 113.4 and 114.0 (^{4b}C), 119.6 and 121.7 (^{4a}C), 123.3 and 123.8 (^{10}C), 124.2 and 124.7 (^{9}C), 142.9 and 145.1 (^{10a}C), 145.4 and 145.6 (^{8a}C). HRMS calcd for $C_{32}H_{54}O_3+H^+$: 487.42; found: 487.42.

3.1.2. 2,2′,2′,2′,4,4′,4′,4′-Octadeutero-2,4,7,9,10-pentamethyl-7-(4,8,12-trimethyltridecyl)-4,5,6,7-tetrahydro-1,3,8-tri-oxaphenanthrene (5). Compound **5** was prepared as a yellow oil (0.18 g, 77%) according to the general procedure employing γ-tocopherol (0.20 g, 0.48 mmol) and CD_3CDO (0.05 g, 0.96 mmol). ^{1}H NMR: δ 1.20 and 1.21 (2×s, 3H, $^{7a}CH_3$), 1.61–1.90 (m, 2H, $^{6}CH_2$), 2.09 and 2.11 (2×s, 2×3H, $^{9a}CH_3$, $^{10b}CH_3$), 2.35–2.71 (m, 2H, $^{5}CH_2$). HRMS calcd for $C_{32}H_{46}O_3D_8+H^+$: 495.46; found: 495.48.

3.1.3. 2,4-Diethyl-7,9,10-trimethyl-7-(4,8,12-trimethyltri-decyl)-4,5,6,7-tetrahydro-1,3,8-trioxaphenanthrene (6). Compound **6** was prepared as a yellow oil (0.19 g, 79%, *cis*/*trans*=1:1) according to the general procedure from γ-tocopherol (0.20 g, 0.48 mmol) and propanal (0.06 g, 1.04 mmol). ^{1}H NMR: δ 0.85 (m, 3H, CH_2CH_3), 1.05 (m, 3H, CH_2CH_3), 1.20 (s, 3H, $^{7a}CH_3$), 1.58–1.91 (m, 6H, CH_2CH_3, CH_2CH_3, $^{6}CH_2$), 2.09 and 2.11 (2×s, 2×3H, $^{9a}CH_3$, $^{10b}CH_3$), 2.34–2.65 (m, 2H, $^{5}CH_2$), 4.60 (t, 1H, ^{3}J=6.1 Hz, *cis*-^{4}CH), 4.67 (tt, 1H, ^{3}J=4.9 Hz, *trans*-^{2}CH), 5.03 (tt, 2H, ^{3}J=7.1 Hz, *cis*-^{2}CH, *trans*-^{4}CH). ^{13}C NMR: δ 8.3 and 9.0 ($^{2}CH_2CH_3$, $^{4}CH_2CH_3$), 10.3; 11.3; 11.4; 11.8 ($^{9a}CH_3$, $^{10b}CH_3$), 19.8 and 20.1 ($^{5}CH_2$), 27.0 and 27.7 (^{4}CH–*C*H$_2$), 28.2 and 28.4 (^{2}CH–*C*H$_2$), 31.4 and 31.6 ($^{6}CH_2$), 74.3 and 74.6 (^{4}CH), 74.9 (^{7a}C), 93.1 and 99.4 (^{2}CH), 113.6 and 114.1 (^{4b}C), 119.3 and 120.4 (^{4a}C), 123.3 and 123.7 (^{10}C), 124.0 and 124.7 (^{9}C), 143.0 and 145.4 (^{10a}C), 146.2 and 146.3 (^{8a}C). HRMS calcd for $C_{34}H_{58}O_3+Na^+$: 537.43; found: 537.45.

3.1.4. 7,9,10-Trimethyl-2,4-dipropyl-7-(4,8,12-trimethyltri-decyl)-4,5,6,7-tetrahydro-1,3,8-trioxaphenanthrene (7). Compound **7** was prepared as a yellow oil (0.19 g, 73%, *cis*/*trans*=1:1.5) according to the general procedure from **2** (0.20 g, 0.48 mmol) and butanal (0.07 g, 0.96 mmol). ^{1}H NMR: δ 0.97 (t, 3H, ^{3}J=6.9 Hz, CH_3 in propyl), 1.00 (t, 3H, ^{3}J=6.9 Hz, CH_3 in propyl), 1.20 (s, 3H, $^{7a}CH_3$), 1.45–1.90 (m, 10H, $^{6}CH_2$, 2×C*H*$_2$–C*H*$_2$ in propyl), 2.09 (s, 3H, $^{9a}CH_3$), 2.11 (s, 3H, $^{10b}CH_3$), 2.43–2.61 (m, 2H, $^{5}CH_2$), 4.70–4.75 (m, 2×1H, *trans*-^{2}CH, *cis*-^{4}CH), 5.04–5.07 (m, 1H, *trans*-^{4}CH), 5.11 (t, 1H, ^{3}J=5.14 Hz, *cis*-^{2}CH). ^{13}C NMR: δ 11.3 and 11.7 ($^{9a}CH_3$, $^{10b}CH_3$), 14.0 and 14.1 (CH_3 in propyl), 17.5 and 18.0 (CH_2 in propyl), 20.1 and 19.9 ($^{5}CH_2$), 22.6 and 22.7 ($^{7a}CH_3$), 31.1 and 31.6 ($^{6}CH_2$), 37.7 and 37.9 (CH_2 in propyl), 74.7 and 74.8 (^{4}CH), 92.1 and

98.5 (^{2}CH), 113.5 and 114.0 (^{4b}C), 119.3 and 120.9 (^{4a}C), 123.3 and 123.7 (^{10}C), 124.0 and 124.6 (^{9}C), 145.3 and 145.5 (^{10a}C), 146.1 and 146.2 (^{8a}C). HRMS calcd for $C_{36}H_{62}O_3+Na^+$: 565.48; found: 565.46.

3.1.5. *trans*-2,4-Diisopropyl-7,9,10-trimethyl-7-(4,8,12-tri-methyltridecyl)-4,5,6,7-tetrahydro-1,3,8-trioxaphenanthrene (8). Compound **8** was prepared as a yellow oil (0.19 g, 73%, *cis*/*trans*=1:8.1) according to the general procedure from **2** (0.20 g, 0.48 mmol) and 2-methylpropanal (0.07 g, 0.96 mmol). ^{1}H NMR: δ 0.66 (d, 3H, ^{3}J=6.9 Hz, CH(CH_3)$_2$), 1.04 (d, 3H, ^{3}J=6.9 Hz, CH(CH_3)$_2$), 1.07 (d, 3H, ^{3}J=6.9 Hz, CH(CH_3)$_2$), 1.13 (d, 3H, ^{3}J=6.9 Hz, CH(CH_3)), 1.61–1.85 (m, 2H, ^{6}CH$_2$), 1.89–2.08 (m, 2×1H, CH(CH$_3$)$_2$), 2.08 (s, 3H, ^{9a}CH$_3$), 2.11 (s, 3H, ^{10b}CH$_3$), 2.43–2.61 (m, 2H, ^{5}CH$_2$), 4.43 (d, 1H, ^{3}J=4.9 Hz, ^{4}CH), 4.93 (d, 1H, ^{3}J=2.5 Hz, ^{2}CH). ^{13}C NMR: δ 11.2; 11.8 (^{9a}CH$_3$, ^{10b}CH$_3$), 14.1; 14.9; 17.0; 17.3 (CH–(*C*H$_3$)$_2$), 20.7 (^{5}CH$_2$), 22.7 (^{7a}CH$_3$), 31.4 (^{4}CH$_2$), 32.6; 32.7 (2×*C*H(CH$_3$)$_2$), 74.7 (^{7}C), 77.3 (^{4}CH), 101.6 (^{2}CH), 114.2 (^{4b}C), 120.7 (^{4a}C), 123.6 (^{10}C); 123.9 (^{9}C); 146.8 (^{10a}C); 146.9 (^{8a}C). HRMS calcd for $C_{36}H_{62}O_3+Na^+$: 565.48; found: 565.46.

3.1.6. 7,9,10-Trimethyl-2,4-diphenyl-7-(4,8,12-trimethyltri-decyl)-4,5,6,7-tetrahydro-1,3,8-trioxaphenanthrene (9). Compound **9** was prepared as a yellow oil (0.17 g, 58%, *cis*/*trans*=1:3.9) according to the general procedure using **2** (0.20 g, 0.48 mmol) and benzaldehyde (0.11 g, 0.96 mmol). ^{1}H NMR: δ 1.21 (s, 3H, ^{7a}CH$_3$), 1.40–1.67 (s, 2H, ^{6}CH$_2$), 2.09 and 2.12 (2×s, 2×3H, ^{9a}CH$_3$, ^{10b}CH$_3$), 2.43–2.64 (m, 2H, ^{5}CH$_2$), 5.77 (s, 1H, *trans*-^{4}CH), and 5.95 (s, 1H, *trans*-^{2}CH), 5.99 (2s, 1H, *cis*-^{4}CH), 6.14 (2s, 1H, *cis*-^{2}CH), 7.28–7.38 (m, 4H, ^{Ar}CH), 7.46–7.49 (m, 4H, ^{Ar}CH), 7.59–7.63 (m, 2H, ^{Ar}CH). ^{13}C NMR: δ 12.1 and 12.4 (^{9a}CH$_3$, ^{10b}CH$_3$), 20.2 and 21.0 (^{5}CH$_2$), 22.2 and 22.7 (^{7a}CH$_3$), 37.3 and 37.4 (^{6}CH$_2$), 74.4 (^{7}C), 75.1 (^{4}CH), 92.1 (^{2}CH), 117.4 and 117.5 (^{4a}C, ^{4b}C), 121.8; 122.1 (^{9}C, ^{10}C), 124.9; 125.6; 126.3; 127.3; 128.0; 128.2; 128.3; 128.5; 128.8; 129.2; 129.5 (^{Ar}CH in phenyl), 140.5 and 141.6 (^{Ar}C in phenyl), 145.6 (^{10a}C), 146.0 (^{8a}C). HRMS calcd for $C_{36}H_{62}O_3+Na^+$: 565.48; found: 565.46.

3.1.7. 7,7,9,10-Tetramethyl-2,4-diphenyl-4,5,6,7-tetrahydro-1,3,8-trioxaphenanthrene (10). Compound **10** was prepared as a white solid (0.23 g, 60%, *cis*/*trans*=1:5, mp=115–117 °C) according to the general procedure using **2a** (0.20 g, 0.97 mmol) and benzaldehyde (0.21 g, 1.92 mmol). ^{1}H NMR: δ 1.21 (s, 6H, ^{7a}CH$_3$), 1.40–1.67 (s, 2H, ^{6}CH$_2$), 2.09 and 2.12 (2×s, 2×3H, ^{9a}CH$_3$, ^{10b}CH$_3$), 2.43–2.64 (m, 2H, ^{5}CH$_2$), 5.77 (s, 1H, *trans*-^{4}CH), and 5.95 (s, 1H, *trans*-^{2}CH), 5.99 (s, 1H, *cis*-^{4}CH), 6.14 (s, 1H, *cis*-^{2}CH), 7.28–7.38 (m, 4H, ^{Ar}CH), 7.46–7.49 (m, 4H, ^{Ar}CH), 7.59–7.63 (m, 2H, ^{Ar}CH). ^{13}C NMR: δ 12.1 and 12.4 (^{9a}CH$_3$, ^{10b}CH$_3$), 20.2 and 21.0 (^{5}CH$_2$), 22.2 (d.i.) and 22.7 (d.i.) (^{7a}CH$_3$), 37.3 and 37.4 (^{6}CH$_2$), 74.4 (^{7}C), 75.1 (^{4}CH), 92.1 (^{2}CH), 117.4 (d.i.), 117.5; 117.6 (^{4a}C, ^{4b}C), 121.8; 121.9; 122.0; 122.1 (^{9}C, ^{10}C), 124.9; 125.6; 126.3; 127.3; 128.0; 128.2; 128.3; 128.5; 128.8; 129.2; 129.5 (^{Ar}CH in phenyl), 140.5 and 141.6 (^{Ar}C in phenyl), 145.6 (^{10a}C), 146.0 (^{8a}C). HRMS calcd for $C_{36}H_{62}O_3+Na^+$: 423.19; found: 423.17.

3.1.8. 2-Polystyryl-4,7,9,10-tetramethyl-7-(4,8,12-trimethyl-tridecyl)-4,5,6,7-tetrahydro-1,3,8-trioxaphenanthrene (11). Merryfield resin (polystyrene, cross-linked with 1% divinylbenzene), containing 2.5–3.0 mmol g^{-1} benzaldehyde groups, 383 mg corresponding to 0.96–1.15 mmol CHO was stirred with 2,4,7,9,10-pentamethyl-1,3,8-trioxaphenanthrene **4** (0.50 g, 1.20 mmol) and 2 drops of concd H_2SO_4 in dichloromethane for 14 h. The trioxaphenanthrene-loaded resin was obtained by filtration and was thoroughly washed sequentially with ethyl acetate, *n*-hexane, and diethyl ether. The resin was finally dried in vacuo for 24 h.

3.1.9. 6,9,10,16,17,20-Hexamethyl-6,20-di(4,8,12-trimethyl tridecyl)-7,12,14,19-tetraoxahexacyclo [11.11.1.0^{2,11}.0^{3,8}.0^{15,24}.0^{18,23}]pentacosa-2,8,10,15(24),16,18(23)-hexaene (12). Compound **12** was prepared as a green oil (0.14 g, 35%) from **2** (0.20 g, 0.48 mmol) and 1,1,3,3-tetramethoxypropan (0.05 g, 0.96 mmol) in 2 mL of trifluro acetic acid. After stirring for 2 h, the reaction mixture was poured into ice-water. Then the aqueous phase was repeatedly extracted with *n*-hexane. The combined organic phases were washed sequentially with water, saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc/*n*-hexane, v/v=1:20). ^{1}H NMR: δ 1.27 (2×s, 2×3H, 2×CH$_3$), 1.65–1.93 (m, 2×2H, ^{3}CH$_2$ in tocopherol), 2.03 (m, 2H, bridge-CH$_2$), 2.06 and 2.15 (4×s, 4×3H, 4×CH$_3$), 2.76–2.93 (m, 2×2H, ^{4}CH$_2$ in tocopherol), 4.16 (t, 1H, ^{3}J=10.0 Hz, Ar-CH-Ar), 6.09 (s, 1H, acetal CH). ^{13}C NMR: δ 11.8; 12.2 (C^{Ar}–CH$_3$); 20.8; 21.0 (^{4}CH$_2$ in tocopherol), 25.0 (Ar-*C*H-Ar), 28.3 (bridge CH$_2$), 31.8 (^{3}CH$_2$ in tocopherol), 74.8 (^{2}C in tocopherol), 91.0 (acetal CH), 114.8; 116.0; 120.7; 120.8; 123.3; 123.4; 124.4 (d.i.); 143.2; 143.3; 145.7; 145.8 (^{Ar}CH). HRMS calcd for $C_{59}H_{96}O_4+Na^+$: 868.73; found: 891.77.

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Tautomeric enhancement of the hyperpolarizability in new acridine-benzothiazolylamine based NLO chromophores

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Abstract—The second order NLO response of a new family of acridine-based chromophores is greatly enhanced due to the presence of a tautomeric minor form with high charge-transfer capabilities.

1. Introduction

Within the field of photonics and opto-electronics[1] non-linear optics stands out due to its important technological applications. In the past few years, major advances in organic materials have led to compounds with high and fast nonlinearities. Push–pull organic chromophores, in which a conjugated π-system contains asymmetrically positioned electron-donor and electron-acceptor substituents, were the first and have been the most widely studied of these molecules.[2] The charge transfer between the functional groups imparts a high degree of polarity to push–pull systems. Nonlinearity in organic chromophores can be synthetically modulated by varying the composition or length of conjugated π-systems, and by evaluating the effects of various electron-donor and -acceptor groups. The literature contains numerous examples of these systems, for which high values of hyperpolarizabilities have been reported.[3] Optimized chromophores have generally been obtained via arduous synthetic pathways,[4] usually based on condensation reactions plagued by low regio- and stereo-selective control.

2. Results and discussion

The aim of the present study was to apply our experience in the synthesis of heterocyclic systems[5] to obtain and evaluate novel push–pull chromophores based on 2-nitroacridine as a π-conjugated system and on benzothiazol-2-yl-amino as an electron-donor group. We made this choice both are well-known systems with well-established synthetic methods, however, their nonlinear properties are rarely studied. From structural standpoint, the influence of the benzothiazol-2-yl amino moiety was expected to present some advantages, for instance, Marder[6] and others have shown that for push–pull systems, less-aromatic heterocycles correlate with high nonlinearities. In addition, the high thermal stability of these heterocycles is desirable for practical applications.

Secondary 2-aminobenzothiazoles have commonly been obtained by the reaction of the corresponding 2-halobenzothiazoles with the primary amines.[7] However, our syntheses comprised the reaction of 2-aminobenzothiazole and 6-fluoro-2-nitroacridine via aromatic nucleophilic substitution as described by Rosevear[7] because of the easy preparation of the 6-fluoro-2-nitroacridine, owing the strongly electron-withdrawing group, nitro group in position 2, useful for our purposes to prepare push–pull systems, and the previously reported method for the synthesis of 2-aminobenzothiazole-6-substituted,[8] a substitution pattern useful to enable polymer linkage of these molecules in later works. The major drawback of the Rosevear method for obtaining the target chromophores was the low nucleophilicity of 2-aminobenzothiazoles, which had to be made more reactive by employing an auxiliary base and a polar aprotic solvent. The best yields for the products **2**, **3**, and **4** were obtained when an equimolar ratio of reactants was used and the reaction was run at approximately 130 °C.

Keywords: Synthesis of nonlinear optical chromophores; Tautomeric equilibria; Surface determination of hyperpolarizabilities.
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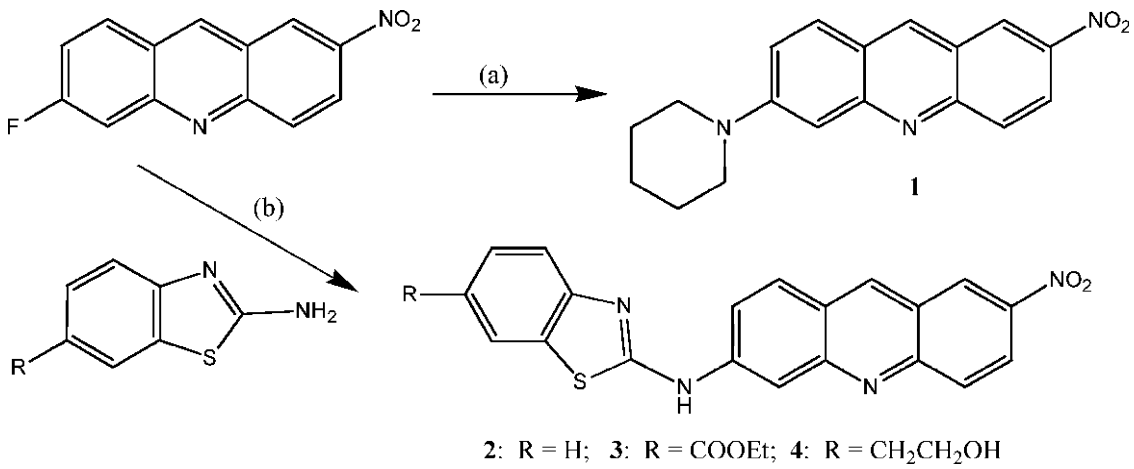

Scheme 1. (a) Refluxing piperidine, 1 h, (95%); (b) K_2CO_3, DMA or NMP, 130 °C, 4 h (55–65) %.

2-Nitro-6-(piperid-1-yl)acridine (**1**) was prepared and studied as a matter of comparison. Scheme 1 shows synthetic routes followed to obtain the chromophores.

The second order optical behavior of **2**, **3**, and **4**, exhibited marked differences as compared to that of **1**, for which the second harmonic generation was clearly inferior. Considering that in all cases the electron-donor group directly linked to the 2-nitroacridine moiety is an amine, the variation in response must be attributed to the presence or absence of the benzothiazole. As the benzothiazole system is slightly π-deficient, the 2-aminobenzothiazole group of chromophores **2**, **3**, and **4** was expected to have a lower electron-donating character than the piperidine present in **1** and, consequently, a lower NLO response. Surprisingly, the experimental results were the opposite. This contradiction may be explained by the existence of tautomeric forms of the 2-aminobenzothiazole moiety (Fig. 1).

Tautomeric equilibria in molecules that contain 2-amino-benzothiazole moiety have typically been described to be predominantly displaced to the aromatic form (Fig. 1a).[9] However, the minor tautomer, benzothiazolin-2-imine (Fig. 1b), could contribute to the hyperpolarizability in the cases of our molecules by increasing the donor strength of the benzothiazole system, because charge transfer increases stability by restoring aromaticity in the benzothiazole ring. This gain in aromaticity could imply an increase in the polarization of the ground-state, another important factor for reaching high hyperpolarizabilities.[10] Nonetheless, the spectroscopic data for our chromophores indicate a very fast tautomeric equilibrium that strongly favors the aromatic tautomer. Charge-transfer bands in the UV-absorption spectra of **2**, **3**, and **4** exhibit a hypsochromic displacement, whereas those of the spectra of **1** do not. This phenomenon suggested the presence of major aromatic tautomers, in which the slightly electron-deficient benzothiazole ring reduces the charge-transfer strength of the amino group. This conclusion was refined and completed by comparing ^{13}C NMR spectra of **2**, **3**, and **4** and their benzothiazole containing precursors with literature data.[9] Unfortunately the low solubility of our compounds in practically all

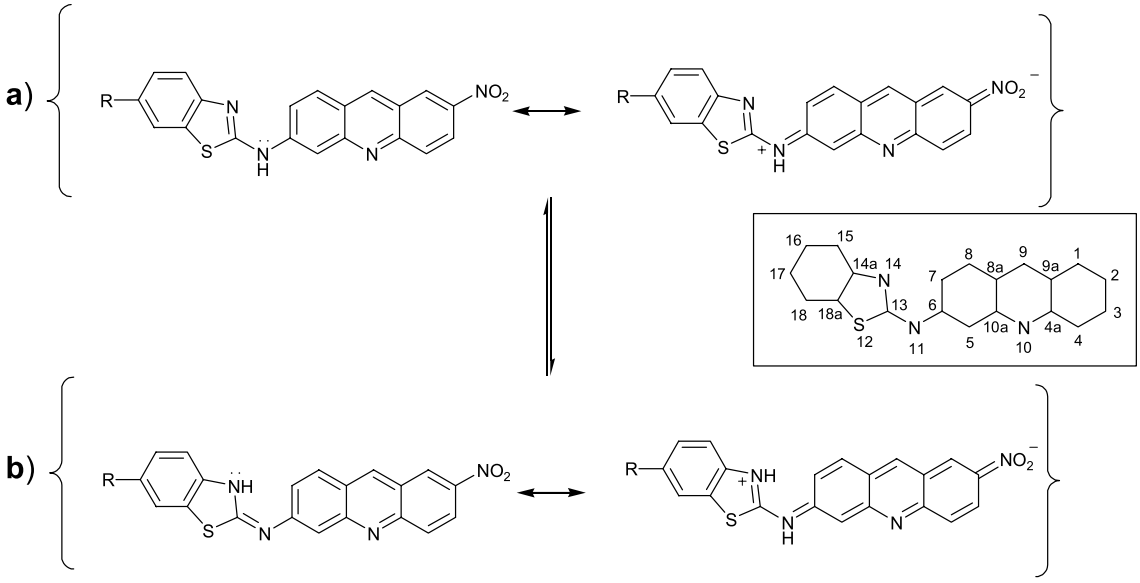

Figure 1. Tautomeric benzothiazol-2-yl-(7-nitroacridin-3-yl)amine (a) and (3*H*-benzothiazol-2-ylidene)-(7-nitroacridin-3-yl)amine (b) and their respective mesomeric forms.

solvents avoid us to perform low temperature and change of solvent NMR experiments to determine the tautomeric population. However, in the paper of Faure et al.,[9a] on prototropic tautomerism in benzothiazoles, the authors reported that the displacement to lower values of ^{13}C shifts for C4[11] upon passing from the aromatic to the non-aromatic tautomer enables the detection and relative quantification of non-aromatic tautomers of the heterocycles. For example, for 2-aminobenzothiazole, in which the aromatic tautomer dominates over the non-aromatic tautomer, C4-δ= 118.4 ppm. In 2-cyanamidebenzothiazole, in which the non-aromatic tautomer is favored but not exclusive, C4-δ=113.9 ppm. Lastly, in 3-methyl-3*H*-benzothiazol-2-yl-ideneamine, which exists in its purely non-aromatic form because tautomerism is blocked by the methyl group in N3, C4-δ=109.3 ppm. Thus, lower δ values translate to higher proportions of non-aromatic tautomers. Upon applying this rule to **2**, **3**, and **4**, a displacement to lower C15-δ values is observed: C15-δ=123.3, 121.8, and 116.6 ppm for **2**, **3**, and **4**, respectively. If we observe now the displacement of C4-δ from 2-aminobenzothiazole to ethyl 2-aminobenzothiazol-6-carboxylate and 2-amino-6-(2-hydroxyethyl)benzothiazole the values are 118.4, 120.0, and 117.9 ppm, respectively. Thus, when the 6-substituent is ethyl carboxylate, a downfield shift in C4 is observed with respect to that of 6-unsubstituted 2-aminobenzothiazole. In contrast, the 2-hydroxyethyl group as a 6-substituent has little or no influence on the C4 chemical shift, contrariwise to the observed in **2**, **3**, and **4**. As the 2-nitroacridine moiety is the same in all cases, the decrease in δ values observed in moving from **2** to **3**, and again from **3** to **4**, only can be explained by the increase in the population of non-aromatic tautomers.

Furthermore, the experimental values for NLO parameters conclusively agreed with the existence of a significant proportion of non-aromatic, imine-type tautomer. This form should present a much higher second-order NLO response than that of the more abundant amino-like tautomer. Spectroscopic data reveal that, under the conditions used, an equilibrium exists in, which the aromatic form dominates. However, if the amount of the non-aromatic tautomer is significant, it must contribute to a higher NLO response; hence higher proportions of the non-aromatic tautomer must yield higher NLO responses. Combining this reasoning with the ^{13}C NMR experimental data led us to the conclusion that lower C15-δ values correspond with higher NLO responses.

The nonlinear optical properties of the chromophores were measured via surface second harmonic generation (SHG).[12] The noncentrosymmetry at the interface between a glass surface and a monolayer of adsorbed molecules, whereby the molecules are uniformly distributed and free of interactions between them, can be used to obtain a considerable second harmonic output.[13] The adsorption of the monolayers of chromophores **1**–**4** and the reference compound 4-dimethylamino-4′-nitrostilbene (DANS) onto glass surfaces was performed by slow (1 mm s^{-1}) withdrawal of a glass plate from a solution of the corresponding molecule in 1-propanol.[14] If we assume that DπA chromophores **1**–**4** have an average rod-like geometry, the molecular nonlinear polarizability tensor would be dominated by the nonlinear axial coefficient along the molecular axis, and then the values for the dominant component of their corresponding microscopic hyperpolarizabilities can be determined.[15]

Briefly, the methodology used consists in measuring the TE and TM second harmonic intensities generated as a function of polarizations of the fundamental field.[16] The exact average orientation of each of the chromophores in the monolayer can be calculated from such measurements. By comparing these values with the measurements obtained for DANS under the same conditions, while taking into account its known hyperpolarizability $\beta(0)$, the values for the second-order nonlinear parameters of the new chromophores were obtained. For each case, the fraction of hyperpolarizability due to the absorption resonance had to be determined for the each chromophore and for DANS.[17] The results are summarized in Table 1.

Chromophores **1**, **2**, and **3** actually exhibited the rod-like nonlinear behavior necessary for the method used to determine static hyperpolarizability. However, a large deviation from said behavior was observed for **4**. The size and conformational freedom of the 2-hydroxyethyl chain enables interaction of the hydroxyl groups with the glass plate surface. The interaction of both hydroxyl and nitro groups with the glass surface confers an angular shape to the adsorbed molecules, whereby the amino group rests at the vertex of the resulting angle that effectively divides each molecule into two sections. Each half-molecule gives an independent NLO response, and the superposition of both vectorial responses leads to non-standard behavior. Hence, neither an average angle of orientation for the adsorbed molecules nor a representative hyperpolarizability value could be obtained in this case. Therefore, only the non-vanishing nonlinear second-order tensor components d_{15}, d_{24}, and d_{33} were possible to determine. The values are given in Table 1. However, the 6-(hydroxyethyl) group in **4** were expected to have a minimal effect on the electronic structure of the π system of the molecule and, consequently, on its NLO properties, and we can legitimately expect an optical behavior similar to **2** and **3**, as, in fact, is observed in

Table 1. NLO parameters of new acridine-benzothiazolylamine chromophores, including DANS as term of comparison

Molecule	λ_{max} (nm)	d_{15} ($\times 10^{-29}$ esu)	d_{24} ($\times 10^{-29}$ esu)	d_{33} ($\times 10^{-29}$ esu)	$(L\cdot\beta)/(L\cdot\beta)_{DANS}$	DπA length, L (Å)[a]	$\beta(0)$ ($\times 10^{-30}$ esu)
1	476	3.92	3.92	6.02	1.18	10.815	43
2	437	3.98	3.98	5.37	1.26	10.795 (12.791)	78
3	430	3.87	3.87	6.40	1.41	10.761 (12.421)	93
4	437	7.83	4.49	4.74	—	10.765 (12.726)	—
DANS	432	3.53	3.53	8.46	1	12.920	55

[a] Values in brackets are the lengths of non-aromatic tautomers.

the calculated values of the hyperpolarizability tensor components (Table 1).

The dipole length of each chromophore was determined using a semi-empiric (AM1) calculation of the geometry of the appropriate charge-separated resonance form. The most widely accepted value for the static hyperpolarizability $\beta(0)$ of DANS is 55×10^{-30} esu.[18] The ratio $(L\cdot\beta)/(L\cdot\beta)_{\mathrm{DANS}}$, in which the hyperpolarizabilities β are wavelength-dependent, can be calculated from the experimental results. In order to determine the static hyperpolarizability $\beta(0)$ of the new chromophores from this ratio, the absorption correction factor derived from the two-state model for the hyperpolarizability must be included.[16] These calculations were far less challenging for the case of **1** than for **2**, **3**, and **4**, all of which contain the benzothiazol-2-yl-amino moiety and are therefore complicated by the presence of two possible tautomers. In addition to unique electronic distributions, each of these tautomeric forms has a corresponding SH that generates a dipole of particular length. Both tautomers must be present in the working mixture, and determining the relative tautomeric populations, as well as the length of the charge-transfer system necessary to calculate the value of β, is not trivial. As previously explained, the position of the tautomeric equilibria could not be established, and was most likely different in solution than in the adsorbed sample, as well as being related to the length of the push–pull system. Fortunately, the second-harmonic generation only depends on the length of dipolar electronic distributions, as shown by Shen,[19] with little or no influence of atoms that do not contribute to resonance. In other words, the dipole 'starts' in the first atom contributing to the resonance of the conjugated system and 'finishes' in the last, functioning independently of atoms that do not contribute to the resonance.

When we combined the aforementioned considerations with the assumption that the aromatic tautomer (i.e., benzothiazol-2-yl-amino) is the predominant form, we established that for all cases, the dipole length is the distance from the nitrogen atom that bridges the acridine and benzothiazole to the oxygen atoms of the nitro group, and is not influenced by the benzothiazole system. In fact, Moylan[20] prepared a broad group of push–pull chromophores, in which the dialkylamino electron-donor groups were substituted by diarylamino groups, obtaining similar SHG values, or in some cases, slightly lower NLO responses due to the lower electron-donating character of the diarylamino groups. We calculated the dipole distances and used them to determine the NLO parameters of our chromophores.

Chromophores **2**, **3**, and **4** should behave similarly to **1** because the electronic distributions of the push–pull systems should themselves be similar. Alternatively, slightly lower intensities could be observed for **2**, **3**, and **4** as compared to **1**, which would be consistent with the findings of Moylan for dialkyl-diarylamino derivatives. Surprisingly the NLO responses of **2**, **3**, and **4** were all greater than that of **1** by nearly 20%. This difference becomes even greater if the relatively higher absorbance at 532 nm for **1** is taken to contribute positively to the final SHG observed. These SHG enhancements can only be caused by the existence of minor tautomeric forms capable of acquiring a stabilized, highly polarized charge-transfer state. Taking into account that spectral characterization did not allow quantification of tautomeric forms, the calculations were performed under the assumption that the dipole length, as previously defined, is approximately the same in all cases (see, Table 1). It is should be noted that the calculated lengths of non-aromatic tautomer dipoles are approximately 2 Å (i.e., ca. 20%) longer than aromatic ones. Hence, in using the ratio $(L\cdot\beta)/(L\cdot\beta)_{\mathrm{DANS}}$ to calculate $\beta(0)$ from the observed SHG, the values obtained for $L_{\mathrm{chromophore}}$ should be inversely proportional to those for $\beta(0)_{\mathrm{chromophore}}$ if all other data are held constant. As the experimental β values were clearly higher than expected, it can be deduced that the β of the longer, minor non-aromatic tautomers are larger than the aromatic ones by at least one order of magnitude.

Static hyperpolarizability [$\beta(0)$] results are shown in the last column of the Table 1. In molecule **1**, a considerable decrease in comparison with β at 1064 nm is observed, in which the $\beta(0)$ was 20% lower than that of the reference compound DANS. Similar decreases were not observed for the other chromophores, in which the enhancement due to the absorption resonance effect is much lower. Chromophores **2** and **3** had $\beta(0)$ values of ca. 142 and 169%, respectively, in relation to DANS and, more importantly, 181 and 216%, respectively, in relation to **1**. The larger value observed for **3** is probably due to an additional favorable effect on the tautomeric equilibrium stemming from the carboxylate group at the position 6. Similar tensor components values were obtained for **2**, **3**, and **4**, indicating that, most likely, the nonlinear polarizabilities of all of them are similar. It should be noted that in the majority of light polarization combinations, the nonlinear performance of **4** would be better or equivalent to that of chromophores **1**–**3**, since the d_{15} and d_{24} values for **4** are larger than the those corresponding to **1**–**3**, and only the d_{33} of chromophore **4** was 25% lower than that of **3**, the best chromophore between **1**, **2**, and **3**.

3. Conclusions

Several new NLO push–pull chromophores have been synthesized via a facile, two-step procedure and their second-order optical behavior was evaluated. The SHG capability of molecules with the benzothiazol-2-yl-amino electron-donating group is considerably enhanced in relation to the analogous piperidyl compound. This phenomena is due to the contribution of a minor non-aromatic tautomer. These tautomers, previously described in the literature, have a less aromatic ground state that enables an aromatic, stabilized and highly polarized charge-transfer state. The $\beta(0)$ of such chromophores are considerably higher than those of similar organic molecules. The surface method used to determine the hyperpolarizability of test compounds was validated and shown to be facile as well as rapid for common DπA rod-like type molecules. Chromophore **4**, with a 2-hydroxyethyl side group, exhibited abnormal optical behavior due to its comb-shaped, non-rod-like geometry in the monolayer due to the simultaneous interaction of nitro and hydroxyl groups with

the glass slide used to perform the measurements. However, **4** has hyperpolarizability tensor component values equal to, or even larger than, those of chromophores **2** and **3**.

4. Experimental

4.1. General

Melting points were determined using a Köfler apparatus equipped with a Reichert Thermovar microscope and are uncorrected. TLC was carried out on SiO_2 (Alugram SIL G/UV_{254} Macherey–Nagel 0.25 mm) and visualized with UV light. Flash chromatography was carried out on SiO_2 (Silica Gel 60 A CC, Merck). Organic extracts were dried over anhydrous $MgSO_4$, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. NMR spectra were measured with Varian Gemini-200 (200 MHz) and Varian Unity-300 (300 MHz) spectrometers, data are given in δ/ppm and referenced to TMS for ^{1}H NMR and to $CDCl_3$ (77.0 ppm) for ^{13}C NMR, and J values are given in Hz. Mass spectra were measured in chemical ionization (CI, NH_3) mode with a Hewlett-Packard 5988A spectrometer, or with a Fisons VG-Quattro spectrometer. The samples were then introduced into a matrix of 2-nitrobenzyl alcohol for FAB analysis.

4.1.1. Synthesis of 6-fluoro-2-nitroacridine.[7] 6-Fluoro-2-nitroacridine was synthesized following the method described in the reference 7 with slightly modifications. 2-Fluoro-5-nitrobenzaldehyde (1.185 g, 7 mmol), 3-fluoroaniline (1.556 g, 14 mmol) and 2 ml of triethylamine were dissolved in 20 ml DMSO and heated to 100 °C under nitrogen atmosphere for 4 h, at which point the reaction mixture was poured into 100 ml of water. The precipitate was filtered off and thoroughly washed with water. The solid was then dissolved in 25 ml of ethanol and 5 ml of dichloromethane, and 5 ml of concentrated hydrochloric acid were subsequently added to the solution. The reaction mixture was refluxed for 30 min, and then poured into 150 ml of a 15% solution of ammonium hydroxide, which precipitated out a pale yellow solid. The solid was filtered off, washed with water and vacuum pump dried. The low solubility of the desired product in ethyl acetate was exploited for the purification. Hence, the solid was solved in a mixture of dichloromethane and ethyl acetate, and the solution was vacuum distilled until the pure title product precipitated. The precipitation was completed by maintaining the solution at 5 °C for a few hours. After several precipitations, 1.215 g (72% yield) of the product was collected; mp 237–238 °C (lit. 237–239 °C). TLC (SiO_2, CH_2Cl_2) R_f=0.48; ^{1}H NMR ($CDCl_3$, TMS_{int}): δ_H (ppm)= 9.02 (s, H8 and H9, 2H), 8.53 (dd, H3, J^{3-4}=10 Hz, J^{3-1}= 3 Hz, 1H), 8.31 (d, H4, J^{4-3}=10 Hz, 1H), 8.11 (dd, H8, J^{8-7}=10 Hz, $J^{8\text{-}F}$=6 Hz, 1H), 7.87 (dd, H5, $J^{5\text{-}F}$=10 Hz, J^{5-7}=2 Hz, 1H), 7.48 (ddd, H7, J^{7-8}=$J^{7\text{-}F}$=10 Hz, J^{7-5}= 2 Hz, 1H); ^{13}C NMR (CD_3OD, TMS_{int}): δ_C (ppm)=165.22 (C6, J^{C-F}=245 Hz), 151.47 (C4a), 149.80 (C2), 144.93 (C10a, J^{C-F}=10 Hz), 142.33 (C9), 133.15 (C8, J^{C-F}= 11 Hz), 130.71 (C4), 127.59 (C1), 124.87 (C9a), 124.81 (C3). 124.41 (C8a), 119.72 (C7, J^{C-F}=28 Hz). 111.66 (C5, J^{C-F}=21 Hz); FTIR (film): ν=1620, 1508, 1341, 1168, 822 cm^{-1}; MS (CI, NH_3): m/z=243.0 ($[M-H]^+$, 100%); HRMS (FAB+): m/z observed 243.056592, calculated for $C_{13}H_8N_2O_2F$ 243.056981.

4.1.2. Synthesis of 2-nitro-6-(piperid-1-yl)-acridine (1). 6-Fluoro-2-nitroacridine (242 mg, 1 mmol) was suspended in 5 ml of piperidine, and the mixture was heated to reflux for 1 h. The resulting red solution was cooled to room temperature and poured into 100 ml of water. The crude product was extracted with dichloromethane (3×100 ml), the organic layer was dried over anhydrous sodium sulfate and evaporated, and the resulting residue was flashed through a short pad of silica gel using dichloromethane as eluent. A major fraction was collected and concentrated by evaporation to afford 291 mg of an intense-red solid; mp 199–200 °C. TLC (SiO_2, DCM) R_f=0.21; ^{1}H NMR ($CDCl_3$, TMS_{int}): δ_H (ppm)=8.83 (d, H1, J^{8-6}=3 Hz, 1H), 8.60 (s, H9, 1H), 8.38 (dd, H3, J^{3-4}=10 Hz, J^{3-1}= 3 Hz, 1H), 8.06 (d, H4, J^{4-3}=10 Hz, 1H), 7.80 (d, H8, J^{8-7}=9 Hz, 1H), 7.40 (dd, H7, J^{7-8}=9 Hz, J^{7-5}=2 Hz, 1H), 7.27 (d, H5, J^{5-7}=2 Hz, 1H), 3.54 (m, –N(CH_2)$_2$–, 4H), 1.75 (m, –(CH_2)$_3$–, 6H); ^{13}C NMR ($CDCl_3$, TMS_{int}): δ_C (ppm)=154.00 (C3), 153.51 (C4a), 150.73 (C10a), 143.14 (C7), 138.12 (C8), 129.75 (C5), 129.59 (C1), 126.34 (C9), 123.28 (C6), 122.70 (C8a), 122.66 (C9a), 121.04 (C2), 106.30 (C4), 49.27 (–N(CH_2)$_2$–), 25.68 (–CH_2–), 24.66 (–CH_2–); UV vis (CH_2Cl_2) λ_{max} (nm)=476 (ε=19,500), 312 (ε=25,100), 270+(ε=41,500); MS (CI, NH_3): m/z= 308.1 ($[M-H]^+$, 100%); HRMS (FAB+): m/z observed 308.139926, calculated for $C_{18}H_{18}N_3O_2$ 308.139902.

4.1.3. Synthesis of ethyl 2-aminobenzothiazole-6-carboxylate.[21] Ethyl *p*-aminobenzoate (5.000 g, 30 mmol) was dissolved in 40 ml of acetic acid, and to the resulting solution was suspended sodium thiocyanate (9.720 g, 120 mmol). A solution of 1.50 ml of bromine in 20 ml of acetic acid was slowly added, and the reaction mixture was stirred at room temperature overnight. A mixture of 100 ml of 30% aqueous ammonium hydroxide and 200 ml of water was then added, and the crude product was extracted by ethyl acetate (5×100 ml). The organic layer was dried over sodium sulfate and concentrated by evaporation, and the resulting solid was purified by flash chromatography (silica gel, 1:4 CH_2Cl_2/ethyl acetate) to obtain 5.970 g of the desired 2-aminobenzothiazole-6-carboxylate; mp 242–243 °C (lit. 243 °C). TLC (SiO_2, AcOEt/CH_2Cl_2 4:1) R_f= 0.58; ^{1}H NMR ($CDCl_3$, TMS_{int}): δ_H (ppm)=8.15 (s, H7, 1H), 7.86 (d, H5, J^{5-4}=8 Hz, 1H), 7.32 (d, H4, J^{4-5}=8 Hz, 1H), 4.38 (q, H8, J^{8-9}=7 Hz, 2H), 1.41 (t, H9, J^{9-8}=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS_{int}): δ_C (ppm)=169.87 (C2), 164.90 (C=O), 156.32 (C3a), 132.01 (C7a), 130.41 (C5), 129.80 (C6), 125.42 (C7), 120.02 (C4), 63.82 (–OCH_2–), 16.82 (–CH_3); FTIR (KBr): 3407, 3332, 1679, 1542, 1458, 1045 cm^{-1}; MS (CI, NH_3): 223.1 ($[M+1]^+$, 100%); HRMS (FAB+): m/z observed 223.054662, calculated for $C_{10}H_{11}N_2O_2S$ 223.054125.

4.1.4. Synthesis of 2-amino-6-(2-hydroxyethyl)-benzothiazole.[22] 4-Aminophenethyl alcohol (4.770 g, 35 mmol), potassium thiocyanate (13.200 g, 140 mmol) and bromine (1.70 ml) were reacted according to a literature procedure to obtain 4.085 g (73% yield) of 2-amino-6-(2-hydroxyethyl)-benzothiazole; mp 176–178 °C (lit.

175–177 °C). TLC (SiO_2, AcOEt/CH_2Cl_2 4:1) R_f=0.47; ^{1}H NMR (DMSO-d_6,TMS_{int}): δ_H (ppm)=7.45 (s, H7, 1H), 7.33 (s, –NH_2, 2H), 7.21 (d, H5, J^{5-4}=8 Hz, 1H), 7.02 (d, H4, J^{4-5}=8 Hz, 1H), 4.61 (t, –OH, J^{OH-9}=4 Hz, 1H), 3.56 (m, H9, 2H), 2.70 (t, H8, J^{8-9}=7 Hz, 3H); ^{13}C NMR (DMSO-d_6 TMS_{int}): δ_C (ppm)=166.34 (C2), 151.59 (C3a), 132.72 (C6), 131.42 (C7a), 126.96 (C5), 121.44 (C7), 117.91 (C4), 63.14 (–CH_2CH_2OH), 39.45 (–CH_2CH_2OH); FTIR (KBr): ν=3427, 3268, 3200–2900 (broad band), 1615, 1532, 1451, 1046 cm^{-1}; MS (FAB+): m/z=195.0 ($[M-H]^+$).

4.1.5. Synthesis of 6-(benzothiazol-2-yl-amino)-2-nitroacridine (2). 6-Fluoro-2-nitroacridine (121 mg, 0.5 mmol) was reacted with 2-aminobenzothiazole (78 mg, 0.6 mmol) and 71 mg of anhydrous potassium carbonate (83 mg, 0.6 mmol, 1.2 equiv) in 10 ml of DMA at 130–140 °C for 4 h. The crude reaction mixture was concentrated under vacuum, then purified by column chromatography (silica gel, 20:1 CH_2Cl_2/MeOH) to afford 92 mg of the title product (yield: 57%); mp >300 °C. TLC (SiO_2, hexane/AcOEt 1:3) R_f=0.47; ^{1}H NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_H (ppm)=9.74 (s, H9, 1H), 9.31 (d, H1, J^{1-3}=2 Hz, 1H), 8.97 (dd, H3, J^{3-4}=9 Hz, J^{3-1}=2 Hz, 1H), 8.56 (s, H5, 1H), 8.54 (d, H4, J^{4-3}=9 Hz, 1H), 8.52 (d, H8, J^{8-7}=9 Hz, 1H), 8.03 (dd, H7, J^{7-8}=9 Hz, J^{7-5}=2 Hz, 1H), 7.98 (d, H14, J^{14-15}=8 Hz), 7.87 (d, H17, J^{17-16}=8 Hz, 1H), 7.77 (dd, H16, J^{16-15}=8 Hz, J^{16-17}=8 Hz, 1H), 7.66 (dd, H15, J^{15-14}=8 Hz, J^{15-16}=8 Hz, 1H); ^{13}C NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_C (ppm)=165.27 (C13), 149.96 (C9), 147.15 (C6), 146.33 (C2), 143.42 (C18a), 141.49 (C4a), 136.60 (C10a), 132.98 (C8), 131.25 (C3), 130.41 (C17), 128.00 (C16), 126.52 (C1), 125.27 (C14a), 124.91 (C7), 124.30 (C8a), 123.35 (C15), 123.17 (C9a), 122.23 (C4), 116.32 (C18), 104.26 (C5); FTIR (KBr): ν=3365 (broad band), 1637, 1609, 1543, 1439, 1339, 1331, 1197 cm^{-1}; MS (MALDI-TOF+): m/z=373.1 ($[M]^+$, 100%); HRMS (FAB+): m/z observed 373.076187, calculated for $C_{20}H_{13}N_4O_2S$ 373.075923; UV vis (MeOH) λ_{max} (nm)= 437 (ε=2.4×10^4), 331 (ε=3.7×10^4).

4.1.6. Synthesis of 6-(6-ethylcarboxylate-benzothiazol-2-yl-amino)-2-nitroacridine (3). Following the method described above, 6-fluoro-2-nitroacridine (242 mg, 1 mmol) was reacted with 2-aminobenzothiazole-6-carboxylate (225 mg, 1.1 mmol) and anhydrous potassium carbonate (165 mg, 1.2 mmol) in 15 ml of DMA to obtain 288 mg (65% yield) of the title product; mp 293–295 °C. TLC (SiO_2, CH_2Cl_2/MeOH 20:1) R_f=0.57; ^{1}H NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_H (ppm)=9.72 (s, H9, 1H), 9.31 (d, H1, J^{1-3}=2 Hz, 1H), 9.29 (dd, H3, J^{3-4}= 10 Hz, J^{3-1}=2 Hz, 1H), 8.99 (d, H18, J^{18-17}=10 Hz, 1H), 8.69 (s, H15, 1H), 8.55 (d, H4, J^{4-3}=10 Hz, 1H), 8.40 (d, H17, J^{17-18}=10 Hz, 1H), 8.35 (s, H5, 1H), 8.05 (d, H8, J^{8-7}=8 Hz, 1H), 7.95 (d, H7, J^{7-8}=8 Hz, 1H), 4.54 (q, CH_3CH_2O, J=6 Hz, 2H), 1.51 (t, CH_3CH_2O, J=6 Hz, 3H); ^{13}C NMR (DMSO-d_6,TMS_{int}): δ_C (ppm)=164.10 (C=O), 160.70 (C13), 152.91 (C9), 150.73 (C18a), 150.47 (C16), 144.38 (C4a), 144.38 (C2), 139.96 (C6), 135.68 (C10a), 135.55 (C9a), 130.72 (C3), 128.03 (C4), 127.97 (C7), 127.85 (C17), 124.46 (C1), 123.94 (14a), 123.68 (C18), 122.52 (C8), 121.81 (C15), 121.05 (C8a), 111.58 (C5), 62.33 (CH_2), 31.27 (CH_3); FTIR (KBr): ν=3268, 1675, 1532, 1451, 1046 cm^{-1}; MS (MALDI-TOF+): m/z=445.1 ($[M+1]^+$, 100%); HRMS (MALDI-TOF+): m/z observed 445.096738, calculated for $C_{24}H_{17}N_4O_4S$ 445.097050. UV vis (MeOH): 430 (ε=2.4×10^4), 331 (ε=3.8×10^4).

4.1.7. Synthesis of the 6-[6-(β-hydroxyethyl)-benzothiazol-2-yl-amino]-2-nitroacridine (4). 6-Fluoro-2-nitroacridine (242 mg, 1 mmol) was reacted with 2-amino-6-(2-hydroxyethyl)-benzothiazole (217 mg, 1.1 mmol) and anhydrous potassium carbonate (165 mg, 1.2 mmol), in 15 ml of DMA to obtain 249 mg (60% yield) of the title product; mp 297–298 °C. TLC (SiO_2, DCM/MeOH 20:1) R_f=0.27;. ^{1}H NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_H (ppm)=9.72 (s, H9, 1H), 9.31 (d, H1, J^{1-3}=2 Hz, 1H), 8.96 (dd, H3, J^{3-4}=10 Hz, J^{3-1}=2 Hz, 1H), 8.54 (d, H18, J^{18-17}=10 Hz, 1H), 8.53 (s, H5, 1H), 8.50 (d, H4, J^{4-3}= 10 Hz, 1H), 8.02 (d, H17, J^{17-18}=10 Hz, 1H), 7.86 (s, H15, 1H), 7.82 (d, H8, J^{8-7}=8 Hz, 1H), 7.60 (d, H7, J^{7-8}=8 Hz, 1H), 4.65 (t, –CH_2CH_2OH, J=6 Hz, 2H), 3.27 (t, –CH_2CH_2OH, J=6 Hz, 2H); ^{13}C NMR ($CDCl_3$+TFA 1 drop, TMS_{int}): δ_C (ppm)=165.14 (C13), 149.80 (C9), 147.19 (C18a), 146.26 (C4a), 143.52 (C2), 141.50 (C6), 137.19 (C10a), 136.09 (C16), 132.92 (C4), 131.27 (C3), 131.15 (C7), 126.52 (C17), 125.24 (C1), 124.92 (C8a), 124.24 (C8), 124.19 (C9a), 123.22 (14a), 122.22 (C18), 116.61 (C15), 103.95 (C5), 67.95 (–CH_2CH_2OH), 34.23 (–CH_2CH_2OH); FTIR (KBr): ν=3427, 3268, 3200–2900 (broad band), 1615, 1532, 1451, 1046 cm^{-1}; MS (MALDI-TOF+): m/z=416.0 ($[M]^+$, 100%); HRMS (MALDI-TOF+): m/z observed 417.10064, calculated for $C_{22}H_{17}N_4O_3S$ 417.10214. UV vis (MeOH) λ_{max} (nm)= 437 (ε=2.5×10^4), 329 (ε=3.8×10^4).

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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.2005.07.045

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Reductive ring opening of dihydrodibenzothiepine and dihydrodinaphtho-oxepine and -thiepine

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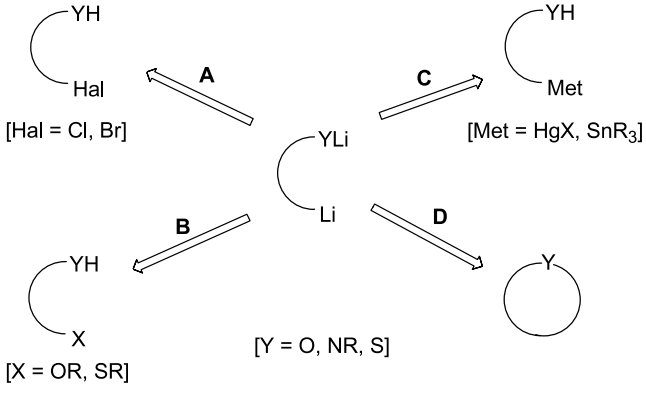
Dedicated to Professor Rafael Suau on the occasion of his 60th birthday

Abstract—The 4,4′di-*tert*-butylbiphenyl (DTBB)-catalysed lithiation of dihydrodibenzothiepine (**1**) at −78 °C for 30 min followed by reaction with a carbonyl compound [^{t}BuCHO, Ph$(CH_2)_2$CHO, PhCHO, (n-$C_5H_{11})_2$CO, $(CH_2)_5$CO, $(CH_2)_7$CO, (−)-menthone] at the same temperature leads, after hydrolysis with 3 M hydrochloric acid, to sulphanyl alcohols **2**. If after addition of a carbonyl compound as the first electrophile [Me_2CO, $(CH_2)_5$CO, (−)-menthone], the resulting dianion of type **II** is allowed to react at room temperature for 30 min, a second lithiation takes place to give an intermediate of type **III**, which by reaction with a second electrophile [Me_2CO, Et_2CO, $(CH_2)_5$CO, $ClCO_2Et$], yields, after hydrolysis, difunctionalised byphenyls **4**. The cyclisation of the sulphanyl alcohol **2c** under acidic conditions yields the eight-membered sulphur containing heterocycle **3**. The lithiation of dihydrodinaphthoheteroepines **7** and **10** with 2.2 equiv of lithium naphthalenide in THF at −78 °C followed by reaction with different electrophiles [H_2O, D_2O, ^{t}BuCHO, Me_2CO, Et_2CO, $(CH_2)_4$CO, $(CH_2)_5$CO] at the same temperature leads, after hydrolysis, to unsymmetrically 2,2′-disubstituted binaphthyls **9** and **12**, respectively. When the lithiation is performed with an excess of lithium in the presence of a catalytic amount of DTBB (10% molar), a double reductive cleavage takes place to give the dianionic intermediate **VII**, which by reaction with different electrophiles [H_2O, Me_2CO, Et_2CO, $(CH_2)_4$CO, $(CH_2)_5$CO], followed by hydrolysis with water, yields symmetrically 2,2′-disubstituted binaphthyls **8** and **11**. In the case of starting from (*R*)- or (*S*)-dihydrodinaphthoheteroepines **7** and **10**, these methodologies allow us to prepare enantiomerically pure compounds **8**, **11** and **12**.

1. Introduction

Among organometallic intermediates in synthetic organic chemistry, organolithium compounds[1] have become of routine use due to their high reactivity even under mild reaction conditions. When the organolithium compound bears a functional group, this type of intermediates[2] are more interesting from a synthetic point of view because in their reaction with an electrophile, the functionality is transferred to this reagent, so polyfunctionalised molecules can be prepared directly, creating at the same time in general a new carbon–carbon bond. Some general procedures to prepare organolithium compounds are also applicable to the corresponding functionalised systems, namely (a) a halogen–lithium exchange (mainly from chlorinated or brominated derivatives; Scheme 1, Method A), (b) an oxygen– or sulphur–lithium exchange (Scheme 1, Method B), or (c) a mercury– or tin–lithium transmetallation (Scheme 1, Method C) have been successfully used to generate functionalised organolithium compounds, being necessary to deprotonate the YH functionality before the



Scheme 1.

Keywords: DTBB-catalysed lithiation; Sulphur–lithium exchange; Dibenzothiepine; Dinaphthothiepine; Electrophilic substitution.
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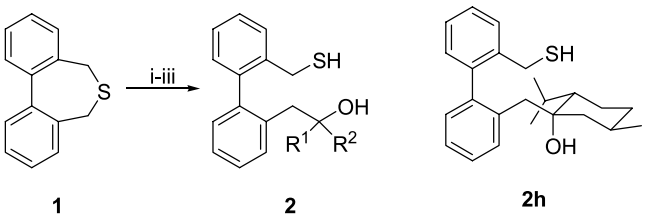


Scheme 2. Reagents and conditions: (i) Li, DTBB (5 mol %), THF, −78 °C, 1 h; (ii) R^1R^2CO=^{t}BuCHO, $Ph(CH_2)_2CHO$, PhCHO, Me_2CO, $(n\text{-}C_5H_{11})_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (−)-menthone, −78 °C; (iii) HCl–H_2O, −78 °C to rt.

lithiation step. On the other hand, the above mentioned procedures are not very efficient from an atom economy point of view.[3] In order to solve this last disadvantage, in the last few years a new methodology has been introduced for the generation of functionalised organolithium compounds consisting in a reductive opening of heterocycles (Scheme 1, Method C).[4] Since in many cases, the corresponding organolithium intermediate is not stable at room temperature, it is necessary to perform the lithiation at low temperature using, for that purpose, a high reactive lithiation agent.[5] For this reason, in the last few years our group has intensively worked in the development of an arene-catalysed lithiation,[6] which, among other applications,[7] can be used to the reductive opening of heterocycles.[8] In this paper we describe the application of this methodology to the ring opening of benzo- and naphtho-condensed sulphur-containing seven-membered rings, comparing in the last case the reactivity of the sulphur- and the oxygen-containing heterocycle.[9] The reaction of the resulting organolithium compounds with electrophiles leads to funtionalised biphenyls and binaphthyls which are mainly prepared by metal-catalysed coupling of aryl halides, triflates or stannanes with appropriate counter pairs,[10] as well as by nucleophilic opening of dinaphthoazepinium[11] and thiepinium[12] salts.

2. Results and discussion

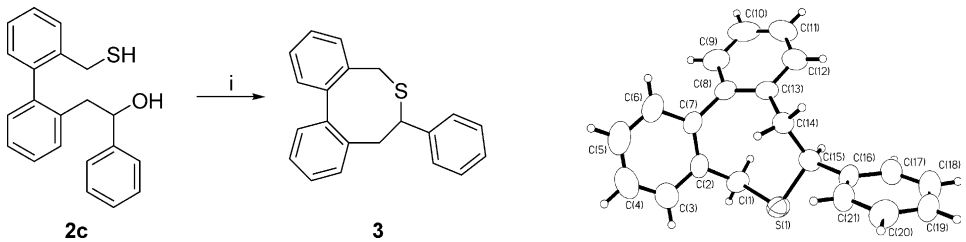
The reaction of 5,7-dihydrodibenzo[*c*,*e*]thiepine (**1**) with an excess of lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB; 5 mol%) in THF at −78 °C followed by treatment with a carbonyl compound [R^1R^2CO=^{t}BuCHO, $Ph(CH_2)_2CHO$, PhCHO, Me_2CO, $(n\text{-}C_5H_{11})_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (−)-menthone] at the same temperature led, after acid hydrolysis at −78 °C to room temperature, to the corresponding hydroxy thiols **2** (Scheme 2 and Table 1). For prostereogenic carbonyl compounds, such as pivalaldehyde, benzaldehyde, 3-phenylpropanal and (−)-menthone, the corresponding 1:1 mixture of diastereomers was obtained (Table 1, entries 1, 2, 3 and 8, respectively, and footnote c). In the case of using (−)-menthone as the electrophile, the attack of the nucleophile took place almost exclusively from the less hindered face of the carbonyl group[13] to give compound **2h** (Scheme 2).

Concerning possible intermediates involved in the reaction shown in Scheme 2, in the lithiation step, a reductive opening of the heterocycle takes place[14] giving intermediate **I**, which by reaction with the carbonyl compound R^1R^2CO used as electrophile gives the second intermediate **II**, precursor of products **2** by final acidic hydrolysis.

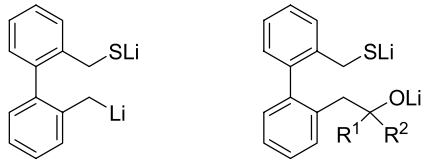
Table 1. Preparation of compounds **2**

Entry	R^1R^2CO	Product[a]			
		No.	R^1	R^2	Yield (%)[b]
1	^{t}BuCHO	**2a**	H	^{t}Bu	71[c]
2	$Ph(CH_2)_2CHO$	**2b**	H	$Ph(CH_2)_2$	75[c]
3	PhCHO	**2c**	H	Ph	82[c]
4	Me_2CO	**2d**	Me	Me	50
5	$(n\text{-}C_5H_{11})_2CO$	**2e**	$n\text{-}C_5H_{11}$	$n\text{-}C_5H_{11}$	76
6	$(CH_2)_5CO$	**2f**	$(CH_2)_5$		72
7	$(CH_2)_7CO$	**2g**	$(CH_2)_7$		47
8	(−)-Menthone	**2h**	—[d]		55

[a] All products **2** were >95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**.
[c] Isolated as a ca. 1:1 diastereomeric mixture (NMR).
[d] See Scheme 2.



Scheme 3. Reagents and conditions: (i) H_3PO_4 (85%), PhMe, 110 °C.

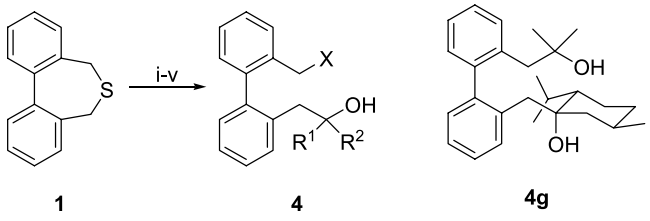


I II

Compound **2** can be easily cyclised under acidic conditions as is exemplified for the benzaldehyde derivative **2c**. Treatment of this compound with 85% phosphoric acid under toluene reflux yielded the corresponding eight-membered ring **3** in 74% isolated yield, whose structure was determined by X-ray crystallography (Scheme 3).[15]

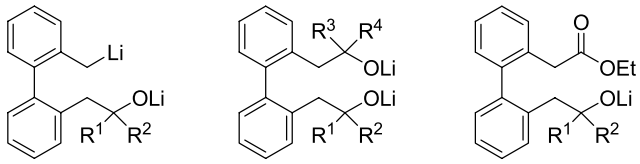
Starting material **1** was easily prepared from commercially available 2,2′-bis(bromomethyl)biphenyl by treatment with sodium sulphide in DMF at 100 °C in almost quantitative yield.[12]

From a synthetic point of view, an interesting variant of the lithiation of the starting material **1** results when a second electrophile is introduced in the molecule. It happens when after the generation of the intermediate **II** instead of hydrolysis a second lithiation took place at temperatures ranging between −78 °C and room temperature. By this treatment, a second carbon–sulphur bond cleavage took place, so a new organolithium intermediate **III** was generated, which by reaction with a second electrophile {E=R^3R^4CO [Me_2CO, Et_2CO, $(CH_2)_5CO$], $ClCO_2Et$} at −78 °C gave, after hydrolysis, the expected products **4** (Scheme 4 and Table 2). Before the final hydrolysis intermediates **IV** (for R^3R^4CO) or **V** (for $ClCO_2Et$) are probably involved in the process. Also here, the use of (−)-menthone as the first electrophile and acetone as the second one yielded almost exclusively the diastereomer **4g**, resulting from the attack of the organolithium intermediate **I** to the first electrophile [(−)-menthone] at the less hindered face, as it was above mentioned for compound **2h** (Scheme 4, Table 2, entry 7).[13]



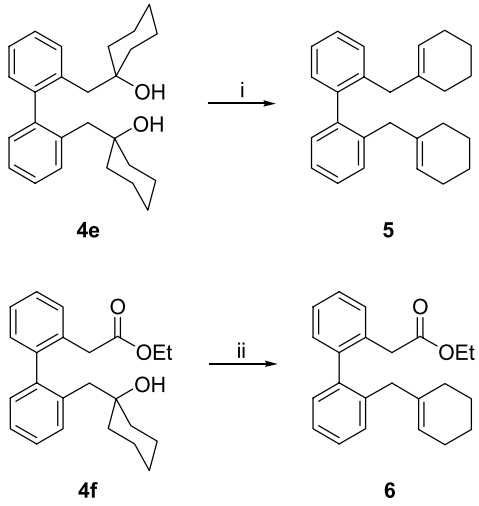
1 4 4g

Scheme 4. Reagents and conditions: (i) Li, DTBB (5 mol %), THF, −78 °C, 1 h; (ii) R^1R^2CO=Me_2CO, $(CH_2)_5CO$, (−)-menthone, −78 °C; (iii) −78 °C to rt; (iv) E=Me_2CO, Et_2CO, $(CH_2)_5CO$, $ClCO_2Et$, −78 °C; (v) H_2O, −78 °C to rt.



III IV V

Compounds of type **4**, especially those derived from carbonyl compounds, could be adequate starting materials for cyclisation processes (see above for compound **3**). However, treatment of compound **4e** (derived from cyclohexanone) with 85% phosphoric acid under toluene reflux gave the corresponding diolefin **5** in 62% isolated yield, without detection of any cyclisation products (Scheme 5). In addition, hydroxyl ester **4f** gave also the dehydration product **6** in 50% yield upon treatment with a catalytic amount of *p*-toluenesulphonic acid under toluene reflux, also without formation of the desired lactone (Scheme 5).



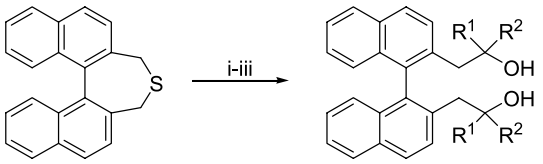
4e 5 4f 6

Scheme 5. Reagents and conditions: (i) H_3PO_4 (85%), PhMe, 110 °C; (ii) TsOH (cat.), PhMe, 110 °C.

Table 2. Preparation of compounds **4**

Entry	R^1R^2CO	Electrophile E	Product[a]				
			No.	R^1	R^2	X	Yield (%)[b]
1	Me_2CO	Me_2CO	**4a**	Me	Me	Me_2COH	40
2	Me_2CO	$ClCO_2Et$	**4b**	Me	Me	CO_2Et	36
3	$(CH_2)_5CO$	Me_2CO	**4c**	$(CH_2)_5$		Me_2COH	45
4	$(CH_2)_5CO$	Et_2CO	**4d**	$(CH_2)_5$		Et_2COH	46
5	$(CH_2)_5CO$	$(CH_2)_5CO$	**4e**	$(CH_2)_5$		$(CH_2)_5COH$	38
6	$(CH_2)_5CO$	$ClCO_2Et$	**4f**	$(CH_2)_5$		CO_2Et	41
7	(−)-Menthone	Me_2CO	**4g**		—[c]		35

[a] All products **4** were >95% pure (GLC and/or 300 MHz ^1H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**.
[c] Isolated as a ca. 1:1 diastereomeric mixture (NMR); see Scheme 4.



7 8

Scheme 6. Reagents and conditions: (i) Li, DTBB (10 mol %), THF, −78 °C; (ii) R^1R^2CO=Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, −78 °C; (iii) HCl–H_2O, −78 °C to rt.

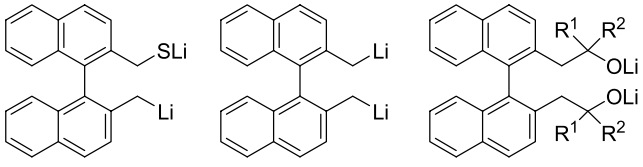
Table 3. Preparation of compounds **8** and **11**

Entry	Starting material	Electrophile E	Product[a]			
			No.	R^1	R^2	Yield (%)[b]
1	**7**	Me_2CO	**8a**	Me	Me	52
2	**7**	Et_2CO	**8b**	Et	Et	57
3	**7**	$(CH_2)_4CO$	**8c**	$(CH_2)_4$		31
4	**7**	$(CH_2)_5CO$	**8d**	$(CH_2)_5$		38
5	**10**	H_2O	**11**	—[c]		96
6	**10**	Me_2CO	**8a**	Me	Me	48

[a] All products **8** and **11** were >95% pure (GLC and/or 300 MHz ^1H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **7** or **10**.
[c] See Scheme 8.

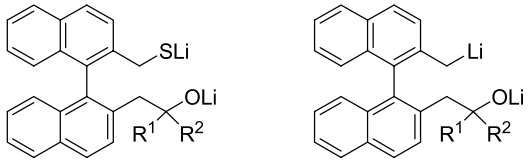
In the second part of this study, we will consider the corresponding dinaphtho derivatives as a heterocycle to be reductively opened, hoping that in this case functionalised chiral binaphthyls could be accessible using this methodology.

The reaction of 4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*] thiepine (**7**) with an excess of lithium and a catalytic amount of DTBB, under the same reaction conditions shown on Scheme 2 (THF, −78 °C), gave, after treatment with a carbonyl compound as electrophile [R^1R^2CO=Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$] at the same temperature, and final hydrolysis, the corresponding compounds **8**, resulting from a double condensation at both benzylic positions (Scheme 6 and Table 3, entries 1–4). In contrast to the behaviour observed for the starting material **1**, in the case of compound **7** it seems that here, after the first reductive ring opening, the first organolithium intermediate **VI** suffers a rapid second lithiation (even in the presence of the electrophile: Barbier type reaction conditions) to give the dilithium compound **VII**, which can survive under the essayed conditions until the addition of the electrophile, so giving the corresponding dialkoxide **VIII**, precursor of the obtained products **8**.



VI VII VIII

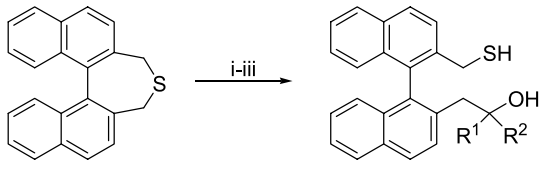
In order to avoid the mentioned second lithiation we used the less active stoichiometric version of the arene-promoted lithiation.[16] Thus, treatment of the starting material **7** with a THF solution of lithium naphthalene (1:2.2 molar ratio) in THF at −78 °C, followed by reaction with the same electrophile mentioned in Scheme 6 at the same temperature gave, after hydrolysis under acidic conditions, the corresponding monosubstituted products **9** (Scheme 7 and Table 4, entries 1–4). In this case, and due to the less energic reduction conditions, the first lithiation product **VI** reacts with the electrophile giving an intermediate of type **IX**, which by hydrolysis afforded sulphanyl alcohols **9**.



IX X

Different attempts to perform a second lithiation of intermediate **IX** under catalytic conditions failed, so in contrast to the results shown in Scheme 4 for the starting material **1** we were not able to introduce two different electrophiles at both benzylic positions (through an intermediate of type **X**). For this reason we decide to investigate for the first time, the behaviour of the corresponding oxygen containing dinaphtho derivative **10** in an arene-promoted lithiation with concomitant ring opening.

Actually, we found a similar behaviour starting from compound **10** than from its sulphur analogue **7** (see Schemes 6 and 7). Thus, using the DTBB-catalysed lithiation (Scheme 6), as for compound **7**, and using water



7 9

Scheme 7. Reagents and conditions: (i) $LiC_{10}H_8$ (2.2 equiv), THF, −78 °C; (ii) R^1R^2CO=Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, −78 °C; (iii) HCl–H_2O, −78 °C to rt.

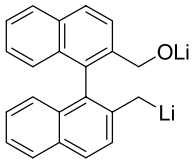
Table 4. Preparation of compounds **9** and **12**

Entry	Starting material	Electrophile E	Product[a]			
			No.	R^1	R^2	Yield (%)[b]
1	**7**	Me_2CO	**9a**	Me	Me	64
2	**7**	Et_2CO	**9b**	Et	Et	56
3	**7**	$(CH_2)_4CO$	**9c**	$(CH_2)_4$		53
4	**7**	$(CH_2)_5CO$	**9d**	$(CH_2)_5$		36
5	**10**	H_2O	**12a** (X=H)	—	—	81
6	**10**	D_2O	**12b** (X=D)	—	—	68[c]
7	**10**	^{t}BuCHO	**12c** (X=^{t}BuCHOH)	—	—	48[d]
8	**10**	Me_2CO	**12d** (X=Me_2COH)	—	—	38
9	**10**	Et_2CO	**12e** (X=Et_2COH)	—	—	51
10	**10**	$(CH_2)_5CO$	**12f** [X=$(CH_2)_5COH$]	—	—	48

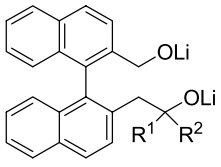
[a] All products **9** and **12** were >95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **7** or **10**.
[c] A ca. 70% deuterium incorporation was obtained (^{13}C NMR).
[d] A ca. 1:1 diastereomeric mixture was obtained and separated by column chromatography (silica gel, hexane/ethyl acetate).

or acetone as electrophiles, compounds **11** and **8a** were, respectively, isolated (Scheme 8 and Table 3, entries 5 and 6). In addition, using the stoichiometric version of the naphthalene-promoted lithiation (Scheme 7), and using different electrophiles [E=H_2O, D_2O, ^{t}BuCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$] under the same reaction conditions than for compound **9**, the expected compounds **12** were isolated (Scheme 8 and Table 4, entries 5–10).

Whereas possible intermediates involved in Scheme 8 would be successively **XI**, **VII**, **X** and **VIII** for compounds **8a**, for compound **12** intermediates **XI** and **XII** (for E=R^1R^2CO) are probably involved in their preparation.



XI

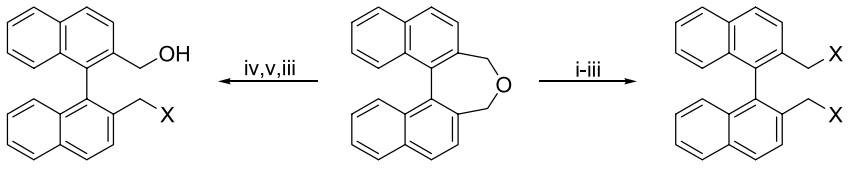


XII

Starting materials **7** and **10** were prepared in ca. 40% overall yield from commercially available 1-bromo-2-methylnaphthalene (**13**) following the reaction sequence: (i) homocoupling of its corresponding Grignard reagent in the presence of a catalytic amount of $(PPh_3)_2NiCl_2$ to give compound **11**;[17] (ii) treatment with *N*-bromosuccinimide in the presence of AIBN to give 2,2′-bis(bromomethyl)-1,1′-binaphthyl (**16**);[18] (iii) reaction of the dibromo derivative with sodium sulphide in DMF,[12] or 5 M NaOH in dioxane in the presence of 2,6-lutidine,[19] to yield compound **7** or **10**, respectively, (Scheme 9).

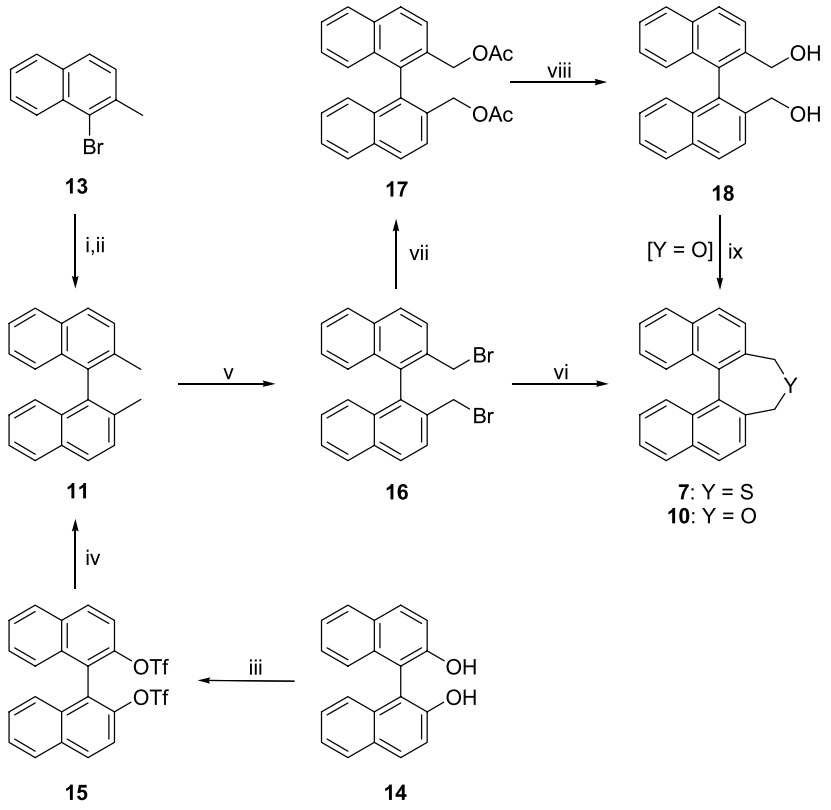
In the last part of this work, we study the use of chiral starting materials **7** and **10** in order to prepare chiral products of type **8**, **9**, **11** and **12**. Scheme 9 summarizes the preparation of those heterocycles: commercially available (*R*)- or (*S*)-binaphthol **14** (>99% ee) was treated with triflic anhydride and pyridine in CH_2Cl_2 at −78 °C to yield the corresponding bistriflate **15**, which was then coupled with methylmagnesium bromide in the presence of a catalytic amount of $(PPh_3)_2NiCl_2$ under ether reflux to yield the corresponding chiral dimethyl derivative **11**.[20] After double radical bromination with NBS catalyzed by AIBN in CCl_4 at 80 °C to give the dibromoderivative **16**, it was transformed into the final compounds **7** and **10** as it was above mentioned for the corresponding achiral systems. Alternatively, compound **10** can be prepared from the dibromo compound **16** by first acetate nucleophilic substitution under PTC reaction conditions to give the diacetate **17**, followed by basic hydrolysis to afford the diol **18** and final cyclisation through a *p*-toluenesulphonic acid-promoted azeotropic dehydration[21] (Scheme 9).

Once chiral compound (*R*)-**7** and (*S*)-**7** or (*R*)-**10** and (*S*)-**10** were prepared, they were submitted to the same protocol used for their racemic mixtures as shown in Schemes 6 and 8. Thus, the expected compounds **8**, **11** and **12** were isolated in high optical purity, the same than the starting materials, so no racemisation occurred during the whole process of the tandem lithiation-S_E reaction. Optical purities of compounds **7** and **10** were assigned on the basis of the starting commercially available (*R*)- and (*S*)-1,1′-bi-2-naphthols (Aldrich, 99% ee). In order to confirm the optical purity of the reaction products, compounds (*S*)-**12a** and (*S*)-**12f** were analysed by HPLC with a Daicel Chiralpack AS column, along with racemic **12a** and **12f**. In both cases a 98% ee was obtained (λ=254 nm, *n*-hexane/2-propanol, 1.0 mL/min; **12a** t_r=7.73 and 10.00 min; **12f** t_r=25.70 and 29.69 min).



12 **10** **8a**,**11** (X = H)

Scheme 8. Reagents and conditions: (i) Li, DTBB (10 mol %), THF, −78 °C; (ii) E=H_2O, Me_2CO, −78 °C; (iii) H_2O, −78 °C to rt; (iv) $LiC_{10}H_8$ (2.2 equiv), THF, −78 °C; (v) E=H_2O, D_2O, ^{t}BuCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, −78 °C.



Scheme 9. Reagents and conditions: (i) Mg, Et_2O–PhH (1/1), 20 °C, 5 h; (ii) **13**, $(Ph_3P)_2NiCl_2$ (cat.), 40 °C, 15 h;(iii) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, −78 °C to rt; (iv) MeMgBr (2.2 equiv), $(Ph_3P)_2NiCl_2$ (cat.), Et_2O, 0 °C to reflux; (v) NBS (2.5 equiv), AIBN (cat.), CCl_4, 80 °C; (vi) $Na_2S\cdot 9H_2O$, DMF, reflux (for Y = S) or 5 M NaOH, 2,6-lutidine, 80 °C (for Y = O); (vii) KOAc, TBAB, DMF, 80 °C; (viii) 5 M NaOH, dioxane, 100 °C; (ix) TsOH (cat.), PhH, 80 °C.

In order to select representative examples, we chose the starting materials (*R*)-**7** or (*S*)-**7** for preparing chiral products **8** and **11** (see Scheme 6; see also Scheme 8 for the structure of compound **11**) and (*R*)-**10** or (*S*)-**10** for achieving compounds **12** (see Scheme 8). The results were consistent and are summarised in Table 5. For the case of using the starting molecule (*S*)-**10** and pivalaldehyde as electrophile a ca. 1:1 mixture of diastereomers was obtained, both of them being separated and purified by column chromatography and analysed (Table 5, entry 9 and footnote c). However, we are not able to assign the absolute configuration of the newly created stereocentre at both alcohol moieties.

Table 5. Preparation of chiral compounds **8**, **11** and **12**

Entry	Starting material	Electrophile E	Product[a]		
			No.	$[\alpha]_D^{rt}$, *c* (solvent)	Yield (%)[b]
1	(*R*)-**7**	H_2O	(*R*)-**11**[c]	−22.0, 0.37 (CH_2Cl_2)	91
2	(*S*)-**7**	H_2O	(*S*)-**11**[c]	+21.2, 0.74 (CH_2Cl_2)	85
3	(*R*)-**7**	Et_2CO	(*R*)-**8b**	−82.9, 1.38 (CH_2Cl_2)	39
4	(*S*)-**7**	Et_2CO	(*S*)-**8b**	+83.7, 1.40 (CH_2Cl_2)	42
5	(*R*)-**7**	$(CH_2)_5CO$	(*R*)-**8d**	−2.1, 1.51 (CH_2Cl_2)	38
6	(*S*)-**7**	$(CH_2)_5CO$	(*S*)-**8d**	+2.2, 1.69 (CH_2Cl_2)	40
7	(*R*)-**10**	H_2O	(*S*)-**12a**[d]	−5.5, 1.00 ($CHCl_3$)	80
8	(*S*)-**10**	H_2O	(*R*)-**12a**[d]	+5.8, 1.00 ($CHCl_3$)	78
9	(*S*)-**10**	^{t}BuCHO	(*R*)-**12c**[d]	−43.1, 1.65 (CH_2Cl_2)	13[e]
				−113.0, 1.40 (CH_2Cl_2)	11[e]
10	(*R*)-**10**	Et_2CO	(*S*)-**12e**[d]	+81.5, 1.00 (CH_2Cl_2)	46
11	(*S*)-**10**	Et_2CO	(*R*)-**12e**[d]	−79.5, 0.76 (CH_2Cl_2)	28
12	(*R*)-**10**	$(CH_2)_5CO$	(*S*)-**12f**[d]	+70.0, 0.80 (CH_2Cl_2)	49
13	(*S*)-**10**	$(CH_2)_5CO$	(*R*)-**12f**[d]	−76.0, 0.91 (CH_2Cl_2)	46

[a] All products **8**, **11** and **12** were > 95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **7** or **10**.
[c] For structure of compound **11**, see Scheme 8.
[d] For the meaning of X see Table 4.
[e] Both diastereomers were isolated and purified by column chromatography (silica gel, hexane/ethyl acetate). We do not know the absolute configuration of the newly created stereocentres at both alcohol moieties.

3. Conclusion

In conclusion, we have described here the use of dihydrodibenzo- or dihydrodinaphthothiepine as starting materials for the reductive ring opening using an arene-promoted lithiation, so either functionalised organolithium compounds or dilithium intermediates are generated, which by reaction with electrophiles give polyfuncionalised biphenyls or binaphthyls. In the second case, the oxygenated analogue has also been studied in order to compare both systems. The lithiation can be directed in the case of the binaphtyl derivatives using either the stoichiometric or the catalytic version of the arene-promoted lithiation. For binaphthyl products, the chiral version of the reaction is also studied, so chiral functionalised biaryl compounds are prepared without observing any racemisation during the tandem process lithiation-S_E reaction. Finally, the reductive opening of the binaphthyl derivatives takes place under milder reaction conditions than in the case of the corresponding biphenyl derivative. We think that this is due to the lower energy of LUMO's of naphthyl derivatives, so electron transfer from the reducing reagent to the substrates takes place easier.[6g–k]

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in oven-dried glassware. All reagents were commercially available (Acros, Aldrich) and were used without further purification. Commercially available anhydrous THF (99.9%, water content $\leq$0.006%, Acros) was used as solvent in all the lithiation reactions. IR spectra were measured (film) with a Nicolet Impact 400 D-FT Spectrometer. NMR spectra were recorded with a Bruker AC-300 or a Bruker ADVANCE DRX-500 using $CDCl_3$ as the solvent. LRMS and HRMS were measured with Shimadzu GC/HS QP-5000 and Finingan MAT95 S spectrometers, respectively. The purity of volatile products and the chromatographic analyses (GLC) were determined with a flame ionisation detector and a 12 m capillary column (0.2 mm diam., 0.33 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$=275 °C, $T_{detector}$=300 °C, T_{column}=60 °C (3 min) and 60–270 °C (15 °C/min), P=40 kPa. HPLC analyses were performed on a Shimadzu LC-10 AD equipped with a chiral column (detailed in the main text), by using mixtures of *n*-hexane/2-propanol as mobile phase, at 25 °C. Specific rotations were determined with a PerkinElmer 341 digital polarimeter.

4.2. Preparation of 5,7-dihydrodibenzo[*c*,*e*]thiepine (1), 4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]thiepine (7) and 4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]oxepine (10)

Isolation of compound **1**. A mixture of 2,2′-bis(bromomethyl)biphenyl (3.4 g, 10 mmol) and sodium sulphide nonahydrate (3.6 g, 15 mmol) in DMF (mL) was stirred at 100 °C for 1 h. After that the reaction mixture was allowed to cool down to room temperature, hydrolysed with water (20 mL), extracted with ethyl acetate (3×40 mL) and the organic layer was dried over anhydrous sodium sulphate and evaporated (15 Torr). The resulting residue was then recrystallised (hexane) to yield pure compound **1** (2.0 g, 94% yield). Physical and spectroscopic data follow.

4.2.1. 5,7-Dihydrodibenzo[*c*,*e*]thiepine (1). Pale yellow solid; mp 95–96 °C (hexane) (lit. mp 89–90 °C);[22] R_f 0.63 (hexane/ethyl acetate: 10:1); ν (KBr) 3050, 3025 cm^{-1} (ArH); δ_H 3.27 (2H, d, J=12.2 Hz, 2×C*H*H), 3.46 (2H, d, J=12.2 Hz, 2×CH*H*), 7.26–7.39 (8H, m, ArH); δ_C 31.3 (CH_2), 127.7, 128.3, 128.4, 128.5, 135.6, 140.5 (ArC); *m*/*z* 212 (M^+, 100%), 211 (28), 197 (19), 184 (21), 179 (67), 178 (53), 166 (37), 165 (61), 152 (15), 89 (26), 76 (20), 63 (13), 51 (10).

Isolation of compounds **7**. *General procedure*. A mixture of 2,2′-bis(bromomethyl)-1,1′-binaphthyl (**16**) (2.20 g, 5.0 mmol) [easily prepared from 1-bromo-2-methyl-bynaphthalene (**13**)[17,18] for racemic **7** or from (*R*)- or (*S*)-binaphthol (**14**)[20] in the case of enantiomerically pure derivatives **7**] and sodium sulphide nonahydrate (3.55 g, 15.0 mmol) in DMF (20 mL) was stirred at 100 °C for 1 h. After that, the reaction mixture was allowed to cool down to room temperature, hydrolysed with water (200 mL), extracted with ethyl acetate (3×200 mL) and the organic layer was dried over anhydrous sodium sulphate and evaporated (15 Torr). The resulting residue was then recrystallised (acetone) to yield pure compounds **7** [1.28 g, 82% yield in the case of (±)-**7**]. Physical and spectroscopic data follow.

4.2.2. (±)-4,5-Dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]thiepine (7). Brown solid; mp 210–212 °C (hexane) (lit. mp 216–218 °C);[12] R_f 0.83 (hexane/ethyl acetate: 2:1); ν (KBr): 3049, 3008 cm^{-1} (ArH); δ_H 3.41 (4H, s, 2×CH_2), 7.23–7.30 (4H, m, ArH), 7.41–7.46 (2H, m, ArH), 7.93 (2H, dd, J=8.4, 3.6 Hz, ArH); δ_C 31.9 (CH_2), 125.1, 125.7, 126.1, 126.4, 127.8, 128.9, 131.2, 132.5, 133.2, 133.4 (ArC); *m*/*z* 312 (M^+, 100), 297 (15), 279 (79), 278 (27), 277 (37), 276 (43), 266 (49), 265 (50), 264 (24), 263 (39), 148 (21), 139 (26), 138 (82), 133 (32), 131 (85), 126 (17), 125 (25), 119 (20).

4.2.3. (*R*)-4,5-Dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]thiepine [(*R*)-7]. Physical and spectroscopic data were found to be the same than for **7**. $[\alpha]_D^{20}$ −259.2 (*c* 1.00, CH_2Cl_2) {lit. $[\alpha]_D^{25}$ −276 (*c* 1.02, $CHCl_3$)}.[12]

4.2.4. (*S*)-4,5-Dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]thiepine [(*S*)-7]. Physical and spectroscopic data were found to be the same than for **7**. $[\alpha]_D^{20}$ +258.4 (*c* 1.00, CH_2Cl_2) {lit. $[\alpha]_D^{23}$ +279 (*c* 0.20, $CHCl_3$)}.[12]

Isolation of compounds **10**. *Preparation from 2,2′-bis(bromomethyl)-1,1′-binaphthyl* **16**. *General procedure*. To a 5 M aqueous NaOH solution (50 mL) was added a solution of 2,2′-bis(bromomethyl)-1,1′-binaphthyl (**16**) (0.95 g, 2.24 mmol) in dioxane (5 mL). The resulting mixture was stirred at 80 °C for 15 h. After that the reaction mixture was allowed to cool down to room temperature, hydrolysed with 3 M HCl (90 mL), extracted with ethyl acetate (3×40 mL) and the organic layer was dried over anhydrous sodium sulphate and evaporated (15 Torr). The resulting residue was then purified by column chromatography

(silica gel, hexane/ethyl acetane, 20:1) to yield pure compounds **10** [0.695 g, 78% yield in the case of (±)-**10**].

Preparation from 2,2′-bis(hydroxymethyl)-1,1′-binaphthyl (**18**). *General procedure*. A mixture of 2,2′-bis(hydroxymethyl)-1,1′-binaphthyl (0.95 g, 3.0 mmol) [easily prepared from 2,2′-bis(bromomethyl)-1,1′-binaphthyl[21]] and *p*-toluenesulphonic acid (0.095 g, 0.5 mmol) in benzene (40 mL) was stirred at 80 °C for 48 h. After that the reaction mixture was allowed to cool down to room temperature and washed with a sodium carbonate saturated aqueous solution (30 mL). Then, the organic layer was dried over anhydrous sodium sulphate and evaporated (15 Torr). The resulting residue was then purified by column chromatography (silica gel, hexane/ethyl acetate: 20:1) to yield pure compounds **10** [0.49 g, 55% yield in the case of (±)-**10**]. Physical and spectroscopic data follow.

4.2.5. (±)-4,5-Dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]oxepine (10). White solid; mp 179–181 °C (hexane/dichloromethane) (lit. mp 188–188.5 °C);[21] R_f 0.69 (hexane/ethyl acetate: 2:1); ν (KBr) 3042 cm^{-1} (ArH); δ_H 4.18 (2H, d, J=11.3 Hz, 2×C*H*HO), 4.63 (2H, d, J=11.3 Hz, 2×CH*H*O), 7.24–7.31 (2H, m, ArH), 7.46–7.54 (4H, m, ArH), 7.61 (2H, d, J=8.3 Hz, ArH), 7.98 (4H, dd, J=9.4, 8.6 Hz, ArH); δ_C 67.4 (CH_2), 125.9, 126.0, 127.3, 127.6, 128.3, 129.1, 131.1, 133.5, 133.6, 135.4 (ArC); *m*/*z* 296 (M^+, 100), 293 (11), 282 (11), 281 (30), 279 (22), 278 (28), 277 (70), 268 (20), 267 (40), 266 (36), 253 (54), 252 (67), 239 (37), 133 (33), 132 (48), 131 (27), 126 (37), 120 (30), 115 (33).

4.2.6. (*R*)-4,5-Dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]oxepine [(*R*)-10]. Physical and spectroscopic data were found to be the same than for **10**. $[\alpha]_D^{20}$ −432.8 (*c* 1.00, CH_2Cl_2).

4.2.7. (*S*)-4,5-Dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]oxepine [(*S*)-10]. Physical and spectroscopic data were found to be the same than for **10**. $[\alpha]_D^{20}$ +428.3 (*c* 1.00, CH_2Cl_2) {lit. $[\alpha]_D^{28}$ +687 (*c* 1.4, benzene)}.[21]

4.3. Reductive lithiation of 5,7-dihydrodibenzo[*c*,*e*]-thiepine (1) and reaction with electrophiles. Preparation of compounds 2

Isolation of compounds **2**. *General procedure*. To a cooled (−78 °C) blue suspension of lithium powder (105 mg, 15.0 mmol) and a catalytic amount of DTBB (26 mg, 0.1 mmol) in THF (3 mL) was added dropwise a solution of compound **1** (212 mg, 1.0 mmol) in THF (1 mL) under argon and the mixture was stirred at the same temperature for 30 min. Then the corresponding electrophile was added dropwise (1.1 mmol) and after 5 min it was hydrolysed carefully with 3 N HCl (5 mL). The resulting mixture was allowed to reach room temperature, extracted with ethyl acetate (3×15 mL) and the organic layer was dried over anhydrous sodium sulphate and evaporated (15 Torr). The residue was then purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure compounds **2**. Yields are given in Table 1, physical, analytical and spectroscopic data follow.

4.3.1. 2-(2-Hydroxy-3,3-dimethylbutyl)-2′-sulphanylmethylbiphenyl (2a). Diastereomeric mixture: colourless oil; R_f 0.58 (hexane/ethyl acetate: 4:1); ν (KBr) 3310–3680 (OH), 3059, 3019 (ArH), 2575 cm^{-1} (SH); δ_H 0.67 [9H, s, $(CH_3)_3C$], 0.69 [9H, s, $(CH_3)_3C$], 1.40–1.72 [4H, m, 2×(OH, SH)], 2.25–2.32 (2H, m, ArCH_2CHOH), 2.66 (1H, d, J=13.6 Hz, ArC*H*HCHOH), 2.87 (1H, d, J=13.6 Hz, ArCH*H*CHOH), 3.12–3.17 (2H, m, 2×C*H*OH), 3.42–3.63 (4H, m, 2×CH_2SH), 7.10–7.45 (16H, m, 2×ArH); δ_C 25.3 [$(CH_3)_3C$], 25.35 [$(CH_3)_3C$], 26.3 (CH_2SH), 34.6 [$(CH_3)_3C$], 34.65 [$(CH_3)_3C$], 35.5 (ArCH_2CHOH), 35.7 (ArCH_2CHOH), 79.1 (CHOH), 79.4 (CHOH), 126.0, 126.2, 126.6, 126.7, 127.6, 127.7, 128.0, 128.9, 129.2, 130.1, 130.15, 130.2, 130.35, 130.4, 130.5, 137.8, 138.6, 138.8, 139.9, 140.2 (ArC); *m*/*z* 282 (M^+-H_2O, 2%), 215 (10), 214 (68), 191 (20), 181 (90), 180 (100), 179 (79), 178 (38), 166 (29), 165 (55), 87 (17), 69 (18), 57 (48); HRMS: M^+-H_2O, found 282.1440. $C_{19}H_{22}S$ requires 282.1442.

4.3.2. 2-(2-Hydroxy-4-phenylbutyl)-2′-sulphanylmethylbiphenyl (2b). Diastereomeric mixture: colourless oil; R_f 0.39 (hexane/ethyl acetate: 4:1); ν (KBr) 3290–3650 (OH), 3060, 3025 (ArH), 2610 cm^{-1} (SH); δ_H 1.44–1.63 [8H, m, 2×(OH, SH), 2×CHCH_2CH_2], 2.43–2.80 (8H, m, 2×ArCH_2, 2×PhCH_2), 3.39–3.65 (6H, m, 2×C*H*OH, 2×CH_2SH), 7.03–7.47 (26H, m, 2×Ph, 2×ArH); δ_C 26.3, 31.7, 38.2, 38.4, 41.4, 41.5 (CH_2), 70.6, 71.1 (CHOH), 125.6, 126.2, 126.3, 126.7, 126.8, 127.7, 127.8, 128.0, 128.2, 128.3, 128.35, 129.0, 129.15, 130.0, 130.1, 130.2, 130.3, 136.4, 136.5, 138.7, 139.8, 140.35, 140.4, 141.7 (ArC); *m*/*z* 330 (M^+-H_2O, 6%), 214 (40), 182 (25), 181 (33), 180 (68), 179 (37), 178 (34), 166 (18), 165 (44), 105 (27), 91 (100), 77 (15), 44 (22); HRMS: M^+-H_2O, found 330.1139. $C_{23}H_{22}S$ requires 330.1442.

4.3.3. 2-(2-Hydroxy-2-phenylethyl)-2′-sulphanylmethylbiphenyl (2c). Diastereomeric mixture: colourless oil; R_f 0.43 (hexane/ethyl acetate: 4:1); ν (KBr) 3300–3645 (OH), 3055, 3022 (ArH), 2590 cm^{-1} (SH); δ_H 1.52–2.07 [4H, m, 2×(OH, SH)], 2.69–2.74 (3H, m, ArCH_2CH, ArC*H*HCH), 2.97 (1H, dd, J=13.9, 4.6 Hz, ArCH*H*CH), 3.36–3.57 (4H, m, 2×CH_2SH), 4.63–4.75 (2H, m, C*H*OH), 6.90–7.45 (26H, m, 2×Ph, 2×ArH); δ_C 26.3, 26.4, 43.4, 43.6 (CH_2), 73.9, 74.4 (CHOH), 125.3, 125.5, 126.3, 126.5, 126.7, 127.2, 127.3, 127.7, 127.75, 128.0, 128.05, 128.2, 128.9, 129.2, 130.1, 130.2, 130.3, 130.6, 136.0, 136.1, 138.7, 138.9, 139.8, 140.3, 140.45, 143.9, 144.0 (ArC); *m*/*z* 302 (M^+-H_2O, 11%), 214 (86), 198 (22), 182 (11), 181 (75), 180 (100), 179 (86), 178 (53), 167 (18), 166 (26), 165 (80), 152 (17), 107 (80), 105 (70), 91 (47), 79 (84), 77 (93), 51 (32); HRMS: M^+-H_2O, found 302.1123. $C_{21}H_{18}S$ requires 302.1129.

4.3.4. 2-(2-Hydroxy-2-methylpropyl)-2′-sulphanylmethylbiphenyl (2d). Colourless oil; R_f 0.33 (hexane/ethyl acetate: 4:1); ν (KBr) 3280–3675 (OH), 3058, 3020 (ArH), 2545 cm^{-1} (SH); δ_H 0.98 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.35–1.61 (2H, m, OH, SH), 2.54 (1H, d, J=13.4 Hz, C*H*HCOH), 2.75 (1H, d, J=13.4 Hz, CH*H*COH), 3.42–3.55 (2H, m, CH_2SH), 7.13–7.47 (8H, m, ArH); δ_C 26.4, 29.2 (CH_3), 29.8, 45.5 (CH_2), 71.5 (COH), 126.3, 126.6, 127.3, 127.8, 128.9, 130.4, 130.7, 131.0, 135.8, 138.9, 140.4, 140.8 (ArC); *m*/*z* 254 (M^+-H_2O, 1%), 215 (11), 214 (64), 181 (65), 180 (83), 179 (67), 178 (35), 167 (11), 166 (28), 165

(65), 152 (12), 59 (100); HRMS: M^+-H_2O, found 254.1126. $C_{17}H_{18}S$ requires 254.1129.

4.3.5. 2-(2-Hydroxy-2-pentylheptyl)-2′-sulphanylmethylbiphenyl (2e). Colourless oil; R_f 0.65 (hexane/ethyl acetate: 4:1); ν (KBr) 3290–3650 (OH), 3058, 3020 (ArH), 2570 cm^{-1} (SH); δ_H 0.81–0.86 (6H, m, 2×CH_3), 1.08–1.29 (17H, m, OH, 8×CH_2), 1.61 (1H, t, J=7.7 Hz, SH), 2.53 (1H, d, J=13.7 Hz, C*H*HCOH), 2.73 (1H, d, J=13.7 Hz, CH*H*COH), 3.40–3.53 (2H, m, CH_2SH), 7.14–7.47 (8H, m, ArH); δ_C 13.9 (CH_3), 22.5, 22.55, 22.9, 23.1, 26.4, 32.2, 32.3, 38.8, 39.3, 41.7 (CH_2), 74.9 (COH), 126.2, 126.7, 127.3, 127.8, 128.9, 130.3, 130.7, 131.2, 135.6, 138.9, 140.5, 141.1 (ArC); *m/z* 366 (M^+-H_2O, 2%), 215 (11), 214 (70), 191 (11), 181 (46), 180 (82), 179 (52), 178 (28), 167 (10), 166 (12), 165 (27), 97 (15), 83 (33), 71 (18), 69 (29), 57 (23), 55 (68), 43 (100); HRMS: M^+-H_2O, found 366.2377. $C_{25}H_{34}S$ requires 366.2381.

4.3.6. 2-(1-Hydroxycyclohexylmethyl)-2′-sulphanylmethylbiphenyl (2f). Colourless oil; R_f 0.48 (hexane/ethyl acetate: 4:1); ν (KBr) 3275–3630 (OH), 3055, 3017 (ArH), 2610 cm^{-1} (SH); δ_H 1.05–1.49 (11H, m, OH, 5×CH_2), 1.60 (1H, t, J=7.7 Hz, SH), 2.53 (1H, d, J=13.7 Hz, C*H*HCOH), 2.73 (1H, d, J=13.7 Hz, CH*H*COH), 3.36–3.50 (2H, m, CH_2SH), 7.14–7.48 (8H, m, ArH); δ_C 21.8, 21.9, 26.5, 26.4, 37.4, 37.8, 45.1 (CH_2), 72.0 (COH), 126.3, 126.7, 127.1, 127.2, 127.9, 130.4, 130.8, 131.4, 135.3, 138.9, 140.6, 141.05 (ArC); *m/z* 294 (M^+-H_2O, 3%), 260 (10), 215 (13), 214 (59), 182 (14), 181 (69), 180 (100), 179 (74), 178 (48), 167 (16), 166 (20), 165 (57), 99 (87), 83 (33), 81 (79), 79 (15), 57 (12), 55 (43), 43 (38); HRMS: M^+-H_2O, found 294.1441. $C_{20}H_{22}S$ requires 294.1442.

4.3.7. 2-(1-Hydroxycyclooctylmethyl)-2′-sulphanylmethylbiphenyl (2g). Colourless oil; R_f 0.49 (hexane/ethyl acetate: 4:1); ν (KBr) 3290–3660 (OH), 3059, 3019 (ArH), 2550 cm^{-1} (SH); δ_H 1.22–1.55 (15H, m, OH, 7×CH_2), 1.62 (1H, t, J=7.8 Hz, SH), 2.56 (1H, d, J=13.6 Hz, C*H*HCOH), 2.72 (1H, d, J=13.6 Hz, CH*H*COH), 3.42–3.55 (2H, m, CH_2SH), 7.14–7.86 (8H, m, ArH); δ_C 21.9, 22.2, 24.8, 26.4, 27.7, 28.2, 36.0, 36.2, 43.5 (CH_2), 75.6 (COH), 126.1, 126.6, 127.2, 127.8, 128.9, 130.3, 130.8, 131.4, 135.6, 139.0, 140.5, 141.1 (ArC); *m/z* 322 (M^+-H_2O, 5%), 215 (14), 214 (50), 197 (11), 192 (10), 191 (12), 182 (13), 181 (57), 180 (100), 179 (95), 178 (67), 166 (25), 165 (64), 127 (52), 109 (32), 83 (11), 81 (18), 69 (27), 67 (70), 57 (19), 55 (82), 43 (42); HRMS: M^+-H_2O, found 322.1754. $C_{22}H_{26}$s requires 322.1755.

4.3.8. (1*R*,2*S*,5*R*)-2-[(1-Hydroxy-2-isopropyl-5-methylcyclohexyl)methyl]-2′-sulphanylmethylbiphenyl (2h). Diastereomeric mixture: colourless oil; R_f 0.71 (hexane/ethyl acetate: 4:1); ν (KBr) 3310–3620 (OH), 3058, 3018 (ArH), 2565 cm^{-1} (SH); δ_H 0.54–0.92 (10H, m, CH, 3×CH_3), 1.23–1.67 (8H, m, OH, SH, 3×CH_2), 1.94–2.00 (1H, m, CH), 2.02–2.11 (1H, m, CH), 2.25 (1H, d, J=13.4 Hz, C*H*HCOH), 2.51 (1H, d, J=13.6 Hz, CH*H*COH), 3.00 (1H, d, J=13.4 Hz, C*H*HCOH), 3.21 (1H, d, J=13.6 Hz, CH*H*COH), 3.40–3.52 (2H, m, CH_2SH), 7.11–7.47 (8H, m, ArH); δ_C 17.7, 17.8 (CH_3), 20.65, 20.7 (CH_2), 22.3, 22.4 (CH_3), 23.5, 23.6 (CH_3), 25.8 (CH_2), 26.4, 26.5, 27.5 (CH), 34.8, 34.9, 42.4, 46.9, 47.0 (CH_2), 49.5, 50.1 (CH), 75.5 (COH), 126.0, 126.2, 126.5, 126.8, 127.15, 127.2, 127.8, 127.9, 128.0, 128.9, 129.0, 130.3, 130.4, 130.8, 130.9, 131.3, 131.6, 135.6, 136.1, 139.2, 140.6, 141.2, 141.25 (ArC); *m/z* 350 (M^+-H_2O, 1%), 215 (16), 214 (99), 181 (52), 180 (90), 179 (47), 178 (24), 166 (15), 165 (33), 155 (50), 137 (35), 95 (40), 81 (100), 69 (40), 67 (14), 57 (14), 55 (48), 43 (59); HRMS: M^+-H_2O, found 350.2063. $C_{24}H_{30}S$ requires 350.2066.

4.4. Sequential double lithiation of 5,7-dihydrodibenzo-[*c*,*e*]thiepine (1) and reaction with electrophiles

Isolation of compounds **4**. *General procedure*. To a cooled (−78 °C) blue suspension of lithium powder (105 mg, 15.0 mmol) and a catalytic amount of DTBB (26 mg, 0.1 mmol) in THF (3 mL) was added dropwise a solution of compound **1** (212 mg, 1.0 mmol) in THF (1 mL) under argon and the mixture was stirred at the same temperature for 30 min. Then the corresponding electrophile was added dropwise (1.1 mmol) and after 5 min at −78 °C the cold bath was removed and the reaction mixture was allowed to react at 20 °C for 30 min. Then the reaction mixture was cooled down to −78 °C and a second electrophile (1.1 mmol) was added dropwise. After 5 min at this temperature, the reaction mixture was hydrolysed with water (4 mL), extracted with ethyl acetate (3×10 mL) once at 20 °C, dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure products **4**. Yields are given in Table 2, physical, analytical and spectroscopic data follow.

4.4.1. 2,2′-Bis-(2-hydroxy-2-methylpropyl)biphenyl (4a). Colourless oil; R_f 0.13 (hexane/ethyl acetate: 4:1); ν (KBr) 3220–3640 (OH), 3059, 3020 cm^{-1} (ArH); δ_H 0.96 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.42 (2H, d, J=13.4 Hz, 2×C*H*HCOH), 2.49 (2H, br s, 2×OH), 2.89 (2H, d, J=13.4 Hz, 2×CH*H*COH), 7.06–7.38 (8H, m, ArH); δ_C 31.1, 32.4 (CH_3), 46.1, 46.4 (CH_2), 71.8 (COH), 126.4, 126.9, 131.0, 131.5, 135.4, 141.5 (ArC); *m/z* 262 (M^+-2H_2O, 7%), 207 (57), 182 (17), 179 (49), 174 (54), 172 (25), 165 (15), 114 (27), 98 (27), 81 (19), 64 (18), 58 (42), 43 (47), 40 (100); HRMS: M^+-2H_2O, found 262.1714. $C_{20}H_{22}$ requires 262.1722.

4.4.2. 2-Ethoxycarbonylmethyl-2′-(2-hydroxy-2-methylpropyl)biphenyl (4b). Colourless oil; R_f 0.17 (hexane/ethyl acetate: 4:1); ν (KBr) 3300–3690 (OH), 3059, 3020 (ArH), 1743 cm^{-1} (C=O); δ_H 0.91 (3H, s, CH_3), 0.96 (3H, s, CH_3), 1.08 (3H, t, J=6.7 Hz, CH_3CH$_2$), 2.30 (1H, br s, OH), 2.45 (1H, d, J=13.4 Hz, C*H*HCOH), 2.67 (2H, d, J=13.4 Hz, CH*H*COH), 3.30 (2H, s, CH_2CO_2), 3.95 (2H, q, J=6.7 Hz, CH_2O), 7.04–7.38 (8H, m, ArH); δ_C 14.0, 29.3, 29.8 (CH_3), 38.7, 45.2 (CH_2), 60.6 (CH_2O), 71.45 (COH), 126.2, 126.7, 127.2, 127.4, 129.9, 130.6, 130.7, 130.9, 132.5, 135.8, 141.1, 141.6 (ArC), 171.6 (C=O); *m/z* 294 (M^+-H_2O, 6%), 254 (37), 208 (40), 181 (31), 180 (65), 179 (70), 178 (38), 166 (29), 165 (56), 59 (100), 43 (44); HRMS: M^+-H_2O, found 294.1586. $C_{12}H_{12}O$ requires 294.1620.

4.4.3. 2-(1-Hydroxycyclohexylmethyl)-2′-(2-hydroxy-2-methylpropyl)biphenyl (4c). Colourless oil; R_f 0.11

(hexane/ethyl acetate: 4:1); ν (KBr) 3250–3680 (OH), 3055, 3018 cm^{-1} (ArH); δ_H 0.80 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.98–1.46 (12H, m, 2×OH, 5×CH_2), 2.46–2.62 (4H, m, 2×CH_2), 7.10–7.34 (8H, m, ArH); δ_C 21.7, 21.9 (CH_3), 25.5, 29.2, 29.8, 37.2, 37.9, 45.0, 45.5 (CH_2), 71.5, 72.0 (COH), 126.2, 126.4, 126.9, 127.0, 127.6, 130.6, 131.0, 131.3, 135.1, 135.7, 142.3, 142.35 (ArC); *m/z* 302 (M^+-2H_2O, 7%), 262 (21), 222 (46), 208 (13), 207 (76), 193 (12), 191 (19), 182 (77), 181 (31), 180 (27), 179 (99), 178 (41), 167 (27), 166 (23), 165 (41), 157 (21), 99 (100), 81 (70), 59 (76), 55 (36), 43 (50); HRMS: M^+-2H_2O, found 302.2039. $C_{23}H_{26}$ requires 302.2035.

4.4.4. 2-(1-Hydroxycyclohexylmethyl)-2′-(2-hydroxy-2-ethylbutyl)biphenyl (4d). Colourless oil; R_f 0.23 (hexane/ethyl acetate: 4:1); ν (KBr) 3360–3540, 3550–3640 (OH), 3056, 3019 cm^{-1} (ArH); δ_H 0.40 (3H, t, J=7.3 Hz, CH_3), 0.65 (3H, t, J=8.0 Hz, CH_3), 0.89–1.63 (16H, m, 2×OH, 7×CH_2), 2.47–2.59 (4H, m, 2×CH_2), 7.12–7.34 (8H, m, ArH); δ_C 7.4, 7.8 (CH_3), 21.7, 21.9, 25.5, 30.3, 31.0, 37.2, 37.9, 40.7 (CH_2), 72.0, 75.25 (COH), 126.3, 126.5, 126.9, 130.9, 131.0, 131.15, 131.2, 131.25, 135.2, 135.4, 142.4, 142.6 (ArC); *m/z* 330 (M^+-2H_2O, 21%), 262 (29), 259 (19), 250 (18), 247 (15), 221 (22), 219 (15), 205 (19), 203 (14), 193 (16), 192 (20), 191 (82), 182 (40), 181 (37), 180 (27), 179 (99), 178 (48), 166 (19), 165 (48), 99 (58), 87 (66), 81 (65), 69 (19), 67 (16), 57 (37), 55 (63), 45 (68), 43 (56), 41 (100); HRMS: M^+-2H_2O, found 330.2332. $C_{25}H_{30}$ requires 330.2348.

4.4.5. 2,2′-Bis-(1-Hydroxycyclohexylmethyl)biphenyl (4e). Colourless oil; R_f 0.26 (hexane/ethyl acetate: 4:1); ν (KBr) 3350–3630 (OH), 3058, 3021 cm^{-1} (ArH); δ_H 0.92–1.47 (20H, m, 10×CH_2), 2.46 (2H, br s, 2×OH), 2.57 (2H, d, J=14.2 Hz, 2×ArC*H*H), 2.63 (2H, d, J=14.2 Hz, 2×ArCH*H*), 7.15–7.41 (8H, m, ArH); δ_C 21.7, 21.9, 25.5, 37.8, 38.7, 45.0 (CH_2), 71.9 (COH), 126.3, 126.8, 131.0, 131.2, 135.1, 142.5 (ArC); *m/z* 342 (M^+-2H_2O, 22%), 259 (30), 217 (16), 203 (15), 192 (22), 191 (100), 179 (43), 178 (33), 166 (16), 165 (51), 95 (15), 81 (32), 79 (28), 67 (24), 55 (30), 41 (53); HRMS: M^+-2H_2O, found 342.2341. $C_{26}H_{30}$ requires 342.2348.

4.4.6. 2-Ethoxycarbonylmethyl-2′-(1-hydroxycyclohexylmethyl)biphenyl (4f). Colourless oil; R_f 0.33 (hexane/ethyl acetate: 4:1); ν (KBr) 3360–3590 (OH), 3059, 3020 (ArH), 1740 cm^{-1} (C=O); δ_H 1.04–1.37 (11H, m, OH, 5×CH_2), 1.08 (3H, t, J=6.7 Hz, CH_3), 2.43 (1H, d, J=13.5 Hz, C*H*HCOH), 2.63 (1H, d, J=13.5 Hz, CH*H*COH), 3.30 (2H, s, CH_2CO_2), 3.95 (2H, q, J=6.7 Hz, CH_2CH_3), 7.03–7.37 (8H, m, ArH); δ_C 14.0 (CH_3), 21.75, 21.8, 25.5, 37.3, 37.7, 38.7, 44.8 (CH_2), 60.5 (CH_2O), 71.8 (COH), 126.0, 126.6, 127.0, 127.4, 129.8, 130.5, 130.7, 131.2, 135.3, 141.2, 141.7 (ArC), 171.6 (C=O); *m/z* 334 (M^+-H_2O, 8%), 254 (22), 208 (30), 181 (17), 180 (45), 179 (100), 178 (40), 166 (16), 165 (32), 99 (17), 81 (31), 79 (11), 55 (27), 41 (32); HRMS: M^+-H_2O, found 334.1928. $C_{23}H_{26}O_2$ requires 334.1933.

4.4.7. (1*R*,2*S*,5*R*)-2-[(1-Hydroxy-2-isopropyl-5-methylcyclohexyl)methyl]-2′-(2-hydroxy-2-methylpropyl)-biphenyl (4g). Diastereomeric mixture: colourless oil; R_f 0.42 (hexane/ethyl acetate: 4:1); ν (KBr) 3340–3660 (OH), 3056, 3019 cm^{-1} (ArH); δ_H 0.40 (3H, d, J=6.7 Hz, CH_3CH), 0.58–0.83 (6H, m, 2×CH_3CH), 0.78 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.15–1.66 (8H, m, 2×OH, 3×CH_2), 1.64–1.81 (1H, m, CH), 2.03–2.15 (1H, m, CH), 2.15 (1H, d, J=13.4 Hz, C*H*HCOH), 2.37 (1H, d, J=13.5 Hz, C*H*HCOH), 2.50 (1H, d, J=13.5 Hz, C*H*HCH$_3$), 2.61 (1H, d, J=13.5 Hz, CH*H*CH$_3$), 2.93 (1H, d, J=13.5 Hz, CH*H*COH), 3.05 (1H, d, J=13.4 Hz, CH*H*COH), 7.08–7.39 (8H, m, ArH); δ_C 17.6, 17.9 (CH_3), 20.7, 20.75 (CH_2), 22.2, 22.4 (CH_3), 23.5, 23.7 (CH_3), 25.8, 25.9 (CH_2), 27.5, 27.55, 29.2 (CH), 29.6, 29.8, 34.8, 35.0, 42.2, 42.4, 45.5, 45.6, 46.9, 47.0 (CH_2), 49.2, 50.4 (CH), 71.6, 75.2, 75.7 (COH), 126.1, 126.2, 126.3, 126.7, 126.8, 126.9, 127.2, 130.5, 130.7, 130.75, 131.2, 131.25, 131.3, 131.5, 131.7, 135.2, 135.65, 135.8, 136.0, 142.4, 142.6 (ArC); *m/z* 358 (M^+-2H_2O, 2%), 222 (46), 207 (51), 182 (34), 180 (15), 179 (68), 178 (23), 166 (12), 165 (21), 155 (50), 137 (34), 95 (35), 81 (78), 69 (40), 67 (16), 59 (68), 57 (16), 55 (63), 43 (100); HRMS: M^+-2H_2O, found 358.2651. $C_{27}H_{34}$ requires 358.2661.

4.5. Attempt of cyclisation of sulphanyl alcohol 2c, diol 4e and hydroxy ester 4f under acidic conditions

Isolation of compounds **3** *and* **5**. *General procedure*. To a solution of sulphanyl alcohol **2c** or diol **4e** (0.2 mmol) in toluene (3 mL) was added 85% phosphoric acid (0.4 mL). The reaction mixture was heated at 110 °C for 4 h, then the toluene was removed by distillation and the resulting residue was hydrolysed with water (4 mL), extracted with ethyl acetate (3×10 mL), dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure products. Yields are given in the text, physical, analytical and spectroscopic data for these compounds follow.

4.5.1. 7-Phenyl-7,8-dihydro-5*H*-dibenzo[*c*,*e*]thiocine (3). Pale yellow solid; mp 143–144 °C (hexane); R_f 0.62 (hexane/ethyl acetate: 10:1); ν (KBr) 3056, 3028 cm^{-1} (ArH); δ_H 2.94–3.03 (1H, m, C*H*HCH), 3.21 (1H, d, J=13.4 Hz, CH*H*CH), 3.43 (1H, d, J=14.6 Hz, C*H*HS), 3.52 (1H, d, J=14.6 Hz, CH*H*S), 4.15 (1H, d, J=9.1 Hz, CHS), 7.12–7.34 (13H, m, ArH); δ_C 33.9 (CH_2), 42.9 (CH_2S), 51.2 (CHS), 126.4, 126.6, 127.4, 127.6, 128.4, 128.6, 128.9, 129.1, 129.6, 129.8, 139.4, 139.7, 140.1, 140.3, 142.6, 142.65, 143.1 (ArC); *m/z* 302 (M^+, 57%), 198 (32), 197 (18), 180 (78), 179 (100), 178 (61), 165 (61), 91 (41); HRMS: M^+, found 302.1121. $C_{21}H_{18}S$ requires 302.1129.

4.5.2. 2,2′-Bis-(1-cyclohexenylmethyl)biphenyl (5). Pale yellow oil; R_f 0.45 (hexane); ν (film) 3055, 3030 cm^{-1} (ArH); δ_H 1.41–1.46 (4H, m, 2×CH_2), 1.58–1.62 (2H, m, CH_2), 1.83–1.87 (2H, m, CH_2), 2.85 (2H, d, J=14.6 Hz, 2×ArC*H*H), 2.94 (2H, d, J=14.6 Hz, 2×ArCH*H*), 5.07 (2H, br s, CH=C), 6.99–7.20 (8H, m, ArH); δ_C 22.4, 22.9, 25.3, 28.2 (CH_2), 41.6 (CHS), 123.2, 125.2, 126.9, 129.1, 129.9, 136.6, 138.1, 141.3 (CH=C, ArC); *m/z* 342 (M^+, 26%), 259 (33), 217 (13), 203 (14), 192 (18), 191 (100), 179 (59), 178 (34), 166 (16), 165 (51), 95 (12), 81 (44), 79 (22), 67 (29), 55 (37), 53 (19); HRMS: M^+, found 342.2339. $C_{26}H_{30}$ requires 342.2348.

Preparation of compound **6**. A solution of hydroxy ester **4f** (70 mg, 0.2 mmol) in toluene (10 mL) in the presence of a catalytic amount of *p*-toluenesulphonic acid (1 mg) was heated at 110 °C in a Dean-Stark apparatus for 4 h, then the toluene was removed by distillation and the resulting residue was hydrolysed with a saturated solution of $CaCO_3$ (5 mL), extracted with ethyl acetate (3×10 mL), dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane) to yield pure product **6**. Yield is given in the text, physical, analytical and spectroscopic data for this compound follow.

4.5.3. Ethyl 2-[2-(1-cyclohexenylmethyl)phenyl]phenylacetate (6). Colourless oil; R_f 0.50 (hexane/ethyl acetate: 10:1); ν (film) 3050, 3027 (ArH), 1730 cm^{-1} (C=O); δ_H 1.16 (3H, t, J=7.0 Hz, CH_3), 1.47–1.51 (4H, m, 2×CH_2), 1.61–1.66 (2H, m, CH_2), 1.85–1.91 (2H, m, CH_2), 2.90 (1H, d, J=15.0 Hz, C*H*HC=CH), 3.03 (1H, d, J=15.0 Hz, CH*H*C=CH), 3.30 (1H, d, J=15.8 Hz, C*H*HCO), 3.38 (1H, d, J=15.8 Hz, CH*H*CO), 4.04 (2H, q, J=7.0 Hz, CH_2CH_3), 5.06 (1H, br s, CH=C), 7.10–7.35 (8H, m, ArH); δ_C 14.1 (CH_3), 22.3, 22.8, 25.3, 28.1, 38.8, 41.5 (CH_2), 60.5 (CH_2O), 121.2, 123.2, 126.5, 127.3, 127.35, 129.5, 129.6, 129.9, 130.0, 132.5, 136.4, 138.0, 140.5, 141.3, 142.9 (CH=C, ArC), 171.7 (C=O); *m/z* 334 (M^+, 11%), 180 (15), 179 (100), 178 (32), 165 (22), 153 (44), 152 (13); HRMS: M^+, found 334.1926. $C_{23}H_{26}O_2$ requires 334.1933.

4.6. Double reductive lithiation of 4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]thiepine (7) and 4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]oxepine (10) and reaction with electrophiles. Preparation of compounds 8 and 11

Isolation of compounds **8** *and* **11**. *General procedure*. To a cooled (−78 °C) blue suspension of lithium powder (105 mg, 15.0 mmol) and a catalytic amount of DTBB (26 mg, 0.1 mmol) in THF (3 mL) was added dropwise a solution of compound **7** or **10** (0.5 mmol) in THF (1 mL) under argon and the mixture was stirred at the same temperature for 1 h. Then the corresponding electrophile was added dropwise (0.6 mmol, 0.25 mL in the case of H_2O) and after 15 min it was hydrolysed with water (5 mL). The resulting mixture was extracted with ethyl acetate (3× 15 mL) and the organic layer was dried over anhydrous sodium sulphate and evaporated (15 Torr). The residue was then purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure compounds **8** and **11**. Yields are given in Tables 3 and 5, specific rotations are given in Table 5, other physical, analytical and spectroscopic data follow.

4.6.1. 2,2′-Bis-(2-hydroxy-2-methylpropyl)-1,1′-binaphthyl (8a). White solid; mp 78–79 °C (dichloromethane/hexane) (lit. mp 80–81 °C);[23] R_f 0.11 (hexane/ethyl acetate: 2:1); ν (KBr): 3510–3390 (OH), 3053 cm^{-1} (ArH); δ_H 0.82 (6H, s, 2×CH_3), 0.99 (6H, s, 2×CH_3), 1.79 (2H, br s, 2×OH), 2.56 (2H, d, J=14.0 Hz, 2×C*H*H), 2.78 (2H, d, J=14.0 Hz, 2×CH*H*), 7.10–7.21 (4H, m, ArH), 7.37–7.42 (2H, m, ArH), 7.81–7.93 (6H, m, ArH); δ_C 29.8, 30.7 (CH_3), 46.1 (CH_2), 71.8 (COH), 125.3, 125.8, 127.5, 127.6, 127.9, 129.1, 132.2, 133.3, 135.4, 135.8 (ArC); *m/z* 362 (M^+-2H_2O, 22), 323 (15), 322 (26), 320 (15), 319 (21), 294 (15), 293 (16), 292 (19), 289 (16), 283 (15), 282 (65), 279 (47), 278 (26), 277 (23), 276 (42), 267 (20), 265 (39), 263 (36), 252 (20), 221 (15), 207 (176), 138 (19), 59 (100).

4.6.2. 2,2′-Bis-(2-hydroxy-2-ethylbutyl)-1,1′-binaphthyl (8b). White solid; mp 121–122 °C (dichloromethane/hexane) (found: C, 84.22; H, 8.43. $C_{32}H_{38}O_2$ requires: C, 84.54; H, 8.42); R_f 0.58 (hexane/ethyl acetate: 2:1); ν (KBr) 3677–3162 (OH), 3062 cm^{-1} (ArH); δ_H 0.13 (6H, t, J=7.5 Hz, 2×CH_3), 0.63 (6H, t, J=7.5 Hz, 2×CH_3), 0.82–1.09 (4H, m, 2×CH_2CH$_3$), 1.24–1.45 (4H, m, 2×CH_2CH$_3$), 2.56 (2H, d, J=14.0 Hz, 2×C*H*HAr), 2.72 (2H, d, J=14.0 Hz, 2×CH*H*Ar), 7.14–7.26 (2H, m, ArH), 7.37–7.42 (2H, m, ArH), 7.79–7.91 (8H, m, ArH); δ_C 7.3, 7.7 (CH_3), 30.7, 31.7 (*C*H_2CH$_3$), 41.2 (*C*H_2COH), 75.6 (COH), 125.3, 125.7, 127.4, 127.5, 127.9, 129.5, 132.3, 133.4, 135.3, 136.2 (ArC); *m/z* 436 [(M^+-H_2O), 0.1], 351 (10), 350 (34), 283 (37), 282 (100), 281 (17), 280 (12), 279 (41), 278 (10), 277 (13), 276 (10), 267 (18), 266 (30), 265 (37), 87 (23); HRMS, M^+-H_2O, found 436.2739. $C_{32}H_{36}O$ requires 436.2766.

4.6.3. 2,2′-Bis-(1-hydroxycyclopentylmethyl)-1,1′-binaphthyl (8c). Pale yellow oil; R_f 0.39 (hexane/ethyl acetate: 2:1); ν (film) 3660–3180 (OH), 3060 cm^{-1} (ArH); δ_H 1.28–1.65 (18H, m, 8×CH_2, 2×OH), 2.66 (2H, d, J=14.5 Hz, 2×C*H*HAr), 2.89 (2H, d, J=14.5 Hz, 2×CH*H*Ar), 7.06 (2H, d, J=8.4 Hz, ArH), 7.16–7.42 (2H, m, ArH), 7.85–7.94 (8H, m, ArH); δ_C 23.0, 23.4, 40.2, 41.2, 43.8 (CH_2), 82.7 (COH), 125.3, 126.0, 126.9, 127.5 127.9, 128.3 132.2, 133.3, 135.8, 135.9 (ArC); *m/z* 450 (M^+, 0.3), 432 (4), 416 (15), 414 (21), 350 (26), 349 (18), 348 (52), 347 (13), 345 (13), 289 (11), 283 (26), 282 (100), 281 (56), 280 (27), 279 (65), 278 (23), 277 (34), 276 (26), 267 (28), 266 (41), 265 (56), 264 (14), 263 (18), 253 (12), 252 (23), 85 (21), 67 (20); HRMS, M^+, found 450.2595. $C_{32}H_{34}O_2$ requires 450.2559.

4.6.4. 2,2′-Bis-(1-hydroxycyclohexylmethyl)-1,1′-binaphthyl (8d). White solid; mp 142–143 °C (dichloromethane/hexane) (found: C, 84.98; H, 8.06. $C_{34}H_{38}O_2$ requires: C, 85.31; H, 8.00); R_f 0.47 (hexane/ethyl acetate: 2:1); ν (KBr) 3655–3145 (OH), 3058 cm^{-1} (ArH); δ_H 0.78–1.68 (20H, m, 10×CH_2), 2.57 (2H, d, J=14.0 Hz, 2×C*H*HAr), 2.74 (2H, d, J=14.0 Hz, 2×CH*H*Ar), 7.10–7.19 (2H, m, ArH), 7.36–7.41 (2H, m, ArH), 7.81–7.91 (8H, m, ArH); δ_C 21.7, 22.0, 37.6, 37.7, 38.7 (CH_2), 72.4 (COH), 125.2, 125.7, 127.3, 127.6, 127.9, 129.6, 132.3, 133.4, 135.0, 136.1 (ArC); *m/z* 460 [($M-H_2O$)$^+$, 0.6], 362 (23), 283 (24), 282 (100), 281 (25), 279 (20), 267 (11), 266 (19), 265 (21), 99 (12), 81 (14); HRMS, M^+-H_2O, found 460.2771. $C_{32}H_{36}O$ requires 460.2766.

4.6.5. 2,2′-Dimethyl-1,1′-binaphthyl (11).[17] Colourless oil; R_f 0.28 (hexane); ν (film) 3053, 3003 cm^{-1} (ArH); δ_H 2.03 (6H, s, 2×CH_3), 7.04 (2H, d, J=8.4 Hz, ArH), 7.19 (2H, dd, J=8.3, 7.0 Hz, ArH), 7.37 (2H, t, J=7.1 Hz, ArH), 7.49 (2H, d, J=8.4 Hz, ArH), 7.85–7.89 (4H, m, ArH); δ_C 20.0 (CH_3), 124.9, 124.4, 125.6, 127.4, 127.9, 128.7, 132.2, 132.8, 134.2, 135.1 (ArC); *m/z* 282 (M^+, 95%), 267 (40), 266 (20), 265 (30), 132 (100), 127 (15), 126 (62), 119 (23).

4.6.6. (*R*)-2,2′-Bis-(2-hydroxy-2-ethylbutyl)-1,1′-binaphthyl [(*R*)-8b]. Physical and spectroscopic data were found to be the same than for **8b**.

4.6.7. (*S*)-2,2′-Bis-(2-hydroxy-2-ethylbutyl)-1,1′-binaphthyl [(*S*)-8b]. Physical and spectroscopic data were found to be the same than for **8b**.

4.6.8. (*R*)-2,2′-Bis-(1-hydroxycyclohexylmethyl)-1,1′-binaphthyl [(*R*)-8d]. Physical and spectroscopic data were found to be the same than for **8d**.

4.6.9. (*S*)-2,2′-Bis-(1-hydroxycyclohexylmethyl)-1,1′-binaphthyl [(*S*)-8d]. Physical and spectroscopic data were found to be the same than for **8d**.

4.6.10. (*R*)-2,2′-Dimethyl-1,1′-binaphthyl [(*R*)-11]. Physical and spectroscopic data were found to be the same than for **11** {lit. $[\alpha]_D^{22}$ −19.0 (*c* 1.3, ethanol)}.[24]

4.6.11. (*S*)-2,2′-Dimethyl-1,1′-binaphthyl [(*S*)-11]. Physical and spectroscopic data were found to be the same than for **11**. {lit. $[\alpha]_D^{23}$ +14.5 (*c* 1.0, toluene)}.[25]

4.7. Reductive lithiation of 4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]thiepine (7) and 4,5-dihydro-3*H*-dinaphtho-[2,1-*c*:1′,2′-*e*]oxepine (10) and reaction with electrophiles. Preparation of compounds 9 and 12

Isolation of compounds **9** *and* **12**. *General procedure*. To a cooled (−78 °C) solution of compounds **7** or **10** (0.5 mmol) in THF (2 mL) was added dropwise a 0.7 M THF solution (1.6 mL, 1.1 mmol) of lithium naphthalenide and the mixture was stirred at the same temperature for 1 h. Then the corresponding electrophile was added dropwise (0.6 mmol, 0.25 mL in the case of H_2O and D_2O) and after 15 min it was hydrolysed with 3 M HCl (5 mL) for compound **9** and with water in the case of **12**. The resulting mixture was extracted with ethyl acetate (3×15 mL) and the organic layer was dried over anhydrous sodium sulphate and evaporated (15 Torr). The residue was then purified by column chromatography (silica gel, hexane/ethyl acetate) to yield pure compounds **9** and **12**. Yields are given in Tables 4 and 5, specific rotations are given in Table 5, other physical, analytical and spectroscopic data follow.

4.7.1. 2-(2-Hydroxy-2-methylpropyl)-2′-sulphanylmethyl-1,1′-binaphthyl (9a). Yellow oil; R_f 0.26 (hexane/ethyl acetate: 2:1); ν (KBr) 3510–3380 (OH), 3055 (ArH), 2560 cm^{-1} (SH); δ_H 0.98 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.55 (1H, dd, *J*=9.1, 7.2 Hz, SH), 2.05 (1H, br s, OH), 2.63 (2H, dd, *J*=24.2, 14.3 Hz, CH_2COH), 3.42–3.53 (2H, m, CH_2SH), 7.03–7.10 (2H, m, ArH), 7.20–7.25 (1H, m, ArH), 7.40–7.47 (3H, m, ArH), 7.53 (1H, d, *J*=8.5 Hz, ArH), 7.75 (1H, d, *J*=8.5 Hz, ArH), 7.86–8.00 (4H, m, ArH); δ_C 27.3 (CH_2), 30.0, 30.7 (CH_3), 46.3 (CH_2), 71.9 (COH), 125.6, 125.8, 126.2, 126.4, 126.6, 126.7, 126.9, 127.1, 127.7, 128.0, 128.1, 128.7, 129.0, 132.4, 132.6, 134.1, 134.8, 135.7, 137.4, 138.2 (ArC); *m/z* 372 (M^+, 2), 354 (M^+-H_2O, 8), 315 (13), 282 (24), 281 (71), 280 (38), 279 (89), 278 (28), 277 (34), 276 (39), 267 (22), 266 (47), 265 (63), 264 (22), 263 (25), 252 (17), 139 (9), 138 (22), 132 (11), 126 (8), 59 (100); HRMS, M^+, found 372.1544. $C_{25}H_{24}OS$ requires 372.1548.

4.7.2. 2-(2-Hydroxy-2-ethylbutyl)-2′-sulphanylmethyl-1,1′-binaphthyl (9b). Pale yellow oil; R_f 0.38 (hexane/ethyl acetate: 2:1); ν (KBr) 3709–3112 (OH), 3058 (ArH), 2546 cm^{-1} (SH); δ_H 0.56 (3H, t, *J*=7.4 Hz, CH_3), 0.73 (3H, t, *J*=7.4 Hz, CH_3), 1.40–1.61 (6H, m, 2×CH_2, OH, SH), 2.47 (1H, d, *J*=14.2 Hz, C*H*HCOH), 2.65 (1H, d, *J*=14.2 Hz, CH*H*COH), 3.29 (1H, d, *J*=12.5 Hz, C*H*HSH), 3.34 (1H, d, *J*=12.6 Hz, CH*H*SH), 7.03–7.08 (2H, m, ArH), 7.37–7.47 (3H, m, ArH), 7.62 (1H, d, *J*=8.6 Hz, ArH), 7.79–8.02 (6H, m, ArH); δ_C 7.6, 8.1 (CH_3), 30.4, 32.0, 41.9, 63.2 (CH_2), 76.0 (COH), 125.5, 125.8, 126.1, 126.2, 126.3, 126.4, 126.8, 127.4, 127.5, 127.6, 127.9, 128.1, 128.4, 129.3, 132.3, 132.5, 133.0, 133.6, 134.2, 138.3 (ArC); *m/z* 382 [(M^+-H_2O), 0.1], 298 (31), 282 (27), 281 (18), 280 (58), 279 (100), 278 (19), 277 (24), 276 (16), 267 (13), 266 (21), 265 (39), 263 (14), 252 (19), 87 (11); HRMS, M^+-H_2O, found 382.1755. $C_{27}H_{26}S$ requires 382.1772.

4.7.3. 2-(1-Hydroxycyclopentylmethyl)-2′-sulphanylmethyl-1,1′-binaphthyl (9c). Pale yellow oil; R_f 0.70 (hexane/ethyl acetate: 2:1); ν (film) 3540–3360 (OH), 3058 (ArH), 2555 cm^{-1} (SH); δ_H 1.30–1.65 (10H, m, 4×CH_2, OH, SH), 2.68 (1H, d, *J*=14.5 Hz, C*H*HCOH), 2.78 (1H, d, *J*=14.5 Hz, CH*H*COH), 3.39–3.54 (2H, m, CH_2SH), 7.03 (1H, d, *J*=8.4 Hz, ArH), 7.09 (1H, d, *J*=8.6 Hz, ArH), 7.14–7.24 (2H, m, ArH), 7.28–7.51 (2H, m, ArH), 7.70–7.76 (2H, m, ArH), 7.81–7.99 (4H, m, ArH); δ_C 23.1, 23.2, 27.3, 29.7, 31.4, 40.7 (CH_2), 82.8 (COH), 125.5, 125.8, 126.2, 126.4, 126.7, 127.1, 127.8, 128.0, 128.1, 132.4, 132.6, 132.9, 133.0, 134.3, 134.7, 136.1, 137.3 (ArC); *m/z* 398 (M^+, 0.5), 380 (17), 350 (11), 338 (24), 314 (20), 298 (14), 296 (13), 283 (25), 282 (100), 281 (57), 280 (34), 279 (74), 278 (24), 277 (38), 276 (23), 267 (35), 266 (41), 265 (62), 264 (16), 263 (27), 253 (16), 252 (36), 251 (10), 250 (11), 249 (14), 207 (13), 149 (17), 138 (11), 132 (13), 126 (14), 85 (18), 71 (14); HRMS, M^+, found 398.1704. $C_{27}H_{26}OS$ requires 398.1704.

4.7.4. 2-(1-Hydroxycyclohexylmethyl)-2′-sulphanylmethyl-1,1′-binaphthyl (9d). Pale yellow oil; R_f 0.70 (hexane/ethyl acetate: 2:1); ν (film) 3600–3340 (OH), 3059 (ArH), 2570 cm^{-1} (SH); δ_H 1.18–1.73 (12H, m, 5×CH_2, OH, SH), 2.70 (1H, d, *J*=14.0 Hz, C*H*HCOH), 2.79 (1H, d, *J*=14.0 Hz, CH*H*COH), 3.41–3.60 (2H, m, CH_2SH), 7.00–7.24 (4H, m, ArH), 7.31–7.55 (2H, m, ArH), 7.74 (2H, m, ArH), 7.80–8.01 (4H, m, ArH); δ_C 21.8, 21.9, 25.5, 31.8, 37.9, 38.9, 45.0 (CH_2), 82.8 (COH), 124.9, 125.6, 126.0, 126.2, 126.5, 126.9, 127.6, 127.9, 128.0, 132.2, 132.3, 132.7, 132.9, 134.1, 134.5, 136.0, 137.1 (ArC); *m/z* 394 [(M^+-H_2O), 2], 328 (10), 315 (11), 314 (42), 312 (28), 297 (17), 296 (18), 295 (26), 282 (34), 281 (84), 280 (28), 279 (73), 278 (26), 277 (41), 276 (32), 267 (45), 266 (87), 265 (100), 253 (12), 252 (30), 239 (10), 138 (18), 132 (19), 131 (28), 126 (14); HRMS, M^+-H_2O, found 394.1760. $C_{28}H_{26}S$ requires 394.1755.

4.7.5. 2-Hydroxymethyl-2′-methyl-1,1′-binaphthyl (12a). Colourless oil; R_f 0.17 (hexane/ethyl acetate: 5:1); ν (film) 3570–3400 (OH), 3047 cm^{-1} (ArH); δ_H 1.54 (1H, br s, OH), 2.05 (3H, s, CH_3), 4.31 (1H, d, *J*=12.9 Hz, C*H*HOH), 4.39 (1H, d, *J*=12.9 Hz, CH*H*OH), 7.03 (1H, d, *J*=8.4 Hz, ArH), 7.09 (1H, d, *J*=8.4 Hz, ArH), 7.18–7.27 (2H, m, ArH), 7.37–7.52 (3H, m, ArH), 7.82 (1H, d, *J*=8.4 Hz, ArH), 7.88–7.95 (3H, m, ArH), 8.01 (1H, d, *J*=8.6 Hz, ArH); δ_C 20.2 (CH_3), 63.4 (CH_2), 125.1, 125.4, 125.8,

125.9, 126.0, 126.4, 126.5, 127.9, 128.1, 128.2, 128.7, 132.2, 132.4, 133.1, 133.2, 133.5, 134.6, 134.7, 136.5 (ArC); *m/z* 298 (M^+, 35), 281 (14), 280 (51), 279 (100), 278 (22), 277 (50), 276 (30), 268 (25), 267 (19), 266 (15), 265 (51), 264 (18), 263 (36), 254 (19), 253 (21), 252 (35), 240 (15), 239 (31), 128 (15), 127 (40), 126 (44), 119 (15), 115 (26), 86 (15), 77 (27), 51 (29), 50 (22), 44 (46); HRMS: M^+, found 298.1346. $C_{22}H_{18}O$ requires 298.1358.

4.7.6. 2-Deuteromethyl-2′-hydroxymethyl-1,1′-binaphthyl (12b). Colourless oil; R_f 0.17 (hexane/ethyl acetate: 5:1); ν (film) 3570–3400 (OH), 3047 cm^{-1} (ArH); δ_H 1.50 (1H, br s, OH), 2.05 (2H, s, CH_2D), 4.32 (1H, d, $J=12.95$ Hz, C*H*HOH), 4.38 (1H, d, $J=12.95$ Hz, CH*H*OH), 7.03 (1H, d, $J=8.4$ Hz, ArH), 7.09 (1H, d, $J=8.4$ Hz, ArH), 7.18–7.27 (2H, m, ArH), 7.37–7.52 (3H, m, ArH), 7.82 (1H, d, $J=8.4$ Hz, ArH), 7.86–7.95 (3H, m, ArH), 8.01 (1H, d, $J=8.4$, ArH); δ_C 20.0 (t, $J_{CD}=19.7$ Hz, CH_2D), 63.4 (CH_2OH), 125.1, 125.4, 125.8, 125.9, 126.0, 126.4, 126.5, 127.9, 128.0, 128.2, 128.7, 132.1, 132.4, 133.0, 133.2, 133.5, 134.6, 134.7, 136.4 (ArC); *m/z* 299 (M^+, 41), 298 (27), 281 (35), 280 (73), 279 (88), 278 (39), 277 (27), 266 (30), 265 (39), 264 (23), 263 (17), 254 (12), 253 (22), 252 (46), 250 (10), 240 (10), 143 (17), 142 (14), 141 (12), 140 (12), 139 (32), 138 (18), 133 (11), 132 (100), 129 (14), 128 (10), 127 (45), 126 (69), 125 (12), 121 (11), 120 (15), 119 (13), 115 (12), 114 (13), 113 (24); HRMS: M^+, found 299.1420. $C_{18}H_{17}DO$ requires 299.1419.

4.7.7. 2-(2-Hydroxy-3,3-dimethylbutyl)-2′-hydroxymethyl-1,1′-binaphthyl (12c). First diastereoisomer: white solid; mp 190–191 °C (hexane/ethyl acetate) (found: C, 84.11; H, 7.44. $C_{27}H_{28}O_2$ requires: C, 84.34; H, 7.34); R_f 0.14 (hexane/ethyl acetate: 5:1); ν (film) 3649–3139 (OH), 3062 cm^{-1} (ArH); δ_H 0.66 [9H, s, $(CH_3)_3$], 2.25 (1H, dd, $J=14.3$, 11.0 Hz, C*H*HCHOH), 2.44 (2H, br s, 2×OH), 2.61 (1H, dd, $J=14.3$, 2.2 Hz, CH*H*CHOH), 3.64 (1H, dd, $J=11.0$, 2.2 Hz, C*H*OH), 4.26 (2H, d, $J=12.2$ Hz, C*H*HOH), 4.33 (1H, d, $J=12.2$ Hz, CH*H*OH), 7.00–7.04 (2H, dd, $J=8.4$, 3.1 Hz, ArH), 7.19–7.25 (2H, m, ArH), 7.40–7.46 (2H, m, ArH), 7.62 (1H, d, $J=8.6$ Hz, ArH), 7.79 (1H, d, $J=8.4$ Hz, ArH), 7.89–8.00 (4H, m, ArH); δ_C 25.3 (CH_3), 30.9 [*C*$(CH_3)_3$], 34.9, 63.1 (CH_2), 80.0 (COH), 125.4, 125.7, 126.0, 126.2, 126.4, 126.5, 126.6, 127.3, 127.9, 128.0, 128.2, 128.3, 132.1, 133.0, 133.5, 134.2, 134.9, 136.5, 137.4 (ArC); *m/z* 384 (M^+, 0.5), 366 (4), 350 (0.2), 298 (36), 281 (29), 280 (66), 279 (100), 278 (18), 277 (22), 276 (15), 267 (17), 266 (25), 265 (44), 264 (10), 263 (14), 252 (22); HRMS: M^+, found 384.2090. $C_{27}H_{28}O_2$ requires 384.2089. Second diastereoisomer: colourless oil; R_f 0.13 (hexane/ethyl acetate: 5:1); ν (film) 3630–3125 (OH), 3060 cm^{-1} (ArH); δ_H 0.53 [9H, s, $(CH_3)_3$], 2.28 (1H, dd, $J=14.0$, 10.7 Hz, C*H*HCHOH), 2.44 (2H, br s, 2×OH), 2.59 (1H, dd, $J=14.0$, 2.2 Hz, CH*H*CHOH), 3.15 (1H, dd, $J=10.7$, 2.2 Hz, C*H*OH), 4.32 (1H, d, $J=13.1$ Hz, C*H*HOH), 4.36 (1H, d, $J=13.1$ Hz, CH*H*OH), 7.12 (1H, d, $J=8.6$ Hz, ArH), 7.18 (1H, d, $J=8.4$ Hz, ArH), 7.23–7.31 (2H, m, ArH), 7.41–7.49 (2H, m, ArH), 7.61 (1H, d, $J=8.4$ Hz, ArH), 7.81 (1H, d, $J=8.6$ Hz, ArH), 7.91–7.96 (3H, m, ArH), 8.02 (1H, d, $J=8.4$ Hz, ArH); δ_C 25.1 (CH_3), 34.6 [*C*$(CH_3)_3$], 36.5, 63.3 (CH_2), 78.9 (COH), 125.4, 125.5, 125.9, 126.0, 126.5, 126.6, 128.0, 128.1, 128.2, 128.5, 129.1, 132.2, 132.4, 133.1, 133.2, 133.9, 134.1, 134.5, 137.2 (ArC); *m/z* 384 (M^+, 0.5), 366 (4), 350 (0.2), 298 (36), 281 (29), 280 (66), 279 (100), 278 (18), 277 (22), 276 (15), 267 (17), 266 (25), 265 (44), 264 (10), 263 (14), 252 (22); HRMS: M^+, found 384.2090. $C_{27}H_{28}O_2$ requires 384.2089.

4.7.8. 2-(2-Hydroxy-2-methylpropyl)-2′-hydroxymethyl-1,1′-binaphthyl (12d). Colourless oil; R_f 0.18 (hexane/ethyl acetate: 2:1); ν (KBr) 3663–3130 (OH), 3058 cm^{-1} (ArH); δ_H 1.06 (3H, s, CH_3), 1.17 (3H, s, CH_3), 2.05 (2H, br s, 2× OH), 2.55 (1H, d, $J=14.2$ Hz, C*H*HCOH), 2.65 (1H, d, $J=14.2$ Hz, CH*H*COH), 4.28 (1H, d, $J=12.9$ Hz, C*H*HOH), 4.32 (1H, d, $J=12.9$ Hz, CH*H*OH), 7.02 (1H, d, $J=8.6$ Hz, ArH), 7.09 (1H, d, $J=8.6$ Hz, ArH), 7.19–7.27 (2H, m, ArH), 7.40–7.47 (2H, m, ArH), 7.66 (1H, d, $J=8.6$ Hz, ArH), 7.82 (1H, d, $J=8.6$ Hz, ArH), 7.89–7.94 (3H, m, ArH), 7.99 (1H, d, $J=8.6$ Hz, ArH); δ_C 28.8, 31.7 (CH_3), 46.7, 63.1 (CH_2), 72.0 (COH), 125.5, 125.8, 126.1, 126.3, 126.4, 126.7, 127.5, 127.9, 128.0, 128.1, 128.4, 129.4, 132.2, 132.4, 132.9, 133.5, 134.1, 135.1, 135.2, 138.2 (ArC); *m/z* 356 (M^+, 0.5), 338 (1), 320 (0.4), 298 (28), 296 (19), 281 (21), 280 (52), 279 (100), 278 (30), 277 (50), 276 (20), 267 (17), 266 (17), 265 (45), 264 (12), 263 (21), 253 (17), 252 (34); HRMS: M^+, found 356.1800. $C_{25}H_{24}O_2$ requires 356.1776.

4.7.9. 2-(2-Hydroxy-2-ethylbutyl)-2′-hydroxymethyl-1,1′-binaphthyl (12e). Colourless oil; R_f 0.26 (hexane/ethyl acetate: 2:1); ν (KBr) 3681–3103 (OH), 3053 cm^{-1} (ArH); δ_H 0.56 (3H, t, $J=7.5$ Hz, CH_3), 0.73 (3H, t, $J=7.5$ Hz, CH_3), 1.20–1.26 (2H, m, C*H*$_2$CH$_3$), 1.39–1.56 (2H, m, C*H*$_2$CH$_3$), 1.98 (2H, br s, 2×OH), 2.46 (1H, d, $J=14.2$ Hz, C*H*HCOH), 2.65 (1H, d, $J=14.2$ Hz, CH*H*COH), 4.28 (1H, d, $J=12.7$ Hz, C*H*HOH), 4.32 (1H, d, $J=12.7$ Hz, CH*H*OH), 7.03–7.08 (2H, m, ArH), 7.20–7.24 (2H, m, ArH), 7.40–7.47 (2H, m, ArH), 7.62 (1H, d, $J=8.6$ Hz, ArH), 7.81–8.00 (5H, m, ArH); δ_C 7.6, 8.1 (CH_3), 30.4, 32.0, 41.9, 63.2 (CH_2), 75.9 (COH), 125.5, 125.8, 126.1, 126.2, 126.3, 126.4, 126.8, 127.5, 127.9, 128.1, 129.3, 132.2, 132.5, 133.0, 133.6, 134.1, 134.7, 135.7, 138.4 (ArC); *m/z* 366 [(M^+-H_2O), 0.2], 298 (34), 281 (14), 280 (61), 279 (100), 278 (16), 277 (19), 276 (12), 267 (10), 266 (16), 265 (34), 263 (12), 252 (16); HRMS: M^+, found 384.2094. $C_{27}H_{28}O_2$ requires 384.2089.

4.7.10. 2-(1-Hydroxycyclohexylmethyl)-2′-hydroxymethyl-1,1′-binaphthyl (12f). Colourless oil; R_f 0.28 (hexane/ethyl acetate: 2:1); ν (KBr) 3672–3148 (OH), 3062 cm^{-1} (ArH); δ_H 0.85–1.57 (10H, m, 5×CH_2), 1.90 (2H, br s, 2×OH), 2.46 (1H, d, $J=14.2$ Hz, C*H*HCOH), 2.58 (1H, d, $J=14.2$ Hz, CH*H*COH), 4.27 (1H, d, $J=12.5$ Hz, CH*H*OH), 4.33 (1H, d, $J=12.5$ Hz, CH*H*OH), 7.00–7.09 (2H, m, ArH), 7.19–7.24 (2H, m, ArH), 7.39–7.46 (2H, m, ArH), 7.62 (1H, d, $J=8.6$ Hz, ArH), 7.83 (1H, d, $J=8.6$ Hz, ArH), 7.88–7.93 (3H, m, ArH), 7.99 (1H, d, $J=8.4$ Hz, ArH); δ_C 21.8, 21.9, 25.5, 36.8, 39.6, 63.2 (CH_2), 72.6 (COH), 125.5, 125.8, 126.1, 126.2, 126.3, 126.4, 126.9, 127.4, 127.9, 128.1, 128.4, 128.5, 132.2, 132.4, 133.0, 133.6, 134.2, 134.5, 135.5, 138.5 (ArC); *m/z* 396 (M^+, 0.1), 378 (0.6), 360 (1), 299 (10), 298 (42), 281 (17), 280 (70), 279 (100), 278 (16), 277 (19), 276 (12), 266 (11), 265 (29), 263 (11), 252 (16); HRMS: M^+, found 396.2077. $C_{28}H_{28}O_2$ requires 396.2089.

4.7.11. (*S*)-2-Hydroxymethyl-2′-methyl-1,1′-binaphthyl [(*S*)-12a]. Physical and spectroscopic data were found to be the same than for **12a**.

4.7.12. (*R*)-2-Hydroxymethyl-2′-methyl-1,1′-binaphthyl [(*R*)-12a]. Physical and spectroscopic data were found to be the same than for **12a**.

4.7.13. (*R*)-2-(2-Hydroxy-3,3-dimethylbutyl)-2′-hydroxymethyl-1,1′-binaphthyl [(*R*)-12c]. Two diastereoisomers were isolated in enantiomericaly pure form and their physical and spectroscopic data were found to be the same than for those isolated in the racemic **12c**.

4.7.14. (*S*)-2-(2-Hydroxy-2-ethylbutyl)-2′-hydroxymethyl-1,1′-binaphthyl [(*S*)-12e]. Physical and spectroscopic data were found to be the same than for **12e**.

4.7.15. (*R*)-2-(2-Hydroxy-2-ethybutyl)-2′-hydroxymethyl-1,1′-binaphthyl [(*R*)-12e]. Physical and spectroscopic data were found to be the same than for **12e**.

4.7.16. (*S*)-2-(1-Hydroxycyclohexylmethyl)-2′-hydroxymethyl-1,1′-binaphthyl [(*S*)-12f]. Physical and spectroscopic data were found to be the same than for **12f**.

4.7.17. (*R*)-2-(1-Hydroxycyclohexylmethyl)-2′-hydroxymethyl-1,1′-binaphthyl [(*R*)-12f]. Physical and spectroscopic data were found to be the same than for **12f**.

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Novel synthesis of *o*-naphthothiophenequinone derivatives via regioselective Diels–Alder reaction

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Abstract—A novel procedure to construct *o*-naphthothiophenequinones has been achieved from readily available *o*-benzothiophenquinones and *N*-dienes via Diels–Alder reaction-aromatization sequence as key steps. The absolute regioselectivity was established via Diels–Alder reaction of *o*-benzothiophenquinones with rich electron *N*-dienes.

1. Introduction

The derivatives of synthetic and natural polycyclic quinoid structure are a large category of very significative compounds, which possess a broad spectrum of biological activities.[1–7] Among heterocyclic quinones with a variety of bioactivities, those containing a thiophene ring fused to a quinone system have received an increasing attention.[8]

As part of our ongoing research for hetero polycyclic *o*-quinones,[9] more structurally diversified *o*-quinoid derivatives were called for. In contrast to extensive study of oxoheterocyclic-fused *o*-quinones, that of thioheterocyclic-fused *o*-quinones was quite scarce.[8c,10] Therefore, synthesis of novel thiophen-fused *o*-quinones was proposed, these novel derivatives were characterized as 3-aryl and 6-acylamino substituted *o*-naphthothiophenquinones **I** (Fig. 1).

However, efficient methods for the synthesis of *o*-naphthothiophenequinones could be seldom found.[11] Furthermore, the reported synthetic procedure[11] was unapplicable for us to prepare the proposed derivatives **I** for unavailable starting materials.

In this paper, we described a novel and regiospecific procedure to synthesize the target substrates **I**. The retrosynthetic analysis (Scheme 1) showed that compounds **I** could be achieved facilely from inexpensive and easily available starting materials **II**, **III**, **VI**, **VII** via condensation, intramolecularly cyclization, deprotection, IBX

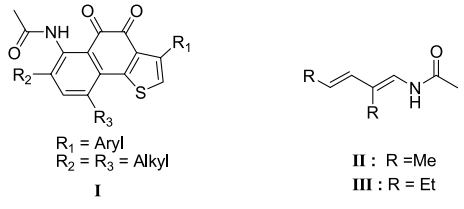
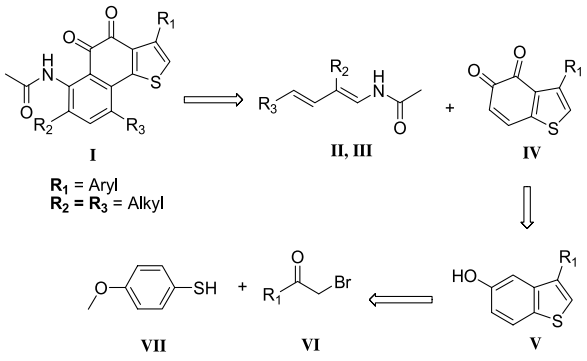


Figure 1.



Scheme 1. Retrosynthesis route of target compounds **I**.

Keywords: *o*-Naphthothiophenequinone; IBX; Diels–Alder; Regioselectivity.
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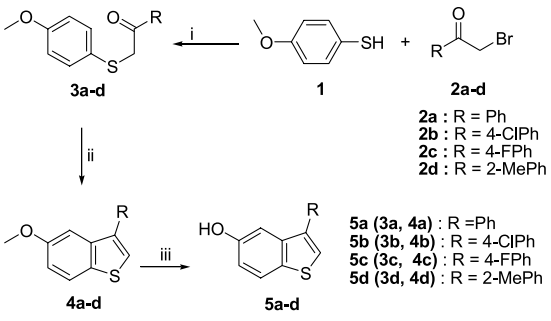
oxidation, and then Diels–Alder reaction-aromatization sequence.

2. Results and discussion

2.1. Synthesis of benzothiophen-5-ols (5a–d)

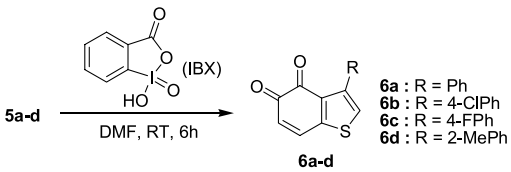
Our strategies were started from synthesis of benzothiophen-5-ol moieties detailed in Scheme 2. Compounds **3a–d** were prepared in MeOH/H_2O by condensing 4-methoxyphenylthiol **1** with an equiv of 2-bromo-1-arylyethanones **2a–d** at 5–10 °C in the presence of an equiv of KOH.[12] Compounds **3a–d** were then cyclized into 3-aryl-5-methoxybenzothiophenes **4a–d** in refluxing toluene by using PPA.[13] Finally, benzothiophene-5-ols **5a–d** were achieved in moderate to good overall yield (see Section 4) after deprotection of **4a–d** by refluxing in a mixture of Ac_2O and 48% HBr (1:1 v/v).



Scheme 2. Conditions: (i) MeOH, equiv KOH, 5–10 °C; (ii) PPA, toluene, RF, 6 h; (iii) AC_2O–HBr (48%) (1:1, v/v), 140 °C, 4 h.

2.2. Synthesis of benzothiophen-4, 5-diones (6a–d)

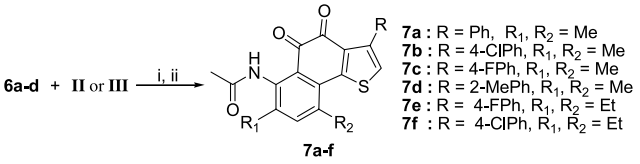
The next step was to convert benzothiophen-5-ols **5a–d** into benzothiophen-4,5-diones **6a–d**. Fremy's salt is well known for its application in transforming single phenolic hydroxyl group into *o*-quinone group.[14] Our first attempt was focused on the oxidation of benzothiophen-5-ols **5a–d** to produce *o*-quinones **6a–d**. However, most of the reaction failed to give the desired products in satisfactory yield. After an in-depth screening of mild oxidants, we found that *o*-iodoxybenzoic acid (IBX) could be a good choice in these reactions, as it was reported that IBX was a good oxidant for transforming phenols to *o*-quinones.[15] However, few reports on transformation of hetero biscyclic phenolic hydroxyl group into *o*-quinone by IBX could be found. Our results indicated that IBX worked very well in our system, the desired product benzothiophen-4,5-diones **6a–d** were obtained regioselectively (Scheme 3) in almost quantitative yields. The isolation of the diquinone intermediates was not pursued as most of these *o*-quinone compounds were volatile and highly reactive.



Scheme 3.

2.3. Synthesis of target *o*-quinones (7a–f)

After the completion of IBX oxidation, the reaction mixture was first diluted with water, and then extracted with benzene. The extraction containing benzothiophen-4,5-diones was dried with anhydrous sodium sulfate and *N*-diene **II** or **III**[16] was added for cycloaddition. The reaction was carried out at 45 °C and monitored by TLC (noticeably, only one new fluorescent substance was found, which indicated that the single regiomer was produced). About 16 h later, the reaction mixtures were subsequently aromatized into the final products by refluxing with DDQ. After purification by chromatography on silica gel ($CHCl_3$/MeOH), regiospecific compounds **7a–f** were obtained in 78–86% yields (Scheme 4).



Scheme 4. Conditions: (i) benzene, 45 °C, 16 h; (ii) DDQ, benzene, RF, 10 h.

Structures of all final products were assigned according to ^1H NMR, ^{13}C NMR, DEPT, HMQC, HMBC, ESI-MS and element analysis data. The structure of **7a** was also proved unanimously by X-ray crystal structure analysis[17] (Fig. 2).

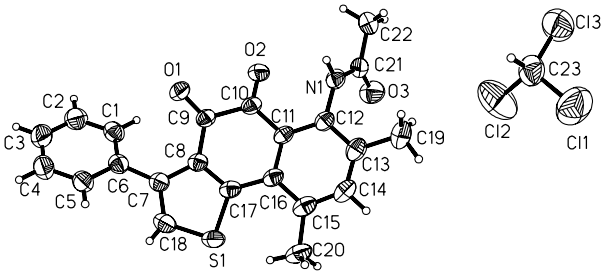


Figure 2. X-ray crystal structure for **7a** (CCDC no. 267293).

It is interesting that the cycloaddition reactions of our procedure were essentially regiospecific and high reactive, which was reasoned that an intermolecular hydrogen bond (HB) would form between the amide group (NH) of the *N*-dienes and the oxygen atom of carbonyl groups in *o*-quinones. The role of intermolecular hydrogen bonding in the regio and stereo-chemical outcome of Diels–Alder reactions has been well recognized.[18]

3. Conclusions

In summary, we developed a novel route to prepare thiophen-fused *o*-naphthoquinone derivatives via the key IBX oxidation–cycloaddition–aromatization sequence. Noticeably, the cycloaddition was regiospecific and highly efficient. To the best of our knowledge, none relative reports have surfaced. Furthermore, this work produced a series of novel thiophene fused *o*-quinoid derivatives. Studies on the bioactivities and further synthesis of these compounds are well under way.

4. Experimental

4.1. General

All reagents were available commercially. Solvents were purified using standard techniques. Reactions were monitored by TLC. Separation by vacuum chromatographic column were performed on Silica gel H. ^{1}H NMR, ^{13}C NMR, DEPT, HMQC and HMBC spectra were measured on a Varian UNITY INOVA 500 or 300 MHz spectrometer using TMS as an internal standard. For the electrospray (ESI) MS analysis, a Finnigan LCQ Deca XP ion trap mass spectrometer was equipped with a Microsoft Windows NT data system and an ESI interface was used. Elementary analysis was recorded on an Elementar Vario EL elementary analysis device. *N*-Dienes **II**, **III** are prepared by using the reported method.[16]

4.2. General procedure for 3-arylbenzothiophen-5-ols (5a–d)

To a freshly prepared solution of 70 mL of MeOH, 30 mL of water, and 3.3 g of KOH (85% purity; 0.05 mol) at room temperature was added 4-methoxybenzenethiol **1** (7.0 g, 0.05 mol) in one portion, and the solution was cooled to between 5 and 10 °C. A saturated solution of 2-bromo-1-arylyethanones (**2a–d**) (0.05 mol) in MeOH was added at a rate that the temperature did not exceed 15 °C. The reaction was continued for further 1 h at 15 °C, and then was allowed to stir overnight at room temperature. The reaction was diluted with water and extracted with ether. The organic layers were washed with 1 M HC1 solution, water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organics were dried over anhydrous Na_2SO_4, filtered, and evaporated to give crude products (**3a–d**) as yellow oils.

A mixture of 2-(4-methoxyphenylthio)-1-arylethanones (**3a–d**), polyphosphoric acid (40 g), and toluene (100 mL) was refluxed for 6 h. The reaction mixture was cooled to room temperature, poured into water, and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation gave crude compounds (**4a–d**), which were used directly for the next reaction without further purification.

Unpurified 3-aryl-5-methoxybenzo[*b*]thiophenes (**4a–d**) were added to mixed solution (40 mL) of 48% HBr and acetic anhydride (1:1, v/v). The mixture was refluxed at 140 °C for 4 h. The reaction mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate solution and extracted with ether. The organic extracts were washed with saturated aqueous sodium chloride and dried over anhydrous Na_2SO_4. Evaporation and purification by chromatography on silica gel (eluent: EtOAc/Petroleum-II 1:8) gave 3-arylbenzo[*b*]thiophene-5-ols (**5a–d**) in moderate to good overall yields.

4.2.1. 3-Phenylbenzo[*b*]thiophene-5-ol (5a). This compound was obtained as a yellow oil in 53% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{14}H_{10}OS$: C, 74.31; H, 4.45; S, 14.17; Found: C, 74.27; H, 4.48; S, 14.14; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 1H, J=8.7 Hz), 7.55–7.58 (m, 2H), 7.41–7.48 (m, 5H), 7.05 (dd, 1H, J=2.4, 8.6 Hz), 6.46 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.0, 114.3, 123.6, 124.8, 127.2, 128.2, 128.4, 133.0, 135.6, 137.1, 138.8, 152.7.

4.2.2. 3-(4-Chlorophenyl)benzo[*b*]thiophene-5-ol (5b). This compound was obtained as a yellow oil in 58% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{14}H_9ClOS$: C, 64.49; H, 3.48; S, 12.30; Found: C, 64.47; H, 3.52; S, 12.27; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 1H, J=8.6 Hz), 7.31–7.41 (m, 6H), 7.00 (dd, 1H, J=2.0, 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.7, 114.6, 123.6, 125.1, 128.6, 129.5, 132.7, 133.1, 134.1, 135.9, 138.6, 153.4.

4.2.3. 3-(4-Fluorophenyl)benzo[*b*]thiophene-5-ol (5c). This compound was obtained as a yellow oil in 60% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{14}H_9FOS$: C, 68.84; H, 3.71; S, 13.12; Found: C, 68.79; H, 3.74; S, 13.09; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 1H, J=8.6 Hz), 7.49 (dd, 1H, J=5.5, 8.5 Hz), 7.37 (s, 1H), 7.29 (d, 1H, J=2.3 Hz), 7.14 (t, 2H, J=8.6 Hz), 6.99 (dd, 1H, J=2.3, 8.6 Hz), 5.65 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.7, 114.5, 115.6 (d, J=21.0 Hz), 123.7, 124.9, 130.0 (d, J=7.3 Hz), 131.8, 132.8, 136.2, 139.0, 153.3, 162.1 (d, J=245.6 Hz).

4.2.4. 3-(2-Methylphenyl)benzo[*b*]thiophene-5-ol (5d). This compound was obtained as a yellow oil in 62% overall yield (eluent: EtOAc/Petroleum-II 1:8). Anal. Calcd for $C_{15}H_{12}OS$: C, 74.97; H, 5.03; S, 13.34; Found: C, 74.94; H, 5.28; S, 13.29; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 1H, J=8.6 Hz), 7.28–7.33 (m, 5H), 6.95 (dd, 1H, J=2.4, 8.6 Hz), 6.84 (d, 1H, J=2.4 Hz), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 108.0, 114.3, 123.4, 125.0, 125.6, 127.8, 130.1, 130.3, 132.1, 135.2, 136.7, 136.9, 140.2, 153.2.

4.3. General procedure for substituted naphtho [1,2-*b*] thiophene-4,5-diones (7a–f)

Compound **5a–d** (1 mmol) and IBX (1.2 mmol) were added to dry DMF (5 mL) and then stirred at the room temperature for 6 h. The reaction mixture was diluted with water (120 mL), extracted with benzene, washed with saturated aqueous sodium chloride, dried over Na_2SO_4, and concentrated to 50 mL, *N*-dienes **II** or **III** (1 mmol) was added and then the mixture was stirred at 45 °C for 16 h. The solution containing cycloaddition products was added DDQ (0.75 mmol) and refluxed for further 16 h. Evaporation and purification by chromatography on silica gel ($CHCl_3$/MeOH) gave **7a–f** in good yields.

4.3.1. 7,9-Dimethyl-3-phenyl-6-acetamidonaphtho[1,2-*b*] thiophene-4,5-dione (7a). This compound was obtained as a red solid in 86% yield (eluent: MeOH/$CHCl_3$ 1:50). Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73; S, 8.54; Found: C, 70.35; H, 4.61; N, 3.70; S, 8.49; MS (ESI) *m/z*: 374 $(M-H)^-$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.0 (br s, 1H), 7.35–7.43 (m, 6H), 7.18 (s, 1H), 2.65 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 24.2, 24.33, 122.0, 125.0, 127.8, 128.1, 128.7, 129.9, 131.6, 132.9, 134.4, 136.8, 139.6, 142.4, 144.4, 151.5, 168.8, 174.9, 185.4.

4.3.2. 7,9-Dimethyl-3-(4-chlorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7b). This compound was obtained as a red solid in 83% yield (eluent: MeOH/$CHCl_3$ 1:50). Anal. Calcd for $C_{22}H_{16}ClNO_3S$: C, 64.47; H, 3.93; N, 3.42; S, 7.82; Found: C, 64.44; H, 3.96; N, 3.39; S, 7.78; MS (ESI) *m/z*: 408 $(M-H)^-$; ^1H NMR (500 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.26 (s, 3H), 2.68 (s, 3H), 7.20 (s, 1H), 7.36 (s, 4H), 7.40 (s, 1H), 10.03 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 24.1, 24.3, 122.2, 125.2, 127.9, 128.2, 129.9, 130.3, 130.6, 131.7, 133.0, 133.1, 134.3, 137.2, 140.0, 142.7, 143.3, 152.0, 169.0, 175.1, 185.5.

4.3.3. 7,9-Dimethyl-3-(4-fluorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7c). This compound was obtained as a red solid in 85% yield (eluent: MeOH/$CHCl_3$ 1:50). Anal. Calcd for $C_{22}H_{16}FNO_3S$: C, 67.16; H, 4.10; N, 3.56; S, 8.15; Found: C, 67.13; H, 4.14; N, 3.54; S, 8.11; MS (ESI) *m/z*: 392 $(M-H)^-$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.25 (s, 3H), 2.67 (s, 3H), 7.06 (t, 2H, $J=8.6$ Hz), 7.17 (s, 1H), 7.36–7.41 (m, 3H), 10.01 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 24.3, 24.4, 114.9 (d, $J=21.6$ Hz), 122.0, 125.0, 129.8, 130.4, 130.6 (d, $J=7.9$ Hz), 131.5, 133.0, 137.0, 139.7, 142.5, 143.3, 151.8, 162.5 (d, $J=247.4$ Hz), 168.9, 174.9, 185.4.

4.3.4. 7,9-Dimethyl-3-(2-methylphenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7d). This compound was obtained as red solid in 80% yield (eluent: MeOH/$CHCl_3$ 1:20). Anal. Calcd for $C_{23}H_{19}NO_3S$: C, 70.93; H, 4.92; N, 3.60; S, 8.23; Found: C, 70.89; H, 4.95; N, 3.57; S, 8.25; MS (ESI) *m/z*: 388 $(M-H)^-$; ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 7.10 (s, 1H), 7.13–7.31 (m, 4H), 7.37 (s, 1H), 9.98 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 20.3, 24.5, 24.6, 122.7, 125.2, 125.6, 128.4, 129.3, 129.9, 130.3, 133.2, 133.3, 135.1, 136.9, 137.2, 140.1, 142.7, 143.7, 151.1, 169.3, 174.5, 185.2.

4.3.5. 7,9-Diethyl-3-(4-fluorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7e). This compound was obtained as a red solid in 78% yield (eluent: MeOH/$CHCl_3$ 1:200). Anal. Calcd for $C_{24}H_{20}FNO_3S$: C, 68.39; H, 4.78; N, 3.32; S, 7.61; Found: C, 68.36; H, 4.82; N, 3.30; S, 7.58; MS (ESI) *m/z*: 420 $(M-H)^-$; ^1H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, 3H, $J=7.5$ Hz), 1.42 (t, 3H, $J=7.4$ Hz), 2.24 (s, 3H), 2.66 (q, 2H, $J=7.5$ Hz), 3.11 (q, 2H, $J=7.4$ Hz), 7.07 (t, 2H, $J=8.7$ Hz), 7.16 (s, 1H), 7.40 (dd, 2H, $J=5.3$, 8.7 Hz), 7.48 (s, 1H), 9.81 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5, 14.3, 24.2, 24.7, 28.8, 114.9 (d, $J=21.7$ Hz), 122.9, 124.8, 129.3, 130.6, 130.7 (d, $J=8.3$ Hz), 131.9, 138.4, 138.8, 139.4, 143.0, 143.2, 150.9, 162.7 (d, $J=247.5$ Hz), 169.5, 175.7, 186.2.

4.3.6. 7,9-Diethyl-3-(4-chlorophenyl)-6-acetamidonaphtho [1,2-*b*]thiophene-4,5-dione (7f). This compound was obtained as red solid in 80% yield (eluent: MeOH/$CHCl_3$ 1:200). Anal. Calcd for $C_{24}H_{20}ClNO_3S$: C, 65.82; H, 4.60; N, 3.20; S, 7.32; Found: C, 65.78; H, 4.65; N, 3.21; S, 7.34; MS (ESI) *m/z*: 436 $(M-H)^-$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, $J=7.5$ Hz), 1.40 (t, 3H, $J=7.4$ Hz), 2.23 (s, 3H), 2.64 (q, 2H, $J=7.5$ Hz), 3.08 (q, 2H, $J=7.4$ Hz), 7.15 (s, 1H), 7.32 (s, 4H), 7.45 (s, 1H), 9.78 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 14.3, 24.3, 24.7, 28.8, 122.8, 125.0, 128.0, 129.1, 130.1, 131.6, 132.8, 134.0, 138.2, 138.6, 139.3, 142.7, 142.9, 150.9, 169.4, 175.4, 185.8.

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17. Crystal data for **7a**: $C_{22}H_{17}NO_3S\cdot CHCl_3$, $M=494.79$, monoclinic, space group $P2(1)/c$, $a=17.413(6)$ Å, $b=16.235(5)$ Å, $c=8.054(3)$ Å, $\alpha=90.00°$, $\beta=95.706(6)°$, $\gamma=90.00°$, $V=2265.8(13)$ Å^3, $Z=4$, $D_c=1.451$ g/m^3, $F(000)=1016$, $1.18°<\theta<27.13°$, $-22\le h\le 22$, $-20\le k\le 14$, $-10\le l\le 10$, $T=293$ K, colorless red, $0.54\times0.42\times0.21$. $R_1=0.0595$ ($[I>2\sigma(I)]$), 0.1040 (all data), $\omega R_2=0.1817$ ($[I>2\sigma(I)]$), 0.2224 (all data). Crystallographic data for the structures in this paper have been deposited with the Cambridge crystallographic data centre as supplementary publication numbers CCDC 267293. 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: eposit@ccdc.cam.ac.uk].
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A versatile route to benzocanthinones

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Abstract—Benzocanthinone (**1**) and five analogs (**10**, **12–15**) were prepared by radical-induced cyclizations of halo *N*-aroyl derivatives of β-carboline and carbazole.

1. Introduction

Benzocanthinone (**1**; 9*H*-benzo[*c*]indolo[3,2,1-*ij*][1,5]-naphthyridin-9-one), derived from *Calycanthus floridus* L., was first reported in 1938.[1] Both **1** and its tetracyclic analog, canthin-6-one (**2**; 6*H*-indolo[3,2,1-*e*][1,5]-naphthyridin-6-one), belong to a large family of β-carboline alkaloids, which exhibit a broad range of pharmacological activity.[2] Of the three reported syntheses of **1**, two proceeded in poor yields (0.4 and 9%),[1,3] and the third involved an isolation step unsuitable for scale-up purposes (filtration of mercury metal).[4] While new routes to **2** and its analogs continue to be developed,[5] there is to date no satisfactory route to pentacyclic alkaloids such as **1** (Fig. 1).

As part of our earlier interest in canthinones, we explored an intramolecular Diels–Alder pathway to **1**, which would simultaneously generate rings C and D.[6] The cycloaddition, however, could not be effected even under stringent conditions.[6a] Retrosynthetic analysis led us to consider the alternative paths shown in Scheme 1. Such disconnections generated β-carboline derivatives containing a pendent ring E. The final step would be closure of ring D by either amide formation or aryl–aryl coupling. Our interest was in devising a methodology not only for **1**, but also for a series of isomers, in which ring E contained the peripheral nitrogen atom. The three prior preparations of **1** were based on condensations of phthalic acid derivatives with tryptophan derivatives and thus, were incompatible with the latter objective.

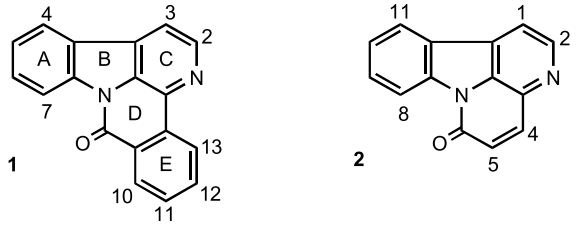

Figure 1. Benzocanthinone (**1**) and canthinone (**2**).

2. Results and discussion

We began by exploring path a and replicating Bracher and Hildebrand's conversion of 1-chloro-β-carboline (**3**) to 1-phenyl-β-carboline by Suzuki coupling.[7] In our hands, this reactivity could not be extended to 2-methoxycarbonylphenylboronic acid (**A**, X=OMe), 2-carboxyphenylboronic acid (**A**, X=OH), or 2-cyanophenylboronic acid (**A**, COX=CN). However, we anticipated that cyclization of either **B** or **C** could be effected by tributylstannane (path b), a process for which there was ample precedent.[8]

Our initial intermediate target was a type **C** molecule, given the ready availability of the starting materials. The subsequent radical-induced ring closure posed regioselectivity options at C(1) and C(8) of the β-carboline moiety, but the strong preference for radical attack at C(1) rather than at C(8) with isoquinoline augured well.[9] In the event, β-carboline (**4**) was converted to **5a–c**, which were subjected to radical, oxidative cyclization (Scheme 2). The reaction mixtures contained two coupling products, **1** and **6**, and, in the case of **5a** and **5c**, appreciable amounts of **4** resulting from reductive cleavage. GC–MS analysis

Keywords: Benzocanthinone; Pentacyclic alkaloids; Radical-induced cyclization.
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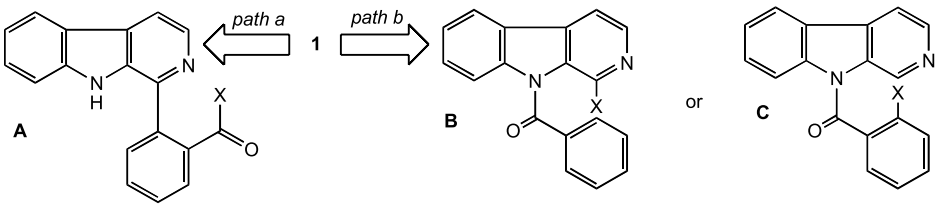
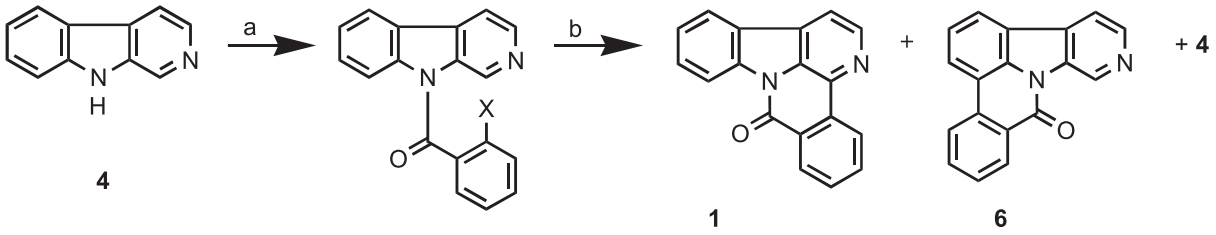


Scheme 1.



5a (X = Cl, 96%)
5b (X = Br, 71%)
5c (X = I, 76%)

Scheme 2. Reagents and conditions: (a) NaH, DMF, rt, then 2-halobenzoyl chloride, DMAP, DMF, 65 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.

established that **1** and **6** had comparable retention times, identical masses, and the same fragmentation pattern. The identity of **1** was assigned by comparison with an authentic sample, and the structure of **6** was based on the above characteristics. The product ratios were a function of the halo substituent (Table 1). The regioselectivities related inversely to the aryl-halogen bond strengths,[10] whereby **5c** afforded the lowest energy aryl radical, which exhibited the highest selectivity between C(1) and C(8) of the β-carboline moiety.

The above results dictated that a type **B** intermediate was necessary for an unambiguous route to **1**. Accordingly, 1-chloro-β-carboline (**3**) was converted to amide **7**, which afforded **1** as the only observed product (Scheme 3).

Table 1. Percent composition of product mixtures in Schemes 2–9[a]

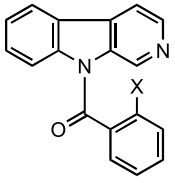
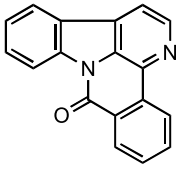
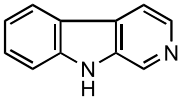
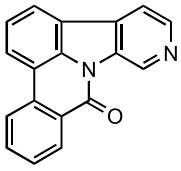
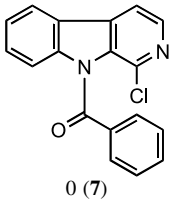
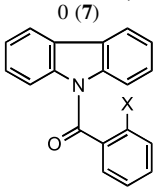
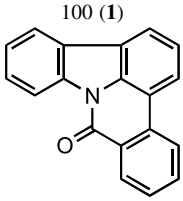
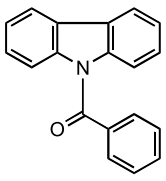
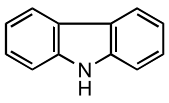
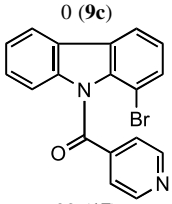
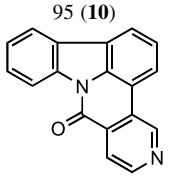
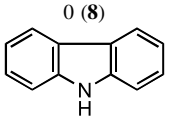
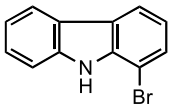
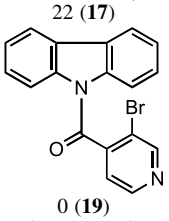
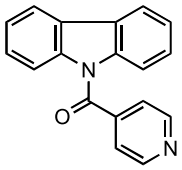
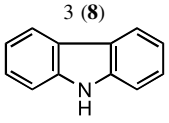
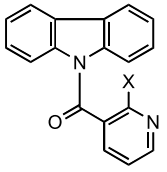
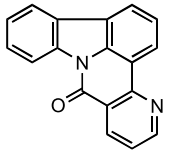
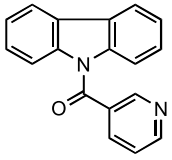
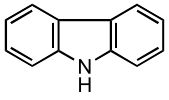
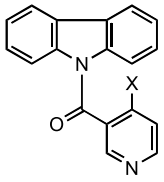
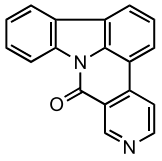
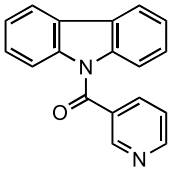
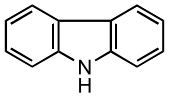
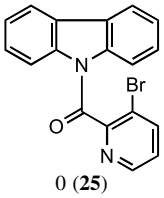
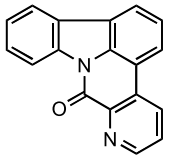
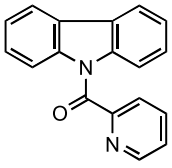
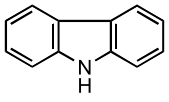
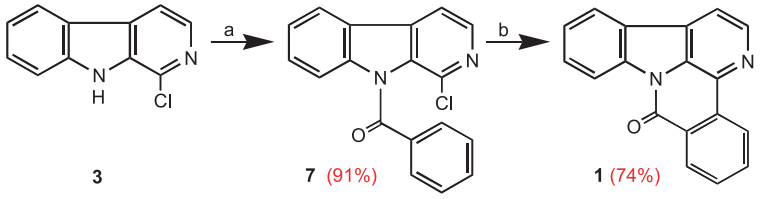
	Amide	Cyclization	Dehalogenation	Amide cleavage	Other
					
X					
Cl	51 (**5a**)	13 (**1**)		22 (**4**)	14 (**6**)
Br	0 (**5b**)	69 (**1**)		0 (**4**)	31 (**6**)
I	0 (**5c**)	42 (**1**)		51 (**4**)	7 (**6**)
					
	0 (**7**)	100 (**1**)			
					
X					
Cl	75 (**9a**)	18 (**10**)	0 (**11**)	7 (**8**)	
Br	0 (**9b**)	>99 (**10**)	0 (**11**)	0 (**8**)	

Table 1 (*continued*)

	Amide	Cyclization	Dehalogenation	Amide cleavage	Other
I	0 (**9c**) 	95 (**10**) 	5 (**11**)	0 (**8**) 	
	22 (**17**) 	69 (**13**)		3 (**8**) 	6 (**16**)
	0 (**19**) 	93 (**13**) 	3 (**20**) 	4 (**8**) 	
X Cl Br	6 (**21a**) 0 (**21b**) 	90 (**12**) 99 (**12**) 	2 (**22**) 1 (**22**) 	2 (**8**) 0 (**8**) 	
X Cl Br	67 (**24a**) 9 (**24b**) 	28 (**14**) 88 (**14**) 	3 (**22**) 2 (**22**) 	2 (**8**) 1 (**8**) 	
	0 (**25**)	37 (**15**)	13 (**26**)	5 (**8**)	16 (**27a**)[b] 14 (**27b**)[b] 8 (**27c**)[b]

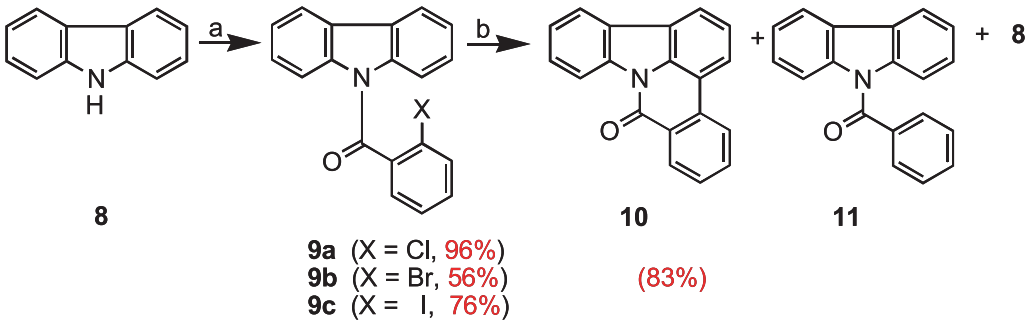
[a] Standard conditions: see Section 4.4.1.
[b] Values not calibrated.



Scheme 3. Reagents and conditions: (a) NaH, DMF, rt, then benzoyl chloride, DMAP, DMF, 120 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversion.

With this new route to **1** achieved, we extended the methodology to analogs and isomers of **1**. Our next objective was **10** (9*H*-indolo[3,2,1-*de*]phenanthridin-9-one), the carbocyclic analog of **1**. It had previously been prepared from carbazole (**8**) via Pschorr cyclization in 1% yield and from the photochemical rearrangement of 9-(2-halobenzoyl)-carbazoles in 23 and 67% yields.[11] Since the latter process paralleled the present route, we prepared three derivatives (**9a–c**) of **8** and converted them to **10** (Scheme 4). Under our standard conditions **9b** and **9c** gave high conversion rates to **10**, but **9a** was poorly reactive. In some cases, minor amounts of carbazole (**8**) and dehalogenated amide (**11**) were generated. The latter process is frequently observed in such cyclizations.[8]

The major application of this methodology was to a family



Scheme 4. Reagents and conditions: (a) NaH, DMF, rt, then 2-halobenzoyl chloride, DMAP, DMF, 65 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.

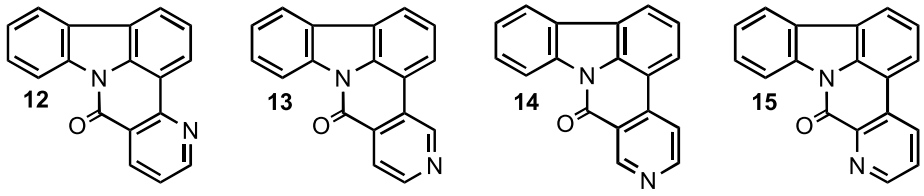


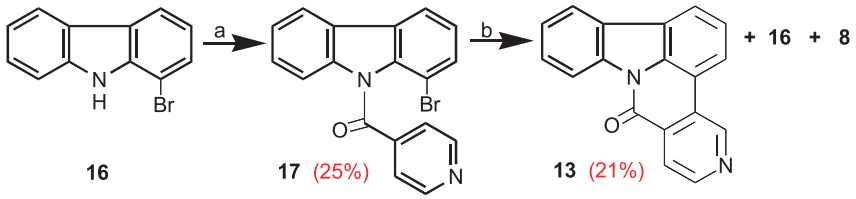
Figure 2.

of isomers **12**–**15**,[12] suitable for structure–activity relationship studies (Fig. 2). Retrosynthetically, the least complicated target was **13**, since the symmetry of the 4-pyridinyl ring E accommodated both type **B** and **C** precursors. The former route, starting from 1-bromocarbazole (**16**), afforded **13** in good yield accompanied by only minor amounts of amide-cleaved side products (Scheme 5). The product mixture contained only a single product (**13**) with *m*/*z* 270. The structure was consistent with a mechanistic process involving 6-*endo* radical cyclization. Although, a 5-*exo* route has been detected in related cyclizations,[13] in the present case such a pathway could only be operative if the spiro radical intermediate never rearranged to **14**. The alternate route to **1** via a type **C** precursor proceeded without ambiguity, starting from 3-bromo-4-pyridinecarboxylic acid (**18**) (Scheme 6).

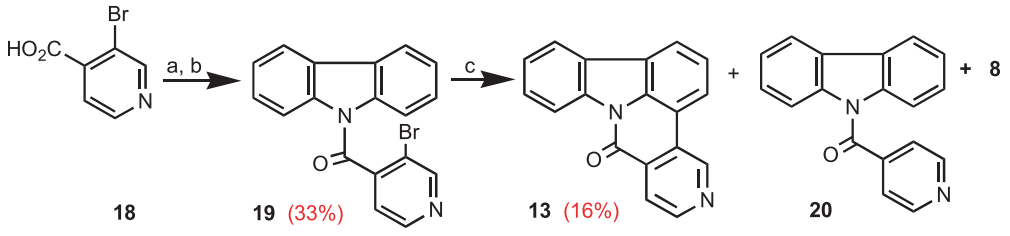
Routes to the remaining isomers (**12**, **14**, **15**) were feasible only with type **C** precursors. For **12**, amide **21a** was converted to **21b** by the method of Schlosser and Cottet.[14] Both amides were readily cyclized to **12** (Scheme 7).

The analogous route to **14** required 4-chloro-3-pyridinecarboxylic acid (**23**). It was converted to **24a** and **24b** and both precursors afforded **14** (Scheme 8).

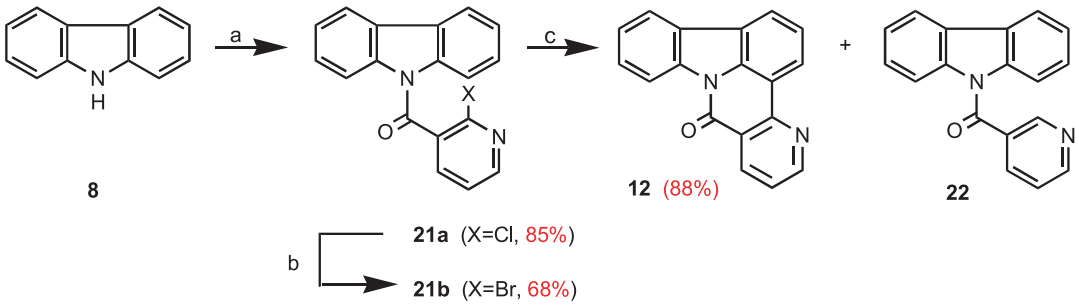
Finally, the standard protocol was utilized for the preparation of **15**. 3-Bromo-2-pyridinecarboxylic acid was



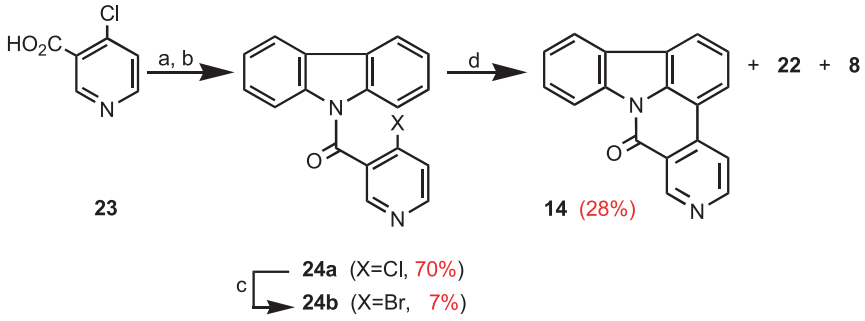
Scheme 5. Reagents and conditions: (a) NaH, DMF, rt, then 4-pyridinecarbonyl chloride, DMAP, DMF, 75 °C; (b) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



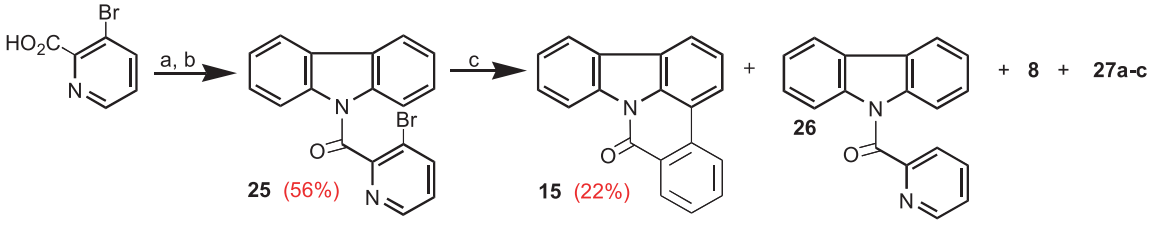
Scheme 6. Reagents and conditions: (a) $SOCl_2$, reflux; (b) **8**, NaH, DMF, rt, then DMAP, DMF, 65 °C; (c) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



Scheme 7. Reagents and conditions: (a) NaH, 15-crown-5, THF, rt, then 2-chloro-3-pyridinecarbonyl chloride, DMAP, DMF, rt; (b) Me_3SiBr, EtCN, reflux; (c) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



Scheme 8. Reagents and conditions: (a) $SOCl_2$, reflux; (b) **8**, NaH, 15-crown-5, THF, rt, then DMAP, rt; (c) Me_3SiBr, EtCN, reflux; (d) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.



Scheme 9. Reagents and conditions: (a) $SOCl_2$, reflux; (b) **8**, NaH, 15-crown-5, THF, rt, then DMAP, rt; (c) Bu_3SnH, ACN, toluene, reflux; see Table 1 for product conversions.

converted without difficulty to amide **25**, but the cyclization step afforded an appreciable amount of side products (Scheme 9). Although the side products (**27a–c**) were not isolated, by GC–MS analysis they consisted of three compounds with the same mass (*m*/*z* 362) and comparable retention times. The reduced amount of **15** (37%) and the increased amounts of **26** (13%) and **27a–c** (38%) can be attributed to the intermediate pyridinyl radical adopting a conformation, which facilitated intermolecular processes leading to **26** and **27a–c** via reaction with tributylstannane and solvent, respectively. This more reactive conformer reflected the reduction in nonbonded interaction between H(1) of the carbazole moiety and the nitrogen atom of ring E compared to all other cases in this study. It was noteworthy that in none of the other five cyclizations was a side product observed with *m*/*z* 362. The isomeric **27a–c** were considered to have resulted from radical pyridinylation of toluene.

3. Conclusion

A short route to a series of isomeric benzocanthinones has been developed. In each case, the key step was an intramolecular, radical-induced, oxidative cyclization. The best reactivities were obtained when the halogen substituent (Br > Cl) was alpha to a pyridinyl nitrogen or a carbonyl group. The conversations, except for **15**, were good to excellent; the isolated yields were poor to good.

4. Experimental

4.1. General procedures

Melting points were taken on a modified Hershberg apparatus with matched Anschütz thermometers and are uncorrected. NMR spectra were measured in $CDCl_3$ on a Bruker Avance DRX 500 spectrometer with a Hewlett Packard (HP) ×1100 Workstation running under XWINMR version 3.5; chemical shifts are reported in ppm downfield relative to internal tetramethylsilane, and coupling constants are reported in hertz (Hz). GC–MS analyses were performed on a HP 6890 gas chromatography system with a HP-5MS crosslinked diphenyl(5%) dimethyl(95%)polysiloxane capillary column (30 m × 0.25 mm × 0.25 μm film), a 5973 mass selective detector,

and a HP Kayak XA computer. FT-IR spectra were recorded on a Perkin Elmer Spectrum One spectrophotometer with a Dell Optiplex GX1 computer. HRMS analyses were performed by the Nebraska Center for Mass Spectrometry at the University of Nebraska-Lincoln. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Liquid injections were made with a KD Scientific 100 Series syringe pump. Tetrahydrofuran (THF) and toluene were purified by the method of Grubbs and co-workers;[15] dimethylformamide (DMF, 99.8%) was sparged with argon for 3 h and stored over 4A molecular sieves. Products were purified by recrystallization or by medium-pressure liquid chromatography with silica gel as stationary phase and hexanes–ethyl acetate as mobile phase; all compounds were determined to be >98% pure by capillary GLC and ^{1}H NMR spectroscopy.

4.2. Starting materials

Compounds **3**,[7] **9ac**,[11] **11**,[11] **16**,[16] **18**,[17] and **24**[18] were prepared by literature procedures; their physical and spectral data matched the reported values. 3-Bromo-2-pyridinecarboxylic acid was a gift from Aventis Pharmaceutical Co. All other chemicals used in this study were commercially available.

4.3. Typical procedures for the preparation of amides

4.3.1. 9-Benzoyl-1-chloro-β-carboline (7). Method A. To a stirred solution of 1-chloro-β-carboline (**3**)[7] (1.317 g, 6.50 mmol) in DMF (100 mL) under argon was added sodium hydride (0.432 g of 60% dispersion in mineral oil; 0.259 g, 10.6 mmol). The slurry was stirred at room temperature for 20 min and to it was added dropwise a solution of benzoyl chloride (1.096 g, 7.80 mmol) and 4-dimethylaminopyridine (DMAP) (0.079 g, 0.65 mmol) in DMF (25 mL). The reaction mixture was stirred at 70 °C for 15 h, concentrated at reduced pressure, diluted with water (150 mL), neutralized with saturated aqueous sodium bicarbonate, and extracted with chloroform. The combined extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure to give a viscous, residual liquid (1.81 g, 91%), which was crystallized to give the analytical sample of **5a**: mp 137.0–138.0 °C (2-propanol); IR (film) 1699 cm^{-1}; ^{1}H NMR δ 8.40 (1H, d, J=5.0 Hz), 8.10 (1H, dd, J=8.0, 0.6 Hz), 7.94 (1H, d, J=5.0 Hz), 7.85 (2H, dd, J=8.0, 1.2 Hz), 7.70 (1H, t, J=7.5 Hz), 7.56–7.47 (3H, m), 7.44–7.37 (2H, m); ^{13}C NMR δ 168.6, 142.1, 141.2, 137.1, 135.0, 134.8, 134.3, 133.5, 130.3, 129.9, 129.2, 123.3, 122.9, 121.7, 113.9, 113.8; MS (*m*/*z*) 308 (M$^+$ ^{37}Cl, 8%), 306 (M$^+$ ^{35}Cl, 24), 105 (100), 77 (37). Calcd for $C_{18}H_{11}Cl\cdot N_2O$: C, 70.48; H, 3.62; N, 9.13. Found: C, 69.79; H, 3.77; N; 9.03.

4.3.2. 9-(2-Chlorobenzoyl)-β-carboline (5a). Colorless solid (0.286 g, 96%): mp 157.0–158.0 °C; IR (film) 1686 cm^{-1}; ^{1}H NMR δ 8.73 (1H, br s), 8.60 (1H, d, J=5.0 Hz), 8.07 (1H, dd, J=10.0, 1.0 Hz), 7.90 (1H, dd, J=5.0, 1.0 Hz), 7.62–7.55 (3H, m), 7.54–7.43 (4H, m); ^{13}C NMR δ 166.1, 144.1, 139.1, 135.7, 135.1, 132.9, 132.4, 131.3, 130.7, 130.0, 128.8, 127.9, 124.6, 121.3, 114.2; MS (*m*/*z*) 308 (M$^+$ ^{37}Cl, 6%), 306 (M$^+$ ^{35}Cl, 18), 141 (34), 139 (100), 111 (25). HRMS for $C_{18}H_{12}Cl\cdot N_2O$ [M+H]$^+$ requires: 307.0638. Found: 307.0642.

4.3.3. 9-(2-Bromobenzoyl)-β-carboline (5b). Pale yellow solid (0.254 g, 71%): mp 139.4–140.0 °C; IR (film) 1685 cm^{-1}; ^{1}H NMR δ 8.61 (1H, s), 8.07 (1H, d, J=8.0 Hz), 7.91 (1H, d, J=4.0 Hz), 7.74 (1H, d, J=8.0 Hz), 7.57 (1H, d, J=4.0 Hz), 7.55–7.51 (4H, m), 7.50–7.43 (3H, m); ^{13}C NMR δ 166.8, 144.0, 139.0, 137.8, 133.8, 132.9, 132.5, 130.1, 128.8, 128.5, 124.6, 121.3, 119.7, 116.3; MS (*m*/*z*) 352 (M$^+$ ^{81}Br, 13%), 350 (M$^+$ ^{79}Br, 13), 185 (99), 183 (100), 157 (23), 155 (24). HRMS for $C_{18}H_{12}Br\cdot N_2O$ [M+H]$^+$ requires: 351.0133. Found: 351.0141.

4.3.4. 9-(2-Iodobenzoyl)-β-carboline (5c). Colorless solid (0.125 g, 76%): mp 135.8–137.0 °C; IR (film) 1684 cm^{-1}; ^{1}H NMR δ 8.68 (1H, br s), 8.59 (1H, d, J=5.0 Hz), 8.04 (1H, d, J=8.0 Hz), 7.96 (1H, d, J=8.0 Hz), 7.87 (1H, d, J=5.0 Hz), 7.58 (1H, t, J=7.4 Hz), 7.53–7.40 (3H, m), 7.32 (1H, t, J=7.7 Hz); ^{13}C NMR δ 168.3, 144.1, 141.7, 140.2, 139.1, 138.0, 135.1, 132.9, 132.3, 130.0, 129.1, 128.5, 124.7, 124.6, 121.3, 116.4, 114.2; MS (*m*/*z*) 398 (M$^+$, 13%), 231 (100), 203 (22). HRMS for $C_{18}H_{12}I\cdot N_2O$ [M+H]$^+$ requires: 398.9994. Found: 398.9981.

4.3.5. 1-Bromo-9-(4-pyridinecarbonyl)-carbazole (17). Pale yellow solid (0.050 g, 25%): mp 129.0–130.5 °C; IR (film) 1697 cm^{-1}; ^{1}H NMR δ 8.81 (2H, d, J=3.9 Hz), 8.03 (2H, m), 7.58 (3H, m), 7.40 (3H, m), 7.29 (1H, m); ^{13}C NMR δ 167.9, 151.1, 151.0, 142.8, 140.3, 138.4, 131.7, 129.1, 127.9, 125.1, 125.0, 123.7, 122.8, 120.6, 120.5, 119.3, 113.4, 108.7; MS *m*/*z* 352 (M$^+$ ^{81}Br, 41%), 350 (M$^+$ ^{79}Br, 43), 165 (21), 164 (22), 106 (100), 78 (33). Calcd for $C_{18}H_{11}Br\cdot N_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 61.50; H, 3.39; N, 7.90.

4.3.6. 9-(3-Bromo-4-pyridinecarbonyl)-carbazole (19). Tan solid (0.175 g, 33%): mp 125.5–126.0 °C; IR (film) 1678 cm^{-1}; ^{1}H NMR δ 8.94 (1H, s), 8.79 (1H, d, J=4.2 Hz), 8.00 (2H, d, J=7.8 Hz), 7.47 (1H, d, J=4.2 Hz), 7.44–7.27 (6H, m); ^{13}C δ 164.7, 153.2, 149.3, 145.4, 138.2, 127.6, 127.0, 124.8, 122.5, 120.1, 115.8; MS *m*/*z* 352 (M$^+$ ^{81}Br, 64%), 350 (M$^+$ ^{79}Br, 67), 271 (60), 186 (88), 184 (100), 166 (25), 158 (26), 140 (28). Calcd for $C_{18}H_{11}Br\cdot N_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 62.02; H, 3.44; N, 7.86.

4.3.7. 9-(2-Bromobenzoyl)-carbazole (9b). Method B. To a stirred slurry of sodium hydride (0.084 g of a 60% dispersion in mineral oil; 0.0504 g, 2.10 mmol) in THF (20 mL) under argon were added a solution of carbazole (0.334 g, 2.00 mmol) and 15-crown-5 (0.463 g, 2.10 mmol) in THF (8 mL). The slurry was stirred at room temperature for 30 min and to it was added dropwise a solution of 2-bromobenzoyl chloride (0.483 g, 2.20 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 17 h, concentrated at reduced pressure, diluted with brine (20 mL), neutralized with saturated aqueous sodium bicarbonate, and extracted with dicloromethane. The combined extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure to give an orange solid, which was recrystallized to give **9b** (0.394 g, 56%): mp 102.5–103.0 °C (95% ethanol);

IR (KBr) 1678 cm^{-1}; ^1H NMR δ 8.01–8.00 (1H, m), 7.99–7.97 (1H, m), 7.73 (1H, dm, $J=7.6$ Hz), 7.55–7.45 (4H, m), 7.41–7.29 (5H, m); ^{13}C NMR δ 167.2, 138.5, 138.4, 133.6, 132.0, 128.8, 128.2, 127.3, 126.7, 124.2, 119.8, 115.9; MS *m/z* 351 (M^+ ^{81}Br, 30%), 349 (M^+ ^{79}Br, 29), 185 (94), 183 (100), 157 (27), 155 (29), 140 (21). Calcd for $C_{19}H_{12}Br{\cdot}NO$: C, 65.16; H, 3.45; N, 4.00. Found: C, 64.88; H, 3.68; N. 4.08.

4.3.8. 9-(4-Pyridinecarbonyl)-carbazole (20). Colorless solid (0.052 g, 21%): mp 184.5–185.0 °C; IR (film) 1679 cm^{-1}; ^1H δ 8.85 (2H, d, $J=5.0$ Hz), 7.98 (2H, d, $J=7.0$ Hz), 7.54 (2H, d, $J=5.0$ Hz), 7.49 (2H, d, $J=8.0$ Hz), 7.37 (2H, t, $J=7.0$ Hz), 7.32 (2H, d, $J=8.0$ Hz); ^{13}C δ 167.4, 151.1, 143.4, 138.7, 127.3, 126.6, 124.3, 122.3, 120.2, 116.0; MS *m/z* 272 (M^+48%), 106 (100), 78 (50). HRMS for $C_{18}H_{13}N_2O$ $[M+H]^+$ requires: 273.1028. Found: 273.1018.

4.3.9. 9-(2-Chloro-3-pyridinecarbonyl)-carbazole (21a). Tan solid (0.987 g, 85%): mp 129.0–131.0 °C; IR (film) 1677 cm^{-1}; ^1H δ 8.67 (1H, dd, $J=5.0$, 2.0 Hz), 8.03–7.97 (2H, m), 7.90 (1H, dd, $J=7.6$, 2.0 Hz), 7.53–7.45 (2H, m), 7.44–7.30 (4H, m); ^{13}C NMR δ 164.7, 151.5, 147.9, 138.2, 137.8, 132.9, 127.5, 126.8, 124.5, 123.0, 120.0, 115.6; MS *m/z* 308 (M^+ ^{37}Cl, 7%), 306 (M^+ ^{35}Cl, 19), 142 (28), 140 (100), 112 (34). Calcd for $C_{18}H_{11}Cl{\cdot}N_2O$: C, 70.48; H, 3.62; N, 9.13. Found: C, 70.26; H, 3.67; N, 9.04.

4.3.10. 9-(2-Bromo-3-pyridinecarbonyl)-carbazole (21b). Prepared from **21a** by the method of Schlosser and Cottet.[14] Tan solid (0.238 g, 68%): mp 143.5–144.5 °C; IR (film) 1686 cm^{-1}; ^1H NMR δ 8.63 (1H, dd, $J=5.0$, 2.0 Hz), 8.00 (2H, d, $J=7.0$ Hz), 7.83 (1H, dd, $J=7.0$, 2.0 Hz), 7.51 (1H, dd, $J=7.0$, 5.0 Hz), 7.40 (2H, t, $J=8.0$ Hz), 7.34 (2H, t, $J=7.0$ Hz); ^{13}C NMR δ 165.3, 151.9, 139.2, 138.5, 137.5, 135.9, 127.7, 127.0, 124.8, 123.4, 120.2, 116.0; MS *m/z* 352 ($M^+$$^{81}Br$, 53%), 350 ($M^+$ ^{79}Br, 54), 186 (96), 184 (100), 158 (29), 156 (30). Calcd for $C_{18}H_{11}Br{\cdot}N_2O$: C, 61.56; H, 3.16; N, 7.98. Found: C, 60.91; H, 3.34; N, 7.90.

4.3.11. 9-(3-Pyridinecarbonyl)-carbazole (22). Colorless solid (0.054 g, 22%): mp 126.0–126.5 °C; IR (film) 1676 cm^{-1}; ^1H NMR δ 8.94 (1H, s), 8.88 (1H, d, $J=5.0$ Hz), 8.05–7.99 (3H, m), 7.54–7.45 (3H, m), 7.40–7.32 (4H, m); ^{13}C NMR δ 167.5, 153.2, 150.2, 139.0, 136.8, 131.9, 127.2, 126.5, 124.1, 123.8, 120.3, 115.9; MS *m/z* 272 (M^+46%), 106 (100), 78 (45). HRMS for $C_{18}H_{13}N_2O$ $[M+H]^+$ requires: 273.1028. Found: 273.1033.

4.3.12. 9-(4-Chloro-3-pyridinecarbonyl)-carbazole (24a). Tan solid (0.147 g, 70%): mp 130.5–131.5 °C; IR (film) 1676 cm^{-1}; ^1H NMR δ 8.76 (1H, s), 8.73 (1H, d, $J=5.0$ Hz), 7.95 (2H, d, $J=8.0$ Hz), 7.48 (1H, d, $J=7.0$ Hz), 7.38–7.30 (5H, m); ^{13}C NMR δ 164.1, 152.4, 149.6, 141.6, 138.3, 132.7, 127.6, 126.8, 125.3, 124.7, 120.2, 115.6; MS *m/z* 308 (M^+ ^{37}Cl, 19%), 306 (M^+ ^{35}Cl, 54), 142 (30), 140 (100), 112 (26). HRMS for $C_{18}H_{12}Cl{\cdot}N_2O$ $[M+H]^+$ requires: 307.0638. Found: 307.0624.

4.3.13. 9-(4-Bromo-3-pyridinecarbonyl)-carbazole (24b). Prepared from **24a** by the method Schlosser and Cottet.[14] Tan solid (0.011 g, 6.9%): mp 143.0–144.0 °C; IR (film) 1670 cm^{-1}; ^1H NMR δ 8.73 (1H, s), 8.66 (1H, d, $J=5.0$ Hz), 8.01 (2H, d, $J=7.0$ Hz), 7.71 (1H, d, $J=6.0$ Hz), 7.58–7.43 (1H, m), 7.40 (2H, t, $J=7.0$ Hz), 7.34 (2H, t, $J=7.0$ Hz); ^{13}C NMR 165.1, 152.1, 149.3, 138.5, 135.2, 130.9, 128.6, 127.7, 127.0, 124.8, 120.3, 115.9; MS *m/z* 352 (M^+ ^{81}Br, 98%), 350 (M^+ ^{79}Br, 97), 186 (98), 184 (00), 166 (31), 158 (88), 156 (90), 140 (38). HRMS for $C_{18}H_{12}Br{\cdot}N_2O$ $[M+H]^+$ requires: 351.0133. Found: 351. 0143.

4.3.14. 9-(3-Bromo-2-pyridinecarbonyl)-carbazole (25). Colorless solid (0.301 g, 56%): mp 142.5–143.0 °C; IR (film) 1683 cm^{-1}; ^1H NMR δ 8.71 (1H, d, $J=5.0$ Hz), 8.09 (1H, d, $J=8.0$ Hz), 7.98 (2H, d, $J=8.0$ Hz), 7.44 (1H, dd, $J=8.0$, 5.0 Hz), 7.38 (2H, t, $J=8.0$ Hz), 7.32 (2H, t, $J=8.0$ Hz); ^{13}C NMR δ 165.4, 154.0, 148.7, 141.5, 138.4, 127.5, 127.0, 126.5, 124.5, 120.1, 118.0, 115.9; MS *m/z* 352 (M^+ ^{81}Br, 90%), 350 (M^+ ^{79}Br, 88), 186 (98), 184 (100), 166 (31), 158 (88), 156 (90), 140 (38). HRMS for $C_{18}H_{12}Br{\cdot}N_2O$ $[M+H]^+$ requires: 351.0133. Found: 351. 0136.

4.3.15. 9-(2-Pyridinecarbonyl)-carbazole (26). Colorless solid (0.145 g, 59%): mp 132.0–132.5 °C; IR (film) 1681 cm^{-1}; ^1H NMR δ 8.71 (1H, d, $J=4.0$ Hz), 8.00–7.95 (3H, m), 7.87 (1H, d, $J=8.0$ Hz), 7.56 (1H, dd, $J=7.0$, 4.0 Hz), 7.38–7.28 (6H, m); ^{13}C NMR δ 168.0, 153.7, 149.9, 139.1, 137.8, 127.0, 126.7, 126.5, 124.3, 124.0, 120.0, 116.1; MS *m/z* 272 (M^+100%), 271 (76), 106 (51), 78 (99). HRMS for $C_{18}H_{13}N_2O$ $[M+H]^+$ requires: 273.1028. Found: 273.1033.

4.4. Typical procedure for cyclization

The procedure reported below was used in all cases. Composition of the crude product mixtures was determined by GC–MS analysis. Detector responses were calibrated with independently prepared samples of all observed products; the percent conversions in Table 1 reflect the normalized values. The reaction conditions were optimized. Product yields were not optimized, since the hexane trituration step to remove tin-containing compounds partially dissolved the desired products.

4.4.1. 9*H*-Benzo[*c*]indolo[3,2,1-*ij*][1,5]naphthyridin-9-one (1). Under an argon atmosphere a solution of tributyltin hydride (0.350 mL, 0.378 g, 0.130 mmol) and azobis-(cyclohexanenitrile) (ACN) (0.244 g, 0.100 mmol) in toluene (5 mL) was added over 1 h via syringe pump to a stirred, refluxing solution of 9-benzoyl-1-chloro-β-carboline (**7**) (0.0306 g, 0.100 mmol) in toluene (50 mL). The reaction solution was stirred at reflux for an additional 2.5 h, and the solvent was removed at reduced pressure. The crude product mixture was analyzed by GC–MS and then triturated with hexanes. The remaining solid was collected, washed, and dried to give **1** (0.020 g, 74%): mp 227.5–229.5 °C [lit.[3] mp 226–227 °C]; IR (film) 1682 cm^{-1}; ^1H NMR δ 8.87 (1H, d, $J=5.0$ Hz), 8.86–8.81 (2H, m), 8.67 (1H, dd, $J=7.5$, 1.0 Hz), 8.16 (1H, d, $J=7.5$ Hz), 7.98 (1H, d, $J=5.0$ Hz), 7.93 (1H, td, $J=7.5$, 1.0 Hz), 7.79–7.73 (2H, m), 7.56 (1H, td, $J=7.5$, 1.0 Hz); ^{13}C NMR δ 159.5, 145.0, 139.3, 136.0, 134.8, 133.6, 130.7, 130.6, 130.4, 130.0, 129.4, 129.2, 125.4, 124.9, 122.5, 117.5, 115.2; MS *m/z* 270 (M^+100%).

4.4.2. 9*H*-Indolo[3,2,1-*de*]phenanthridin-9-one (10). Colorless solid (0.056 g, 83% from **5c**): mp 229.5–230.0 °C ($CHCl_3$–pet. ether) [lit.[11b] mp 227 °C]; IR (film) 1666 cm^{-1}; ^1H NMR δ 8.83 (1H, d, J=8.0 Hz), 8.68 (1H, d, J=7.7 Hz), 8.30 (1H, d, J=8.0 Hz), 8.15 (1H, d, J=7.7 Hz), 8.07–8.03 (2H, m), 7.81 (1H, t, J=7.0 Hz), 7.67–7.54 (3H, m), 7.49 (1H, t, J=7.4 Hz); ^{13}C NMR δ 160.1, 138.6, 134.2, 133.8, 133.0, 129.3, 128.3, 128.1, 127.8, 126.4, 125.0, 124.5, 124.1, 122.5, 121.0, 120.8, 120.3, 117.3, 117.2; MS *m/z* 269 (M^+100%).

4.4.3. 8*H*-[1,6]Naphthyridino[8,7,6-*jk*]carbazol-8-one (12). Yellow solid (0.057 g, 88%): mp 196.0–196.5 °C; IR (film) 1685 cm^{-1}; ^1H NMR δ 9.04 (1H, dd, J=4.6, 2.0 Hz), 8.89 (1H, dd, J=8.0, 2.0 Hz), 8.77 (1H, dt, J=8.0, 1.0 Hz), 8.58 (1H, dd, J=8.0, 1.0 Hz), 8.15 (1H, d, J=1.0 Hz), 8.13 (1H, d, J=1.0 Hz), 8.09–8.05 (1H, m), 7.67–7.47 (4H, m); ^{13}C NMR δ 159.6, 153.9, 151.1, 138.2, 137.2, 135.4, 128.2, 126.6, 125.4, 124.6, 124.2, 123.7, 123.1, 122.8, 122.3, 121.0, 118.2, 117.3; MS *m/z* 270 (M^+100%). HRMS for $C_{18}H_{11}N_2O$ $[M+H]^+$ requires: 271.0871. Found: 271.0861.

4.4.4. 8*H*-[2,6]Naphthyridino[4,3,2-*jk*]carbazol-8-one (13). Pale yellow solid (0.022 g, 16%): mp 249.5–250.0 °C; IR (film) 1677 cm^{-1}; ^1H NMR δ 9.77 (1H, s), 8.94 (1H, d, J=5.2 Hz), 8.84 (1H, d, J=8.0 Hz), 8.48 (1H, d, J=5.2 Hz), 8.34 (1H, d, J=8.0 Hz), 8.18 (1H, d, J=7.6 Hz), 8.13 (1H, d, J=7.5 Hz), 7.67 (2H, m), 7.56 (1H, d, J=7.5 Hz); ^{13}C NMR δ 149.0, 146.2, 138.5, 128.5, 126.6, 125.7, 124.9, 124.8, 122.0, 121.5, 121.0, 120.2, 117.5, 115.2; MS *m/z* 270 (M^+100%). Calcd for $C_{18}H_{10}N_2O$: C, 79.99; H, 3.73; N, 10.36. Found: C, 79.61; H, 3.80; N, 10.11.

4.4.5. 8*H*-[2,7]Naphthyridino[4,3,2-*jk*]carbazol-8-one (14). Colorless solid (0.035 g, 28%): mp 274.0–275.0 °C; IR (film) 1674 cm^{-1}; ^1H NMR δ 9.87 (1H, s), 8.97 (1H, d, J=2.0 Hz), 8.82 (1H, d, J=8.0 Hz), 8.21 (2H, t, J=7.0 Hz), 8.14–8.08 (2H, m), 7.65 (2H, t, J=8.0 Hz), 7.54 (1H, t, J=7.0 Hz); ^{13}C NMR δ 159.4, 152.8, 152.4, 140.6, 138.6, 135.7, 128.8, 126.3, 125.6, 125.2, 124.7, 123.6, 122.7, 121.4, 121.7, 117.6, 116.2, 115.3; MS *m/z* 270 (M^+100%), 242 (16). HRMS for $C_{18}H_{11}N_2O$ $[M^++H]$ requires: 271.0871. Found: 271.0864.

4.4.6. 8*H*-[1,7]Naphthyridino[5,6,7-*jk*]carbazol-8-one (15). Colorless solid (0.025 g, 22%): mp 252.0–255.0 °C with decomp.; IR (film) 1686 cm^{-1}; ^1H NMR δ 8.96 (1H, s), 8.81 (1H, d, J=8.5 Hz), 8.48 (1H, d, J=8.0 Hz), 7.93 (3H, q, J=7.0 Hz), 7.66 (1H, s), 7.58 (1H, t, J=8.0 Hz), 7.45 (2H, q, J=7.0 Hz); ^{13}C NMR δ 158.1, 150.5, 143.8, 138.5, 133.6, 131.0, 130.3, 128.4, 126.8, 126.1, 125.4, 124.5, 124.3, 122.0, 121.0, 120.4, 117.8, 115.1; MS *m/z* 270 (M^+100%), 242 (38), 121 (20). HRMS for $C_{18}H_{11}N_2O$ $[M^++H]$ requires: 271.0871. Found: 271.0859.

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A highly fluorescent water-soluble boronic acid reporter for saccharide sensing that shows ratiometric UV changes and significant fluorescence changes

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Abstract—One water-soluble naphthalene-based fluorescent boronic acid, 6-(dimethylamino)-naphthalene-2-boronic acid (6-DMANBA, **1**), has been synthesized. 6-DMANBA shows significant ratiometric UV absorbance changes upon addition of a sugar. For example, addition of 50 mM fructose shifted the UV absorption wavelengths of 6-DMANBA from 306 and 251 to 280 and 244 nm, respectively. In addition, 6-DMANBA is highly fluorescent with a quantum yield of 89% in the absence of a sugar and shows significant fluorescence intensity changes with the addition of a saccharide in aqueous phosphate buffer at physiological pH. For example, with the addition of 50 mM fructose, 6-DMANBA shows an 80% fluorescent intensity decrease at 432 nm. All these spectroscopic properties make compound **1** unique and useful.

1. Introduction

Fluorescent sensors that can selectively recognize various biologically important ions and compounds are very useful for a wide range of applications.[1] This field typically has two major directions: sensors for metal ions and for organic compounds. Recent years have seen a major surge in interest in developing sensors for biologically important organic compounds such as neurotransmitters,[2] amino acids,[3] nucleic acids,[4] and carbohydrates.[5] Among these activities, the carbohydrate sensing and recognition field is especially active. In the design and synthesis of carbohydrate sensors for application in aqueous solution, the boronic acid functional group is quite often used as the key recognition moiety because of its strong and reversible interactions with 1,2- or 1,3-diols to form five- or six-membered rings, respectively.[6] Our laboratory[7] and other research groups[8] have been actively pursuing fluorescent carbohydrate sensors based on boronic acid.

Recently, our laboratory has demonstrated that boronic acid-based saccharide sensors can be used for the recognition of cancer-related mammalian cell surface saccharide biomarkers.[9a,b] Other laboratories such as those of Hageman,[8r] Smith,[9c,d] and Houston,[9e,f] have also reported using boronic acids as a way to enhance cell affinity and/or fusion. We termed these boronic acid-based carbohydrate sensors as fluorescent boronolectins because of their similarity in functions with lectins.[10] Because saccharide biomarkers[11] are implicated in various physiological and pathological processes including cancer,[12] immune responses,[13] and viral and bacterial infection,[14] such boronolectins have a wide variety of potential applications in the diagnosis, detection, and therapeutic intervention of human diseases.[12,15] Critical to our effort in developing fluorescent boronolectins is the availability of reporter compounds that change fluorescent properties upon binding.[8a,b,e,f,16–17] In our continuing work in this area, we are interested in developing a combinatorial approach for the synthesis of fluorescent boronolectins selective for various biologically important carbohydrates and for multiplex sensing. For this effort and increased diversity of the combinatorial libraries, we are in need of a large number of boronic acid-based fluorescent reporter compounds that are (1) water soluble and (2) chemically and photochemically stable.[16,17]

Herein we describe the synthesis and evaluation of one highly fluorescent boronic acid, 6-(dimethylamino)-naphthalene-2-boronic acid (6-DMANBA, **1**, Fig. 1), which shows ratiometric UV property changes and significant fluorescence changes upon sugar binding. This

Keywords: Boronic acid; Fluorescent sensor; Carbohydrate; Ratiometric UV; Boronolectin.
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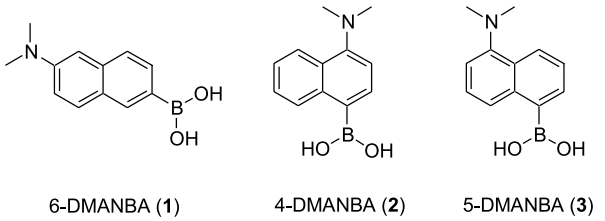


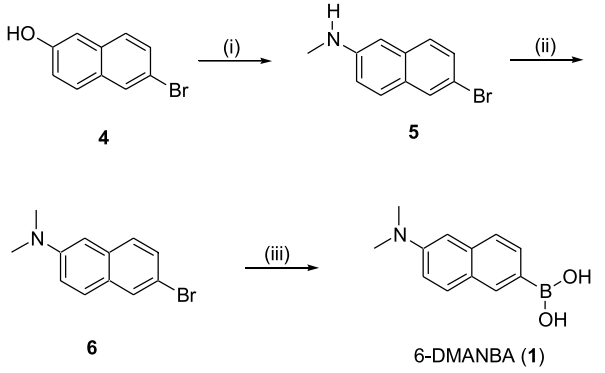
Figure 1. Structure of naphthalene-based boronic acids.

boronic acid reporter will be useful for the combinatorial synthesis of boronolectins.

2. Results and discussions

2.1. Synthesis

The synthesis of 6-(dimethylamino)-naphthalene-2-boronic acid (6-DMANBA, **1**) is shown in Scheme 1. The intermediate, compound **5**, was synthesized from the commercially available **4** by substitution of the hydroxyl group with methylamine following a literature procedure.[18] Reaction of **5** with methyl iodide in the presence of NaH in THF at 60 °C gave 6-bromo-2-(dimethylamino)-naphthalene (**6**). 6-DMANBA (**1**) was synthesized from **6** through lithiation and reaction with trimethylborate. Purification of the crude product by silica gel chromatography afforded **1** as a white powder in 64% yield.



Scheme 1. Synthesis of 6-DMANBA (**1**): (i) CH_3NH_2, $Na_2S_2O_5$, 140 °C, 77%; (ii) CH_3I, NaH, 60 °C, 84%; (iii) *n*-BuLi, $(MeO)_3B$, HCl, 64%.

2.2. UV absorbance properties of 6-DMANBA (1)

The effect of carbohydrates on the UV absorbance property of 6-DMANBA (**1**) was studied. 6-DMANBA (**1**) showed two absorbance maxima at 306 and 251 nm, respectively, in 0.1 M aqueous phosphate buffer at pH 7.4. Addition of a carbohydrate resulted in a significant absorbance change of compound **1**. For example, with the addition of 50 mM fructose, compound **1** shifted its UV λ_{max} from 306 and 251 to 280 and 244 nm, respectively (Fig. 2A). The two isosbestic points for the 306/280 nm and 251/244 nm shifts were observed at 288 and 250 nm, respectively. In addition, there is another isosbestic point at 271 nm.

Significant ratiometric absorbance changes of compound **1** were observed at four wavelengths upon addition of a sugar (Fig. 2A and B). For example, the ratio of the absorbance at 280 nm to that at 306 nm was 0.56:1 before addition of a sugar and 2.7:1 after addition of 50 mM fructose. This is a 4.8-fold change. In addition, the ratio of the absorbance at 244 nm to that at 251 nm changed from 0.87:1 before addition of a sugar to 1.1:1 after addition of 50 mM fructose. Other carbohydrates (galactose and glucose) also exhibited significant changes in this ratio at different concentrations (Fig. 2B). Therefore, compound **1** can be used as a ratiometric UV sensor for carbohydrates.

The effect of carbohydrates on the UV absorbance property of 4-DMANBA (**2**) and 5-DMANBA (**3**) was also studied in a fashion similar to that of 6-DMANBA (**1**), and no similar changes were observed (Fig. 2C and D).

We also studied the pH induced UV spectral changes of **1**. Figure 3A and B show the results in the absence of a sugar in the pH range of 2.00–7.40 and 7.40–11.00, respectively. When the pH was increased from 2.00 to 7.40, the absorbance of **1** at 251 and 306 increased significantly with an absorbance decrease at 230 nm (Fig. 3A). When the pH was further increased from 7.40 to 11.00, the absorbance at 306 and 251 nm decreased significantly with a significant absorbance increase at another two wavelengths, 280 and 244 nm, respectively (Fig. 3B). It is well known that the increase of pH from 7.40 to 11.00 can change the boronic acid moiety from its neutral trigonal form to the anionic tetrahedral form. These results indicate that the neutral trigonal form of **1** has absorbance maxima of 306 and 251 nm, while the anionic tetrahedral form has absorbance maxima of 280 and 244 nm. The absorbance changes of **1** with increasing pH from 7.40 to 11.00 are very similar to the absorbance changes of **1** induced by addition of a sugar.

The pH induced UV absorbance property changes of 4-DMANBA (**2**) and 5-DMANBA (**3**) were also studied in a fashion similar to that of 6-DMANBA (**1**). Although significant UV absorbance changes were observed for **2** and **3** when pH increased from 3.00 to 7.40, no significant absorbance changes were observed for them when pH increased from 7.40 to 11.00 (Fig. 3C and D).

2.3. Fluorescent properties of 6-DMANBA (1)

The fluorescence properties of 6-DMANBA (**1**) was studied in neutral aqueous solution (0.1 M aqueous phosphate buffer, pH 7.4). Under such condition, compound **1** shows emission maximum of 432 nm with a quantum yield of 89% (8-quinoline boronic acid was used as the reference compound[19]). This is the highest quantum yield so far among all the water-soluble fluorescent boronic reporter compounds discovered in our laboratory.[16,17]

Since compound **1** shows unique UV changes upon addition of a sugar and different excitation wavelengths would induce different emission changes upon addition of a sugar, we first searched for the optimal excitation wavelength for its fluorescence studies using fructose as a model sugar. Table 1 shows the fluorescence intensity changes of **1** at the emission wavelength of 432 nm with different excitation wavelengths upon addition of 50 mM fructose. The emission intensity changes of **1** with an excitation

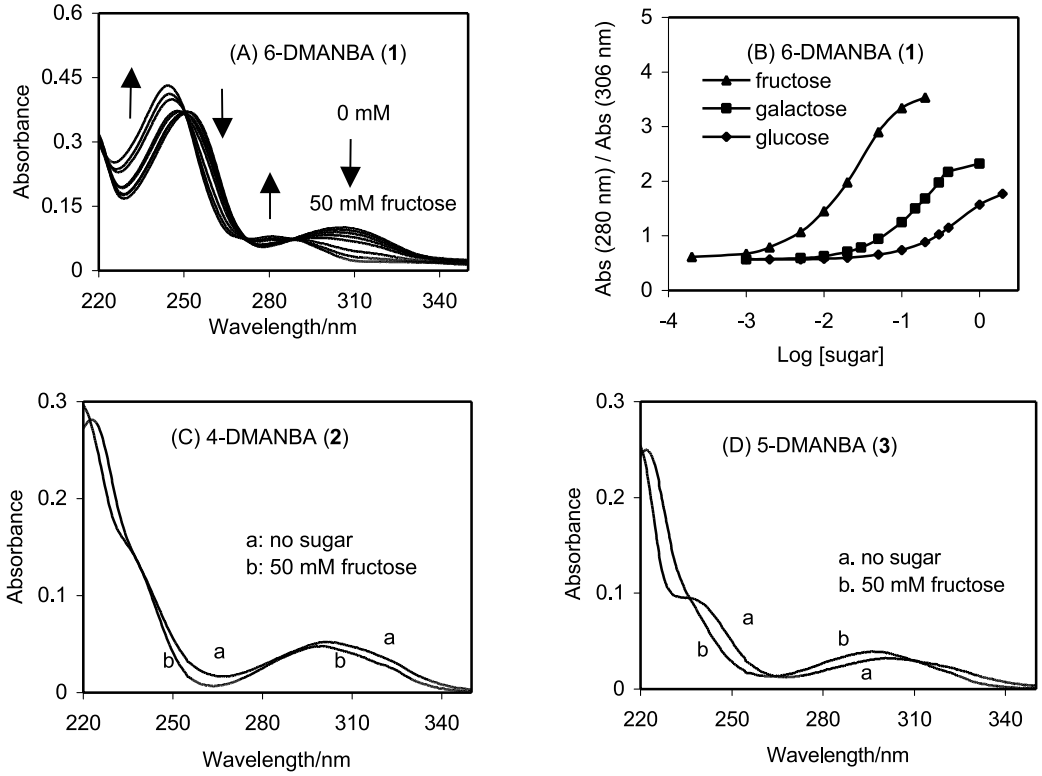


Figure 2. UV absorbance changes of **1**, **2**, and **3** upon addition of a sugar in 0.1 M aqueous phosphate buffer at pH 7.4. (A) UV absorbance spectral changes of 6-DMANBA (**1**) (1.0×10^{-5} M) with different concentrations of D-fructose (0–50 mM). (B) Absorbance ratiometric changes (Abs (280 nm)/Abs (306 nm)) of 6-DMANBA (**1**) (1.0×10^{-5} M) as a function of sugar concentrations. (C) UV absorbance spectral changes of 4-DMANBA (**2**, 1.0×10^{-5} M) in the absence and presence of 50 mM D-fructose. (D) UV absorbance spectral changes of 5-DMANBA (**3**, 1.0×10^{-5} M) in the absence and presence of 50 mM D-fructose.

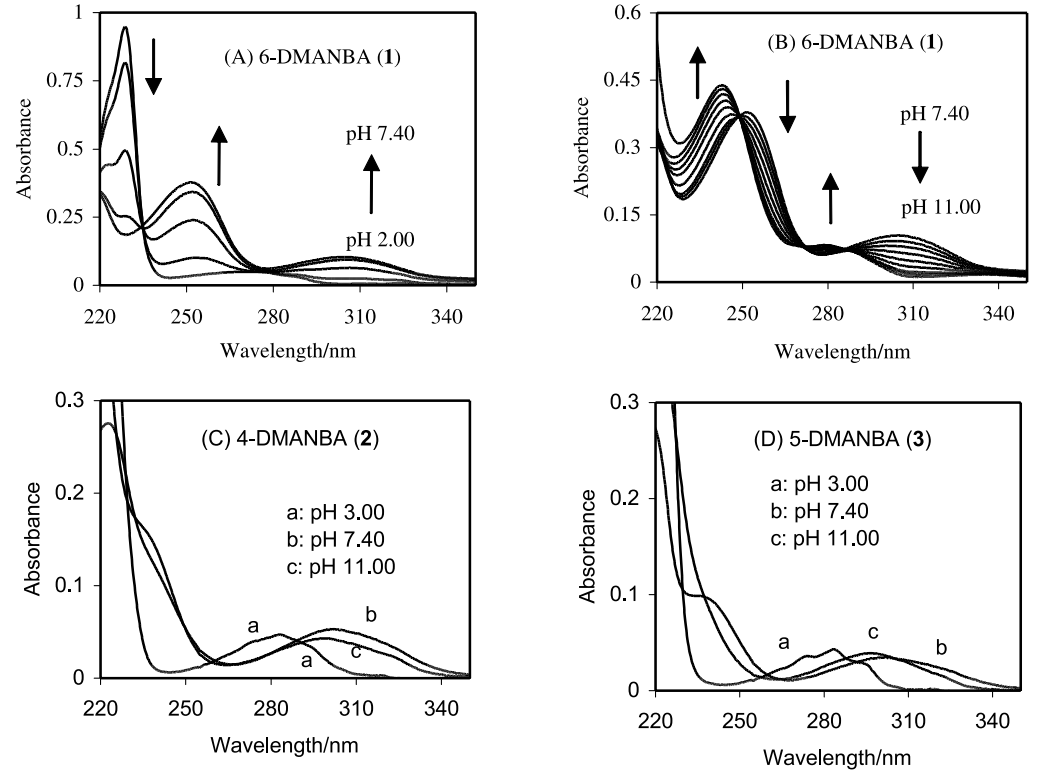


Figure 3. UV absorbance spectral changes of **1**, **2**, and **3** at different pH in 0.1 M aqueous phosphate buffer. (A) 6-DMANBA (**1**) (1.0×10^{-5} M) at different pH (from 2.00 to 7.40). (B) 6-DMANBA (**1**) (1.0×10^{-5} M) at different pH (pH from 7.40 to 10.0). (C) 4-DMANBA (**2**) (1.0×10^{-5} M) at different pH. (D) 5-DMANBA (**3**) (1.0×10^{-5} M) at different pH.

Table 1. Fluorescence intensity changes ($\Delta I/I_0$) of 6-DMANBA (**1**) at the emission wavelength of 432 nm with different excitation wavelengths upon addition of 50 mM D-fructose

Excitation wavelength (λ_{ex}, nm)	$\Delta I/I_0$	Excitation wavelength (λ_{ex}, nm)	$\Delta I/I_0$
250	−0.314	290	−0.440
260	−0.588	300	−0.665
270	−0.497	310	−0.801
271	−0.185	320	−0.743
280	−0.035	330	−0.592
288	−0.366	340	−0.495

wavelength at its three UV isosbestic points of 250, 271, and 288 nm were −0.314, −0.185, and −0.366, respectively (Table 1). Understandably, excitation at the isosbestic points did not give the largest fluorescent intensity changes up sugar addition. Instead, the largest fluorescence changes occurred when the excitation wavelength was at the absorption λ_{max}, 310 nm. Therefore, excitation at 310 nm was used for further fluorescence studies of compound **1**.

With the optimal excitation wavelength established, we studied the concentration-dependent fluorescent changes of **1** with the addition of sugars. With the addition of fructose and four other sugars (sorbitol, tagatose, galactose, and glucose) at different concentrations to the solution of 6-DMANBA in 0.1 M aqueous phosphate buffer (pH 7.4), significant decreases in fluorescent intensity were observed. For example, with the addition of fructose, the fluorescent intensity decreased by 80% (Fig. 4).

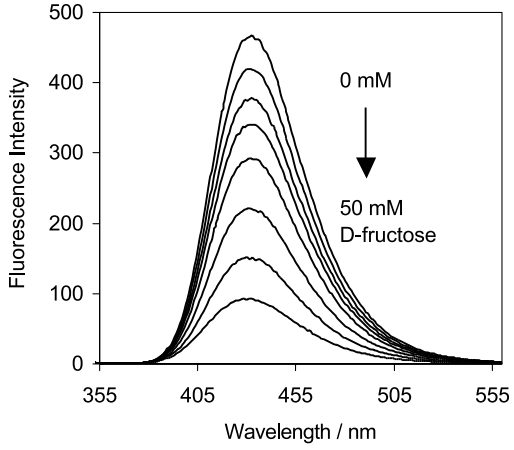


Figure 4. Fluorescence spectral changes of 6-DMANBA (**1**) (1.0×10^{-6} M) with different concentrations of D-fructose (0–50 mM) in 0.1 M aqueous phosphate buffer at pH 7.4, $\lambda_{ex}=310$ nm.

The results of such fluorescent studies are summarily presented in Table 2 and Figure 5. Addition of sorbitol, fructose, and tagatose induced fluorescence intensity changes at much lower sugar concentrations than that of galactose and glucose due to their difference in binding affinity. However, it is important to note that they all eventually reach about the same level, indicating that all these complexes have similar fluorescent intensities.

The apparent association constants (K_a) between **1** and these five carbohydrates were determined assuming the formation of a 1:1 complex.[20] As expected, the affinity trend of various

Table 2. Apparent association constants (K_a) and fluorescence intensity changes ($\Delta I/I_0$) of 6-DMANBA (**1**) with different sugars

Sugar	K_a (M^{-1})	$\Delta I/I_0$ (Sugar concentration, M)
Sorbitol	227±5	−0.825 (0.10)
Fructose	120±2	−0.801 (0.05)
Tagatose	103±3	−0.853 (0.10)
Galactose	8.0±0.3	−0.772 (1.0)
Glucose	2.4±0.2	−0.610 (1.0)

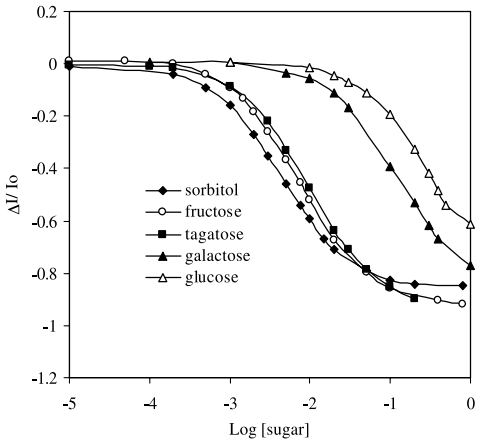


Figure 5. Fluorescence intensity changes ($\Delta I/I_0$) of 6-DMANBA (**3**) (1.0×10^{-6} M) as a function of sugar concentrations in 0.1 M aqueous phosphate buffer at pH 7.4; $\lambda_{ex}=310$ nm, $\lambda_{em}=432$ nm.

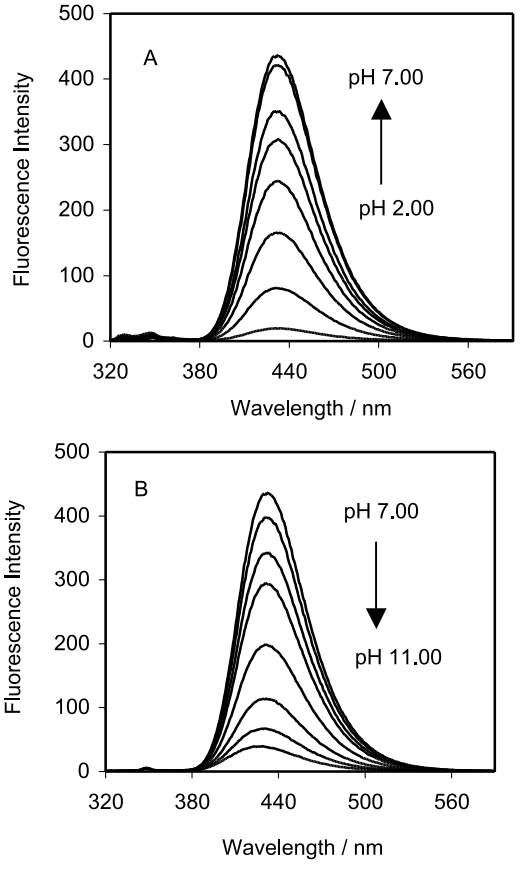
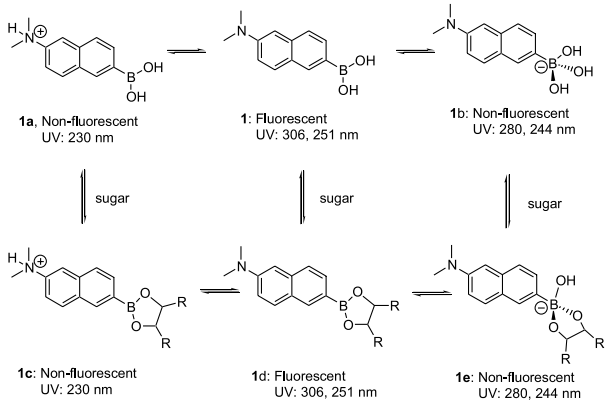


Figure 6. Fluorescence spectral changes of 6-DMANBA (**1**) (1.0×10^{-6} M) in the absence of sugar at different pH in 0.1 M aqueous phosphate buffer, $\lambda_{ex}=310$ nm. (A) pH from 2.00 to 7.00; (B) pH from 7.00 to 11.00.

sugars with **1** followed that of simple monoboronic acid in the order of sorbitol > fructose ≅ tagatose > galactose > glucose (Table 2). For example, the observed association constants with different sugars show the same binding trend as **2** and **3** as well as other monoboronic acids.[6c,d,17] The different binding properties of these sugars are attributed to the different dihydral angles of the diol of these sugars.

The pH induced fluorescent spectral changes of **1** in the absence and presence of fructose or glucose at a fixed concentration (50 mM) were studied to examine the relationship between the fluorescence intensity changes and the different ionization states. Figure 6 shows the fluorescence spectral changes of **1** at different pH in the absence of a sugar. It can be seen that the fluorescence intensity of **1** at 432 nm increased when pH increased from 2 to 7 (Fig. 6A). After that, increasing pH caused a decrease in fluorescence intensity at 432 nm (Fig. 6B). Such results indicate that the free form (**1**) is the fluorescent species (**1**), and neither the protonated form (**1a**) nor the boron ionized form (**1b**) is fluorescent (Scheme 2). With the deprotonation of the aniline group, the proportion that exists in the neutral form increases, which gives the increased fluorescence. At higher pH, the boronic acid moiety becomes ionized, which causes a drop in fluorescence.



Scheme 2. The spectroscopic properties of 6-DMANBA (**1**) at its different ionization states.

The fluorescence intensity profile of **1** versus pH in the presence of 50 mM fructose or glucose were also studied (Fig. 7). It can be seen from this figure that the situation with the esters is similar to that of the free boronic acid, that is, only the neutral form (**1d**, Scheme 2) is fluorescent. Neither the protonated form (**1c**) nor the boron-ionized form (**1e**) has appreciable fluorescence. The fluorescence intensity changes observed with the addition of a sugar is largely due to a decrease in the boron pK_a with ester formation, which converts the boron to the sp^3 hybridized form that is non-fluorescent. For example, the apparent pK_a of the boronic acid group of **1** in the absence of a sugar is about 9.0, while its apparent pK_a dropped to about 6.8 in the presence of 50 mM fructose. In such a case, at neutral pH the boron is ionized in the presence of fructose and neutral in the absence of a sugar. Since the ionized form is non-fluorescent, addition of fructose causes a significant decrease in fluorescent intensity. For glucose, because its binding constant is much smaller than that of fructose (Table 1), it

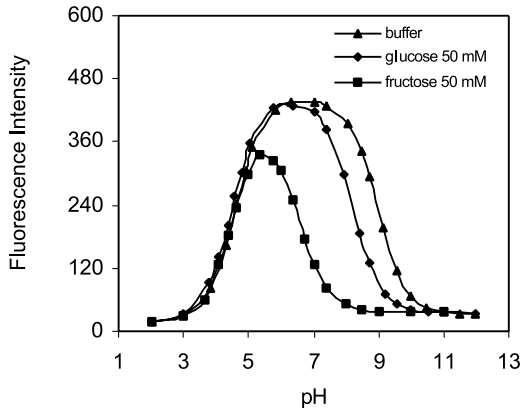


Figure 7. pH titration of the fluorescence intensity of 6-DMANBA (**1**) (1×10^{-6} M) at 432 nm in the absence and presence of 50 mM fructose or glucose in 0.1 M aqueous phosphate buffer, $\lambda_{ex}=310$ nm.

requires a much higher concentration for the boronic acid to be converted to its complexed form, which has a lower pK_a than the free boronic acid.

It should be noted that the pH induced fluorescence changes of **1** are different from its analogs, 4-dimethylamino-naphthaleneboronic acid (4-DMANBA, **2**)[17a] and 5-dimethylaminonaphthaleneboronic acid (5-DMANBA, **3**)[17b]. In 4-DMANBA, the neutral form is not fluorescent, but the boron-ionized form is, which gives a fluorescent intensity increase upon sugar addition. In 5-DMANBA, the boron ionized form is also very fluorescent, but has a different emission wavelength than the neutral form, which gives fluorescent ratiometric sensing. It should also be noted that 6-DMANBA only has one emission wavelength no matter what protonation state it is in. This again is in direct contrast to 4-DMANBA and 5-DMANBA, which also showed an emission peak at 336 nm in the protonated form. It is interesting to see that with the same chromophore, naphthalene, the functional group substitution positions can bestow very different spectroscopic properties on these boronic acid compounds.

3. Conclusions

One new water-soluble naphthalene-based boronic acid fluorescent saccharide sensor, 6-DMANBA (**1**), was synthesized and studied. 6-DMANBA (**1**) shows significant ratiometric UV absorbance changes upon addition of a sugar. In addition, 6-DMANBA (**1**) is a very fluorescent compound with a high fluorescence quantum yield ($\phi_F=89\%$) in the absence of a sugar. Addition of a sugar significantly decreases fluorescence intensity of **1**. All these properties make compound **1** special and useful in our effort of synthesizing combinatorial libraries in search of new fluorescent boronolectins.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz with tetramethylsilane as the internal

standard. Mass spectral analyses were performed by the mass spectrometry facilities of Georgia State University. Fluorescence spectra were recorded on a Shimadzu RF-5301 PC spectrofluorometer. Absorption spectra were recorded on a Shimadzu UV-1700 UV–vis spectrophotometer. All pH values were determined by a UB-10 Ultra Basic Benchtop pH meter (Denver Instrument). Column chromatography was performed on silica gel (200–400 mesh) from Aldrich. Tetrahydrofuran (THF) was distilled over Na before use.

4.2. Synthesis

4.2.1. 6-(*N*-Methyl)-2-bromo-naphthalene (5).[18] A mixture of **4** (1.0 g, 4.5 mmol), $Na_2S_2O_5$ (1.6 g, 8.7 mmol), and H_2O (4 mL) was placed in a pressure reactor. To the solution was added aqueous methylamine (40%) (2.0 mL, 22 mmol). The reaction mixture was stirred at 140 °C for 4 days. After cooling, the reaction mixture was dissolved in 50 mL CH_2Cl_2, washed with 5% $NaHCO_3$ (3×30 mL) and dried over Na_2SO_4. After evaporation of solvent, the crude was purified on a silica gel column, eluting with CH_2Cl_2/hexanes (1:1), to give compound **5** as a white powder (0.82 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J=1.2 Hz, 1H), 7.46–7.36 (m, 3H), 6.80–6.76 (dd, J=8.7, 0.6 Hz, 1H), 6.54 (d, J=2.1 Hz, 1H), 3.83 (s, 1H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 134.1, 129.9, 129.7, 128.7, 128.2, 127.9, 119.1, 115.2, 103.7, 30.9; HR ESI-MS (*m*/*z*) Calcd for $C_{11}H_{11}BrN$ 236.0075 $(M+H)^+$, found 236.0079.

4.2.2. 6-(*N*-Dimethyl)-2-bromo-naphthalene (6). To the solution of compound **5** (0.33 g, 1.2 mmol) and CH_3I (0.75 mL, 12 mmol) in THF (50 mL) was added NaH (60%) (0.58 g, 14 mmol). The reaction mixture was stirred at 60 °C overnight. The precipitate was removed by filtration. After evaporation of solvent, the residue was dissolved in 50 mL CH_2Cl_2 and washed with 5% $NaHCO_3$ (3×30 mL) and dried over Na_2SO_4. After evaporation of solvent, the crude was purified on a silica gel column, eluting with CH_2Cl_2/hexanes (1:1), to give compound **6** as a white powder (0.25 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=1.8 Hz, 1H), 7.51 (d, J=9.3 Hz, 1H), 7.45 (d, J=8.6 Hz, 1H), 7.36 (dd, J=9.0, 2.7 Hz, 1H), 7.07 (dd, J=9.0, 2.7 Hz, 1H), 6.80 (d, J=2.4 Hz, 1H), 2.98 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 133.8, 129.7, 129.6, 128.2, 128.1, 128.0, 117.3, 115.3, 106.3, 41.0; HR ESI-MS (*m*/*z*) Calcd for $C_{12}H_{13}BrN$ 250.0231 $(M+H)^+$, found 250.0239.

4.2.3. 6-(Dimethylamino)-naphthalene-2-boronic acid (1). The solution of 6-(dimethylamino)-2-bromo-naphthalene (**6**) (0.10 g, 0.40 mmol) in THF (5 mL) was cooled to −78 °C. To the solution was added dropwise *n*-BuLi in hexanes (1.5 M) (0.31 mL, 0.56 mmol). The reaction mixture was stirred at −78 °C for 45 min and $(MeO)_3B$ (0.13 mL, 1.2 mmol) was added. After the mixture was stirred at −78 °C for 1 h, the temperature was warmed to room temperature and stirring was continued overnight. The solvent was removed in vacuum. The residue was dissolved in 50 mL CH_2Cl_2 and washed with 5% $NaHCO_3$ (3×20 mL) and dried over Na_2SO_4. After evaporation of solvent, the crude was purified on a silica gel column, eluting with CH_2Cl_2/MeOH (20:1), to give compound **1** as white powder (0.055 g, 64%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.11 (s, 0.5H), 7.97 (s, 0.5H), 7.55–7.70 (m, 3H), 7.16 (d, J=9.0 Hz, 1H), 6.91 (s, 1H), 3.00 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 150.8, 137.9, 135.8, 131.7, 130.5, 127.9, 127.2, 126.3, 117.4, 107.4, 41.1; HR ESI-MS (*m*/*z*) Calcd for $C_{12}H_{15}BNO_2$ 216.1196 $(M+H)^+$, found 216.1215.

4.3. Procedures for the binding studies

Distinct solutions of the sensors (2×10^{-6} M for fluorescence and 2×10^{-5} M for UV absorbance) and the sugars (various concentrations) were prepared in 0.1 M phosphate buffer at pH 7.40. Then, 2 mL of a sensor solution was mixed with 2 mL of a sugar solution. After stirring for 20 min, the mixture was transferred into a 1 cm quartz cell and the fluorescence intensity or UV absorbance was recorded immediately.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.035. ^{1}H and ^{13}C NMR of 6-DMANBA (**1**) and two intermediates (**5** and **6**) are available.

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1,2,3-Triazoles and related glycoconjugates as new glycosidase inhibitors

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Abstract—A series of saccharidyl-triazoles structurally related to acarbose were prepared and tested as inhibitors of glycosidases. They share in common a 1,4,5-trisubstituted 1,2,3-triazole heterocycle as a functional element able to interact with the active site of the target enzymes. First, it was established that the heterocyclic core exhibits a moderate but highly selective α-glucosidase inhibitory activity. Then, it was confirmed that the inhibitory properties could be modulated by conjugation from one to five carbohydrate residues. The present study includes the regio- and stereocontrolled synthesis of novel non-fused 1,2,3-triazolo-pseudooligosaccharides as well as their evaluation as new glycosidase inhibitors.

1. Introduction

The wide range of physiological and pathological events involving the rupture or the construction of glycosidic linkages has spurred an aggressive effort aimed at the identification of inhibitors of glycosidases and glycosyl transferases that catalyze these processes.[1] On one hand, such inhibitors represent useful tools to understand the mechanism of action of these enzymes.[2] On the other hand, they exhibit a high promise as therapeutic agents for the treatment of ailments as varied as diabetes,[3] viral infections[4] or cancer metastasis.[5]

Polysubstituted five-membered azaheterocycles rank among the most potent glycosidase inhibitors.[6] The battery of structures on record include pyrrolo-,[7] imidazolo-,[8] triazolo-[9] and tetrazolo-glyco-derivatives,[10] their biological activity being dependent on the nature and the orientation of the functional groups present onto the ring.[2b,11] Most of the syntheses of these compounds, however, are rather complex and often feature modest overall yields. Our research efforts aim at an efficient, high-yielding synthesis of triazole-containing oligosaccharide mimetics, via [3+2] cycloaddition between azide and acetylene derivatives ('click reactions').[12] This reaction generally results in the corresponding 1,4-disubstituted 1,2,3-triazoles in high yields, is particularly well adapted to combinatorial synthetic strategies[13,14] and has already been successfully used in carbohydrate chemistry for the preparation of pseudooligosaccharide structures.[15]

In the present study, we were interested in the evaluation of the glycosidase inhibitory potential of new 1,4,5-trisubstituted 1,2,3-triazoles derived from 2-butyn-1,4-diol derivatives and 4-azido-4-deoxysugars. In a preliminary screening, the heterocyclic core showed a moderate but rather specific α-glycosidase competitive inhibitory activity. The possibility of introducing molecular diversity with a relatively low synthetic cost offers then a possibility to explore the effect of different substituents that might provide aglyconic or satellite interactions with binding subsites of the enzyme. To probe the viability of our approach, various saccharidyl-triazole derivatives have been prepared and assayed against a panel of glycosidases.

Keywords: Carbohydrates; Triazoles; Glycosylation; Glycosidase inhibition.
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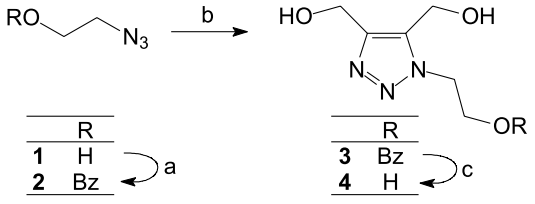
2. Results and discussion

2.1. Synthesis and properties of non-glycosylated 1,4,5-trisubstituted 1,2,3-triazoles

We have selected 2-butyn-1,4-diol as the dipolarophile reagent in our synthetic design in order to introduce some hydrophilicity on the aromatic ring via the hydroxyl groups and so to offset the high hydrophobicity around the basic part of the final adducts. Moreover, the hydroxyl functions are useful anchoring points for further conjunction with additional saccharide residues in the preparation of bis(glycosylated) derivatives. In order to check the activity of the resulting 1,4,5-trisubstituted 1,2,3-triazole core, we first undertook the synthesis of the trihydroxylated derivative **4**, bearing no saccharidyl residues. For its preparation, 2-azidoethanol (**1**) and 2-butyn-1,4-diol were first heated at 80 °C (Scheme 1). Although the desired triazole was obtained, it could not be separated from the starting alkyne neither by selective crystallization nor by chromatography. Hence, **1** was first benzoylated and the resulting product **2** was treated with the dipolarophile under heating to give **3**. Further transesterification afforded **4** in 79% yield.



Scheme 1. (a) BzCl, Et_3N, CH_2Cl_2 (90%); (b) 2-butyn-1,4-diol, 80 °C (65%); (c) NaOMe, MeOH (79%).

Both triazoles **3** and **4** were tested as inhibitors against α-glucosidase (baker yeast), isomaltase (yeast), amyloglucosidase (*Aspergillus niger*), β-glucosidase (almonds), trehalase (pig kidney), α-mannosidase (jack bean), α-galactosidase (green coffee) and β-glucosidase/β-galactosidase (bovine liver, cytosolic). The benzoylated triazole **3** presented no inhibitory effect for any of the studied enzymes, even at 2 mM concentration. On the contrary, the trihydroxylaled derivative **4** exhibited a moderate but highly selective yeast α-glucosidase competitive inhibition (inhibition constant, $K_i = 294$ μM). The fact that the triazole element is able to compete with natural glycosides for the active site of α-glucosidase, the inhibitory activity being promoted by hydrophilic substituents at position N-1, encouraged us to investigate the possibility of introducing saccharidyl residues to modulate the inhibition properties.

2.2. Synthesis and properties of saccharidyl-triazoles

The nature of the sugar substituents in the saccharidyl-triazoles included in this study has been inspired in the structure of the potent α-glucosidase inhibitor acarbose (Fig. 1), for which the existence of an oligosaccharide portion containing quinovosyl (6-deoxyglucosyl) and maltosyl subunits results in a extremely high enzyme selectivity.[16] The quinovosyl derivatives **9** and **10** were obtained in 81% overall yield from the known azido-

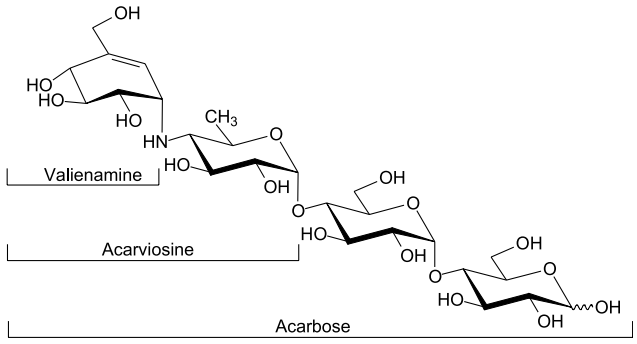
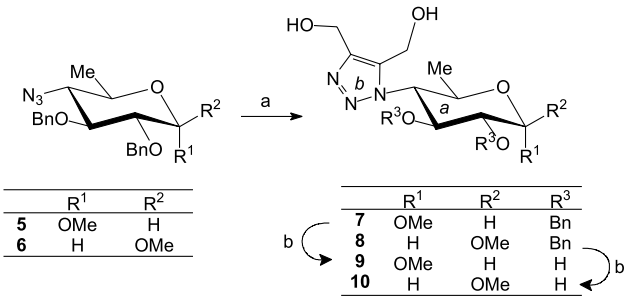


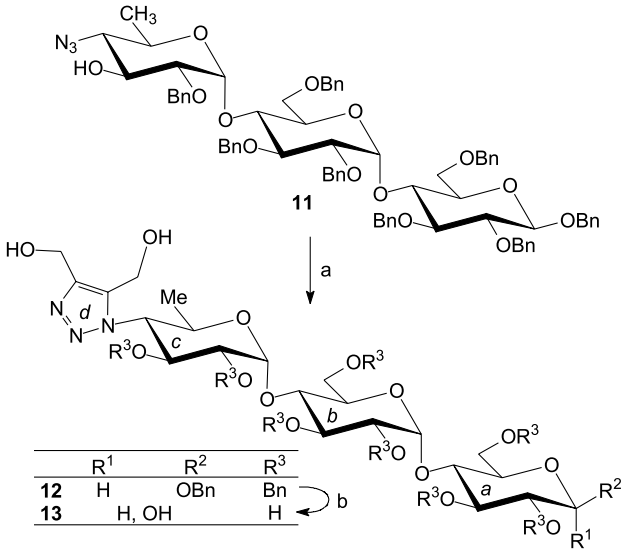
Figure 1. Structure of acarbose.

deoxyglycosides **5**[17] and **6**,[18] respectively, and 2-butyn-1,4-diol, under thermal activation followed by hydrogenolysis of the resulting intermediates **7** and **8** (Scheme 2).



Scheme 2. (a) 2-Butyn-1,4-diol, 120 °C (**7**: 85%; **8**: 85%); (b) H_2, Pd/C (**9**: 93%; **10**: 95%).

The synthesis of the saccharidyl derivative **13**, which incorporates the trisaccharide element present in acarbose, was based on the condensation of the trisaccharidic azide **11**, previously prepared in our laboratory[19] and the same acetylenic diol (Scheme 3). The cycloaddition reaction proceeded smoothly in chlorobenzene and provided the corresponding triazol adduct **12** in 70% yield. Removal of the benzyl protecting groups in **12** by classical catalytic hydrogenation was, however, unsuccessful. Nevertheless,

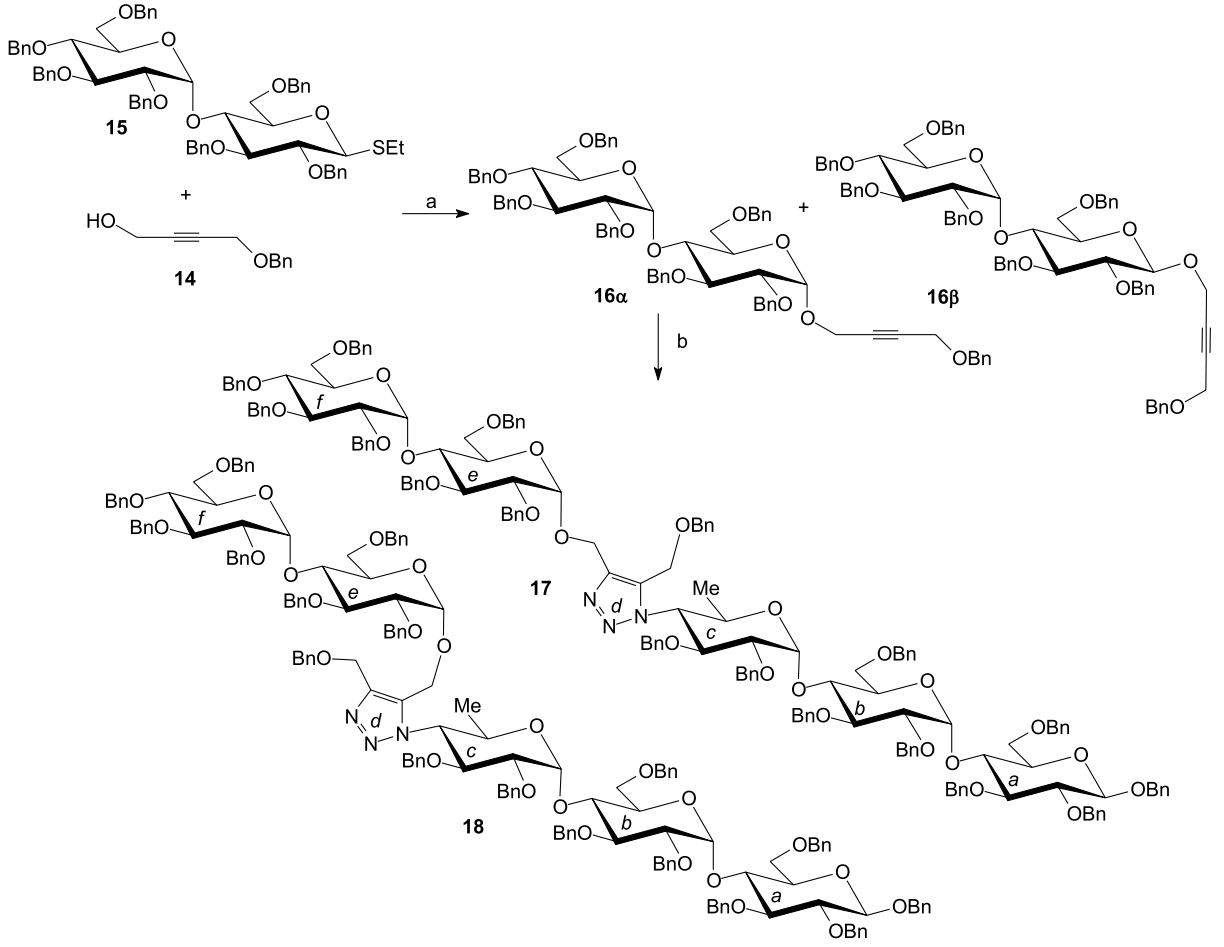


Scheme 3. (a) 2-Butyn-1,4-diol, chlorobenzene, 130 °C (70%); (b) cyclohexene, MeOH, cat. $Pd(OH)_2$, 90 °C (95%).

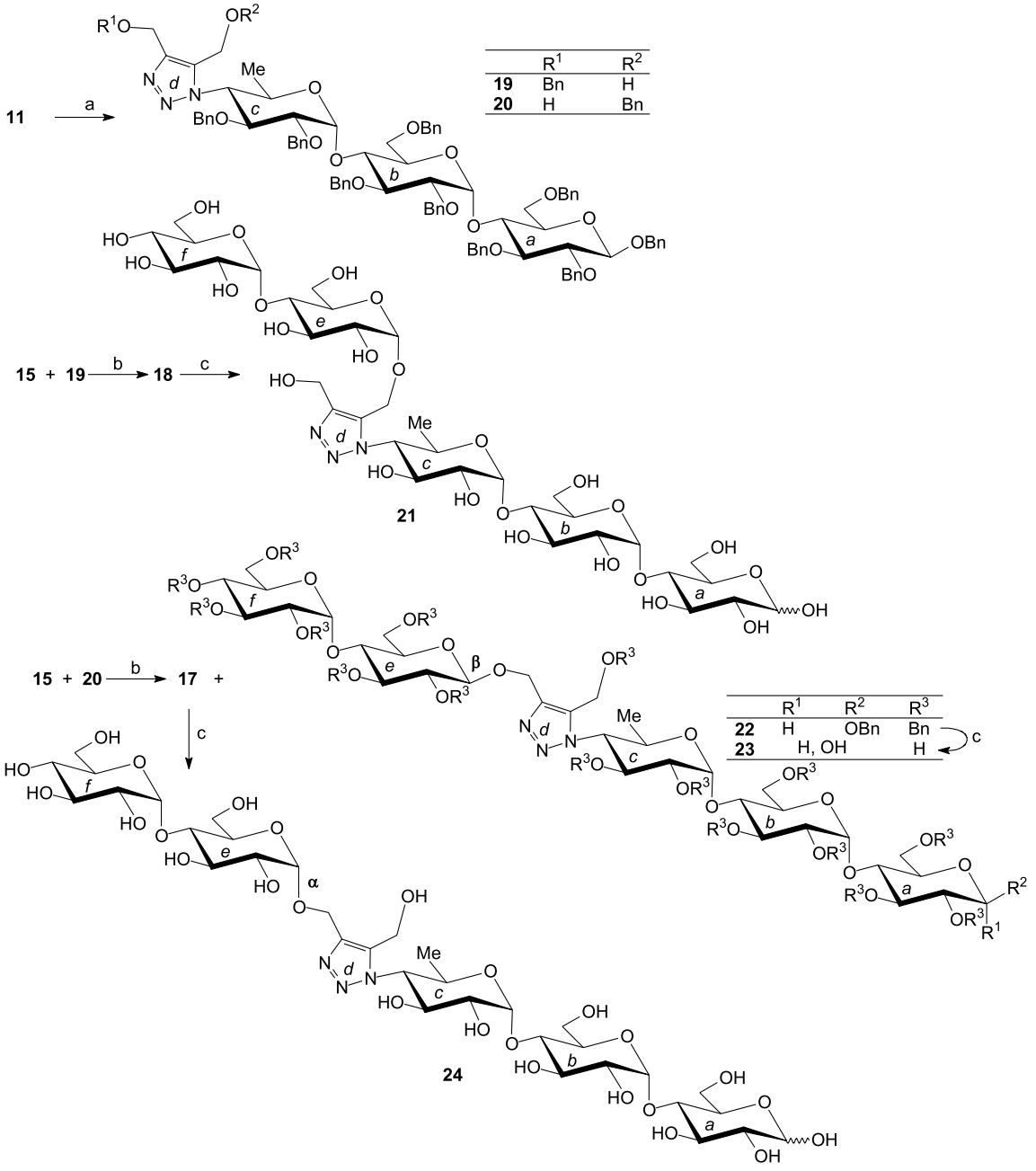
hydrogenolysis could be performed by hydrogen transfer from cyclohexene in the presence of Pearlman's catalyst [palladium(II) hydroxide] at 90 °C, providing the target fully unprotected conjugate **13** in 95% yield.

In order to obtain pseudooligosaccharide derivatives incorporating the 1,2,3-triazole unit in the backbone for structure–activity studies, the convergent route depicted in Scheme 4 was explored. The first step implied glycosylation of the known 4-benzyloxybut-2-yn-1-ol (**14**)[20] using the perbenzylated thiomaltoside **15**[21] as the glycosyl donor. After experimentation, the best compromise between diastereoselectivity and yield was obtained when the glycosylation reaction was promoted by *N*-iodosuccinimide (NIS) and a catalytic amount of the very mild Lewis acid copper(II) trifluoromethanesulfonate. These conditions afforded a 4.6:1 anomeric mixture of **16**α and **16**β, which could be chromatographically separated. Subsequent cycloaddition reaction of the major alkyne **16**α and azide **11** gave the isomeric adducts **17** and **18** in 54% yield as an inseparable 1.2:1 mixture.

In view of the difficulties to obtain the pure pseudo-oligosaccharides by the above approach, the linear strategy depicted in Scheme 5 was examined. Click conjugation of the trisaccharide azide **11** and the asymmetric alkyne **14** afforded the expected regioisomers **19** and **20**, which could be separated by simple silica gel chromatography. The chemical structures of these isomeric triazoles were established on the grounds of NMR data. In the ^{13}C NMR spectra, the signal corresponding to C-4d is typically observed at lower field than that for C-5d.[22] Moreover, etherification of a hydroxyl function leads to a large downfield shift of the α-carbon atom (6–9 ppm) and a less pronounced high-field shift of the β-carbon atom (3–4 ppm).[23] Comparison of the corresponding ^{13}C NMR data for the dihydroxymetyl derivative **12** with those for the monobenzyloxymethylated counterparts **19** and **20**, by combining both types of informations, allowed unambiguous differentiation between them. Further glycosylation of acceptor **19** with donor **15** using NIS/$Cu(OTf)_2$ as promotor proceeded with a moderate 20% yield but with an excellent diastereocontrol, providing exclusively the α-anomer **18**. A lower diastereoselectivity was, however, observed in the glycosylation of **20** under identical reaction conditions. The corresponding diastereomers **17** and **22**, characterized by $J_{1e,2e}$ coupling constant values of 3.6 and 8.0 Hz, respectively, were obtained in 30% yield as a 1.5:1 mixture. This result may be ascribed to the greater accessibility, and therefore higher reactivity, of the hydroxyl group of the hydroxymethyl substituent at position C-4d as compared with that at position C-5d in the triazole ring. Finally, removal of the benzyl protecting groups under hydrogen transfer conditions afforded the target glycomimetics **21**, **23** and **24** in 95% yield.



Scheme 4. (a) NIS, cat. $Cu(OTf)_2$ (61%; **16α/16β**=4.6:1); (b) **11**, 110 °C (54%; **17/18**=1.2:1).



Scheme 5. (a) **14**, 130 °C (39%; **19/20**=1.5:1); (b) NIS, cat. $Cu(OTf)_2$ [(**18**: 20%); (30%, **17/22**=1.5:1)]; (c) cyclohexene, MeOH, cat. $Pd(OH)_2$ (**21**: 95%; **23**: 95%; **24**: 95%).

The inhibitory activities of the new saccharidyl-triazoles **9**, **10**, **13**, **21**, **23** and **24** against a series of glycosidases are collected in Table 1. None of the prepared compounds inhibited invertase, galactosidase, mannosidase and fucosidase, which is in agreement with the configurational specificity previously observed for the triazole core as well as with the known specificity of the related pseudo-oligosaccharide inhibitor acarbose. The total lack of inhibitory properties for the trisaccharidyl-triazole **13** and the low α-glucosidase inhibition activities of the higher pseudooligosaccharides **21**, **23**, **24** indicated that the bis(hydroxymethyl)triazole unit is not a functional surrogate of the natural aminocyclitol moiety (valienamine) present in acarbose.

The results show that the introduction of glucosyl-type residues directly linked to the triazole moiety could modulate the inhibitory properties. Actually, compound **9** turned to be a rather good competitive inhibitor of α-glucosidase (K_i=73 μM), four-fold more potent as compared to unglycosylated triazole **4** and twice more active than acarbose for this particular enzyme. Moreover, the enzyme specificity of this family of compounds seems to be strongly dependent upon the nature of the substituents at the triazole ring. Thus, a change in the anomeric configuration of the quinovosyl residue, from α (**9**) to β (**10**), totally abolished the biological activity. The specificity of the pseudooligosaccharides **21**, **23**, **24** was also dependent on the linking position of the non-reducing

Table 1. Glycosidase inhibitory activities (K_i, μM) for triazolo-glycomimetics **9**, **10**, **13**, **21**, **23** and **24** in comparison with data for acarbose[a]

	Acarbose	**9**	**10**	**13**	**21**	**23**	**24**
α-Glucosidase (yeast)[b]	148	73	n.i.[c]	n.i.	n.i.	1158	1416
Isomaltase (yeast)[a]	n.i.	1925	n.i.	n.i.	1028		n.i.
Amyloglucosidase (*A. niger*)[d]	<20	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
β-Glucosidase (almonds)[e]	n.i.	534	n.i.	n.i.	n.i.	n.i.	n.i.
β-Glucosidase/β-Galactosidase (bovine liver)[f]	n.i.	597	n.i.	n.i.	n.i.	n.i.	n.i.

[a] The inhibition, when detected, was of the competitive type. None of the compounds **9**, **10**, **13**, **21**, **23** and **24** showed inhibitory properties against invertase (yeast), α-galactosidase (green coffee beans), α-mannosidase (Jack beans), and α-fucosidase (bovine kidney) at their optimal pHs.
[b] pH 6.8.
[c] No inhibition detected.
[d] pH 4.5.
[e] pH 5.5.
[f] pH 7.3.

maltosyl substituent at the triazole core, the C-4d′ linked derivatives **23** and **24** being weak inhibitors of α-glucosidase while the positional isomer **21** weakly inhibited isomaltase, instead.

It is worth mentioning that, contrary to other azaheterocycle glycomimetics, the 1,2,3-triazole ring has a low basicity ($pK_a = 1.1–1.3$)[24] and, consequently, the sp^2-hybridized nitrogen atoms will not be protonated at the pH of the inhibition assays (the optimal for each of the enzymes considered in this study). Recent results have shown that sp^2-azaheterocyclic glycomimetics may actually behave as more specific glycosidase inhibitors than the corresponding basic iminosugars, probably by mimicking the partial positive charge at the anomeric region in the transition state of enzymatic glycosidase hydrolysis.[25] Though weak, the activities measured in this study seem to follow this general trend.

3. Conclusion

In summary, the methodology developed herein provides a new direction to the development of 1,2,3-triazole-based pseudooligosaccharidic glycosidase inhibitors that allows the effective introduction of molecular diversity to modulate the biological activity. The high efficiency of the proposed transformation, in combination with the plethora of readily available azide and acetylene reagents, makes the approach particularly well suited for combinatorial library schemes, which should facilitate the identification of more active compounds. Work in that direction is currently under way in our laboratories.

4. Experimental

4.1. General

Melting points were determined on a Reichert microscope and are uncorrected. TLC analyses were conducted on E. Merck 60 F_{254} Silica Gel non activated plates and compounds were revealed using a 5% solution of H_2SO_4 in EtOH followed by heating. For column chromatography, Geduran Si 60 (40–63 μm) Silica Gel was used. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. ^1H, ^{13}C, HMQC and COSY NMR spectra were recorded on a Brüker ARX 400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C analyses. Chemical shifts are given in δ-units measured from Me_4Si, generated from the $CHCl_3$ lock signal at δ 7.26. Coupling constants are given in Hz. Microanalyses were performed by the Service de Microanalyse de l'ICSN (Gif sur Yvette, France) and by the Service de Microanalyse de l'Institut de Chimie de Rennes (CRMPO, Rennes, France). LSIMS High-resolution mass spectra were recorded on a MS/MS ZabSpec TOF Micromass spectrometer at the CRMPO using the fast atom bombardment technique in positive mode.

4.2. Materials

The azidodeoxy sugars **5**, **6** and **11** were prepared according to the previously reported procedures.[17–19] The glycosidases α-glucosidase (from yeast), β-glucosidase (from almonds), β-glucosidase/β-galactosidase (from bovine liver, cytosolic), trehalase (from pig kidney), isomaltase (from yeast), α-galactosidase (from green coffee beans), α-mannosidase (from Jack beans), invertase (from yeast), amyloglucosidase (from *A. Niger*) and α-fucosidase (from pig kidney), used in the inhibition studies, as well as sucrose and the corresponding *o*- and *p*-nitrophenyl glycoside substrates were purchased from Sigma Chemical Co.

4.3. General procedure for inhibition assay

Inhibitory potencies were determined by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases against the respective *o*- (for β-glucosidase/β-galactosidase from bovine liver) or *p*-nitrophenyl α- or β-D-glycopyranoside in the presence of the corresponding 1,2,3-triazole derivative. Each assay was performed in phosphate buffer or phosphate-citrate buffer (for α-mannosidase and amyloglucosidase) at the optimal pH for each enzyme. The reactions were initiated by addition of enzyme to a solution of the substrate in the absence or presence of various concentrations of inhibitor. After the mixture was incubated for 10–30 min at 37 or 55 °C (for amyloglucosidase) the reaction was quenched by addition of 1 M Na_2CO_3. The absorbance of the resulting mixture was determined at 405 nm. The K_i value and enzyme inhibition mode were determined from the slope of Lineweaver–Burk plots and double reciprocal analysis using a Sigma Plot program (version 4.14, Jandel Scientific).

4.3.1. 1-(2-*O*-Benzoxyethyl)-4,5-dihydroxymethyl-1*H*-1,2,3-triazole 3. To a solution of 2-azidoethanol **1** (1.00 g,

11.5 mmol) and triethylamine (2.0 mL, 14.2 mmol) in CH_2Cl_2 (20 mL), benzoyl chloride (1.6 mL, 13.8 mmol) was added. After stirring for 4 h at rt, the solution was successively washed with a 5% HCl aqueous solution, a saturated aqueous solution of $NaHCO_3$ and water. The organic layer was then dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatographic purification (CH_2Cl_2) gave the desired product **2** (1.98 g, 90%), which was directly used for the next cycloaddition reaction without further purification; TLC (EtOAc) R_f 0.7; δ_H ($CDCl_3$) 8.08–8.05 (m, 2H, C_6H_5), 7.59–7.54 (m, 1H, C_6H_5), 7.47–7.43 (m, 1H, C_6H_5), 4.48 (t, 2H, $J=5.1$ Hz, CH_2O), 3.59 (t, 2H, CH_2N); δ_C ($CHCl_3$) 166.2 (CO), 133.3, 129.7, 128.5 (C_6H_5), 63.7 (CH_2O), 50.0 (CH_2N).

Compound **2** (423 mg, 2.2 mmol) and 2-butyn-1,4-diol (190 mg, 2.2 mmol) were heated at 80 °C for 19 h. After cooling at rt, EtOAc (2 mL) was added and the mixture stirred for 10 min. The resulting solid was washed with EtOAc and finally filtered to give **3** (402 mg, 65%); TLC (EtOAc) R_f 0.3; δ_H ($CDCl_3$) 7.95 (d, 2H, $J=7.4$ Hz, H_o–C_6H_5), 7.58 (t, 1H, $J=7.4$ Hz, H_p–C_6H_5), 7.44 (d, 2H, H_m–C_6H_5), 4.91–471 (m, 8H, CH_2O, CH_2N); δ_C ($CDCl_3$) 167.4 (CO), 145.9 (C-4), 136.2 (C-5), 134.4, 130.8, 130.6, 129.5 (C_6H_5), 64.1 (CH_2OCO), 55.6 (CH_2–C-4), 52.4 (CH_2–C-5), 48.6 (CH_2CH_2–N-1). Found: C, 56.04; H, 5.23; N, 14.92. $C_{13}H_{15}N_3O_4$, requires C, 56.31; H, 5.45; N, 15.15.

4.3.2. 1-(2-Hydroxyethyl)-4,5-dihydroxymethyl-1*H*-1,2,3-triazole 4. Debenzoylation of triazole **3** (70 mg, 0.25 mmol) was achieved in a 0.1 M solution of sodium methylate in methanol (2 mL) for 2 h. The reaction media was neutralized with an acidic resin (IR 120, H^+-form), filtered, concentrated and subjected to chromatographic purification (EtOAc and then 7:3 EtOAc/MeOH) to give **4** (39 mg, 89%); TLC (EtOAc) R_f 0.1; δ_H (CD_3OD) 4.75 (s, 2H, CH_2–C-5), 4.65 (s, 2H, CH_2–C-4), 4.50 (t, 2H, $J=5.4$ Hz, CH_2CH_2–N-1), 3.91 (t, 2H, CH_2CH_2–N-1); δ_C (CD_3OD) 145.8 (C-4), 136.6 (C-5), 61.9 (CH_2CH_2–N-1), 55.7 (CH_2–C-4), 52.4 (CH_2–C-5), 51.9 (CH_2CH_2–N-1). Found: C, 41.71; H, 6.34; N, 24.08. $C_6H_{11}N_3O_3$, requires C, 41.62; H, 6.40; N, 24.27.

4.3.3. 4,5-Dihydroxymethyl-1-(methyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosid-4-yl)-1*H*-1,2,3-triazole 7. 2-Butyn-1,4-diol (56 mg, 0.65 mmol) and azide **5** (50 mg, 0.13 mmol) were heated at 120 °C for 4 h. Purification by flash chromatography (CH_2Cl_2/MeOH, 19:1) afforded **7** (47 mg, 85%) as a white solid; TLC (light petroleum/ethyl actetate, 1:2) R_f 0.2; mp 98 °C; $[\alpha]_D^{20}$ +72 (*c* 1.0 in CH_2Cl_2); δ_H ($CDCl_3$) 7.32–6.80 (m, 10H, C_6H_5), 5.20–4.89 (m, 7H, OCH_2Ph, H-4′b, H-5′b), 5.03 (d, 1H, $J_{1a,2a}=4.3$ Hz, H-1a), 4.96 (dq, 1H, $J_{5a,6a}=8.6$ Hz, $J_{4a,5a}=9.0$ Hz, H-5a), 4.78 (dd, 1H, $J_{3a,4a}=9.0$ Hz, H-4a), 4.40 (d, 1H, $J=14.0$ Hz, OCH_2Ph), 4.39 (dd, 1H, $J_{2a,3a}=9.0$ Hz, H-3a), 4.16 (dd, 1H, H-2a), 3.98 (s, 3H, OCH_3), 1.91 (d, 3H, H-6a); δ_C ($CDCl_3$) 136.3 (C-4b), 130.8, 130.3 [$C_{ipso}(C_6H_5)$], 129.3 (C-5b), 122.6–122.1 (C_6H_5), 95.8 (C-1a), 80.2 (C-3a), 79.5 (C-2a), 76.0, 73.7 (OCH_2Ph), 66.8 (C-5a), 66.3 (C-4a), 58.1 (OCH_3, C-4′b), 54.8 (C-5′b), 24.2 (C-6a). Found: C, 63.92; H, 6.51; N, 8.91. $C_{25}H_{31}N_3O_6$ requires C, 63.95; H, 6.65; N, 8.94.

4.3.4. 4,5-Dihydroxymethyl-1-(methyl 2,3-di-*O*-benzyl-4,6-dideoxy-β-D-glucopyranosid-4-yl)-1*H*-1,2,3-triazole 8. 2-Butyn-1,4-diol (56 mg, 0.65 mmol) and azide **6** (50 mg, 0.13 mmol) were heated at 120 °C for 4 h. Column chromatography (CH_2Cl_2/MeOH, 19:1) gave **8** (47 mg, 85%) as a white solid; TLC (CH_2Cl_2/MeOH, 19:1) R_f 0.2; mp 85 °C; $[\alpha]_D^{20}$ +43 (*c* 1.0 in CH_2Cl_2); δ_H ($CDCl_3$) 7.30–6.81 (m, 10H, C_6H_5), 5.29 (d, 1H, $J=15.6$ Hz, OCH_2Ph), 5.10–4.08 (m, 6H, OCH_2Ph, H-4′b, H-5′b), 4.95 (d, 1H, $J_{1a,2a}=9.4$ Hz, H-1a), 4.76 (dq, 1H, $J_{4a,5a}=8.9$ Hz, $J_{5a,6a}=8.5$ Hz, H-5a), 4.57 (dd, 1H, $J_{3a,4a}=8.4$ Hz, H-4a), 4.55, (dd, 1H, $J_{2a,3a}=8.9$ Hz, H-3a), 4.41 (d, 1H, $J=15.3$ Hz, OCH_2Ph), 4.10 (s, 3H, OCH_3), 4.08 (dd, 1H, H-2a), 1.97 (d, 3H, H-6a); δ_C ($CDCl_3$) 136.9 (C-4b), 131.6, 130.6 [$C_{ipso}(C_6H_5)$], 129.9 (C-5b), 121.9–122.3 (C_6H_5), 101.9 (C-1a), 82.5 (C-2a), 82.2 (C-3a), 76.4, 75.2 (OCH_2Ph), 71.2 (C-5a), 66.5 (C-4a), 60.1 (OCH_3), 58.4 (C-4′b), 55.2 (C-5′b), 24.7 (C-6a). Found: C, 63.76; H, 6.37; N, 8.91. $C_{25}H_{31}N_3O_6$ requires C, 63.95; H, 6.65; N, 8.94.

4.3.5. 4,5-Dihydroxymethyl-1-(methyl 4,6-dideoxy-α-D-glucopyranosid-4-yl)-1*H*-1,2,3-triazole 9. A suspension of compound **7** (45 mg, 0.09 mmol) in dry MeOH (1 mL) and Pd/C (30 mg) was stirred for 4 h under H_2 at atmospheric pressure, then filtered over a bed of Celite. The resulting filtrate was dried ($MgSO_4$) and concentrated. Chromatographic purification (9:1 CH_2Cl_2/MeOH) afforded **9** (25 mg, 93%) as a white foam; TLC (CH_2Cl_2/MeOH, 9:1) R_f 0.3; $[\alpha]_D^{20}$ +208 (*c* 0.8 in CH_2Cl_2); δ_H (CD_3OD) 4.84–4.73 (m, 2H, H-4′b), 4.78 (d, 1H, $J_{1a,2a}=3.7$ Hz, H-1a), 4.69 (s, 2H, H-5′b), 4.60–4.56 (m, 1H, H-5a), 4.22–4.17 (m, 2H, H-3a, H-4a), 3.56 (dd, 1H, $J_{2a,3a}=9.0$ Hz, H-2a), 3.46 (s, 3H, OCH_3), 0.97 (d, 3H, $J_{5a,6a}=6.2$ Hz, H-6a); δ_C (CD_3OD) 137.8 (C-4b), 130.5 (C-5b), 101.8 (C-1a), 74.8 (C-3a), 73.6 (C-2a), 67.5 (C-4a, C-5a), 56.2 (OCH_3), 56.1 (C-4′b), 52.5 (C-5′b), 18.0 (C-6a). Found: C, 45.54; H, 6.53; N, 14.35. $C_{11}H_{19}N_3O_6$ requires C, 45.67; H, 6.62; N, 14.52.

4.3.6. 4,5-Dihydroxymethyl-1-(methyl 4,6-dideoxy-β-D-glucopyranosid-4-yl)-1*H*-1,2,3-triazole 10. Compound **10** (20 mg, 95% yield) was obtained from **8** (34 mg, 0.07 mmol) following the procedure above described for the preparation of **9** and isolated a white foam; TLC (CH_2Cl_2/MeOH, 4:1) R_f 0.3; $[\alpha]_D^{20}$ −8 (*c* 0.8 in CH_2Cl_2); δ_H (CD_3OD) 4.84–4.72 (m, 4H, H-4′b, H-5′b), 4.45 (d, 1H, $J_{1a,2a}=7.9$ Hz, H-1a), 4.38 (dq, 1H, $J_{4a,5a}=9.7$ Hz, $J_{5a,6a}=6.1$ Hz, H-5a), 4.28 (dd, 1H, $J_{3a,4a}=9.4$ Hz, H-4a), 4.05 (dd, 1H, $J_{2a,3a}=9.0$ Hz, H-3a), 3.69 (s, 3H, OCH_3), 3.39 (dd, 1H, H-2a), 0.99 (d, 1H, H-6a); δ_C (CD_3OD) 145.6 (C-4b), 138.2 (C-5b), 105.8 (C-1a), 76.5 (C-3a), 76.3 (C-2a), 72.0 (C-5a), 67.3 (C-4a), 57.7 (OCH_3), 56.0 (C-4′b), 52.5 (C-5′b), 18.0 (C-6a). Found: C, 45.55; H, 6.50; N, 14.51. $C_{11}H_{19}N_3O_6$ requires C, 45.67; H, 6.62; N, 14.52.

4.3.7. 1-[Benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosid-4c-yl]-4,5-dihydroxymethyl-1*H*-1,2,3-triazole 12. A solution of the trisaccharidic azide **11** (100 mg, 0.08 mmol) and 2-butyn-1,4-diol (35 mg, 0.40 mmol) in chlorobenzene (1 mL) was heated at 130 °C for 24 h. The solvent was then removed under reduced pressure and the resulting crude oil was purified by column chromatography (light petroleum/EtOAc, 2:3) to give the desired adduct **12** (82 mg, 70%) as a colourless oil; TLC (light petroleum/

EtOAc, 1:1) R_f 0.3; $[\alpha]_D^{20}$ +208 (*c* 0.8 in CH_2Cl_2); δ_H ($CDCl_3$) 7.40–7.06 (m, 43H, C_6H_5), 6.82–6.78 (m, 2H, C_6H_5), 5.83 (d, 1H, $J_{1c,2c}$=3.3 Hz, H-1c), 5.61 (d, 1H, $J_{1b,2b}$=3.3 Hz, H-1b), 5.03–4.91 (m, 4H, OCH_2Ph), 4.82–4.44 (m, 17H, OCH_2Ph, H-4′d, H-5′d), 4.78–4.70 (m, 1H, H-5c), 4.54 (d, 1H, $J_{1a,2a}$=7.6 Hz, H-1a), 4.39 (dd, 1H, $J_{2c,3c}$=9.4 Hz, $J_{3c,4c}$=9.9 Hz, H-3c), 4.22 (dd, 1H, $J_{3b,4b}$=9.1 Hz, $J_{4b,5b}$=8.9 Hz, H-4b), 4.14–4.05 (m, 2H, H-4a, H-3b), 4.05–3.95 (m, 2H, H-6′a, H-5b), 3.92 (dd, 1H, H-4c), 3.88–3.84 (m, 1H, H-6a), 3.83–3.76 (m, 2H, H-3a, H-6b), 3.79 (d, 1H, *J*=10.0 Hz, OCH_2Ph), 3.65–3.62 (m, 5H, H-2a, H-5a, H-2b, H-6′b, H-2c), 0.82 (d, 3H, $J_{5c,6c}$=6.4 Hz, H-6c); δ_C ($CDCl_3$) 144.0 (C-4d), 138.7–137.2 [9C, $C_{ipso}(C_6H_5)$], 135.9 (C-5d), 128.4–126.5 (45C, C_6H_5), 102.4 (C-1a), 95.8 (C-1c), 96.4 (C-1b), 84.6 (C-3a), 82.0 (C-3b), 81.9 (C-2a), 80.2 (C-2c), 79.7 (C-3c), 79.4 (C-2b), 75.7 (O*C*H_2Ph), 74.7 (C-5a), 74.6, 73.9 (O*C*H_2Ph), 73.3 (C-4a), 72.9, 72.7, 71.0 (O*C*H_2Ph), 71.2 (C-4b), 70.5 (C-5b), 68.8 (C-6a), 68.2 (C-6b), 66.2 (C-5c), 64.9 (C-4c), 55.5 (C-4′d), 51.8 (C-5′d), 17.3 (C-6c). Found: C, 72.66; H, 6.65; N, 3.05. $C_{85}H_{91}N_3O_{16}$ requires C, 72.37; H, 6.50; N, 2.98.

4.3.8. 1-[4,6-Dideoxy-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranos-4c-yl]-4,5-dihydroxymethyl-1*H*-1,2,3-triazole 13. A solution of **12** (190 mg, 0.13 mmol) in a 1:1 mixture of cyclohexene/MeOH (4 mL) was heated under reflux in the presence of $Pd(OH)_2$ (200 mg) for 12 h. After removal of the catalyst by filtration over a bed of Celite, chromatographic purification (EtOAc/MeOH/water, 7:2:1→5:3:2) yielded **13** as a white foam; TLC (EtOAc/MeOH/water, 5:3:2) R_f 0.2; $[\alpha]_D^{20}$ +145 (*c* 1.0 in H_2O); δ_H (D_2O) 5.48 (d, 1H, $J_{1c,2c}$=3.3 Hz, H-1c), 5.39 (d, 1H, $J_{1b,2b}$=3.6 Hz, H-1b α-anomer), 5.20 (d, 1H, $J_{1a,2a}$=3.8 Hz, H-1a), 4.80–4.70 (m, 2H, H-5′d), 4.71 (s, 2H, H-4′d), 4.63 (d, 1H, $J_{1a,2a}$=7.6 Hz, H-1a β-anomer), 4.60–4.54 (m, 1H, H-5c), 4.32–4.27 (m, 2H, H -3c, H-4c), 4.00–3.52 (m, 12H, H carbohydrate), 3.62 (dd, 1H, $J_{2a,3a}$=9.7 Hz, H-2a α-anomer), 3.25 (dd, 1H, $J_{2a,3a}$=8.4 Hz, H-2a β-anomer), 0.96 (d, 3H, *J*=6.1 Hz, H-6c); δ_C (D_2O) 144.5 (C-4d), 136.7 (C-5d), 100.2 (C-1c), 99.8 (C-1b), 96.1 (C-1a β-anomer), 92.2 (C-1a α-anomer), 77.4, 77.3, 77.1, 76.5, 74.9, 73.7, 73.6, 71.9, 71.8, 71.6, 70.2 (C carbohydrate), 74.3 (C-2a β-anomer), 72.5 (C-2a α-anomer), 71.4 (C-3c), 67.7 (C-5c), 65.3 (C-4c), 60.8, 60.7 (C-6a, C-6b), 54.0 (C-4′d), 50.8 (C-5′d), 16.4 (C-6c). Found: C, 41.05; H, 6.37; N, 6.20. $C_{22}H_{37}N_3O_{16}\cdot 2.5\ H_2O$ requires C, 40.99; H, 6.57; N, 6.52.

4.3.9. 4-Benzyloxy-2-butynyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α- and β-D-glucopyranoside 16α and 16β. To a solution of maltosyl donor **15**[16] (100 mg, 0.10 mmol) and 4-benzyloxybut-2-yn-1-ol **14** (35 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) were successively added NIS (222 mg, 0.10 mmol) and $Cu(OTf)_2$ (7 mg, 0.02 mmol). The reaction was stirred at rt for 10 min before neutralization by adding a few drops of Et_3N. The reaction media was then diluted with Et_2O and successively washed with an aqueous solution of sodium thiosulfate and water. After drying ($MgSO_4$) and removal of the solvents, flash chromatography (light petroleum/EtOAc, 4:1) gave **16**α (55 mg, 50%) and **16**β (12 mg, 11%). Compound **16**α: TLC (light petroleum/EtOAc, 4:1) R_f 0.24; δ_H ($CDCl_3$) 7.28–6.99 (m, 40H, C_6H_5), 5.65 (d, 1H, $J_{1b,2b}$=3.6 Hz, H-1b), 5.00 (d, 1H, $J_{1b,2b}$=3.6 Hz, H-1a), 4.98 (d, 1H, *J*=11.2 Hz, OCH_2Ph), 4.81 (d, 1H, *J*=10.7 Hz, OCH_2Ph), 4.77–3.30 (m, 31H, H carbohydrate, CH_2Ph, CH_2CCCH_2); δ_C ($CDCl_3$) 138.9, 138.8, 138.5, 138.2, 138.0, 137.9, 137.8, 137.3 [8C, $C_{ipso}(C_6H_5)$], 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.8, 126.7 (C_6H_5), 96.7 (C-1b), 94.9 (C-1a), 82.7, 82.1 (C-3a, C-3b), 82.0, 81.8 (*C*H_2CC*C*H_2), 79.7 (C-2), 79.4 (C-2b), 77.6 (C-4b), 75.6, 75.0, 74.5, 73.5, 73.4, 73.3, 73.2 (CH_2Ph), 73.0 (C-4a), 71.9, 71.7 (CH_2Ph), 71.0 (C-5b), 70.2 (C-5a), 68.8, 68.1 (C-6a, C-6b), 57.4, 54.7 (CH_2CCCH_2). Found: C, 77.66; H, 6.65. $C_{72}H_{74}O_{11}$ requires C, 77.53; H, 6.69. Compound **16**β: TLC (light petroleum/EtOAc, 4:1) R_f 0.20; δ_H ($CDCl_3$) 7.35–7.09 (m, 40H, C_6H_5), 5.67 (d, 1H, $J_{1b,2b}$=3.6 Hz, H-1b), 4.98–4.72 (m, 6H, OCH_2Ph), 4.65 (d, 1H, $J_{1a,2a}$=7.6 Hz, H-1a), 4.61–4.19 (m, 14H, OCH_2Ph), 4.07 (t, 1H, *J*=8.9 Hz, H-4a), 3.89 (t, 1H, *J*=9.7 Hz, H-3b), 3.82–3.57 (m, 8H, H-2a, H-3a, H-5a, H-4b, H-5b, H-6), 3.48 (dd, 1H, H-2b), 3.41 (br d, 1H, *J*=9.9 Hz, H-6); δ_C ($CDCl_3$) 138.9, 138.8, 138.5, 138.2, 138.0, 137.9, 137.8, 137.3 [8C, $C_{ipso}(C_6H_5)$], 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.8, 126.7 (C_6H_5), 101.3 (C-1a), 96.8 (C-1b), 84.8 (C-3a), 82.8 (C-2a or C-2b), 82.0 (*C*H_2CC*C*H_2), 81.9 (C-3b), 79.4 (C-2a or C-2b), 77.7 (C-4b), 75.6, 75.1 (*C*H_2Ph), 74.6 (C-5a, *C*H_2Ph), 74.1, 73.5, 73.4, 73.3 (*C*H_2Ph), 72.6 (C-4a), 71.7 (*C*H_2Ph), 71.1 (C-5b), 69.1, 68.2 (C-6a, C-6b), 57.4, 56.2 (CH_2CCCH_2). Found: C, 77.46; H, 6.55. $C_{72}H_{74}O_{11}$ requires C, 77.53; H, 6.69.

4.3.10. 1-[Benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosid-4c-yl]-4-benzyloxymethyl-5-hydroxymethyl-1*H*-1,2,3-triazole and 1-[benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosid-4c-yl]-5-benzyloxymethyl-4-hydroxymethyl-1*H*-1,2,3-triazole 19 and 20. Heat-promoted 1,3-dipolar cycloaddition between azide **11** (1.00 g, 0.75 mmol) and alkyne **14** (530 mg, 3.00 mmol) for 4 h, following the procedure above described for the preparation of **12**, and subsequent purification of the crude product by column chromatography (7:3 light petroleum/EtOAc) afforded **19** (270 mg, 24%) and **20** (170 mg, 15%) as colourless oils. Compound **19**: TLC (light petroleum/EtOAc, 2:1) R_f 0.3; $[\alpha]_D^{20}$ +30 (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.06 (m, 48H, C_6H_5), 6.82–6.78 (m, 2H, C_6H_5), 5.83 (d, 1H, $J_{1c,2c}$=3.6 Hz, H-1c), 5.61 (d, 1H, $J_{1b,2b}$=3.3 Hz, H-1b), 5.03–4.92 (m, 4H, OCH_2Ph), 4.82–4.45 (m, 19H, OCH_2Ph, H-4′d, H-5′d), 4.56 (d, 1H, $J_{1a,2a}$=6 Hz, H-1a), 4.75–4.70 (m, 1H, H-5c), 4.44 (dd, 1H, $J_{2c,3c}$=9.9 Hz, $J_{3c,4c}$=11.7 Hz, H-3c), 4.22 (dd, 1H, $J_{3b,4b}$=9.2 Hz, $J_{4b,5b}$=9.2 Hz, H-4b), 4.12–4.06 (m, 2H, H-4a, H-3b), 4.06–3.98 (m, 2H, H-6′a, H-5b), 3.99–3.92 (m, 1H, H-4c), 3.88 (dd, 1H, $J_{5a,6a}$=4.1 Hz, $J_{6a,6a'}$=11.2 Hz, H-6a), 3.85–3.78 (m, 2H, H-3a, H-6b), 3.81 (d, 1H, *J*=10.0 Hz, OCH_2Ph), 3.66–3.54 (m, 4H, H-2a, H-5a, H-2b, H-6′b), 3.53 (dd, 1H, H-2c), 0.82 (d, 3H, $J_{5c,6c}$=6.1 Hz, H-6c); δ_C ($CDCl_3$) 141.4 (C-4d), 138.8, 138.4, 138.3, 138.2, 137.7, 137.5, 137.4, 137.1, 136.4 [10C, $C_{ipso}(C_6H_5)$], 136.3 (C-5d), 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 127.2, 126.7, 126.6 (50C, C_6H_5), 102.4 (C-1a), 95.9 (C-1c), 96.4

(C-1b), 84.7 (C-3a), 82.0 (C-2a, C-3b), 80.2 (C-2c), 79.7 (C-3c), 79.4 (C-2b), 75.8, 74.7 (O*C*H$_2$Ph), 74.6 (C-5a), 74.0, 73.9, 73.4 (O*C*H$_2$Ph), 73.3 (C-4a), 72.8, 72.7 (O*C*H$_2$Ph), 71.2 (C-4b), 71.0 (O*C*H$_2$Ph), 70.5 (C-5b), 68.8 (C-6a), 68.2 (C-6b), 66.2 (C-5c), 65.0 (C-4c), 63.5 (C-4′d), 52.2 (C-5′d), 17.4 (C-6c). Found: C, 73.57; H, 6.46; N, 2.80. $C_{92}H_{97}N_3O_{16}$ requires C, 73.63; H, 6.51; N, 2.80. Compound **20**: TLC (light petroleum/EtOAc, 2:1) R_f 0.2; $[\alpha]_D^{20}$ 47 (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.04 (m, 48H, C_6H_5), 6.82–6.78 (m, 2H, C_6H_5), 5.83 (d, 1H, $J_{1c,2c}$=3.6 Hz, H-1c), 5.61 (d, 1H, $J_{1b,2b}$=3.6 Hz, H-1b), 5.02–4.92 (m, 4H, OC*H*$_2$Ph), 4.82–4.35 (m, 19H, OC*H*$_2$Ph, H-4′d, H-5′d), 4.55 (d, 1H, $J_{1a,2a}$=7.6 Hz, H-1a), 4.75–4.67 (m, 1H, H-5c), 4.37 (dd, 1H, *J*=10.9 Hz, H-3c), 4.22 (dd, 1H, $J_{3b,4b}$=9.4 Hz, $J_{4b,5b}$=9.4 Hz, H-4b), 4.12–4.06 (m, 2H, H-4a, H-3b), 4.04–3.94 (m, 2H, H-6′a, H-5b), 4.00–3.95 (m, 1H, H-4c), 3.86 (dd, 1H, $J_{5a,6a}$=4.2 Hz, $J_{6a,6'a}$=10.7 Hz, H-6a), 3.83–3.76 (m, 2H, H-3a, H-6b), 3.78 (d, 1H, *J*=10.0 Hz, OC*H*$_2$Ph), 3.65–3.55 (m, 4H, H-2a, H-5a, H-2b, H-6′b), 3.46 (dd, 1H, H-2c), 0.82 (3H, $J_{5c,6c}$=6.1 Hz, H-6c); δ_C ($CDCl_3$) 145.2 (C-4d), 138.9, 138.8, 138.4, 138.3, 138.2, 137.9, 137.8, 137.7, 137.5, 136.8 [10C, $C_{ipso}(C_6H_5)$], 132.8 (C-5d), 127.8, 127.7, 127.6, 127.5, 127.3, 126.8, 126.6 (50C, C_6H_5), 102.4 (C-1a), 97.0 (C-1c), 96.5 (C-1b), 84.6 (C-3a), 82.0 (C-2a, C-3b), 80.6 (C-2c), 80.1 (C-3c), 79.4 (C-2b), 75.6, 74.7 (O*C*H$_2$Ph), 74.6 (C-5a), 73.9 (O*C*H$_2$Ph), 73.5 (C-4a), 73.3, 72.9, 72.7, 72.4 (O*C*H$_2$Ph), 71.2 (C-4b), 71.0 (O*C*H$_2$Ph), 70.5 (C-5b), 68.8 (C-6a), 68.2 (C-6b), 66.4 (C-5c), 65.1 (C-4c), 58.8 (C-5′d), 56.0 (C-4′d), 17.4 (C-6c). Found: C, 73.96; H, 6.55; N, 2.93. $C_{92}H_{97}N_3O_{16}$ requires C, 73.63; H, 6.51; N, 2.80.

4.3.11. 1-[Benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosid-4c-yl]-4-benzyloxymethyl-5-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazole 18. To a solution of donor **15** (176 mg, 0.17 mmol) and acceptor **19** (130 mg, 0.087 mmol) in toluene (1 mL) at rt were successively added NIS (39 mg, 0.173 mmol) and Cu(OTf)$_2$ (6.3 mg, 0.017 mmol). After stirring for 30 min, the reaction was quenched by adding Et_3N (10 μL) and diluted with Et_2O (25 mL). The mixture was then washed with a 20% aqueous solution of sodium thiosulfate (2×10 mL) and water (2×10 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the residue was purified by column chromatography (light petroleum/EtOAc, 4:1) to give **18** (42 mg, 20%) as a colourless oil; TLC (light petroleum/EtOAc, 7:3) R_f 0.3; $[\alpha]_D^{20}$ +55 (*c* 1.0 in $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.04 (m, 83H, C_6H_5), 6.81–6.78 (m, 2H, C_6H_5), 5.81 (d, 1H, *J*=3.3 Hz, H-1c), 5.65 (d, 1H, *J*=3.6 Hz, H-1f), 5.59 (d, 1H, *J*=3.3 Hz, H-1b), 5.00 (d, 1H, *J*=3.6 Hz, H-1e), 5.00–3.38 (m, 34H OC*H*$_2$Ph, 28H carbohydrate, H-4′d, H-5′d), 4.55 (d, 1H, *J*=7.6 Hz, H-1a), 0.80 (d, 3H, *J*=6.1 Hz, H-6c); δ_C ($CDCl_3$) 141.9 (C-4d), 138.9, 138.8, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 137.9, 137.8, 137.5, 137.2 [17C, $C_{ipso}(C_6H_5)$], 134.2 (C-5d), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.9, 126.8, 126.6 (85C, C_6H_5), 102.4 (C-1a), 96.9 (C-1f), 96.6 (C-1b), 96.1 (C-1c), 95.2 (C-1e), 84.7, 82.0, 81.9, 80.2, 79.9, 79.8, 79.5, 79.4, 77.7, 75.6, 75.0, 74.7, 74.2, 74.0, 73.7, 73.5, 73.3, 73.1, 72.9, 72.8, 72.4, 72.0, 71.3, 71.0, 70.6, 70.1, 69.0, 68.8, 68.2, 66.6, 65.9, 65.0 (28C carbohydrate, 34 O*C*H$_2$Ph), 59.7 (C-4′d), 58.3 (C-5′d), 17.4 (C-6c). Found: C, 75.25; H, 6.59; N, 1.79. $C_{153}H_{159}N_3O_{26}$ requires C, 74.83; H, 6.52; N, 1.71.

4.3.12. 1-[Benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosid-4c-yl]-5-benzyloxymethyl-4-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazole and 1-[benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosid-4c-yl]-5-benzyloxymethyl-4-[2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazole 17 and 22. NIS (45 mg, 0.20 mmol) and Cu(OTf)$_2$ (10 mg, 0.03 mmol) were successively added to a solution of donor **15** (203 mg, 0.20 mmol) and acceptor **20** (200 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) at rt. After stirring for 30 min and quenching with Et_3N (10 μL), the reaction mixture was diluted with Et_2O (25 mL), washed with a 20% aqueous solution of sodium thiosulfate (2×10 mL) and water (2×10 mL), dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting crude oil was purified by column chromatography (light petroleum/EtOAc, 4:1) to give **17** (60 mg, 18%) and **22** (40 mg, 12%) as colourless oils. Compound **17**: TLC (hexane/Et_2O, 3:2) R_f 0.2; $[\alpha]_D^{20}$ +49 (*c* 1.4 in $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.04 (m, 83H, C_6H_5), 6.81–6.78 (m, 2H, C_6H_5), 5.81 (d, 1H, $J_{1c,2c}$=3.0 Hz, H-1c), 5.69 (d, 1H, $J_{1f,2f}$=3.6 Hz, H-1f), 5.60 (d, 1H, $J_{1b,2b}$=3.3 Hz, H-1b), 5.00 (d, 1H, $J_{1e,2e}$=3.6 Hz, H-1e), 5.01–3.38 (m, 34H OC*H*$_2$Ph, 28H carbohydrate, H-4′d, H-5′d), 4.55 (d, 1H, $J_{1a,2a}$=7.6 Hz, H-1a), 0.80 (d, 3H, $J_{5c,6c}$=5.8 Hz, H-6c); δ_C ($CDCl_3$) 141.9 (C-4d), 138.9, 138.8, 138.5, 138.4, 138.3, 138.2, 138.0, 137.9, 137.8, 137.7, 137.5, 137.2 [17C, $C_{ipso}(C_6H_5)$], 134.2 (C-5d), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 126.7, 126.6 (85C, C_6H_5), 102.4 (C-1a), 96.9 (C-1f), 96.6 (C-1b), 96.1 (C-1c), 95.2 (C-1e), 84.7, 82.0, 81.9, 80.2, 79.9, 79.8, 79.4, 77.6, 75.6, 75.0, 74.7, 74.2, 74.0, 73.7, 73.5, 73.3, 73.2, 73.1, 72.9, 72.8, 72.4, 72.0, 71.3, 71.0, 70.5, 70.1, 69.0, 68.8, 68.1, 66.6, 65.9, 65.0 (28C carbohydrate, 34 O*C*H$_2$Ph), 59.7 (C-4′d), 58.3 (C-5′d), 17.4 (C-6c); *m/z* (ESMS) 2477.1124 ([M+Na]$^+$. $C_{153}H_{159}N_3O_{26}Na$ requires 2477.1110). Compound **22**: TLC (hexane/Et_2O, 3:2) R_f 0.1; $[\alpha]_D^{20}$ +35 (*c* 1.4 in $CHCl_3$); δ_H ($CDCl_3$) 7.40–7.04 (m, 83H, C_6H_5), 6.81–6.78 (m, 2H, C_6H_5), 5.80 (d, 1H, $J_{1c,2c}$=3.6 Hz, H-1c), 5.68 (d, 1H, $J_{1f,2f}$=3.6 Hz, H-1f), 5.59 (d, 1H, $J_{1b,2b}$=3.6 Hz, H-1b), 5.08–3.38 (m, 34H OC*H*$_2$Ph, 28H carbohydrate, H-4′d, H-5′d), 4.56 (d, 1H, $J_{1e,2e}$=8.0 Hz, H-1e), 4.55 (d, 1H, $J_{1a,2a}$=7.6 Hz, H-1a), 0.80 (d, 3H, $J_{5c,6c}$=6.1, Hz, H-6c); δ_C ($CDCl_3$) 142.0 (C-4d), 138.9, 138.8, 138.4, 138.3, 138.2, 138.1, 137.9, 137.8, 137.7, 137.5, 137.0 [17C, $C_{ipso}(C_6H_5)$], 134.0 (C-5d), 128.5, 128.4, 128.3, 127.8, 127.6, 127.3, 127.1, 126.7, 126.6 (85C, C_6H_5), 102.6 (C-1e), 102.4 (C-1a), 96.8 (C-1f), 96.6 (C-1b), 96.1 (C-1c), 84.7, 82.0, 80.0, 79.8, 79.5, 79.3, 77.7, 75.6, 75.4, 75.1, 74.7, 74.6, 74.5, 74.0, 73.4, 73.3, 72.9, 72.8, 72.4, 72.2, 71.2, 71.0, 70.5, 68.8, 68.1, 66.5, 65.9, 65.0 (28C carbohydrate, 34 O*C*H$_2$Ph), 61.6 (C-4′d), 58.4 (C-5′d), 17.3 (C-6c); *m/z*

(ESMS) 2477.1126 $[M+Na]^+$. $C_{153}H_{159}N_3O_{26}Na$ requires 2477.1110.

4.3.13. 1-[4,6-Dideoxy-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranos-4c-yl]-4-hydroxymethyl-5-[α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazole 21. Pseudohexasaccharide **21** (35 mg, 95%) was obtained from **18** (100 mg, 0.04 mmol), following the procedure above described for the preparation of **13**, as a white foam; $[\alpha]_D^{20}$ +227 (*c* 1.5 in H_2O); TLC (EtOAc/MeOH/water, 5:3:2) R_f 0.2; δ_H (D_2O) 5.48 (d, 1H, $J_{1c,2c}$=3.3 Hz, H-1c), 5.38 (d, 1H, $J_{1b,2b}$=3.6 Hz, H-1b), 5.32 (d, 1H, $J_{1f,2f}$=3.6 Hz, H-1f), 5.19 (d, 1H, $J_{1a,2a}$=3.6 Hz, H-1a α-anomer), 5.05 (d, 1H, $J_{1e,2e}$=3.3 Hz, H-1e), 4.97 (d, 1H, J=12.2 Hz, H-5′d), 4.74 (d, 1H, H-5′d′), 4.65 (s, 2H, H-4′d), 4.63–4.54 (m, 1H, H-5c), 4.62 (d, 1H, $J_{1a,2a}$=8.1 Hz, H-1a β-anomer), 4.33 (t, 1H, $J_{2c,3c}=J_{3c,4c}$=9.7 Hz, H-3c), 4.26 (dd, 1H, $J_{4c,5c}$= 9.9 Hz, H-4c), 4.00–3.48 (m, 24H, H carbohydrate, H-2a α-anomer), 3.37 (t, 1H, $J_{3f,4f}=J_{4f,5f}$=9.7 Hz, H-4f), 3.24 (dd, 1H $J_{2a,3a}$=8.9 Hz, H-2a β-anomer), 0.97 (d, 3H, J= 6.1 Hz, H-6c); δ_C (D_2O) 144.0 (C-4d), 133.9 (C-5d), 100.2 (C-1c), 100.1 (C-1f), 99.8 (C-1b), 98.4 (C-1e), 96.1 (C-1a β-anomer), 92.2 (C-1a α-anomer), 81.7, 81.5, 77.8, 77.6, 77.3, 76.6, 75.8, 75.1, 74.8, 74.7, 74.3 (C-2a β-anomer), 73.9, 73.8, 73.3, 73.0, 70.2 (C carbohydrate), 71.4 (C-3c), 69.6 (C-4f), 67.7 (C-5c), 65.6 (C-4c), 60.9–60.6 (C-6a, C-6b, C-6e, C-6f), 56.5 (C-5′d), 54.1 (C-4′d), 16.4 (C-6c). Found: C, 39.87; H, 6.24. $C_{34}H_{57}N_3O_{26}\cdot 5.5\ H_2O$ requires C, 39.92; H, 6.70.

4.3.14. 1-[4,6-Dideoxy-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranos-4c-yl]-5-[α-D-glucopyranosyl-(1→4)-β-D-glucopyranosyloxymethyl]-4-hydroxymethyl-1*H*-1,2,3-triazole 23. Compound **23** (12 mg, 95%) was obtained from **22** (35 mg, 0.01 mmol) as a white foam following the procedure above described for the preparation of **13**. *m/z* (ESMS) 946.3128 ($[M+Na]^+$). $C_{34}H_{57}N_3O_{26}Na$ requires 946.3128; $[\alpha]_D^{20}$ +8 (*c* 0.1 in H_2O); TLC (EtOAc/MeOH/water, 5:3:2) R_f 0.2; δ_H (D_2O) 5.48 (d, 1H, $J_{1c,2c}$=3.6 Hz, H-1c), 5.39 (d, 1H, $J_{1b,2b}$= 3.8 Hz, H-1b), 5.36 (d, 1H, $J_{1f,2f}$=3.8 Hz, H-1f), 5.19 (d, 1H, $J_{1a,2a}$=3.6 Hz, H-1a α-anomer), 4.99 (d, 1H, J= 12.7 Hz, H-4d′), 4.87 (d, 1H, H-4′d′), 4.80 (s, 2H, H-5d′), 4.63–4.56 (m, 1H, H-5c), 4.61 (d, 1H, $J_{1a,2a}$=7.9 Hz, H-1a β-anomer), 4.53 (d, 1H, $J_{1e,2e}$=7.9 Hz, H-1e), 4.33–4.25 (m, 2H, H-3c, H-4c), 4.00–3.48 (m, 23H, H carbohydrate, H-2a α-anomer), 3.37 (t, 1H, $J_{3f,4f}=J_{4f,5f}$=9.5 Hz, H-4f), 3.27 (dd, 1H, $J_{2e,3e}$=12.5 Hz, H-2e), 3.23 (dd, 1H, $J_{2a,3a}$= 9.4 Hz, H-2a β-anomer),0.96 (d, 3H, J=6.1 Hz, H-6c); δ_C (D_2O) 142.0 (C-4d), 137.5 (C-5d), 101.6 (C-1e), 100.2 (C-1c), 99.8 (C-1b, C-1f), 96.1 (C-1a β-anomer), 92.2 (C-1a α-anomer), 77.2, 77.0, 75.4, 74.8, 73.7, 73.5, 72.5, 71.9, 70.1, 60.7 (C carbohydrate), 61.5 (C-4′d), 51.0 (C-5′d), 16.5 (C-6c); *m/z* (ESMS) 946.3128 ($[M+Na]^+$). $C_{34}H_{57}N_3O_{26}Na$ requires 946.3128.

4.3.15. 1-[(4,6-Dideoxy-α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→4)-D-glucopyranos-4c-yl)]-4-[α-D-glucopyranosyl-(1→4)-α-D-glucopyranosyloxymethyl]-5-hydroxymethyl-1*H*-1,2,3-triazole 24. Compound **24** (19 mg, 95%) was obtained from **17** (50 mg, 0.02 mmol) as a white foam following the procedure above described for the preparation of **13**; $[\alpha]_D^{20}$ +111 (*c* 0.8 in H_2O); TLC (EtOAc/MeOH/water, 5:3:2) R_f 0.2; δ_H (D_2O) 5.48 (d, 1H, $J_{1c,2c}$=3.6 Hz, H-1c), 5.39 (d, 1H, $J_{1b,2b}$=3.8 Hz, H-1b), 5.34 (d, 1H, $J_{1f,2f}$=3.6 Hz, H-1f), 5.19 (d, 1H, $J_{1a,2a}$= 3.8 Hz, H-1a α-anomer), 5.00 (d, 1H, $J_{1e,2e}$=3.6 Hz, H-1e), 4.86–4.70 (m, 2H, H-4′d), 4.76 (s, 2H, H-5′d), 4.62 (d, 1H, $J_{1a,2a}$=7.8 Hz, H-1a β-anomer), 4.60–4.56 (m, 1H, H-5c), 4.30–4.25 (m, 2H, H-3c, H-4c), 3.97–3.50 (m, 24H, H carbohydrate, H-2a α-anomer), 3.36 (dd, 1H, $J_{3f,4f}=J_{4f,5f}$= 9.5 Hz, H-4f), 3.20 (dd, 1H, $J_{2a,3a}$=9.4 Hz, H-2a β-anomer), 0.96 (d, 3H, J=6.1 Hz, H-6c); δ_C (D_2O) 141.9 (C-4d), 137.6 (C-5d), 100.2 (C-1c), 99.9 (C-1f), 99.8 (C-1b), 98.2 (C-1e), 96.1 (C-1a β-anomer), 92.2 (C-1a α-anomer), 77.8, 77.6, 77.3, 77.0, 75.4, 74.3 (C-2 β-anomer), 74.2, 74.1, 73.7, 73.0, 72.5, 72.4, 72.3, 72.1, 71.9, 71.8, 70.7, 70.1 (C carbohydrate), 71.3 (C-3c), 67.7 (C-5c), 65.4 (C-4c), 61.0–60.6 (C-6a, C-6b, C-6e, C-6f), 60.1 (C-4′d), 50.9 (C-5′d), 16.5 (C-6c); *m/z* (ESMS) 946.3150 ($[M+Na]^+$). $C_{34}H_{57}N_3O_{26}Na$ requires 946.3128.

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Dialkyl quinone-2,3-dicarboxylates in the Nenitzescu reaction

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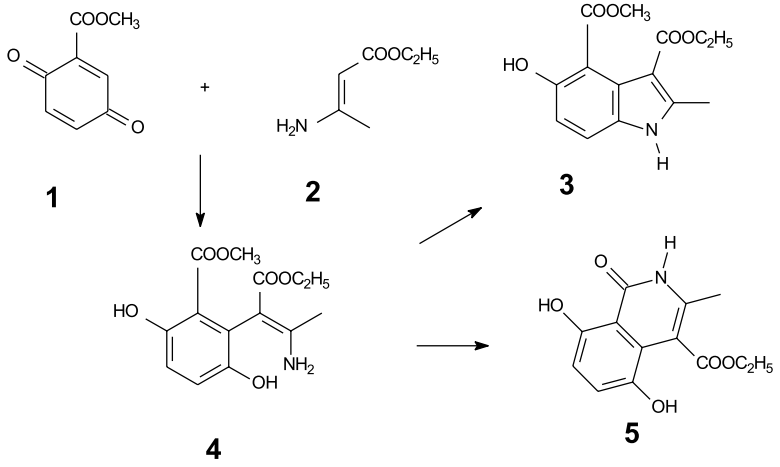
Abstract—Diethyl naphthoquinone-2,3-dicarboxylate reacts with different enamines to give 5-oxo-1,5-dihydro-benzo[*g*]indole-3,4,9b-tricarboxylate derivatives by migration of one ethoxycarbonyl group. These new products aromatize to planar indoles by elimination of one ethoxycarbonylgroup. With an *N*,*N*-dimethyl-enamine cyclization yields a 5-oxo-4,5-dihydro-cyclopenta[*a*]naphthalene-3,3a,4-tricarboxylate as well as a naphthyl-malonic acid derivative by migration of an ethoxycarbonylgroup.

1. Introduction

Continuing our work in the Nenitzescu reaction we have investigated the reaction of dialkyl quinone dicarboxylates with enamines, not known so far. In the literature some experience is available with monoalkyl benzoquinone carboxylate **1**. According to Allen and Weiss[1] methyl benzoquinone-2-carboxylate **1** and 3-aminocrotonate **2** yield (Scheme 1) the hydroquinone adduct **4**, which can be cyclized to indole **3** in a normal Nenitzescu reaction. Furthermore, the isoquinoline derivative **5** was, isolated, which is produced by intramolecular aminolysis of **4**.

In connection with our efforts to synthesize new heterocyclic compounds **9** with cytostatic activity[2–4], presumed to act via DNA-intercalation, we developed a special Nenitzescu reaction (Scheme 2),[2,5–7] starting with enaminones **7** completely substituted in position 2 instead of the 3-amino-crotonates **2** normally used. This reaction was accomplished by intramolecular rearrangement of a spiro-intermediate **8**[2,5–7] with ring enlargement by 1,2-shift of carbonyl and subsequent oxidation to **9**.

Continuing this work, we have investigated the reaction of alkyl β-aminocrotonates **11** with a completely substituted



Scheme 1.

Keywords: Quinones; Nenitzescu; Ethoxycarbonyl migration; Sigmatropic 1,2-shift.
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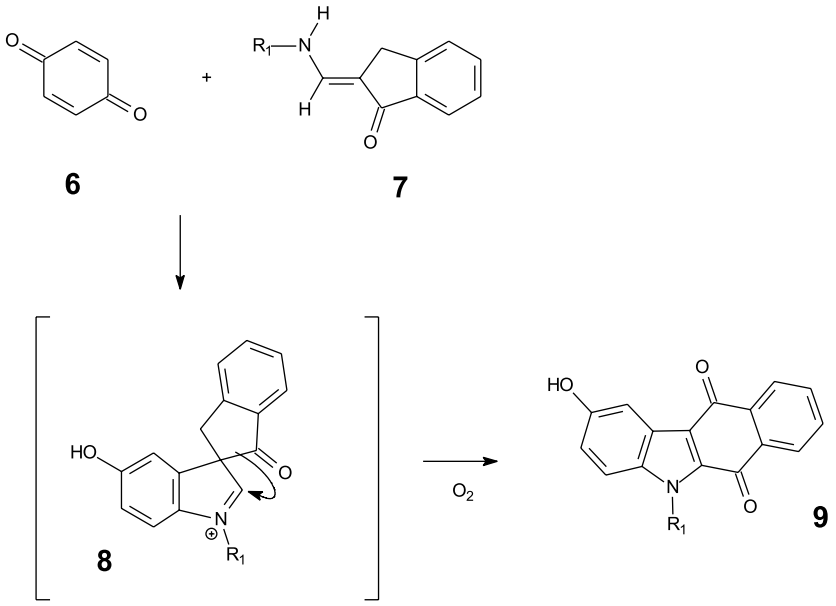


Scheme 2.

quinone-structure **10** activated by two electron-withdrawing substituents. Being aware of the fact that the normal Nenitzescu reaction would not be possible, we were hoping to get further insight into the mechanism of this reaction, to increase the chemical potency of this simple reaction and to obtain new heterocyclic structures with potential cytostatic activity.

2. Chemical results and discussion

The reaction (Scheme 3) of diethyl naphthoquinone-2,3-dicarboxylate **10**[8] and enaminones **11a**,**b**,**c** could lead to indole-5-one derivatives **14** or **15a**,**b**,**c**. Products were isolated in yields of 23–56%.

The reaction involves attack on a completely substituted quinone-C=C-bond and the unusual migration of an ethoxycarbonyl group. First,[9] we assumed a rearrangement of the adduct **13** to indolone **15**, because migration to position 4 appeared to be reasonable (structure **13b**).

This structure seemed to be confirmed by ^{13}C NMR-spectroscopy of the *N*-benzyl derivative showing an sp^2-singlet for the ketocarbonyl group (C-5) $\delta=181.35$ ppm and an sp^3-singlet for C-4 $\delta=79.47$ ppm. However, the λ_{max} 434 nm (log $\varepsilon=4.1$) did not fit this structure, because no corresponding conjugation between donor and acceptor atom is possible. However, structure **14** explains the UV–vis absorption due to the aminodienone part. Now we have checked the structure by X-ray-analysis, which clearly shows migration of an ethoxycarbonyl group not to C-4 but to C-9b. Hence we obtained benzindolone—structure **14** (Fig. 1) and not **15**.

Correspondingly the ^{13}C NMR signal as singlet ($\delta=$ 79.5 ppm) had to be assigned to C-9b of **14b**. Migration of the ethoxycarbonyl group may have occurred at the stage of the iminium ion **13a** via 1,2-shift similar to the synthesis of the carbazole derivative **9**.[2]

Reaction of the *N*-unsubstituted enaminone **11d** and the quinone **10** gives a product, for which the ^{1}H and ^{13}C NMR-spectroscopic data as well as the UV absorption maximum at 334 nm, log $\varepsilon=4.0$ are in accordance with structure **17**. The corresponding UV–vis maximum of **14b** is observed at longer wavelengths.

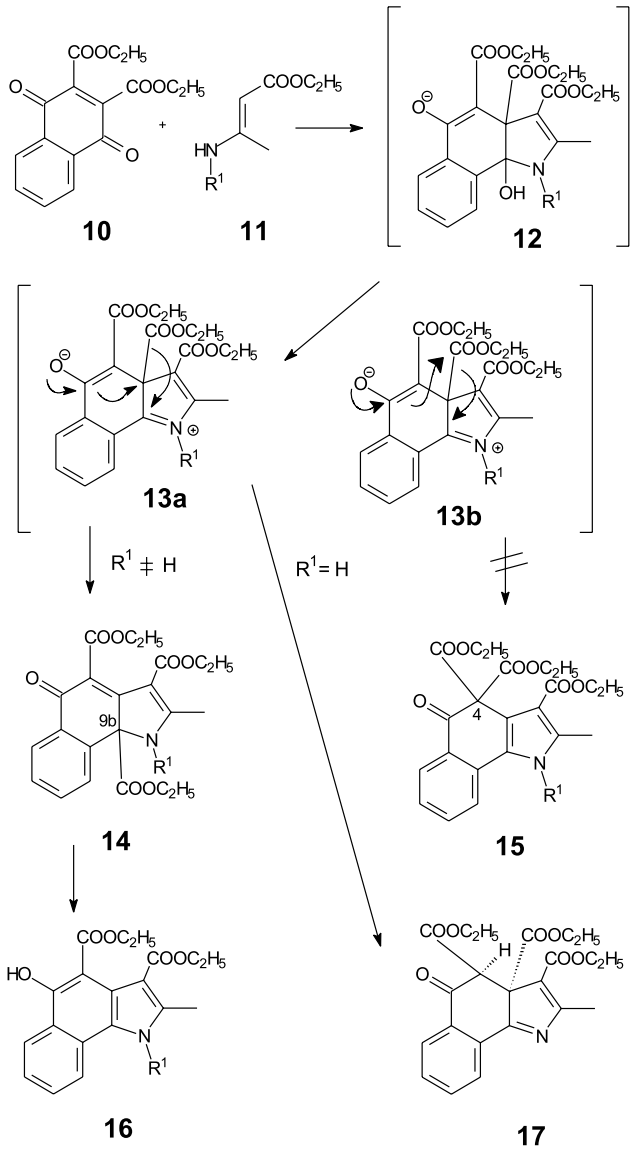
In the case of the intermediate **13** ($R^1=H$) deprotonation to indolone **17** is possible without ethoxycarbonyl migration.

Compounds **14a**,**b**,**c** and **17** are unstable in boiling acetic acid and thus, yielded flat aromatic indoles **16a**,**b**,**c** and **d** via elimination of an ethoxycarbonyl group. The loss of aminodienone structure is accompanied by hypsochromic shift of the UV–vis maximum to 367 nm.

In the reaction of quinone **10** with *N*-unsubstituted β-cyano-enamine **18** indolone **22** and indole **20** as well as another product of a different structure could be isolated. Due to the greater—M-effect of the cyano group the electrophilic character in position 9b is increased in intermediate **19** with the consequence of ethoxycarbonyl migration to indolone **22**. Due to the similar chromophor of indolones **14** and **22** the UV–vis maximum for **22** is observed at similar wavelength: 420 nm (log $\varepsilon=4.05$). Again a hypsochromic shift to 368 nm (log $\varepsilon=3.82$) is observed for indole **20**. Indolone **22** is unstable in acetic acid (100 °C/10 min) and yields (87%) indole **20** (Scheme 4).

Spectroscopic investigation of the third product showed no signal for the enamine methyl group in the range of $\delta=2.0$–2.5 ppm. According to MS- and ^{1}H NMR-spectroscopic data the product results from the reaction of two quinone molecules **10** with enaminone **18**. Spectral data support the existence of structure **21** since the ^{1}H NMR-spectrum in $CDCl_3$ shows an AB-system for a CH_2-group ($\delta=3.2$ and 3.7 ppm, $J=13$ Hz).

Final proof is given by the X-ray-analysis of **21** shown in Figure 2.



Scheme 3.

Apparently, the enaminonemethyl group can react by nucleophilic addition to quinone **10**.

On this basis it seemed reasonable to investigate the reaction of enaminone **23** with a tertiary nitrogen group in order to limit the reaction to the methyl group with no possibility for further reaction at nitrogen. Thus, we attempted the synthesis of **24** (Scheme 5).

However, the reaction between enaminone **23** and quinone **10** did not yield the expected compound **24** resulting from ethoxycarbonyl migration but two isomeric cyclopentanaphthalene derivatives **27** and **28** were isolated instead. Isomer **27** was unstable and rearranged to epimer **28** in $CDCl_3$ or DMSO. The structure assignement of **28** is based on the ^{1}H NMR-spectrum ($CDCl_3$), which shows a singlet for an sp^3-C–H group at 4.85 ppm. The singlet for the corresponding group in the unstable isomer **27** appeared at 3.30 ppm. The ^{13}C NMR-spectrum ($CDCl_3$) of **28** shows a

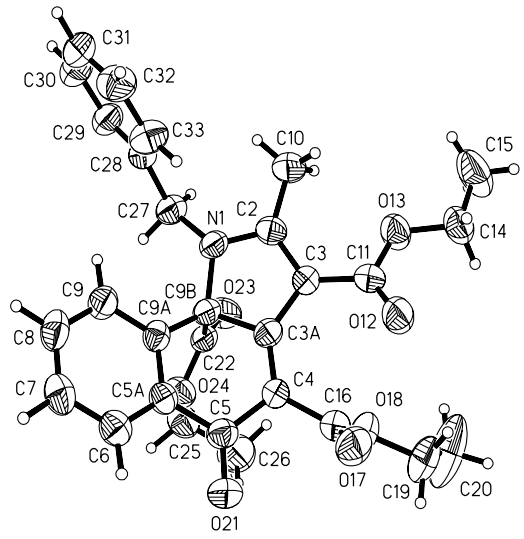
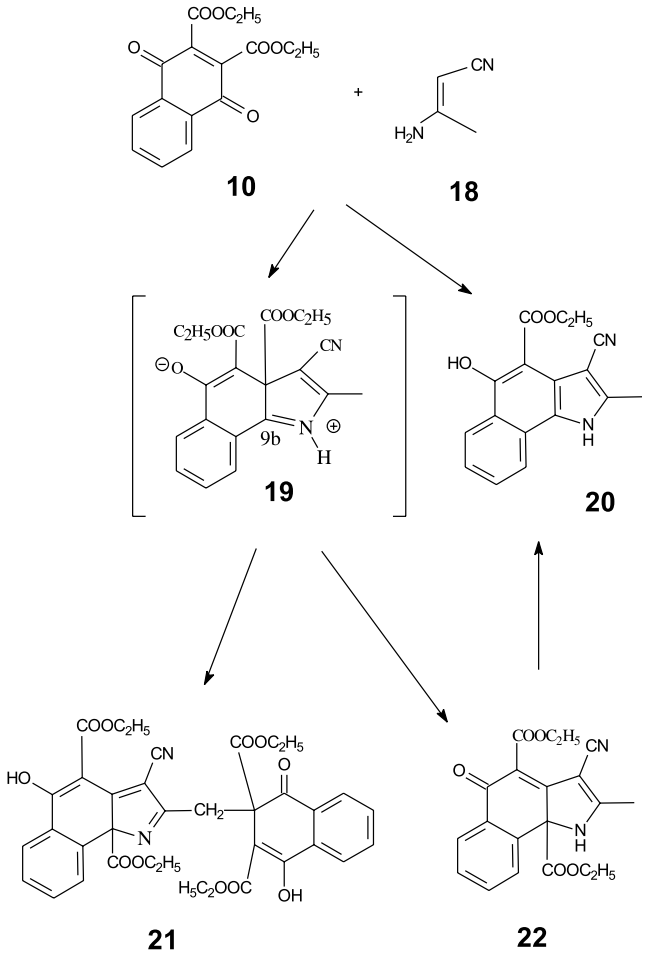


Figure 1. The X-ray crystal structure of **14b**. Displacement ellipsoids are drawn at the 30% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. **14b** is racemic; only one enantiomer is shown.

doublet at 60.2 ppm for C-4 and a singlet at 65.6 ppm for C-3a. Structure **28** was proven by X-ray-analysis (Fig. 3).

The change in the ^{1}H NMR-spectrum of **27** to **28** is caused by the configurational change of C-4 due to



Scheme 4.

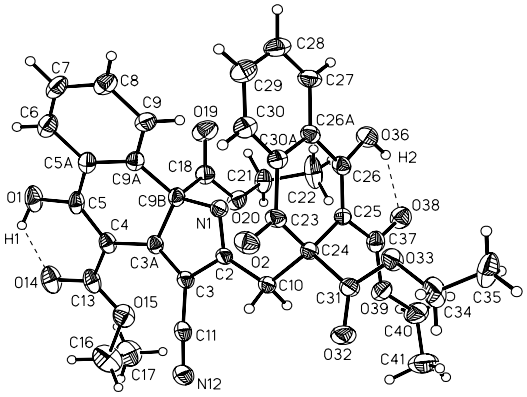


Figure 2. Structure of **21** crystallized with 0.5 mol C_6H_{12}. Displacement ellipsoids are drawn at the 20% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. Note that a conformational disorder of the ethoxycarbonyl group at C9B in the crystal was found. Only the higher populated conformation is drawn. **21** is racemic; only one enantiomer is shown.

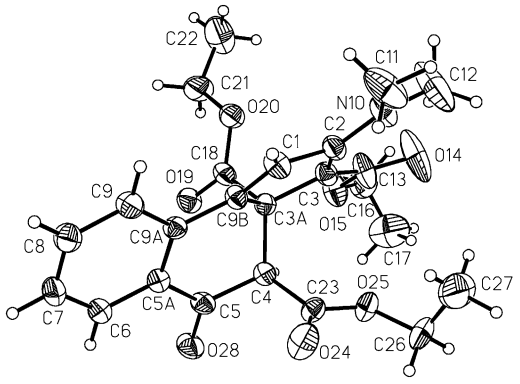
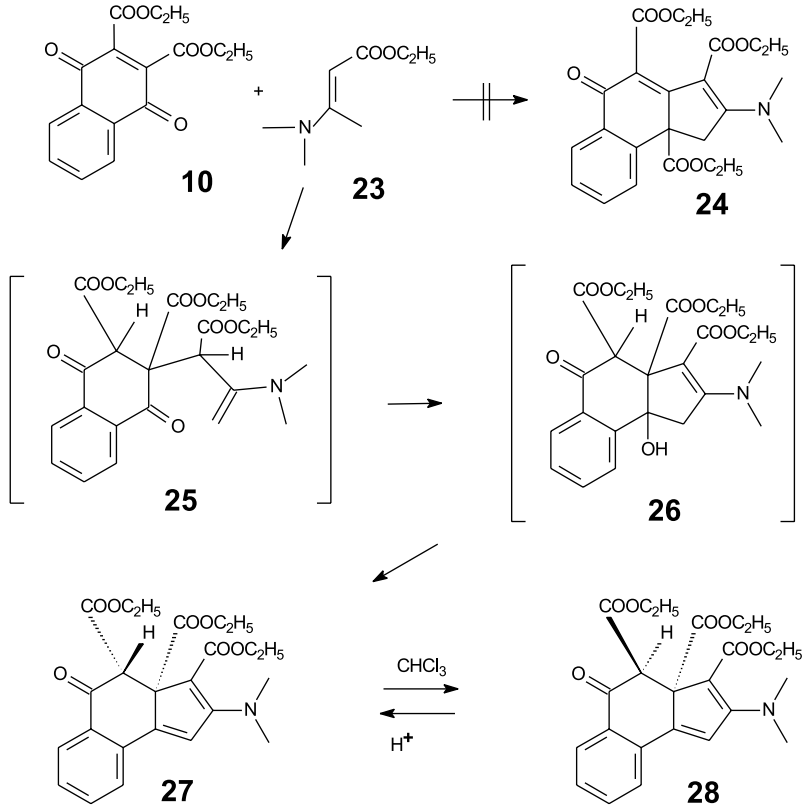


Figure 3. X-ray crystal structure of **28**. Displacement ellipsoids are drawn at the 30% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. **28** is racemic, only one enantiomer is shown.

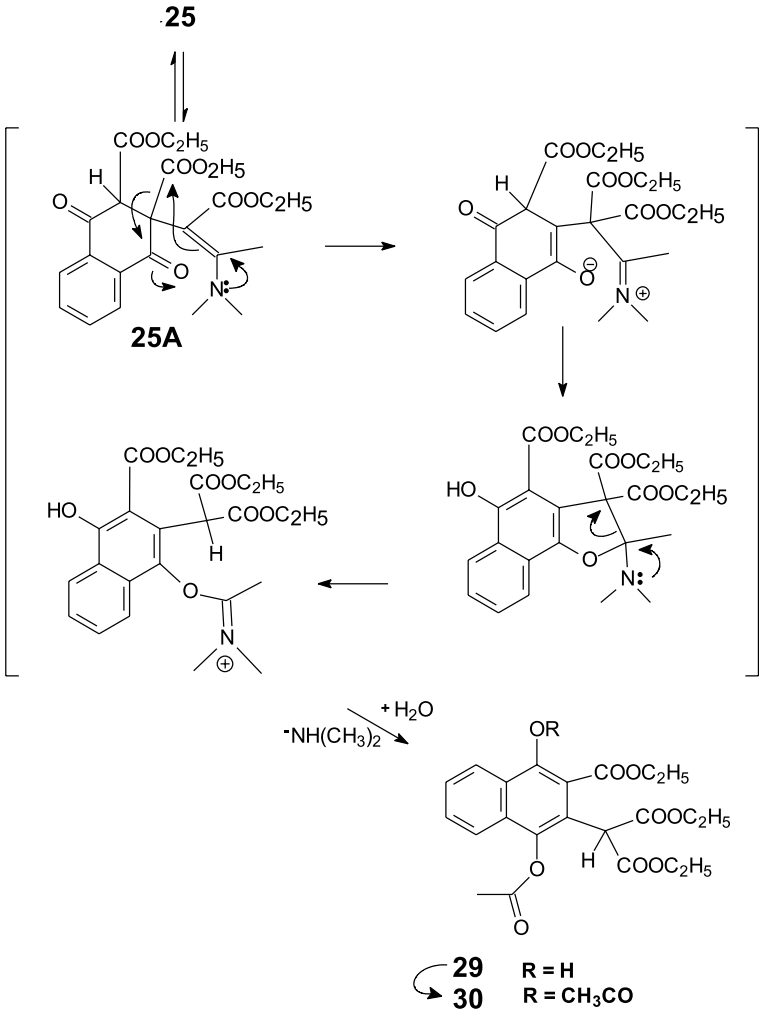
keto-enol-tautomerism. In agreement with the *trans*-position of 4-H and 3a-$COOC_2H_5$ in structure **27** the signal for 4-H appears in the ^1H NMR-spectrum at $\delta = 3.3$ ppm. Corresponding to the *cis*-position of 4-H and the 3a-carbonyl group in structure **28** a downfield shift to $\delta =$ 4.85 ppm was observed. The rearrangement of **27** to **28** is reversible. Treatment of **28** with acetic acid yields **27**. Upon treating **27** with perchloric or trifluoracetic acid no ethoxycarbonyl migration could be observed.

From the reaction of quinone **10** and enaminone **23** a colourless product was isolated in addition to **27** and **28**. The elemental analysis indicated no presence of nitrogen in the product. Spectroscopic investigation did not fit possible structures **31** or **32**. In the end spectral analysis lead to malonester structure **29**, which was in agreement with all data. The same was the case with the acetyl-derivative **30**, which was syntesized from **29** with acetic anhydride. In Scheme 6 a mechanism for the formation of structure **29** is proposed, which is initiated by intramolecular ethoxycarbonyl migration to the enamine structure in the primary adduct **25A**.

During our efforts to establish the structure of **29**, we investigated the reaction of quinone **10** and ethyl acetoacetate under the same conditions, however, the



Scheme 5.

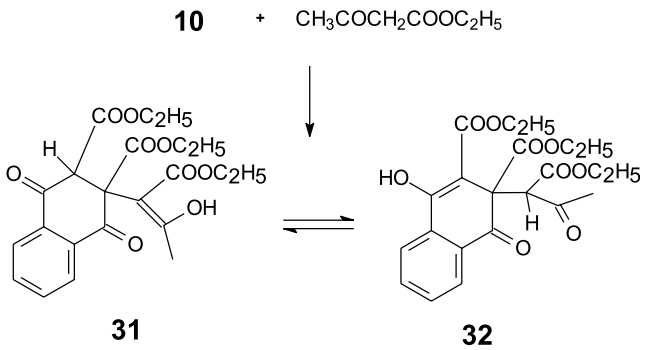


Scheme 6.

product was not identical with the nitrogen free compound from quinone **10** and enamine **23**. (Scheme 7).

^{13}C NMR-spectroscopic data of this product corresponds to structure **32** since signals for the acetyl group were observed: 202.2s (CO) and 33.1q (CH_3) ppm.

After successful realization of these reactions we investigated the reaction of simple dimethyl benzoquinone-2,3-dicarboxylate **33**[10,11] instead of the benzocondensed system **10** with alkyl aminocrotonates **11a**,**b**,**c**.



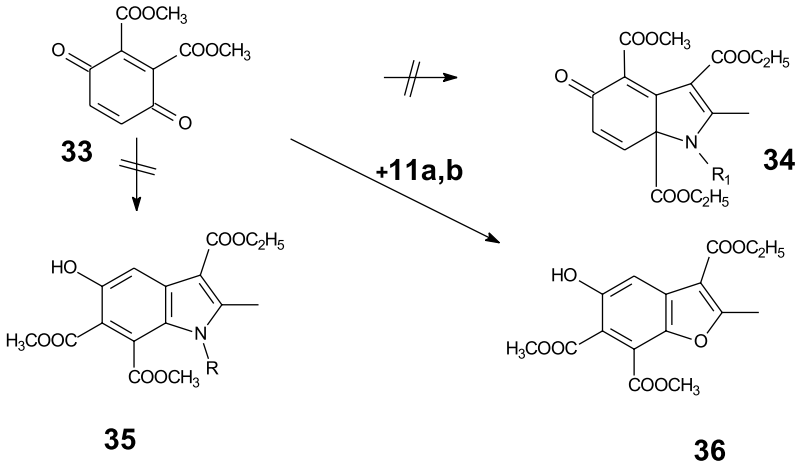
Scheme 7.

Quinone **33** can react by two alternative routes: attack of enamine on C-2 yielding indolone **34** (in analogy to formation of indolone **14** from quinone **10**) or attack on C-5 leading to the normal Nenitzescu product **35**.

The results with enamines **11a–c** were different. *N*-Alkylaminocrotonates **11a**,**b** followed the pathway via attack on C-5. Benzofuran **36** was isolated (Scheme 8), due to fast aromatization to a phenolic intermediate and nucleophilic attack of oxygen to iminium ion yielding the furanring. No formation of indolone **34** or indole **35** was observed.

The reaction (Scheme 9) of ethyl-3-(4-tolylamino)crotonate **11c** and quinone **33** was the result of an attack at C-6 and C-2 of the quinone by addition of two enaminone molecules yielding a dipyrroloindole.

According to MS-, ^{1}H NMR-spectra and elemental analysis three structures **39**, **40** or **41** were possible, but only **41** was in agreement with all spectroscopic data, for example, the signal for one aromatic proton (4-H) $\delta = 9.07$ ppm was shifted paramagnetic by two carbonyl groups and the



Scheme 8.

signal for methoxycarbonylgroup $\delta = 2.50$ ppm (shifted diamagnetic by two aromatic rings).

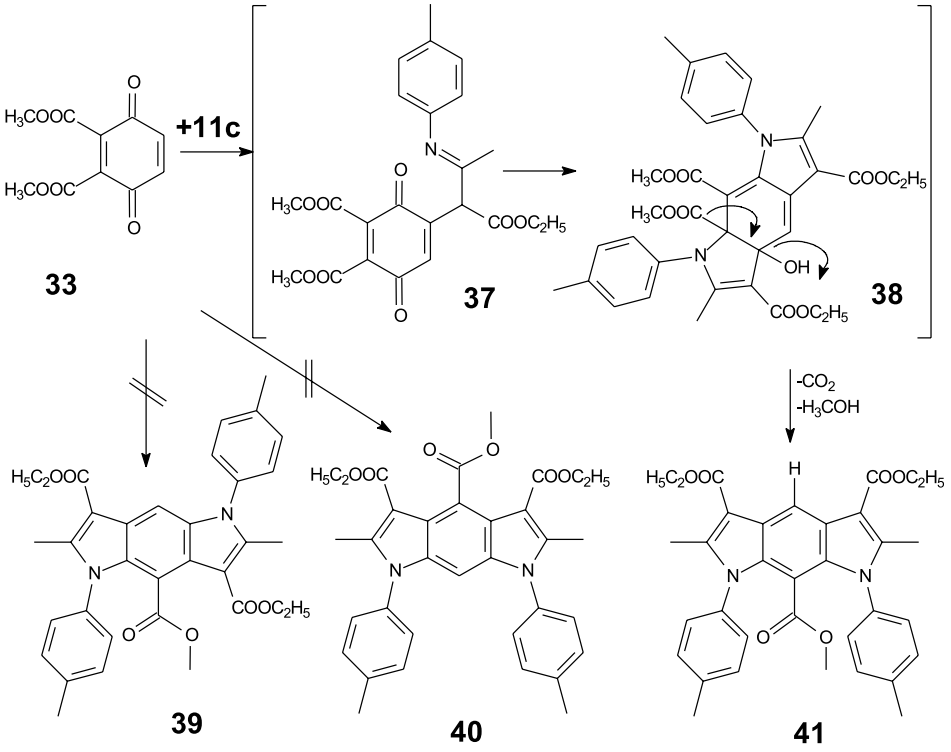
3. Pharmacological results

Contrary to our expectation the planar indole **16b** was inactive as anticancer agent in the initial NCI-assay in a concentration of 1×10^{-4} mol/l against NCI-H460-, MCF-7 and SF-268-carcinom cell lines. The same was observed with pyrroloindole **41**.

The non-planar indol-5-one **14c**, however, reached the mean test of the NCI and showed a significant anticancer response in the 60 cell line in vitro test: log GI50 (growth inhibition of 50%): -4.61, however, the log GI50 value -6.13 for the drug Mitomycin was not reached.

4. Conclusion

The chemistry of quinones with electron-withdrawing substituents and enamines opened new ways to interesting new heterocyclic structures. The structure of benzo[*g*] indolone derivatives **14** can be regarded as a new leader to develop cytostatic drugs. It was shown that tertiary aminocrotonates, usually producing benzo-furanes in the Nenitzescu reaction[12] are able to cyclize to cyclopent[*a*]-naphthalene derivatives via a methyl group as nucleophile, if quinone carbonyl is not able to enolize (as in structure **25**).



Scheme 9.

This opens new possibilities in addition and cyclization chemistry of aminocrotonates.

Furthermore, the easy migration of the ethoxycarbonyl group via anionotropic 1,2-shift to iminium-carbon in 3*H*-pyrrol ring (intermediate **13** and **20**) could be demonstrated. Cationotropic 1,2-shift of ethoxycarbonyl group to enamine-β-C-atom apparently is possible too, as shown in intermediate **25A**.

5. Experimental

5.1. General methods

Melting points were taken on Gallenkamp apparatus and are uncorrected. IR spectra were recorded as frequency in cm^{-1} on a Perkin–Elmer 1600 series FT-IR. ^1H and ^{13}C NMR spectra were recorded using Bruker AC-200 instrument (200 and 50 MHz), shift in ppm, coupling constants in Hz. UV–vis spectra were recorded on Perkin–Elmer Lamda 16 λ_{max} nm (log ε). Mass spectra were performed with Finnigan MAT 8200 or MAT 311A (EI, 70 eV) *m/z* (% rel intensity). Microanalysis was performed on Perkin–Elmer PE2400 CHN analysator.

5.1.1. 1,2-Dimethyl-5-oxo-1,5-dihydro-benzo[*g*]indol-3,4,9b-tricarboxylic acid triethyl ester (14a). Diethyl1,4-dioxo-1,4-dihydro-naphthalene-2,3-dicarboxylate **10** (0.300 g (1.0 mmol)) were dissolved in 3 mL acetic acid p.a. The solution of 0.142 g (1.0 mmol) ethyl 3-methyl-aminocrotonate **11a** in 3 mL acetic acid p.a. was given dropwise to a solution of quinone and stirred for 1 day at rt. Then this solution was poured onto ice and extracted with diethylether. After evaporating the solvent in vacuo, the residue was stirred 4 h at rt with petrolether 60/80. Yellow needles crystallized in the refrigerator overnight. Yield: 0.1 g (23%). Mp=162 °C (from petrolether 60/80). IR (KBr) 1736, 1726, 1699, 1633, 1596, 1562. ^1H NMR ($CDCl_3$) δ 8.20 ('d',1H, 6-H), 7.57–7.38 (m, 3H, 7-H, 8-H, 9-H), 4.37–4.13 (2×q, 4H, O–CH_2 ^3J=7.1 Hz), 4.02 (q, 2H, O–CH_2, ^3J=7.1 Hz), 3.57 (s, 3H, N–CH_3), 2.56 (s, 3H, CH_3), 1.29 (2×t, 6H, O–C–CH_3, ^3J=7.1 Hz), 1.12 (t, 3H, O–C–CH_3, ^3J=7.1 Hz). UV–vis (MeOH) 282 (4.15), 442 (4.20). MS 427 (2, $M^+\cdot$), 382 (4, $M^+\cdot-OC_2H_5$), 354 (67, $M^+\cdot-COOC_2H_5$), 309 (98), 281 (100, 309-CO_2), 263 (24), 252 (50), 236 (28), 208 (49), 181 (41), 179 (64), 166 (18), 151 (53), 138 (28), 126 (16), 116 (14), 90 (17), 77 (31), 62 (12), 54 (22), 41 (66). Anal. Calcd for $C_{23}H_{25}NO_7$ (427.45): C 64.63, H 5.90, N 3.28. Found: C 64.43, H 6.02, N 3.15.

5.1.2. 1-Benzyl-2-methyl-5-oxo-1,5-dihydro-benzo[*g*]indol-3,4,9b-tricarboxylic acid triethyl ester (14b). (c/r. **14a**): 0.3 g (1.0 mmol) diethyl 1,4-dioxo-1,4-dihydro-naphthalene-2,3-dicarboxylate **10**, 0.22 g (1.0 mmol) ethyl 3-benzylaminocrotonate **11b**. Yield: 0.28 g (56%). Mp=198 °C (from $CHCl_3$/ethylacetate 8:2). IR (KBr) 1736, 1727, 1702, 1642, 1598, 1569. ^1H NMR ($CDCl_3$) δ 8.21 ('d', 1H, 6-H), 7.46–7.18 (m, 9H, 7-H, 8-H, 9-H, phenyl-H), 5.21d and 5.07d (^2J=18.5 Hz, 2H, CH_2phe); 4.39–4.22 (2×q, 4H, O–CH_2, ^3J=7.0 Hz), 4.03 (q, 2H, O–CH_2 ^3J=7.0 Hz), 2.38 (s, 3H, 2-CH_3), 1.34 (t, 3H, O–C–CH_3, ^3J=7.0 Hz), 1.29 (t, 3H, O–C–CH_3, ^3J=7.0 Hz), 1.13 (t, 3H, O–C–CH_3, ^3J=7.0 Hz). ^{13}C NMR ($CDCl_3$) 181.35 (s, C=O, C-5), 174.77 (s, C=O), 167.20 (s, C=O), 165.80 (s, C=O), 163.61 (s, C-2), 156.94s, 136.34s, 134.66s, 133.60s, 130.44 (d, ^1J=162.8 Hz), 129.25 (d, ^1J=160.6 Hz), 128.90 (d, ^1J=162.7 Hz), 128.23 (d, ^1J=164.7 Hz), 127.95 (d, ^1J=161.4 Hz), 126.12 (d, ^1J=160.3 Hz), 122.74 (d, ^1J=159.4 Hz), 116.30s, 104.09s, 79.47 (s, C-9b), 64.66 (t, O–CH_2, ^1J=149.5 Hz), 60.63 (t, O–CH_2, ^1J=147.4 Hz), 60.24 (t, O–CH_2, ^1J=147.1 Hz), 52.70 (t, N–CH_2, ^1J=138.9 Hz), 14.68 (q, O–C–CH_3, ^1J=126.9 Hz), 14.28 (q, O–C–CH_3, ^1J=127.0 Hz), 14.20 (q, O–C–CH_3, ^1J=130.4 Hz), 13.56 (q, O–C–CH_3, ^1J=128.2 Hz). UV–vis (MeOH) 282 (4.15), 434 (4.10). MS 503 (5, $M^+\cdot$), 458 (9, $M^+\cdot-OC_2H_5$), 430 (39, $M^+\cdot-COOC_2H_5$), 385 (46), 357 (18, 385-CO_2), 310 (18), 294 (25), 266 (26), 222 (24), 194 (13), 164 (17), 129 (15), 126 (7), 91 (100), 64 (30), 43 (19). Anal. Calcd for $C_{29}H_{29}NO_7$ (503.55): C 69.17, H 5.80, N 2.78. Found: C 69.20, H 5.89, N 2.80.

Crystal structure determination of compound **14b.**[13] Crystals of **14b**, suitable for X-ray study, were selected by means of a polarisation microscope. One was investigated on a Stoe Imaging Plate Diffraction System, using graphite monochromatized Mo Kα radiation (λ=0.71073 Å). Unit cell parameters were determined by a least-squares refinement on the positions of 6754 strong reflections distributed equally in reciprocal space. A monoclinic lattice was found, and space group $P2_1/n$ was uniquely determined. Crystal data of **13b**: $M_r(C_{29}H_{29}NO_7)$=503.53, a=10.4204(7) Å, b=13.0135(7) Å, c=19.2358(12) Å, β=104.614(7)°, V=2524.1(3) Å^3, Z=4, D_x=1.325 g cm^{-3}, μ=0.095 mm^{-1}, T=291 K, yellow plate of dimensions 0.25 mm×0.25 mm×0.1 mm. 16979 intensity data (Θ_{min}=2.04°, Θ_{max}=25.00°) were collected and Lp corrections were applied. The structure was solved by direct methods,[14] and approximate positions of all hydrogen atoms were found via difference Fourier-synthesis. Refinement (419 parameters, all of 4249 unique reflections used, 0 restraints) by full-matrix least-squares calculations on F^2,[15] converged to the following final indicators: $R_1[F_o^2>2\sigma(F_o^2)]$=0.039, wR_2=0.060 (all data), $w=1/[\sigma^2(F_o^2)+(0.09P)^2+0.1P]$ where $P=(F_o^2+2F_c^2)/3$, S=1.018, largest peak and hole in the final difference map are 0.140 e/Å^2 and −0.118 e/Å^3, respectively.

Anisotropic displacement parameters were used for all non-hydrogen atoms. Individual isotropic displacement parameters were refined for all H atoms, individual coordinates for all but the H atoms of methyl groups that were allowed to ride on their parent carbon atom and to move collectively around the neighbouring C–C axis. Furthermore, the C–H distances were allowed to vary, the same shifts being applied along the three C–H bonds of a group.

Selected geometric features [Å;°]: N1–C27 1.464(3), N1–C2 1.347(3), N1–C9B 1.458(2), C2–C3 1.381(3), C3–C3A 1.430(3), C3A–C9B 1.526(3), C3A–C4 1.351(3), C4–C5 1.460(3), C5–C5A 1.490(3), C5A–C9A 1.386(3), C9A–C9B 1.514(3), O21–C5 1.219(2), C2–C10 1.491(3), C3–C11 1.453(3), C4–C16 1.490(3), C9B–C22 1.564(3); O12–C11–C3–C2 154.5(2), O17–C16–C4–C3A 115.5(3), O21–C5–C4–C16–17.4(4), O21–C5–C5A–C6 21.3(3), N1–C9B–C9A–C9 25.9(3), N1–C27–C28–C29 174.4(2),

C2–C3–C3A–C9B 8.1(3), C3–C2–N1–C9B–10.7(3), C3A–C9B–C9A–C9 145.1(2), C5–C4–C3A–C9B–12.4(3), C9A–C9B–N1–C27–70.3(3), C9B–N1–C2–C10 171.2(2), C10–C2–C3–C11 8.2(4).

5.1.3. 2-Methyl-5-oxo-1-(4-tolyl)-1,5-dihydro-benzo[*g*]indol-3,4,9b-tricarboxylic acid triethyl ester (14c). (c/r. **14a**) 0.30 g (1.0 mmol) diethyl 1,4-dioxo-1,4-dihydro-naphthalene-2,3-dicarboxylate **10**, 0.22 g (1.0 mmol) ethyl 3-(4-tolylamino)-crotonate **11c**. Yield: 0.14 g (28%). Mp = 164 °C (from petrolether 60/80). IR (KBr) 1740, 1688, 1629, 1596, 1571. ^{1}H NMR ($CDCl_3$) δ 8.21 ('d', 1H, 6-H), 7.40 ('d', 1H, 8-H), 7.33 (m, 4H, 2′-H, 3′-H, 5′-H, 6′-H), 7.08 ('dt', 1H, 9-H), 6.36 ('d', 1H, 7-H), 4.33 (q, 2H, O–CH_2, ^3J = 6.9 Hz), 4.24 (q, 2H, O–CH_2, ^3J = 6.9 Hz), 4.18 (q, 2H, O–CH_2, ^3J = 7.1 Hz), 2.49 (s, 3H, 2-CH_3), 2.27 (s, 3H, Tol–CH_3), 1.36 (t, 3H, O–C–CH_3, ^3J = 6.9 Hz), 1.31 (t, 3H, O–C–CH_3, ^3J = 6.9 Hz), 1.05 (t, 3H, O–C–CH_3, ^3J = 7.1 Hz). UV–vis (MeOH) 279 (4.17), 430 (4.10). MS 503 (2, $M^+\cdot$), 458 (3, $M^+\cdot - OC_2H_5$), 431 (76, $M^+\cdot - COOC_2H_5$–H), 385 (100, 458-$COOC_2H_5$), 357 (79, 385-CO), 328 (44), 284 (63, 328-CO_2), 269 (46), 256 (54), 241 (48), 214 (19), 192 (16), 164 (24), 140 (16), 126 (23), 113 (17), 91 (57), 77 (10), 64 (47), 49 (9), 43 (25), 41 (63), 40 (51). Anal. Calcd for $C_{29}H_{29}NO_7$ (503.55): C 69.17, H 5.81, N 2.78. Found: C 69.00, H 5.86, N 2.66.

5.1.4. 5-Hydroxy-1,2-dimethyl-1*H*-benz[*g*]indol-3,4-dicarboxylic acid diethyl ester (16a). Triethyl 1,2-dimethyl-5-oxo-1,5-dihydrobenzo[*g*]indole-3,4,9b-tricarboxylate **13a** (0.085 g (0.2 mmol)) were refluxed for 3 h in 12 mL acetic acid p.a. After evaporating the solvent in vacuo, the oily residue was stirred 4 h at rt with petrolether 60/80. Yellow needles crystallized in the refrigerator overnight. Yield: 0.05 g (70%). Mp = 165 °C. IR (KBr) 3391 OH, 1694, 1618, 1582. ^{1}H NMR ($CDCl_3$) δ 11.05 (s, 1H, OH), exchangeable with D_2O, 8.52 ('d', 1H, 6-H), 8.36 ('d', 1H, 9-H), 7.66 ('dt', 1H, 7-H), 7.49 ('dt', 1H, 8-H), 4.38 (q, 2H, O–CH_2, ^3J = 7.0 Hz), 4.29 (q, 2H, O–CH_2, ^3J = 7.2 Hz), 4.12 (s, 3H, N–CH_3), 2.67 (s, 3H, 2-CH_3), 1.35 (t, 3H, O–C–CH_3, ^3J = 7.0 Hz), 1.34 (t, 3H, O–C–CH_3, ^3J = 7.2 Hz). UV–vis (MeOH) 222 (4.41), 242 (4.55), 259 (4.50), 276 (4.60), 367 (3.75). MS 355 (23, $M^+\cdot$), 309 (94, $M^+\cdot - OC_2H_5$ + H), 281(100, $M^+\cdot - COOC_2H_5$ + H), 263 (62, 281-H_2O), 237 (43), 235 (25, 263-CO_2), 208 (47, 281-$COOC_2H_5$), 180 (98, 208-CO_2), 166 (35), 152 (54), 139 (29), 117 (22), 104 (23), 90 (47), 77 (54), 45 (93), 44 (53). Anal. Calcd for $C_{20}H_{21}NO_5$ (355.39): C 67.59, H 5.96, N 3.94. Found: C 67.37, H 6.06, N 3.90.

5.1.5. 5-Hydroxy-1-benzyl-2-methyl-1*H*-benzo[*g*]indol-3,4-dicarboxylic acid diethyl ester (16b). (c/r. **16a**) 0.04 g (0.08 mmol) triethyl 1-benzyl-2-methyl-5-oxo-1,5-dihydro-benzo[*g*]indol-3,4,9b-tricarboxylate **14b**. Yield: 0.01 g (29%). Mp = 177 °C. IR (KBr) 3408, 1694, 1659, 1620, 1583. ^{1}H NMR ($CDCl_3$) δ 11.09 (s, 1H, OH, exchangeable with D_2O), 8.50 (mc, 1H, 6-H), 7.92 (mc, 1H, 9-H), 7.46–7.28 (m, 6H, 7-H, 8-H, 1′-H, 3′-H, 4′-H, 5′-H), 7.14 (m, 2H, 2′-H, 6′-H), 5.73 (s, 2H, N–CH_2), 4.41 (q, 2H, O–CH_2, ^3J = 7.0 Hz), 4.34 (q, 2H, O–CH_2, ^3J = 7.1 Hz), 2.61 (s, 3H, 2-CH_3), 1.38 (t, 3H, O–C–CH_3, ^3J = 7.1 Hz), 1.36 (t, 3H, O–C–CH_3, ^3J = 7.0 Hz). UV–vis (MeOH) 243 (3.90), 265 (4.00), 276 (4.05), 276 (4.13), 367 (4.05). MS 431 (22, $M^+\cdot$), 385 (56, $M^+\cdot - OC_2H_5$ + H), 357 (35, $M^+\cdot - COOC_2H_5$ + H), 313 (13, 357-CO_2), 294 (40, 385-$C_7H_7^+$), 266 (42), 249 (15), 222 (60), 194 (23), 165 (23), 151 (10), 139 (19), 129 (21), 126 (9), 124 (12), 91 (100), 77 (8), 64 (44), 56 (17), 43 (16). Anal. Calcd for $C_{26}H_{25}NO_5$ (431.48): C 72.37, H 5.84, N 3.25. Found: C 72.25, H 5.91, N 3.22.

5.1.6. 5-Hydroxy-2-methyl-1-(4-tolyl)-1*H*-benzo[*g*]indol-3,4-dicarboxylic acid diethyl ester (16c). (c/r. **16a**) 0.10 g (0.2 mmol) triethyl 2-methyl-5-oxo-1-(4-tolyl)-1,5-dihydrobenzo[g]indol-3,4,9b-tricarboxylate **14c**. Yield: 0.07 g (81%). Mp = 77 °C. IR (KBr) 3429, 1707, 1659, 1621, 1583. ^{1}H NMR ($CDCl_3$) δ 11.10 (s, 1H, OH, exchangeable with D_2O), 8.44 ('d', 1H, 6-H), 7.48–7.18 (m, 6H, 7-H, 8-H, 2′-H, 3′-H, 5′-H, 6′-H), 6.97 ('d', 1H, 9-H), 4.41 (q, 2H, O–CH_2, ^3J = 7.1 Hz), 4.35 (q, 2H, O–CH_2), ^3J = 7.1 Hz), 2.54 (s. 3H, 2-CH_3), 2.34 (s, 3H, Tol–CH_3), 1.39 (t, 3H, O–C–CH_3, ^3J = 7.1 Hz), 1.37 (t, 3H, O–C–CH_3, ^3J = 7.1 Hz). UV–vis (MeOH) 243 (4.55), 262 (4.52), 269 (sh), 367 (3.80). MS 431 (10, $M^+\cdot$), 385 (81, $M^+\cdot - OC_2H_5$ + H), 357 (87, $M^+\cdot - COOC_2H_5$ + H), 340 (16, $M^+\cdot - C_7H_7$ +), 339 (22), 313 (24), 284 (92, 357-$COOC_2H_5$), 270 (32), 254 (29), 240 (41), 193 (20), 165 (13), 139 (16), 127 (38), 120 (23), 102 (12), 91 (47), 89 (29), 77 (11), 45 (100), 44 (87). Anal. Calcd for $C_{26}H_{25}NO_5$ (431.48): C 72.37, H 5.84, N 3.25. Found; C 72.02, H 6.06, N 3.68.

5.1.7. 5-Hydroxy-2-methyl-1*H*-benzo[*g*]indol-3,4-dicarboxylic acid diethyl ester (16d). (c/r. **16a**) 0.041 g (0.1 mmol) 2-methyl-5-oxo-4,5-dihydrobenzo[*g*]indole-3,3a,4-tricarboxylic acid triethyl ester **17** was heated under reflux in 2 mL acetic acid for 45 min. On cooling **16d** crystallized. Yield 0.025 g (73%). Mp = 280 °C. IR (KBr) 3235 (NH/OH), 1662, 1631. ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 6H, O–C–CH_3), 2.62 (s, 3H, CH_3), 4.28 (m, 4H, OCH_2), 7.49 ('t', 1H), 7.70 ('t', 1H), 8.28 ('t', 2H), 10.10 (s, NH), 12.36 (s, OH). MS 341 (40), 295 (100), 267 (85), 249 (36), 223 (38), 195 (50). Anal. Calcd for $C_{19}H_{19}NO_5$ (341.36): C 66.85, H 5.60, N 4.10. Found: C 66.65, H 5.80, N 3.96.

5.1.8. 2-Methyl-5-oxo-4,5-dihydro-benzo[g]indole-3,3a,4-tricarboxylic acid triethyl ester (17). (v. **14a**) From 1.050 g (3.5 mmol) quinone **10** and 0.225 g (1.74 mmol) enamine **11d**. Yield 0.300 g (42%). Mp = 123 °C. IR (KBr) 1740, 1731, 1713, 1688, 1610. ^{1}H NMR ($CDCl_3$) δ 1.03 (m, 6H, 2×O–C–CH_3), 1.34 (t, 3H, O–C–CH_3), 2.72 (s, 3H, 2-CH_3), 4.00 (m, 4H, 2×O–CH_2), 4.30 (m, 2H, O–CH_2), 4.81 (s, 1H), 7.71mc (2H), 8.16mc (2H). ^{13}C NMR ($CDCl_3$) 13.7q, 13.8q, 17.0q, 60.3d, 60.5t, 61.8t, 63.0t, 70.8s, 125.5s, 125.7d, 128.2d, 131.3s, 132.5s, 133.0d, 134.4d 162.7s, 165.5s, 167.0s, 170.7s, 174.7s, 189.0s. UV–vis($CHCl_3$) 334 (4.00). MS 413 (6), 367 (34), 340 (13), 295 (43), 238 (56), 222 (100). Anal. Calcd for $C_{22}H_{23}NO_7$ (413.42): C 63.92, H 5.61, N 3.39. Found: C 64.01, H 5.50, N 3.34.

5.1.9. 3-Cyano-2-methyl-5-oxo-1,5-dihydro-benzo[*g*]indole-4,9b-dicarboxylic acid diethyl ester (22). Procedure **a**: 0.74 g (2.5 mmol) quinone **10** and 0.20 g (2.4 mmol) enamine **18** were stirred in 4 mL acetic acid for 3 h. The precipitation was fractionally crystallized to give **20**, **21** and **22**. Procedure **b**: under stirring enamine **18**

is added slowly to a solution of quinone **10** in acetic acid. After 3 h the mixture is diluted with water and extracted with diethylether. Evaporation under reduced pressure at 30 °C gives yellow solid. Procedure **c**: quinone **10** is slowly added to the solution of enamine **18** in acetic acid. Yield **22**: $a=0.030$ g (3.4%), $b=0.250$ mg (28%). Mp=136 °C. IR (KBr): 3486, 2217, 1744, 1696, 1643. ^{1}H NMR (d_6-DMSO) δ 1.03 (t, 3H) and 1.27 (t, 3H, O–C–CH_3), 2.45 (s, 3H, 2-CH_3), 4.0–4.3 (m, 4H, O–CH_2), 7.6 (m, 3H), 7.95 (m, 1H), 11.47 (s, NH). UV–vis (MeOH) 262 (4.08) 420 (4.05). MS 366 (36), 320 (81), 248 (100), 220 (50), 192 (20), 178 (38). $C_{20}H_{18}N_2O_5$ (366.37): C 65.57, H 4.95, N 7.64. Found: C 65.39, H 4.93, N 7.69.

5.1.10. 3-Cyano-5-hydroxy-2-methyl-1*H*-benzo[*g*]indole-4-carboxylic acid ethyl ester (20). (c/r. **22**). Yield $a=$ 0.03 g (3.4%), $c=0.260$ mg (35%). Mp=298 °C. IR (KBr) 3253, 2204, 1662, 1652, 1638. ^{1}H NMR(d_6-DMSO) δ 1.44 (t, 3H, O–C–CH_3), 2.62 (s, 3H, 2-CH_3), 4.57 (q, 2H, O–CH_2), 7.56 ('t', 1H), 7.80 ('t', 1H), 8.32 ('d', 1H), 12.28s and 12.86s (OH and NH). UV–vis (MeOH) 274 (4.46), 368 (3.82) MS 294 (21), 248 (100), 192 (43). Anal. Calcd for $C_{17}H_{14}N_2O_3$ (294.30): C 69.38, H 4.79, N 9.52. Found: C 69.16, H 4.96, N 9.46.

5.1.11. 3-Cyano-2-(4-hydroxy-2,3-bisethoxy-carbonyl-1-oxo-1,2-dihydro-naphthalen-2-yl)-methyl-5-hydroxy-9a*H*-benz[*g*]indol-4,9b-dicarboxylic acid diethyl ester (21). (c/r. **22**). Yield $a=$ 0.250 g (29.9%). Mp=150 °C. IR (KBr) 2217, 1750, 1683, 1652. ^{1}H NMR (d_6-DMSO) δ 0.90 (t, 3H) and 1.13 (t, 3H, 2×O–C–CH_3), 1.29 (t, 6H, 2× O–C–CH_3), 3.2 (d, 1H, $J=13$ Hz) and 3.7 (d, 1H, $J=13$ Hz, CH_2), 4.0–4.5 (m, 8H, 4×O–CH_2), 7.0 (m, 2H), 7.3 (m, 2H), 7.6 (m, 3H), 7.83 ('d', 1H), 11.13s and 13.05s (OH and NH). MS 668 (20), 365 (100), 319 (15), 247 (45). Anal. Calcd for $C_{36}H_{32}N_2O_{11}$ (668.65): C 64.67, H 4.82, N 4.19. Found: C 64.92, H 5.13, N 3.92.

Crystal structure determination of compound **21** $\times 0.5C_6H_{12}$[13] Only weak diffracting crystals of limited quality were available. Some were selected by means of a polarisation microscope and investigated on a Stoe Imaging Plate Diffraction System using graphite mono-chromatized Mo Kα radiation ($\lambda=0.71073$ Å). Unit cell parameters were determined by a least-squares refinement on the positions of 8000 reflections, distributed equally in reciprocal space. An anorthic lattice was found compatible with space groups $P1$ and $P\bar{1}$. The latter was confirmed in the course of the structure refinement. Crystal data of **22**: $M_r(C_{39}H_{38}N_2O_{11})$-=710.71, $a=11.072(2)$ Å, $b=12.989(3)$ Å, $c=$ 13.628(3) Å, $\alpha=74.38(3)°$, $\beta=82.62(3)°$, $\gamma=76.25(3)$, $V=1829.1(8)$ Å^3, $Z=2$, $D_x=1.291$ g cm^{-3}, $\mu=$ 0.095 mm^{-1}, $T=291$ K, yellow prism of dimensions 0.5 mm×0.4 mm×0.3 mm. 20546 intensity data ($\Theta_{min}=$ 1.98°, $\Theta_{max}=25.00°$) were collected and Lp corrections were applied. The structure was solved by direct methods,[14] and approximate positions of all the hydrogen atoms were found via difference Fourier-synthesis. Taking into account disorder of the ethoxycarbonyl group at C9B in the ratio 0.679(14)–0.321(14), refinement (510 parameters, all of 5561 unique reflections used, 73 restraints) by full-matrix least-squares calculations on F^2,[15] converged to the following final indicators: $R_1[F_o^2>2\sigma(F_o^2)]=0.070$, $wR_2=$ 0.169 (all data), $w=1/[\sigma^2(F_o^2)+(0.01P)^2+1.0P]$ where $P=(F_o^2+2F_c^2)/3$, $S=1.011$,[14] largest peak and hole in the final difference map are 0.216 e/Å^2 and −0.133 e/Å^3, respectively. Anisotropic displacement parameters were used for all non-hydrogen atoms. Appropriate same distance and same U_{ij} restraints were needed to achieve resonable parameters for the atoms of the disordered group, appropriate 1,2 and 1,3 distance restraints for the carbon atoms of the solvent cyclohexane molecule. Together with their parent carbon and oxygen atoms all H atoms were treated as rigid groups with fixed idealised C–H and O–H distances, respectively. The riding model was applied for all but the H atoms of selected methyl groups, that in addition could be allowed to move collectively around the neighbouring C–C axis. The isotropic displacement parameters of the H atoms were kept equal to 120% of the equivalent isotropic displacement parameters of the parent 'aromatic', tertiary or secondary carbon atom and equal to 150% of the parent primary carbon atom, respectively. Isotropic displacement parameters of H atoms at oxygen were allowed to refine.

Selected geometric features [Å;°]: N1–C2 1.264(5), N1–C9B 1.455(6), C2–C3 1.460(6), C3–C3A 1.326(7), C3A–C9B 1.482(7), C3A–C4 1.454(7), C4–C5 1.381(8), C5–C5A 1.449(8), C5A–C9A 1.371(7), C9A–C9B 1.487(7), O1–C5 1.325(6), O1–H1 0.82, O14···H1 1.90, O1···O14 2.516(8), C2–C10 1.490(6), C3–C11 1.404(8), C11–N12 1.173(7), C4–C13 1.442(9), C9B–C18 1.590(8), C10–C24 1.532(6), O2–C23 1.206(6), C23–C30A 1.450(7), C23–C24 1.532(7), O36–C26 1.324(6), O36–H2 0.82, O38···H2 1.80, O36···O38 2.518(8), C26–C26A 1.441(7), C26–C25 1.321(7), C24–C31 1.532(7), C25–C37 1.411(8); O1–C5–C4–C13–4.1(10), O1–C5–C4–C3A–179.7(5), O2–C23–C24–C10 57.5(6), O2–C23–C24–C31–57.5(7), O14–C13–C4–C5–0.3(11), O19–C18–C9B–C9A 23.2(14), O32–C31–C24–C10–6.8(9), O36–C26–C25–C37 4.6(9), O38–C37–C25–C26–4.9(9), N1–C2–C10–C24–5.1(8), N1–C9B–C9A–C9 29.3(8), N1–C9B–C3A–C4 167.1(5), C2–N1–C9B–C9A 133.4(6), C2–C10–C24–C23 61.5(6), C3A–C4–C5–C5A–1.9(9), C4–C5–C5A–C9A 8.0(10), C5–C4–C3A–C9B–21.7(8).

5.1.12. 2-Dimethylamino-5-oxo-4,5-dihydro-cyclopenta[*a*]naphthalene-3,3a,4-tricarboxylic acid triethyl ester (27 and 28). Quinone **10** (1.40 g (4.6 mmol)) and 0.78 g (5.0 mmol) enamine **23** are stirred in acetic acid for 2.5 h. Extraction with petrolether yielded **29**. The acetic acid fraction was evaporated and treated with diethylether. Fractionated crystallization afforded **27** and **28**.

Compound **27**. Yield 0.05 g (2.5%). Mp=160 °C. IR (KBr) 1756, 1725, 1675, 1623. ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, O–C–CH_3), 1.24 (t, 3H) and 1.30 (t, 3H, 2×O–C–CH_3), 3.19 (s, 6H, N–$(CH_3)_2$), 3.26 (s, 1H, 4-H), 4.00 and 4.26 (m, 6H, 4×O–CH_2), 6.85 (s, 1H, 1-H), 7.45 (m, 1H, 9-H), 7.56 (m, 2H, 7-H, 8-H), 8.12 ('d', 1H, 6-H). UV–vis ($CHCl_3$) 425 (3.5). MS 441 (39), 396 (9), 368 (100), 322 (16), 295 (7), 276 (15), 251(27). Anal. Calcd for $C_{24}H_{27}NO_7$(441.48): C 65.29, H 6.16, N 3.17. Found: C 65.05, H 6.11, N 2.95.

Compound 28. Yield 0.30 g (15%). Mp=113 °C. IR (KBr) 1727, 1683, 1622. ^{1}H NMR ($CDCl_3$) 1.01 (t, 3H) 1.12 (t,

3H), 1.28 (t, 3H, O–C–CH_3), 3.21 (s, 6H, N–$(CH_3)_2$), 3.95 (m, 4H) and 4.15 (m, 2H, 3×O–CH_2), 4.85 (s, 1H, 4-H), 6.89 (s, 1H, 1-H), 7.45 (m, 1H, 9-H), 7.60 (m, 2H, 7-H, 8-H), 8.12 ('d', 1H, 6-H). ^{13}C NMR ($CDCl_3$) 191.49s, 171.49s, 167.00s, 164.27s, 163.00s, 146.26s, 133.84d, 133.65s 130.22s, 129.76d, 128.02d, 125.52d, 125.09d, 101.48s, 65.57s, 61.90t, 61.02t, 60.23d, 59.04t, 43.37q, 14.53q, 13.96q, 13.82q. MS 441 (61), 396 (64), 369 (100), 322 (71), 295 (67), 276 (64), 250 (75). Anal. Calcd for $C_{24}H_{27}NO_7$(441.48): C 65.29, H 6.16, N 3.17. Found: C 65.35, H 6.14, N 3.04.

Crystal structure determination of compound **28.**[13] Crystals of **28** suitable for X-ray study were selected by means of a polarisation microscope. One was investigated on a Stoe Imaging Plate Diffraction System using graphite monochromatized Mo Kα radiation (λ=0.71073 Å). Unit cell parameters were determined by a least-squares refinement on the positions of 2316 strong reflections, distributed equally in reciprocal space. A monoclinic lattice was found and space group $P2_1/n$ was uniquely determined. Crystal data of **28**: $M_r(C_{24}H_{27}NO_7)$=441.47, a=8.4857(10) Å, b=14.5085(11) Å, c=18.819(2) Å, β=98.964(14)°, V=2288.6(4) Å^3, Z=4, D_x=1.281 g cm^{-3}, μ=0.094 mm^{-1}, T=291 K, yellow plate of dimensions 0.4 mm×0.2 mm×0.05 mm. 15854 intensity data (Θ_{min}=2.19°, Θ_{max}=25.00°) were collected and Lp corrections were applied. The structure was solved by direct methods,[14] and approximate positions of all the hydrogen atoms were found via difference Fourier-synthesis. Refinement (300 parameters, all of 4016 unique reflections used, 0 restraints) by full-matrix least-squares calculations on F^2,[15] converged to the following final indicators: $R_1[F_o^2>2\sigma(F_o^2)]$=0.048, wR_2=0.080 (all data), $w=1/[\sigma^2(F_o^2)+(0.025P)^2]$ where $P=(F_o^2+2F_c^2)/3$, S=0.654,[15] largest peak and hole in the final difference map are 0.169 e/Å^2 and −0.138 e/Å^3, respectively. Anisotropic displacement parameters were used for all non-hydrogen atoms. Together with their parent carbon atoms all H atoms were treated as rigid groups with fixed idealised C–H distances. The H atoms of methyl groups were allowed to move collectively around the neighbouring C–C axis. For the H atoms at C1 and C4 allowance was made for variation of the C–H bond direction, and for all other H atoms, the riding model was applied. The isotropic displacement parameters of the H atoms were kept equal to 120% of the equivalent isotropic displacement parameters of the parent 'aromatic', tertiary or secondary carbon atom and equal to 150% of the parent primary carbon atom, respectively.

Selected geometric features [Å;°]: C1–C2 1.440(5), C1–C9B 1.318(5), C2–C3 1.382(5), C3–C3A 1.485(5), C3A–C9B 1.502(5), C3A–C4 1.560(5), C4–C5 1.499(5), C5–C5A 1.477(5), C5A–C9A 1.394(5), C9A–C9B 1.432(5), O28–C5 1.216(4), N10–C2 1.346(5), N10–C11 1.445(5), N10–C12 1.394(5), C3–C13 1.392(6), C3A–C18 1.519(5), C4–C23 1.502(6); C1–C2–N10–C12–172.0(5), C1–C9B–C9A–C5A–149.3(5), C1–C9B–C9A–C9 30.8(7), C2–C3–C3A–C4–120.0(4), C3–C3A–C4–C5 165.1(4), C9A–C9B–C3A–C4–49.8(5), C9B–C3A–C4–C5 49.6(5), O28–C5–C4–C3A 153.9(4), O28–C5–C4–C23–83.3(5).

5.1.13. 2-(1-Acetoxy-3-ethoxycarbonyl-4-hydroxy-naphthalen-2-yl)-malonic acid diethyl ester (29). (c/r. Section 5.1.12) Yield 0.250 g (12.6%). mp=94 °C. IR (KBr) 1775, 1748, 1724, 1655. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 6H) and 1.38 (t, 3H, 3×O–C–CH_3), 2.39 (s, 3H, CH_3CO), 4.21 (q, 4H) and 4.44 (q, 2H, 3×O–CH_2), 5.35 (s, 1H), 7.60 (m, 3H), 8.41 (m, 1H), 12.50 (s, OH). ^{13}C NMR ($CDCl_3$) 170.94s, 168.76s, 167.62s, 160.27s, 139.18s, 130.32d, 129.93s, 126.88d, 125.59s, 124.60d, 122.02d, 120.94s, 105.67s, 62.23t, 61.69t, 52.52d, 20.59q 14.06q. MS 432 (3), 390 (38), 344 (41), 298 (100), 252 (58), 225 (67), 141 (15), 113 (21). Anal. calcd. for $C_{22}H_{24}O_9$ (432.42): C 61.11, H 5.59. Found: C 60.98, H 5.40.

5.1.14. 2-(1,4-Diacetoxy-3-ethoxycarbonyl-naphthalen-2-yl)-malonic acid diethyl ester (30). Acetic acid anhydride (0.043 g (0.1 mmol) **29** and 5 mL) were heated (100 °C) for 1.5 h, evaporated and recrystallized with petrolether. Yield: 0.020 g (42%). mp=95 °C. IR (KBr) 1783, 1769, 1752, 1732, 1706. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 6H) and 1.38 (t, 3H, O–C–CH_3), 2.40 (s, 3H) and 2.45 (s, 3H, CH_3CO), 4.22 (q, 4H) and 4.39 (q, 2H, 3×O–CH_2), 7.65 (mc, 3H), 7.85 (mc, 1H). MS 474 (12), 432 (30), 390 (100), 344 (39), 298 (90), 252 (54), 225 (54). Anal. Calcd for $C_{24}H_{26}O_{10}$ (474.46): C 60.75, H 5.52. Found: C 60.78, H 5.71.

5.1.15. 2-(1-Ethoxycarbonyl-2-oxo-propyl)-4-hydroxy-1-oxo-1,2-dihydro-naphthalen-2,3-dicarboxylic acid diethyl ester (32). Quinone **10** (0.79 g (2.6 mmol)) and 0.34 g (2.6 mmol) ethyl acetoacetate were stirred in 3 mL acetic acid for 24 h at rt, evaporated and treated with diethylether/petrolether. Yield. 0.25 g (22%). Mp=108 °C. IR (KBr) 1755, 1740, 1715, 1679, 1654. ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 3H), 1.12 (t, 3H) and 1.28 (t, 3H, 3×O–C–CH_3), 2.53 (s, 3H, CH_3), 3.91 (q, 2H) and 4.25 (mc, 4H, O–CH_2), 5.23 (s, 1H), 7.60 (m, 1H) 7.75 (m, 1H), 8.04 ('dd', 1H), 8.16 ('dd', 1H), 13.22 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) 202.20s, 191.89s, 170.55s, 168.85s, 167.29s, 164.02s, 134.54d, 133.21s, 131.47d, 131.23s,126.82d, 125.53d, 98.52s, 63.15d, 62.28t, 61.59t, 61.24t, 60.31s, 33.09q, 13.85q, 13.79q, 13.64q. MS 432 (1), 359 (0.3), 343 (1), 304 (7), 302 (10), 258 (11), 230 (33), 212 (100). Anal. Calcd for $C_{22}H_{24}O_9$ (432.42): C 61.11, H 5.59. Found: C 61.33, H 5.45.

5.1.16. 5-Hydroxy-2-methyl-benzofuran-3,6,7-tri-carboxylic acid 3-ethyl 6,7-dimethyl ester (36). p-Benzoquinone-2,3-dicarboxylic acid dimethyl ester (**33**) (0.224 g (1.0 mmol)) was disssolved in 3 mL acetic acid. A solution of 0.142 g (1.0 mmol) ethyl-3-alkylaminocrotonate **11a** or **11b** in 3 mL acetic acid was added dropwise. This mixture was stirred for 8 h at rt. The white ppt. was recrystallized from CH_2Cl_2/hexane (20:80). Yield: 0.2 g (59.5%). Mp=135 °C. IR (KBr) 3454, 1734, 1712, 1704, 1597. ^{1}H NMR ($CDCl_3$) δ 10.76 (s, 1H, OH, exchangeable with D_2O), 7.57 (s, 1H, 4-H), 4.40 (q, 2H, O–CH_2, ^3J=7.1 Hz), 4.00 (s, 3H, $COOCH_3$), 3.96 (s, 3H, $COOCH_3$), 2.78 (s, 3H, 2-CH_3), 1.45 (t, 3H, O–C–CH_3, ^3J=7.1 Hz). MS: 336 (27), 304 (86), 277 (10), 259 (11), 246 (100), 218 (36), 202 (8), 190 (6), 173 (7). Anal. Calcd for $C_{16}H_{16}O_8$ (336.29): C 57.14, H 4.80. Found: C 56.87, H 4.73.

5.1.17. 1,7-Dihydro-2,6-dimethyl-1,7-di(4-tolyl)pyrrolo[3,2-*f*]indole-3,5,8-tricarboxylic acid 3,5-diethyl

8-methyl ester (41). (c/r. **36**) 0.545 g (2.5 mmol) ethyl-3-(4-tolylamino)-crotonate (**11c**), 0.224 g (1.0 mmol) p-benzoquinone-2,3-dicarboxylic acid dimethyl ester **33**. Yield: 0.15 g (26.5%). Mp = 297 °C (CH_2Cl_2/hexane (20:80). IR (KBr) 3065, 1732, 1698, 1557. ^{1}H NMR ($CDCl_3$) δ 9.07 (s, 1H, 4-H), 7.23–7.05 (m, 8H, Tol-H), 4.50 (q, 4H, 2×O–CH_2, ^3J = 7.2 Hz), 2.50 (s, 3H, $COOCH_3$), 2.45 (s, 6H, 2-CH_3, 6-CH_3), 2.37 (s, 6H, 2×Tol–CH_3), 1.54 (t, 6H, 2×O–C–CH_3, ^3J = 7.2 Hz). MS: 566 (100), 537 (7), 521 (9), 494 (10), 477 (5), 433 (6), 389 (5), 361 (7), 239 (10), 187 (6). Anal. Calcd for $C_{34}H_{34}N_2O_6$ (566.65): C: 72.07, H 6.05, N 4.94. Found: C 72.03, H 5.84, N 4.83.

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A facile synthesis of highly functionalized dihydrofurans based on 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed reaction of halides with enones

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Abstract—Treatment of halides **5** with electrophilic alkenes **2** afforded the corresponding dihydrofurans **3** and **4** in the presence of 1, 4-diazabicyclo[2.2.2]octane (DABCO) with good to excellent yields and in a stereoselective manner in most cases. Moreover, the stereoisomers **3** and **4** could be easily transformed each other in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

1. Introduction

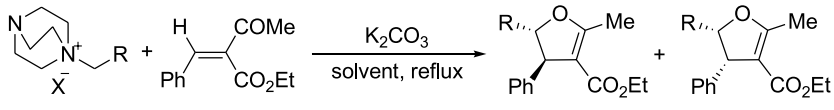
Dihydrofurans are among the most important heterocycles for the construction of a wide range of naturally occurring substances and possess a multiplicity of biological activities.[1] They are also potentially useful intermediates in organic synthesis.[2] For these reasons, the development of new and efficient methods for the synthesis of dihydrofurans remains an area of strong interest.[3]

Recently, the reactions of sulfonium[4] and arsonium[5] ylides with enones to afford dihydrofurans have been reported. However, arsonium compounds are strong hazardous materials; the reactions of sulfonium ylides gave dihydrofurans accompanying with cyclopropane byproducts. On the other hand, in the above processes, the ylide precursor was usually generated in a separate step.

In this paper, we report a novel synthetic route to form dihydrofurans via ammonium ylides[6] in one-step based on a catalytic process. Surprisingly, there was no report on this catalytic method for synthesis of dihydrofurans.

2. Results and discussion

We began our study by investigating the reactivity of preformed quaternary ammonium salts **1** with (*Z*)-ethyl-2-benzyliden-3-oxobutanoate (**2b**) under different conditions (Scheme 1). The preliminary studies demonstrated that the reaction of the ammonium ylides with the enone in the presence of anhydrous K_2CO_3 under reflux yielded dihydrofurans without the formation of cyclopropane. The results are presented in Table 1, which show that the R group of salts **1** played an important role in the stereoselectivity of the procedure. Generally, when R was a strong electron-withdrawing group, the trans-isomer was formed preferentially. As we seen, there is a higher trans-selectivity in entries 5–8 than in entries 1–4 (Table 1).



1a-d **2b** **3b, 3e, 3h, 3k** **4b,4e,4h**

Scheme 1. Reaction of salts **1** with (*Z*)-ethyl-2-benzyliden-3-oxobutanoate.

Keywords: DABCO; Ylides; Enones; Dihydrofurans; Furans.
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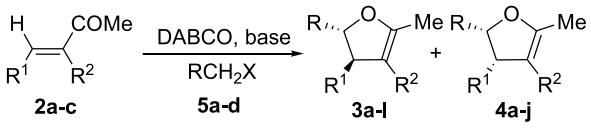
Table 1. Reaction of salts **1** with alkene **2b**[a]

Entry	Salt	X	R	Solvent	Product	Yield %[b]	Product	Yield %[b]
1	**1a**	Cl	CN	CH_2Cl_2/DMSO[c]	**3b**	67	**4b**	25
2	**1a**	Cl	CN	CH_3CN	**3b**	65	**4b**	24
3	**1b**	Cl	CO_2Et	CH_2Cl_2/DMSO[c]	**3e**	46	**4e**	37
4	**1b**	Cl	CO_2Et	CH_3CN	**3e**	47	**4e**	36
5	**1c**	Br	COPh	CH_2Cl_2/DMSO[c]	**3h**	85	**4h**	7
6	**1c**	Br	COPh	CH_3CN	**3h**	76	**4h**	6
7	**1d**	Cl	Thiophene-2-carbonyl	CH_2Cl_2/DMSO[c]	**3k**	86	None	
8	**1d**	Cl	Thiophene-2-carbonyl	CH_3CN	**3k**	75	None	

[a] Salt **1** (1.5 equiv), enone **2b** (1.0 equiv), K_2CO_3 (2.0 equiv), solvent, reflux.
[b] Isolated yield.
[c] v/v=4/1.



Scheme 2. DABCO-catalyzed reaction.

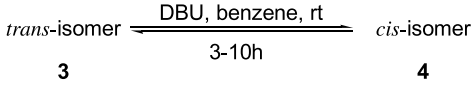
Encouraged by the above results, we then investigated a catalytic process utilizing 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst, in which the ammonium salts **1**, and hence, the ylides could be generated in situ from readily available halides **5**. The reaction worked well for a range of halides and enones (Scheme 2), and the results of which are summarized in Table 2. Chloroacetonitrile (**5a**) and ethyl chloroacetate (**5b**) gave a separable mixture of trans- and cis-dihydrofurans in good yields in CH_2Cl_2/DMSO (4:1) in the presence of K_2CO_3. The α-halo carbonyl compounds **5c** and **5d** gave mostly trans-substituted products in acetonitrile at 80 °C (Table 2). It is worth noting that no reaction took place in the absence of DABCO, which suggests that the tertiary amine is required as the catalyst in these reactions.

Although different stereoisomers were obtained in most cases, **3** and **4** could be separated from one another on silica gel with petroleum ether–ethyl acetate as eluent and the isomers pair **3** and **4** could be readily transformed each other in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[3h] in benzene (Scheme 3). The transformation could eventually reach a thermodynamic equilibrium whether a pure cis- or trans-isomer was used as the starting material (Table 3).

The dihydrofurans structure was identified by ^1H and ^{13}C NMR, MS, HRMS and IR spectral data. The five-membered heterocyclic structures of **3j** and **4j** were further confirmed by a single-crystal X-ray diffraction analysis (Figs. 1 and 2).[7,8]

The mechanism of formation of **3** and **4** could be explained by the following pathway (Scheme 4), based on the previous mechanism of Moorhoff.[9] A halide source **5** undergoes S_N2 displacement with the tertiary amine **8** to form quaternary ammonium salt **1**. Deprotonation of **1** with a mild base forms the ylide **6**, which undergoes Michael addition with **2** to afford the intermediate **7**. The intermediate **7** would readily undergo ring-closing reaction by internal S_N2 displacement of the tertiary amine **8** from the enolate oxygen to give dihydrofurans **3** and **4**. The yield of the trans-isomer is higher than that of the cis-isomer probably due to the major thermodynamic stability of the trans-isomer. This result is different from that of Fan et al.[10]

Moreover, the obtained dihydrofurans **3** and **4** could be further converted into the corresponding furans using mild



Scheme 3. Transformation.

Table 2. Synthesis of dihydrofurans

Entry	Halide	X	R	Enone	R^1	R^2	Conditions	Product	Yield %[a]	Product	Yield %[a]
1	**5a**	Cl	CN	**2a**	Ph	COMe	**A**[b]	**3a**	63	**4a**	35
2	**5a**	Cl	CN	**2b**	Ph	CO_2Et	**A**[b]	**3b**	69	**4b**	26
3	**5a**	Cl	CN	**2c**	4-Cl-C_6H_4	COMe	**A**[b]	**3c**	64	**4c**	29
4	**5b**	Cl	CO_2Et	**2a**	Ph	COMe	**A**[b]	**3d**	45	**4d**	35
5	**5b**	Cl	CO_2Et	**2b**	Ph	CO_2Et	**A**[b]	**3e**	50	**4e**	39
6	**5b**	Cl	CO_2Et	**2c**	4-Cl-C_6H_4	COMe	**A**[b]	**3f**	48	**4f**	34
7	**5c**	Br	COPh	**2a**	Ph	COMe	**B**[c]	**3g**	89	**4g**	9
8	**5c**	Br	COPh	**2b**	Ph	CO_2Et	**B**[c]	**3h**	88	**4h**	8
9	**5c**	Br	COPh	**2c**	4-Cl-C_6H_4	COMe	**B**[c]	**3i**	85	**4i**	9
10	**5d**	Cl	Thiophene-2-carbonyl	**2a**	Ph	COMe	**B**[c]	**3j**	85	**4j**	11
11	**5d**	Cl	Thiophene-2-carbonyl	**2b**	Ph	CO_2Et	**B**[c]	**3k**	88	None	
12	**5d**	Cl	Thiophene-2-carbonyl	**2c**	4-Cl-C_6H_4	COMe	**B**[c]	**3l**	80	None	

[a] Isolated yield.
[b] Enone (1.0 equiv), halide (1.0 equiv), DABCO (0.2 equiv), K_2CO_3 (1.5 equiv), CH_2Cl_2/DMSO, reflux.
[c] Enone (1.0 equiv), halide (1.0 equiv), DABCO (0.2 equiv), Na_2CO_3 (1.5 equiv), CH_3CN, 80 °C.

Table 3. Transformation of either isomer

Entry	Starting material	Product	Yield %[a]	Entry	Starting material	Product	Yield %[a]
1	**4a**	**3a**	63	11	**3a**	**4a**	34
2	**4b**	**3b**	69	12	**3b**	**4b**	26
3	**4c**	**3c**	67	13	**3c**	**4c**	29
4	**4d**	**3d**	54	14	**3d**	**4d**	44
5	**4e**	**3e**	59	15	**3e**	**4e**	39
6	**4f**	**3f**	53	16	**3f**	**4f**	41
7	**4g**	**3g**	76	17	**3g**	**4g**	18
8	**4h**	**3h**	88	18	**3h**	**4h**	7
9	**4i**	**3i**	82	19	**3i**	**4i**	14
10	**4j**	**3j**	84	20	**3j**	**4j**	11

[a] Isolated yield.

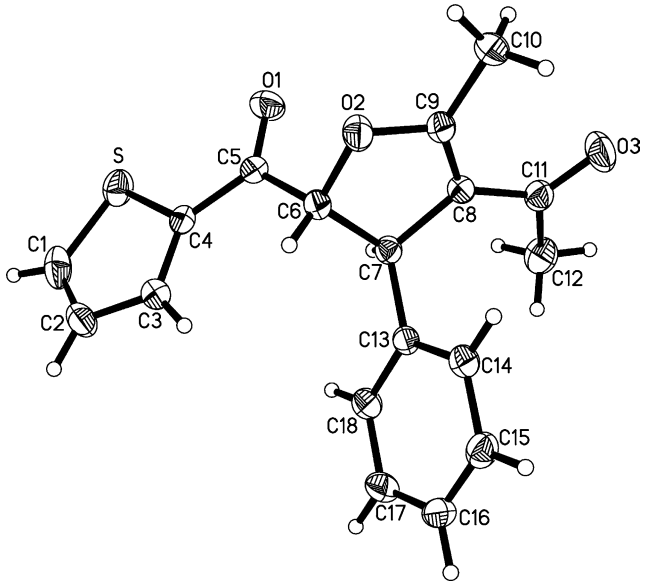


Figure 1. Molecular structure of **3j**.

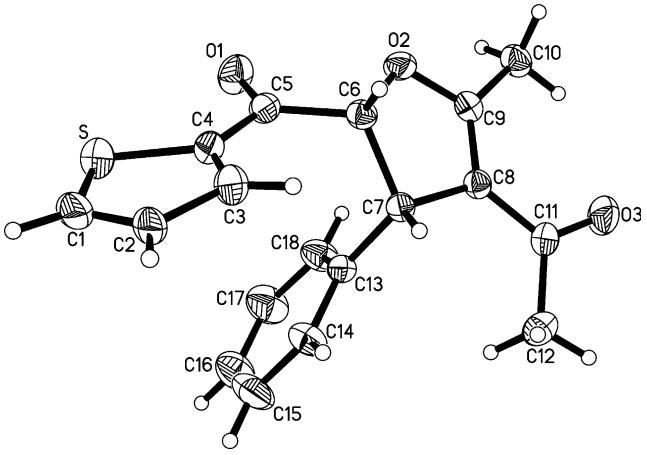
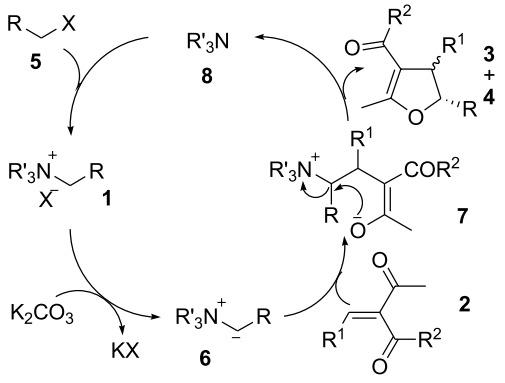
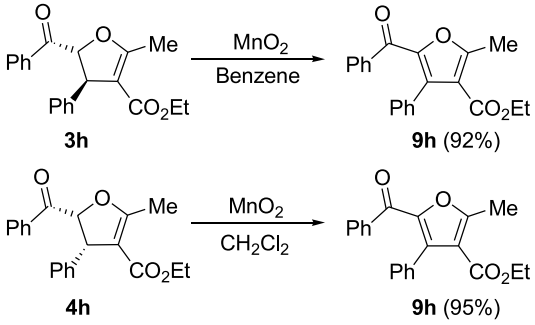


Figure 2. Molecular structure of **4j**.

oxidant, chemical manganese dioxide (CMD).[11] For example, a benzene solution of **3h** was refluxed for 48 h or a dichloromethane solution of **4h** was refluxed for 12 h in the presence of an excess of activated MnO_2 (10–15 equiv), both affording the tetrasubstituted furan **9h** in high yield (Scheme 5).



Scheme 4. Formation of dihydrofurans.



Scheme 5. Oxidation.

3. Conclusions

In this work, we have developed a facile and economical synthetic method of tetrasubstituted dihydrofurans as well as furans via the reaction of ammonium ylides in a catalytic process. Moreover, one stereoisomer of the two result dihydrofurans can be conveniently transformed to the other as required. We believe that this method would give a new viable entry to highly functionalized dihydrofurans.

4. Experimental

4.1. General

Melting points were determined on a microscopic apparatus and were uncorrected. Column chromatography was carried out on silica gel. The ^{1}H and ^{13}C NMR spectra were

recorded at 300 and 75 MHz, respectively. IR spectra were obtained using an FT-IR spectrometer and only major peaks are reported in cm^{-1}. Mass spectra were recorded by the EI method. HRMS spectra were obtained with a Bruker APEX instrument. All reagents were used directly as obtained commercially unless otherwise noted. All mixed solvent systems are reported as v/v solutions. Alkenes **2** (**2a**, **2b** and **2c**) were easily prepared using a literature procedure.[12]

4.2. Typical procedure for the preparation of ammonium salts 1[13]

DABCO (1.12 g, 10 mmol) was added to a solution of chloroacetonitrile (0.755 g, 10 mmol) in THF (50 mL). The reaction was stirred at room temperature for 1 h. After evaporating the solvent under reduced pressure, the resulting solid was washed with petroleum ether and then dissolved in a mixture of MeOH (5 mL) and PhH (5 mL). The solvents were removed under reduced pressure to afford the ammonium salt **1a** as a white solid (1.8 g, 96%).

4.3. General procedure for the reaction of ammonium salts 1 with enone 2b

The mixture of **1** (1.5 mmol), **2b** (1 mmol) and K_2CO_3 (2 mmol) in CH_3CN or in CH_2Cl_2/DMSO (v/v, 4/1) (10 mL) was stirred vigorously at refluxing temperature. Once the reaction was completed, checked by TLC analysis, the reaction was quenched with 15–20 mL of water and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with water and brine, and dried ($MgSO_4$). After evaporating the solvent under reduced pressure, the residue was purified on silica gel with petroleum ether–ethyl acetate (30/1–10/1) as eluent to give first the trans-isomer **3**, while further elution to yield the cis-isomer **4**.

4.4. General procedure for DABCO-catalyzed reaction of halides 5 with enones 2

DABCO (0.2 mmol) was added to a stirred solution of **5** (1 mmol) in CH_3CN or in CH_2Cl_2/DMSO (v/v, 4/1) (10 mL) at room temperature. After stirred for 30 min, the inorganic base (1.5 mmol) was added, followed by the enone **2** (1 mmol). The reaction was vigorously stirred at refluxing temperature. Once completed, checked by TLC analysis, the reaction was quenched with water (15–20 mL) and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with water and brine, and dried ($MgSO_4$). After evaporating the solvent under reduced pressure, the residue was purified on silica gel with petroleum ether–ethyl acetate (30/1–10/1) as eluent to give first the trans-isomer **3**, while further elution to yield the cis-isomer **4**.

4.4.1. trans-4-Acetyl-2-cyano-5-methyl-3-phenyl-2,3-dihydrofuran (3a). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.39 (m, 5H), 4.96 (d, J=4.5 Hz, 1H), 4.66 (d, J=4.2 Hz, 1H), 2.40 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.8, 167.2, 139.9, 129.6, 128.7, 127.3, 117.1, 115.9, 74.9, 55.2, 29.9, 14.9. IR (KBr): 3022, 2922, 2852, 2147, 1679, 1608, 1494, 1452, 1379, 1217, 757, 703 cm^{-1}. MS (EI, 70 eV): m/z (%) 227 (M^+, 8.58), 212 (3.87), 200 (9.42), 170 (15.78), 43 (100). HRMS: m/z [M+H] calcd for $C_{14}H_{13}NO_2$: 228.1019; found: 228.1015.

4.4.2. cis-4-Acetyl-2-cyano-5-methyl-3-phenyl-2,3-dihydrofuran (4a). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20–7.42 (m, 5H), 5.44 (d, J=10.2 Hz, 1H), 4.60 (d, J=10.2 Hz, 1H), 2.39 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 167.5, 137.4, 129.4, 129.1, 128.2, 116.0, 114.6, 74.0, 52.3, 29.8, 14.8. IR (KBr): 3022, 2922, 2218, 1676, 1606, 1495, 1381, 1216, 757, 705 cm^{-1}. MS (EI, 70 eV): m/z (%) 227 (M^+, 28.17), 212 (10.28), 200 (18.46), 170 (30.26), 43 (100). HRMS: m/z [M+H] calcd for $C_{14}H_{13}NO_2$: 228.1019; found: 228.1012.

4.4.3. trans-5-Cyano-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (3b). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–7.34 (m, 5H), 5.01 (d, J=4.2 Hz, 1H), 4.60 (d, J=3.9 Hz, 1H), 4.04 (q, J=7.2 Hz, 2H), 2.38 (s, 3H), 1.09 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 163.9, 140.0, 128.9, 128.0, 126.9, 117.0, 107.4, 74.5, 60.0, 54.3, 13.9, 13.8. IR (KBr): 3030, 2983, 2255, 1704, 1658, 1605, 1492, 1453, 1378, 1213, 1087, 758, 701 cm^{-1}. MS (EI, 70 eV): m/z (%) 257 (M^+, 24.57), 230 (5.66), 212 (15.06), 211 (19.74), 169 (83.64), 43 (100). HRMS: m/z [M+NH_4] calcd for $C_{15}H_{15}NO_3$: 275.1390; found: 275.1394.

4.4.4. cis-5-Cyano-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (4b). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.39 (m, 5H), 5.44 (d, J=10.2 Hz, 1H), 4.55 (d, J=10.2 Hz, 1H), 4.03 (q, J=7.2 Hz, 2H), 2.37 (s, 3H), 1.05 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 164.3, 137.7, 129.0, 128.6, 128.0, 114.7, 107.7, 73.8, 60.2, 51.8, 14.2, 14.0. IR (KBr): 2983, 2928, 2247, 1703, 1656, 1501, 1452, 1379, 1215, 1091, 1021, 755, 702 cm^{-1}. MS (EI, 70 eV): m/z (%) 257 (M^+, 26.33), 230 (3.75), 215 (14.25), 212 (14.15), 211 (18.12), 169 (68.66), 43 (100). HRMS: m/z [M+NH_4] calcd for $C_{15}H_{15}NO_3$: 275.1390; found: 275.1384.

4.4.5. trans-4-Acetyl-3-(4-chlorophenyl)-2-cyano-5-methyl-2,3-dihydrofuran (3c). Solid; mp 107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 4.92 (d, J=4.5 Hz, 1H), 4.64 (d, J=4.5 Hz, 1H), 2.41 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2, 167.1, 138.3, 134.5, 129.7, 128.6, 116.8, 116.1, 74.6, 54.4, 29.8, 14.9. IR (KBr): 3030, 2921, 2844, 2263, 1679, 1632, 1608, 1491, 1381, 1216, 1091 cm^{-1}. MS (EI, 70 eV): m/z (%) 261 (M^+, 14.20), 246 (4.79), 234 (16.26), 226 (2.69), 219 (12.15), 204 (12.67), 43 (100). HRMS: m/z [M+H] calcd for $C_{14}H_{12}ClNO_2$: 262.0629; found: 262.0632.

4.4.6. cis-4-Acetyl-3-(4-chlorophenyl)-2-cyano-5-methyl-2,3-dihydrofuran (4c). Solid; mp 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, J=8.4 Hz, 2H), 7.15 (d, J=8.4 Hz, 2H), 5.42 (d, J=9.9 Hz, 1H), 4.58 (d, J=9.9 Hz, 1H), 2.38 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4, 167.5, 135.9, 134.9, 129.6, 129.5, 116.1, 114.3, 73.6, 51.7, 29.7, 14.8. IR (KBr): 2924, 2247, 1677, 1629, 1605, 1491, 1381, 1213, 1090 cm^{-1}. MS (EI, 70 eV): m/z (%) 261 (M^+, 15.23), 246 (4.20), 234 (14.25), 226 (2.39),

219 (11.39), 204 (10.88), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{14}H_{12}ClNO_2$: 262.0629; found: 262.0625.

4.4.7. trans-4-Acetyl-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (3d). Solid; mp 51–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.38 (m, 5H), 4.78 (d, J=4.8 Hz, 1H), 4.49 (d, J=4.5 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.96 (s, 3H), 1.34 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 170.1, 168.8, 142.4, 129.3, 127.9, 127.4, 115.3, 86.2, 62.1, 53.5, 29.9, 15.1, 14.4. IR (KBr): 2983, 1753, 1674, 1604, 1494, 1449, 1380, 1197, 1037, 764, 703 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 274 (M^+, 5.22), 231 (5.27), 201 (24.20), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{18}O_4$: 275.1278; found: 275.1278.

4.4.8. cis-4-Acetyl-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (4d). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.28 (m, 5H), 5.32 (d, J=10.2 Hz, 1H), 4.62 (d, J=10.2 Hz, 1H), 3.62–3.82 (m, 2H), 2.45 (s, 3H), 1.91 (s, 3H), 0.86 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 168.9, 167.6, 138.1, 128.7, 128.6, 128.1, 116.1, 83.9, 61.3, 52.1, 29.8, 15.1, 13.8. IR (KBr): 2985, 2931, 1752, 1674, 1603, 1494, 1450, 1379, 1210, 1043, 757, 703 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 274 (M^+, 7.49), 259 (1.53), 231 (3.71), 201 (15.96), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{18}O_4$: 275.1278; found: 275.1279.

4.4.9. trans-5-Methyl-3-phenyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (3e). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.34 (m, 5H), 4.83 (d, J=4.8 Hz, 1H), 4.41 (d, J=4.5 Hz, 1H), 4.26 (q, J=6.9 Hz, 2H), 4.09 (q, J=6.9 Hz, 2H), 2.40 (s, 3H), 1.32 (t, J=7.2 Hz, 3H), 1.06 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 168.5, 165.0, 142.8, 128.8, 127.3, 106.6, 85.9, 61.9, 59.7, 52.9, 14.2. IR (KBr): 2982, 2923, 1755, 1702, 1651, 1452, 1379, 1209, 1090, 1034, 759, 700 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 304 (M^+, 23.17), 259 (16.66), 258 (28.86), 231 (29.75), 230 (78.31), 202 (27.90), 201 (28.88), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{17}H_{20}O_5$: 305.1384; found: 305.1380.

4.4.10. cis-5-Methyl-3-phenyl-2,3-dihydrofuran-2,4-dicarboxylic acid diethyl ester (4e). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.26 (m, 5H), 5.30 (d, J=10.5 Hz, 1H), 4.56 (d, J=10.5 Hz, 1H), 3.99 (q, J=7.2 Hz, 2H), 3.64–3.78 (m, 2H), 2.41 (s, 3H), 1.03 (t, J=7.2 Hz, 3H), 0.83 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 167.9, 165.0, 138.7, 128.4, 128.2, 127.7, 127.5, 107.5, 83.7, 61.2, 59.7, 51.6, 14.2, 13.7. IR (KBr): 2984, 1729, 1662, 1624, 1494, 1448, 1379, 1212, 1095, 1042, 757, 697 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 304 (M^+, 37.41), 259 (13.63), 258 (11.54), 231 (43.33), 230 (40.86), 202 (15.30), 201 (11.85), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{17}H_{20}O_5$: 305.1384; found: 305.1378.

4.4.11. trans-4-Acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (3f). Sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J=8.1 Hz, 2H), 7.18 (d, J=8.1 Hz, 2H), 4.74 (d, J=4.8 Hz, 1H), 4.48 (d, J=4.5 Hz, 1H), 4.29 (q, J=6.9 Hz, 2H), 2.44 (s, 3H), 2.00 (s, 3H), 1.32 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 169.8, 168.8, 140.9, 133.6, 129.4, 128.7, 115.4, 85.8, 62.1, 52.8, 29.7, 15.1, 14.3. IR (KBr): 2985, 2919, 1754, 1675, 1626, 1602, 1490, 1380, 1199, 1092, 1039, 832 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 308 (M^+, 10.27), 265 (10.95), 235 (47.84), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{17}ClO_4$: 309.0888; found: 309.0888.

4.4.12. cis-4-Acetyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydrofuran-2-carboxylic acid ethyl ester (4f). Sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J=8.4 Hz, 2H), 7.11 (d, J=8.4 Hz, 2H), 5.30 (d, J=10.5 Hz, 1H), 4.61 (d, J=10.5 Hz, 1H), 3.69–3.87 (m, 2H), 2.44 (s, 3H), 1.96 (s, 3H), 0.92 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 168.9, 167.4, 136.8, 133.9, 130.0, 128.7, 116.2, 83.6, 61.4, 51.4, 29.7, 15.1, 13.8. IR (KBr): 2986, 2936, 1753, 1719, 1675, 1599, 1490, 1381, 1210, 1092, 1043, 855 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 308 (M^+, 9.99), 293 (2.16), 265 (6.74), 235 (29.83), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{16}H_{17}ClO_4$: 309.0888; found: 309.0886.

4.4.13. trans-4-Acetyl-2-benzoyl-5-methyl-3-phenyl-2,3-dihydrofuran (3g). Solid; mp 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.89 (m, 10H), 5.66 (d, J=4.5 Hz, 1H), 4.53 (d, J=4.5 Hz, 1H), 2.47 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ194.4, 193.5, 168.6, 142.4, 134.3, 133.7, 129.3, 129.1, 127.9, 127.8, 116.0, 89.7, 52.2, 29.8, 15.2. IR (KBr): 2921, 1693, 1671, 1601, 1490, 1382, 1224, 1069, 1017, 757, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 306 (M^+, 0.46), 263 (78.90), 201 (13.42), 105 (35.77), 77 (41.48), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{18}O_3$: 307.1329; found: 307.1332.

4.4.14. cis-4-Acetyl-2-benzoyl-5-methyl-3-phenyl-2,3-dihydrofuran (4g). Sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79–7.56 (m, 10H), 6.23 (d, J=10.2 Hz, 1H), 4.73 (d, J=10.2 Hz, 1H), 2.52 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 193.8, 169.2, 137.4, 135.9, 133.7, 128.8, 128.4, 127.9, 127.7, 116.8, 87.6, 53.2, 29.8, 15.3. IR (KBr): 2924, 1697, 1667, 1601, 1494, 1446, 1386, 1217, 1071, 1021, 755, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 306 (M^+, 2.44), 263 (42.31), 201 (18.35), 105 (64.63), 77 (46.59), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{18}O_3$: 307.1329; found: 307.1331.

4.4.15. trans-5-Benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (3h). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.85 (m, 10H), 5.73 (d, J=4.5 Hz, 1H), 4.40 (d, J=4.5 Hz, 1H), 3.96 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.04 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.7, 168.6, 165.1, 142.8, 134.2, 133.7, 129.2, 129.0, 127.8, 127.6, 107.2, 89.5, 59.7, 52.0, 14.3. IR (KBr): 3024, 2924, 2855, 1698, 1651, 1601, 1453, 1380, 1218, 1091, 757, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 336 (M^+, 9.34), 321 (9.59), 293 (17.50), 263 (34.69), 231 (22.87), 105 (100), 77 (70.78), 43 (65.56). HRMS: *m/z* [M+H] calcd for $C_{21}H_{20}O_4$: 337.1434; found: 337.1433.

4.4.16. cis-5-Benzoyl-2-methyl-4-phenyl-4,5-dihydrofuran-3-carboxylic acid ethyl ester (4h). Solid; mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81–7.55 (m, 10H), 6.20 (d, J=10.5 Hz, 1H), 4.68 (d, J=10.2 Hz, 1H), 3.99 (q, J=6.9 Hz, 2H), 2.49 (s, 3H), 1.03 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ194.1, 168.8, 165.1, 138.0, 135.9,

133.6, 128.7, 128.0, 127.9, 127.3, 108.0, 87.8, 59.8, 52.8, 14.4, 14.2. IR (KBr): 2927, 1696, 1648, 1600, 1449, 1385, 1212, 1096, 1021, 756, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 336 (M^+, 12.41), 321 (10.08), 293 (16.07), 263 (15.99), 231 (31.87), 105 (100), 77 (84.08), 43 (79.71). HRMS: *m/z* [M+H] calcd for $C_{21}H_{20}O_4$: 337.1434; found: 337.1434.

4.4.17. trans-4-Acetyl-2-benzoyl-3-(4-chloro-phenyl)-5-methyl-2,3-dihydrofuran (3i). Sticky oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.18–7.86 (m, 9H), 5.61 (d, J=4.8 Hz, 1H), 4.54 (d, J=4.5 Hz, 1H), 2.44 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.72, 193.14, 168.48, 140.92, 134.24, 133.52, 129.37, 129.14, 129.05, 128.99, 116.06, 89.20, 51.37, 29.62, 15.09. IR (KBr): 3067, 3017, 2924, 1697, 1672, 1623, 1598, 1490, 1446, 1381, 1223, 1093, 830, 756, 694 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 340 (M^+, 0.20), 297 (68.54), 235 (13.68), 105 (42.96), 77 (37.74), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{17}ClO_3$: 341.0939; found: 341.0943.

4.4.18. cis-4-Acetyl-2-benzoyl-3-(4-chloro-phenyl)-5-methyl-2,3-dihydrofuran (4i). Solid; mp 125–127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.59 (m, 5H), 6.99 (d, J=8.1 Hz, 2H), 6.74 (d, J=8.4 Hz, 2H), 6.20 (d, J=10.2 Hz, 1H), 4.72 (d, J=10.2 Hz, 1H), 2.52 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 193.5, 169.2, 136.1, 135.7, 133.9, 133.6, 130.0, 128.9, 128.6, 127.9, 117.0, 87.4, 52.6, 29.7, 15.3. IR (KBr): 3015, 2924, 1698, 1671, 1623, 1597, 1489, 1446, 1384, 1214, 1088, 756, 694 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 340 (M^+, 1.67), 297 (26.85), 235 (10.66), 105 (69.69), 77 (39.45), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{20}H_{17}ClO_3$: 341.0939; found: 341.0931.

4.4.19. trans-4-Acetyl-5-methyl-3-phenyl-2-(thiophene-2-carbonyl)-2,3-dihydrofuran (3j). Solid; mp 148–150 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.12–7.74 (m, 8H), 5.40 (d, J=4.8 Hz, 1H), 4.64 (d, J=4.5 Hz, 1H), 2.46 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 187.6, 168.4, 142.4, 140.5, 135.6, 134.0, 129.4, 128.6, 127.9, 127.8, 115.8, 90.5, 52.7, 29.9, 15.2. IR (KBr): 2924, 1674, 1606, 1382, 1229, 1067, 1028, 758, 703 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 312 (M^+, 0.92), 269 (100), 201 (19.94), 111 (53.90), 43 (89.76). HRMS: *m/z* [M+H] calcd for $C_{18}H_{16}O_3S$: 313.0893; found: 313.0890.

4.4.20. cis-4-Acetyl-5-methyl-3-phenyl-2-(thiophene-2-carbonyl)-2,3-dihydrofuran (4j). Solid; mp 79–81 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.93–7.64 (m, 8H), 5.90 (d, J=10.5 Hz, 1H), 4.76 (d, J=10.5 Hz, 1H), 2.53 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 186.9, 169.0, 141.7, 137.2, 134.6, 132.8, 128.8, 128.5, 128.0, 127.8, 116.5, 88.4, 53.6, 29.8, 15.2. IR (KBr): 3104, 2924, 1670, 1602, 1515, 1383, 1219, 1068, 1031, 754, 704 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 312 (M^+, 2.50), 269 (62.00), 201 (19.31), 111 (66.74), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{18}H_{16}O_3S$: 313.0893; found: 313.0894.

4.4.21. trans-2-Methyl-4-phenyl-5-(thiophene-2-carbonyl)-4,5-dihydrofuran-3-carboxylic acid ethyl ester (3k). Sticky oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.08–7.71 (m, 8H), 5.47 (d, J=4.8 Hz, 1H), 4.53 (d, J=4.8 Hz, 1H), 3.97 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 1.03 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 168.2, 164.9, 142.7, 140.3, 135.3, 133.6, 128.8, 128.5, 127.6, 127.4, 107.1, 90.0, 59.6, 52.4, 14.2. IR (KBr): 3092, 3024, 2982, 2931, 1694, 1652, 1514, 1452, 1380, 1217, 1090, 1031, 756, 702 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 342 (M^+, 10.56), 327 (3.99), 299 (14.18), 269 (24.60), 231 (15.21), 111 (100), 43 (44.77). HRMS: *m/z* [M+H] calcd for $C_{19}H_{18}O_4S$: 343.0999; found: 343.0995.

4.4.22. trans-4-Acetyl-3-(4-chloro-phenyl)-5-methyl-2-(thiophene-2-carbonyl)-2,3-dihydrofuran (3l). Sticky oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.14–7.76 (m, 7H), 5.36 (d, J=4.8 Hz, 1H), 4.64 (d, J=4.8 Hz, 1H), 2.46 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 187.3, 168.4, 141.0, 140.3, 135.8, 134.1, 133.7, 129.5, 129.1, 128.7, 116.0, 90.2, 52.0, 29.8, 15.2. IR (KBr): 3097, 3015, 2911, 1672, 1625, 1599, 1514, 1490, 1380, 1228, 1090, 1022, 830 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 346 (M^+, 0.55), 303 (76.85), 235 (13.68), 111 (53.83), 43 (100). HRMS: *m/z* [M+H] calcd for $C_{18}H_{15}ClO_3S$: 347.0503; found: 347.0505.

4.5. General procedure for the transformation of either stereoisomer

The mixture of the cis-isomer **4** (0.1 mmol) and DBU (0.01 mmol) in benzene (2 mL) was stirred at room temperature for 3 h. After evaporating the solvent under reduced pressure, the residue was purified on silica gel with petroleum ether–ethyl acetate (30/1–10/1) as eluent to give first the trans-isomer **3**, while further elution to yield the cis-isomer **4**. When the starting material was a trans-isomer, the reaction took longer.

4.6. Typical procedure for oxidation to tetrasubstituted furans[11b]

To 8 mL benzene solution of dihydrofuran **3h** (0.4 mmol) was added 0.52 g (6 mmol) of CMD, and the suspension was refluxed for 48 h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified on silica gel with petroleum–ethyl acetate (20/1) as eluent to give 122.9 mg (92%) of tetrasubstituted furan **9h**.

To 5 mL dichloromethane solution of dihydrofuran **4h** (0.2 mmol) was added 174 mg (2 mmol) of CMD, and the suspension was refluxed for 12 h. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified on silica gel with petroleum ether–ethyl acetate (20/1) as eluent to give 63.5 mg (95%) of tetrasubstituted furan **9h**.

4.6.1. 5-Benzoyl-2-methyl-4-phenylfuran-3-carboxylic acid ethyl ester (9h). Solid; mp 75–77 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.71 (m, 10H), 4.12 (q, J=7.2 Hz, 2H), 2.74 (s, 3H), 1.06 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.5, 163.0, 162.0, 146.1, 136.9, 135.0, 132.1, 131.3, 129.8, 129.2, 127.7, 127.6, 127.2, 116.0, 60.2, 14.6, 13.6. IR (KBr): 3060, 2983, 2932, 1712, 1648, 1593, 1541, 1487, 1447, 1411, 1246, 1180, 1092, 1011, 731, 696 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 334 (M^+, 3.66), 333 (3.09), 305 (2.57), 159 (8.16), 115 (10.39), 105

(100), 77 (66.74), 43 (45.41). HRMS: *m/z* [M+H] calcd for $C_{21}H_{18}O_4$: 335.1278; found: 335.1276.

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7. Crystal data for **3j**: $C_{18}H_{16}O_3S$, M_W=312.37, T=291(2) K, λ=0.71073 Å, monoclinic space group $P2(1)/n$, a=9.804(1) Å, b=10.474(1) Å, c=15.324(2) Å, α=90.00°, β=102.860(2)°, γ=90.00°, V=1534.0(3) Å^3, Z=4, D_c=1.353 mg/m^3, μ=0.221 mm^{-1}, $F(000)$=656, crystal size 0.38×0.29×0.21 mm, independent reflections 2860 [R(int)=0.0142], reflections collected 7885, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.105, final R indices [$I>2\sigma(I)$] R_1=0.0373, wR_2=0.1067, R indices (all data) R_1=0.0427, wR_2=0.1092, extinction coefficient 0.0117(18), largest diff. peak and hole 0.243 and −0.424 e Å^{-3}. Crystallographic data for **3j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-268616. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].
8. Crystal data for **4j**: $C_{18}H_{16}O_3S$, M_W=312.37, T=288(2) K, λ=0.71073 Å, triclinic space group P-1, a=6.407(1) Å, b=11.386(2) Å, c=11.936(2) Å, α=88.60(1)°, β=75.35(1)°, γ=75.53(1)°, V=815.05(21) Å^3, Z=2, D_c=1.273 mg/m^3, μ=0.208 mm^{-1}, $F(000)$=328, crystal size 0.46×0.34×0.26 mm, independent reflections 3025 [R(int)=0.0084], reflections collected 3432, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.073, final R indices [$I>2\sigma(I)$] R_1=0.0540, wR_2=0.1669, R indices (all data) R_1=0.0761, wR_2=0.1814, extinction coefficient 0.013(6), largest diff. peak and hole 0.340 and −0.509 e Å^{-3}. Crystallographic data for **4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-268617. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].
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A formal synthesis of (±)-physostigmine via 3,3-rearrangement of a bis-enamine☆

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Abstract—A new flexible approach to hexahydropyrrolo[2,3-*b*]indole system via the [3,3]-sigmatropic rearrangement of 1-(2′-methoxycarbonyl-*N*-methylvinylamino)skatole, culminating in the synthesis of (±)-desoxyeseroline, is described.

1. Introduction

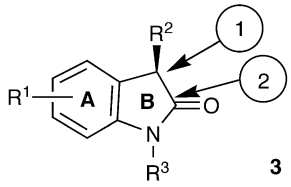
(−)-Physostigmine (**1a**) (Fig. 1), the major alkaloid of *Physostigma venenosum* (Balf.) seeds (Calabar beans)[2] is a member of a class of natural products incorporating the hexahydropyrrolo[2,3-*b*]indole nucleus. Some representative natural products, excluding those containing a diketopiperazine ring,[3] are (−)-debromoflustramine B (**2a**),[4] (−)-flustramine A (**2b**)[5] and (−)-pseudophrynaminol (**2c**).[6] (−)-Physostigmine shows wide biological activity[7] and the finding that suitably altering its carbamate side chain, for example, **1d**, afforded a derivative of much improved pharmacological profile in the fight against Alzheimer disease[8] has stimulated, during the last decade, studies aimed at constructing the skeleton of the alkaloid by expeditious and novel routes.

Amongst many syntheses[9] of alkaloid **1a** and related substances reported to date, a number of them involve an appropriate 1,3-dimethyloxindole (**3**, $R^2=R^3=Me$) playing a central role[10] (Scheme 1).

Introduction of the aminoethyl side chain or its synthetic equivalent with chiral induction,[9a–n] or otherwise,[9o–w] achieved in a variety of interesting ways, still necessitated a number of trivial, but nonetheless, obligatory functional group transformations to construct ring C.

During our studies on pericyclic reactions over a period of years, we have reported their applications to the synthesis of a variety of heterocycles.[11] It was shown that the rearranging system **5** (Scheme 2), generated from an aromatic hydroxamic acid derivative **4** containing a SPh functionality acting as an anion stabilising group,[12] underwent smooth rearrangement to the substituted *o*-aminophenylacetic acid derivative **6**, which was subsequently elaborated, via **7**, to **1c**.[9u]

It was anticipated that the aminoethyl side chain equivalent could be directly introduced by a similar sigmatropic process involving cleavage of the N–N bond of an



3

1 *chiral or non-chiral introduction of* **C—C—NR⁴** *or equivalent*

2 *cyclisation to ring* **C**

Scheme 1.

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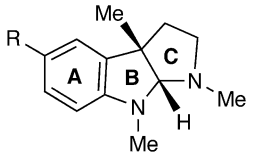


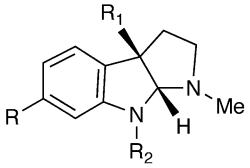
1

a: R = OCONHMe; (-)-physostigmine

b: R = OH; (-)-eseroline

c: R = H; (-)-desoxyeseroline

d: R = OCONHPh; (-)-phenserine



2

a: R = H; $R^1 = R^2 = CH_2CH{=}CMe_2$; (-)-debromoflustramine B

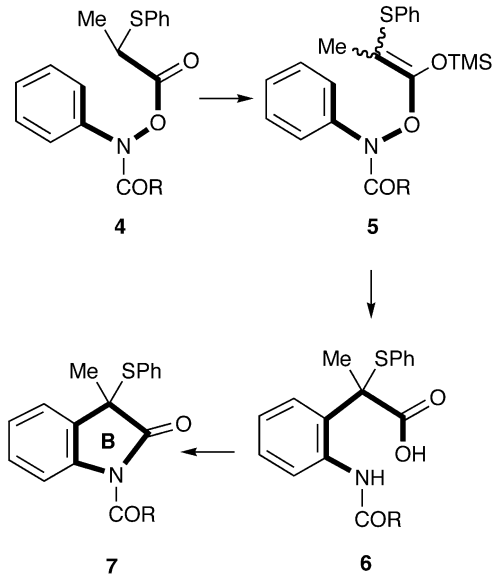
b: R = Br; $R^1 = R^2 = CH_2CH{=}CMe_2$; (-)-flustramine A

c: R = H ; $R^1 = CH_2CH{=}C(Me)CH_2OH$; R^2 = H; (-)-pseudophrynaminol

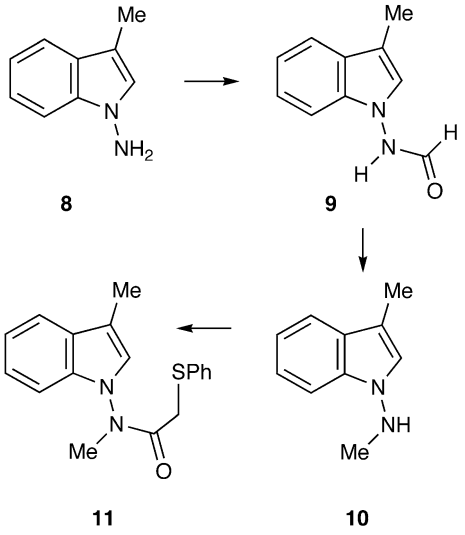
Figure 1. Molecules related to physostigmine, containing the hexahydropyrrolo[2,3-*b*]indole nucleus.

appropriate indole derivative. It was further expected that, should such a reaction occur, the appositely generated electrophilic and nucleophilic centres would cyclise[13] to install rings B and C in cis fusion in one step.[14]

The requisite starting material for the contemplated synthesis, the phenylthioacetamide **11** (Scheme 3) was secured by *N*-amination of skatole[15] followed by conversion



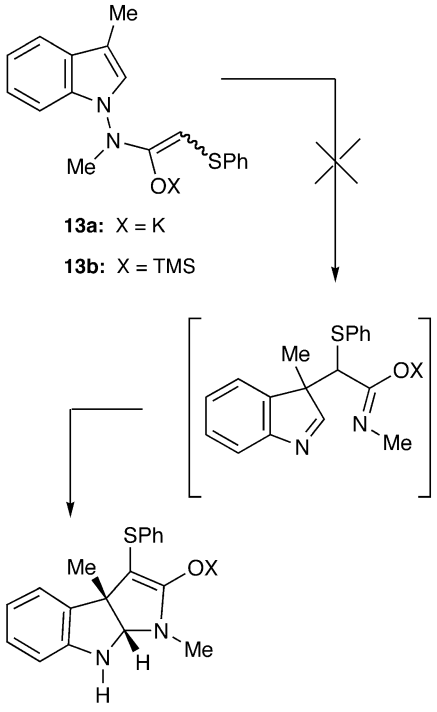
Scheme 2.



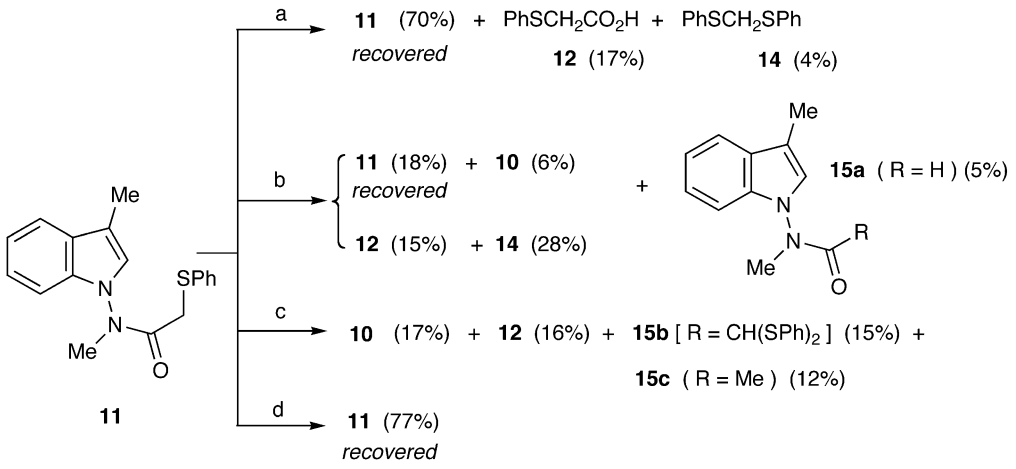
Scheme 3.

of the resulting hydrazine **8** (40% yield), into the formamide **9**[16] with formic acid under reflux. Its ^{1}H NMR spectrum disclosed the presence of two rotamers (1:2) with the major isomer attributed the trans structure on the basis of the coupling constant (J = 10.4 Hz) of the formamide protons NH–C(O)H. LAH reduction of formamide **9** yielded **10**,[16] which on reaction with 2-(phenylsulfanyl)acetic acid (**12**) in the presence of DCC and 4-DMAP, provided **11** in 70% yield.

However, all efforts to induce the desired rearrangement of the derived enolate **13a** (Scheme 4) or the corresponding silyl ether **13b** generated in situ, under a variety of conditions, only met with failure; either the starting material



Scheme 4.



Scheme 5. Reagents and conditions: (a) KHMDS (1.1 equiv), THF, −80 °C to rt, 1 h, rt, 2 h, 45 °C, 2 h, reflux, 50 h; (b) KH (1.1 equiv), THF, −80 °C to rt, 2 h, reflux 30 h; (c) KHMDS (1.1 equiv), $(MeOCH_2CH_2)_2O$, 120–130 °C, 3 h (d) KHMDS (1.1 equiv), TMSCl (2.0 equiv), $(MeOCH_2CH_2)_2O$, −80 °C to rt, 1 h, 120–130 °C, 32 h, reflux, 27 h.

was largely returned or a complex mixture of products obtained.

Scheme 5 summarises the results obtained under different experimental conditions and indicates that radical processes are most probably involved in the formation of some of the products, especially **14** and those of type **15**.

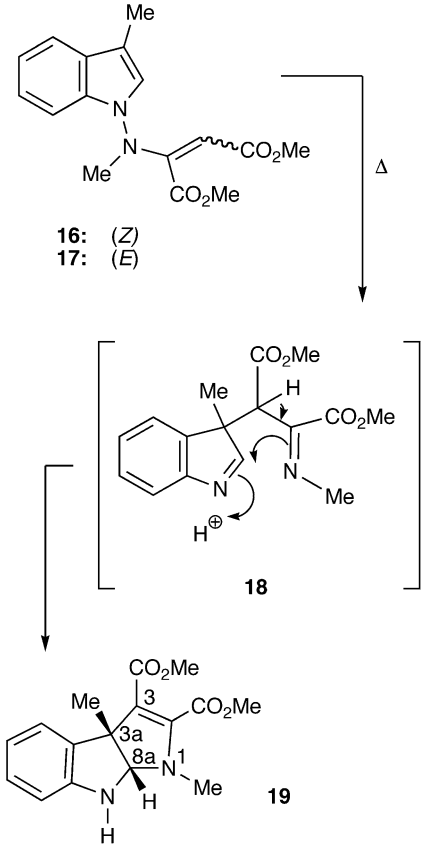
It was thought that the failure of **11** to undergo a 3,3-shift could be overcome if the relatively weak N–N bond is further weakened by incorporation of an EWG at the terminal position in the pendant *N*-vinyl group. In the event this minor structural modification led to a successful synthesis of (±)-desoxyeseroline (**1c**), which we had earlier reported in a preliminary communication.[1] Full details of the work are described herein.

Dimethyl acetylenedicarboxylate was initially chosen for the study. Addition of **10** to the diester in methanol at rt, cleanly provided in a near quantitative yield a mixture of **16** (*Z*-isomer, 32%) and **17** (*E*-isomer, 63%) (Scheme 6).

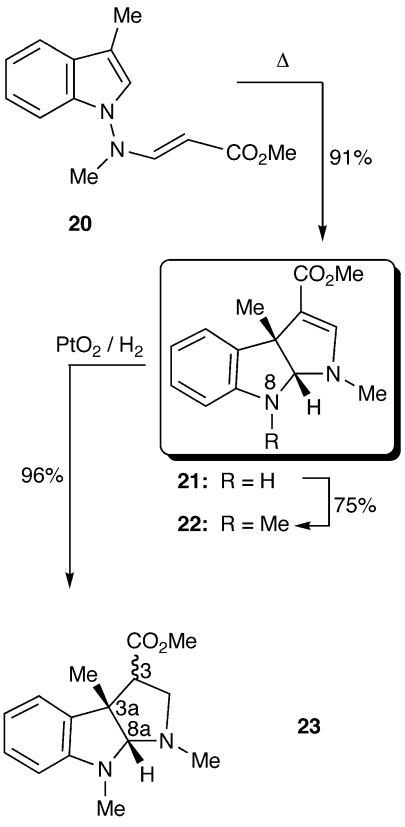
Their olefinic hydrogens resonated at δ 5.48 and 4.73, respectively. The attribution of the *E*-geometry for the isomer with lower δ value was based on the comparison of its chemical shift with that of similar olefinic hydrogen δ (4.60) in the ^{1}H NMR spectra of dimethyl 2-(methylamino) maleate.[17] The olefinic mixture on thermolysis in diphenyl ether at 180–200 °C (ca. 8 h) afforded, probably via **18**, the tricyclic compound **19** (45%) as a yellow oil. Its molecular formula as determined by accurate mass measurement and IR spectrum were fully consistent with the proposed structure. More importantly, the resonance signals (^{1}H NMR) at δ 1.67 (C_{3a}–CH_3) and δ 5.12 (C_{8a}–*H*) uniquely defined its structure.

A similar addition to methyl propiolate, a less reactive Michael acceptor, required a higher temperature and extended reaction time (MeOH, reflux, 14 h) to give the enaminoester **20**. Thermolysis of finely ground **20** in diphenyl ether at 210–220 °C (3 h) furnished the tricycle **21** in 51% yield (Scheme 7). Significant improvement in yield (91%) was achieved when the rearrangement was carried out in *o*-dichlorobenzene under reflux (35 h).

As in **19**, the C_{8a}–*H* in **21** resonated at δ 5.05 as a singlet indicating that ring C of hexahydropyrrolo[2,3-*b*]indole ring system had been established in one step. Although in principle the synthesis of DL-desoxyeseroline (**1c**) from the tricycle **21** involved four simple steps, namely N^8-methylation, saturation of the double bond and removal of the ester functionality, in actual practice the last step in this sequence could not be realised. Thus, the *N*-methyl



Scheme 6.



Scheme 7.

compound **22** secured in 75% yield (NaH, DMF, 15-crown-5, THF, MeI, 92%), on reduction (PtO_2–H_2; rt) furnished the corresponding dihydro compound **23** of undetermined stereochemistry in high yield.

Although the Na salt of the acid was readily formed by base hydrolysis of the ester **23**, the corresponding Barton ester could not be obtained in any synthetically meaningful yield via the activated carboxylic acid derivatives with the usual coupling agents, such as isobutylchloroformate[18] or $(EtO)_2$-P(O)CN[19] and the anion of *N*-hyroxypyridine-2-thione.

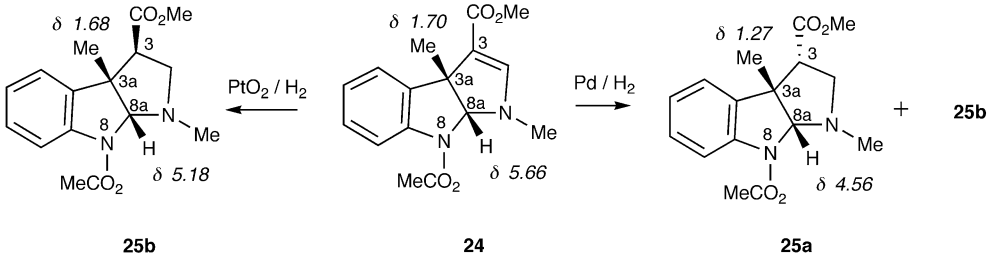
On the assumption that the nucleophilicity of N^8 could be responsible for the observed failure, **21** was first converted into its methylcarbamate derivative **24** (81%) (Scheme 8). Whilst saturation of the double bond of **24** with Pt°–H_2 provided **25b** (β-ester: C_{3a}–CH_3, δ 1.68; C_{8a}–*H*, δ 5.18) as the exclusive product (98%), the use of Pd produced a diastereomeric mixture of **25a** (α-ester: 58%: C_{3a}–CH_3, δ 1.27; C_{8a}–*H*, δ 4.56) and **25b** (35%). In view of the lower δ values of the C_{3a}–CH_3 and C_{8a}–*H* resonances for **25a** vis à vis **25b** the β configuration is assigned to the latter. Consistent with this attribution, is the observation that a pure sample of **25b** on exposure to a methanolic sodium methoxide solution epimerises to the more stable **25a**.

Selective hydrolysis of the ester group in **25a** or in **25a**, **25b** mixture with aqueous methanolic NaOH (1 N; 1 equiv) followed by evaporation of the solvents gave the corresponding salt **26a** (Scheme 9), which was thoroughly dried in high vacuum prior to use. The derived acid chloride **26b**, formed in situ with oxalyl chloride, on reaction with the anion of *N*-hydroxypyridine-2-thione yielded the Barton ester **27** that on decarboxylation in the usual manner (AIBN, TBSH)[20] afforded the product **28** in poor yield (24%). Compound **27**, obtained via the mixed anhydride **26c**, on photolysis in the presence of *tert*-butylthiol as the hydrogen donor[21] underwent decarboxylation to afford an improved yield of **28** (51%). A considerable improvement in this yield (92%) was achieved on irradiating[22] the benzophenone oxime ester **29** secured in 75% yield via the mixed anhydride **26c**, in a THF–isopropanol mixture containing a large excess of *tert*-butylthiol (10 mmol).

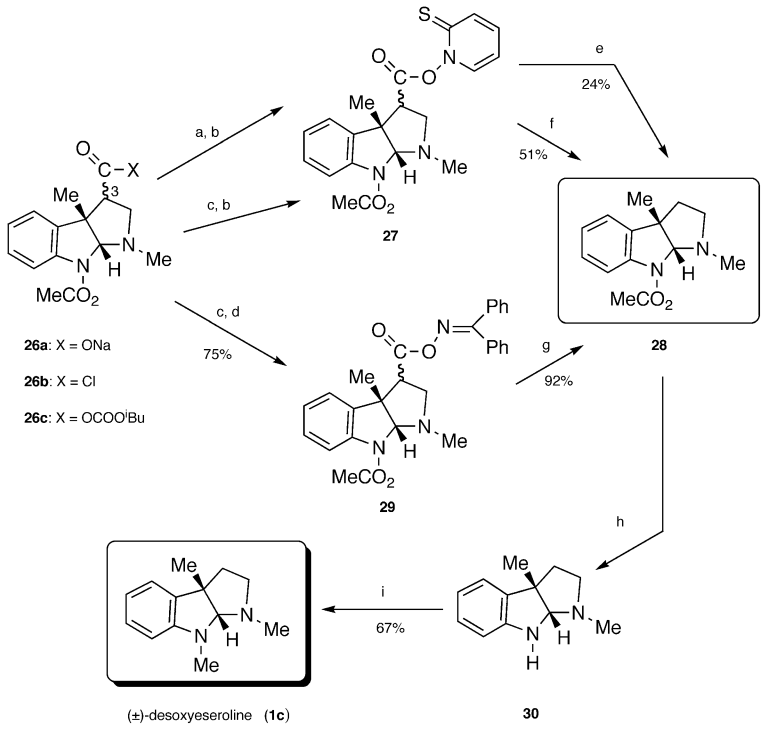
The presence of a 2H triplet centred at δ 2.04 (C_3–*H*) in its ^{1}H NMR spectrum and a single CO absorption (IR) taken in conjunction with the elemental analysis confirmed the structure assigned to **28**. Although LAH reduction of *N*,*N*-disubstituted carbamates in general provides the corresponding tertiary amines,[23] such a reduction of **28** yielded N^8-nordesoxyeseroline (**30**) (mp 110–112 °C; 69% lit.[24] 111–112 °C) with δ values in its ^{13}C NMR spectrum coincident with those reported for such compound.[25] *N*-methylation, carried out at pH≈6, with aqueous formalin and $NaBH_3CN$,[26] furnished (±)-desoxyeseroline (**1c**) as a pale yellow oil (PTLC; 67% yield). It formed a picrate, mp 183–184 °C (from EtOH), lit.[10] mp 179–180 °C, and the δ values of the various hydrogens in its ^{1}H NMR spectrum were in full accordance with those reported.[14b]

Since (−)-desoxyeseroline (**1c**) had been previously converted into (−)-eseroline (**1b**) and hence to (−)-physostigmine (**1a**)[27] this work constitutes also a formal synthesis of (±)-physostigmine.

In summary, a novel route to 3a-methyl hexahydropyrrolo[2,3-*b*]indole nucleus involving a pericyclic reaction of a *N*-aminoskatole derivative as the starting material is described. The protocol employed above is applicable, in principle, to the diastereoselective synthesis of alkaloids by using chiral Michael acceptors (e.g., a chiral acetylene sulphoxide or a chiral propiolic ester).



Scheme 8.



Scheme 9. Reagents and conditions: (a) oxalyl chloride, C_6H_6, reflux; (b) *N*-hydroxpyridine-2-thione sodium salt, reflux; (c) $ClCO_2CH_2CH(CH_3)_2$, THF, −20 °C; (d) $Ph_2C{=}NOH/Et_3N$; (e) AIBN, $^nBu_3SnH$; (f) hν, THF, ^{t}ButSH; (g) hv, Me_2CHOH, THF, ^{t}BuSH; (h) LAH, THF, reflux, (69%) or aqueous NaOH 5 N MeOH, reflux, (66%); (i) aqueous formalin, $NaBH_3CN$; pH 6.

2. Experimental

2.1. General

Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. IR spectra were measured on a Buck Scientific 500 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brucker ARX 400 spectrometer unless otherwise stated. Chemical shifts are reported relative to tetramethylsilane as internal reference (δ 0.00) for ^1H spectra and to $CDCl_3$ (δ 77.00) for ^{13}C spectra. The solvent used was $CDCl_3$, unless stated otherwise. Ordinary mass spectra were recorded on a Fisons TRIO 2000 or AEI MS-9 spectrometer. High resolution mass spectra were recorded on a AutoSpecQ spectrometer. Elemental analyses were performed by the National Institute of Engineering and Industrial Technology, Lisbon. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh). Hydrogenation reactions were carried out in a Parr 3911 hydrogenator, at rt. Usual work up implies drying the water or brine washed organic extracts over anhydrous sodium sulphate or magnesium sulphate, followed by filtration and evaporation of the solvent from the filtrate under reduced pressure. Anhydrous solvents were dried[28] and freshly distilled.

2.1.1. 1-[*N*-Methyl-2′-(phenylsulfanyl)acetamido]-3-methylindole (11). To a solution of 3-methyl-1-(methylamino)indole (**10**) (2.45 g, 15.3 mmol), 2-(phenylsulfanyl)-acetic acid (**12**) (2.85 g, 16.9 mmol) and 4-DMAP (0.38 g, 3.1 mmol) in anhydrous CH_2Cl_2 (80 mL), under vigorous stirring at rt, was added dropwise a solution of DCC (3.32 g, 16.1 mmol) in the same solvent (50 mL). After being stirred for 3 h 30 min, the reaction mixture was filtered at reduced pressure and the filtrate evaporated to dryness. To the residue was added Et_2O and the resulting mixture again filtered to remove the residual *N*,*N*-dicyclohexylurea. The filtrate was then washed sequentially with 5% aqueous $NaHCO_3$, 5% aqueous HCl and water. The oil obtained on usual work-up was purified by preparative TLC (silica, CH_2Cl_2/*n*-hexane 1:1) to give, after recrystallization from Et_2O/*n*-hexane, **11** (3.32 g, 70%), as colourless needles: mp 75.0–75.5 °C; IR (KBr) ν_{max} 1686 (s, C=O) cm^{-1}; ^1H NMR δ 7.58 (1H, d, J=7.8 Hz, Ar*H*), 7.36–7.14 (8H, m, Ar*H*), 6.73 (1H, s, NC*H*=C), 3.50/3.47 (2H, *AB* system, J=14.9 Hz, CH_2SPh), 3.30 (3H, s, NCH_3), 2.30 (3H, d, J= 1.2 Hz, CCH_3); MS (EI) *m/z* 310 (M^+, 93.6), 160 (32.0), 159 (100.0). Anal. Calcd for $C_{18}H_{18}N_2OS$: C 69.65; H 5.85; N 9.03. Found: C 69.76; H 5.97; N 9.00.

2.2. Reaction of 11 with base

2.2.1. KHMDS in THF. To a stirred suspension of KH (0.78 mmol, 89 mg of a 35% dispersion, washed free of mineral oil with anhydrous THF), in anhydrous THF (8 mL), at rt under N_2 atmosphere, was added bis(trimethylsilyl)amine (0.15 mL, 0.71 mmol). After further stirring for 2 h, the suspension was cooled to −80 °C and a solution of **11** (200 mg, 0.65 mmol) in the same solvent (5 mL) was added dropwise. The reaction mixture was stirred for 1 h, while the temperature was allowed to rise slowly to rt. After being stirred for 2 h at rt, 2 h at 45 °C and 50 h under reflux, the reaction mixture was cooled, diluted with water, neutralized with 5% aqueous HCl and extracted with ethyl acetate. The combined organic layers were washed with 5% aqueous $NaHCO_3$ and water and dried. After removal of the solvent at reduced pressure, the resulting brown oil was

subjected to preparative TLC (silica, Et_2O/*n*-hexane 1:1) to give, in increasing order of polarity: bis(phenylsulfanyl)-methane (**14**) (6 mg, 4%), as a yellow solid: mp 33–37 °C (from *n*-hexane) (lit.[29] mp 36–38 °C); IR (film) ν_{max} 1588, 1484, 1442, 1268, 1204, 1092, 1028, 744 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.47–7.44 (4H, m, Ar*H*), 7.37–7.33 (4H, m, Ar*H*), 7.29–7.25 (2H, m, Ar*H*), 4.56 (2H, s, CH_2); MS (EI) *m*/*z* 232 (M^+, 74.3), 123 (85.3), 109 (13.8), 51 (38.5), 45 (100.0); and recovered **11** (74 mg, 37%). From the original base extract 2-(phenylsulfanyl)acetic acid (**12**) was obtained (after neutralisation with 5% aqueous HCl) in 17% yield (19 mg).

2.2.2. KH in THF. To a stirred suspension of KH (0.76 mmol, 87 mg of a 35% dispersion, washed free of mineral oil with anhydrous THF) in anhydrous THF (8 mL), cooled to −80 °C, under N_2 atmosphere, was added dropwise a solution of **11** (202 mg, 0.65 mmol) in the same solvent (5 mL). The reaction mixture was stirred for 2 h, while the temperature was left to rise slowly to rt. After being stirred for 2 h at rt and 30 h under reflux, the reaction mixture was worked-up as above. Evaporation of the combined ethyl acetate extracts, left an oil, which was subjected to preparative TLC (silica, Et_2O/*n*-hexane 1:1) to give, **14** (21 mg, 28%), as a pale-yellow solid, which was identical with a sample previously isolated; recovered **11** (36 mg, 18%), 3-methyl-1-(*N*-methylformamido)indole (**15a**) (6 mg, 5%), as a white solid: mp 83–85 °C, on recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1692 (f, C=O) cm^{-1}; ^1H NMR δ 8.42 (1H, s, C*H*O), 7.60 (1H, d, J=8.1 Hz, Ar*H*), 7.3–7.20 (3H, m, Ar*H*), 6.88 (1H, s, NC*H*=C), 3.29 (3H, s, NCH_3), 2.32 (3H, s, CCH_3); MS (EI) *m*/*z* 188 (M^+, 91.3), 159 (45.0), 130 (100.0); exact mass calcd for $C_{11}H_{12}N_2O$: 188.094963. Found: 188.095597; and 3-methyl-1-(methylamino)indole (**10**) (6 mg, 6%), as a yellowish oil: IR (film) ν_{max} 3310 (br, NH) cm^{-1}; ^1H NMR δ 7.54 (1H, d, J=7.6 Hz, Ar*H*), 7.39 (1H, d, J=7.6 Hz, Ar*H*), 7.21 (1H, *t*, J=7.6 Hz, Ar*H*), 7.10 (1H, *t*, J=7.6 Hz, Ar*H*), 6.96 (1H, s, NC*H*=C), 4.23 (1H, br s, N*H*, D_2O exchangeable), 2.92 (3H, s, NCH_3), 2.30 (3H, d, J=1.0 Hz, CCH_3); MS (EI) *m*/*z* 160 (M^+, 100.0). From the aqueous $NaHCO_3$ extracts was isolated 2-(phenylsulfanyl)acetic acid (**12**) (16 mg, 15%).

2.2.3. KHMDS in bis(2-methoxyethyl) ether. To a suspension of KHMDS (0.71 mmol) in anhydrous bis(2-methoxyethyl) ether (8 mL), prepared as previously described, stirred at rt under N_2 atmosphere, was added dropwise a solution of **11** (200 mg, 0.65 mmol) in the same solvent (5 mL). After the addition was complete, the reaction mixture was heated at 120–130 °C for 3 h and then worked-up as in procedure (a). Removal of the solvent from the ethyl acetate extracts left an oil, which was purified by preparative TLC (silica, Et_2O/*n*-hexane 1:1) to give, 1-[bis(2′-phenylsulfanyl)-*N*-methylacetamido]-3-methylindole (**15b**) (20 mg, 15%), as a yellowish oil: IR (film) ν_{max} 1692 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 7.54 (1H, d, J=7.5 Hz, Ar*H*), 7.40–7.14 (10H, m, Ar*H*), 7.09–7.03 (3H, m, Ar*H*), 6.56 (1H, s, NC*H*=C), 4.50 (1H, s, COC*H*), 3.31 (3H, s, NCH_3), 2.15 (3H, d, J=0.8 Hz, CCH_3); MS (EI) *m*/*z* 418 (M^+, 38.5), 309 (100.0); exact mass calcd for $C_{24}H_{22}N_2OS_2$: 418.117357. Found: 418.116225; **10** (18 mg, 17%), 3-methyl-1-(*N*-methylacetamido)indole (**15c**) (16 mg, 12%), as a colourless solid: mp 140–141 °C, after recrystallization form Et_2O/*n*-hexane (lit.[30] mp 140.5–141.0 °C); IR (KBr) ν_{max} 1684 (C=O) cm^{-1}; ^1H NMR δ 7.60 (1H, d, J=7.8 Hz, Ar*H*), 7.31–7.18 (3H, m, Ar*H*), 6.84 (1H, s, NC*H*=C), 3.33 (3H, s, NCH_3), 2.33 (3H, J=1.0 Hz, CCH_3), 1.85 (3H, s, $COCH_3$); MS (EI) *m*/*z* 202 (M^+, 100.0). From the aqueous $NaHCO_3$ extracts was isolated, as in procedure (a), 2-(phenylsulfanyl)acetic acid (**12**) (17 mg, 16%), as a colourless solid, which was identical with an authentic sample.

2.2.4. KHMDS and TMSCl in bis(2-methoxyethyl) ether. To a stirred suspension of KHMDS (0.71 mmol) in anhydrous bis(2-methoxyethyl) ether (8 mL), prepared as described above, cooled to −80 °C, under N_2 atmosphere, were added a solution of **11** (199 mg, 0.64 mmol) in the same solvent (5 mL) and TMSCl (0.16 mL, 1.25 mmol). The reaction mixture was stirred for 1 h, while the temperature was left to rise slowly to rt. After being stirred for 1 h at rt, 32 h at 120–130 °C and 27 h under reflux, the reaction mixture was cooled, neutralized with 5% aqueous HCl and the organic layer, separated by decantation, washed with water and dried. Removal of the solvent at reduced pressure and purification of the resulting residue by preparative TLC (silica, Et_2O/*n*-hexane 1:1), furnished **11** (157 mg, 77%).

2.2.5. 1-[1′,2′-Bis(methoxycarbonyl)-*N*-methylvinylamino]-3-methylindole (16,17). To a stirred solution of 3-methyl-1-(methylamino)indole (**10**) (117 mg, 0.73 mmol) in MeOH (8 mL), at rt, was added dropwise dimethyl acetylenedicarboxylate (0.1 mL, 0.82 mmol). After being stirred for 3 h 10 min, the reaction mixture was evaporated to dryness and the resulting residue subjected to preparative TLC (silica, CH_2Cl_2), to give two isomers: *Z* isomer **16** (71 mg, 32%), as a yellow solid: mp 89.5–90.5 °C, after recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1732 (s, C=O), 1708 (s, C=O) cm^{-1}; ^1H NMR δ 7.50 (1H, d, J=7.5 Hz, Ar*H*), 7.45 (1H, d, J=7.5 Hz, Ar*H*), 7.25 (1H, *t*, J=7.5 Hz, Ar*H*), 7.14 (1H, *t*, J=7.5 Hz, Ar*H*), 6.99 (1H, s, NC*H*=C), 5.48 (1H, s, NC=C*H*), 3.76 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.29 (3H, s, NCH_3), 2.27 (3H, d, J=0.8 Hz, CCH_3); MS (EI) *m*/*z* 302 (M^+, 100.0). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.55; H 6.00; N.9.27. Found: C 63.78; H 6.14; N 9.29; *E* isomer 17 (139 mg, 63%), as a colourless solid: mp 93.0–94.5 °C, after recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1744 (s, C=O), 1704 (s, C=O) cm^{-1}; ^1H NMR δ 7.53 (1H, d, J=7.8 Hz, Ar*H*), 7.29–7.15 (3H, m, Ar*H*), 6.84 (1H, s, NC*H*=C), 4.73 (1H, br s, NC=C*H*), 3.71 (3H, br s, OCH_3), 3.64 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 2.27 (3H, d, J=0.7 Hz, CCH_3); MS (EI) *m*/*z* 302 (M^+, 100.0). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.55; H 6.00; N 9.27. Found: C 64.05; H 6.11; N 9.35.

2.2.6. 2,3-Bis(methoxycarbonyl)-1,3a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (19). A solution containing the two isomers **16** and **17** (1/1.8 mixture, 322 mg, 0,11 mmol) in diphenyl ether (15 mL) was heated at 180–200 °C in an oil bath, for 7 h 45 min. The solvent was removed at reduced pressure and the resulting dark residue purified by preparative TLC (silica, CH_2Cl_2/*n*-hexane 2:1) to give 19 (145 mg, 45%), as a yellowish oil: IR (KBr) ν_{max} 3365 (br, NH), 1748 (s, 2-*CO*OMe), 1684 (s, 3-*CO*OMe)

cm^{-1}; ^1H NMR δ 7.56 (1H, d, $J=7.6$ Hz, Ar*H*), 7.05 (1H, *t*, $J=7.6$ Hz, Ar*H*), 6.80 (1H, *t*, $J=7.6$ Hz, Ar*H*), 6.68 (1H, d, $J=7.6$ Hz, Ar*H*), 5.12 (1H, s, NC*H*N), 4.46 (1H, br s, N*H*, D_2O exchangeable), 3.88 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 2.83 (3H, s, NCH_3), 1.67 (3H, s, CCH_3); MS (EI) *m/z* 302 (M^+, 100.0); exact mass calcd for $C_{16}H_{18}N_2O_4$: 302.126657. Found: 302.125918.

2.2.7. 1-(2′-Methoxycarbonyl-*N*-methylvinylamino)-3-methylindole (20). Methyl propiolate (1.5 mL, 16.86 mmol) was added to a solution of 3-methyl-1-(methylamino)indole (**10**) (0.75 g, 4.69 mmol) in MeOH (20 mL), at rt. The reaction mixture was heated under reflux for 14 h and then evaporated to dryness at reduced pressure to give **20** (1.08 g, 94%), as colourless needles: mp 112.0–112.5 °C, after recrystallization from Et_2O/*n*-hexane; IR (KBr) ν_{max} 1698 (s, C=O) cm^{-1}; ^1H NMR δ 7.65 (1H, d, $J=13.2$ Hz, NC*H*=CH), 7.57 (1H, d, $J=7.8$ Hz, Ar*H*), 7.26–7.15 (3H, m, Ar*H*), 6.86 (1H, s, NC*H*=CMe), 4.61 (1H, br d, $J=13.2$ Hz, NCH=C*H*), 3.64 (3H, s, OCH_3), 3.31 (3H, s, NCH_3), 2.30 (3H, d, $J=0.8$ Hz, CCH_3); MS (EI) *m/z* 244 (M^+, 100.0). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C 68.82, H 6.61, N 11.47. Found C 68.96, H 6.66, N 11.48.

2.2.8. 3-Methoxycarbonyl-1,3a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (21). To diphenyl ether (8 mL) at 210–220 °C was added finely powdered 20 (625 mg, 2.56 mmol) and the mixture while being stirred was kept at that temperature, for 2 h 50 min. The solvent was then removed at reduced pressure and the dark residue subjected to column chromatography (Et_2O/*n*-hexane 1:1) to give **21** (319 mg, 51%), as a yellowish oil: IR (film) ν_{max} 3355 (br, NH), 1674 (s, C=O) cm^{-1}; ^1H NMR δ 7.62 (1H, d, $J=$ 7.5 Hz, Ar*H*), 7.05–7.01 (2H, m, Ar*H* and NC*H*=C), 6.79 (1H, *t*, $J=7.5$ Hz, Ar*H*), 6.67 (1H, d, $J=7.5$ Hz, Ar*H*), 5.05 (1H, s, NC*H*N), 4.48 (1H, br s, N*H*, D_2O exchangeable), 3.66 (3H, s, OCH_3), 2.90 (3H, s, NCH_3), 1.65 (3H, s, CCH_3); MS (EI) *m/z* 244 (M^+, 100.0); exact mass calcd for $C_{14}H_{16}N_2O_2$: 244.121178. Found: 244.121673.

Compound **20** (1.61 g, 6.6 mmol) in *o*-dichlorobenzene (distilled, 30 mL) was heated under reflux in an argon atmosphere (35 h). Evaporation of the solvent under reduced pressure followed by chromatographic purification of the resulting residue (EtOAc/*n*-hexane 3:7) furnished **21** (1.47 g, 91%) as a colourless solid mp 120–122 °C, identical in all respects with the sample above.

2.2.9. 3-Methoxycarbonyl-1,3a,8-trimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (22). *Compound* **21** (240 mg, 0.98 mmol) in anhydrous dichloromethane (15 mL) containing 15-crown-5-ether (2 mg) and NaH (80%; 87 mg, 3 mmol) was treated with an excess of MeI (5 mmol) and the mixture heated under reflux (15 h). Evaporation of the solvent followed by purification of the resulting residue by column chromatography (EtOAc/*n*-hexane 1:6) gave the *N*-alkylated product **22** (190 mg, 75%) as a colourless solid, mp 52–53 °C; IR (KBr) ν_{max} 1722, 1671 cm^{-1}; ^1H NMR δ 7.58 (1H, d, $J=8.0$ Hz, Ar*H*), 7.08 (2H, m, Ar-*H* and NC*H*=C), 6.73 (1H, *t*, $J=8.0$ Hz, Ar-*H*), 6.47 (1H, d, $J=$ 8.0 Hz, Ar*H*), 4.71 (1H, s, NC*H*N), 3.65 (3H, s, OCH_3), 3.02 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 1.63 (3H, s, CCH_3); exact mass calcd for $C_{15}H_{18}N_2O_2$: 258.12682. Found: 258.13674.

2.2.10. 3-Methoxycarbonyl-1,3a,8-trimethyl-2,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (23). *Compound* **22** (264 mg, 1.02 mmol) in MeOH (10 mL), was hydrogenated in the presence of PtO_2 (26 mg) at 25 psi (8 h). After removal of the catalyst by filtration, the solvent was evaporated at reduced pressure and the resulting residue purified by column chromatography (EtOAc/*n*-hexane 1:4) to give the title compound **23** (255 mg; 96%) as a colourless solid, mp 48–50 °C; IR (KBr) ν_{max} 1743 (s, C=O) cm^{-1}; ^1H NMR δ 7.14 (1H, *t*, $J=8.0$ Hz/br s, Ar*H*), 6.86 (1H, d, $J=8.0$ Hz, Ar*H*), 6.62 (1H, *t*, $J=8.0$ Hz, Ar*H*), 6.44 (1H, d, $J=8.0$ Hz, Ar-*H*), 4.33 (1H, br s, NC*H*N), 3.54 (3H, s, OCH_3), 2.90 (3H, s, NCH_3), 2.55 (3H, s, NCH_3), 1.65 (3H, s, CCH_3); exact mass calcd for $C_{15}H_{20}N_2O_2$: 260.15247. Found: 260.15228.

2.2.11. 3,8-Bis(methoxycarbonyl)-1,3a-dimethyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (24). A solution of methyl chloroformate (0.09 mL, 1.16 mmol) in anhydrous Et_2O (2 mL) was added dropwise to an ice-cooled solution of **21** (283 mg, 1.16 mmol) and 4-DMAP (142 mg, 1.16 mmol), in the same solvent (10 mL). The mixture was stirred at rt for 2 h 30 m and then washed with water and dried. The solvent was evaporated at reduced pressure and the residue purified by preparative TLC (Et_2O/*n*-hexane 2:1) to give **24** (284 mg, 81%), as a white solid: mp 180.0–180.5 °C, after recrystallization from acetone/Et_2O; IR (KBr) ν_{max} 1722 (s, N*CO*OMe), 1678 (s, 3-*CO*OMe) cm^{-1}; ^1H NMR δ 7.74–750 (2H, d, $J=7.5$ Hz/br s, Ar*H*), 7.20 (1H, *t*, $J=7.5$ Hz, Ar*H*), 7.03 (1H, *t*, $J=7.5$ Hz, Ar*H*), 6.99 (1H, s, NC*H*=C), 5.66 (1H, br s, NC*H*N), 3.90 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.02 (3H, s, NCH_3), 1.70 (3H, s, CCH_3); MS (EI) *m/z* 302 (M^+, 100.0). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C 63.55, H 6.00, N 9.27. Found: C 63.56, H 5.97, N 9.21.

2.2.12. 3,8-Bis(methoxycarbonyl)-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (25a+25b). A solution of **24** (583 mg, 1.93 mmol) in MeOH (180 mL), containing 10% palladium on carbon (179 mg, 0.17 mmol), was shaken under hydrogen pressure (45 Psi) for 16 h. After removal of the catalyst by filtration over Celite, the solvent was evaporated at reduced pressure and the residue subjected to preparative TLC (Et_2O/*n*-hexane 2:1) to give the less polar diastereoisomer **25a** (340 mg, 58%), as a colourless solid: mp 154.0–154.5 °C, after recrystallization from *n*-hexane; IR (KBr) ν_{max} 1740 (s, 3-*CO*OMe), 1712 (s, N*CO*OMe) cm^{-1}; ^1H NMR δ 7.66 (1H, br s, Ar*H*), 7.37 (1H, d, $J=7.6$ Hz, Ar*H*), 7.23 (1H, *t*, $J=7.6$ Hz, Ar*H*), 7.06 (1H, *t*, $J=7.6$ Hz, Ar*H*), 4.56 (1H, br s, NC*H*N), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.23–3.18 (1H, m, NCH_2CH), 3.08–3.04 (1H, m, NCH_2CH), 2.94 (1H, *t*, $J=9.8$ Hz, NCH_2CH), 2.59 (3H, br s, NCH_3), 1.27 (3H, s, CCH_3); MS (EI) *m/z* 304 (M^+, 32.9), 273 (8.2), 245 (7.3), 189 (50.7), 158 (23.4), 144 (14.2), 130 (23.4), 115 (100.0). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C 63.13; H 6.63; N 9.21. Found: C 63.07; H 6.33; N 9.22; and the more polar diastereoisomer **25b** (205 mg, 35%), as a colourless solid: mp 73.5–75.0 °C, after recrystallization from acetone/Et_2O; IR (KBr) ν_{max} 1734 (s, 3-*CO*OMe), 1720 (s, N*CO*OMe) cm^{-1}; ^1H NMR δ 7.70 (1H, br s, Ar*H*), 7.24–7.20 (1H, m, Ar*H*), 6.98–6.94 (2H, m,

Ar*H*), 5.18 (1H, s, NC*H*N), 3.86 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.20–3.16 (1H, m, NCH_2CH), 2.90–2.82 (2H, m, NCH_2CH and NCH$_2$C*H*), 2.56 (3H, s, NCH_3), 1.68 (3H, s, CCH_3); MS (EI) *m*/*z* 304 (M^+, 27.4), 273 (14.6), 245 (7.8), 189 (81.3), 158 (25.1), 144 (34.7), 130 (19.1), 115 (100.0). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C 63.13; H 6.63; N 9.21. Found: C 63.23; H 6.70; N 9.21.

The diastereomer **25b**, obtained as the exclusive product with Pt° as the hydrogenating catalyst in anhydrous MeOH, was found to isomerise to **25a** on exposure to 1 N methanolic sodium methoxide.

2.3. Sodium salt of 8-methoxycarbonyl-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-3-carboxylic acid (26a)

To a mixture of the diastereoisomers **25a** and **25b** (144 mg, 0.47 mmol) in MeOH (6 mL), was added 1 N aqueous NaOH (0.48 mL, 0.48 mmol) and the mixture heated under reflux for 5 h. The solvents were removed at reduced pressure, benzene was added to the residue and the resulting mixture evaporated to dryness at reduced pressure. The process was repeated several times. The resulting solid, presumably a mixture of the sodium salts **26a** was dried over phosphorous pentoxide in vacuo.

2.3.1. 8-Methoxycarbonyl-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (28). *Method a*. A suspension of the above sodium salts **26a** (49.9 mg, 0.16 mmol) in benzene was treated with oxalyl chloride (0.015 mL, 0.18 mmol) in benzene (3 mL) and the mixture refluxed (2 h). Subsequent to the addition of the sodium salt of *N*-hydroxythiopyridine-2-thione (28.6 mg, 0.19 mmol) to the above mixture at rt, reflux was continued for 30 min. To the resulting yellow solution, under reflux, was added a mixture of AIBN (4 mg, 0.024 mmol) and *n*-Bu_3SnH (0.13 mL, 0.48 mmol) in benzene (2 mL). On completion of the reaction (1 h 30 m), the mixture was taken to dryness and the residue obtained was purified by preparative TLC (Et_2O/*n*-hexane 1:1) to give **28** as an oil (9.4 mg, 24%); IR (film) ν_{max} 1712 (s, C=O) cm^{-1}; ^1H NMR δ 7.66 (1H, br s, Ar*H*), 7.19 (1H, *t*, *J*=7.3 Hz, Ar*H*), 7.12 (1H, d, *J*=7.3 Hz, Ar*H*), 7.02 (1H, *t*, *J*=7.3 Hz, Ar*H*), 4.89 (1H, s, NC*H*N), 3.86 (3H, s, OCH_3), 2.71–2.60 (2H, m, NCH_2CH$_2$), 2.56 (3H, s, NCH_3), 2.04 (2H, *t*, *J*=6.2 Hz, NCH$_2$CH_2), 1.43 (3H, s, CCH_3); MS (EI) *m*/*z* 246 (M^+, 100.0). exact mass calcd for $C_{14}H_{18}N_2O_2$: 246.136828. Found 246.136829.

Method b. To a mixture of sodium salts **26a** (488 mg, 1.56 mmol) in anhydrous THF (6 mL), cooled to −20 °C and under N_2 atmosphere, was added isobutyl chloroformate (0.2 mL, 1.56 mmol). After stirring for 2 h, finely powdered sodium salt of *N*-hydroxypyridine-2-thione (280 mg, 1.88 mmol) was added and the suspension stirred at −20 °C, sheltered from light, for 1 h 30 min. The resulting yellow mixture was irradiated in the presence of *tert*-butylthiol (1 mL) with a 125 W high-pressure mercury lamp at rt, under N_2 atmosphere, until the yellow color disappeared (2 h). The reaction mixture was then diluted with Et_2O and washed sequentially with 0.1 N aqueous $NaHCO_3$, water and brine. The organic phase was dried, the solvent removed at reduced pressure and the residue subjected to preparative TLC (Et_2O/*n*-hexane 1:1) to afford **28** (196 mg, 51%), identical with that obtained by Method a.

Method c. Via oxime ester **29**. To a mixture of sodium salts **26a** (64 mg, 0.21 mmol) in DMF (3 mL) containing a catalytic amount of 15-crown-5-ether cooled to 0 °C, was added with stirring freshly distilled isobutyl chloroformate (0.026 mL, 0.20 mmol) under N_2 atmosphere. After stirring for 1 h, the mixture was treated with benzophenone oxime (38 mg, 0.2 mmole) and Et_3N (0.12 mL, 0.6 mmol) and the reaction allowed to stand at rt overnight. It was then diluted with EtOAc (25 mL) and washed with water. Usual work up led to a solid residue which was purified by preparative TLC (EtOAc/*n*-hexane 1:1) to afford the oxime ester **29** as a pale yellow solid (72 mg, 75%), mp 38–40 °C; IR (KBr) ν_{max} 1766 (s, C=O), 1711 (NC*O*OMe) cm^{-1}; ^1H NMR δ 7.66–7.36 (11H, m, Ar*H*), 7.15 (1H, *t*, *J*=7.6 Hz, Ar*H*), 6.77 (1H, *t*, *J*=7.6 Hz, Ar*H*), 6.43 (1H, d, *J*=7.6 Hz, Ar*H*), 4.44 (1H, s, NC*H*N), 3.84 (3H, s, OCH_3), 3.14 (1H, d, *J*=10.2, 6.6 Hz, NCH$_2$C*H*), 3.04 (1H, d, *J*=9.4, 6.6 Hz), 2.95 (1H, t, CHCOO, *J*=10 Hz), 2.52 (3H, s, NCH_3), 1.21 (3H, s, CCH_3). exact mass calcd for $C_{28}H_{27}N_3O_4$: 469.20014 46. Found 469.2002452.

The above oxime-ester **29** (50 mg, 1.07 mmol) and *t*-BuSH (0.2 mL,10 mmol) in a mixture of iso-propanol/THF (2:1, 3 mL) was irradiated (Philips HPR 125 W HG) at 25 °C for 20 h. Evaporation of solvents and excess reagent under reduced pressure gave a residue, which was taken up in EtOAc and washed with ice-cold 1 N aqueous NaOH and then with water and dried (Na_2SO_4). The yellow solid obtained on removal of the solvent and after purification by column chromatography (EtOAc/*n*-hexane 1:50) gave **28** (23 mg, 92%) identical with that obtained by Method a.

2.3.2. 1,3a-Dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole [(±)-N^8-nordesoxyeseroline] (30). *By reduction of* **28**. To a solution of **28** (53.0 mg, 0.22 mmol) in anhydrous THF (8 mL) was added $LiAlH_4$ (15.1 mg, 0.40 mmol) and the resulting suspension heated under reflux for 50 min. The reaction mixture was cooled in an ice-bath and 5 N aqueous NaOH was added. The mixture was heated under reflux for 1 h, extracted with boiling AcOEt and the combined organic layers were dried and concentrated under reduced pressure. Purification of the resulting residue by preparative TLC (AcOEt/MeOH 20/1) afforded **30** (28.1 mg, 69%), as a colourless solid: mp 110–112 °C (lit.[24] mp 111–112 °C), after recrystallization from *n*-hexane; IR (KBr) ν_{max} 3180 (br, NH), 1620 cm^{-1}; ^1H NMR δ 7.05–6.99 (2H, m, Ar*H*), 6.73 (1H, *t*, *J*=7.6 Hz, Ar*H*), 6.58 (1H, d, *J*=7.6 Hz, Ar*H*), 4.36 (1H, s, NC*H*N), 4.18 (1H, br s, N*H*, D_2O exchangeable), 2.71–2.60 (2H, m, NCH_2CH$_2$), 2.45 (3H, s, NCH_3), 2.01–1.98 (2H, m, NCH$_2$CH_2), 1.45 (3H, s, CCH_3); ^{13}C NMR δ 149.5 (C-7a), 137.0 (C-3b), 127.5 (C-6), 122.8 (C-4), 118.8 (C-5), 109.0 (C-7), 89.7 (C-8a), 53.5 (C-3a), 52.5 (C-2), 40.9 (C-3), 37.0 (1-*C*H$_3$), 27.0 (3a-*C*H$_3$); MS (FAB, glycerol) *m*/*z* 189 ([M+H]$^+$, 100.0).

By hydrolysis of **28**. To a solution of **28** (31.0 mg, 0.13 mmol) in MeOH (3 mL) was added 5 N aqueous NaOH (0.1 mL, 0.5 mmol) and the resulting suspension heated under reflux for 3 h. The reaction mixture was

cooled, diluted with water and extracted with Et_2O. The combined organic layers were washed with brine and dried. After removal of the solvent at reduced pressure, the resulting residue was subjected to preparative TLC (AcOEt/MeOH 20/1) to give **30** (15.7 mg, 66%), which was identical with a sample prepared by method a.

2.3.3. 1,3a,8-Trimethyl-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole [(±)-desoxyeseroline] (1c). To an ice-cooled solution of **30** (13.5 mg, 0.07 mmol) in MeOH (3 mL) was added $NaBH_3CN$ (9.1 mg, 0.14 mmol). The mixture was then adjusted to pH≈6 with 1% aqueous HCl and 35% aqueous formalin (2.1 mL, 24.5 mmol) added. After being stirred at rt for 1 h 10 min, the reaction mixture was evaporated to dryness under reduced pressure and the residue basified with 25% aqueous NH_4OH. The resulting mixture was extracted with AcOEt, the combined organic extracts washed with brine, dried and the solvent removed under reduced pressure. Purification of the residue by preparative TLC (alumina, Et_2O/*n*-hexane 1.5:9), afforded **1c** (9.7 mg, 67%), as a yellowish oil: IR (film) ν_{max} 1605, 1495, 1450, 1345, 1300, 1255, 1120, 1035, 1020, 955, 735 cm^{-1}; ^1H NMR (300 MHz) δ 7.08 (1H, *td*, $J=1.1$, 7.5 Hz, Ar*H*), 7.00 (1H, d, $J=1.1$, 7.5 Hz, Ar*H*), 6.68 (1H, dt, $J=1.1$, 7.5 Hz, Ar*H*), 6.42 (1H, d, $J=7.5$ Hz, Ar*H*), 4.12 (1H, s, NC*H*N), 2.95 (3H, s, NCH_3), 2.77–2.59 (2H, m, NCH_2CH_2), 2.55 (3H, s, NCH_3), 1.99–1.95 (2H, m, NCH_2CH_2), 1.44 (3H, s, CCH_3); ^{13}C NMR (75 MHz) δ 151.9, 136.6, 127.7, 122.2, 117.5, 106.6, 97.5 (C-8a), 53.2 (C-2), 52.7 (C-3a), 40.8 (C-3), 38.4 (8-CH_3), 36.5 (1-CH_3), 27.3 (3a-CH_3); MS (EI) *m*/*z* 202 (M^+, 100.0); exact mass calcd for $C_{13}H_{18}N_2$: 202.146999. Found: 202.147656.

The picrate of **1c**, obtained as yellow crystals, had: mp 182.5–184 °C (lit.[10] mp 179–180 °C), on recrystallization from EtOH; IR (KBr) ν_{max} 1635, 1615, 1565 (s, NO_2), 1490, 1430, 1360, 1320 (s, NO_2), 1275, 1165, 1075, 1005, 910, 785, 740 cm^{-1}; ^1H NMR (300 MHz) δ 11.30 (1H, br s, N*H*), 8.93 (2H, s, Ar*H*), 7.24 (1H, t, $J=7.2$ Hz, Ar*H*), 7.11 (1H, d, $J=7.2$ Hz, Ar*H*), 6.92 (1H, t, $J=7.2$ Hz, Ar*H*), 6.66 (1H, d, $J=7.2$ Hz, Ar*H*), 5.16 (1H, d, $J=3.0$ Hz, NC*H*N),3.71–3.65 (1H, m, NCH_2CH_2), 3.19 (3H, s, NCH_3), 2.83 (3H, d, $J=4.5$ Hz, NCH_3), 2.71–2.61 (1H, m, NCH_2CH_2), 2.57–2.47 (1H, m, NCH_2CH_2), 2.35–2.30 (1H, m, NCH_2CH_2), 1.55 (3H, s, CCH_3).

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Solvent-assisted thiocarboxylation of amines and alcohols with carbon monoxide and sulfur under mild conditions

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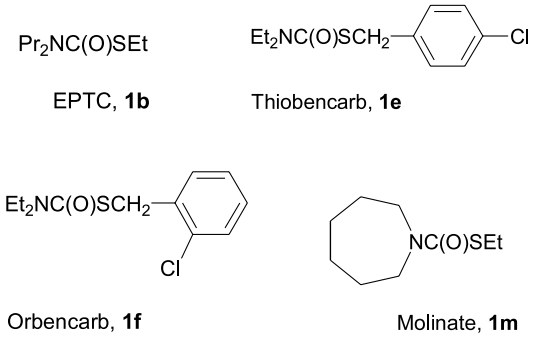
Abstract—DMSO or DMF as a solvent strongly accelerated the thiocarboxylation of amines and alcohols with carbon monoxide and sulfur. Under mild conditions (1 atm, 20 °C), this thiocarboxylation of amines assisted by DMSO with carbon monoxide and sulfur has been developed into a practical and convenient synthetic method for *S*-alkyl thiocarbamates in good to excellent yields, including EPTC, thiobencarb, orbencarb, and molinate (herbicides). DMF also showed the similar solvent effect. NMP slightly decreased the effect for the thiocarboxylation of amines, and the yield of *S*-alkyl thiocarbamate was lowered in DMAc. Surprisingly, no formation of *S*-alkyl thiocarbamate was observed at the use of the other solvents, such as THF, hexane, toluene, AcOEt, MeCN, MeOH, and H_2O. The present solvent-assisted thiocarboxylation with carbon monoxide and sulfur could be also applied to a new synthesis of *S*-alkyl *O*-alkyl carbonothioates from alcohols under mild conditions (1 atm, 20 °C) in DMF using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).

1. Introduction

The development of useful and practical synthetic methods of *S*-alkyl thiocarbamates **1** is of importance, because a series of *S*-alkyl thiocarbamates is well known as useful herbicides, and these herbicides (e.g., EPTC (**1b**), thiobencarb (**1e**), orbencarb (**1f**), and molinate (**1m**)) have been produced in an industrial large-scale.[1–3]



Many methods for the synthesis of *S*-alkyl thiocarbamates **1** have been reported. Among them, the reaction of amines **2** with thiols and phosgene or with carbonyl sulfide, followed by alkylation with alkyl halides has been known as the general routes.[4–6] Indeed, *S*-alkyl thiocarbamate herbicides **1** are industrially produced two steps reaction, which includes the generation of carbonyl sulfide from carbon monoxide and sulfur under high temperature, and the reaction of carbonyl sulfide with amines **2** and alkyl halides.[2]

Direct thiocarboxylation of primary amines with carbon monoxide and sulfur to form urea derivatives was introduced by Monsanto group in 1961.[8–10] Furthermore, Grisley and Stephens developed *S*-alkyl thiocarbamate **1** synthesis from secondary amines, carbon monoxide, sulfur, and alkyl halides in similar manners.[11] However, these reactions require high temperature and pressurized carbon monoxide.

Our research group has found that selenium exhibits an excellent catalytic activity toward the thiocarboxylation of amines with carbon monoxide and sulfur in 1989. This selenium-catalyzed thiocarboxylation of amines **2** smoothly proceeded under mild conditions (1 atm, 30 °C) to give thiocarbamate salts **3**. Then, the alkylation of **3** by alkyl halides, led to the formation of *S*-alkyl thiocarbamates **1** in excellent yields.[12,13] Owing to the toxicity of elemental selenium, however, use of this preparative method was considerably limited for industrial production of herbicides.

Next, we also found a high-yield synthesis of *S*-alkyl thiocarbamate **1** by the reaction of carbamoyl lithiums, which were prepared in situ from lithium amides and carbon

Keywords: *S*-Alkyl thiocarbamates; *S*-Alkyl *O*-alkyl carbonothioates; DMSO; DMF; Carbon monoxide; Sulfur; Thiocarboxylation.
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monoxide (1 atm) at low temperature (−78 °C), with elemental sulfur and alkyl halides, or disulfides.[14–16] However, this synthetic method may not be suitable for industrial production of *S*-alkyl thiocarbamate herbicide, because of the production cost of **1**.

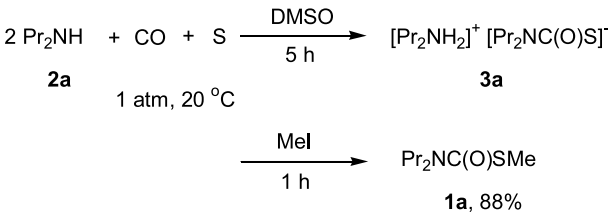
Recently, we reported the thiocarboxylation of amines **2** with carbon monoxide and sulfur, assisted by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to provide *S*-alkyl thiocarbamates **1** in excellent yields in THF under mild conditions (1 atm, 20 °C).[17] But, this method also seemed to be not attractive for industrial production of *S*-alkyl thiocarbamate herbicides **1**, because of the price of DBU compared with inorganic bases, such as K_2CO_3. Furthermore, a more useful synthetic method for *S*-alkyl thiocarbamate herbicides **1** has been developed in 2004.[18] Under mild conditions (1 atm, 20 °C), in which the thiocarboxylation of amines **2** with carbon monoxide and sulfur was powerfully assisted by K_2CO_3 and DMSO as a solvent. However, still weak point of this procedure was the need of an excess amount of K_2CO_3 as a base.

Then, thiocarboxylation of alcohols **5** with carbon monoxide and sulfur to give *S*-alkyl carbonothioates **4** was also established by us, using base such as DBU[19–21] and triethylamine,[22,23] and selenium-catalyst.[24] However, these thiocarboxylation reactions from alcohols **5** proceeded under high temperature and pressurized carbon monoxide using an autoclave.

Therefore, in our strategy, we explored a new practical synthetic method to the *S*-alkyl thiocarbamates **1** including herbicides under mild conditions (1 atm, 20 °C) without using additional base, and useful route of *S*-alkyl *O*-alkyl carbonothioates (**4**) under similar mild conditions.

2. Results and discussion

Our trial employing DMSO or DMF as a solvent, which is cheap and commercially available, led to a successful thiocarboxylation of dipropylamine (**2a**) with carbon monoxide and sulfur without other base. Dipropylamine (**2a**) smoothly reacted with carbon monoxide (1 atm) and sulfur (1.0 equiv) at 20 °C for 5 h in DMSO solvent. Then, color of solution was changed from reddish black to green, the resulting thiocarbamate salt (**3a**) in DMSO solution was esterified by methyl iodide (1.2 equiv) under an ambient pressure at 20 °C for 1 h. Finally, *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) was obtained in 88% yield (Eq. 1) (Table 1, entry 1).



(1)

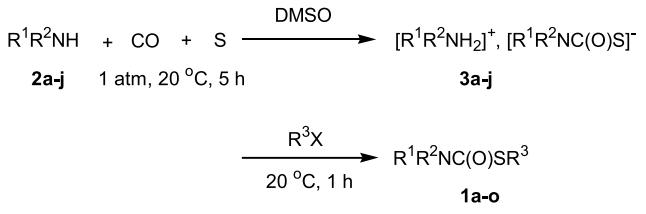
To examine the influence of solvent on this thiocarboxylation of dipropylamine (**2a**) with carbon monoxide and sulfur, various solvents were screened (Table 1). When DMF was employed as a solvent for this thiocarboxylation, DMF also showed the similar solvent effect to afford *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) in good yields (82%) (entry 2). NMP used as solvent somewhat weakly accelerated the carboxylation of **2a** to give *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) in moderate yield (67%) (entry 3). In DMAc, the yield of **1a** was lowered (entry 4). In contrast, we surprisingly observed that the use of other solvents (THF, hexane, toluene, AcOEt, MeCN, MeOH, and H_2O) resulted in no formation of the desired **1a** at all (entries 5–11). Therefore, we believe that solvents are a predominant factor for reactivity of the present thiocarboxylation of amines with carbon monoxide and sulfur.

Table 1. Influence of solvent on the synthesis of *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**)

Entry	Solvent	Isolated yield[a]
1	DMSO	88
2	DMF	82
3	NMP	67
4	DMAc	30
5	THF	0
6	Hexane	0
7	Toluene	0
8	AcOEt	0
9	MeCN	0
10	MeOH	0
11	H_2O	0

[a] Reaction conditions: dipropylamine (2.74 mL, 20 mmol), sulfur (321 mg, 10 mmol), methyl iodide (0.75 mL, 12 mmol), solvent (20 mL), CO (1 atm), 20 °C, 5 h for carbonylation and 1 h for alkylation.

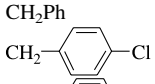
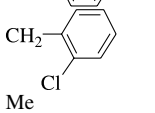
To demonstrate the efficiency and scope of the present method, a variety of *S*-alkyl thiocarbamates **1a–o** were synthesized from the corresponding amines **2a–j** and alkyl halides (Eq. 2, Table 2). Under 1 atm of carbon monoxide at 20 °C for 5 h in DMSO, ammonium salts of thiocarbamates **3a–j** were formed from amines **2a–j** with carbon monoxide and sulfur, followed by quenching by alkyl halides to afford the corresponding *S*-alkyl thiocarbamates **1a–o** in good to excellent yields.



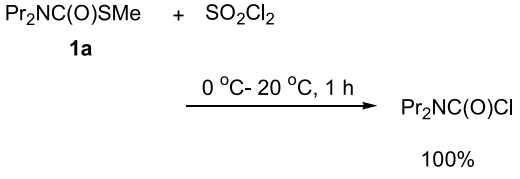
(2)

Secondary amines **2a–c**, **2e–h** were suitable for this thiocarboxylation to provide *S*-alkyl thiocarbamates **1a–g**, **1i–m** in good to excellent yields under mild conditions (1 atm, 20 °C) (entries 1–8 and 10–14). Even in 10 times large scale, *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) was obtained in excellent yield (91%) for longer reaction time (entry 2). Furthermore, the chlorination of *S*-alkyl *N*,*N*-dialkylthiocarbamates **1** from secondary amines was successfully performed using sulfuryl chloride, to afford the corresponding carbamoyl chlorides in good yields (Eq. 3).[17]

Table 2. Synthesis of *S*-alkyl thiocarbamates (**1a–o**)

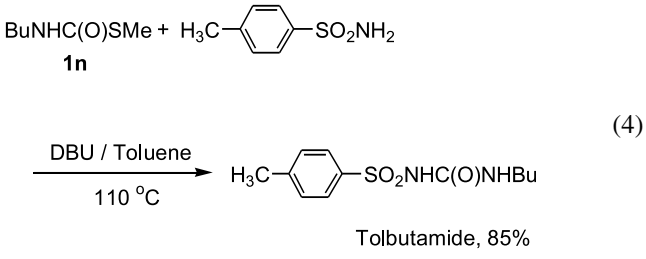
Entry	R^1	R^2		R^3	X		Yield%[a]
1	Pr	Pr	**2a**	Me	I	**1a**	88
2	Pr	Pr	**2a**	Me	I	**1a**	91[b]
3	Pr	Pr	**2a**	Et	I	**1b**[c]	82
4	Pr	Pr	**2a**	CH_2Ph	Cl	**1c**	95[d]
5	Et	Et	**2b**	CH_2Ph	Cl	**1d**	94[d,e]
6	Et	Et	**2b**		Cl	**1e**[f]	83[d,e], 39[g], 99[g,h], 80[d,i]
7	Et	Et	**2b**		Cl	**1f**[j]	86[d,e]
8	Bu	Bu	**2c**	Me	I	**1g**	68
9	*i*-Pr	*i*-Pr	**2d**	Me	I	**1h**	42, 45[i]
10	$-(CH_2)_4-$		**2e**	Me	I	**1i**	83
11	$-(CH_2)_5-$		**2f**	Me	I	**1j**	84
12	$-(CH_2)_2O(CH_2)_2-$		**2g**	Me	I	**1k**	76
13	$-(CH_2)_6-$		**2h**	Me	I	**1l**	88
14	$-(CH_2)_6-$		**2h**	Et	I	**1m**[k]	86
15	Bu	H	**2i**	Me	I	**1n**	73 (10)[l]
16	Ph	H	**2j**	Me	I	**1o**	0, 82[i]

[a] Reaction conditions: amine (20 mmol), sulfur (321 mg, 10 mmol), alkyl halide (12 mmol), DMSO (20 mL), CO (1 atm), 20 °C, 5 h for thiocarboxylation and 1 h for alkylation.
[b] Reaction conditions: dipropylamine (27.4 mL, 200 mmol), sulfur (3.21 g, 100 mmol), methyl iodide (7.5 mL, 120 mmol), DMSO (50 mL), CO (1 atm), 20 °C, 20 h for carbonylation and 1 h for alkylation.
[c] EPTC.
[d] Alkyl halides (10 mmol) was used.
[e] Reaction time: 8 h for thiocarboxylation and 1 h for alkylation.
[f] Thiobencarb.
[g] 4-Chlorobenzyl chloride (1.39 mL, 11 mmol) was used.
[h] K_2CO_3 (2.07 g, 15 mmol) was added.
[i] Amine (10 mmol) and DBU (1.50 mL, 10 mmol) were used.
[j] Orbencarb.
[k] Molinate.
[l] Yield of *N*,*N*′-dibutylurea.



(3)

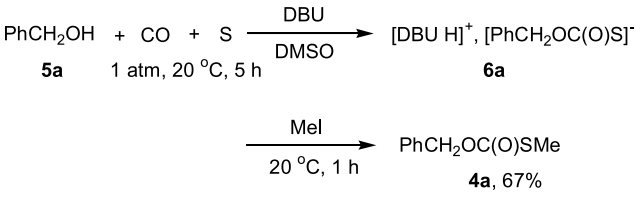
S-Alkyl diethylthiocarbamates **1d–f** synthesis from diethylamine (**2b**) occurred in considerably good yields, but this thiocarboxylation for **2b** needed slightly longer reaction time (8 h for thiocarboxylation). Without using other base, thiocarboxylation of **2b** did not finished perfectly to give **1e** in diminished yield (39%) in shorter reaction time (5 h for thiocarboxylation).[18] Addition of K_2CO_3 or DBU for this reaction system was also effective, **1e** was obtained in better yields for shorter reaction time (99[18] and 80%, respectively) (entry 6). Then, di-*i*-propylamine (**2d**) gave *S*-methyl *N*,*N*-di-*i*-propylthiocarbamate (**1h**) in low yield (42%), because of steric hindrance of di-*i*-propylamine (**2d**). Furthermore, in the presence of DBU, **1h** was given in similar yield (45%) (entry 9). Using this procedure, herbicides, such as EPTC (**1b**),[1,3] thiobencarb (**1e**),[1–3] orbencarb (**1f**),[1–3] and molinate (**1m**)[1,3] could be successfully synthesized in good yields (82–86%) (entries 3, 6, 7, and 14). The yield of *S*-methyl *N*-butylthiocarbamate (**1n**) from the primary amine (butylamine, **2i**) was somewhat diminished, accompanied with the formation of the corresponding urea derivative (entry 15).[25] Recently, we showed a methodology for useful medicine synthesis that these *N*-alkylthiocarbamates smoothly reacted with bezenesulfonamides in the presence of DBU, to afford the corresponding sulfonylurea derivatives in good yields, in which are used as oral antidiabetics (tolbutamide and chlorpropamide) (Eq. 4).[27]



(4)

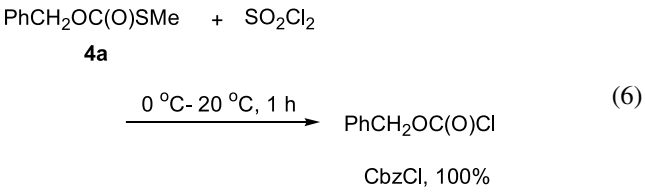
Furthermore, in spite of the low basicity of aniline (**2j**), *S*-methyl *N*-phenylthiocarbamate (**1o**) was obtained in good yield, in the case of using DBU (entry 16).[17]

Extension of this thiocarboxylation has yielded promising results. Then, we tested the effect of solvent DMSO on the thiocarboxylation of benzyl alcohol (**5a**) by carbon monoxide and sulfur under mild conditions (1 atm, 20 °C). This trial was easily performed for the thiocarboxylation of benzyl alcohol (**5a**) in the presence of DBU under 1 atm at 20 °C, followed by esterification using methyl iodide to afford the corresponding *S*-methyl *O*-benzyl carbonothioate (**4a**) in good yield (67%) (Eq. 5).



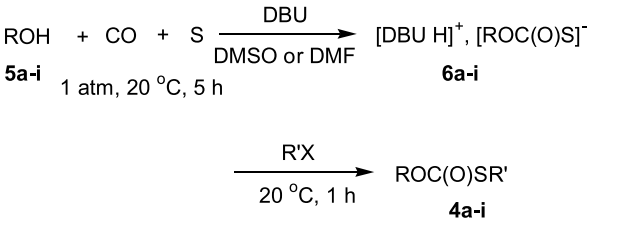
(5)

Also, we described *S*-methyl *O*-benzyl carbonothioate (**4a**) was a useful materials for further synthetic manipulation. *S*-Methyl *O*-benzyl carbonothioate (**4a**) was easily converted with sulfuryl chloride into the corresponding *O*-benzyl chloroformate (CbzCl) used as an *N*-protective reagent for amino group in peptide synthesis (Eq. 6).[20,21]



(6)

A variety of *S*-alkyl *O*-alkyl carbonothioates **4a–i** were synthesized from the corresponding alcohols and phenol **5a–i** and alkyl halides (Eq. 7, Table 3).

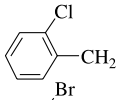
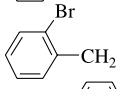
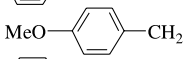
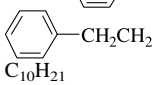


(7)

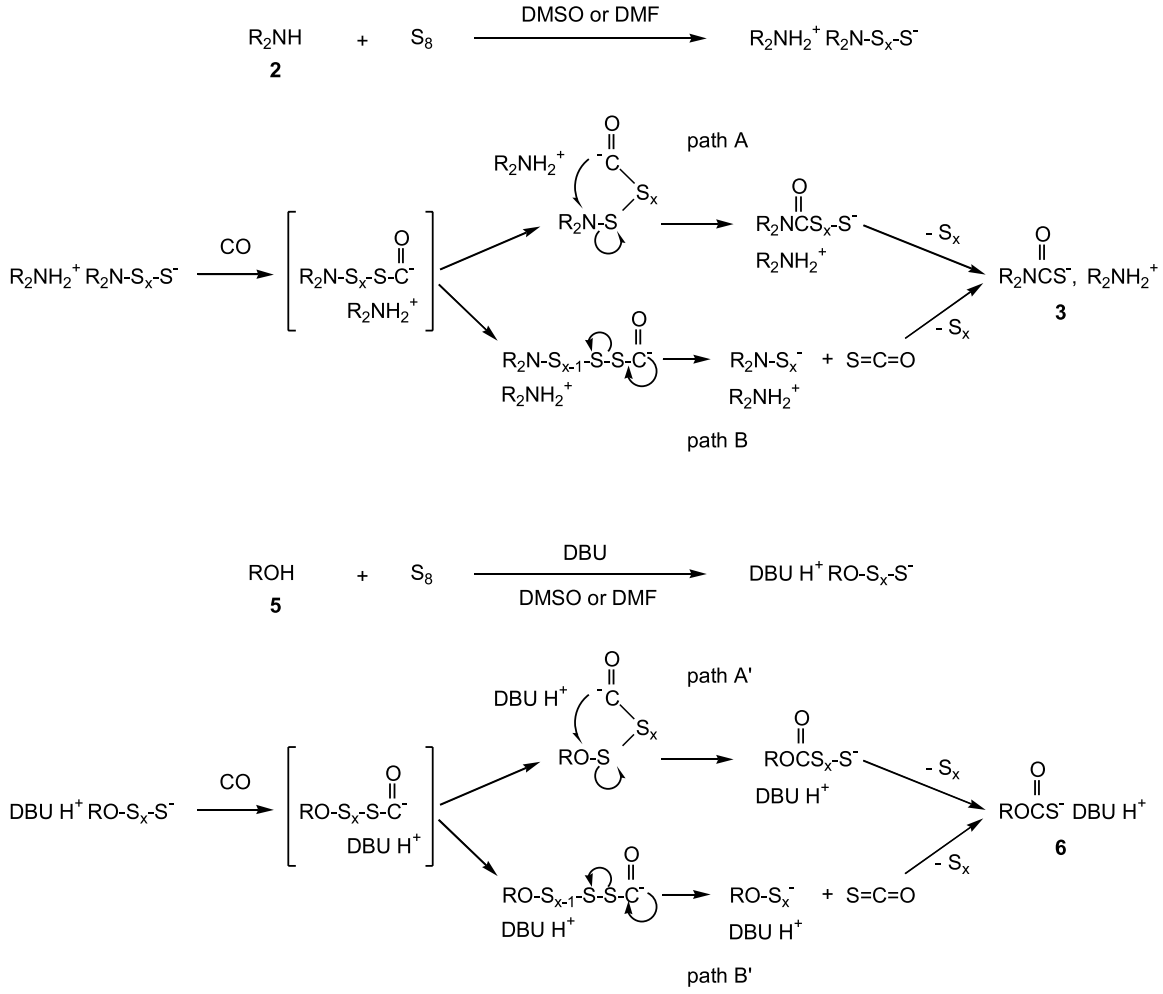
DMF using as a solvent, thiocarboxylation of benzyl alcohol (**5a**) with carbon monoxide and sulfur in the presence of DBU smoothly proceeded to give *S*-methyl *O*-benzyl carbonothioate (**4a**) in almost similar yield (65%) (entry 2), compared with that of **4a** using DMSO and DBU (entry 1). K_2CO_3 was weakly affected for this thiocarboxylation of benzyl alcohol (**5a**) to afford **4a** in poor yield (entry 3). DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and triethylamine were not effective for this thiocarboxylation of **5a** in DMSO (entries 4 and 5). In the absence of base, no formation of salts of *O*-benzyl carbonothioate (**6a**) was observed (entry 6). Nevertheless, *S*-methyl *O*-benzyl carbonothioate (**4a**) was obtained successfully from benzyl alcohol (**5a**) in DBU/DMSO system (entry 1), the trials of synthesis of *S*-methyl *O*-(2-chloro)benzyl carbonothioate (**4b**), *S*-methyl *O*-(2-bromo)benzyl carbonothioate (**4c**), and *S*-methyl *O*-(4-methoxy)benzyl carbonothioate (**4d**) using DBU/DMSO system gave poor results (entries 7–9). It seemed that the products **4b–d** were easily decomposed into alcohols and thiol under very strong basic conditions (DBU/DMSO). However, using DMF as a solvent, **4b–d** were fortunately given in moderate to good yields (52–63%) in the presence of DBU (entries 7–9). According to these results, thiocarboxylation of various alcohols **5a–i** was performed with carbon monoxide and sulfur using 1 equiv of DBU under 1 atm at 20 °C for 5 h in DMF. Quenching by alkyl halides (1 h), the corresponding *S*-alkyl *O*-alkyl carbonothioates **4a–h** were afforded in good yields (52–68%) (entries 2, 7–13). However, the yield of *S*-methyl *O*-phenyl carbonothioate (**4i**) lowered (29%), because of very low basicity of phenol (**5i**) (entry 14).

Scheme 1 shows a plausible pathway for this thiocarboxylation. Based on our finding of the ready reaction for salts of thiolates with carbon monoxide to convert into salts of thiocarbamates **3**,[28] we suggest a plausible pathway via thiolate anions for this solvent-assisted thiocarboxylation of amines or alcohols with carbon monoxide and sulfur. In the case of thiocarboxylation on amines **2**, elemental sulfur is readily subject to S–S bond fission by the reaction with amines strongly assisted by DMSO[29] or DMF, to form ammonium salts of thiolate anions. The reaction of thiolate

Table 3. Synthesis of *S*-alkyl *O*-alkyl carbonothioates (**4a–i**)

Entry	R		Base	R′X		Yield%[a]
1	$PhCH_2$	**5a**	DBU	MeI	**4a**	67
2	$PhCH_2$	**5a**	DBU	MeI	**4a**	65[b]
3	$PhCH_2$	**5a**	K_2CO_3	MeI	**4a**	35
4	$PhCH_2$	**5a**	DBN	MeI	**4a**	5
5	$PhCH_2$	**5a**	Et_3N	MeI	**4a**	0
6	$PhCH_2$	**5a**	None	MeI	**4a**	0[c]
7		**5b**	DBU	MeI	**4b**	0, 61[b]
8		**5c**	DBU	MeI	**4c**	0, 63[b]
9		**5d**	DBU	MeI	**4d**	9, 52[b]
10		**5e**	DBU	MeI	**4e**	58[b]
11	$C_{10}H_{21}$	**5f**	DBU	EtI	**4f**	68[b]
12	$C_{18}H_{37}$	**5g**	DBU	EtI	**4g**	66[b]
13	$C_4H_9CHEtCH_2$	**5h**	DBU	EtI	**4h**	62[b]
14	Ph	**5i**	DBU	MeI	**4i**	29[b]

[a] Reaction conditions: alcohol (10 mmol), sulfur (321 mg, 10 mmol), base (10 mmol), alkyl halide (12 mmol), DMSO (20 mL), CO (1 atm), 20 °C, 5 h for thiocarboxylation and 1 h for alkylation.
[b] DMF (20 mL) was used as a solvent, instead of DMSO.
[c] Benzyl alcohol (20 mmol) was used.



Scheme 1.

anions with carbon monoxide gives the carbonylated species. Through an intramolecular rearrangement of the carbonylated species (path A) or elimination of carbonyl sulfide from the carbonylated species (path B), thiocarbamate salts **3** are generated. A plausible pathway for thiocarboxylation of alcohols **5** is the similar to that of amines **2**. But, in this case of alcohols **5**, solvents and DBU assist the thiocarboxylation of **5** to form DBU salts of thiolates and carbonothioates **6** as intermediates.

3. Conclusion

A useful synthetic method for *S*-alkyl thiocarbamates **1** has been developed under mild conditions (1 atm, 20 °C) without using additional base, in which the carboxylation of amines with carbon monoxide and sulfur was powerfully assisted by solvent DMSO or DMF. This thiocarboxylation was employed successfully for the synthesis of EPTC (**1b**), thiobencarb (**1e**), orbencarb (**1f**), and molinate (**1m**) used as herbicides. Also, synthesis of *S*-alkyl *O*-alkyl carbonothioates **4a–h** from alcohols **5a–h** and alkyl halides with carbon monoxide and sulfur, assisted by DMF have been explored in the presence of DBU under mild condition (1 atm, 20 °C). From the viewpoint of application to actual industrial production of *S*-alkyl thiocarbamates **1** such as herbicides, the present reaction is very significant, in terms of the use of easily available and cheap carbon monoxide, sulfur, and DMSO (or DMF), and mild reaction conditions.

4. Experimental

4.1. General

Melting points were determined on a Mettler FP 5 instrument and were uncorrected. FT-IR spectra were recorded on a JASCO FT/IR-4100 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300 (300, 75 MHz) instrument. Chemical shifts were reported in ppm relative to tetramethylsilane (δ-units). Mass and exact mass spectra were recorded on a JEOL JMS-600 spectrometer. Amines **2a–j**, alcohols **5a–i**, alkyl halides, DMSO, other solvent, DBU, other bases, sulfur (99.5%), and carbon monoxide (99.9%) were used as purchased.

4.2. Typical procedure for the synthesis of *S*-methyl *N*,*N*-dipropylthiocarbamate (1a) from dipropylamine (2a), carbon monoxide, sulfur, and methyl iodide

A DMSO (20 mL) solution containing dipropylamine (**2a**) (2.74 mL, 20 mmol), and powdered sulfur (321 mg,

10 mmol) was vigorously stirred under carbon monoxide (1 atm) at 20 °C for 5 h. Into the DMSO solution of thiocarbamate salt (**3a**), methyl iodide (0.75 mL, 12 mmol) was added slowly at 0 °C under argon atmosphere. The reaction mixture was stirred for additional 1 h at 20 °C. The resulting mixture was then poured into 1 N HCl (100 mL) and extracted with *t*-butyl methyl ether (100 mL, 50 mL×2). After evaporation of solvents and purification by short-column chromatography (silica gel, toluene/AcOEt=1:1), *S*-methyl *N*,*N*-dipropylthiocarbamate (**1a**) was afforded in 88% yield (1.54 g).

4.2.1. *S*-Methyl *N*,*N*-dipropylthiocarbamate (1a).[4,12,13,17] Oil; IR (neat) 2965, 1655, 1405, 1225, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=7 Hz, 6H), 1.60 (br s, 4H), 2.32 (s, 3H), 3.28 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 12.8, 21.4, 49.3, 168.2; MS (*m*/*z*, %) 175 (M^+, 100), 128 (89), 86 (79), 75 (65). Exact MS calcd for $C_8H_{17}NOS$: 175.1031. Found: 175.1012.

4.2.2. *S*-Methyl perhydroazepin-1-carbothioate (1l). Oil; IR (neat) 2925, 1650, 1405, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.54–1.58 (m, 4H), 1.74 (br s, 4H), 2.33 (s, 3H), 3.45 (q, J=6 Hz, 2H), 3.57 (t, J=6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 26.9, 27.2, 27.9, 28.4, 47.4, 47.6, 168.2; MS (*m*/*z*, %) 173 (M^+, 41), 126 (100), 83 (18), 55 (48). Exact MS calcd for $C_8H_{15}NOS$: 173.0874. Found: 173.0861.

Identification of the other *S*-alkyl thiocarbamates **1b–k**, **1m–o** was performed by comparison of the IR, NMR, MS spectra, and mp of **1b–k**, **1m–o** with those of authentic samples, which were prepared according to the literatures, **1b**, **1g–k**, **1n**, **1o**,[17] **1c**, **1e**, **1f**, **1m**,[18] and **1d**.[13]

4.3. General synthetic method of *S*-methyl *O*-benzyl carbonothioate (4a) under mild conditions

Into DMSO (20 mL), benzyl alcohol (**5a**) (1.03 mL, 10 mmol), powdered sulfur (321 mg, 10 mmol) and DBU (1.50 mL, 10 mmol) were added. The solution was very vigorously stirred under carbon monoxide (1 atm) at 20 °C for 5 h. Then, methyl iodide (0.75 mL, 12 mmol) was added carefully at 0 °C under argon atmosphere in the DMSO solution of carbonothioate salt (**6a**). The solution was stirred for additional 1 h at 20 °C. The resulting mixture was then poured slowly into 1 N HCl (100 mL), and extracted with *t*-butyl methyl ether (100 mL, 50 mL×2). After evaporation of solvents and purification by short-column chromatography (silica gel, toluene), *S*-methyl *O*-benzyl-carbonothioate (**4a**) was obtained in 67% yield (1.23 g).

4.3.1. *S*-Methyl *O*-benzyl carbonothioate (4a).[20,21] Oil; IR (neat) 1710, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 5.24 (s, 2H), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 68.9, 128.4, 128.5, 135.5, 171.6; MS (*m*/*z*, %) 182 (M^+, 69), 92 (48), 91 (100), 77 (27), 65 (36). Exact MS calcd for $C_9H_{10}O_2S$: 182.0402. Found: 182.0368.

4.3.2. *S*-Methyl *O*-2-phenylethyl carbonothioate (4e). Oil; IR (neat) 1710, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.98 (t, J=7 Hz, 2H), 4.42 (t, J=7 Hz, 2H), 7.20–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 35.2, 67.8, 126.7, 128.6, 128.9, 137.3, 171.6; MS (*m*/*z*, %) 196 (M^+, 0.2), 105 (100), 104 (100), 91 (99), 77 (68). Exact MS calcd for $C_{10}H_{12}O_2S$: 196.0558. Found: 196.0547.

4.3.3. *S*-Ethyl *O*-decyl carbonothioate (4f). Oil; IR (neat) 2925, 2855, 1715, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7 Hz, 3H), 1.26–1.34 (m, 17H), 1.61–1.68 (m, 2H), 2.86 (q, J=7 Hz, 2H), 4.20 (t, J=7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.0, 22.7, 25.3, 25.8, 28.7, 29.2, 29.3, 29.5, 29.5, 31.9, 67.5, 171.2; MS (*m*/*z*, %) 246 (M^+, 7), 185 (28), 85 (59), 71 (80), 57 (100). Exact MS calcd for $C_{13}H_{26}O_2S$: 246.1654. Found: 246.1637.

4.3.4. *S*-Ethyl *O*-stearyl carbonothioate (4g). Oil; IR (neat) 2925, 2850, 1715, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J=7 Hz, 3H), 1.26–1.34 (m, 33H), 1.63–1.68 (m, 2H), 2.86 (q, J=7 Hz, 2H), 4.20 (t, J=7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.0, 22.7, 25.3, 25.8, 28.7, 29.2, 29.4, 29.5, 29.5, 29.6, 29.7, 29.7, 31.9, 67.4, 171.1; MS (*m*/*z*, %) 358 (M^+, 14), 297 (43), 85 (74), 71 (83), 57 (100). Exact MS calcd for $C_{21}H_{42}O_2S$: 358.2906. Found: 358.2909.

4.3.5. *S*-Ethyl *O*-2-ethylhexyl carbonothioate (4h). Oil; IR (neat) 2960, 2930, 1710, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J=7 Hz, 6H), 1.29–1.41 (m, 11H), 1.53–1.62 (m, 1H), 2.86 (q, J=7 Hz, 2H), 4.13 (d, J=6 Hz, 1H), 4.14 (d, J=6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 14.0, 15.0, 22.9, 23.7, 25.3, 28.9, 30.2, 38.9, 69.7, 171.2; MS (*m*/*z*, %) 218 (M^+, 4), 157 (8), 112 (24), 71 (92), 57 (100). Exact MS calcd for $C_{11}H_{22}O_2S$: 218.1341. Found: 218.1341.

Identification of the other *S*-methyl *O*-alkyl carbonothioates **4b–d** and *S*-methyl *O*-phenyl carbonothioate (**4i**) was performed by comparison of the IR, NMR, and MS spectra of **4b–d** and **4i** with those of authentic samples, which were prepared according to the literatures.[20,21]

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Synthesis of cordiaquinone J and K via *B*-alkyl Suzuki–Miyaura coupling as a key step and determination of the absolute configuration of natural products

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Abstract—A versatile methodology for the synthesis of various terpenoids via *B*-alkyl Suzuki–Miyaura coupling as a key step is established. Synthesis of cordiaquinone J and K, new antifungal and larvicidal meroterpenoids, was achieved by using this methodology. The absolute configurations of cordiaquinone J and K were confirmed by the synthesis.

1. Introduction

Cordiaquinones are antifungal and larvicidal meroterpenoids isolated from Panamanian plants such as *Cordia linnaei*. In 1990, Messana and co-workers reported the isolation and structures of cordiaquinones A (**1**) and B (**2**) (Fig. 1).[1] After their identification of cordiaquinones from the plant, several cordiaquinones have been isolated.[2,3] In 2000, Hostettmann and co-workers reported the structures of cordiaquinones J (**3**) and K (**4**) isolated from *C. curassavica* (Fig. 1).[4] These compounds exhibit antifungal activities against phytopathogenic fungus such as *Cladosporium cucumerinum* and larvicidal activity against the larvae of the yellow fever-transmitting mosquito *Aedes aegypti*. The structures of cordiaquinone J and K were established on the basis of HRMS, UV and 1D and 2D NMR spectra. In connection with our synthetic studies of biologically active natural terpenoids,[5] we became interested in clarifying the absolute configuration of cordiaquinones. The synthesis and absolute configuration of cordiaquinone B were reported by

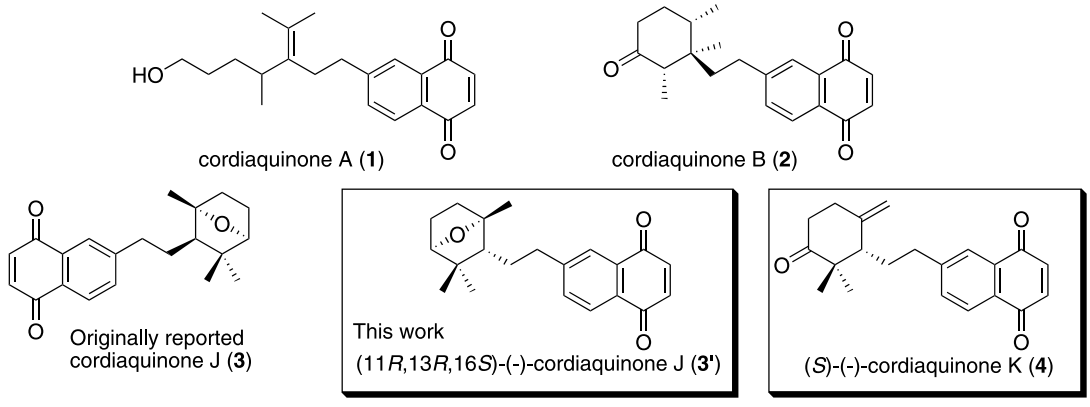

Figure 1. Structures of cordiaquinones.

Keywords: Synthesis; *B*-Alkyl Suzuki–Miyaura coupling; Cordiaquinones; Absolute configuration.
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Asaoka and his co-workers.[6] In previous communications, we reported the synthesis of (*R*)-(+)-cordiaquinone K employing one-pot *B*-alkyl Suzuki–Miyaura coupling as a key step and the determination of the absolute configuration of the natural product.[7] Although the absolute configuration of cordiaquinone K was determined to be *S* as shown in Figure 1, the absolute configuration of cordiaquinone J remained unknown. In recent structural studies of natural products, NOE studies are a powerful tool, especially for relative stereochemistry determination. However, Hostettmann provided no clear information on the relative stereochemistry of cordiaquinone J, including NOE experiment.[4] To clarify the stereochemistry, we decided to synthesize cordiaquinone J. This paper describes details of the synthesis of (*R*)-(+)-cordiaquinone K, (11*R*,13*S*,16*R*)- and (11*S*,13*R*,16*S*)-cordiaquinone J employing one-pot *B*-alkyl Suzuki–Miyaura coupling[8] as a key step. This paper also describes the determination of the relative and absolute configuration of the natural products.

2. Results and discussion

Our synthetic plans for the synthesis of cordiaquinone J and K are shown in Scheme 1. Appropriate transformations of the oxygen functionality at C-13 led to hydroxyolefines **A** and **B**, respectively. Disconnection between C-6 and C-9 gave γ-cyclohomogeranyl units **D** and **E**, respectively, and naphtoquinone derivative **C**. We planned to apply *B*-alkyl Suzuki–Miyaura coupling reaction to connect these units. This methodology would be useful for not only the synthesis of cordiaquinones but also various terpenoids such as ambrein,[9] luffarin W,[10] penlanpallescensin.[11] (Fig. 2), because these compounds have a common structural feature with cordiaquinones, namely, a γ-cyclohomogeranyl unit connecting with an aryl or a vinyl unit. Optically active γ-cyclohomogeranyl units could be derived from known hydroxyketone **F**, [12] obtained by yeast-mediated asymmetric reduction of the corresponding diketone. Naphtoquinone derivative **C** would be synthesized from known 6-bromonaphtoquinone.[13]

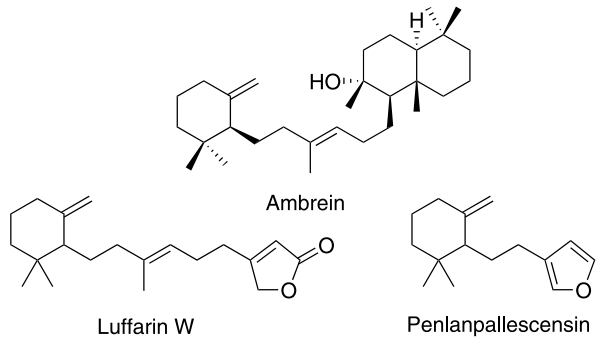
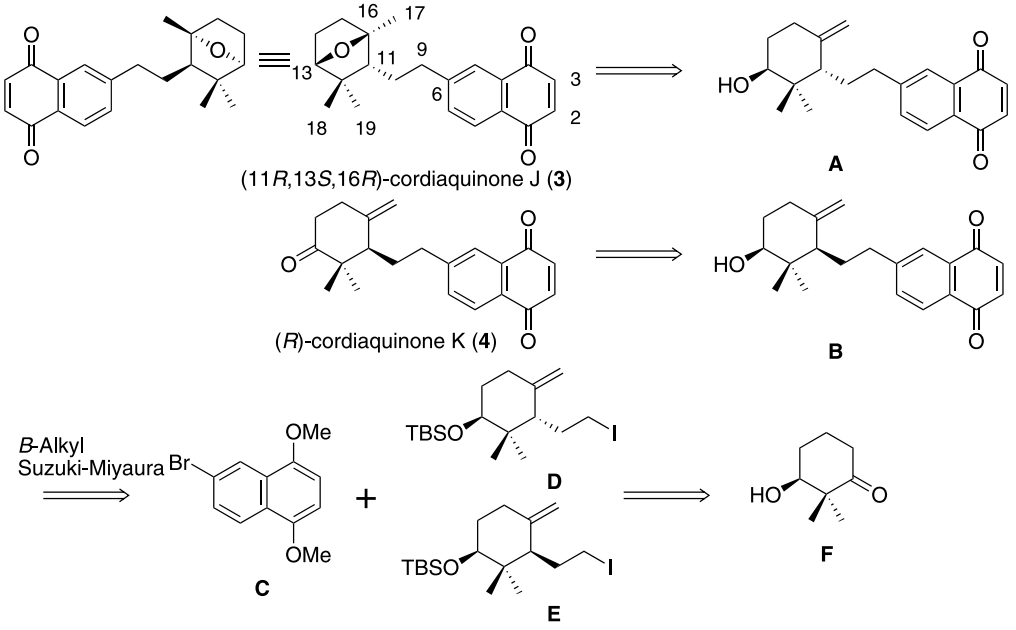
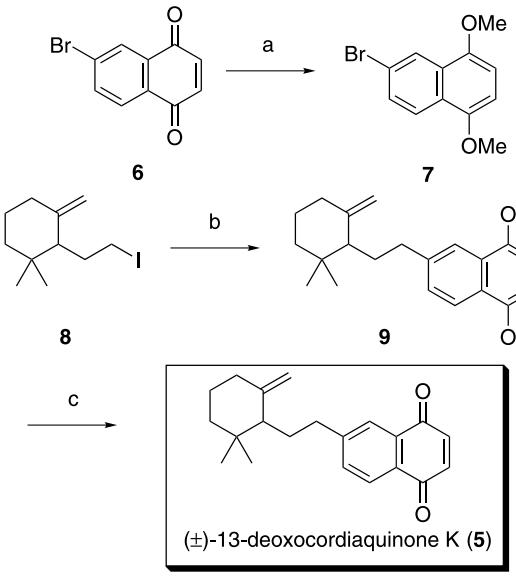


Figure 2. Structures of natural products with related structure of cordiaquinones.

As our target, we first chose (±)-13-deoxocordiaquinone K (**5**), since there was an urgent need to establish the appropriate conditions of the coupling reaction. Scheme 2 summarizes our synthesis of (±)-13-deoxocordiaquinone K (**5**). 6-Bromonaphtoquinone[13] (**6**) and (±)-γ-cyclohomogeranyl iodide[5a,14] (**8**) were selected as the starting materials. 6-Bromonaphtoquinone (**6**) was first hydrogenated with PtO_2 followed by methylation of the resulting hydroxyl groups to give **7**. (±)-γ-Cyclohomogeranyl iodide (**8**) was derived from the corresponding alcohol.[15] To connect the γ-cyclohomogeranyl unit (**8**) and the naphtoquinone derivative (**7**), we examined one-pot *B*-alkyl Suzuki–Miyaura coupling reaction. As a preliminary experiment for the coupling of **8** with **7**, the conditions reported by Marshall and Johns[16] {$PdCl_2$(dppf) as a catalyst} were examined to give the desired product (**9**) in only 10% yield based on **8**. Then we examined various conditions. Table 1 summarizes reaction conditions and yields of **9**. Although $PdCl_2$(dppf) was not an effective catalyst (entries 1–3), $Pd(PPh_3)_4$ was superior in yield (entry 4). Moreover, by heating the reaction mixture to



Scheme 1. Retrosynthetic analyses of cordiaquinone J and K.



Scheme 2. Synthesis of (±)-13-deoxocordiaquinone K. Reagents, conditions and yields. (a) (1) H_2, PtO_2, EtOAc; (2) NaH, MeI, DMF (89%, two steps); (b) (i) 2 equiv *t*-BuLi, ether, −78 °C; (ii) 2.5 equiv B-MeO-9-BBN, hexane, THF; (iii) 2.5 equiv base; (iv) 5 mol% Pd catalyst, **7**, DMF (see Table 1); (c) CAN, CH_3CN, 0 °C (73%).

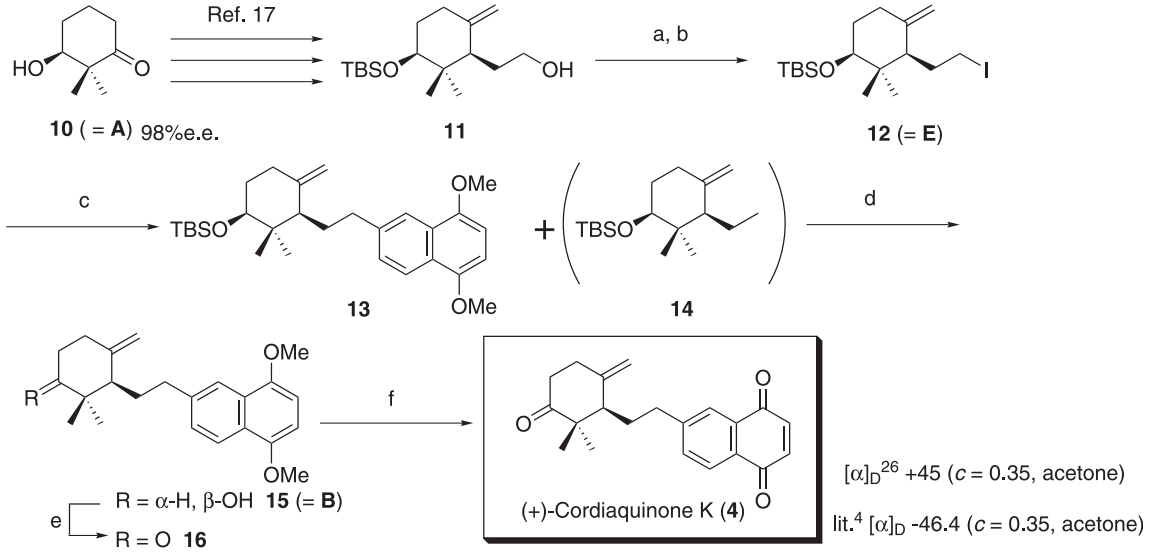
80 °C, 50% yield of **9** was obtained (entry 6). This indicates that the yield based on **7** was quantitative. Increasing the stoichiometry of **7**, however, showed only a slight improvement (55%, entry 7). Other palladium catalysts such as $Pd_2(dba)_3$, $PdCl_2(dppe)$, $PdCl_2(dppp)$, $Pd(PEt_3)_2Cl_2$, $Pd(OAc)_2+2Cy_3P$ and allylpalladium chloride dimer or other bases such as $Ba(OH)_2$, TlOEt and Cs_2CO_3 were also examined, but we found $Pd(PPh_3)_4$ with K_3PO_4 is the best choice for the coupling reaction. With the desired product (**9**) in hand (Scheme 2), the aromatic ring of **9** was oxidized with ceric ammonium nitrate (CAN) to afford (±)-13-deoxocordiaquinone K (**5**). The spectroscopic data of synthetic **5** are in perfect accordance with the structure of **5**.

By using this established methodology as described above, the synthesis of optically active cordiaquinone K was investigated (Scheme 3). The known alcohol (**11**)[17] derived from the known hydroxyketone (**10**)[12] was selected as the starting material. Alcohol **11** was converted to the corresponding iodide **12** (=**E**) in two steps (68%). The resulting iodide **12** was coupled with **7** by using the optimized conditions described above to give coupled product **13** (50%). In the ^1H NMR spectrum of the crude product, we observed the signals of side products with the terminal ethyl group. The yield of the product was estimated to be 20–35%. Although the

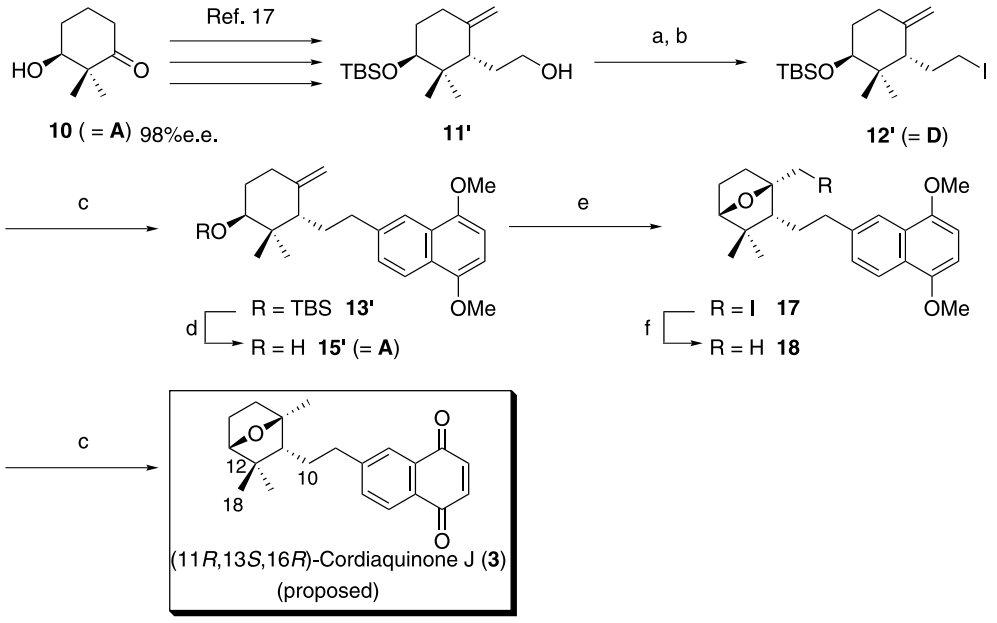
Table 1. Reaction conditions and yields of **9**

Entry	Pd catalyst[a]	Equiv of **7**	Temp. (°C)	Time (h)	Yield based on **8** (%)	Yield based on **7** (%)
1	$PdCl_2(dppf)$	0.5	rt	16	10	20
2		0.5	rt	120	13	26
3		0.5	80	16	12	24
4	$Pd(PPh_3)_4$	0.5	rt	16	24	48
5		0.5	rt	72	22	44
6		0.5	80	16	50	Quant.
7		1	80	16	55	55
8		2	80	16	50	25

[a] Five mole percent of catalysts with 2.5 equiv of K_3PO_4 were used.



Scheme 3. Synthesis of (+)-cordiaquinone K. Reagents, conditions and yields. (a) TsCl, Py.; (b) NaI, acetone, reflux (68%, two steps); (c) (i) 2 equiv *t*-BuLi, ether, −78 °C; (ii) 2.5 equiv B-MeO-9-BBN, hexane, THF; (iii) 3 M K_3PO_4; (iv) 5 mol% $Pd(PPh_3)_4$, **7**, DMF, 80 °C, 16 h (50%); (d) TBAF, THF, 60 °C (90%); (e) PCC, MS4A, CH_2Cl_2 (63%); (f) CAN, CH_3CN, 0 °C (quant.).



Scheme 4. Synthesis of (11*R*,13*S*,16*R*)-cordiaquinone J. Reagents, conditions and yields. (a) TsCl, Py.; (b) NaI, acetone, reflux (77%, two steps); (c) (i) 2 equiv *t*-BuLi, ether, −78 °C; (ii) 2.5 equiv B-MeO-9-BBN, hexane, THF; (iii) 3 M K_3PO_4; (iv) 5 mol% $Pd(PPh_3)_4$, **7**, DMF, 80 °C, 16 h (43%); (d) TBAF, THF, 60 °C (93%); (e) NIS, CH_3CN, (75%); (f) *n*-Bu_3SnH, AIBN, benzene, reflux (84%); (g) CAN, CH_3CN, 0 °C (72%).

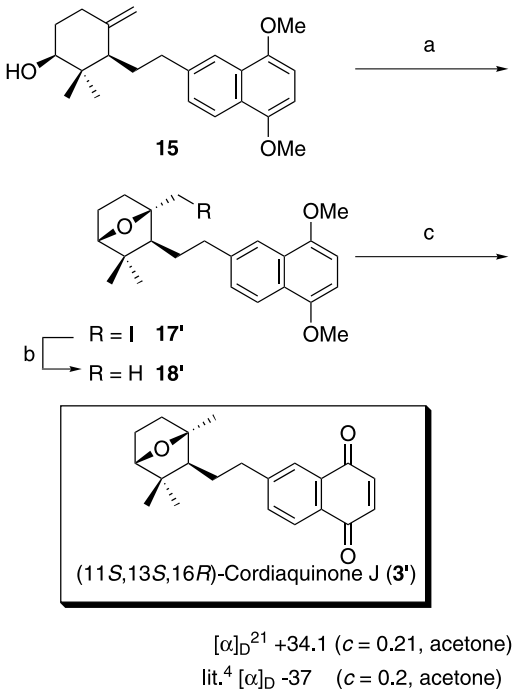
isolation of this compound was unsuccessful due to other side products, this compound was presumed to be compound **14**, which might be produced by protonation of lithiated **12**. This result indicates that optimization of the lithium–boron exchange procedure could improve the yield of this step.[18] The obtained coupling product **13** was treated with TBAF at 60 °C to give alcohol **15** (=**B**) (90%). Finally, the resulting hydroxyl group was oxidized with PCC (63%) and subsequent oxidation of the aromatic ring with CAN at 0 °C gave (*R*)-(+)-cordiaquinone K (**4**) as a pale yellow gum in quantitative yield. The overall yield of (+)-**4** was 19% in six steps from known alcohol (**11**). The ^1H and ^{13}C NMR and MS spectra are identical with those of reported data[4]. Synthetic cordiaquinone K (**4**) shows $[\alpha]_D^{26}$ +45 (*c* 0.35, acetone), while natural cordiaquinone K shows $[\alpha]_D$ −46.4 (*c* 0.35, acetone)[4]. This means that our synthetic cordiaquinone K is the antipode of the natural product. The absolute configuration of natural cordiaquinone K is, therefore, determined to be *S*.

In order to determine the relative and absolute configuration, we set out to synthesize cordiaquinone J (Scheme 4). We first choose (11*R*,13*S*,16*R*)-**3** as a candidate of the natural product. This compound possesses a cis naphtoquinone-substituted side chain at C-11 and a methyl group at C-16 as originally indicated by Hostettmann (Fig. 1).[4] The absolute configuration at C-11 of **3** was presumed to be the same as that of natural (*S*)-(−)-cordiaquinone K, because cordiaquinones could be biosynthesized from a common intermediate. For the synthesis of **3**, we selected known alcohol **11′**, diastereomer of the intermediate of our synthesis of cordiaquinone K (**4**), as a starting material. Alcohol **11′** was converted to the corresponding iodide **12′** (=**D**) as described above (77%, in two steps). The iodide **12′** was coupled with **7** using one-pot *B*-alkyl Suzuki–Miyaura coupling strategy to give **13′** (43%). Removal of the TBS group to give **15′** (93%) was followed by construction of an oxabicyclo ring system. Namely, intermolecular iodo-etherification by treatment with *N*-iodosuccinimide (NIS) gave **17** (75%), then radical reduction of **17** by tri-*n*-butyltinhydride afforded **18** with the desired oxabicyclo ring system (84%). Finally, oxidation of the aromatic ring with CAN gave (11*R*,13*S*,16*R*)-cordiaquinone J (**3**) in 72% yield. The overall yield of (11*R*,13*S*,16*R*)-**3** was 14% in seven steps from known alcohol **11′**. The ^1H NMR and IR spectra of synthetic (11*R*,13*S*,16*R*)-cordiaquinone J (**3**) are in good accordance with those of the natural product. But the ^{13}C NMR spectrum of synthetic **3** is not identical with those of the natural product. Table 2 summarizes selected ^{13}C NMR chemical shift values of synthetic and natural cordiaquinone J. Remarkable differences are observed at C-10, C-12 and C-18, which are located around the oxabicyclo ring system. So, we concluded that our synthetic **3** is a diastereomer of the natural cordiaquinone J.

To prove this hypothesis, we decided to synthesize a diastereomer of **3**. Since we have already synthesized compound **15** as an intermediate of (*R*)-(+)-cordiaquinone K (Scheme 1), we chose **15** as starting material for the

Table 2. 100 MHz ^{13}C NMR chemical shifts of synthetic (11*R*,13*S*,16*R*)- and natural cordiaquinone J

Carbon number	Synthetic (ppm)	Natural (ppm)
9	29.6	36.8
10	27.3	30.3
11	57.6	56.2
12	42.5	46.0
13	86.5	86.4
14	29.5	26.3
15	36.5	39.7
16	88.2	86.9
17	20.0	19.2
18	32.8	26.2
19	21.8	23.6



Scheme 5. Synthesis of (11*S*,13*S*,16*R*)-cordiaquinone J. Reagents, conditions and yields. (a) NIS, CH_3CN, 0 °C (74%); (b) *n*-Bu_3SnH, AIBN, benzene, reflux (quant.); (c) CAN, CH_3CN (70%).

synthesis of (11*S*,13*S*,16*R*)-cordiaquinone J (**3′**). Scheme 5 summarizes the synthesis of (11*S*,13*S*,16*R*)-cordiaquinone J (**3′**). In the same manner of the synthesis of (11*R*,13*S*,16*R*)-isomer, **15** was converted to **3′** in three steps. All spectral data such as IR and ^1H and ^{13}C NMR of synthetic **3′** are identical with those of the natural product. Synthetic **3′** shows $[\alpha]_D^{21}$ +34 (*c* 0.21, acetone), while the natural cordiaquinone J shows $[\alpha]_D$ −37 (*c* 0.2, acetone)[4]. This means that our synthetic cordiaquinone J is the antipode of the natural product. The absolute configuration of natural cordiaquinone J is, therefore, determined to be 11*R*,13*R*,16*S*.

3. Conclusion

A versatile methodology for terpenoid synthesis was established by using one-pot *B*-alkyl Suzuki–Miyaura coupling reaction. With this methodology, synthesis of (*R*)-cordiaquinone K was achieved. The absolute configuration of the natural cordiaquinone K (**4**) was determined to be *S* by a comparison of optical rotations of the synthetic and natural products. We also synthesized (11*R*,13*S*,16*R*)- and (11*S*,13*S*,16*R*)-cordiaquinone J (**3** and **3′**). The absolute stereochemistry of natural cordiaquinone J was determined to be 11*R*,13*R*,16*S*. Both the natural cordiaquinone K and J possess the same stereochemical feature at C-11. This suggests that cordiaquinones would be biosynthesized from a common intermediate.

4. Experimental

4.1. General

Optical rotations were measured on a Jasco DIP-140. IR spectra were measured for samples as films for oils or as KBr plates for solids on a Shimadzu IR-470 spectrometer. ^1H NMR spectra were taken with Jeol JNM-A400 (400 MHz) spectrometer using $CDCl_3$ at $\delta=7.24$ or acetone-d_6 at $\delta=2.04$ as an internal standard. ^{13}C NMR spectra were taken with Jeol JNM-A400 (100 MHz) spectrometer using $CDCl_3$ at $\delta=77.0$ or acetone-d_6 at $\delta=29.8$ as an internal standard. HRMS spectra were measured on a Jeol-MS700 spectrometer and Jeol-HX110/110A spectrometer. Elemental compositions were analyzed on a J-Science MICROCORDER JM10. Column chromatography was performed with silica gel Wakogel-C200.

4.1.1. 6-Bromo-1,4-dimethoxynaphthalene (7). To a solution of **6** (700 mg, 2.95 mmol) in EtOAc (10 ml), PtO_2 (15 mg) was added. The stirred suspension was degassed by evacuating, and filled with H_2. After stirring for 3 h, the suspension was filtered through Celite pad and concentrated in vacuo. The residue was dissolved in DMF (10 ml), and added MeI (460 µl, 11.8 mmol) and 60% NaH in oil (443 mg, ca. 12 mmol) to the solution. After stirring overnight, the mixture was poured into water and extracted with EtOAc three times. The combined organic extracts were washed with water and dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (hexane/EtOAc=100:1) to afford 700 mg (89%) of **7** as a colorless amorphous solid. IR (KBr) ν_{max} (cm^{-1})=3000 (w, H–C=C), 2950 (m, C–H), 1625 (m), 1590 (s), 1460 (s), 1420 (s), 1365 (s), 1330 (m), 1150 (m), 1100 (s), 1080 (s), 960 (m), 860 (m), 830 (m), 800 (s), 760 (m), 720 (m), 440 (s); ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.92$ (s, 6H, 1, 4-OCH_3), 6.66 (d, $J=8.3$ Hz, 1H, 2-H), 6.69 (d, $J=8.3$ Hz, 1H, 3-H), 7.54 (dd, $J=2.4$, 8.8 Hz, 1H, 7-H), 8.05 (d, $J=8.8$ Hz, 1H, 8-H), 8.35 (d, $J=2.4$ Hz, 1H, 5-H). Found C, 53.95%; H, 4.15%. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96%; H, 4.15%.

4.1.2. *B*-Alkyl Suzuki–Miyaura coupling reaction of iodide (8, 12 and 12′) and bromonaphthoquinone derivative (7). *General procedure*. To a stirred and cooled (−78 °C) solution of iodide in dry ether was added dropwise *tert*-BuLi in pentane (2.5 equiv) under Ar. After stirring for 30 min, *B*-methoxy-9-borabicyclo[3.3.1]nonane in hexane (1.5 equiv) was added dropwise, followed by addition of dry THF. After stirring for 10 min at the same temperature, the resulting solution was allowed to warm to rt for 75 min To the mixture, aqueous 3 M K_3PO_4 solution (2.5 equiv) was added, followed by a solution of **7** (1 equiv) in DMF. After addition of $Pd(PPh_3)_4$ (0.05 equiv), the mixture was stirred at 80 °C for 16 h. After cooling to rt, the mixture was diluted with ether. The organic layer was washed with water and brine, and the combined aqueous layers were extracted with ether three times. The combined organic layers were dried with Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (hexane) to afford **9**, **12** or **12′** as a colorless oil or amorphous solid.

4.1.3. (±)-6-[2′-(6″,6″-Dimethyl-2″-methylenecyclohexyl)-ethyl]-1,4-dimethoxynaphthalene (9). Yield: 55%; amorphous solid; IR (KBr) ν_{max} (cm^{-1})=3080 (m, H–C=C), 2920 (s, C–H), 1645 (m), 1635 (m), 1610 (s, Ar–O–CH_3), 1460 (s), 1390 (s), 1345 (m), 1270 (s), 1165 (m), 1090 (m), 1000 (m), 970 (m), 895 (s), 825 (s), 795 (s), 715

(m); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (s, 3H, 6″-CH_3), 0.89 (s, 3H, 6″-CH_3), 1.71–1.99 (m, 7H, 2′, 4″, 5″-CH_2), 2.05 (m, 1H, 3″-C*H*H), 2.06 (m, 1H, 3″-CH*H*), 2.50 (m, 1H, 1′-C*H*H), 2.75 (m, 1H, 1′-CH*H*), 3.93, 3.94 (2×s, 6H, 2×CH_3–O), 4.64 (br s, 1H, H–C=C), 4.83 (br s, 1H, H–C=C), 6.60, 6.66 (d, J=8.6 Hz, 2H, 2,3-H), 7.29 (dd, J=2.0, 8.8 Hz, 1H, 7-H), 7.94 (d, J=2.9 Hz, 1H, 5-H), 8.07 (d, J=8.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.7, 26.4, 28.3, 28.7, 32.4, 34.88, 34.93, 36.1, 53.9, 55.70, 55.70, 102.3, 103.2, 109.3, 120.2, 121.7, 124.7, 126.4, 127.3, 141.0, 149.19, 149.23, 149.6; HRFABMS: Calcd for $C_{23}H_{30}O_2$ $[M]^+$: 338.2246, found: 338.2243.

4.1.4. (1″*R*,3″*S*)-6-[2′-(3″-*tert*-Butyldimethylsilyloxy-2″,2″-dimethyl-6″-methlenecyclohexyl)-ethyl]-1,4-dimethoxynaphthalene (13). Yield: 50%; oil; $[\alpha]_D^{25}$ +3.9° (c=0.98, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=3080 (w, H–C=C), 2950 (s, C–H), 2850 (s, C–H), 1645 (m), 1635 (s), 1605 (s), 1460 (s), 1385 (s), 1270 (s), 1240 (s), 1210 (w), 1190 (w), 1140 (w), 1030 (w), 1000 (m), 985 (s), 845 (s), 795 (m), 770 (s), 720 (m), 670 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.00 (s, 3H, $SiCH_3$), 0.01 (s, 3H, Si–CH_3), 0.76 (s, 3H, 2″-CH_3), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.89 (s, 3H, 2″-CH_3), 1.48–2.08 (m, 6H, 2′, 5″-CH_2, 1″-H, 4″-C*H*H), 2.39 (m, 1H, 4″-CH*H*), 2.51 (m, 1H, 1′-C*H*H), 2.87 (m, 1H, 1′-CH*H*), 3.41 (dd, J=3.7, 7.6 Hz, 1H, 3″-H), 3.94 (s, 6H, 1, 4-CH_3O), 4.69 (br s, 1H, H–C=C), 4.89 (br s, 1H, H–C=C), 6.61 (d, J=8.3 Hz, 1H, 2-H), 6.68 (d, J=8.3 Hz, 1H, 3-H), 7.33 (dd, J=1.3, 8.8 Hz, 1H, 7-H), 7.95 (d, J=1.3 Hz, 1H, 5-H), 8.09 (d, J=8.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−5.0, −4.2, 18.0, 18.8, 25.8, 26.9, 28.1, 29.7, 30.8, 32.2, 37.1, 40.5, 52.1, 55.6, 102.2, 103.1, 108.7, 120.2, 121.6, 124.6, 126.4, 127.3, 140.9, 148.1, 149.2, 149.5.

4.1.5. (1″*S*,3″*S*)-6-[2′-(3″-*tert*-Butyldimethylsilyloxy-2″,2″-dimethyl-6″-methlenecyclohexyl)-ethyl]-1,4-dimethoxynaphthalene (13′). Yield: 40%; oil; $[\alpha]_D^{21}$ +14.4° (c 0.202, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=3080 (w, C=C–H), 2950 (s, C–H), 2850 (s, C–H), 1645 (m, C=C), 1600 (s, C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ=−0.02 [s, 6H, $Si(CH_3)_2$], 0.84 [s, 9H, $SiC(CH_3)_3$], 0.85 [s, 6H, 2″-$(CH_3)_2$], 1.48–2.08 (m, 6H, 2′, 5″-CH_2, 1″-H, 4″-C*H*H), 2.39 (m, 1H, 4″-CH*H*), 2.51 (m, 1H, 1′-C*H*H), 2.87 (m, 1H, 1′-CH*H*), 3.56 (dd, J=4.2, 9.0 Hz, 1H, 3″-H), 3.93 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 4.66 (br s, 1H, H–C=C), 4.86 (br s, 1H, H–C=C), 6.62 (d, J=8.3 Hz, 1H, 2-H), 6.66 (d, J=8.3 Hz, 1H, 3-H), 7.33 (dd, J=1.3, 8.8 Hz, 1H, 7-H), 7.95 (d, J=1.3 Hz, 1H, 5-H), 8.11 (d, J=8.8 Hz, 1H, 8-H). Found C, 74.47%; H, 9.21%. Calcd for $C_{29}H_{44}SiO_3$: C, 74.31%; H, 9.46%.

4.1.6. (±)-13-Deoxocordiaquinone K (5). To a stirred solution of **9** (100 mg, 300 μmol) in MeCN/water=4:1 (15 ml) at 0 °C was added ceric ammonium nitrate (329 mg, 600 μmol) in several portions and the mixture was stirred for 30 min Then, the mixture was poured into water and extracted with ether three times. The extract was washed with water and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (AcOEt/hexane=1:50) to afford **5** (65 mg, 73%) as a pale yellow gum; IR (film) ν_{max} (cm^{-1})=3070 (w, H–C=C), 2930 (s, C–H), 2860 (m, C–H), 1670 (s, C=O), 1600 (s), 1450 (m), 1390 (w), 1370 (m), 1305 (s), 1140 (w), 1045 (m), 890 (m), 835 (m), 735 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.82 (s, 3H, 19-CH_3), 0.89 (s, 3H, 18-CH_3), 1.22–1.80 (m, 7H, 10,13,14-CH_2, 11-H), 2.05 (m, 2H, 15-CH_2), 2.50 (m, 1H, 9-C*H*H), 2.14 (m, 1H, 9-CH*H*), 4.60 (br s, 1H, H–C=C), 4.84 (br s, 1H, H–C=C), 6.93 (s, 2H, 2,3-H), 7.52 (dd, J=1.5, 8.3 Hz, 1H, 7-H), 7.86 (d, J=1.5 Hz, 1H, 5-H), 7.97 (d, J=8.3 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.6, 26.5, 28.1, 28.3, 32.2, 34.8, 34.9, 35.9, 53.8, 109.7, 126.1, 126.7, 129.9, 131.2, 134.1, 138.5, 138.8, 148.7, 150.5, 184.9, 185.5; HRFABMS: Calcd for $C_{21}H_{24}O_2$ $[M]^+$: 308.1777, found: 308.1810.

4.2. Synthesis of (*R*)-(+)-cordiaquinone K (4)

4.2.1. (1′*R*,3′*S*)-2-(3′-*tert*-Butyldimethylsilyloxy-2′,2′-dimethyl-6′-methylenecyclohexyl)iodoethane (12). To a stirred and ice-cooled solution of **11** (990 mg, 3.32 mmol) in dry pyridine (10 ml), *p*-TsCl (769 mg, 4.03 mmol) was added in one portion. The mixture was stirred overnight at 4 °C, then poured into water. The aqueous layer was extracted with ether three times. The combined extracts were washed with satd $CuSO_4$ aq, water and brine, and dried with $MgSO_4$. After concentration in vacuo, the residue was dissolved in dry acetone (15 ml). To the solution, NaI (970 mg, 6.47 mmol) was added, and the mixture was refluxed for 4 h. After being cooled to rt, the mixture was poured into water, and extracted with pentane three times. The combined extracts were washed with satd $NaHCO_3$ aq, satd $Na_2S_2O_3$ aq, water and brine, and dried with Na_2SO_4. After concentration in vacuo, the residue was purified by column chromatography (pentane) to give 923 mg of **12** (68%) as a colorless oil; IR (film) ν_{max} (cm^{-1})=2950 (s, C–H), 2850 (s, C–H), 1645 (m), 1470 (s), 1385 (m), 1360 (m), 1250 (s), 1080 (s), 1000 (m), 990 (m), 935 (s), 875 (s), 670 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.01 [s, 6H, $Si(CH_3)_2$], 0.82 (s, 3H, 2′-CH_3), 0.87 [s, 9H, $SiC(CH_3)_3$], 0.89 (s, 3H, 2′-CH_3), 1.46 (m, 1H, 4′-C*H*H), 1.72 (m, 1H, 4′-CH*H*), 1.82 (dd, J=2.4, 11.7 Hz, 1H, 1′-H), 1.95 (m, 2H, 5′-CH_2), 2.18 (m, 1H, 2-C*H*H), 2.31 (m, 1H, 2-CH*H*), 2.91 (ddd, J=7.3, 9.3, 16.6 Hz, 1H, 1-C*H*HI), 3.26 (ddd, J=3.9, 8.8, 16.6 Hz, 1H, 1-CH*H*I), 3.50 (dd, J=3.9, 5.9 Hz, 1H, 3′-H), 4.62 (br s, 1H, H–C=C), 4.81 (br s, 1H, H–C=C). This was employed in the next step without further purification.

4.2.2. (1″*R*,3″*S*)-6-[2′-(3″-Hydroxy-2″,2″-dimethyl-6″-methlenecyclohexyl)-ethyl]-1,4-dimethoxynaphthalene. (15). A solution of **6** (235 mg, 503 μmol) and TBAF (1 ml, 1 mmol, 1.0 M in THF) in dry THF (2 ml) was stirred at 50–60 °C for 6 h under Ar. After being cooled to rt, water was added, and the mixture was extracted with ether three times. The organic extracts were washed with water and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (AcOEt/hexane=1:10) to furnish **7′** (160 mg, 90%) as a colorless oil; $[\alpha]_D^{21}$ −21° (c 0.56, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=3450 (br m, O–H), 3080 (w H–C=C), 2950 (s, C–H), 2850 (s, C–H), 1645 (m), 1610 (s) 1460 (s), 1370 (s), 1275 (s), 1240 (s), 1210 (m), 1195 (m), 1160 (w), 1095 (s), 1020 (m), 1005 (m), 990 (m), 930 (m), 900 (s), 820 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.71 (s, 3H, 2″-CH_3), 1.00 (s, 3H, 2″-CH_3), 1.53 (m, 1H, 4″-C*H*H), 1.75 (br d, J=11.7 Hz,

1H, 1″-H), 1.81–1.95 (m, 3H, 2′-CH_2, 4″-CH*H*), 2.03 (ddd, J=4.9, 11.7, 13.2 Hz, 1H, 5″-C*H*H), 2.36 (ddd, J=4.9, 4.9 13.2 Hz, 1H, 5″-CH*H*), 2.56 (ddd, J=7.3, 9.3, 14.2 Hz, 1H, 1′-CH*H*), 2.93 (ddd, J=4.9, 9.8, 14.2 Hz, 1H, 1′-CH*H*), 3.39 (dd, J=4.4, 9.8 Hz, 1H, 3″-H), 3.94 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 4.77 (br s, 1H, H–C=C), 4.98 (br s, 1H, H–C=C), 6.62 (d, J=8.3 Hz, 1H, 2-H), 6.66 (d, J=8.3 Hz, 1H, 3-H), 7.34 (dd, J=1.7, 8.3 Hz, 1H, 7-H), 7.96 (d, J=1.7 Hz, 1H, 5-H), 8.11 (d, J=8.3 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.6, 25.9, 27.5, 32.1, 32.9, 35.2, 40.5, 51.1, 55.7, 102.3, 103.2, 108.7, 120.2, 121.8, 124.7, 126.4, 127.2, 140.6, 147.1, 149.1, 149.5. Found: C, 77.96%; H, 8.47%. Calcd for $C_{23}H_{30}O_3$: C, 77.93%; H, 8.53%.

4.2.3. (*R*)-6-[2′-(2″,2″-Dimethyl-6″-methylen-3″-oxocyclohexyl)ethyl]-1,4-dimethoxynaphthalene (16). To a stirred solution of **15** (65 mg, 0.18 mmol) in dry CH_2Cl_2 (1.5 ml), powdered MS 4A (24 mg) and PCC (80 mg, 0.37 mmol) were added, respectively, at rt. After stirring for 30 min, the mixture was filtered through Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (AcOEt/hexane=50:1) to give **16** (41 mg, 63%) as a colorless oil; $[\alpha]_D^{24}$ +55.0° (c 0.34, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=3080 (w, H–C=C), 2950 (s, C–H), 2850 (s, C–H), 1710 (s, C=O), 1610 (s), 1460 (s), 1370 (s), 1270 (s), 1100 (s), 900 (s), 800 (s), 720 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.97 (s, 3H, 2″-CH_3), 1.13 (s, 3H, 2″-CH_3), 1.51 (m, 1H, 2′-C*H*H), 1.85 (m, 1H, 2′-CH*H*), 2.16 (dd, J=3.4, 8.3 Hz, 1H, 1″-H), 2.27 (m, 1H, 4″-C*H*H), 2.43–2.60 (m, 4H, 1′,5″-CH_2), 2.73 (m, 1H, 4″-CH*H*), 3.88, 3.89 (2×s, 6H, 2×CH_3O), 4.86 (br s, 1H, H–C=C), 5.05 (br s, 1H, H–C=C), 6.57 (d, J=8.8 Hz, 1H, 2-H), 6.62 (d, J=8.3 Hz, 1H, 3-H), 7.24 (dd, J=1.5, 6.8 Hz, 1H, 7-H), 7.84 (d, J=1.5 Hz, 1H, 5-H), 8.05 (d, J=8.3 Hz, 1H, 8-H). This was employed in the next step without further purification.

4.2.4. (*R*)-(+)-Cordiaquinone K (4). To a stirred solution of **16** (37 mg, 106 μmol) in MeCN/water=4:1 (0.5 ml) at 0 °C was added ceric ammonium nitrate (126 mg, 229 μmol) in several portions and the mixture was stirred for 2.5 h. Then, the mixture was poured into water and extracted with ether three times. The extract was washed with water and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (AcOEt/hexane=1:40) to afford **4** (36 mg, quant.) as a pale yellow gum; $[\alpha]_D^{26}$ +44.9 (c 0.35, acetone), lit.[4]: $[\alpha]_D$ −46.4° (c 0.35, acetone); IR (film) ν_{max} (cm^{-1})=3080 (w, H–C=C), 2950 (s, C–H), 2850 (s, C–H), 1710 (s, C=O), 1670 (m), 1600 (s), 1420 (s), 1310 (m), 935 (m), 900 (m); ^{1}H NMR (400 MHz, acetone-d_6): δ=0.99 (s, 3H, 19-CH_3), 1.18 (s, 3H, 18-CH_3), 1.49 (m, 1H, 10-C*H*H), 1.94 (m, 1H, 10-CH*H*), 2.24 (m, 1H, 14-C*H*H), 2.34 (dd, J=3.7, 12.0 Hz, 1H, 11-H), 2.55–2.98 (m, 5H, 9, 15-CH_2, 14-CH*H*), 4.94 (br s, 1H, H–C=C), 5.13 (br s, 1H, H–C=C), 6.88 (s, 2H, 2, 3-H), 7.58 (dd, J=1.8, 6.4 Hz, 1H, 7-H), 7.71 (d, J=1.8 Hz, 1H, 5-H), 7.82 (d, J=7.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, acetone-d_6): δ=21.6 (C-19), 27.4 (C-18), 29.9 (C-10), 31.1 (C-15), 34.6 (C-9), 38.0 (C-14), 49.4 (C-12), 56.7 (C-11), 113.9 (C-17), 126.5 (C-5), 127.0 (C-8), 130.9 (C-8a), 132.9 (C-4a), 134.9 (C-7), 139.3 (C-3), 139.5 (C-2), 150.2 (C-6), 185.4 (C-4), 185.7 (C-1), 213.6 (C-13); HREIMS: Calcd for $C_{21}H_{22}O_3$ $[M]^+$: 322.1569, found: 322.1581; ^{1}H and ^{13}C NMR spectra are identical with those of reported natural product.

4.3. Synthesis of (11*R*,13*S*,16*R*)-cordiaquinone J (3)

4.3.1. (1′*S*,3′*S*)-2-(3′-*tert*-Butyldimethylsilyloxy-2′,2′-dimethyl-6′-methylenecyclohexyl)-iodoethane (12′). In the same manner as described above for (1′*R*,3′*S*)-isomer, 5.28 g (18.8 mmol) of **11′** was converted to **12′** to give 5.91 g (77%, two steps); IR (film) ν_{max} (cm^{-1})=3080 (w, H–C=C), 2950 (s, C–H), 2850 (s, C–H), 1645 (m, C=C), 1600 (s, C=C), 1485 (s, Si–CH_3), 1385 (s, Si–CH_3), 1285 (s, Si–CH_3), 1240 (s, C–I), 1100 (s, Si–O), 680 (w, C–I); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.01 [s, 6H, Si(CH_3)$_2$], 0.82 (s, 3H, 2′-CH_3), 0.86 [s, 12H, 2′-CH_3, SiC(CH_3)$_3$], 1.45 (m, 1H, 4′-C*H*H), 1.63 (m, 1H, 4′-CH*H*), 1.80–2.05 (m, 3H, 2-CH_2, 5′-C*H*H), 2.08 (dd, J=3.2, 11.5 Hz, 1H, 1′-H), 2.19 (ddd, J=5.4, 5.4, 13.7 Hz, 1H, 5′-CH*H*), 2.92 (dd, J=8.3, 17.6 Hz, 1H, 1-C*H*HI), 3.22 (ddd, J=3.9, 8.8, 17.6 Hz, 1H, 1-CH*H*I), 3.49 (dd, J=3.9, 8.8 Hz, 1H, 3′-H), 4.63 (br s, 1H, H–C=C), 4.82 (br s, 1H, H–C=C). This was employed in the next step without further purification.

4.3.2. (1″*S*,3″*S*)-6-[2′-(3″-hydroxy-2″,2″-dimethyl-6″-methlenecyclohexyl)-ethyl]-1,4-dimethoxynaphthalene (15′). In the same manner as described above for (1′*R*,3′*S*)-isomer, 117 mg (244 μmol) of **13′** was converted to **15′** (83 mg, 93%) as a colorless oil; $[\alpha]_D^{21}$ −15.7° (c 0.328, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=3450 (br m, O–H), 3080 (w, H–C=C), 2950 (s, C–H), 2850 (s, C–H), 1645 (m, C=C), 1610 (s, C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (s, 3H, 2″-CH_3), 0.97 (s, 3H, 2″-CH_3), 1.45–1.91 (m, 4H, 2′, 4″-CH_2), 2.00 (dd, J=3.0, 12.2 Hz, 1H, 1″-H), 2.25 (m, 2H, 5″-CH_2), 2.49 (ddd, J=6.3, 10.7, 14.2 Hz, 1H, 1′-C*H*H), 2.72 (ddd, J=4.4, 10.7, 14.2 Hz, 1H, 1′-CH*H*), 3.63 (dd, J=4.4, 10.3 Hz, 1H, 3″-H), 3.93 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 4.69 (br s, 1H, H–C=C), 4.88 (br s, 1H, H–C=C), 6.62 (d, J=8.3 Hz, 1H, 2-H), 6.66 (d, J=8.3 Hz, 1H, 3-H), 7.31 (d, J=8.3 Hz, 1H, 7-H), 7.94 (s, 1H, 5-H), 8.09 (d, J=8.3 Hz, 1H, 8-H). Found: C, 78.00%, H, 8.48%. Calcd for $C_{23}H_{30}O_3$: C, 77.93%, H, 8.53%.

4.3.3. (1*R*,2*S*,4*S*)-2-[2′-(5″,8″-Dimethoxynaphthalene-2″-yl)-ethyl]-1-iodomethyl-3,3,-dimethyl-7-oxabicyclo[2.2.1]heptane (17). A solution of **15** (253 mg, 0.72 mmol) and *N*-iodosuccinimide (290 mg, 1.28 mmol) in dry MeCN (3 ml) was stirred at rt in the dark overnight. The resulting mixture was poured into water and extracted with ether. The extract was washed successively with $Na_2S_2O_4$ aq, water, satd $NaHCO_3$ and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (AcOEt/hexane=1:40) to afford 284 mg of **17** (83%) as a colorless oil; $[\alpha]_D^{21}$ −36.2° (c 0.302, $CHCl_3$); IR (film) υ_{max} (cm^{-1})=2950 (s, C–H), 1635 (m), 1600 (s), 1465 (s), 1425 (m), 1365 (s), 1340 (w), 1270 (s), 1245 (s), 1215 (m), 1195 (s), 1160 (w), 1095 (s), 1000 (m), 980 (m), 965 (w), 950 (m), 820 (m), 795 (s), 715 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.00 (s, 3H, 3-CH_3), 1.15 (s, 3H, 3-CH_3), 1.52 (m, 2H, 1′-CH_2), 1.68 (m, 4H, 6-CH_2, 5-C*H*H, 2-CH), 1.95 (m, 1H, 5-CH*H*), 2.68 (m, 1H, 2′-C*H*H), 2.82 (ddd, J=4.0, 9.2, 9.2 Hz, 1H, 2′-CH*H*), 3.48 (d, J=10.7 Hz, 1H, C*H*H-I), 3.53 (d, J=10.7 Hz, 1H, CH*H*-I), 3.85 (d, J=4.9 Hz, 1H, 4-H), 3.93, 3.95 (2×s, 3H,

2×CH_3O), 6.63 (d, J=8.3 Hz, 1H, 6″-H), 6.68 (d, J=8.3 Hz, 1H, 7″-H), 7.32 (d, J=8.3 Hz, 1H, 3″-H), 7.95 (s, 1H, 1″-H), 8.12 (d, J=8.3 Hz, 1H, 4″-H). Found: C, 57.52%; H, 6.04%. Calcd for $C_{23}H_{29}O_3I$: C, 57.51%; H, 6.08%.

4.3.4. (1*R*,2*S*,4*S*)-2-[2′-(5″,8″-Dimethoxynaphthalene-2″-yl)-ethyl]-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane (18). To a stirred solution of **16** (57 mg, 119 μmol) in dry benzene (1.5 ml) was added *n*-Bu_3SnH (80 μl, 297 μmol) and AIBN (32 mg, 196 μmol) under Ar. Then the mixture was stirred at reflux for 5 h. After cooling to rt, the mixture was poured into water and extracted with ether. The extract was washed with water, satd $NaHCO_3$ and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (AcOEt/hexane=1:50) to afford **18** (98 mg, 84%) as a colorless oil; $[\alpha]_D^{21}$ −9.3° (*c* 0.33, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=2950 (s, C–H), 1635 (s), 1605 (s), 1465 (s), 1425 (s), 1370 (s), 1340 (m), 1270 (s), 1245 (s), 1215 (s), 1195 (s), 1160 (m), 1140 (w), 1095 (s), 1000 (s), 980 (m), 965 (w), 950 (m), 895 (w), 860 (w), 820 (m), 795 (s), 715 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.98 (s, 3H, 3-CH_3), 1.11 (s, 3H, 3-CH_3), 1.14–1.24 (m, 2H, 2-H, 6-C*H*H), 1.35 (m, 1H, 6-CH*H*), 1.39 (s, 3H, 1-CH_3), 1.50–1.70 (m, 3H, 5-C*H*H, 1′-CH_2), 1.80 (m, 1H, 5-CH*H*), 2.68 (ddd, J=6.3, 10.7, 13.7 Hz, 1H, 2′-C*H*H), 2.78 (ddd, J=4.9, 11.2, 13.7 Hz, 1H, 2′-CH*H*), 3.80 (d, J=5.9 Hz, 1H, 4-H), 3.93 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 6.62 (d, J=8.3 Hz, 1H, 6″-H), 6.67 (d, J=8.3 Hz, 1H, 7″-H), 7.33 (dd, J=2.0, 8.8 Hz, 1H, 3″-H), 7.95 (d, J=2.0 Hz, 1H, 1″-H), 8.15 (d, J=8.8 Hz, 1H, 4″-H). Found: C, 77.96%; H, 8.46%. Calcd for $C_{23}H_{30}O_3$: C, 77.93%; H, 8.53%.

4.3.5. (11*R*,13*S*,16*R*)-Cordiaquinone J (3). To a stirred solution of **17** (60 mg, 169 μmol) in MeCN/water=4:1 (1 ml) at 0 °C was added CAN (187 mg, 341 μmol) in several portions and the mixture was stirred for 2 h. Then, the mixture was poured into water and extracted with ether three times. The extract was washed with water and brine, then dried with $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography (AcOEt/hexane=1:40) to afford **3** (39 mg, 72%) as a pale yellow gum; $[\alpha]_D^{21}$ –20° (*c* 0.05, acetone); IR (film) ν_{max} (cm^{-1})=3080 (w, H–C=C), 2950 (s, C–H), 2855 (m, C–H), 1665 (s, C=C–C=O), 1600 (s, C=C–C=O), 1465 (m), 1385 (m), 1340 (w), 1335 (m), 1305 (s), 1190 (w), 1135 (w), 1080 (w), 1045 (m), 995 (m), 870 (m), 835 (s); ^{1}H NMR (400 MHz, acetone-d_6): δ=1.00 (s, 3H, 19-CH_3), 1.07 (s, 3H, 18-CH_3), 1.12 (ddd, J=2.0, 3.9, 12.2 Hz, 1H, 15-C*H*H), 1.31 (ddd, J=1.9, 4.4, 9.3 Hz, 1H, 14-C*H*H), 1.50 (dddd, J=5.4, 5.4, 12.7, 12.7 Hz, 1H, 10-C*H*H), 1.54–1.74 (m, 3H, 11-H, 10, 15-CH*H*), 1.83 (dddd, J=3.9, 4.9, 8.8, 12.2 Hz, 1H, 14-CH*H*), 2.75 (ddd, J=6.8, 11.3, 13.7 Hz, 1H, 9-C*H*H), 2.85 (dd, J=4.9, 10.3, 13.7 Hz, 1H, 9-CH*H*), 3.72 (d, J=4.9 Hz, 1H, 13-H), 7.00 (s, 2H, 2, 3-H), 7.66 (dd, J=2.0, 7.8 Hz, 1H, 7-H), 7.83 (d, J=2.0 Hz, 1H, 5-H), 7.88 (d, J=7.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, acetone-d_6): δ=20.0 (C-17), 21.8 (C-19), 27.3 (C-14), 30.3 (C-10), 30.4 (C-9), 32.9 (C-18), 36.6 (C-15), 42.6 (C-12), 57.6 (C-11), 86.6 (C-13), 88.3 (C-16), 126.4 (C-5), 127.1 (C-8), 130.9 (C-8a), 132.9 (C-4a), 134.8 (C-7), 139.4 (C-3), 139.5 (C-2), 150.6 (C-6), 185.3 (C-2), 185.7 (C-1). Found: C, 77.77%, H, 7.40%. Calcd for $C_{21}H_{24}O_3$: C, 77.75%, H, 7.46%.

4.4. Synthesis of (11*S*,13*S*,16*R*)-(+)-cordiaquinone J (3′)

4.4.1. (1*R*,2*R*,4*S*)-2-[2′-(5″,8″-Dimethoxynaphthalene-2″-yl)-ethyl]-1-iodomethyl-3,3,-dimethyl-7-oxabicyclo[2.2.1]heptane (17′). In the same manner as described above for (1*R*,2*S*,4*S*)-isomer, 160 mg (452 μmol) of **15′** was converted to **17′** (160 mg, 74%) as a colorless oil; $[\alpha]_D^{21}$ +48.8° (*c* 0.81, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=2950 (s, C–H), 1635 (s), 1600 (s), 1460 (br s), 1365 (s), 1270 (s), 1240 (s), 1210 (m), 1195 (m), 1160 (m), 1095 (s), 1000 (s), 970 (m), 955 (m), 900 (w), 860 (w), 830 (m), 800 (s), 720 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.12 (s, 3H, 3-CH_3), 1.15 (s, 3H, 3-CH_3), 1.50–1.75 (m, 5H, 6, 1′-CH_2, 5-C*H*H), 1.85 (m, 1H, 5-CH*H*), 1.88 (dd, J=1.9, 11.2 Hz, 1H, 2-H), 2.63 (ddd, J=6.4, 9.8, 13.7 Hz, 1H, 2′-C*H*H), 2.80 (ddd, J=4.9, 10.7, 13.7 Hz, 1H, 2′-CH*H*), 3.26 (d, J=10.3 Hz, 1H, 1-C*H*H), 3.47 (d, J=10.3 Hz, 1H, 1-CH*H*), 3.86 (d, J=4.4 Hz, 1H, 4-H), 3.88, 3.89 (2×s, 6H, 2×CH_3O), 6.58 (d, J=8.3 Hz, 1H, 6″-H), 6.62 (d, J=8.3 Hz, 1H, 7″-H), 7.30 (dd, J=1.9, 8.3 Hz, 1H, 3″-H), 7.91 (br s, 1H, 1″-H), 8.06 (d, J=8.3 Hz, 1H, 4″-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=8.00, 23.5, 25.6, 26.4, 29.3, 36.2, 38.0, 46.0, 54.3, 55.7, 86.7, 87.3, 102.5, 103.3, 120.2, 122.0, 124.8, 126.4, 127.0, 139.7, 149.1, 149.5. Found: C, 57.58%; H, 6.13%. Calcd for $C_{23}H_{29}O_3I$: C, 57.51%; H, 6.08%.

4.4.2. (1*R*,2*R*,4*S*)-2-[2′-(5″,8″-Dimethoxynaphthalene-2″-yl)-ethyl]-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane (18′). In the same manner as described above for (1*R*,2*S*,4*S*)-isomer, 160 mg (452 μmol) of **17′** was converted to **18′** (106 mg, quant.) as a colorless oil; $[\alpha]_D^{21}$ +27.8° (*c* 0.63, $CHCl_3$); IR (film) ν_{max} (cm^{-1})=2950 (s, C–H), 1600 (s), 1460 (s), 1425 (m), 1365 (s), 1270 (s), 1240 (m), 1195 (m), 1095 (s), 1000 (w), 990 (m), 985 (w), 830 (w), 800 (s), 720 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.10 (s, 6H, 2×3-CH_3), 1.30 (dd, J=5.9, 8.3 Hz, 1H, 2-H), 1.39–1.53 (m, 2H, 5, 6-C*H*H), 1.68 (m, 3H, 6-CH*H*, 1′-CH_2), 1.91 (ddd, J=4.9, 8.5, 12.5 Hz, 1H, 5-CH*H*), 2.69 (ddd, J=6.3, 9.8, 13.7 Hz, 1H, 2′-C*H*H), 2.78 (ddd, J=5.9, 10.2, 13.7 Hz, 1H, 2′-CH*H*), 3.80 (d, J=5.9 Hz, 1H, 4-H), 3.93, 3.95 (2×s, 6H, 2×CH_3O) 6.62 (d, J=8.3, 1H, 6″-H), 6.67 (d, J=8.3, 1H, 7″-H) 7.34 (dd, J=2.0, 8.8 Hz, 1H, 3″-H), 7.95 (d, J=2.0 Hz, 1H, 1″-H), 8.15 (d, J=8.8 Hz, 1H, 4″-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.0, 23.5, 25.7, 26.1, 29.9, 36.4, 36.5, 39.0, 45.3, 55.5, 55.7, 86.1, 86.7, 102.4, 103.3, 120.1, 121.9, 124.7, 126.4, 127.0, 140.4, 149.1, 149.5. Found: C, 77.93%; H, 8.41%. Calcd for $C_{23}H_{30}O_3$: C, 77.93%; H, 8.53%.

4.4.3. (11*S*,13*S*,16*R*)-(+)-Cordiaquinone J (3′). In the same manner as described above for (11*R*,13*S*,16*R*)-isomer, 79 mg (309 μmol) of **17′** was converted to **3′** (71 mg, 70%) as a pale yellow gum; $[\alpha]_D^{21}$ +34.1° (*c* 0.205, acetone), lit.[4]; $[\alpha]_D$ −37° (*c* 0.2, acetone); IR (film) ν_{max} (cm^{-1})=3080 (w, H–C=C), 2995 (s, C–H), 2975 (m, C–H), 1665 (s, C=C–C=O), 1600 (s, C=C–C=O), 1460 (m), 1380 (m), 1345 (w), 1310 (s), 1190 (w), 1180 (w), 1135 (m), 1045 (m), 995 (m), 875 (m), 835 (s); ^{1}H NMR (400 MHz, acetone-d_6): δ=1.08 (s, 3H, 19-CH_3), 1.12 (s, 3H, 18-CH_3), 1.32 (s, 3H, 17-CH_3), 1.33–1.4 (m, 2H, 11-H, 15-C*H*H), 1.51–1.6 (m, 1H, 15-CH*H*), 1.55–1.67 (m, 2H, 10, 14-C*H*H), 1.72 (m, 1H, 10-CH*H*), 1.93 (ddd, J=4.9, 8.5, 12.2 Hz, 1H, 14-CH*H*), 2.80 (m, 2H, 9-CH_2), 3.67 (d, J=5.4 Hz, 1H, 13-H), 7.00 (s, 2H,

2, 3-H), 7.72 (br d, $J=7.8$ Hz, 1H, 7-H), 7.85 (s, 1H, 5-H), 7.95 (d, $J=7.8$ Hz, 1H, 8-H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta=19.2$ (C-17), 23.6 (C-19), 26.1 (C-18), 26.3 (C-14), 30.3 (C-10), 36.8 (C-9), 39.7 (C-15), 46.0 (C-12), 56.3 (C-11), 86.4 (C-13), 86.9 (C-16), 126.3 (C-5), 127.1 (C-8), 130.9 (C-8a), 132.9 (C-4a), 134.7 (C-7), 139.3 (C-3), 139.5 (C-2), 150.7 (C-6), 185.3 (C-4), 185.7 (C-1). Found: C, 77.71%; H, 7.42%. Calcd for $C_{21}H_{24}O_3$: C, 77.75%; H 7.46%; ^{1}H and ^{13}C NMR spectra are identical with those of reported natural product.

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Chemoselective reduction of β-butyltellanyl α,β-unsaturated carbonyl compounds to allylic alcohols

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Abstract—(*Z*)-β-Butyltellanyl α,β-unsaturated carbonyl compounds were stereoselectively produced by hydrotelluration of alkynones or by an addition/elimination sequence from enol tosylates. The β-butyltellanyl-enones were chemoselectively reduced with $NaBH_4$/MeOH, $NaBH_4 \cdot CeCl_3 \cdot 7H_2O$/MeOH and DIBAL-H systems to the corresponding allylic alcohols with retention of the *Z* stereochemistry.

1. Introduction

The organic chemistry of tellurium experienced a great development in the last decade.[1] One of the most studied classes of organotellurium compounds are the vinylic tellurides.[1,2] Recently two of such species have been employed in the total synthesis of two structurally complex natural products.[3] The vinylic telluride **1** used in one of these synthesis[3b] presents a hydroxyl group at one end, which allows the chain elongation by appropriate manipulation of the functionality. At the other end of the molecule, the vinyltellurium moiety constitutes an equivalent of vinyl organometallics.[1,2] This bifunctional character of functionalized vinylic tellurides makes them extremely versatile synthetic building blocks (Fig. 1).

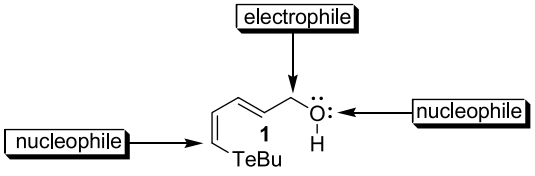
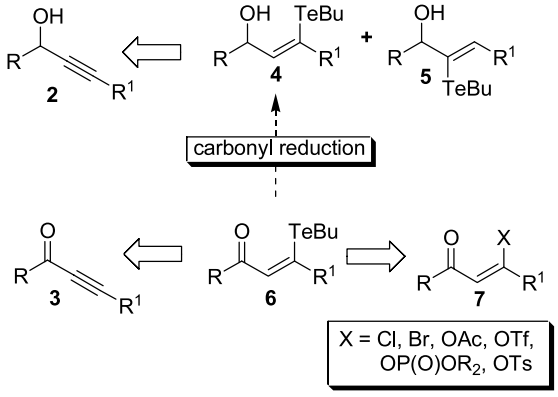


Figure 1. Bifunctional character of functionalized vinylic tellurides.

In view of this fact, in recent years we have dedicated special attention to the development of general methodologies to prepare functionalized tellurides.[1a,2] To date, two methods to prepare functionalized vinylic tellurides can be considered of general character, the hydrotelluration of activated alkynes **3**[1a,2] and the vinylic substitution of vinyl halides, triflates, phosphates and acetates[4] **7** bearing electron stabilizing groups at the β position (Scheme 1). Both methods give one single regioisomer of the *Z* configuration **6** exclusively.[1,2,4] Contrary to the hydrotelluration of alkynones **3**, propargyl alcohols **2** give mixtures of vinylic tellurides **4** and **5** on hydrotelluration (Scheme 1).[5]



Scheme 1. Preparation of functionalized vinylic tellurides.

A good approach to prepare vinylic tellurides **4** in pure form would be the reduction of **6**. However, sodium borohydride usually promotes the reduction of the carbon–carbon double bond of α,β-unsaturated ketones.[6] The presence of cerium chloride in the reaction medium avoids this side

Keywords: Vinylic tellurides; Chemoselective reduction; Enones and allylic alcohols.
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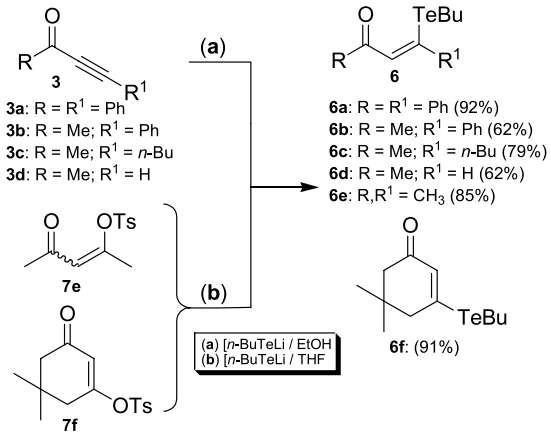
reaction.[7] Another way to circumvent the 1,4-reduction was recently described by Zeynizadeh and Yahyaei, where sodium borohydride in THF under ultrasonic irradiation performs high selective reduction of enones to the corresponding allylic alcohols.[7c]

In this paper, we describe a systematic study on the reduction of α,β-unsaturated carbonyl compounds bearing a butyltellanyl group at the β-position, as a route to vinylic tellurides of the type **4** (Scheme 1).

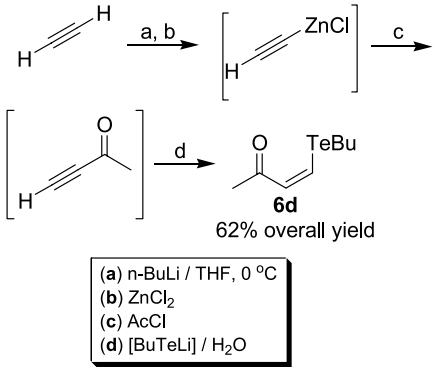
As a very often mentioned drawback to the use of organotellurium compounds is their alleged bad smell, it is important to point out that all the compounds described in this paper are not bad smelling. Most of them are almost odourless or present a smell not more unpleasant than most of the laboratory chemicals normally used in an organic synthesis laboratory. In the last few years our laboratory has devoted efforts to avoid the use of bad smelling low molecular weight alkyl tellurium compounds as starting materials in the preparation of more complex tellurium compounds. Elemental tellurium and *n*-butyllithium have been used instead in our new synthetic methodologies to introduce tellurium into organic substrates.[1a,4b–d,8] All the compounds described in this paper, are stable to the ambient light and can be manipulated in the air. However, long contact of the compounds with air, especially when in solution, must be avoided, since alkyltellurides react with oxygen to give an amorphous white powder, presumably a telluroxide. After evaporation of the solvents the pure compounds can be manipulated in the presence of air with no need of special precautions. Finally, it must be pointed out that the compounds described here were not tested for their toxicity. A recent review[9] on the pharmacology and toxicology of organic tellurium compounds mention that the few studies on this matter indicate that tellurium compounds are toxic to mammals, in the same way as are many other widely used compounds of, for example, phosphorous[10] and tin,[11] elements routinely used in any organic synthesis laboratory. In this way, the obvious safety cautions recommended in the manipulation of laboratory chemicals must be taken in handling organotellurium compounds.

2. Results and discussion

Two routes were used to prepare the β-butyltellanyl alkenones used in this study. The first one was the hydrotelluration of alkynones **3**.[2] The hydrotellurating agent was prepared by addition of *n*-butyllithium to a suspension of elemental tellurium in THF at 0 °C under nitrogen. A clear yellow solution was formed with the consumption of the grey tellurium powder. Deoxygenated water or ethanol was added to this solution and then the alkynone **3a–d** (Scheme 2). The β-butyltellanyl enone **6d** was prepared by an efficient sequential large scale (0.1 mol) procedure (Scheme 3). To pre-generated monolithium acetylide in THF at 0 °C was added $ZnCl_2$ and the resulting solution was stirred for 30 min at 0 °C. Then acetylchloride in THF was added and after 30 min at room temperature the mixture was transferred to a pre-formed hydrotelluration system prepared as described above. The β-butyltellanyl enone **6d** was obtained in 62% overall yield (Scheme 3).



Scheme 2. Preparation of the β-butyltellanyl enones.

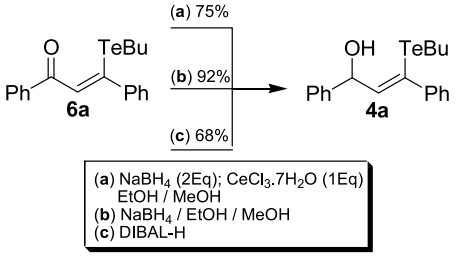


Scheme 3. Large scale preparation of **6d**.

The β-butyltellanyl enones **6e** and **6f** were prepared by a vinylic substitution reaction using enol tosylates **7e** and **7f** and lithium *n*-butyltellurolate, prepared by addition of *n*-butyllithium to elemental tellurium in THF at 0 °C.[4b–e] The substitution reaction was completed in few minutes. Both methods gave the β-butyltellanyl ketones as yellow or orange oils in good yields after purification by silica gel column chromatography. As commented before, **6a–f** are almost odourless compounds.

All compounds were formed as a single *Z* stereoisomer. The stereochemistry was assigned by spectroscopic and chromatography analysis and was in agreement with previous reports.[4b–e]

With the β-butyltellanyl enones **6a–f** in hands we initiated the study of their reduction to the vinylic tellurides **4** (Scheme 4). The reducing systems used were sodium



Scheme 4. Reduction of compound **6a** by different reducing systems.

borohydride in methanol/ethanol, sodium borohydride/cerium chloride in methanol/ethanol, and diisobutylaluminum hydride (DIBAL-H) in tetrahydrofuran. The β-butyltellanyl enone **6a** was used in this exploratory study (Scheme 4).

It is worth mentioning that DIBAL-H has been used in highly chemoselective reductions of conjugated aldehydes and ketones, leading to the corresponding allylic alcohols.[12] On the other hand, when conjugated ketones are reduced with sodium borohydride, a mixture of the allylic and the corresponding saturated alcohol is formed.[6b] As mentioned before, the high selective formation of allylic alcohols is possible by the addition of cerium chloride to the sodium borohydride reducing systems.[7]

In view of these literature reports, the results shown in Scheme 4 are noteworthy, since the reduction of only the carbonyl group was observed in the three reducing systems. More interesting in a practical point of view is the fact that comparable good yields were obtained when sodium borohydride only was used as the reducing agent. As the substituent at the β-position of the conjugated system plays an important role in the chemoselectivity of the reduction process,[6b] we can presume that the high chemoselectivity in the present case can be attributed to the butyltellanyl group. In order to test the generality of this behaviour of the butyltellanyl enones **6**, the whole series of compounds **6** was submitted to the same reaction conditions described in Scheme 4. The results are summarized in Table 1. Also in this case, the obtained alcohols are almost odourless yellow oils.

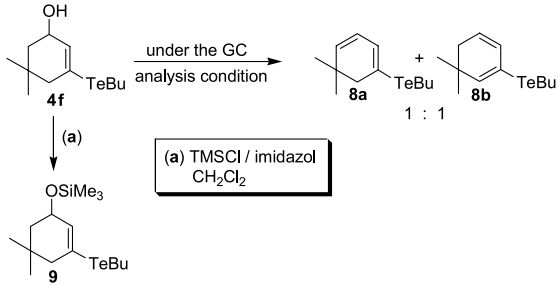
Table 1. Reduction of β-butyltellanyl enones **6a–f** under the reduction conditions shown in Scheme 4

Enone	Product	(a) Yield (%)[a,b]	(b) Yield (%)[a,b]	(c) Yield (%)[a,c]
6a	**4a**	75	92	68
6b	**4b**	98	95	84
6c	**4c**	84	70	76
6d	**4d**	80	93	76
6e	**4e**	60[d]	96	70
6f	**4f**	86	70	78

[a] Isolated yields after column chromatography on silica gel.
[b] The reactions were performed at 0 °C.
[c] The reactions were performed at −20 °C.
[d] The reaction was performed at room temperature.

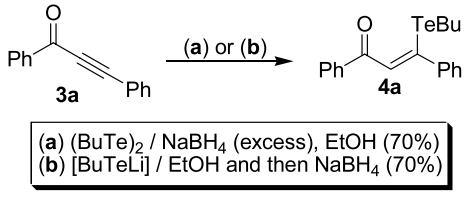
As can be observed, results very similar to those obtained for compound **6a** (Scheme 4) were obtained for all β-butyltellanyl enones **6**. In all cases it was not observed any trace of the saturated alcohol. The analytical data of all compounds showed that only one isomer was formed from the corresponding *Z* enone. The NOESY experiments of compounds **6c** and **6e** showed that the stereochemistry of the double bond remains *Z*.

It was also observed that the alcohols **4a–f** are thermally unstable under GC analysis conditions producing probably the corresponding water elimination products **8** (from **4f**), since two peaks of equal mass and similar fragmentation patterns appeared in the GC–MS spectra of these compounds. This assumption was confirmed by derivatizing the allylic alcohol **4f** as the trimethylsilyl ether **9**. In this case only one peak was observed by GC analysis (Scheme 5).



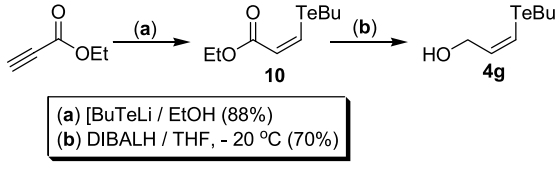
Scheme 5. Thermal decomposition of **4f** under GC–MS analysis conditions and its derivatization to TMS ether **9**.

In one case (alkynone **3a**) the hydrotelluration was performed using the classical conditions employed for this transformation.[1a,2] Dibutylditelluride was reduced with sodium borohydride in ethanol and then **3a** was added to the hydrotellurating system containing an excess of sodium borohydride. The alcohol **4a** of the *Z* configuration was obtained as the only product, indicating that the hydrotelluration and the carbonyl reduction can be performed in a one pot operation. In order to avoid the use of the malodorous dibutylditelluride, the hydrotelluration reaction was performed using the lithium butyltellurolate/ethanol method,[8] and then sodium borohydride was added to the reaction mixture. Results similar to the obtained by the preceding method were obtained (Scheme 6).



Scheme 6. Sequential one pot hydrotelluration/reduction of alkynone **3a** to the allylic alcohol **4a**.

As an extension of the studies reported above, the hydrotelluration of ethyl propiolate was performed using the lithium butyltellurolate/ethanol method.[8] The vinylic telluride **10** of the *Z* configuration was formed as the only product in 88% yield (Scheme 7), which was then reduced with DIBAL-H in THF at −20 °C leading to the alcohol **4g** in 70% yield as the only product. It is worth mentioning that the preparation of alcohol **4g** by hydrotelluration of propargyl alcohol gives a mixture of regioisomers **4** and **5** (Scheme 1).[5]



Scheme 7. Chemoselective reduction of the ester **10** to the alcohol **4g**.

3. Conclusions

In conclusion, the chemoselective reduction of β-butyltellanyl enones constitutes a good method to prepare allylic alcohols containing a butyltellanyl group at the γ-position to the hydroxyl function. Cerium trichloride is a dispensable additive in the chemoselective reduction of β-butyltellanyl enones to the corresponding allylic alcohols.

4. Experimental

4.1. Materials

All reagents and solvents used were previously purified and dried in agreement with the literature.[13] THF was distilled from sodium/benzophenone under nitrogen immediately before use. *n*-Butyllithium was titrated using 1,10-phenanthroline as indicator prior to use.[14] Nitrogen gas used in the reactions was deoxygenated and dried. All operations were carried out in flame-dried glassware. Column chromatography separations were performed with Vetec silicagel 60 (0.063–0.200 mm, 70–230 mesh) or Acros Organics silicagel (0.035–0.075 mm, pore diameter ca. 6 nm). Tellurium metal of 200 mesh was dried overnight in an over at 100 °C, sodium borohydride, cerium trichloride heptahydrate and DIBAL-H (1 mol L^{-1} in hexanes) were purchased from Aldrich Chemical Co. The following reagents were pepared according to literature procedures: (**7e**), 4-oxopent-2-en-2-yl 4-methylbenzenesulfonate [435294-87-4];[4e] (**7f**), 5,5-dimethyl-3-oxocyclohex-1-enyl 4-methylbenzenesulfonate [77708-65-7];[4c,e] (**6e**), (*Z*)-4-(*n*-butyltellanyl)pent-3-en-one [251991-67-9];[4c,e] (**6f**), 3-(*n*-butyltellanyl)-5,5-dimethylcycloex-2-enone [849595-89-7];[4c,e] (**10**), (*Z*)-ethyl 3-butyltellanyl)acrylate [185841-09-2];[15] (**4g**), (*Z*)-3-(butyltellanyl)prop-2-1-ol [185841-11-6].[15] These last compounds presented analytical data, which agree with the proposed structures. The remaining chemicals were obtained from commercial sources.

4.2. Analysis

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-200 (200 MHz, ^{1}H; 50 MHz, ^{13}C) or DRX-500 (500 MHz, ^{1}H; 125 MHz, ^{13}C) or on a Varian INOVA 300 (300 MHz, ^{1}H; 75 MHz, ^{13}C) Spectrometers. All spectra were taken in $CDCl_3$ and the chemical shifts are given in ppm with respect to tetramethylsilane (TMS) used as internal standard. ^{125}Te NMR spectra were obtained on a Bruker DRX-500 (157 MHz, ^{125}Te) spectrometer using $CDCl_3$ as solvent. The chemical shifts refer to diphenyl ditelluride $(PhTe)_2$ in $CDCl_3$ (1 mol L^{-1}) ($\delta = 420$ ppm at 25 °C) as external standard. Low resolution mass spectra were obtained on a Shimadzu CG-17A/CG/MS-QP5050A instrument. Near IR spectra were obtained on a Bomen MB-100 spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Institute of Chemistry, Universidade de São Paulo. The IUPAC names were obtained using the software ChemDraw, version 8.0.

4.3. Typical procedures

4.3.1. Preparation of alkynones 3a–c.[16] To a 100 mL two-necked round-bottomed flask equipped with magnetic stirring under nitrogen atmosphere at −70 °C were added the terminal alkyne (10 mmol) and THF (50 mL). To the solution was slowly added *n*-butyllithium (1 equiv, 1.24 mol L^{-1} solution in hexanes). The solution was warmed up to 0 °C, stirred at this temperature for 30 min and then cooled at −70 °C prior to the addition of a solution of $ZnCl_2$ (1 equiv, 1 mol L^{-1} solution in THF). The solution was warmed and stirred at room temperature for additional 15 min and then recooled at −70 °C. Benzoyl or acetyl chloride was added in one portion. The reaction mixture was warmed to room temperature and stirred for additional 40 min, then diluted with hexane (10 mL) and washed with brine (3×10 mL). The organic phase was dried over magnesium sulphate and filtered. The solvents were evaporated and the residue purified by silica gel column chromatography eluting with hexane/ethyl ether 70:1 yielding 1.83 g (89%) of (**3a**), 1,3-diphenylprop-2-yn-1-one [7338-94-5]; (**3b**), 4-phenylbut-3-yn-2-one [1817-57-8]; (**3c**), oct-3-yn-2-one [1119-58-0].

4.3.2. Preparation of alkenones 6e–f.[4c,e] To a suspension of elemental tellurium (1.9 g, 15 mmol) in THF (30 mL) under nitrogen at 0 °C was slowly added *n*-butyllithium (from a 1.4 mol L^{-1} in hexanes, 10.5 mL, 15 mmol). A clear yellow solution was formed. Then the appropriated enol sulfonate (**7e** or **7f**) was added (13 mmol) and the mixture was stirred at 0 °C until the consumption of the enol (the reaction was monitored by TLC). After this, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with brine (3×50 mL). The organic phase was dried with magnesium sulfate and the solvents were evaporated. The residue was purified by silica gel chromatography eluting with hexane/ethyl acetate 19:1. All spectral data agree with those of the literate.

4.3.3. Preparation of the β-butyltellanyl enone (6d). A 500 mL, septum capped, round-bottomed flask, equipped with a magnetic stir bar and purged under N_2 was charged 200 mL of dry THF. The apparatus was cooled at 0 °C, and the solution saturated with acetylene by means of a 10-mm needle approximately 30 cm in length inserted through the septum of the flask. *n*-Butyllithium (50 mmol, 38 mL of a 1.31 mol L^{-1} solution in hexanes) was introduced dropwise into the reaction flask over a period of 20 min by means of a syringe. The inlet end of the needle was pushed below the surface of the liquid to avoid contact of the organolithium with the acetylene atmosphere and formation of dilithium carbide on the needle tip. The contents were resaturated with acetylene, and zinc chloride (50 mmol, 50 mL of a 1.00 mol L^{-1} solution in THF) was introduced dropwise via syringe. The solution was warmed to ambient temperature, and stirred for 30 min then recooled to 0 °C. A solution of acetyl chloride (50 mmol, 3.55 mL in 10 mL of THF) was introduced dropwise via syringe. The resulting solution was stirred for additional 30 min at 0 °C and then warmed to room temperature. To a second 1 L-flask containing a suspension of elemental tellurium (52 mmol, 6.63 g) in THF (150 mL) at 0 °C *n*-butyllithium (52 mmol, 39.5 mL of a 1.31 mol L^{-1}) was added. A clear yellow solution was formed. To this solution was added deoxygenated water (10 mL). The resulting red solution was stirred for 10 min at room temperature. The in situ above prepared alkynone was

transferred via cannula to the second flask containing the hydrotellurating system. The progress of the reaction was monitored by TLC. After 5 min the reaction mixture was diluted with hexane (200 mL) and the organic phase was washed with brine (3×100 mL) and then dried with magnesium sulphate. The solvents were evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 20:1 to give 3.1 g (62%) of the pure telluride *(Z)-4-(butyltellanyl)but-3-en-2-one* (**6d**): (Found: C, 38.03; H, 5.38. $C_8H_{14}OTe$ requires C, 37.86; H, 5.38%); ν_{max} (film) 2957, 2922, 2730, 2376, 2064, 1852, 1750, 1644, 1506, 1360, 1334, 1189, 973, 709, 669. δ_H (200 MHz, $CDCl_3$) 0.92 (t, J=7.5 Hz, 3H); 1.40 (sext., J=7.5 Hz, 2H); 1.80 (quint., J=7.0 Hz, 2H); 2.24 (s, 3H); 2.51 (t, J=7.5 Hz, 2H); 7.53 (d, J=9.2 Hz, 1H); 8.78 (d, J=9.2 Hz, 1H); δ_C (50 MHz, $CDCl_3$) 197.1; 139.8; 129.5; 33.7; 29.9; 24.9; 13.3; 10.5; δ_{Te} (157.79 MHz/300 K/Ph_2Te_2) 606.7; (*m/z* (EI, 70 kV) 256 (8, M^++3); 254 (8, M^++1); 252 (5); 251 (2); 200 (2); 199 (46); 196 (45); 195 (25); 193 (10); 192 (7); 190 (3); 57 (10); 55 (11); 43 (100).

4.3.4. Hydrotelluration of 3a–c by the [BuTeLi/EtOH] method. To a suspension of elemental tellurium (0.96 g, 7.5 mmol) in THF (15 mL) under nitrogen at 0 °C was slowly added *n*-butyllithium (7 mmol, 5.25 mL of a 1.4 mol L^{-1} solution in hexanes). A clear yellow solution was formed. After 5 min the alkynone (**3a**, **3b** or **3c**) was added in deoxygenated ethanol (2 mL). After 30 min the reaction mixture was diluted with hexane (30 mL) and washed with water (2×10 mL) then with brine (2×10 mL), the phases were separated and the organic phase was dried with magnesium sulphate. The solvents were evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 20:1.

(Z)-3-(Butyltellanyl)-1,3-diphenylprop-2-en-1-one (**6a**) (92%)

(Found: C, 58.39; H, 5.21. $C_{19}H_{20}OTe$ requires C, 58.16; H, 5.10%); ν_{max} (film) 2957, 2864, 2864, 1958, 1899, 1813, 1615, 1573, 1513, 1480, 1337, 1238, 1045. δ_H (300 MHz, $CDCl_3$) 0.75 (t, J=7.5 Hz, 3H); 1.17 (sext., J=7.5 Hz, 2H); 1.47 (quint., J=7.8 Hz, 2H); 2.1 (t, J=7.2 Hz, 2H); 7.29–7.60 (m, 8H); 8.02 (s, 1H); 8.04–8.10 (2H); δ_C (75 MHz, $CDCl_3$) 188.1; 160.4; 142.8; 138.1; 132.3; 128.6; 128.1; 127.9; 127.3; 126.4; 32.9; 25.1; 13.2; 10.5; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 686.0; *m/z* (EI, 70 kV) 390 (1); 337 (31); 333 (17); 207 (17); 205 (10); 180 (10); 105 (10); 77 (100); 51 (22).

(Z)-4-(Butyltellanyl)-4-phenylbut-3-en-2-one (**6b**) (62%)

(Found: C, 51.13; H, 5.35. $C_{14}H_{18}OTe$ requires C, 50.97; H, 5.50%); ν_{max} (film) 3058, 2957, 2923, 1614, 1575, 1518, 1238, 1059, 774, 699. δ_H (200 MHz, $CDCl_3$) 0.70 (t, J=7.5 Hz, 3H); 1.10 (sext., J=7.0 Hz, 2H); 1.38 (quint., J=7.5 Hz, 2H); 2.00 (t, J=7.5 Hz, 2H); 2.27 (s, 3H); 7.18–7.42 (m, 5H); δ_C (75 MHz, $CDCl_3$) 196.1; 156.3; 142.2; 130.0; 128.0; 127.9; 127.3; 33.0; 30.1; 25.0; 13.2; 9.8; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 578.0; *m/z* (EI, 70 kV) 275 (100); 145 (20); 105 (70); 77 (85).

(Z)-4-(Butyltellanyl)oct-3-en-2-one (**6c**) (79%)

(Found: C, 46.61; H, 7.09. $C_{12}H_{22}OTe$: C, 46.51; H, 7.16%); ν_{max} (film) 2928, 2867, 1644, 1523, 1461, 1359, 1333, 1249, 1207, 992. δ_H (500 MHz, $CDCl_3$) 0.91 (t, J=7.3 Hz, 3H); 0.92 (t, J=7.3 Hz, 3H); 1.36–1.42 (m, 4H); 1.50–1.54 (m, 2H); 1.60–1.69 (m, 2H); 2.16 (s, 3H), 2.53 (t, J=7.7 Hz, 2H); 2.61 (t, J=7.6 Hz, 2H); 7.16 (s, 1H); δ_C (50 MHz, $CDCl_3$) 196.2; 159.1; 127.5; 39.4; 33.4; 32.9; 29.8; 25.3; 22.1; 13.8; 13.4; 5.9; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 451.4; *m/z* (EI, 70 kV) 312 (M^++2, 2); 310 (M^++1, 25); 255 (100); 254 (10); 253 (91); 251 (53); 250 (21); 249 (13); 211 (8); 95 (21).

4.3.5. Sequential hydrotelluration/reduction procedure of 3a to 4a by the Bu_2Te_2/$NaBH_4$ method. To a solution of dibutyl ditelluride (5 mmol, 1.85 g) in ethanol (7 mL) was added sodium borohydride (5.2 mmol, 0.19 g) at room temperature. A solution of ketone **3a** (5 mmol, 1.03 g) in ethanol (2 mL) was then added dropwise. After 30 min, the reaction mixture was cooled to 0 °C and an ethanolic solution of sodium borohydride (10 mmol, 0.34 g in 10 mL of ethanol) was added dropwise. Thirty minutes latter the reaction mixture was diluted with ethyl ether (100 mL) and washed with water (2×10 mL) and brine (10 mL). The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 5:1, yielding 1.37 g (70%) of **4a**.

4.3.6. Sequential hydrotelluration/reduction procedure of 3a to 4a by the [BuTeLi/EtOH] method. To a suspension of elemental tellurium (0.19 g, 1.5 mmol) in THF (5 mL) under nitrogen at 0 °C, was slowly added *n*-butyllithium (from a 1.4 mol L^{-1} solution in hexanes, 1.2 mL, 1.5 mmol). A clear yellow solution was formed. Then an ethanolic solution of alkynone **3a** was added (2 mL, 0.31 g, 1.5 mmol) and the mixture was stirred at room temperature for 30 min. After 30 min, the reaction mixture was cooled to 0 °C and an ethanolic solution of sodium borohydride (10 mmol, 0.34 g in 10 mL of ethanol) was added dropwise. Thirty minutes latter the reaction mixture was diluted with ethyl ether (100 mL) and washed with water (2×10 mL) and brine (10 mL). The organic phase was dried with magnesium sulphate and the solvents were evaporated. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate 5:1, yielding 0.42 g (70%) of **4a**.

4.3.7. General procedure for reduction of enones to the corresponding allylic alcohol by $NaBH_4$. To a solution of the appropriate enone (1 mmol) in methanol (5 mL) at 0 °C, a solution of $NaBH_4$ in ethanol was added by means of a dropping funnel (usually 2 equiv was needed; 2 mL from a 1 mol L^{-1}, 2 mmol, 2 equiv). The reaction was monitored by thin layer chromatography. After total consumption of the starting material, the reaction mixture was diluted with a mixture of hexane/diethyl ether (1:1, 15 mL) and washed with water (3×10 mL) and brine (2×10 mL). The solvents were evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 5:1.

(Z)-3-(Butyltellanyl)-1,3-diphenylprop-2-en-1-ol (**4a**) (92%)

(Found: C, 58.02; H, 5.71. $C_{19}H_{20}OTe$ requires C, 57.92; H, 5.59%); ν_{max} (film) 3361, 3057, 2957, 2926, 1949, 1882, 1806, 1755, 1677, 1599, 1488, 1447, 1013, 759. δ_H (200 MHz, $CDCl_3$) 0.74 (t, $J=7.0$ Hz, 3H); 1.20 (sext., $J=7.0$ Hz, 2H); 1.52 (quint., $J=7.5$ Hz, 2H); 2.02 (sl, 1H); 1.30–1.36 (m, 2H); 5.61 (d, $J=7.5$ Hz, 1H), 6.16 (d, $J=7.9$ Hz, 1H); 7.22–7.48 (m, 10H); 7.16 (s, 1H); δ_C (50 MHz, $CDCl_3$) 143.0; 142.9; 140.8; 128.8; 128.6; 128.1; 127.6; 127.5; 126.3; 124.3; 77.6; 33.8; 24.8; 13.2; 8.3; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 361.7.

(Z)-4-(Butyltellanyl)-4-phenylbut-3-en-2-ol (**4b**) (95%)

(Found: C, 51.09; H, 6.16. $C_{14}H_{22}OTe$ requires C, 50.75; H, 6.04%); ν_{max} (film) 3326, 3019, 2866, 1947, 1883, 1805, 1754, 1676, 1598, 1445, 1247, 1136, 1089, 1059, 759, 698. δ_H (200 MHz, $CDCl_3$) 0.74 (t, $J=7.0$ Hz, 3H); 1.07–1.30 (m, 2H); 1.34 (d, $J=6.6$ Hz, 3H); 1.50 (quint., $J=7.9$ Hz, 2H); 2.30 (ta, $J=9.2$ Hz, 2H); 4.65 (quint., $J=6.6$ Hz, 1H), 5.96 (d, $J=7.5$ Hz, 1H); 7.10–7.50 (m, 5H); δ_C (50 MHz, $CDCl_3$) 142.9; 142.7; 128.6; 128.0; 127.3; 121.9; 71.5; 33.7; 24.7; 23.0; 13.1; 7.8; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 355.3; *m/z* (EI, 70 kV) 334 ($M^+ +3$, 24); 332 ($M^+ +2$, 23); 330 (13); 277 (14); 275 (14); 147 (45); 145 (16); 131 (19); 130 (17); 129 (64); 128 (34); 127 (12); 103 (100); 102 (29); 77 (45); 76 (11); 69 (45); 57 (51); 55 (18); 51 (15).

(Z)-4-(Butyltellanyl)oct-3-en-2-ol (**4c**)[17] (70%)

ν_{max} (film) 3339, 2959, 2926, 2866, 1618, 1459, 1370, 1057, 865. δ_H (200 MHz, $CDCl_3$) 0.92 (ta, $J=7.0$ Hz, 6H); 1.20–1.50 (m, 8H); 1.65–1.80 (m, 2H); 2.01 (sl, 1H); 2.32 (ta, $J=7.9$ Hz, 2H); 2.68 (td, $J=7.9$, 2.2 Hz, 2H), 4.56 (quint. a, $J=6.2$ Hz, 1H); 5.70 (d, $J=7.9$ Hz, 1H); δ_C (50 MHz, $CDCl_3$) 140.5; 121.4; 71.7; 41.5; 34.2; 32.0; 31.9; 25.0; 23.0; 21.8; 13.9; 13.3; 5.2; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 265.6; *m/z* (EI, 70 kV) 314 (25); 312 (24); 311 (2); 310 (15); 257 (39); 255 (40); 253 (26); 188 (4); 127 (42); 126 (92); 111 (11); 110 (21); 109 (45); 98 (4); 97 (54); 93 (12); 84 (11); 83 (23); 81 (50); 79 (21); 71 (58); 69 (35); 68 (47); 67 (80); 65 (11); 57 (94); 55 (100).

(Z)-4-(Butyltellanyl)but-3-en-2-ol (**4d**) (93%)

(Found: C, 37.16; H, 5.80. $C_8H_{16}OTe$ requires C, 37.54; H, 6.20%); ν_{max} (film) 3349, 2960, 2925, 2868, 1597, 1457, 1282, 1108, 1046, 706. δ_H (300 MHz, $CDCl_3$) 0.92 (t, $J=7.2$ Hz, 3H); 1.27 (d, $J=6.3$ Hz, 3H); 1.39 (sext., $J=7.8$ Hz, 2H); 1.78 (q, $J=7.8$ Hz, 2H); 1.94 (sl, 1H); 2.65 (td, $J=7.5$ Hz, 2H), 4.34 (quint. a, $J=6.3$ Hz, 1H); 6.28 (dd, $J=6.6$, 9.9 Hz, 1H); 6.70 (dd, $J=1.2$, 9.9 Hz, 1H); δ_C (50 MHz, $CDCl_3$) 141.8; 103.4; 70.5; 34.0; 24.9; 22.4; 13.3; 7.2; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 280.9; *m/z* (EI, 70 kV) 258 (13); 256 (12); 201 (15); 199 (15); 71 (100); 57 (60); 55 (40); 53 (35); 45 (22); 43 (81); 41 (55).

(Z)-4-(Butyltellanyl)pent-3-en-2-ol (**4e**) (70%)

(Found: C, 40.00; H, 6.30. $C_9H_{18}OTe$ requires C, 40.06; H, 6.67%); ν_{max} (film) 3350, 2959, 2933, 2348, 1443, 1264, 1109, 1058, 939. δ_H (300 MHz, $CDCl_3$) 0.92 (t, $J=7.5$ Hz, 3H); 1.26 (d, $J=6.3$ Hz, 3H); 1.39 (sext, $J=7.5$ Hz, 2H); 1.75 (quint a, $J=7.2$ Hz, 2H); 2.26 (d, $J=1.8$ Hz, 3H); 2.67–2.80 (m, 2H), 4.45 (q, $J=6.3$ Hz, 1H); 1.80–1.82 (dq, $J=7.8$, 1.2 Hz, 1H); δ_C (50 MHz, $CDCl_3$) 140.2; 114.4; 71.4; 34.4; 29.1; 25.0; 22.9; 13.4; 4.8; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 326.5; *m/z* (EI, 70 kV) 272 (5); 270 (5); 268 (2); 215 (9); 213 (11); 85 (36); 69 (19); 67 (58); 57 (43); 55 (14); 45 (35); 43 (100).

3-(Butyltellanyl)-5,5-dimethylcyclohex-2-enol (**4f**) (96%)

(Found: C, 46.30; H, 6.97. $C_{12}H_{22}OTe$ requires C, 46.60; H, 7.11%); ν_{max} (film) 3340, 2952, 2924, 1618, 1461, 1161, 1098, 1038, 1001, 940, 803. δ_H (500 MHz, $CDCl_3$) 0.92 (t, $J=7.4$ Hz, 3H); 0.94 (s, 3H); 0.99 (s, 3H); 1.06 (sl, 1H); 1.31 (dd, $J=12.5$, 3.2 Hz, 1H); 1.39 (sext., $J=7.4$ Hz, 2H), 1.77 (quint. a, $J=7.6$ Hz, 2H); 1.80–1.82 (m, 1H); 2.05 (dd, $J=17.4$, 1.3 Hz, 1H); 2.19 (dt, $J=17.4$, 2.6 Hz, 1H); 2.72–2.78 (m, 2H); 4.28 (m, 1H); 6.14 (s, 1H); δ_C (125 MHz, $CDCl_3$) 137.6; 113.9; 67.9; 49.2; 44.7; 33.9; 32.9; 31.5; 30.9; 25.9; 2.1; 24.7; 13.7; 13.4; 5.8; δ_{Te} (157.79 MHz/295.3 K/Ph_2Te_2) 452.8; *m/z* (EI, 70 kV) 312 (7); 310 (7); 308 (4); 125 (94); 107 (36); 91 (29); 83 (12); 81 (15); 79 (27); 69 (43); 67 (12); 57 (56); 55 (52); 43 (100).

4.3.8. General procedure for reduction of the enones to the corresponding allylic alcohol by $NaBH_4 \cdot CeCl_3$. To a solution of cerium trichloride heptahydrate (1 mmol, 0.372 g) in methanol was added the appropriated enone (1 mmol) at 0 °C. To the resulting mixture, a solution of $NaBH_4$ in ethanol was added by means of a dropping funnel (usually 2 equiv was needed; 2 mL from a 1 mol L^{-1}, 2 mmol, 2 equiv). The reaction was monitored by TLC. After total consumption of the starting material, the reaction mixture was diluted with a mixture of hexane/diethyl ether (1:1, 15 mL) and washed with water (3×10 mL) and brine (2×10 mL). The solvents were evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 5:1. (*Z*)-(Butyltellanyl)-1,3-diphenylprop-2-en-1-ol (**4a**), 92%. (*Z*)-4-(Butyltellanyl)-4-phenylbut-3-en-2-ol (**4b**), 98%. (*Z*)-4-(Butyltellanyl)oct-3-en-2-ol (**4c**), 84%. (*Z*)-4-(Butyltellanyl)but-3-en-2-ol (**4d**), 80%. 3-(Butyltellanyl)-5,5-dimethylcyclohex-2-enol (**4f**), 60%. (*Z*)-4-(Butyltellanyl)pent-3-en-2-ol (**4e**), 86%. The spectral data are identical to those described in Section 4.3.7 for the same compounds.

4.3.9. General procedure for reduction of the enones to the corresponding allylic alcohol by DIBAL-H. To a solution of the appropriate enone (1 mmol) in dry THF (5 mL) at −20 °C, was slowly added a solution of DIBAL-H (1.1 equiv from a 1 mol L^{-1} in hexane). The reaction was monitored by TLC. After total consumption of the starting material, to the cooled solution was added 0.5 mL of methanol, 0.5 mL of water, 0.7 g of magnesium sulphate and 0.7 g of Celite®. The reaction mixture was stirred at 0 °C for additional 30 min. The solid was separated by filtration and the solid residue washed with ethyl acetate. The organic layer was washed with brine (2×5 mL) and dried with magnesium sulphate. The solvents were evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 5:1. (*Z*)-(Butyltellanyl)-1,3-diphenylprop-2-en-1-ol (**4a**), 68%. (*Z*)-4-(butyltellanyl)-4-phenylbut-3-en-2-ol (**4b**), 84%. (*Z*)-4-(butyltellanyl)oct-3-en-2-ol (**4c**), 76%.

(*Z*)-4-(Butyltellanyl)but-3-en-2-ol (**4d**), 76%. 3-(butyltellanyl)-5,5-dimethylcyclohex-2-enol (**4f**), 70%. (*Z*)-4-(Butyltellanyl)pent-3-en-2-ol (**4e**), 78%. The spectral data are identical to those described in Section 4.3.7 for the same compounds.

4.3.10. Reduction of (*Z*)-ethyl 3-(butyltellanyl)acrylate (10) to (*Z*)-3-(butyltellanyl)prop-2-en-1-ol with DIBAL-H. To a solution of ester **10** (1 mmol, 0.283 g) in dry THF (5 mL) at −20 °C, was slowly added a solution of DIBAL-H (2 mmol, 2 mL, 1 mol L^{-1} solution in hexane). The reaction was monitored by TLC. After total consumption of the starting material, to the cooled solution was added 0.5 mL of methanol, 0.5 mL of water, 0.7 g of magnesium sulphate and 0.7 g of Celite®. The reaction mixture was stirred at 0 °C for additional 30 min. The solid was separated by filtration and washed with ethyl acetate. The organic layer was washed with brine (2×5 mL) and dried with magnesium sulphate. The solvents were evaporated and the residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate 5:1, affording 0.169 g (70%).

4.3.11. Derivatization of the allylic alcohol 3e with chlorotrimethylsilane. To a 2.5 mL round-bottomed flask, was added imidazol (0.25 mmol, 17 mg) in dichloromethane (1 mL). The resulting solution was cooled to 0 °C, and then chlorotrimethylsilane (0.25 mmol, 0.03 mL) was slowly added. The resulting mixture was stirred for 10 min and the alcohol (**4e**) (0.03 mmol, 10 mg) was introduced via syringe. The mixture was diluted in hexane and analyzed by gas chromatography.

4.3.12. Derivatization of alcohol 4c to the corresponding acetate 4c′. To a solution of **4c** (0.560 g, 1.8 mmol) in pyridine (3 mL) under nitrogen at room temperature, was added acetic anhydride (0.36 g, 0.34 mL, 3.6 mmol, 2 equiv). The resulting solution was warmed at 45 °C for 2 h and then cooled to room temperature, diluted with hexane (10 mL) and washed with a 10% solution of cooper sulfate (5×5 mL). The organic phase was dried with magnesium suphate and the solvents were evaporated. The residue was purified by silica gel column chromatography eluting with hexane/ethyl acetate 19:1, yielding 0.54 g (85%) of (*Z*)-4-(butyltellanyl)oct-3-en-2-yl acetate (**4c′**) as a clear yellow oil. (Found: C, 47.71; H, 6.90. $C_{14}H_{26}O_2Te$ requires C, 47.51; H, 7.35%); ν_{max} (film) 2958, 2928, 2871, 1739, 1460, 1370, 1239, 1044. δ_H (200 MHz, $CDCl_3$) 0.90 (t, J=7.2 Hz, 6H); 1.28 (d, J=6.6 Hz, 3H); 1.32–1.8 (m, 10); 2.02 (s, 3H); 2.33 (t, J=7.0 Hz, 2H); 2.68 (t, 7.5 Hz, 2H); 5.55 (quint., J=6.2 Hz, 1H), 5.68 (d., J=7.9 Hz, 1H); δ_C (50 MHz, $CDCl_3$) 170.1; 136.3; 123.6; 75.2; 41.5; 34.11; 31.8; 25.0; 21.8; 21.1; 20.5; 13.9; 13.3; 5.3.

Acknowledgements

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17. Compound **4c** was very unstable under GC and GS–MS analysis conditions. No acceptable elemental analysis was obtained for this compound. In this way it was converted into the corresponding acetate **4c′**, which presented ^1H NMR, ^{13}C NMR, elemental analysis and IR in agreement with the proposed structure.

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Bu_3SnH-mediated 5-exo selective radical cyclization of *N*-vinyl-α,β-unsaturated amides leading to γ-lactams

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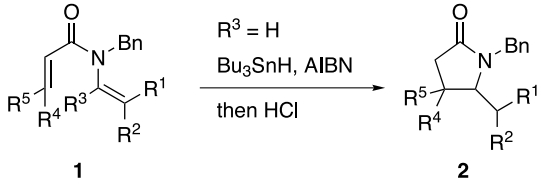
Abstract—Treatment of *N*-vinyl-α,β-unsaturated amides **1a–h** with Bu_3SnH and a catalytic amount of AIBN in boiling benzene caused 5-exo cyclization of allylic *O*-stannyl ketyl radicals generated by addition of $Bu_3Sn\cdot$ on the amide-oxygen atoms to provide γ-lactams **2a–h** after acidic workup. When enamide **1d** was treated with Bu_3SnH in the presence of AIBN followed by aldehydes **3a–d**, sequential radical cyclization and aldol reactions occurred to afford *anti*-adducts **4a–d** and *syn*-adducts **5a**,**b**.

1. Introduction

Bu_3SnH-mediated reductive radical cyclizations of ω-haloalkenes are widely used in organic synthesis.[1] However, one of the drawbacks of these radical cyclizations is the loss of halogen functionalities. From this point of view, cyclizations of allylic *O*-stannyl ketyl radicals [$Bu_3SnOC(R)=CH-CHR'$ radicals] generated from α,β-unsaturated ketones having activated olefin moieties under standard Bu_3SnH-mediated radical conditions appear to be attractive due to without the use of halogen atoms.[2–4] Recently, Leśniak et al. reported that treatment of *N*-(1-substituted ethenyl)cinnamamides **1** ($R^2=R^4=H$, $R^3=$ mainly Ph or RS, $R^5=Ph$) with Bu_3SnH and AIBN produced allylic *O*-stannyl ketyl radicals to give 6-endo radical cyclization products, δ-lactams.[5] We have now found that Bu_3SnH-mediated cyclization of enamides **1** ($R^3=H$) gave 5-exo radical cyclization products, γ-lactams **2**, via allylic *O*-stannyl ketyl radicals (Scheme 1).[6] The aldol reaction of intermediary tin(IV) enolates is also described.



Scheme 1.

2. Results and discussion

The starting enamides **1a–d** and **1f–h** (for structures of enamides **1**, see Tables 1 and 2) were readily prepared by direct acylation of imines derived from aldehydes and benzylamine with acyl chlorides in the presence of Et_3N (Scheme 2). Enamide **1e** having non-substituted *N*-vinyl group was synthesized from crotonic acid by three step; condensation with *N*-benzyl-*N*-(2-phenylthioethyl)amine, oxidation of phenylthio group to phenylsulfinyl group and β-elimination of the phenylsulfinyl group.

Our investigation on radical cyclization of **1** began with reaction of enamide **1a–d** bearing 2,2-diphenylethenyl group known as a good radical acceptor (Table 1).[7] Treatment of acrylamide **1a** with Bu_3SnH (2 equiv) in the presence of AIBN (0.2 equiv) in boiling benzene for 8 h gave γ-lactam **2a** in 10% yield after workup with 10% HCl (entry 1). Compound **1a** was not recovered and the 6-endo cyclization product was not detected. The formation of lactam **2a** may involve cyclization of allylic *O*-stannyl radical **A** (Scheme 3). $Bu_3Sn\cdot$ attacks the carbonyl oxygen atom of amide **1a** to generate radical **A**, which undergoes 5-exo cyclization to give radical **B** stabilized by two phenyl groups. Radical **B** is trapped with Bu_3SnH to give tin(IV) enolate **C**, whose hydrolysis by acidic workup affords γ-lactam **2a**. The radical reaction of **1a** might suffer from addition of $Bu_3Sn\cdot$ at the β-position of amide **1a**,[8] giving radical **D**, which is likely to cause side reactions.

Keywords: *N*-Vinyl-α,β-unsaturated amides; Radical cyclization; Allylic *O*-stannyl ketyl radical; Aldol reaction; Tin(IV) enolate.
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Table 1. Radical cyclization of *N*-(2,2-diphenylethenyl)amides

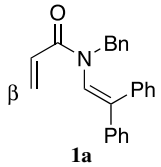
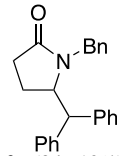
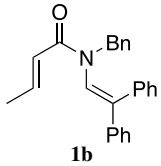
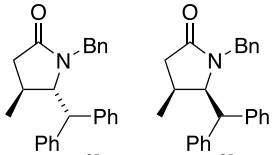
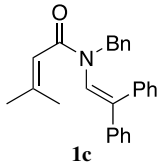
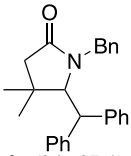
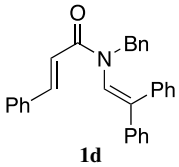
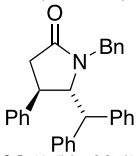
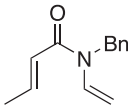
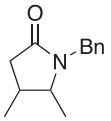
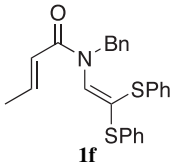
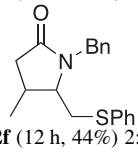
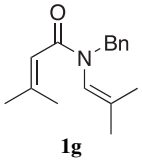
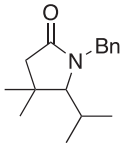
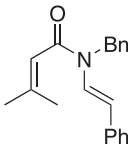
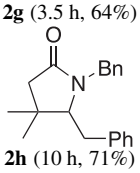
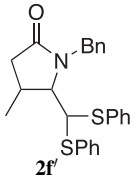
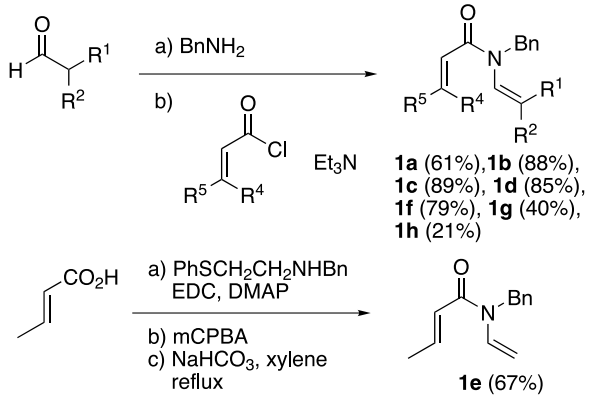
Entry	Enamide	Product (time, yield)
1	 **1a**	 **2a** (8 h, 10%)
2	 **1b**	 *trans*-**2b** *cis*-**2b** (7 h,91%; *trans*:*cis*=1.4:1)
3	 **1c**	 **2c** (9 h, 97%)
4	 **1d**	 **2d** (1.5 h, 93%)

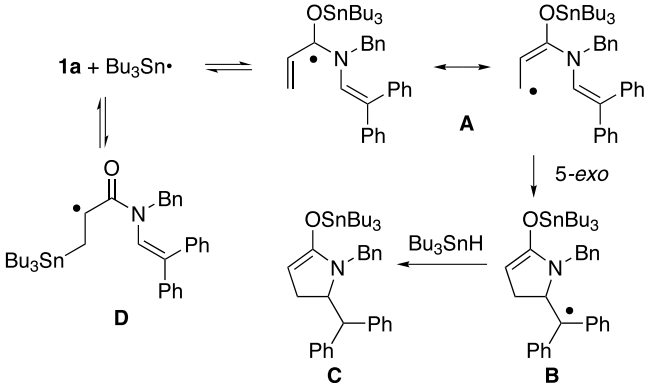
Table 2. Radical cyclization of varius *N*-vinylamides

Entry	Enamide	Product (time, yield)
1	 **1e**	 **2e** (8.5 h, 26%) 3:1
2	 **1f**	 **2f** (12 h, 44%) 2:1
3	 **1g**	 **2g** (3.5 h, 64%)
4	 **1h**	 **2h** (10 h, 71%)


2f′



Scheme 2.



Scheme 3.

Introduction of a substituent at the β-position of α,β-unsaturated amide **1** might prevent undesired β-addition of $Bu_3Sn\cdot$ due to steric reason and/or stabilize the allyic *O*-stannyl ketyl radical intermediate and result in improvement of the yield of cyclization product **2**. Indeed, reaction of crotonamide **1b** gave a mixture of cyclization products *trans*-**2b** and *cis*-**2b** in dramatically improved yield (91%) (entry 2). Under conditions similar to those for **1a** and **1b**, 3,3-dimethylacrylamide **1c** and cinnamoylamide **1d** afforded excellent yields of γ-lactams **2c** (97%) and **2d** (93%), respectively (entries 3 and 4).

The stereostructures of *trans*-**2b** and *cis*-**2b** were deduced by means of NOE and coupling constants in their ^{1}H NMR spectra (Fig. 1). Compound *trans*-**2b** exhibited an NOE between methyl group and C5–H and very a small coupling constant $J_{4,5}$ (~0 Hz) whereas *cis*-**2b** showed a relatively large coupling constant ($J_{4,5}$=6.6 Hz) (Fig. 1). The stereostructure of compound **2d** was also deduced to be trans on the basis of the small coupling constant ($J_{4,5}$= 1.0 Hz).

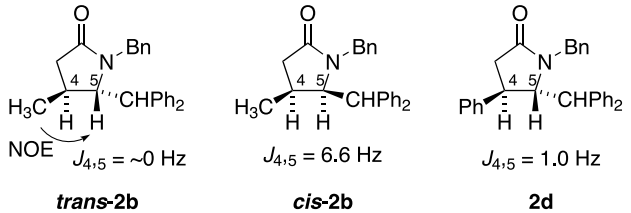
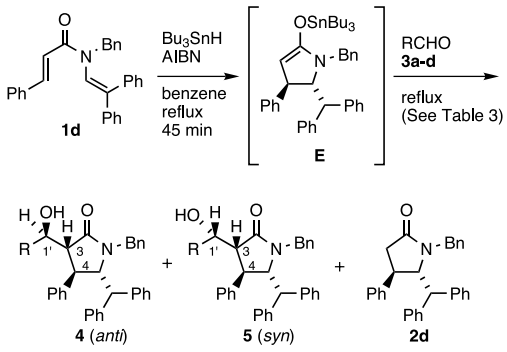


Figure 1.



Scheme 4.

aliphatic aldehydes **3c** and **3d** appear to have good selectivities (entries 3 and 4). Although aldol reaction of heptanal (**3c**) with enolate **E** took a long time, exclusive formation of adduct **4c** resulted in 45% yield along with **2d** (53%). The reaction with cyclohexylcarboaldehyde (**3d**) required the use of high boiling toluene as a solvent, and therefore, the radical cyclization of **1d** was performed in toluene in the presence of ACN having a long half-life period. These conditions gave adduct **4d** in 27% yield along with cyclization product **2d** (47%).

In principle, four stereoisomers are possible for the aldol reaction. C4-Phenyl group, however, effectively shields β-face, hence aldehydes **3a–d** may approach from α-face to

Table 3. Radical cyclization and aldol reaction of enamide **1d**

Entry	Aldehyde (R)	Reaction time (h)	Yield (%)		
			4	**5**	**2d**
1	**3a** (Ph)	12	42	33	
2	**3b** (PhCH=CH–)	10	54	15	20
3	**3c** (*n*-hexyl)	25	45		53
4[a]	**3d** (cyclohexyl)	24	27		47

[a] The reaction was carried out by using toluene and ACN (1,1′-azobis(cyclohexane-1-carbonitrile).

We next examined the effect of the substituent(s) at the terminus of *N*-vinyl-moieties of **1** (Table 2). In contrast to the reaction of amide **1b** (Table 1, entry 2), reaction of amide **1e** having a non-substituted *N*-vinyl group with Bu_3SnH (3 equiv) and AIBN (2.5 equiv) gave an inseparable 3:1 diastereomeric mixture of γ-lactams **2e** in only 26% yield (Table 2, entry 1). This result suggests that a radical stabilizing group at the terminus of the *N*-vinyl group would be required for efficient cyclization. Treatment of amide **1f** bearing an *N*-2,2-bis(phenylthio)ethenyl group with a large excess of Bu_3SnH (8 equiv) and AIBN afforded lactam **2f** as an inseparable mixture of diastereomers in a moderate yield (44%) probably via desulfurization of the initial cyclization product **2f′** (entry 2). Partial desulfurization of **2f′** giving **2f** may be explained by assuming that the radical intermediate formed by an attack of tin radical on the sulfur atom is highly stabilized by an adjacent phenylthio group. *N*-2,2-Dimethylethenyl and *N*-2-phenylethenyl groups also appear to be efficient as radical acceptors for the present cyclization. The reactions of amides **1g** and **1h** gave γ-lactams **2g** and **2h** in 64 and 71% yields, respectively (compare to Table 1, entry 3).

Enholm et al. reported aldol reaction of tin(IV) enolates generated from α,β-unsaturated ketones with Bu_3SnH.[9] Since tin(IV) enolates should be also generated in the present reactions, radical cyclization–aldol reaction sequence of **1d** was next examined (Scheme 4 and Table 3). Enamide **1d** was treated with Bu_3SnH and AIBN in refluxing benzene for 45 min to form tin(IV) enolate **E**, to which benzaldehyde (**3a**) was added. Further heating the resulting mixture caused aldol reaction of enolate **E** with aldehyde **3a** to afford *anti*-adduct **4a** and *syn*-adduct **5a** in 42 and 33% yields, respectively (entry 1). In a similar manner, reaction of *trans*-cinnamaldehyde (**3b**) gave adduct **4b** in 54% yield along with **5b** (15%) and simple cyclization product **2d** (20%) (entry 2). Compared to aromatic aldehyde **3a** or α,β-unsaturated aldehyde **3b**, give C3–C4 trans-adducts **4** and **5** (Fig. 2). The C3–C4 trans-relationship of **4b** was supported by an NOE as illustrated in Figure 2. Stereostructures of C3–C1′positions for adducts **3a–d** and **4a**,**b** were deducted on the basis of their ^1H NMR spectra. In general, the β-proton referred to the carbonyl group of an *anti*-aldol resonates in upper field and exhibits a larger *J*-value than does the corresponding *syn*-aldol.[10] In fact, H_B of *anti*-aldol **6a** related to **4a** shows the signal at δ 4.71 (J_{AB}=9.0 Hz), whereas H_B of *syn*-aldol **6b** does at δ 5.30 (J_{AB}=2.9 Hz) (Fig. 3).[11] The tendencies of NMR data for adducts **4a–d** and **5a**,**b** listed in Table 4

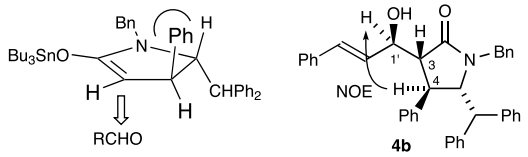


Figure 2.

Figure 3.

Table 4

	δ C1′–H	$J_{1'3}$ (Hz)
4a	4.17	9.2
5a	5.33	3.3
4b	3.79	8.5
5b	4.75	3.5
4c	4.30	8.6
4d	3.00	9.2

well accord with those for **6a** and **6b**. The predominant formation of the *anti* adducts **4** by the aldol reaction of **E** with aldehydes **3a–d** (RCHO) may be explained by considering the six-membered transition state in which R is equatorial.

3. Conclusion

We have explored 5-exo selective Bu_3SnH-mediated radical cyclization of *N*-vinyl α,β-unsaturated amides leading to γ-lactams. Sequential radical cyclization and aldol reaction of an intermediary tin(IV) enolate have been also demonstrated. Further studies on cascade-type cyclization[12] are in progress.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H and ^{13}C NMR spectra were measured on JEOL JNM-EX 270 and JEOL JNM-GSX 500 spectrometers. δ values quoted are relative to TMS (tetramethylsilane). High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX 102A instrument. All new compounds determined to be >95% pure by microanalyses or ^1H NMR spectra. Column chromatography was performed on Silica gel 60 PF_{254} under pressure. 2-(Phenylthio)ethylamine,[13] and bis(phenylthio)acetaldehyde[14] were prepared by reported methods.

4.1.1. *N*-Benzyl-*N*-(2,2-diphenylvinyl)acrylamide, 1a. A solution of diphenylacetaldehyde (366 μL, 2.00 mmol) and $BnNH_2$ (223 μL, 2.00 mmol) in benzene (7 mL) was heated at reflux for 1 h, and then the mixture was cooled to 0 °C. To the mixture were successively added a solution of Et_3N (509 μL, 3.60 mmol) in benzene (5 mL) and a solution of acryloyl chloride (255 μL, 3.00 mmol) in benzene (5 mL) at the same temperature, then the mixture was stirred at room temperature for 30 min. The mixture was washed with a saturated aqueous NH_4Cl, and the aqueous phase was further extracted with $CHCl_3$. The organic phases were combined, washed successively with a saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was chromatographed on silica gel with (hexane/AcOEt 15:1) to give **1a** (414 mg, 61%) as a colorless oil. IR ($CHCl_3$) 1655, 1610 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.51 (2H, s), 5.59 (1H, dd, J= 10.2, 2.0 Hz), 6.31 (1H, dd, J=16.8, 2.0 Hz), 6.48 (1H, s), 6.67 (1H, dd, J=16.8, 10.2 Hz), 7.07–7.39 (15H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 50.1, 125.6, 127.9, 128.7, 128.8, 128.9, 129.1, 129.2, 130.0, 137.7, 138.0, 140.6, 140.8, 166.5; HRMS calcd for $C_{24}H_{21}NO$ 339.1623, found 339.1620.

4.1.2. (2*E*)-*N*-Benzyl-*N*-(2,2-diphenylvinyl)but-2-enamide, 1b. Using a procedure similar to that for the preparation of **1a**, the crude material was obtained from diphenylacetaldehyde (732 μL, 4.00 mmol), $BnNH_2$ (446 μL, 4.00 mmol), Et_3N (1.02 mL, 7.20 mmol) and *trans*-crotonyl chloride (639 μL, 6.00 mmol). Chromatography on silica gel (hexane/AcOEt 20:1) gave **1b** (1.25 g, 88%) as a colorless oil. IR ($CHCl_3$) 1665, 1610 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.80 (3H, dd, J=6.9, 1.7 Hz), 4.48 (2H, s), 6.36 (1H, dd, J=15.2, 1.7 Hz), 6.49 (1H, s), 6.87 (1H, dq, J=15.2, 6.9 Hz), 7.08–7.40 (15H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.6, 49.8, 123.5, 126.1, 127.7, 128.6, 128.7, 128.8, 129.0, 130.0, 138.0, 138.3, 139.7, 141.0, 143.0, 166.9; HRMS calcd for $C_{25}H_{23}NO$ 353.1780, found 353.1777.

4.1.3. *N*-Benzyl-*N*-(2,2-diphenylvinyl)-3-methylbut-2-enamide, 1c. Using a procedure similar to that for the preparation of **1a**, the crude material was obtained from diphenylacetaldehyde (366 μL, 2.00 mmol), $BnNH_2$ (223 μL, 2.00 mmol), Et_3N (509 μL, 3.60 mmol) and 3,3-dimethylacryloyl chloride (344 μL, 3.00 mmol). Chromatography on silica gel (hexane/AcOEt 20:1) gave **1c** (651 mg, 89%) as a colorless oil. IR ($CHCl_3$) 1650, 1610 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.75 (3H, s), 1.91 (3H, s), 4.50 (2H, s), 5.99 (1H, s), 6.45 (1H, s), 7.05–7.37 (15H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 20.1, 27.1, 48.9, 118.1, 126.0, 127.2, 127.9, 128.2, 128.3, 128.4, 128.5, 129.5, 137.8, 138.1, 138.4, 140.8, 151.8, 167.3; HRMS calcd for $C_{26}H_{25}NO$ 367.1936, found 367.1937.

4.1.4. *N*-Benzyl-*N*-(2,2-diphenylvinyl)cinnamamide, 1d. Using a procedure similar to that for the preparation of **1a**, the crude material was obtained from diphenylacetaldehyde (366 μL, 2.00 mmol), $BnNH_2$ (223 μL, 2.00 mmol), Et_3N (509 μL, 3.60 mmol) and cinnamoyl chloride (526 mg, 3.00 mmol). Chromatography on silica gel (hexane/AcOEt 15:1) gave **1d** (705 mg, 85%) as yellow crystals: mp 93–95 °C (hexane). IR ($CHCl_3$) 1650, 1605 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.59 (2H, s), 6.58 (1H, s), 6.93 (1H, d, J=15.5 Hz), 7.08–7.45 (20H, m), 7.59 (1H, d, J=15.5 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 49.9, 118.6, 125.3, 127.4, 127.9, 128.2, 128.3, 128.4, 128.6, 128.7, 128.8, 129.5, 129.7, 135.1, 137.4, 137.7, 140.0, 140.4, 143.0, 166.3. Anal. Calcd for $C_{30}H_{25}NO$: C, 86.71; H, 6.06; N, 3.37. Found: C, 86.47; H, 6.09; N, 3.21.

4.1.5. (2*E*)-*N*-Benzyl-*N*-vinylbut-2-enamide, 1e. To a stirred solution of *trans*-crotonic acid (522 mg, 6.00 mmol) and *N*-benzyl-*N*-(phenylthio)ethylamine (1.53 g, 6.30 mmol) in CH_2Cl_2 (30 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.76 g, 9.00 mmol) and DMAP (147 mg, 1.20 mmol) at 0 °C and the mixture was further stirred at room temperature for 1 h. The mixture was washed with a saturated aqueous solution of NH_4Cl, and the aqueous phase was further extracted with $CHCl_3$. The organic phases were combined, washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give crude (2*E*)-*N*-benzyl-*N*-[2-(phenylthio)ethyl]but-2-enamide. This material was dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C. To this solution was added a solution of *m*CPBA (1.36 g, 6.30 mmol) in CH_2Cl_2 (100 mL) at the same temperature over 1 h and the resulting mixture was further stirred for 30 min. A 10% aqueous solution of $Na_2S_2O_3$ (20 mL) was added to the mixture and the resulting mixture was vigorously stirred for 30 min. The organic phase was separated, washed successively with a saturated aqueous

solution of $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give crude (2*E*)-*N*-benzyl-*N*-[2-(phenylsulfinyl)ethyl]but-2-enamide. A mixture of this crude sulfoxide and $NaHCO_3$ (1.01 g, 12.0 mmol) in xylene (150 mL) was heated at reflux for 18 h. After cooling, the mixture was filtered, and then the filtrate was washed successively with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was cromatographed on silica gel (hexane/AcOEt 10:1) to give **1e** (808 mg, 67%) as a colorless oil. IR ($CHCl_3$) 1665, 1620 cm^{-1}; The ^1H and ^{13}C NMR spectra of **1e** showed the presence of two rotamers; ^1H NMR (270 MHz, $CDCl_3$) δ 1.91 (3H, br), 4.27–4.47 (2H, br), 4.90 (2H, br s), 6.08–6.51 (1H, br), 6.88–7.10 (1H+1H×3/5, br), 7.10–7.40 (5H, m), 7.64 (1H×2/5H, br s); ^{13}C NMR (68 MHz, $CDCl_3$) δ: 15.5, 18.3, 36.3, 46.1, 48.3, 94.8, 65.7, 121.6, 122.2, 125.6, 126.8, 126.9, 128.5, 132.2, 132.8, 133.4, 136.4, 136.9, 137.9, 144.3, 144.5, 165.8; HRMS calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1156.

4.1.6. (2*E*)-*N*-Benzyl-*N*-[2,2-bis(phenylthio)vinyl]but-2-enamide, 1f. A solution of bis(phenylthio)acetaldehyde (521 mg, 2.00 mmol) and $BnNH_2$ (223 μL, 2.00 mmol) in benzene (12 mL) was heated at reflux for 1.5 h. To the mixture were added Et_3N (509 μL, 3.60 mmol) and a solution of *trans*-crotonyl chloride (319 μL, 3.00 mmol) in benezene (5 mL), then the mixture was further refluxed for 1.5 h. Since the reaction was not completed, additional Et_3N (509 μL, 3.60 mmol) and a solution of *trans*-crotonyl chloride (319 μL, 3.00 mmol) in benezene (5 mL), were added to the mixture, then the mixture was further refluxed for 1 h. Workup similar to that for the preparation of **1a** gave a crude material, which was chromatographed on silica gel (hexane/AcOEt 20:1→15:1→10:1) to give **1f** (622 mg, 79%) as colorless crystals: mp 73–74 °C (hexane). IR ($CHCl_3$) 1665, 1630 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.89 (3H, dd, J=6.9, 1.7 Hz), 4.88 (2H, s), 6.17 (1H, dd, J=15.2, 1.7 Hz), 6.81–7.33 (17H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.3, 49.9, 122.7, 127.5, 127.8, 128.5, 128.5, 128.8, 131.1, 132.0, 132.5, 133.7, 134.1, 137.0, 143.3, 166.1. Anal. Calcd for $C_{25}H_{23}NOS$: C, 71.91; H, 5.55; N, 3.35. Found: C, 71.88; H, 5.58; N, 3.36.

4.1.7. *N*-Benzyl-*N*-(2,2-dimethylvinyl)-3-methylbut-2-enamide, 1g. To a stirred mixture of $BnNH_2$ (223 μL, 2.00 mmol) and $MgSO_4$ (300 mg) in Et_2O (2 mL) was added isobutyraldehyde (335 μL, 3.69 mmol) at 0 °C, then the mixture was stirred at the same temperature for 1.5 h. The mixture was filtered, and filtrate was concentrated to give a residue, which was dissolved in benzene (3 mL). To the solution were added Et_3N (509 μL, 3.6 mmol) and 3,3-dimethylacryloyl chloride (344 μL, 3.00 mmol) at 0 °C and the mixture was stirred at the same temperature for 2 h. Workup similar to that for the preparation of **1a** gave a crude material, which was chromatographed on silica gel (hexane/AcOEt 20:1) to give **1g** (193 mg, 40%) as a colorless oil. IR ($CHCl_3$) 1650, 1615 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.36 (3H, d, J=1.3 Hz), 1.67 (3H, d, J=1.3 Hz), 1.81 (3H, d, J=1.0 Hz), 2.13 (3H, d, J=1.0 Hz), 4.62 (2H, s), 5.74 (1H, t, J=1.3 Hz), 5.85 (1H, t, J=1.3 Hz), 7.21–7.28 (5H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.5, 20.0, 21.9, 27.2, 50.1, 117.7, 123.3, 126.9, 128.1, 128.5, 135.3, 137.7, 150.0, 167.1; HRMS calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1629.

4.1.8. *N*-Benzyl-*N*-[(1*E*)-2-phenylvinyl]-3-methylbut-2-enamide, 1h. Using a procedure similar to that for the preparation of **1a**, the crude material was obtained from phenylacetaldehyde (248 μL, 2.00 mmol), $BnNH_2$ (223 μL, 2.00 mmol), Et_3N (509 μL, 3.60 mmol) and 3,3-dimethylacryloyl chloride (344 μL, 3.00 mmol). Chromatography on silica gel (hexane/AcOEt 20:1) gave **1h** (121 mg, 21%) as colorless crystals: mp 87.5–88.5 °C (hexane). IR ($CHCl_3$) 1660; 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.83–2.08 (6H, br), 4.98 (2H, br), 5.78–6.10 (2H, br), 7.16 (10H+1H×2/3, m), 8.23 (1H×1/3, br). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.08; H, 7.27; N, 4.81.

4.1.9. 5-Benzhydryl-1-benzylpyrrolidin-2-one, 2a: general procedure for radical reaction of enamides 1. A mixture of **1a** (136 mg, 0.400 mmol), Bu_3SnH (219 μL, 0.800 mmol) and AIBN (6.7 mg, 0.040 mmol) in benzene (4 mL) was heated at reflux for 5 h. Since the reaction was not completed, a solution of AIBN (6.7 mg, 0.040 mmol) in benzene (1 mL) was added, then the mixture was further refluxed for 3 h. After cooling the mixture was concentrated to give a residue, which was partitioned between 10% HCl and AcOEt, and the aqueous phase was extracted with AcOEt. The organic phases were combined, stirred vigorously with an 8% aqueous KF overnight. After filtration to remove precipitates, the organic phase was separated and the aqueous phase was further extracted with AcOEt. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude material was chromatographed on silica gel (hexane/AcOEt 4:1→3:1) to give **2a** (9.6 mg, 10%) as a colorless oil. IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.86–2.26 (4H, m), 3.28 (1H, d of a pair of ABq, J=15.2 Hz), 4.18–4.27 (2H, m), 5.06 (1H, d of a pair of ABq, J=15.2 Hz), 6.99–7.35 (15H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.1, 29.8, 45.2, 54.1, 60.0, 127.4, 127.5, 127.9, 128.3, 128.9, 129.0, 129.1, 129.2, 131.7, 141.6, 141.9, 176.2; HRMS calcd for $C_{24}H_{23}NO$ 341.1780, found 341.1781.

4.1.10. (4*R,5*R**)-5-Benzhydryl-1-benzyl-4-methylpyrrolidin-2-one, *trans*-2b and its (4*R**,5*S**)-isomer, *cis*-2b.** Following the general procedure, the crude material was obtained from **1b** (141 mg, 0.400 mmol), Bu_3SnH (219 μL, 0.800 mmol) and AIBN (6.7 mg, 0.040 mmol). Chromatography on silica gel (hexane/AcOEt 4:1) gave a 1.4:1 mixture of *trans*-**2b** and *cis*-**2b** (129 mg, 91%). Analytical samples of *trans*-**2b** and *cis*-**2b** were obtained by further chromatography on silica gel (hexane/AcOEt 6:1). *trans*-**2b**: IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, d, J=6.9 Hz), 1.80 (1H, d, J=15.8 Hz), 2.13–2.27 (2H, m), 2.95 (1H, d of a pair of ABq, J=14.8 Hz), 3.69 (1H, d, J=7.9 Hz), 4.11 (1H, d, J=7.9 Hz), 5.04 (1H, d of a pair of ABq, J=14.8 Hz), 7.01–7.37 (15H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 30.5, 37.5, 44.7, 54.5, 67.1, 126.9, 127.0, 127.4, 128.2, 128.4, 128.6, 128.7, 128.8, 136.5, 141.4, 141.6, 174.9; HRMS calcd for $C_{25}H_{25}NO$ 355.1936, found 355.1932. *cis*-**2b**: IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (3H, d, J=6.9 Hz), 2.09 (1H, dd, J=15.8, 10.2 Hz), 2.38 (1H, dd, J=15.8, 7.3 Hz), 2.42–2.56 (1H, m), 2.71 (1H, d of a pair of ABq, J=15.2 Hz), 4.14 (1H, d, J=8.3 Hz), 4.23 (1H, dd, J=8.3,

6.6 Hz), 4.78 (1H, d of a pair of ABq, J=15.2 Hz), 6.77–6.80 (2H, m), 7.17–7.33 (13H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4, 34.2, 38.0, 45.1, 51.4, 63.1, 126.5, 127.0, 127.1, 127.6, 128.1, 128.3, 128.6, 128.8, 129.4, 136.9, 140.9, 142.2, 175.5; HRMS calcd for $C_{25}H_{25}NO$ 355.1936, found 355.1938.

4.1.11. 5-Benzhydryl-1-benzyl-4,4-dimethylpyrrolidin-2-one, 2c. Following the general procedure, the crude material was obtained from **1c** (147 mg, 0.400 mmol), Bu_3SnH (219 μL, 0.800 mmol) and AIBN (6.7 mg, 0.040 mmol). Chromatography on silica gel (hexane/AcOEt 4:1) gave **2c** (144 mg, 97%) as colorless crystals: mp 84–86 °C (hexane). IR ($CHCl_3$) 1675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.76 (3H, s), 0.86 (3H, s), 1.90 (1H, d of a pair of ABq, J= 16.2 Hz), 2.24 (1H, d of a pair of ABq, J=16.2 Hz), 2.42 (1H, d of a pair of ABq, J=14.5 Hz), 3.68 (1H, d, J= 7.6 Hz), 4.21 (1H, d, J=7.6 Hz), 4.90 (1H, d of a pair of ABq, J=14.5 Hz), 6.88–6.92 (2H, m), 7.19–7.38 (13H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.1, 29.3, 38.2, 44.6, 45.2, 52.7, 69.2, 126.5, 127.1, 127.4, 128.2, 128.3, 128.6, 128.7, 129.1, 130.0, 136.2, 140.4, 142.4, 174.5; HRMS calcd for $C_{26}H_{27}NO$ 369.2093, found 369.2095.

4.1.12. (4*R,5*S**)-5-Benzhydryl-1-benzyl-4-phenylpyrrolidin-2-one, 2d.** Following the general procedure, the crude material was obtained from **1d** (166 mg, 0.400 mmol), Bu_3SnH (219 μL, 0.800 mmol) and AIBN (6.7 mg, 0.040 mmol). Chromatography on silica gel (hexane/AcOEt 5:1→4:1) gave **2d** (155 mg, 93%) as colorless crystals: mp 148–150 °C (AcOEt). IR ($CHCl_3$) 1675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.25 (1H, dd, J=17.5, 1.7 Hz), 2.48 (1H, dd, J=17.5, 8.6 Hz), 3.14 (1H, d of a pair of ABq, J=14.5 Hz), 3.23 (1H, d, J=8.9 Hz), 4.19 (1H, dd, J=7.3, 1.0 Hz), 4.29 (1H, d, J=7.5 Hz), 5.07 (1H, d of a pair of ABq, J=14.5 Hz), 6.74–6.77 (2H, m), 7.01–7.35 (18H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 37.7, 41.0, 45.2, 55.2, 67.7, 126.4, 126.7, 127.1, 127.5, 128.3, 128.6, 128.7, 128.8, 128.9, 136.0, 141.0, 144.3, 174.7. Anal. Calcd for $C_{30}H_{27}NO$: C, 86.30; H, 6.52; N, 3.35. Found: C, 86.32; H, 6.56; N, 3.39.

4.1.13. 1-Benzyl-4,5-dimethylpyrrolidin-2-one, 2e. Following the general procedure, the crude material was obtained from **1e** (80.5 mg, 0.400 mmol), Bu_3SnH (219 μL, 0.800 mmol) and AIBN (6.7 mg, 0.040 mmol). Chromatography on silica gel (hexane/AcOEt 20:1) gave **2e** (20.8 mg, 26%) as an inseparable ca. 3:1 mixture of diastereomers. IR ($CHCl_3$) 1670 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H×3/4, d, J=6.6 Hz), 1.02 (3H×3/4, d, J=6.9 Hz), 1.04 (3H×1/4, d, J=6.9 Hz), 1.15 (3H×1/4, d, J= 6.3 Hz), 1.92 (1H×1/4, br sep, J=7.6 Hz), 2.06 (1H×1/4, dd, J=16.5, 7.6 Hz), 2.14 (1H×3/4, ddd, J=15.0, 7.3, 1.0 Hz), 2.41 (1H×3/4, br sep, J=7.3 Hz), 2.50 (1H×3/4, dd, J=16.5, 8.3 Hz), 2.64 (1H×1/4, ddd, J=16.5, 8.3, 1.0 Hz), 3.03 (1H×1/4, qd, J=6.3, 5.9 Hz), 3.49 (1H×3/4, qd, J=6.9, 6.6 Hz), 3.93 (1H×3/4, d of a pair of ABq, J= 15.2 Hz), 3.96 (1H×1/4, d of a pair of ABq, J=15.2 Hz), 4.97 (1H×1/4, d of a pair of ABq, J=15.2 Hz), 4.99 (1H×3/4, d of a pair of ABq, J=15.2 Hz), 7.21–7.35 (5H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.0 (major), 14.7 (major), 18.2 (minor), 18.5 (minor), 31.0 (major), 35.0 (minor), 38.0 (major), 38.7 (minor), 43.9 (minor), 44.0 (major), 55.7 (major), 60.0 (minor), 127.3 (both isomers), 127.8 (major), 128.0 (minor), 128.6 (both isomers), 136.8 (minor), 137.0 (major), 174.3 (major), 174.4 (minor); HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1305.

4.1.14. 1-Benzyl-4-methyl-5-(phenylthiomethyl)pyrrolidin-2-one, 2f. Following the general procedure, the crude material was obtained from **1f** (167 mg, 0.400 mmol), Bu_3SnH (438 μL, 1.60 mmol) and AIBN (13.4 mg, 0.080 mmol). Chromatography on silica gel (hexane/AcOEt 5:1→4:1) gave **2f** (54.3 mg, 44%) as an inseparable ca. 2:1 mixture of diastereomers. IR ($CHCl_3$) 1675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H×2/3, d, J= 6.9 Hz), 1.11 (3H×1/3, d, J=6.6 Hz), 2.03 (1H×2/3, dd, J=17.0, 3.8 Hz), 2.27–2.37 (1H, m), 2.47–2.56 (2H×1/3, m), 2.77 (1H×2/3, dd, J=17.3, 8.9 Hz), 2.85 (1H×2/3, dd, J=13.9, 8.2 Hz), 2.99 (1H×1/3, dd, J=13.5, 7.6 Hz), 3.07–3.15 (2H×2/3+1H×1/3, m), 3.61 (1H×1/3, td, J= 7.3, 3.6 Hz), 3.81 (1H×1/3, d of a pair of ABq, J= 15.2 Hz), 3.83 (1H×2/3, d of a pair of ABq, J=15.2 Hz), 4.95 (1H×2/3, d of a pair of ABq, J=15.2 Hz), 4.97 (1H×1/3, d of a pair of ABq, J=15.2 Hz), 7.12–7.30 (5H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.7, 20.5, 29.6, 30.5, 30.7, 33.3, 36.6, 38.1, 38.6, 44.3, 44.4, 58.8, 63.3, 126.6, 126.7, 127.4, 127.5, 127.8, 128.1, 128.6, 128.8, 129.0, 129.8, 130.0, 135.3, 135.6, 136.3, 136.5, 174.2, 174.7; HRMS calcd for $C_{19}H_{21}NOS$ 311.1344, found 311.1342.

4.1.15. 1-Benzyl-5-isopropyl-4,4-dimethylpyrrolidin-2-one, 2g. Following the general procedure, the crude material was obtained from **1g** (97.3 mg, 0.400 mmol), Bu_3SnH (219 μL, 0.800 mmol) and AIBN (6.7 mg, 0.040 mmol). Chromatography on silica gel (hexane/AcOEt 4:1) gave **2g** (63.2 mg, 64%) as a colorless oil. IR ($CHCl_3$) 1665 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, s), 0.95 (3H, d, J= 6.9 Hz), 1.09 (3H, d, J=7.3 Hz), 1.09 (3H, s), 2.03 (1H, d of a pair of ABq, J=16.5 Hz), 2.02–2.11 (1H, m), 2.41 (1H, d of a pair of ABq, J=16.5 Hz), 2.84 (1H, d, J=2.0 Hz), 3.86 (1H, dd, J=14.9, 1.0 Hz), 5.31 (1H, d, J=14.9 Hz), 7.25–7.36 (5H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.3, 22.1, 23.5, 29.8, 31.0, 36.6, 45.6, 45.8, 70.7, 127.4, 128.4, 128.7, 136.4, 174.5.

4.1.16. 1,5-Dibenzyl-4,4-dimethylpyrrolidin-2-one, 2h. Following the general precedure, the crude material was obtained from **1h** (117 mg, 0.400 mmol), Bu_3SnH (219 μL, 0.800 mmol) and AIBN (6.7 mg, 0.040 mmol). Chromatography on silica gel (hexane/AcOEt 5:1) gave **2h** (83.8 mg, 71%) as colorless crystals: mp 74–75 °C (hexane). IR ($CHCl_3$) 1675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.82 (3H, s), 1.07 (3H, s), 2.12 (1H, d of a pair of ABq, J= 16.3 Hz), 2.38 (1H, d of a pair of ABq, J=16.3 Hz), 2.81 (2H, m), 3.30 (1H, dd, J=7.9, 6.3 Hz), 3.34 (1H, d of a pair of ABq, J=14.8 Hz), 4.95 (1H, d of a pair of ABq, J= 14.8 Hz), 6.96–6.99 (2H, m), 7.11–7.14 (2H, m), 7.23–7.33 (6H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.3, 28.0, 36.3, 36.9, 44.9, 45.3, 67.0, 126.5, 127.3, 128.4, 128.6, 129.1, 136.5, 138.5, 174.1. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.81; H, 7.90; N, 4.77. Found: C, 81.83; H, 8.03; N, 4.65.

4.1.17. (3*R,4*R**,5*S**)-5-Benzhydryl-1-benzyl-3-[(*S**)-hydroxy(phenyl)methyl]-4-phenylpyrrolidin-2-one, 4a and its 3-[(*R**)-hydroxy(phenyl)methyl] isomer, 5a:**

general procedure for sequential radical cyclization and aldol reaction. A solution of enamide **1d** (200 mg, 0.48 mmol), Bu_3SnH (0.26 mL, 0.96 mmol) and AIBN (7.7 mg, 0.048 mmol) in benzene (5 mL) was heated at reflux for 45 min. After cooling, a solution of aldehyde **3a** (0.195 mL, 0.192 mmol) in benzene was added to the mixture and the resulting mixture was refluxed for 12 h and allowed to cool to room temperature. According to Enholm's procedure for workup, the mixture was concentrated under reduced pressure and diluted with Et_2O. To the mixture were added DBU (0.32 mL) followed a solution of iodine in Et_2O until the iodine color persisted. The mixture was filtered through a pad of silica gel and the filtrate was concentrated under reduced pressure. The crude material was chromatographed (hexane/AcOEt 7:1→5:1→3:1) to give **4a** (108 mg, 43%) and **5a** (84 mg, 33%). Compound **4a**: mp 188–190 °C (hexane/AcOEt). IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.67 (1H, dd, J=4.9, 3.3 Hz), 2.73 (1H, dd, J=9.2, 4.9 Hz), 3.42 (1H, d of a pair of ABq, J=14.5 Hz), 4.06 (1H, d, J=6.6 Hz), 4.17 (1H, d, J=9.2 Hz), 4.29 (1H, dd, J=6.6, 3.3 Hz), 4.75 (1H, s), 5.21 (1H, d of a pair of ABq, J=14.5 Hz), 6.11 (2H, br d, J=7.3 Hz), 6.87–7.35 (23H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 44.0, 45.7, 56.5, 57.9, 67.6, 75.6, 126.3, 126.6, 127.0, 127.4, 127.8, 128.0, 128.1, 128.4, 128.5, 128.6, 128.7, 129.0, 129.2, 135.8, 140.0, 140.2, 140.7, 144.4, 176.4. Anal. Calcd for $C_{37}H_{33}NO_2$: C, 84.86; H, 6.35; N, 2.67. Found: C, 84.80; H, 6.49; N, 2.61. Compound **5a**: mp 179–180 °C (hexane/AcOEt). IR ($CHCl_3$) 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.88 (1H, dd, J=4.6, 3.0 Hz), 2.89 (1H, d of a pair of ABq, J=14.9 Hz), 2.96 (1H, dd, J=4.6, 3.3 Hz), 4.09 (1H, d, J=9.9 Hz), 4.24 (1H, dd, J=9.9, 3.0 Hz), 4.35 (1H, br s), 4.98 (1H, d of a pair of ABq, J=14.9 Hz), 5.33 (1H, d, J=3.3 Hz), 6.07 (2H, br d, J=7.3 Hz), 6.83–7.28 (23H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 43.2, 45.9, 58.2, 59.5, 67.5, 72.1, 126.0, 126.1, 126.4, 126.6, 127.0, 127.3, 127.5, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 136.5, 141.6, 141.7, 142.5, 145.6, 175.7. Anal. Calcd for $C_{37}H_{33}NO_2$: C, 84.86; H, 6.35; N, 2.67. Found: C, 84.56; H, 6.46; N, 2.60.

4.1.18. (3*R,4*R**,5*S**)-5-Benzhydryl-1-benzyl-3-[(*R**,*E*)-1-hydroxy-3-phenylallyl]-4-phenylpyrrolidin-2-one, 4b and its 3-[(*S**,*E*)-1-hydroxy-3-phenylallyl] isomer, 5b.** Following general procedure, the crude material was obtained from **1d** (200 mg, 0.48 mmol), Bu_3SnH (262 μL, 0.96 mmol), AIBN (7.7 mg, 0.048 mmol) and **3b** (259 mg, 1.92 mmol). The crude product was chromatographed (hexane/AcOEt 7:1). The first fraction gave a 2.6:1 inseparable mixture (183 mg) of **4b** and **2d** on the basis of intensities of signals, δ 5.07 (d, J=14.9 Hz, one of benzylic H, **4b**) and 5.19 (d, J=14.9 Hz, **2d**), in the ^1H NMR spectrum of the mixture. The yields of **4b** and **2d** were calculated to be 54 and 20%, respectively. The second fraction gave **5b** (58 mg, 15%). To obtain analytical sample, **4b** was silylated. The mixture of **4b** and **2d** was dissolved in DMF (0.5 mL), and TBDPSCl (0.062 mL, 0.24 mmol) and imidazole (33 mg, 0.48 mmol) were added to the mixture at room temperature. After being stirred for 3 h, the mixture was diluted with water, and the whole was extracted with AcOEt. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt 7:1→3:1) to give silylated **4b**, which was dissolved in THF (1 mL). To the solution was added a 1 M solution of TBAF in THF (0.3 mL, 0.3 mmol) at room temperature, and the mixture was stirred for two days. The mixture was diluted with water, and whole was extracted with AcOEt, washed successively with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt 7:1) to give **4b**. Compound **4b**: IR ($CHCl_3$) 3450, 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.63 (1H, dd, J=8.5, 5.4 Hz), 2.91 (1H, dd, J=5.4, 4.0 Hz), 3.51 (1H, d, J=14.6 Hz), 3.79 (1H, t, J=8.5 Hz), 4.26, (1H, d, J=6.3 Hz), 4.33 (1H, dd, J=6.3, 4.0 Hz), 4.47 (1H, br s), 5.19 (1H, d, J=14.6 Hz), 5.82, (1H, dd, J=15.8, 8.5 Hz), 6.35 (1H, d, J=15.8 Hz), 6.60–7.59 (25H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 44.7, 45.7, 56.2, 56.3, 67.7, 74.7, 126.6, 126.7, 127.1, 127.3, 127.8, 128.4, 128.6, 128.7, 128.8, 129.0, 129.1, 132.9, 135.8, 136.3, 140.2, 140.7, 144.4, 176.1; HRMS calcd for $C_{39}H_{35}NO_2$ 549.2668, found 549.2668. Compound **5b**: IR ($CHCl_3$) 3400, 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.88 (1H, dd, J=5.6, 3.5 Hz), 3.06 (1H, dd, J=5.6, 4.0 Hz), 3.16 (1H, d, J=14.9 Hz), 3.42 (1H, br), 4.26 (1H, d, J=9.2 Hz), 4.33 (1H, dd, J=9.2, 4.0 Hz), 4.75 (1H, br), 5.02 (1H, d, J=14.9 Hz), 6.08 (1H, dd, J=15.8, 6.3 Hz), 6.64 (1H, d, J=15.8 Hz), 6.90–7.34 (25H, m, Ph); ^{13}C NMR (68 MHz, $CDCl_3$) δ 43.8, 45.9, 57.3, 58.0, 67.5, 71.4, 126.4, 126.5, 127.0, 127.2, 127.5, 127.7, 128.1, 128.4, 128.6, 128.7, 128.9, 129.3, 131.5, 136.6, 141.9, 144.9, 175.5. Anal. Calcd for $C_{39}H_{35}NO_2$: C, 85.21; H, 6.42; N, 2.55. Found: C, 84.99; H, 6.44; N, 2.53.

4.1.19. (3*R,4*R**,5*S**)-5-Benzhydryl-1-benzyl-3-[(*R**)-1-hydroxyheptyl]-4-phenylpyrrolidin-2-one, 4c.** Following general procedure, the crude material was obtained from **1d** (200 mg, 0.48 mmol), Bu_3SnH (0.26 mL, 0.96 mmol), AIBN (7.7 mg, 0.048 mmol), and **3c** (231 mg, 1.92 mmol) and. After workup, the crude product was chromatographed (hexane/AcOEt 7:1→3:1) to give **4c** (114 mg, 45%) and **2d** (107 mg, 53%). Compound **4c**: IR ($CHCl_3$) 3450, 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.80–1.38 (13H, m), 2.51 (1H, dd, J=8.6, 5.3 Hz), 2.85 (1H, dd, J=5.3, 4.0 Hz), 3.29 (1H, br), 3.49 (1H, d, J=14.9 Hz), 4.21 (1H, d, J=6.9 Hz), 4.29 (1H, dd, J=6.9, 4.0 Hz), 5.12 (1H, d, J=14.9 Hz), 6.67–7.33 (20H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.0, 22.5, 24.5, 29.1, 31.7, 34.6, 45.6, 55.3, 56.8, 67.9, 72.7, 126.7, 127.0, 127.1, 127.3, 127.6, 128.5, 128.7, 128.8, 129.0, 136.0, 140.4, 176.8; HRMS calcd for $C_{37}H_{41}NO_2$ 531.3137, found 531.3109.

4.1.20. (3*R,4*R**,5*S**)-5-Benzhydryl-1-benzyl-3-[(*R**)-cyclohexyl(hydroxy)methyl]-4-phenylpyrrolidin-2-one, 4d.** Following general procedure, the reaction was carried out by using **1d** (200 mg, 0.48 mmol), Bu_3SnH (0.26 mL, 0.96 mmol), ACN (12 mg, 0.048 mmol) and **3d** (0.24 mL, 1.9 mmol) in toluene (5 mL). The crude product was chromatographed (hexane/AcOEt 7:1→3:1) to give **4d** (49.9 mg, 20%) and **2d** (150 mg, 75%). Compound **4d**: mp 144–145 °C (hexane). IR ($CHCl_3$) 3450, 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.66–1.77 (11H, m), 2.63 (1H, dd, J=9.2, 5.6 Hz), 2.87 (1H, dd, J=5.6, 4.3 Hz), 2.98 (1H, d, J=9.2 Hz), 3.46 (1H, d, J=14.9 Hz), 4.25 (1H, J=6.6 Hz), 4.31 (1H, dd, J=6.6, 4.3 Hz), 5.13 (1H, d, J=14.9 Hz), 6.68–7.32 (20H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.9, 25.7, 26.2, 30.0, 40.0, 45.2, 45.5, 52.6, 56.3, 67.8,

76.6, 126.7, 127.0, 127.2, 127.6, 128.1, 128.4, 128.6, 128.7, 128.8, 128.9, 129.0, 135.9, 140.4, 140.8, 144.3, 177.4. Anal. Calcd for $C_{37}H_{39}NO_2$: C, 83.89; H, 7.42; N, 2.64. Found: C, 83.86; H, 7.50; N, 2.66.

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