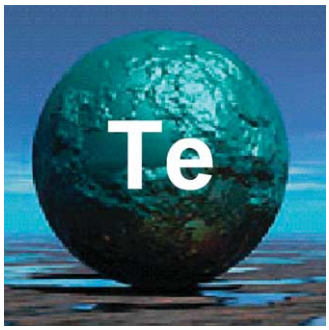
ELSEVIER

Tetrahedron

Tetrahedron Vol. 61, No. 7, 2005

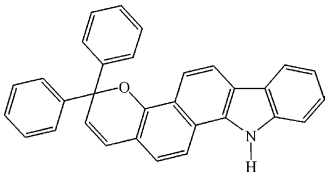
Contents

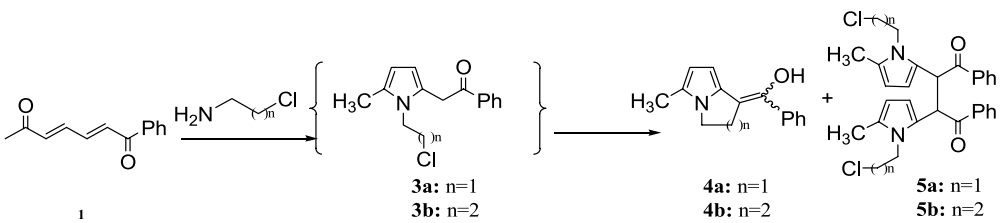
REPORT

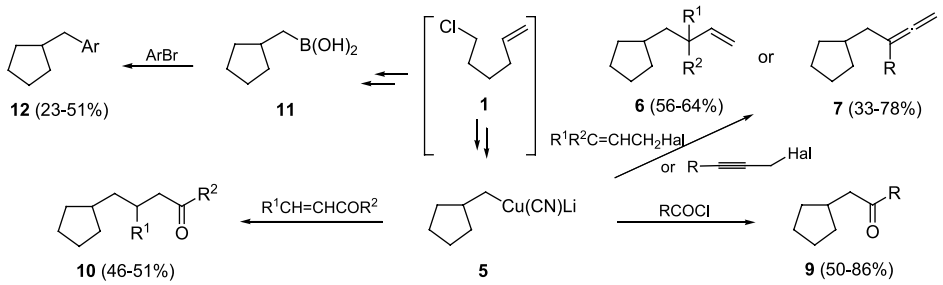


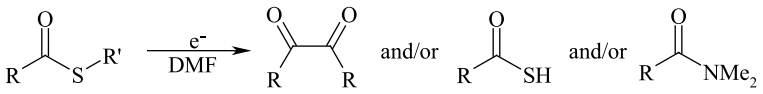
The present review focuses mainly on reports starting from the early 90s, including specific topics such as vinylic tellurides, tellurium–heteroatom exchanges, free radical chemistry deserved special attention.

ARTICLES

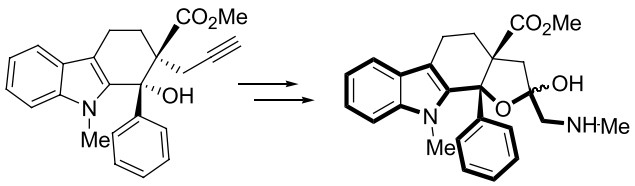


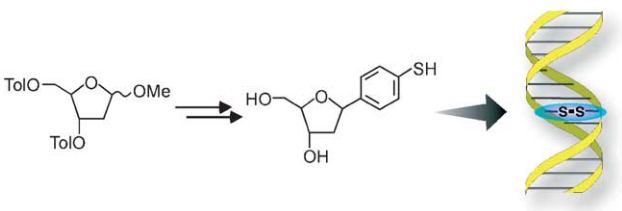


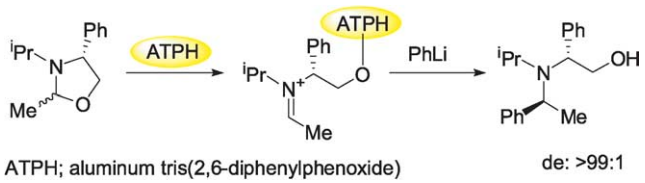


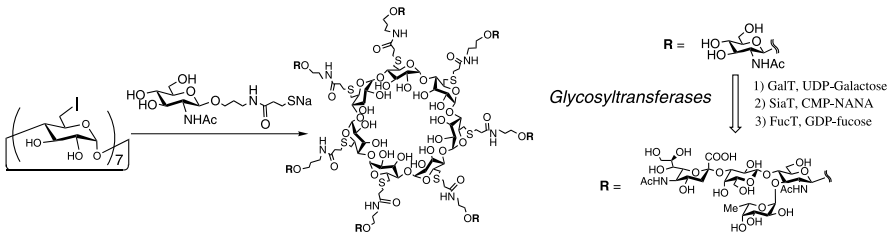


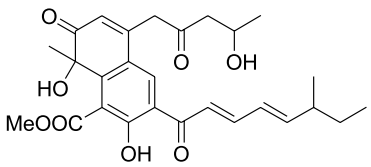
Thioester compounds ($RCOSR'$) undergo highly regioselective cleavage upon electroreduction, depending on the alkyl or aryl nature of the two R and R' groups. Aromatic α-diketones, aliphatic thioacids or amides can be selectively obtained in moderate to good yields.





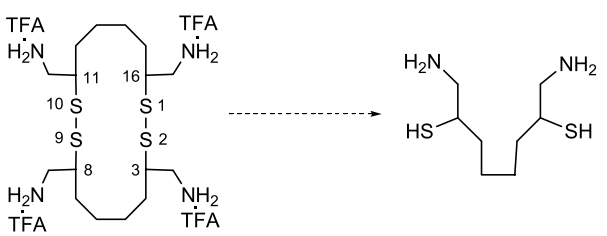


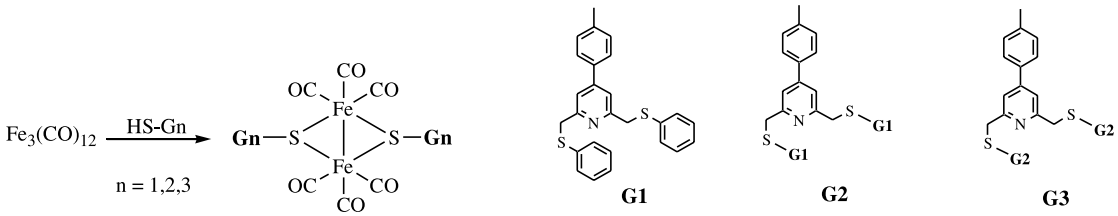


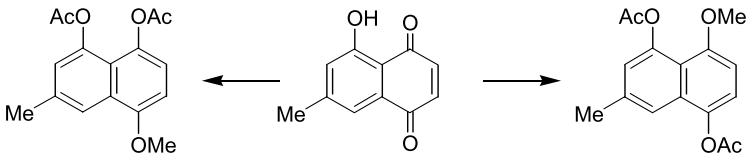


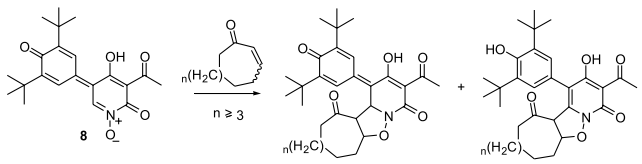
Four new azaphilones named sassafrins A–D (**1**–**4**), which showed the antimircobial activity have been isolated from the methanol extract of the stromata of the fungus *Creosphaeria sassafras*.

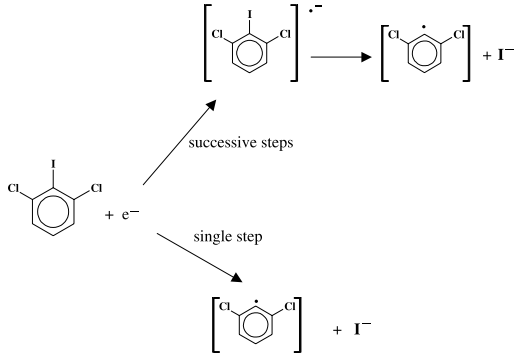
Preparation and characterization of 3,8,11,16-tetrakis(aminomethyl)-1,2,9,10-tetrathia-cyclohexadecane tetra-trifluoroacetic acid, a synthetic precursor to a novel diamine that can be attached to organic and inorganic supports.

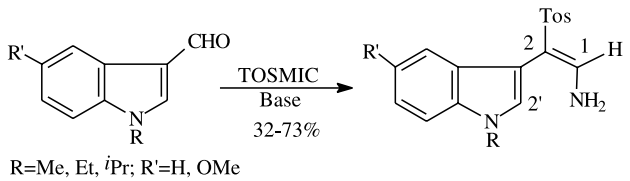




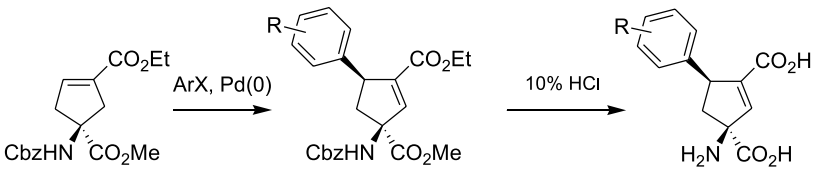


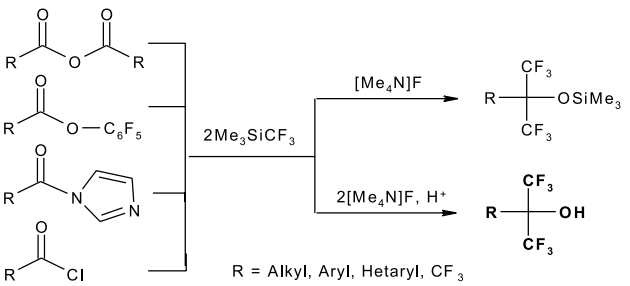


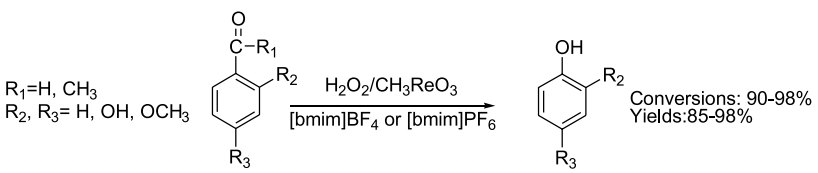


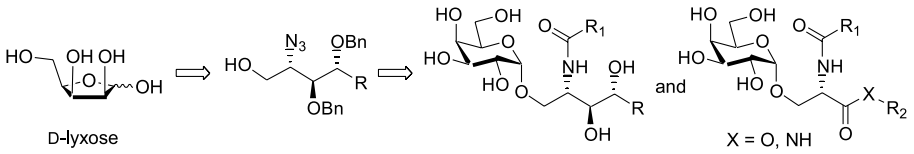


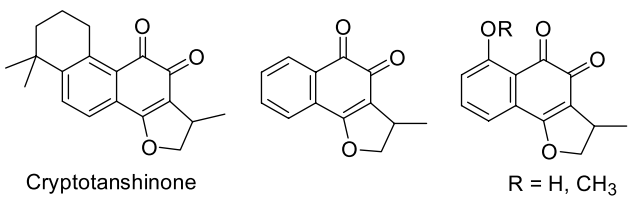
R=Me, Et, ^{i}Pr; R'=H, OMe

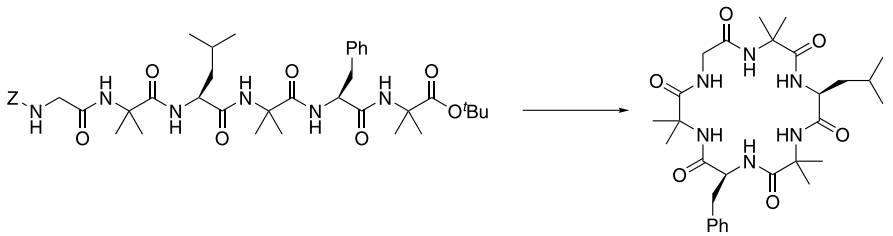


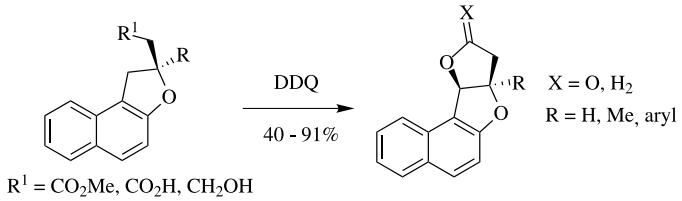


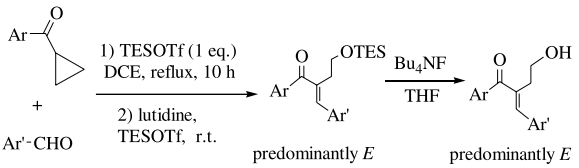




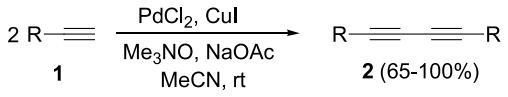


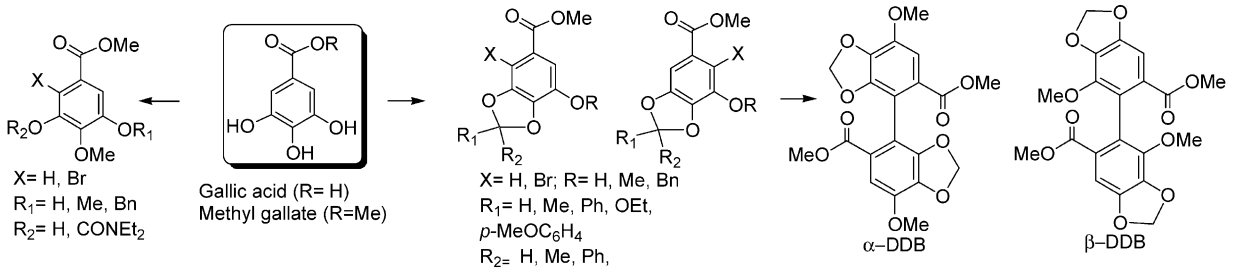


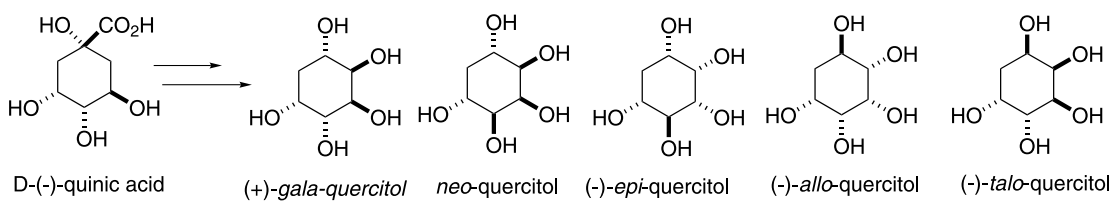




In the presence of Lewis acid TMSOTf, ring-opening reaction of aryl cyclopropyl ketone with arylaldehyde took place under mild conditions to give 2-(2-hydroxyethyl)-1,3-diarylpropenone in good yield through an atom-economic process. Protection of hydroxy group with triethylsilyl group (TES), the corresponding ring-opened product **7** was obtained in high yield with good geometrical selectivity.







OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Advances in organic tellurium chemistry

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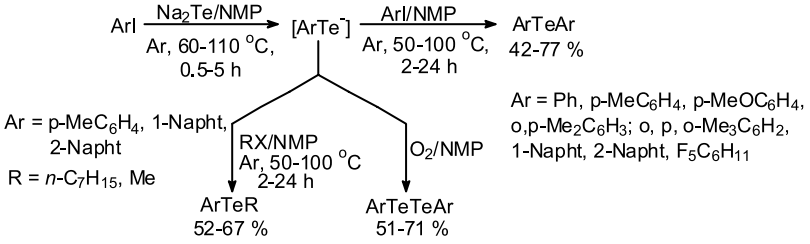
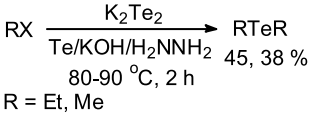
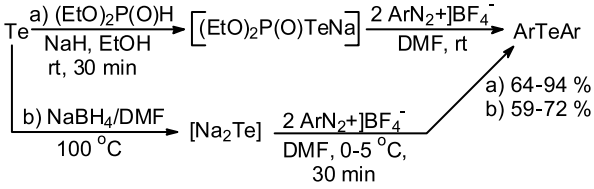


Scheme 1.



Scheme 2.



Scheme 3.

1. Introduction

Four decades after the pioneering use of tellurium compounds in organic synthesis, it is unnecessary to emphasize the rising interest directed toward this field of chemistry. This is clearly documented by the impressive number of publications and the relevant participation of tellurium chemistry in international conferences.

Several research groups in north and south America, Europe and asiatic countries attained an international reputation, introducing new roles for tellurium in structure manipulations and optimizing well-established synthetic methods.

The impressive amount of reports motivated the present review, as a supplement to our previous contributions, i.e. three reviews,[1–3] a monography,[4] and a chapter in Vol. 11 of 'Comprehensive Organometallic Chemistry II'.[5]

The present review focuses mainly on reports starting from the early 90s, including also some previous ones that were omitted in the earlier reviews. Specific topics such as vinylic tellurides, tellurium–heteroatom exchanges, free radical chemistry deserved special attention.

We would like to apologize for any possible omissions of papers that have escaped our review.

Several references that beside tellurium also concern selenium chemistry, are designated at the beginning of the reference section.

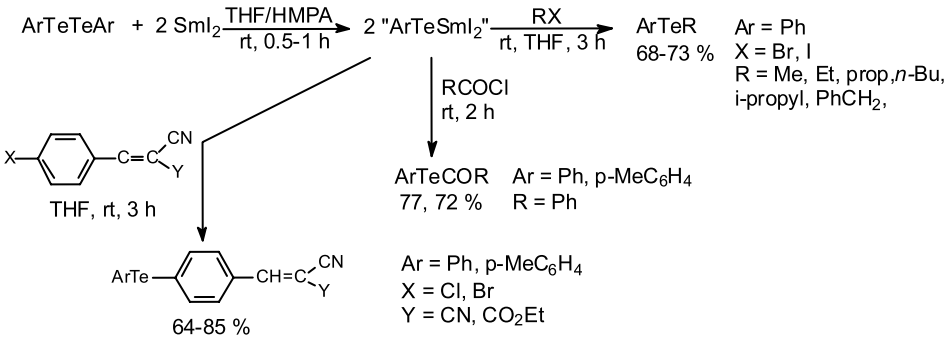
2. Preparation of some classes of organic tellurium compounds

2.1. Aromatic tellurides and ditellurides

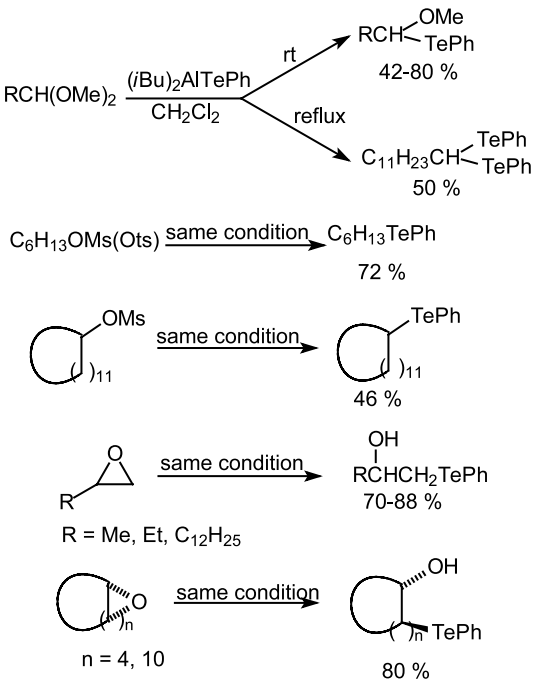
2.1.1. Starting from nucleophilic tellurium reagents. Sodium telluride (Na_2Te) prepared in situ from elemental Te and NaH in *N*-methyl-2-pyrrolidone (NMP), reacts successfully with non-activated aromatic iodides or alkyl iodides providing a variety of diaryl tellurides and aryl alkyl tellurides. Air oxidation of the intermediary aryl tellurolate gives the corresponding diaryl ditellurides[6] (Scheme 1).

The method exhibits some advantages toward previous procedures to prepare Na_2Te.[7]

An old preparative method of synthesis of dialkyl tellurides employing sodium ditelluride generated in situ from elemental Te, aqueous sodium hydroxide and hydrazine



Scheme 4.



Scheme 5.

hydrate,[8] was recently revived replacing sodium ditelluride by potassium ditelluride[9] (Scheme 2).

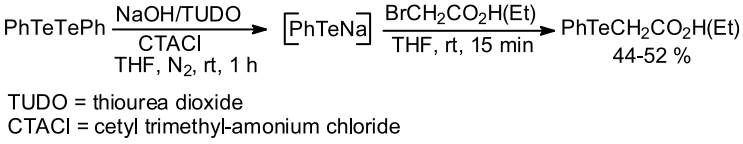
Two related methods for the preparation of diaryl telluride have been reported evolving the reaction of arenediazonium tetrafluoroborates with Na_2Te or with a reagent prepared in a one-pot procedure from elemental Te, diethyl phosphite and NaH in ethanol[10] (Scheme 3).

Aryl ditellurides are cleaved by samarium diiodide (SmI_2) to generate the new nucleophilic species diiodosamarium aryl tellurolate which react smoothly with alkyl and acyl halides, and even with aryl halides to afford the corresponding tellurides and telluroesters[11–13] (Scheme 4).

Diisobutylaluminum benzenetellurolate, generated in situ from diphenyl ditelluride and DIBAL, reacts with acetals, alkyl sulfonates and oxiranes, giving the expected tellurides in high yields.[14] Scheme 5 shows selected examples.

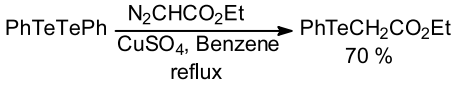
Sodium phenyl tellurolate, prepared in situ from diphenyl ditelluride under a liquid–solid system,[15] reacts with bromoacetic acid or its ethyl ester giving the corresponding phenyl telluro derivative[16] (Scheme 6).

The same telluride was prepared also upon treatment of the



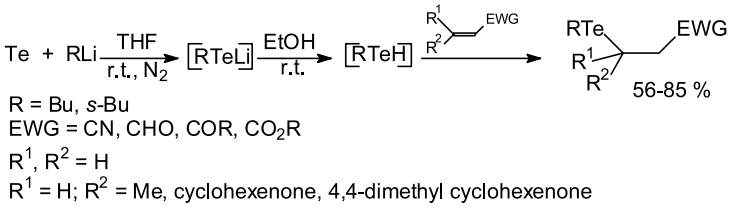
Scheme 6.

ditelluride with ethyl diazoacetate in the presence of $CuSO_4$ (Scheme 7).

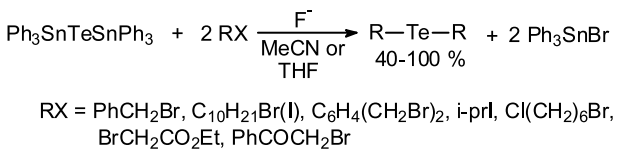


Scheme 7.

Alkyl tellurols, generated in situ by the reaction of elemental Te with alkyl lithiums followed by addition of a proton source, add to olefins conjugated to electron withdrawing groups giving the corresponding β-functionalized tellurides[17] (Scheme 8).



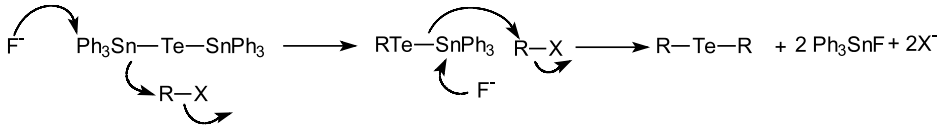
Scheme 8.



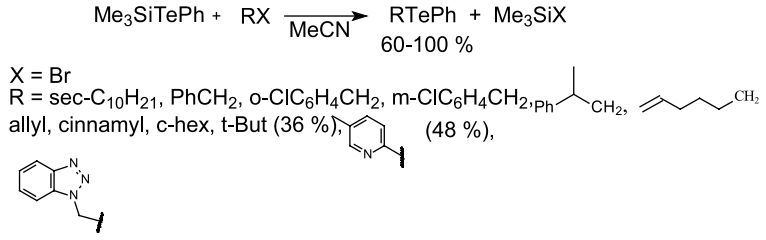
Scheme 9.

The reaction failed with the trisubstituted olefins ($R^1=R^2=$ Me; EWG=CHO and 3,5,5-trimethyl-2-*c*-hexenone).

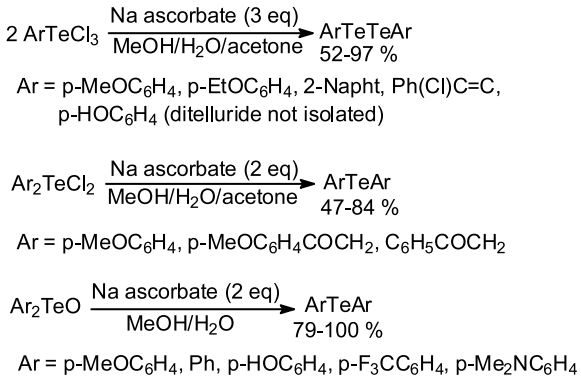
Diorganyl tellurides have been prepared by the reaction of organyl halides with bis(triphenylstannyl)telluride[18] (Scheme 9) or with trimethylsilylphenyl telluride[19] (Scheme 11).



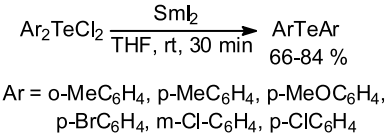
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

The most common halides need to be activated with cesium fluoride (Scheme 10). The reaction involves an attack of a nucleophilic Te species promoted by the F^- anion (Scheme 11).

A polar mechanism has been proposed.

The reactivity of the halides decreases in the order RBr > RCl > RI. It must be pointed out that the preparation of telluroesters by the similar reaction of trimethylsilylphenyl telluride with acylchlorides was reported several years ago.[20]

2.1.2. Reduction of organyl tellurium trichlorides, diaryl tellurium dichlorides and telluroxides. Sodium ascorbate has been introduced as new reagent for the reduction of aryl tellurium trichlorides, diaryl tellurium dichlorides and telluroxides to the corresponding diorganyl ditellurides and tellurides (Scheme 12).[21]

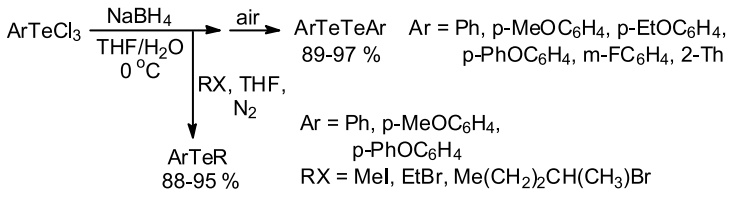
Samarium diiodide also affords the reduction of diaryl tellurium dichlorides to the corresponding tellurides, under mild conditions[22] (Scheme 13).

The reaction of aryl tellurium trichlorides with $NaBH_4$ followed by appropriate manipulations of the intermediate aryl tellurolate is an useful method to prepare diaryl ditellurides, and several types of mixed diorganyl tellurides[23] (Scheme 14).

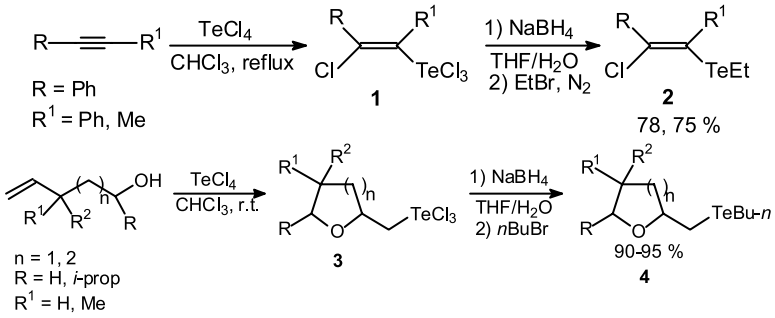
Application of the precedent protocol to vinylic trichlorides **1** and to cyclic compounds **3** (obtained, respectively, by the addition of tellurium tetrachloride to alkynes and by the tellurocyclization of unsaturated alcohols[24]) gives the expected products **2** and **4** in good yields (Scheme 15).

The above described procedure is the first described one-pot transformation of organotellurium trichlorides into diorganotellurides, and is therefore strongly advantageous toward the early precedent methods.[25]

2.1.3. Bis-(phenylethynyl)telluride as Te^{2+} equivalent. On the basis that bis-organyl tellurides undergo Te/Li

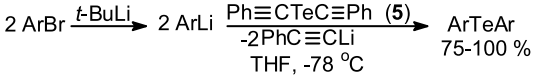


Scheme 14.



Scheme 15.

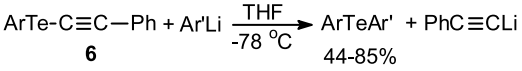
exchange by treatment with an organolithium reagent, if a thermodinamically more stable organolithium moiety is released, bis-(phenylethynyl)telluride[26] **5**, has been employed as starting material for the synthesis of diaryl tellurides[27] (Scheme 16).



Ar = Ph, p-$Me_2NC_6H_4$, p-$MeOC_6H_4$, p-HOC_6H_4, p-MeC_6H_4 m-MeC_6H_4, o,m-$Me_2C_6H_3$, o,p,o-$Me_3C_6H_3$, 2-thienyl, p-$F_3CC_6H_4$, 2-thianapftenyl

Scheme 16.

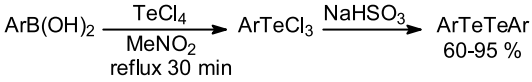
Unsymmetrical diaryl tellurides are afforded by a similar protocol, treating arylethynyl tellurides[28] **6** with aryllithiums (Scheme 17).



Ar = p-$Me_2NC_6H_4$, p-$MeOC_6H_4$
Ar' = Ph, p-$MeOC_6H_4$, p-MeC_6H_4, p-FC_6H_4, p-$F_3CC_6H_4$

Scheme 17.

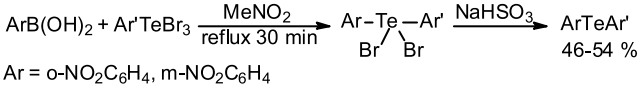
2.1.4. Diaryl ditellurides from aryl boronic acids. Aryl boronic acids treated with $TeCl_4$ generate aryl tellurium trichlorides which are reduced to diaryl ditellurides without prior isolation[29] (Scheme 18).



Ar = Ph, o-$NO_2C_6H_4$, o-ClC_6H_4, m-$NO_2C_6H_4$, p-MeC_6H_4

Scheme 18.

Starting from aryl tellurium tribromides non-symmetrical diaryl ditellurides are formed by similar procedure, but with lower yields (Scheme 19).

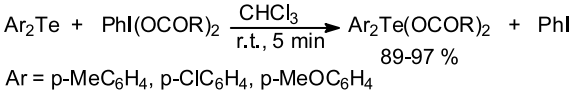


Ar = o-$NO_2C_6H_4$, m-$NO_2C_6H_4$
Ar' = m,m-$Me_2C_6H_3$

Scheme 19.

2.2. Diaryl tellurium dicarboxylates

Diaryl tellurium dicarboxylates are obtained in high yields by treatment of diaryl tellurides with phenyliodine (III) dicarboxylates in $CHCl_3$ at room temperature[30] (Scheme 20).



Ar = p-MeC_6H_4, p-ClC_6H_4, p-$MeOC_6H_4$
R = CF_3, CH_3, Ph

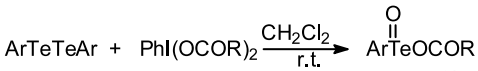
Scheme 20.

This method seems to be more attractive than the preceding ones which start from diaryl tellurium dichlorides or diaryl telluroxide, or are limited to diacetates as the reaction of the parent tellurides with lead tetracetate.

2.3. Arenetellurinic anhydrides

Arenetellurinic anhydrides are synthetic useful reagents.[31]

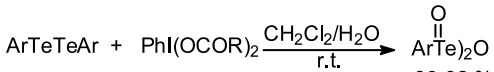
Arenetellurinic mixed anhydrides have been prepared from diaryl tellurides and phenyliodine (III) dicarboxylates[32] (Scheme 21).



Ar = p-MeC_6H_4, p-MeOPh, Ph
R = Ph, Me, CF_3, CH_2Cl

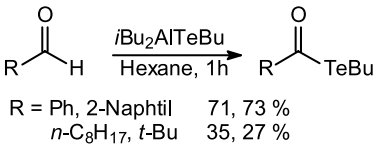
Scheme 21.

Arenetellurinic anhydrides are formed from the mixed anhydrides by hydrolysis, but a more convenient one-pot procedure for their preparation involves the reaction of phenyliodine (III) dicarboxylate with diaryl ditellurides in the two phase system CH_2Cl_2/H_20 10% (Scheme 22).



Ar = p-MeC_6H_4, p-MeOPh, Ph, 1-Naphtyl
R = CF_3, CH_3

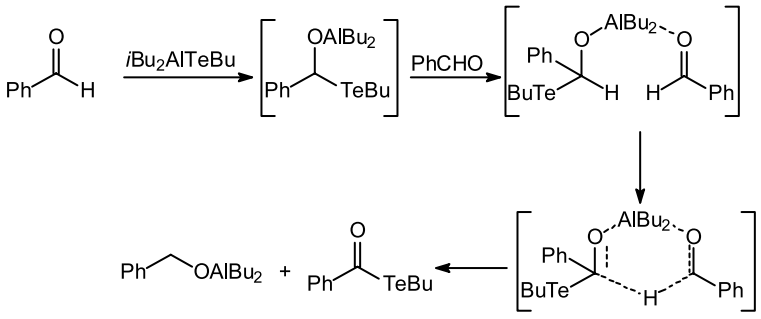
Scheme 22.



Scheme 23.

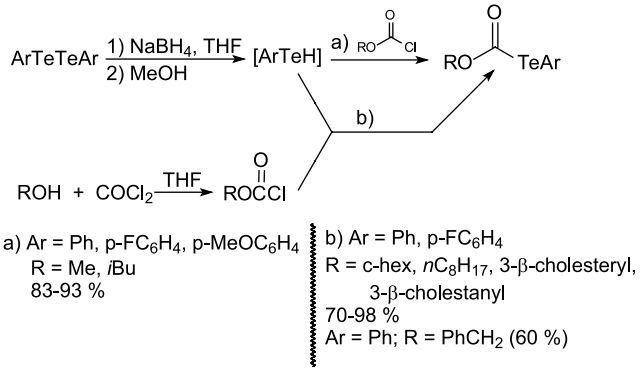
2.4. Telluroesters

Telluroesters (acyl tellurides), a class of compounds of promising synthetic utility,[33] are obtained by the reaction of aldehydes with *i*-Bu_2AlTeBu, prepared in situ from dibutyl ditelluride and diisobutyl aluminum hydride (*i*-Bu_2AlH) in hexane[33,34] (Scheme 23).



Scheme 24.

Butyl telluroesters are obtained satisfactorily from aromatic aldehydes, the yield being improved appreciably by the addition of Et_2AlCl, whereas aliphatic aldehydes are less efficient and Et_2AlCl is ineffective. The reaction probably proceeds via the addition of *i*-Bu_2AlTeBu to aldehyde to form an adduct which then undergoes an intramolecular hydride shift giving the telluroester. The role of the Et_2AlCl is unclear (Scheme 24).

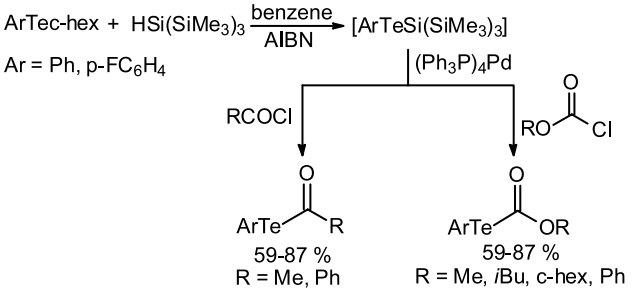


Scheme 25.

2.5. Aryl telluroformates

Aryl telluroformates have been prepared by the following methods:

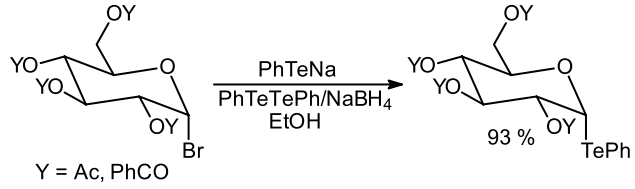
(a) reaction of aryl tellurols with alkyl chloroformates
(b) reaction of aryl tellurols with alkyl chloroformates prepared in situ from alcohols and $COCl_2$ (Scheme 25)[35]
(c) reaction of aryl tellurotris(trimethylsilyl)silane, generated in situ from the corresponding aryl telluro-cyclohexane and tris(trimethylsilyl)silane with chloroformates in the presence of tetrakis-(triphenyl-phosphine)palladium. The same procedure, performed with acyl chlorides, affords telluroesters[36,37] (Scheme 26).



Scheme 26.

2.6. Telluroglucopyranosides

The reaction of protected α,D-glucopyranosyl bromides with sodium arene tellutolates gives rise to the corresponding telluro β-*d*-glucopyranosides[38] (Scheme 27).



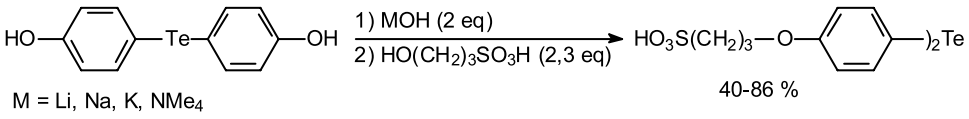
Scheme 27.

2.7. Water soluble diorganyl tellurides

Water soluble diorganyl tellurides with thiolperoxide and autoxidant activity[39] have been prepared as depicted in Scheme 28.

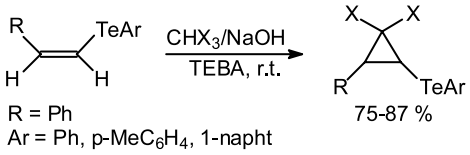
2.8. Dihaloaryltelluro cyclopropanes

Dihalocarbenes generated under phase transfer catalysis add



Scheme 28.

to vinylic tellurides to give the corresponding gem-dihaloaryltelluro cyclopropanes[40] (Scheme 29).



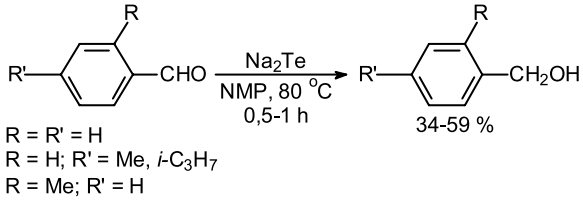
Scheme 29.

3. Reactivity and synthetic applications of tellurium compounds

3.1. Tellurium reagents in functionality transformations

3.1.1. Reduction of organic substrates and fission of C-heteroatom bonds by tellurium reagents. Sodium hydrogen telluride (NaHTe) and Na_2Te, well-established as efficient and selective reagent in a variety of functional transformations,[41] have found further applications in recent years.

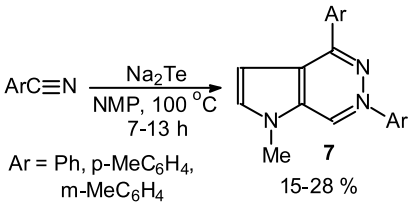
Aromatic aldehydes are reduced to alcohols by Na_2Te in NMP[42] (Scheme 30).



Scheme 30.

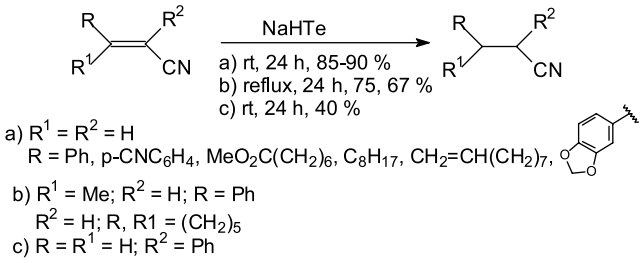
Benzophenone gives benzhydrol in 89%.

The attempted reduction of aromatic nitriles was unsuccessful, giving only the pharmacological important products (7-deaza-9*H*-purines) **7** in low yields (Scheme 31).

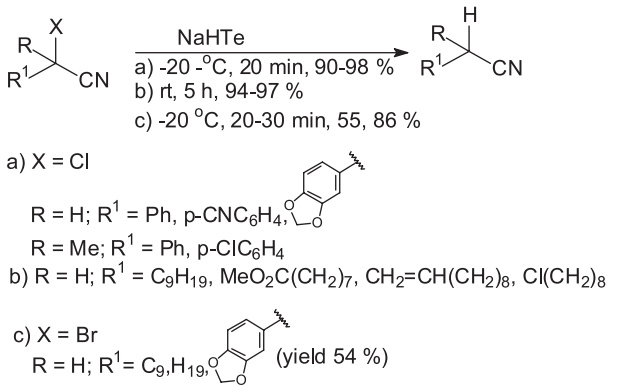


Scheme 31.

α,β-Unsaturated nitriles and α-halonitriles are reduced to the corresponding nitriles[43] (Schemes 32 and 33).

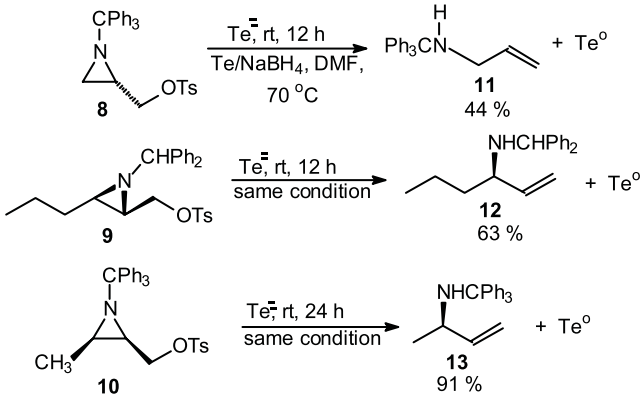


Scheme 32.



Scheme 33.

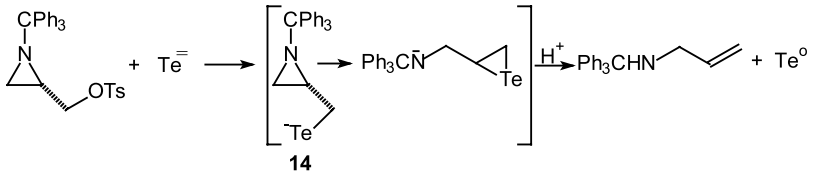
Aziridine sulfonates bearing a trityl or benzydryl group at the N-atom **8–10** are converted to allylic amines upon treatment with Na_2Te[44] (prepared from $Te/NaBH_4$ in DMF[45]) (Scheme 34).



Scheme 34.

The reaction, named 'nucleophilic reduction', involves the opening of the unactivated aziridine ring by the powerful telluride nucleophile as depicted in Scheme 35.

The products **12** and **13** obtained from the optical active **9** and **10** are also optically active.



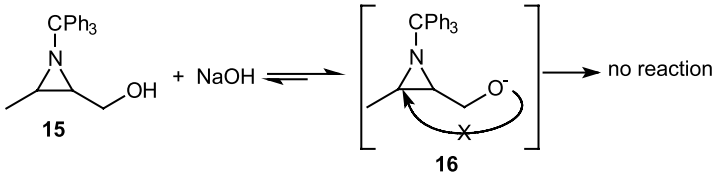
Scheme 35.

Activated aziridinas, bearing a Ph or a carbethoxy group instead of an alhyl group at the aziridine ring furnishes mixtures in the telluride process.

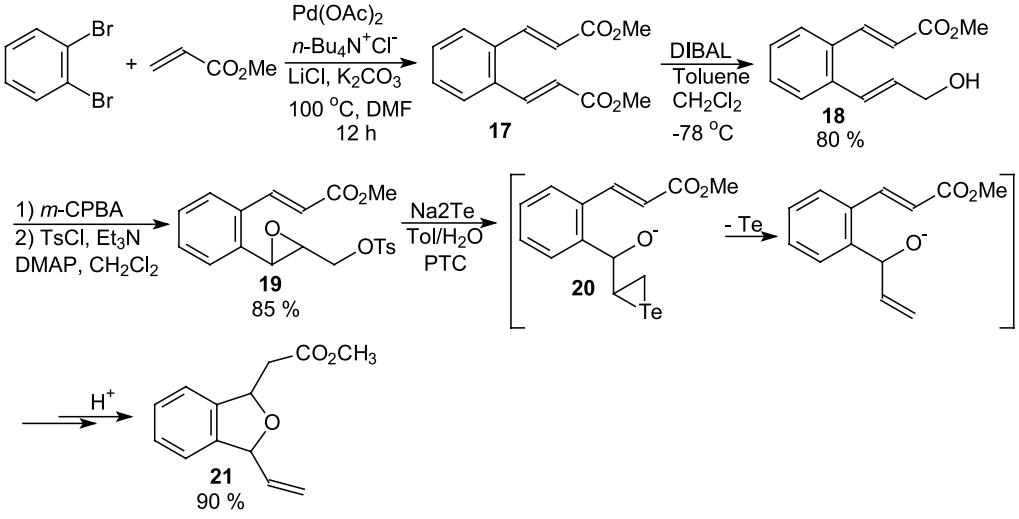
It must be emphasized that the aziridine **15** is stable toward NaOH showing that the intermediate **16**, oxygen analogous of **14**, is unable to open the aziridine ring (Scheme 36).

The 1-substituted-3-vinyl-1,3-dihydroisobenzofuran **21** was synthesized by treatment of epoxide **19** (prepared from 1,2-dibromobenzene via a double Heck reaction giving **17**, reduction of one ester group, monoepoxidation and tosylation) with Na_2Te giving the intermediate epitelluride **20** which is trapped by the adjacent α,β-unsaturated ester[46] (Scheme 37).

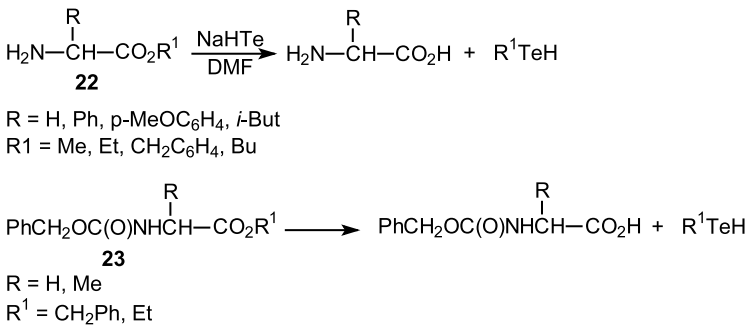
Asymmetric epoxidation of **18** followed by the same sequence gives two diastereomeric products **21** in a 56:44 ratio.



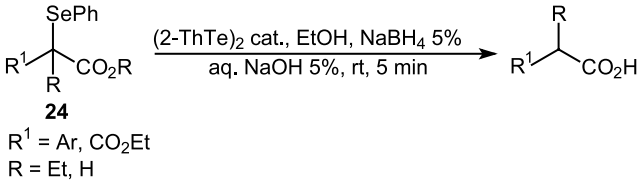
Scheme 36.



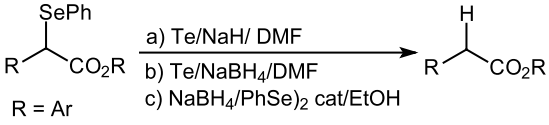
Scheme 37.



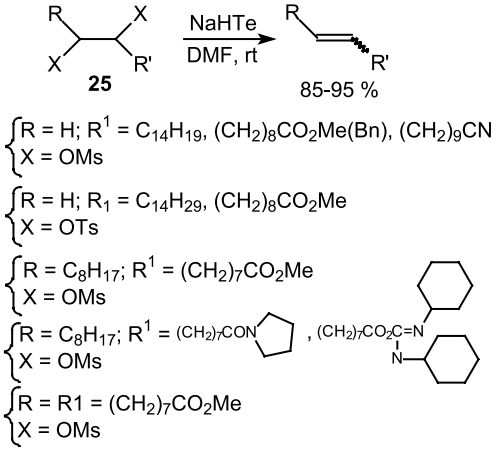
Scheme 38.



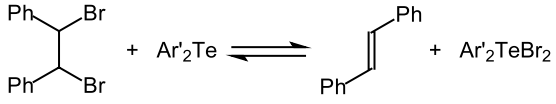
Scheme 39.



Scheme 40.



Scheme 41.



Scheme 42.

NaHTe affords the selective carbalcoxy group dealkylation of C-protected and C and N-protected α-aminoacids[47] **22** and **23**(Scheme 38).

$NaBH_4$ in aqueous NaOH in the presence of catalytic amounts of dithienyl ditelluride converts α-phenylselenocarboxylic esters and diethyl α-phenylselenomalonates **24** to the corresponding seleno free acids[48] in good yields. The yield is lower when the esters are sterically hindered.

α-Phenylseleno carboxylic acids are deselenylated also by this procedure (Scheme 39).

The selective removal of the phenylseleno group without dealkylation of the ester group is achieved by using the system Te/NaH/DMF (method a), Te/$NaBH_4$/DMF (method b), and $NaBH_4$/$PhSe)_2$ cat. (method c) (Scheme 40).

Each of the reactions take rise in medium to good yields.

α-Phenylseleno ketones and β-ketoesters are also deselenylated by similar methods.

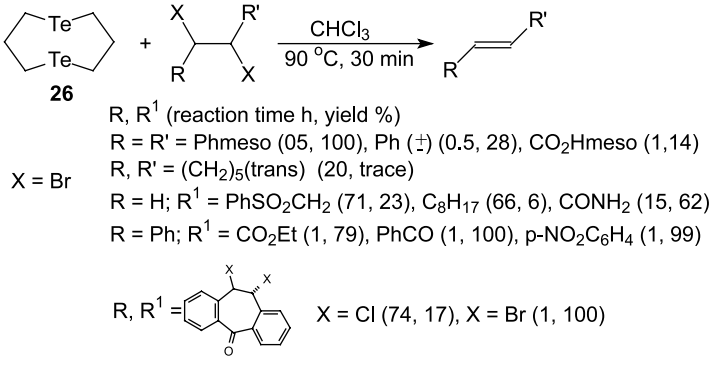
The 1,2-elimination of vicinal disubstituted substrates has been the subject of several investigations. *vic*-Dimesylates and *vic*-ditosylates **25** are desulfonated to alkenes[49] (Scheme 41).

The reaction is stereospecific, *threo* and *erythro* isomers giving, respectively, *trans* and *cis* alkenes only.

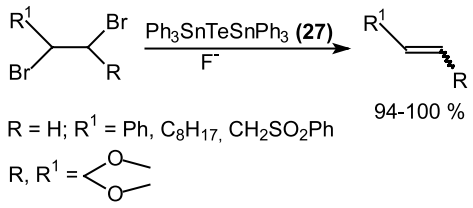
The debromination of *vic*-dibromides to give alkenes by means of a reducing agent, catalyzed by *p*-methoxyphenyl telluride[50] has been reinvestigated.[51] It was shown that the use of more electron-rich diorganotellurides such as *p*-$Me_2NC_6H_4)_2Te$, $(C_6H_{13})_2Te$, 2-$(Me_2NCH_2)C_6H_4$ associated to different reducing agents [reduced glutathione (GSH) or sodium ascorbate] are better debrominating systems than the previous employed *p*-$MeOC_6H_4)_2Te$. By this modification, the debromination is more general and is not restricted to substrates bearing at least one benzylic bromide, as in the old procedure.

It was suggested that halogenation–dehalogenation with diaryltellurium derivatives is an equilibrium process (Scheme 42).

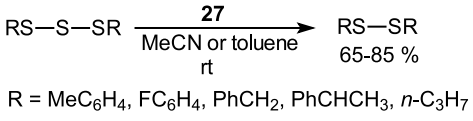
The dehalogenation by 1,5-ditelluracyclooctane **26** is induced and accelerated by transannular Te–Te interaction, as supported by a longer time required if the debromination of the same dibromide is effected with di-*n*-hexyl telluride[53] (Scheme 43).



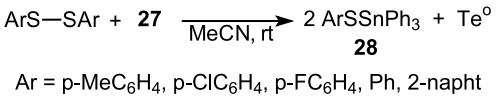
Scheme 43.



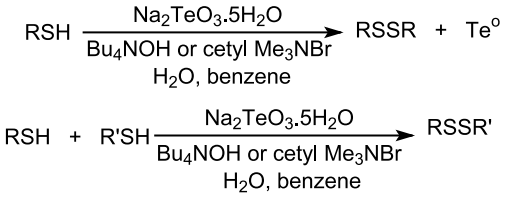
Scheme 44.



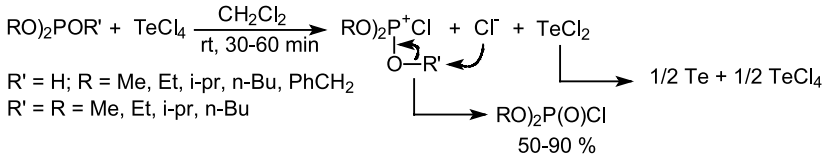
Scheme 45.



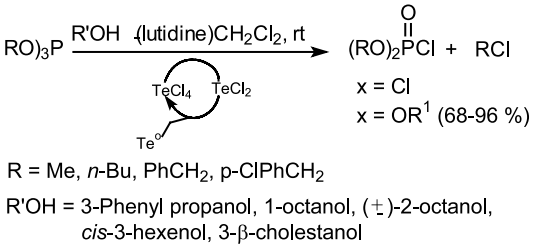
Scheme 46.



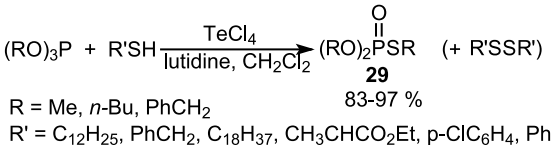
Scheme 47.



Scheme 48.



Scheme 49.



Scheme 50.

For practical purposes, the above described method does not seem to be greatly advantageous compared with the previous described ones.

Bis-(triphenylstannyl)telluride **27** is also efficient to afford the *vic*-debromination[18] (Scheme 44).

The same reagent has also been used for the monodesulfurization of diorganyl trisulfides[54] (Scheme 42) and for the preparation of arylthiostannanes **28** from diaryl disulfides[55] (Schemes 45 and 46).

Alkyl and benzyl disulfides fail to react.

3.1.2. Oxidation reactions. Sodium tellurite (Na_2TeO_2) has been recognized as a mild and selective oxidizing agent of thiols under phase transfer conditions.[56]

The reagent oxidizes instantaneously aromatic thiols, and rapidly benzylic thiols, whereas primary thiols are slow, *sec*-thiols are sluggish and *tert*-thiols fail to react at all.

Unsymmetrical disulfides are formed by oxidative cross-coupling of two different thiols (Scheme 47).

Sodium tellurate (Na_2TeO_4) exhibits similar oxidizing properties toward thiols.

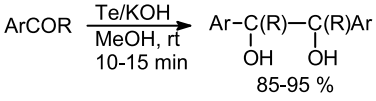
Di- and trialkyl phosphites react with $TeCl_4$ under a typical Arbuzov reaction to give dialkylchlorophosphates in high yields[57] (Scheme 48).

Trialkyl phosphites react with $TeCl_4$ in the presence of an alcohol and *tert*-amines to afford the corresponding trialkyl phosphates in high yields. Elemental tellurium is formed as by-product[58] (Scheme 49).

The reaction was considered as an oxidation–reduction process, where the phosphate and $TeCl_4$ are converted into phosphorochloridate and tellurium dichloride, respectively. $TeCl_2$ suffers a disproportionation into Te and $TeCl_4$ which can participate again in the reaction.

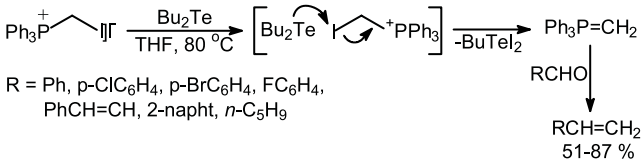
The intriguing feature of this reaction is how the alcohol participates in the proposed cycle, since in accordance with former reports,[57] trialkyl phoshites react with $TeCl_4$, as a preparation method of phosphorochloridates, but a solution containing dibutyl phosphorochloridate is hardly converted to tributyl phosphate when butanol is added.

Following the same procedure, phosphoric thiol esters **29** are prepared by the treatment of trialkyl phosphites with thiols in the presence of $TeCl_4$ and lutidine[59] (Scheme 50).



R = H; Ar = Ph, p-ClC$_6$H$_4$, p-MeC$_6$H$_4$, p-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$
R = Me; Ar = Ph, p-MeC$_6$H$_4$

Scheme 51.



R = Ph, p-ClC$_6$H$_4$, p-BrC$_6$H$_4$, FC$_6$H$_4$, PhCH=CH, 2-napht, *n*-C$_5$H$_9$

Scheme 52.

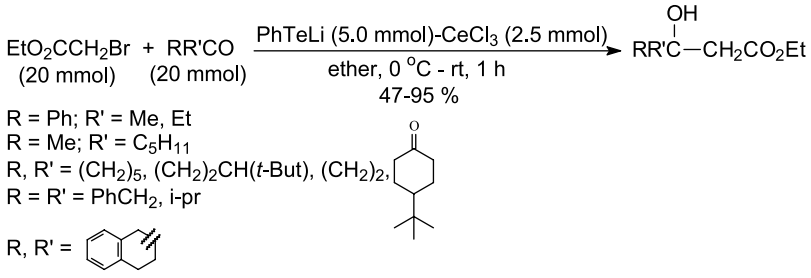
In the presence of dibutyl telluride, iodomethyltriphenyl phosphonium iodide reacts with aldehydes upon a Wittig-type olefination, via the intermediacy of the methylene phosphorane[61] (Scheme 52).

The previously described Reformatsky-type reaction promoted by Na_2Te and *i*-Bu_2Te[62] was later improved by the use of the system PhTeLi/$CeCl_3$[62] (Scheme 53).

Scheme 54 rationalizes the reaction.

Tellurium tetrachloride is an efficient catalyst in the Knoevenagel reaction of non-enolisable aldehydes with active methylene compounds[63] (Scheme 55).

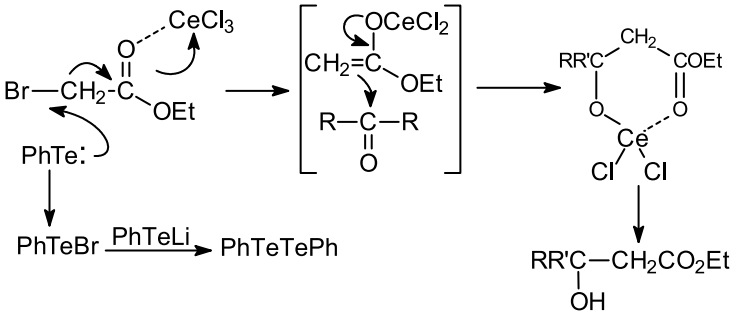
3.1.4. Miscellaneous. Diaryl tellurium dibromides undergo



R = Ph; R' = Me, Et
R = Me; R' = C_5H_{11}
R, R' = $(CH_2)_5$, $(CH_2)_2CH(t\text{-But})$, $(CH_2)_2$,
R = R' = $PhCH_2$, i-pr

R, R' =

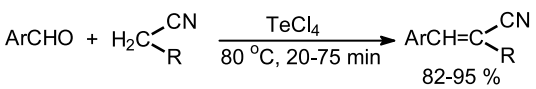
Scheme 53.



Scheme 54.

High yields are achieved with alkane thiols, but to ensure good results with arene thiols, $CaCO_3$ is employed as acid captor instead of lutidine, avoiding the side reaction forming disulfides.

3.1.3. Tellurium promoted carbon–carbon bond formation. Tellurium powder/KOH is an efficient system for the pinacolization of aromatic carbonyl compounds.[60] The method exhibits some advantages over others since it is a very fast reaction (Scheme 51).

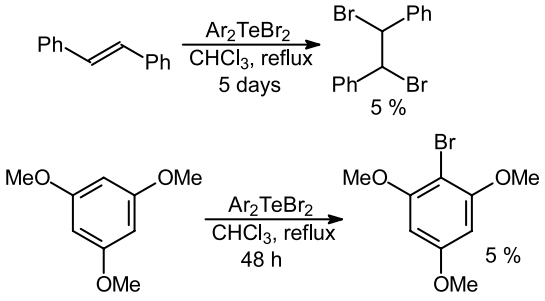


Ar = Ph and substituted Ph, 2-furyl, E-C$_6$H$_5$CH=CH
R = CO_2Et, CN, $CONH_2$

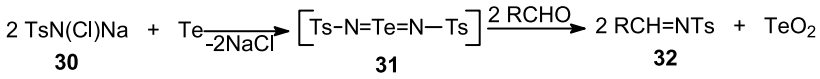
Scheme 55.

bromination of *trans*-stilbene and 1,3,5-trimethoxybenzene giving, respectively, low yield of the corresponding *erythro* dibromide and bromoarene[52] (Scheme 56).

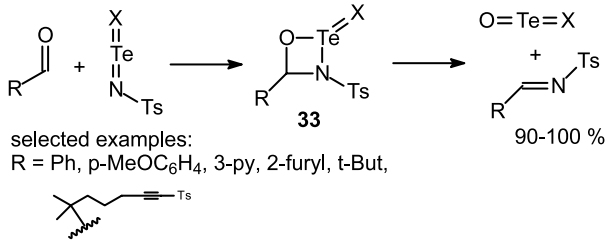
The diaryl tellurium dichloride (Ar=*p*-ClC$_6$H$_4$) is



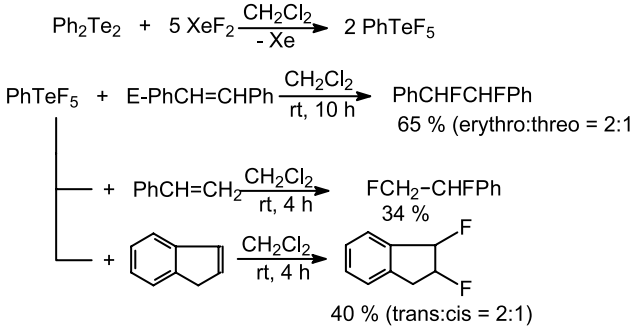
Scheme 56.



Scheme 57.



Scheme 58.



Scheme 59.

unreactive with *c*-hexane, *trans*-stilbene and 1,3,5-trimethylbenzene.

A convenient protocol for their synthesis of *N*-sulfonylimines **32**, which are important synthetic building blocks,[64] involves the reaction of *N*,*N*′-ditosyltellurodiimide **31**, generated in situ from elemental Te and Chloramine T **30**, with aldehydes in polar or non-polar solvents[65] (Scheme 57).

The mechanism of the reaction is assumed to involve a cycloaddition to a four-membered ring **33** followed by cycloreversion giving the product (Scheme 58).

Phenyl tellurium pentafluoride, is easily prepared from diphenyl ditelluride and xenon difluoride (XeF_2), reacts smoothly with olefins affording the corresponding 1,2-difluorides[66] (Scheme 59).

3.2. Conversion of organotellurium compounds into tellurium free compounds—synthetic applications

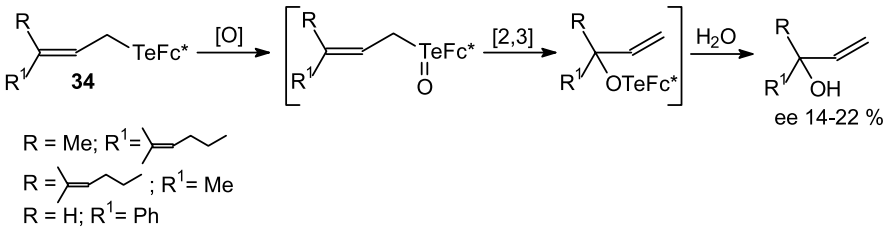
3.2.1. Telluroxide eliminations. Although not so well known as the familiar selenoxide elimination, the corresponding telluroxide elimination has gained more attention in the last years becoming a well-established method for the synthesis of olefins.[67] Some noteworthy results have been reported recently with regard to this matter.

The addition of Et_3N and other amines exhibits a remarkable effect on the telluroxide elimination, improving the alkene yields, suppressing the formation of side-products and promoting the elimination even from primary alkylphenyl telluroxides. Moreover the 2-pyridyltelluro moiety was shown to be a better leaving group than the usual phenyltelluro moiety.[68]

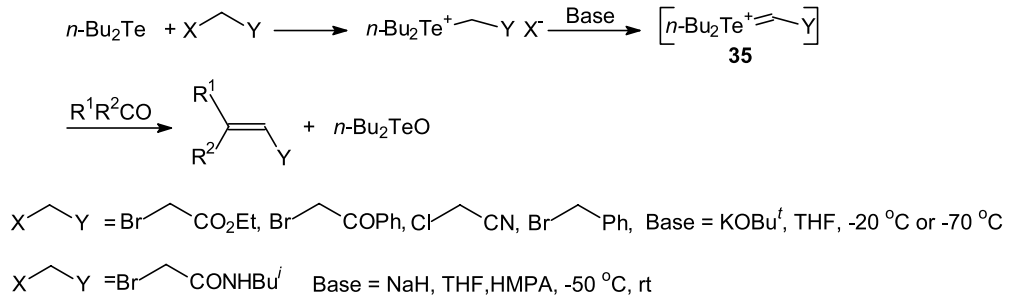
The well known correlate oxidation of allyl tellurides, which proceeds via a [2.3]-sigmatropic rearrangement and affords allylic alcohols after hydrolysis,[69] was performed on chiral allylic ferrocenyl tellurides **34**, giving evidence of chirality transference to the allylic alcohol[70] (Scheme 60).

3.2.2. Alkenes from telluronium ylides.[71]

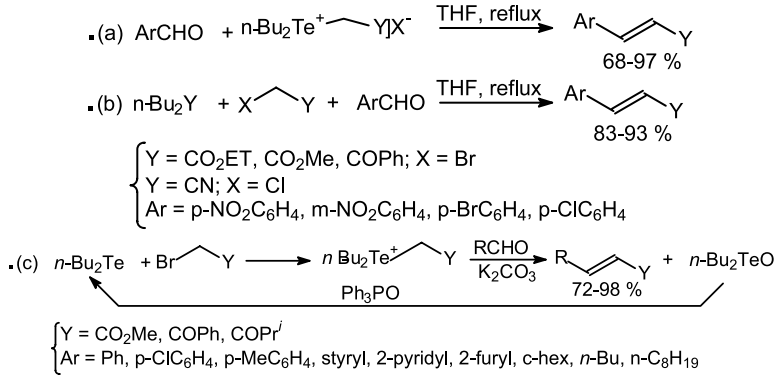
3.2.2.1. Stabilized telluronium ylides. Dibutyltelluronium methylides **35** stabilized by electron-attracting groups, such as carbethoxy,[72] phenacyl,[73] cyano[73] and carbamoyl,[74] and dibutyltelluronium benzylide[75] (easily prepared by the reaction of dibutyl telluride with the appropriate substituted methyl halide, followed by base treatment), undergoes typical Wittig olefination with a variety of aldehydes and ketones to give the expected alkenes in satisfactory yields (Scheme 62). It must be pointed out that, by contrast, stabilized sulfonium ylides are inert toward carbonyl compounds. Noteworthy features of these tellurium reactions are the high predominance of (*E*)-sterochemistry in the case of aldehydes and the good results obtained even with highly enolizable ketones (cyclopentanone), α,β-epoxyketones (isophorone oxide) and α,β-unsaturated compounds such as benzalacetophenone and cinnamaldehyde. In the case of carbamoyl derivatives (Y = $CONHBu^i$), phase-transfer catalysis conditions can be employed by simply treating aromatic aldehydes with the telluronium salt (itself behaving as a phase-transfer catalyst in wet THF) in the presence of K_2CO_3, at 50–60 °C[76] (Scheme 61).



Scheme 60.



Scheme 61.



Scheme 62.

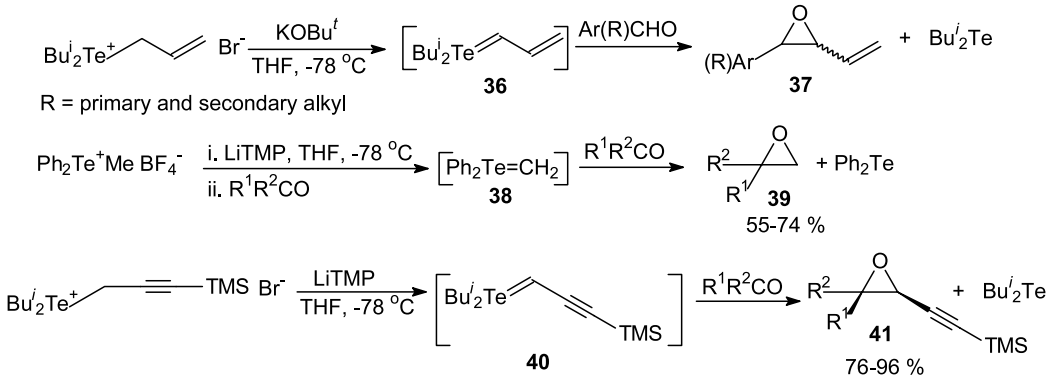
Two simplified high-yielding procedures have been described exploiting the low energy and high polarity of the Te–C bond.[73,77] In the first one (a), the reaction is performed with telluronium salts under neutral conditions, instead of the ylides. In the second one (b), the preparation of the telluronium salts and the olefination step are combined in a 'one-pot' operation. A further procedure (c) is also effective, which uses dibutyl telluride in catalytic amount, and the addition of triphenyl phosphite reduces the telluroxide formed[78] (Scheme 62).

3.2.2.2. Semi and non-stabilized telluronium ylides. Semi- and non-stabilized telluronium ylides such as dibutyltelluronium allylide[79] **36**, diphenyltelluronium methylide[80] **38** (the first non-stabilized telluronium ylide) and di-*i*-butyltelluronium trimethylsilyl propynylide[81] **40** react with aldehydes and ketones to give epoxides **37**, **39** and **41** in medium to high yields(in analogy to non-stabilized sulfonium and selenonium ylides) (Scheme 63).

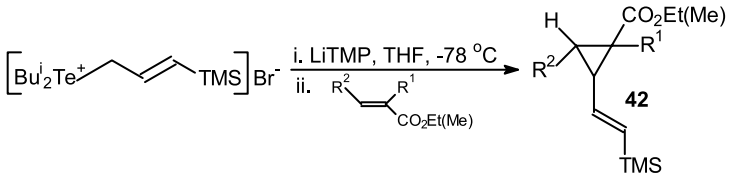
Intensive investigations have been devoted to the synthesis of vinyl cyclopropanes by using allylic telluronium salts.[82] Vinyl cyclopropanes are important compounds as versatile synthetic intermediates and also as participants in the structure of several biological active natural compounds.[83]

3-Trimethylsilyl diisobutyltelluronium prop-2-enylide reacts with α,β-unsaturated esters to give trimethylsilylvinyl cyclopropane derivatives[84] **42** (Scheme 64).

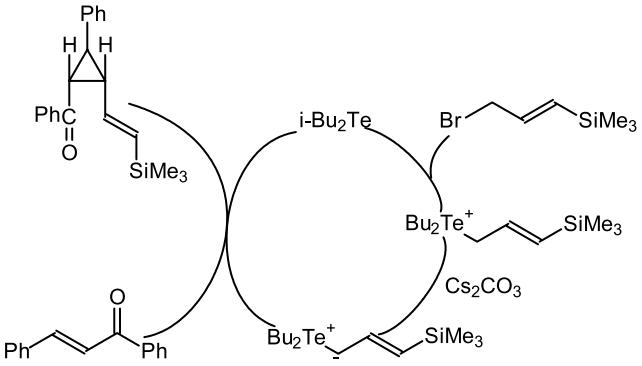
A useful and practical version of the above protocol involves a catalytic process in which the enone, a bromoallyl silane, cesium carbonate and diisobuty ltelluride react in a one-pot procedure to give the desired cyclopropanes[85] with a high *cis* stereoselectivity (Scheme 65).



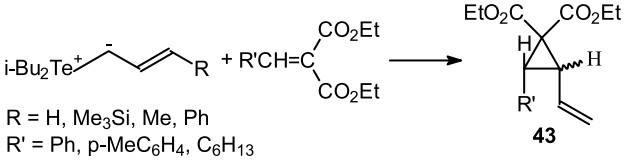
Scheme 63.



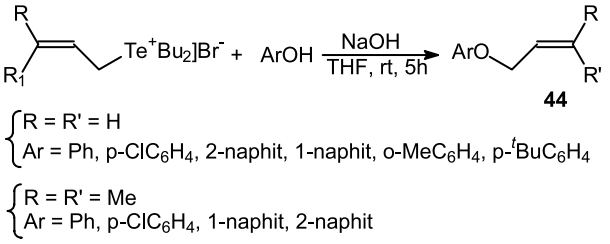
Scheme 64.



Scheme 65.



Scheme 66.



Scheme 67.

Further investigation showed that the presence of lithium salts plays an important role in the stereochemistry of these reactions.[86]

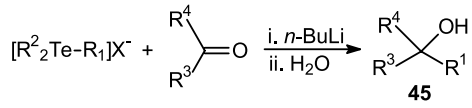
Thus, allyl telluronium ylides generated in situ from the corresponding telluronium salts in the presence of Li salts react with α,β-unsaturated esters and amides to afford *trans*-2-vinyl-*trans*-3-substituted cyclopropyl compounds. Employing sodium and potassium salts instead of lithium the corresponding *cis–trans* compounds are obtained as main product. Temperature and solvent are also influential factors in the stereochemical outcome.

Similar cyclopropanation reactions with benzylidene and alkylidene malonic esters give **43**[87] (Scheme 66).

Propargylic silylated telluronium ylides react analogously.

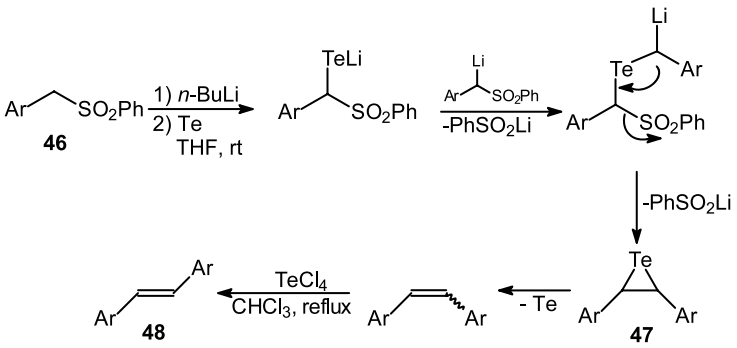
The reaction of allyl telluronium salts with phenols in the presence of solid NaOH in THF leads to allylic ethers **44** in excellent yields[88] (Scheme 67).

Many different types of telluronium salt reacts with carbonyl compounds on treatment with organolithiums to give alcohols **45** instead of alkenes.[75,81,89,90] This reaction proceeds via the intermediacy of a tetraorganotellurium, which generates a carbanionic species suitable for addition to the carbonyl group (Scheme 69). Phenyl, benzyl, cyanomethyl and trimethylsilylpropargyl groups are transferred in preference to other groups. The β-hydroxynitriles obtained from the cyanomethyl telluronium salts are of great importance.[91] Similarly, the relevant role of propargylic anions in synthetic chemistry enhances the

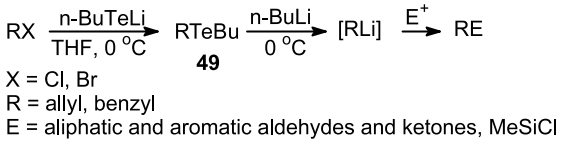


Telluronium salt	Carbonyl compound	Yield %	
$Me_3Te^+]I^-$, $Ph_2Te^+Me]BF_4^-$	-Benzaldehyde and derivatives, 2-NapthCHO, 2-pyridylCHO	56-85	(ref. 89)
n-$Bu_2Te^+CH_2Ph]Br^-$	-Benzaldehyde and derivatives, cinnamaldehyde, 2-pyridylCHO, c-hexanone	58-96	(ref. 75)
n-$Bu_2Te^+CH_2CN]Cl^-$	-Benzaldehyde and derivatives, aliphatic aldehydes, benzophenone, acetophenone	85-98	(ref. 90)
i-$Bu_2Te^+CH_2C{\equiv}CSiMe_3]Br^-$	-Benzaldehyde and derivatives, 2-NapthCHO, 2-pyridylCHO, c-hexylCHO, acetophenone, c-hexanone, 2-c-hexenone	67-93	(ref. 81)

Scheme 68.



Scheme 69.



Scheme 70.

importance of the propargyl-substituted telluronium salt[92] (Scheme 68).

Benzylic sulfones **46** are converted into diaryl ethylenes **48** on treatment with butyllithium in the presence of elemental tellurium; an epitelluride **47** is the intermediate[93] (Scheme 69). The *cis–trans* mixture which is obtained is converted into the pure *trans*-isomer by treatment with $TeCl_4$.

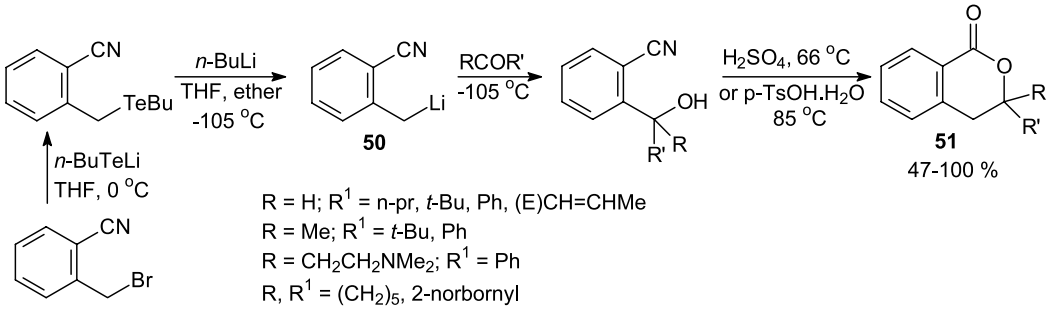
3.2.3. Tellurium–lithium exchange. The well known one-pot generation of allyl- and benzyllithiums **49** followed by capture with electrophiles[94] has been investigated in more detail[95] (Scheme 70).

It was observed that in the case of bromo or iodo substituted benzylic tellurides the lithium–Br exchange and/or the halogen displacement by the butyllithium competes with the Te/Li exchange, resulting in lower yields of the desired products. This drawback is avoided using ether as solvent.

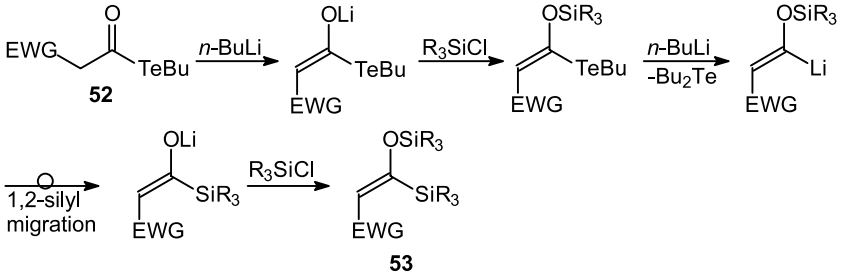
The reaction of *o*-cyanobenzyllithium **50**, generated by Te/Li exchange in the corresponding telluride, with aldehydes or ketones followed by acid promoted lactonization of the obtained hydroxyderivatives, affords 3,4-dihydroisocoumarins compounds[96] **51** (Scheme 71).

Telluroesters bearing an α-anion stabilizing group **52**, upon treatment with BuLi (2 equiv) in the presence of chlorosilanes give enolsilyl ethers of the corresponding acyl silanes **53** exhibiting main *Z* geometry at the double bond.[97] The reaction pathway is depicted in Scheme 72.

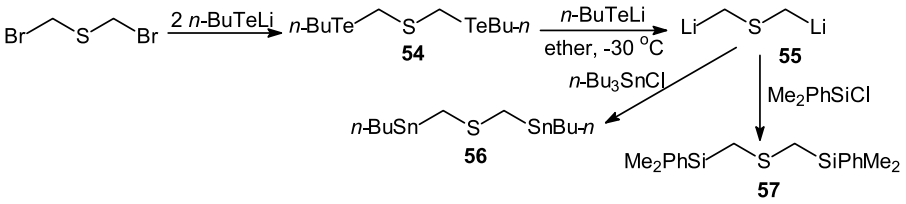
Bis(butyl tellurium)methyl sulfide **54**, prepared from bis(bromomethyl)sulfide and *n*-BuTeLi, by treatment with 2 equiv of *n*-BuLi gives rise to the dilithioderivative **55** which can be isolated under vacuum as a colorless powder.



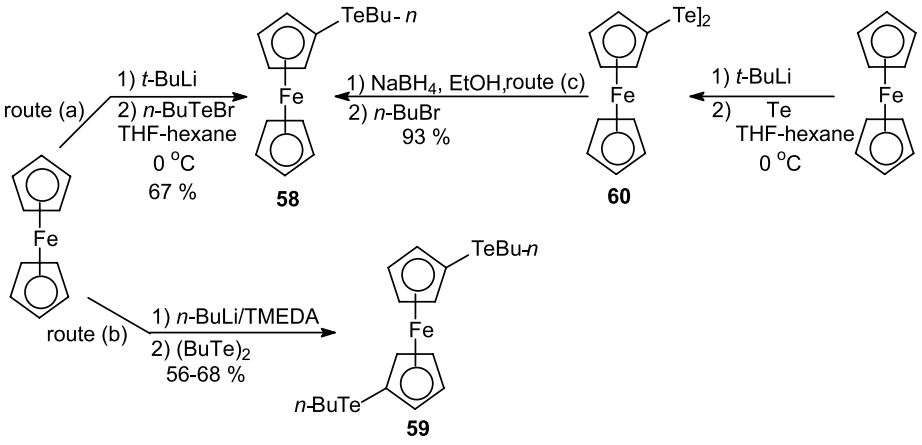
Scheme 71.



Scheme 72.



Scheme 73.



Scheme 74.

Compound **55** ignites explosively upon contact with traces of air, and decomposes under argon at 60 °C but can be stored at −20 °C for six months.

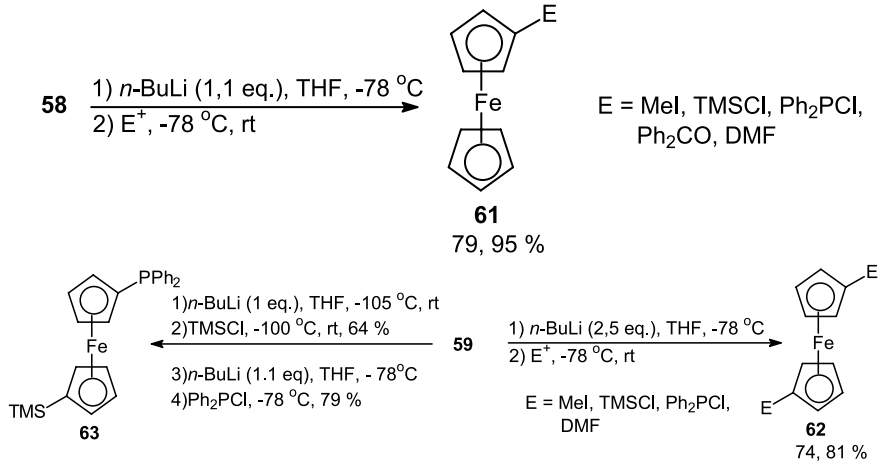
Reaction with Bu_3SnCl and $Me_2PhSiCl$ leads to compounds **56** and **57**[98] (Scheme 73).

Mono- and bis-tellurenyl ferrocenes **58** and **59** are achieved by treatment of lithiated ferrocenes with butyltellurenyl bromide (route a) or dibutyl ditelluride (route b). Mono tellurenyl ferrocene **58** is also obtained in a two-step procedure by treating lithiated ferrocene with Te to give ditelluride **60** followed by reductive alkylation (route c)[99,100] (Scheme 74).

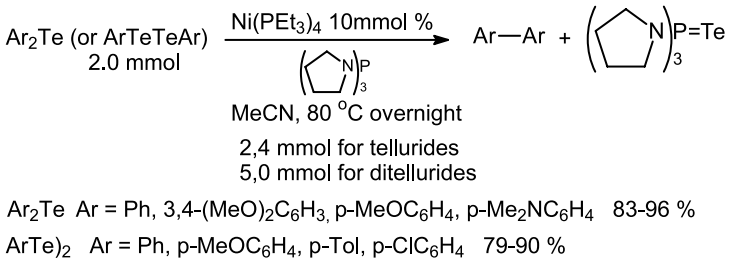
Tellurium/lithium exchanges in the mono- and bis-tellurderivatives **58** and **59** are a suitable route for the preparation of mono and disubstituted ferrocenes **61**, **62** and **63**[99] (Scheme 75).

3.2.4. Nickel-catalyzed detelluration of diaryl tellurides and ditellurides. The previous reported[101] detelluration of organotellurides and ditellurides with Pd(0) and Pd^{+2} is experimentally objectionable since it requires one or more equivalents of the catalyst.

Recent reports describes the use of the $Ni(PEt_3)_4$ system in the presence of phospines as a successful catalyst for the



Scheme 75.



Scheme 76.

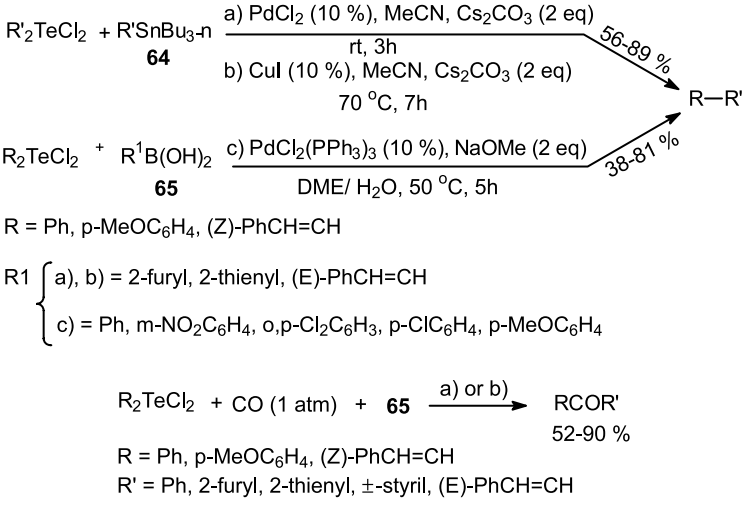
detelluration of organotellurides and ditellurides[102] (Scheme 76).

3.2.5. Palladium and copper catalyzed cross-coupling of organotellurium dichlorides with organostannanes and organoboronic acids. Diaryl and divinyl tellurium dichlorides undergo cross-coupling reactions with organostannanes **64** and organoboronic acids[103] **65**, catalyzed, respectively, by $PdCl_2$ or CuI in the presence of Cs_2CO_3, and $PdCl_2(PPh_3)_3$. The reaction was extended to carbonylative cross-coupling (Scheme 77).

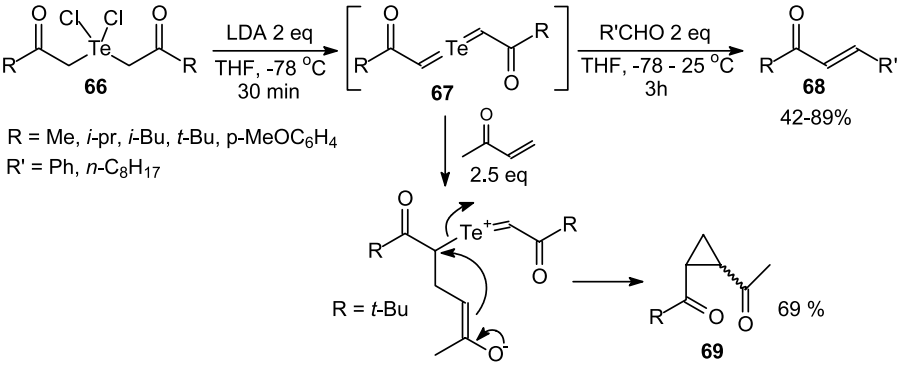
3.2.6. Synthesis of enones and cyclopropanes from bis(oxoalkyl)tellurium dichlorides. The sequential treatment of bis(2-oxomethyl)tellurium dichlorides **66** with 2 equiv of LDA in THF at −78 °C and 2 equiv of an aldehyde, followed by heating at 25 °C, affords the enones **68** with *E*-geometry in good yields. The same reaction performed with methyl vinyl ketone gives rise to the cyclopropane **69**.[104]

These reactions involve the intermediacy of the bis-ylide **67** which undergoes a Wittig reaction with aldehydes or a Michael 1,4-addition to the enone (Scheme 78).

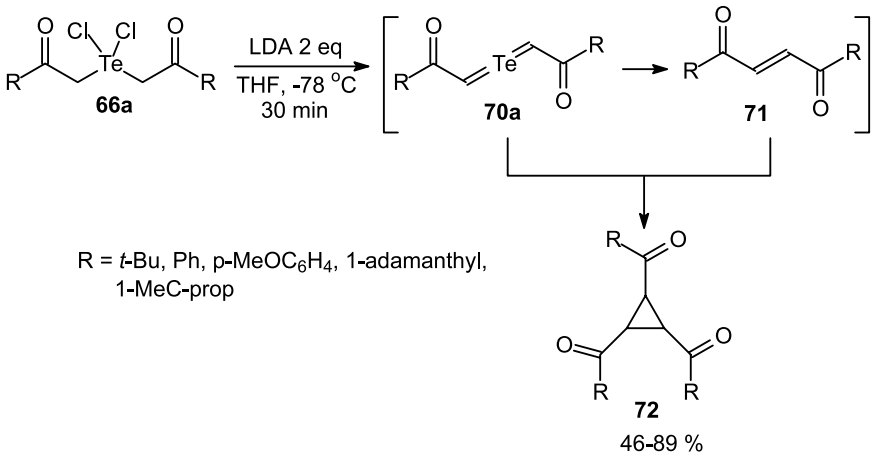
Moreover by heating **66a** bearing one phenyl or *tert*-butyl



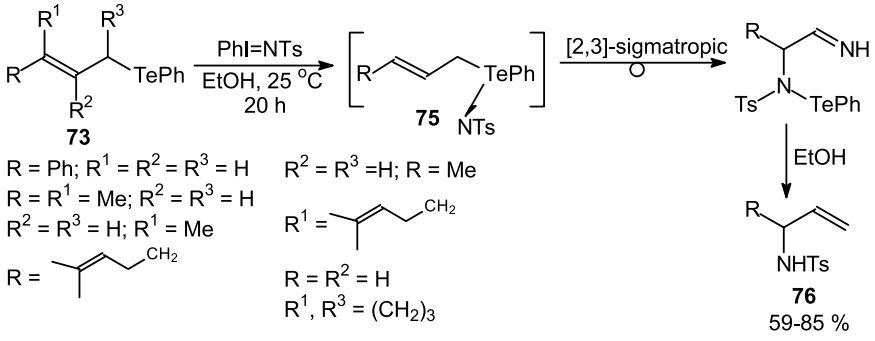
Scheme 77.



Scheme 78.



Scheme 79.



Scheme 80.

group with 2 equiv of LDA at −78 °C and then warming at room temperature, the triacylsubstituted cyclopropane **72** are formed.

This result was rationalized as involving a Michael addition of the bis-ylide **70a** to the 1,2-diacylethylene **71** generated in situ (Scheme 79).

Since compounds **66** are prepared by the reaction of $TeCl_4$ with enolates,[105] the cyclopropanes **72** and the diacylalkenes **71** can be prepared also by a one-pot procedure starting from the corresponding ketones, LDA and $TeCl_4$.

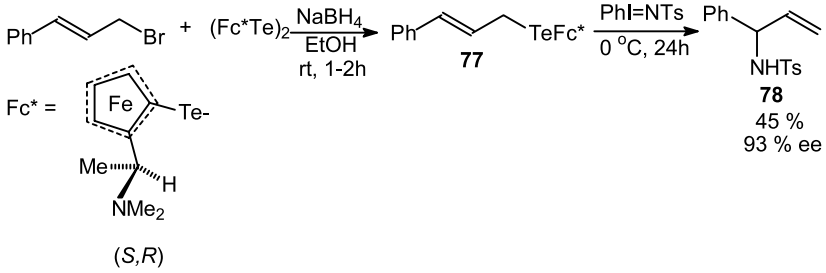
3.2.7. Allylic amine by imination of allylic tellurides. Allylic phenyl tellurides **73** are converted to the corresponding allylic amines **76** by imination with [*N*-(*p*-toluenesulphonyl)imino] phenyliodinane **74**. The reaction proceeds via [2,3]-sigmatropic rearrangement[106] of a tellurimide intermediate **75** (Scheme 80).

Similar results are obtained with chloramine T (TsNClNa).

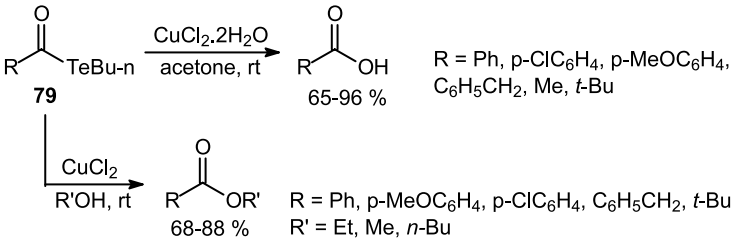
Chiral allylic amines **78** are isolated with high ee, by submitting chiral ferrocenyltellurides **77** to the above described protocol (Scheme 81).

This chirality transference parallels that observed in the oxidation of chiral allylic ferrocenyl tellurides.[70]

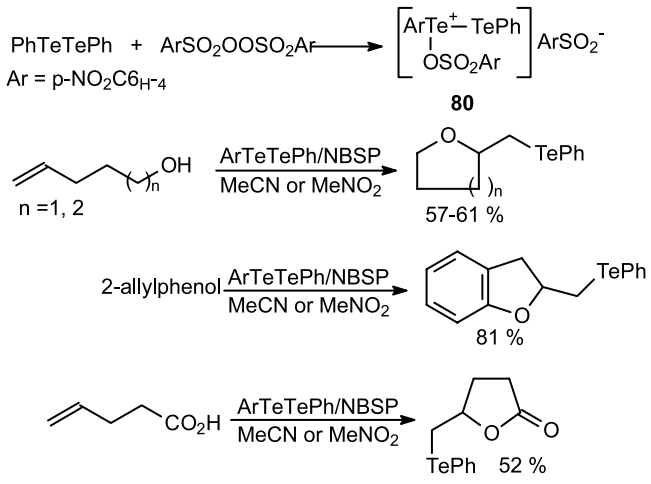
3.2.8. Hydrolysis of telluroesters to carboxylic acids and esters. Telluroesters[107] **79** can be easily hydrolyzed or converted to the corresponding oxygenated esters by treatment with $CuCl_2 \cdot$dihydrate in acetone or anhydrous $CuCl_2$ in dry ethanol or methanol[108] (Scheme 82).



Scheme 81.



Scheme 82.



Scheme 83.

3.2.9. Catalytic activity of diorganyl tellurides in oxidation reactions. Mechanistic studies have been reported concerning the oxidation of glutathione to gluthatione disulfide with diorganyl telluroxides or their hydrates[109] and the catalytic activity of diorganyl tellurides in several oxidative processes such as:

(a) oxidation of thiols with hydrogen peroxide[110]

(b) glutathione peroxidase-like activity as potent peroxide decomposing and chain-breaking anti-oxidative capacity of water soluble diorganyl tellurides[39]

(c) oxidation of sodium halides to positive halogens with hydrogen peroxide in two-phase system.[111]

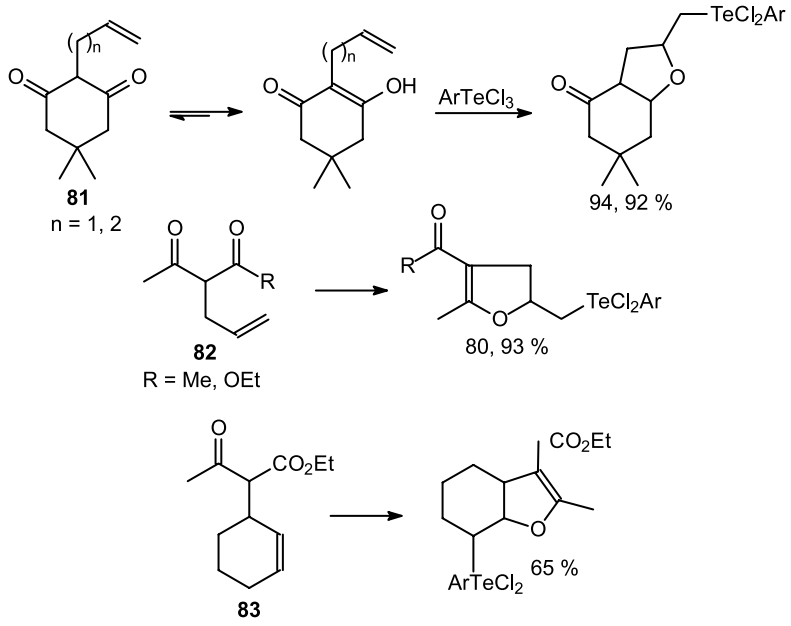
4. Tellurocyclofunctionalization of unsaturated organic substrates.[112]

Old, well-established reactions, such as lactonization of alkene carboxylic acids[113] and cyclization of unsaturated alcohols with electrophiles,[114,115] have been the subject of further investigation.

The combination of diphenyl ditelluride/*p*-nitrobenzenesulfonyl peroxide (NBSP) generates the new reagent benzenetellurenyl *p*-nitro benzenesulfonate **80** which is a remarkable eletrophilic species for tellurocyclization since it has the weak nucleophilic nitrobenzenesulfonate as a counter ion[116] (Scheme 83).

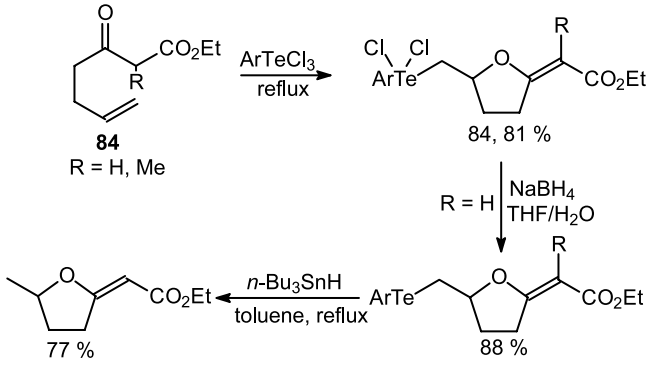
α-Alkenylsubstituted β-dicarbonyl compounds **81**–**83** undergo tellurocyclofunctionalization via an *exo*-mode process of their enolic form[117] (Scheme 84).

γ-Alkenyl substituted β-dicarbonyl compounds **84**, upon



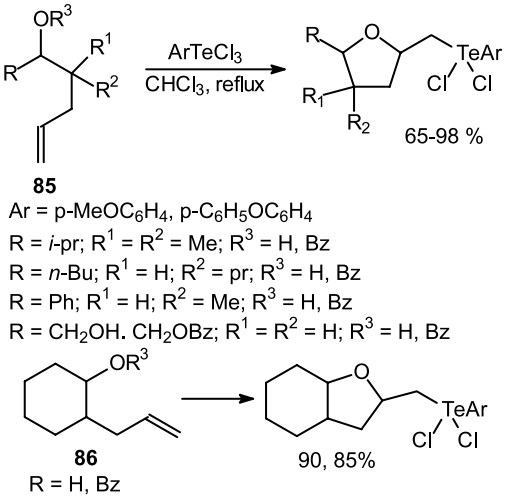
Scheme 84.

the same conditions, give rise to 2,5-disubstituted tetrahydrofurans bearing exocyclic double bonds (Scheme 85). The products, upon treatment with $NaBH_4$, are reduced to the corresponding tellurides which in turn are converted to tellurium free methyl derivatives by treatment with tributyltin hydride.[118]



Scheme 85.

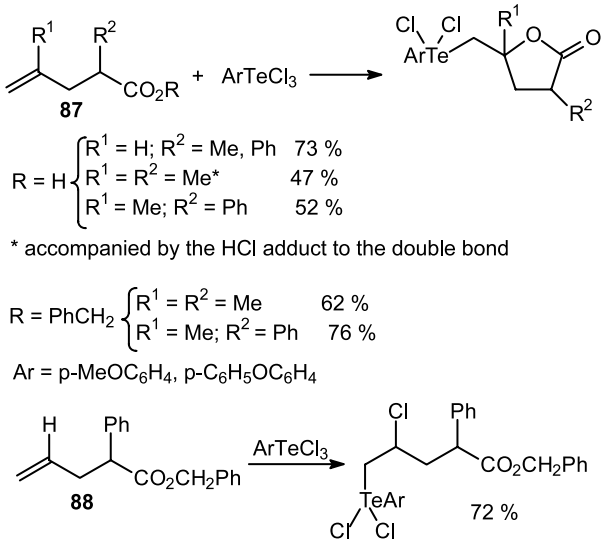
Olefinic benzyl ethers **85** and **86** have shown to be suitable substrates for ethercyclization with aryltellurium trichlorides. The yields and the reaction times are close to those observed for the cyclization of the corresponding alcohols. The stereoselectivity of the reaction is low[119] (Scheme 86).



Scheme 86.

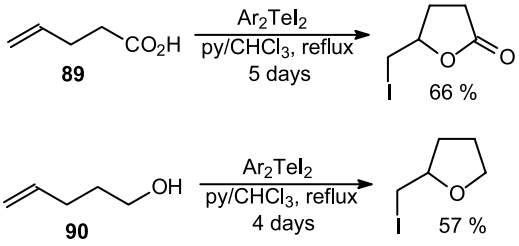
A recent report describes the influence of the substrate structure in the tellurofunctionalization reaction of γ,δ-unsaturated carboxylic acids and corresponding benzylesters.[120]

γ,δ-Unsaturated carboxylic acids **87** with monosubstituted carbon–carbon double bond react with aryltellurium trichlorides to give the expected tellurolactone, while the corresponding benzyl esters **88** give the addition products of the aryltellurium trichlorides to the double bond. 1,1-Disubstituted double bond give a mixture of tellurolactones with the HCl adducts to the double bond, whereas the corresponding benzyl ester give only the tellurolactones (Scheme 87).



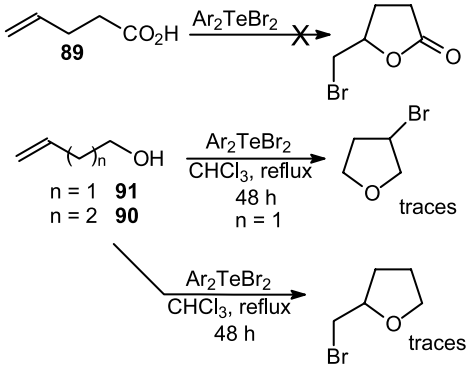
Scheme 87.

Diaryl tellurium diiodides (Ar=*p*-ClC_6H_4) afford the iodocyclization of 4-pentenoic acid **89** and 4-pentenol **90** after 5 and 4 days reflux in $CHCl_3$ in the presence of pyridine[52] (Scheme 88).



Scheme 88.

Diaryl tellurium dibromides are unreactive toward 4-pentenoic acid **89** and give only traces of bromo tetrahydrofurans with 3-butenol and 4-pentenol[52] **90–91** (Scheme 89).



Scheme 89.

5. Telluroheterocycles

5.1. 3-Benzotellurepine

3-Benzotellurepine **92** has been prepared by the addition of Na_2Te to *o*-diethynylbenzene in the presence of hydrazine hydrate, under PTC conditions. The compound is quite unstable but is converted to the more stable dihalides **93** by treatment with SO_2Cl_2 or Br_2. The dihalides regenerate the tellurepine by reduction with Na_2S[121] (Scheme 90).

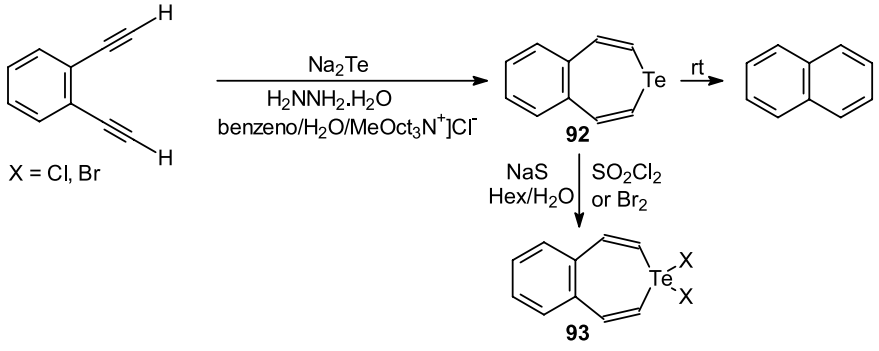
5.2. 1-Benzotellurepines, benzotellurochromenes, benzo[*b*]tellurophenes and tellurochromones

The intramolecular version of the anti-hydrotelluration of alkynes has been applied to synthesize 1-benzotellurepine **95** and benzotellurochromenes[122] **96** (Scheme 91), benzo[*b*]tellurophene[123] **98** (Scheme 92) and tellurochromones[124] **100** (Scheme 93).

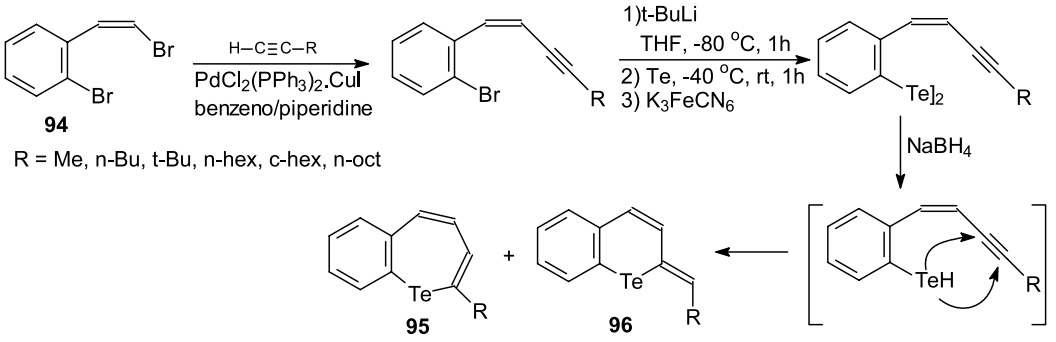
The starting acetylene substrates are prepared by the Pd^{+2} catalyzed coupling of the alkynes with the apropriate *o*-substitutes bromobenzenes **94**, **97** and **99**.

The coupling of **99** with trimethylsilylacetylene (route a) does not proceed, but a Stille reaction of **99** with a tin derivative gives the desired product **100**. In this case the desilylated tellurochromone **101** (R=H) was formed in 5% due to the reductive removal of the TMS group.

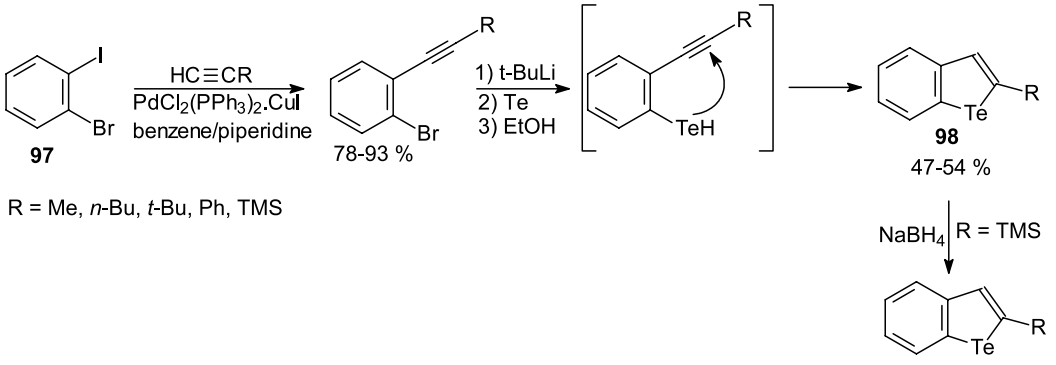
The 2-*tert*-butyl-1-benzotellurepine **95**. (R=*tert*-But) was submitted to several synthetically interesting manipulations[122b] (Scheme 94).



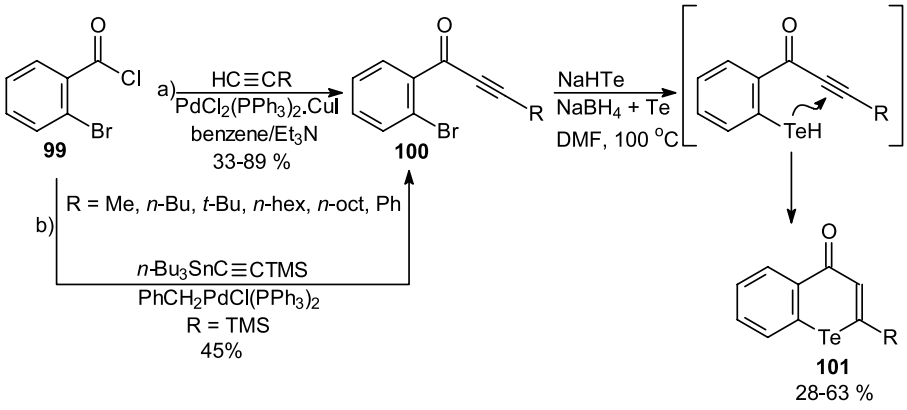
Scheme 90.



Scheme 91.



Scheme 92.



Scheme 93.

5.3. Benzo[*c*]tellurophenes

Benzo[*c*]tellurophenes have been synthesized starting from *o*-bishalomethyl benzenes[125] **102** as depicted in Scheme 95.[126]

The following features are noteworthy.

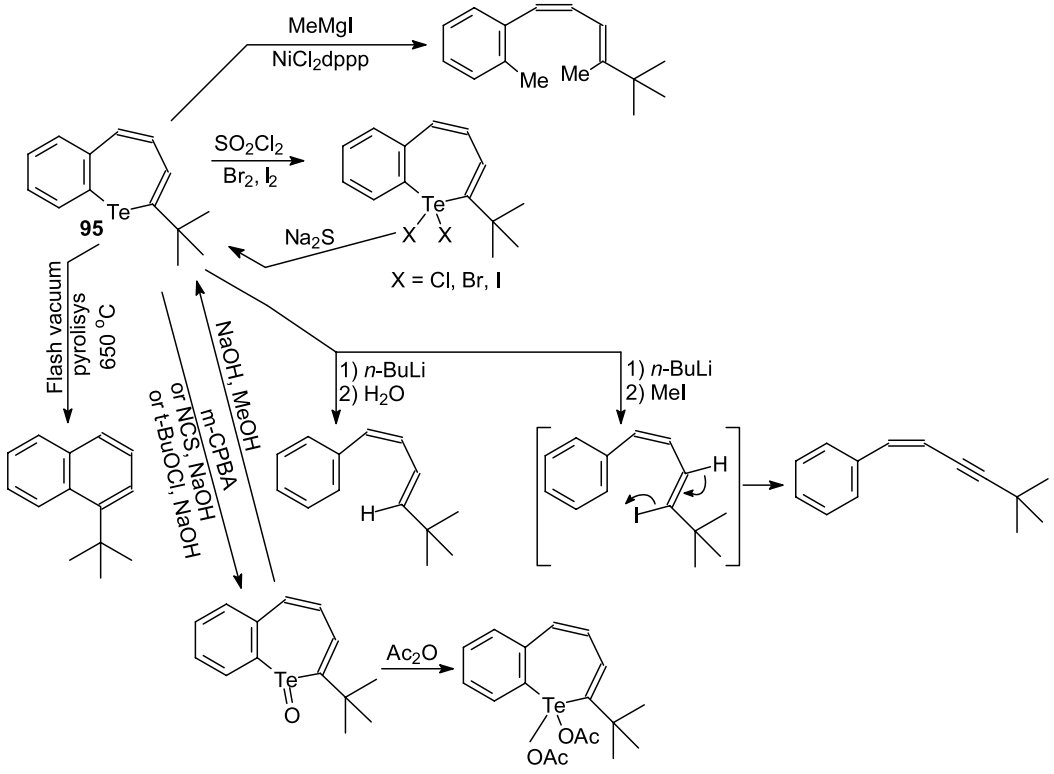
In the case of R=H and MeO, all the attempts to convert the diiodide **103** to the tellurophene **105** by direct elimination of HI with a base, failed. Such conversion was attained via the bistrifluoroacetate **104**. However, as expected, the nitro derivative **103** (R=NO_2) undergoes facile dehydroiodination upon treatment with Et_3N.

Benzotellurophene **105** (R=H) is stable only in benzene solution at low temperature. The derivatives **106** and **107** are more stable, as well as the nitro-derivative **105** (R=NO_2). Medium to good yields are reported in all the steps of Scheme 94.

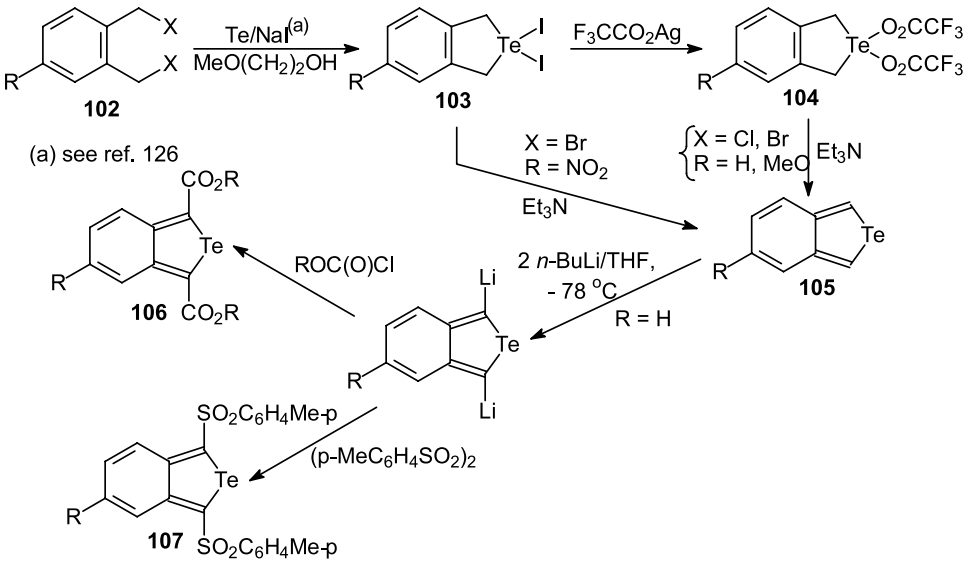
The same protocol was applied to the dibromomethyl thiophene derivative **108** to give **109** and the anellated thiophene–tellurophene compound **110**, which is the first Te-containing diheteropentalene[127] (Scheme 96).

Compound **110**, recognized by NMR, cannot be isolated but gives the dimeric product **111** and the reduced compound **112**.

Treatment of the dimeric **111** with dimethylacetylene dicarboxylate (DMAD) gives the adduct **113**, resulting from the addition to the tellurophene portion of **110**. The addition of dimethylacetylene dicarboxylate (DMAD) to the thiophene portion to give **114** does not work.



Scheme 94.



Scheme 95.

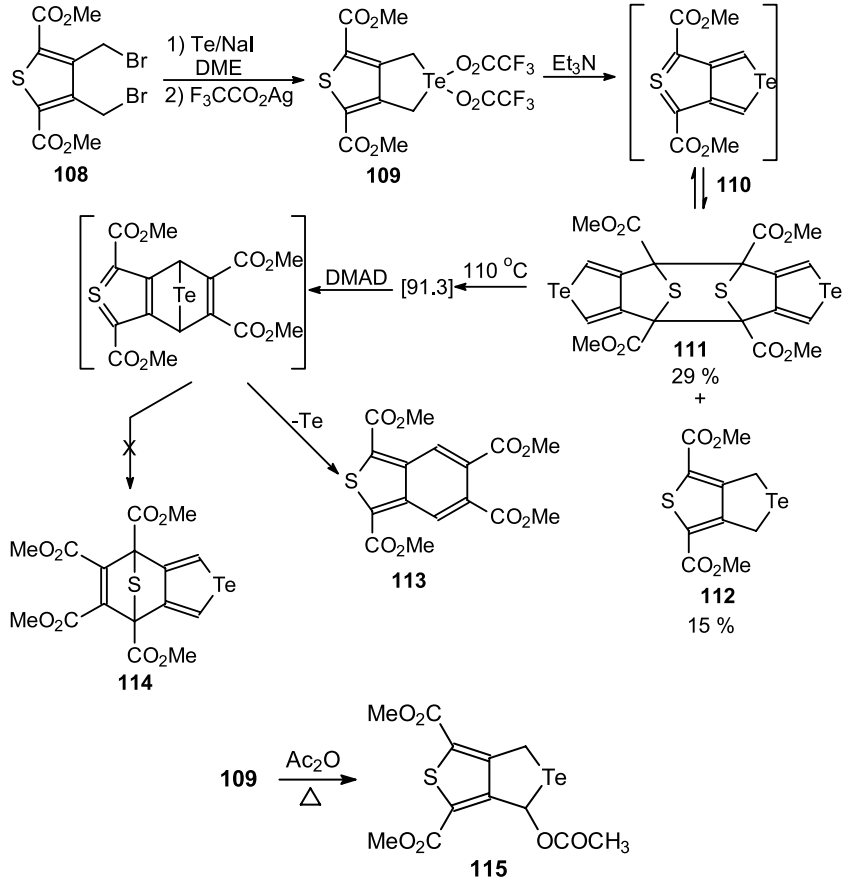
The attempted Ac_2O-catalized Pummerer reaction of **109** furnished only compound **115** in low yield, identified by NMR and MS.

5.4. Benzene fused five membered heterocycles containing tellurium, selenium and sulfur.[128]

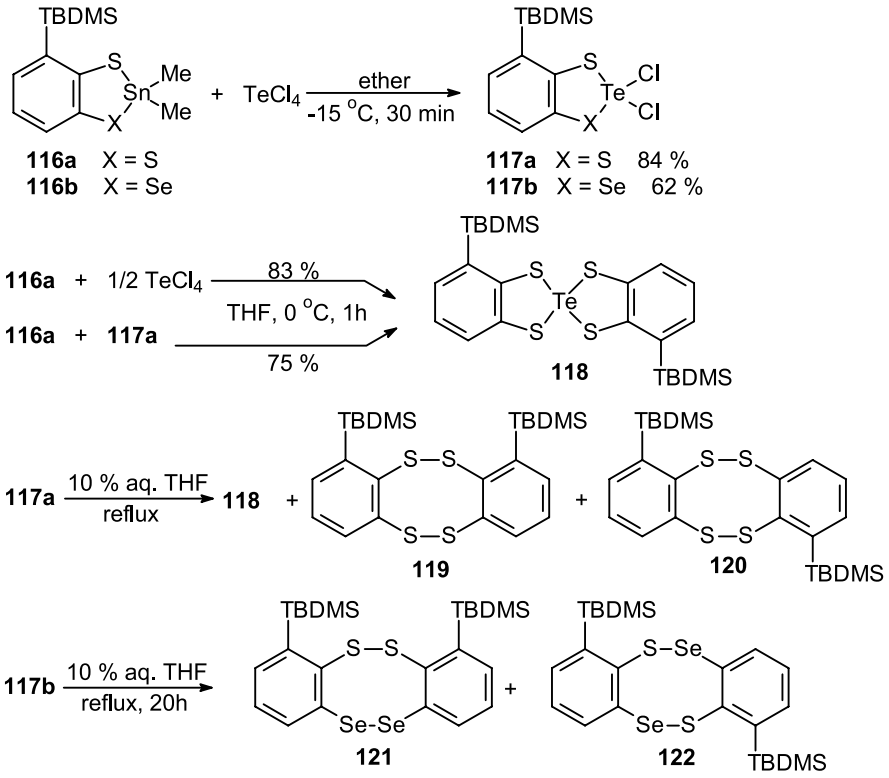
The reaction of the stannoles **116a** and **116b** with $TeCl_4$ affords the substitution of the dimethyltin moiety by the dichlorotelluro group to give the thio and selenodichloro tellurole **117a** and **117b**.

The spiro tellurole **118** is obtained by treatment of **116a** and **116b**, respectively, with 0.5 equiv of $TeCl_4$ or with **117b**.

When **117a** is treated with aqueous THF at reflux a mixture



Scheme 96.



Scheme 97.

of **118** and tetrathiocins **119** and **120** is formed in ratios which depend from the heating time.

Even more **117b**, submitted to the same treatment, yields a mixture of **121** and **122**, tetrachalcogenines containing both sulfur and selenium in the eight membered ring[128] (Scheme 97).

5.5. 3-Iodotellurophenes by iodocyclization of *Z*-butyltellurobutenines

Treatment of *Z*-butyltellurobutenines **123** with iodine in petroleum ether produces 3-iodotellurophenes[129] **126** (Scheme 98).

This conversion involves the intermediacy of the iodonium ion **124** which suffers the attack of the iodide anion, promoting cyclization through the tellurenyl iodide **125** (pathway a) or by the direct pathway b, giving **126a**.

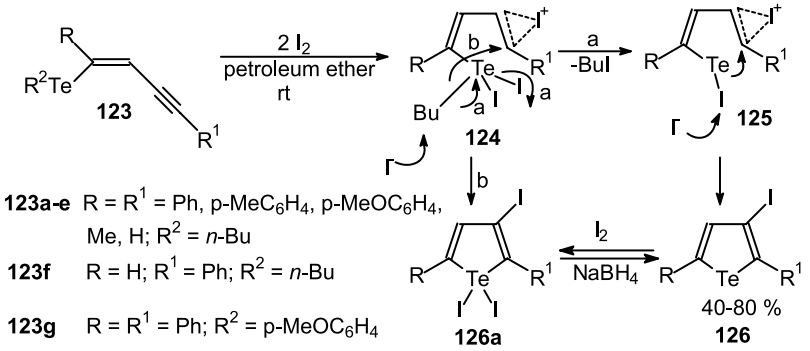
The crude products are treated with aqueous $NaBH_4$ to remove excess of I_2 and reduce the formed diiodide **126a** to **126**.

The treatment of **126** with 0.75 equiv of *n*-BuLi at −78 °C leads to the ditelluride **127**, whereas telluride **128** is formed by the slow addition of 2 equiv of *n*-BuLi at room temperature. These conversions have been rationalized as depicted in Scheme 99.

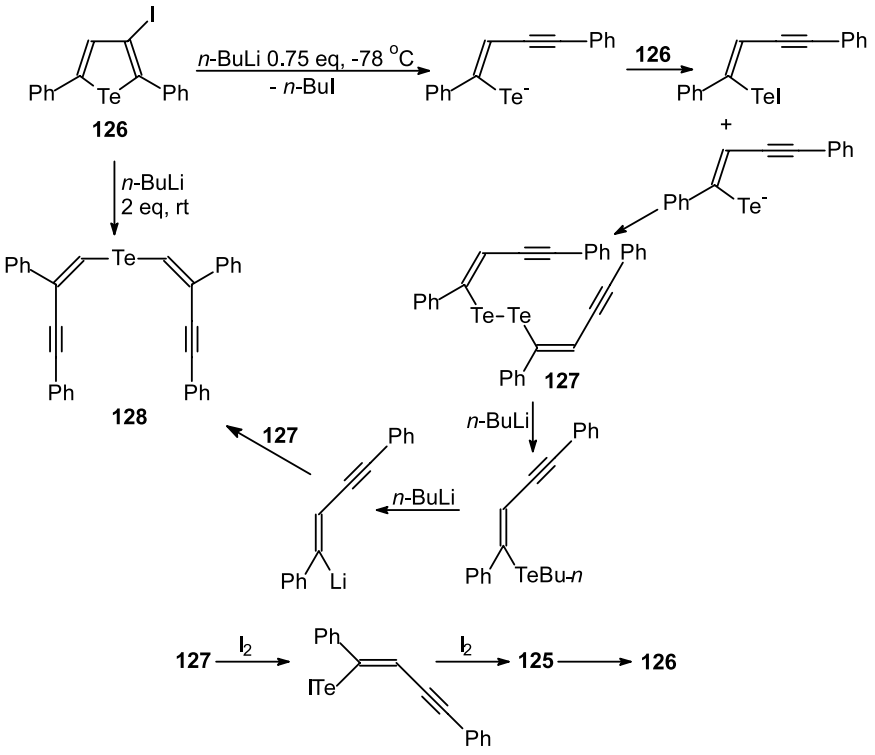
An additional evidence of the intermediacy of **125** (pathway a, Scheme 97) is the formation of **126** by treatment of **127** with iodine.

The structures of **126** (R=R^1=Ph) and **123g** were elucidated by X-ray crystallography.

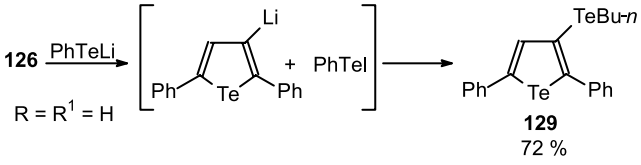
In additional experiments the iodotellurophene **126** was treated with 1.0 equiv of *n*-BuTeLi to give the



Scheme 98.



Scheme 99.



Scheme 100.

corresponding butyltelluro substituted compound **129** (Scheme 100), which is the result of an unexpected nucleophilic substitution.

5.6. Tellurophenes from tellurobutenines under Rupe reaction conditions

The *Z*-butyltellurobutenines **123** upon treatment with boiling 85% formic acid is converted in to the 3-telluro-substituted tellurophene **130**. The structure was confirmed by X-ray crystallography of the corresponding dichloride[130] **131**.

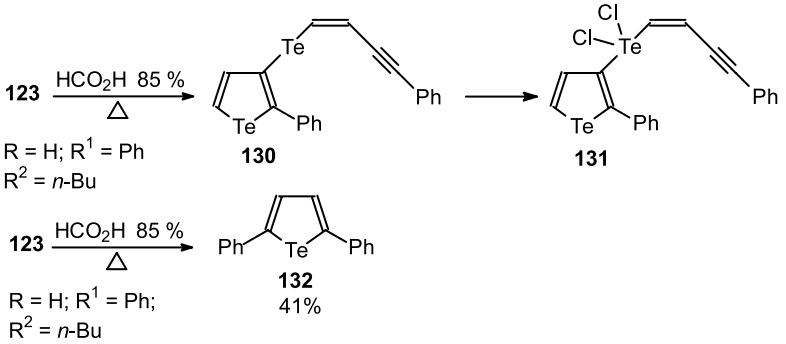
Under the same conditions the phenyl substituted substrate **123** is partially converted into the diphenyl tellurophene **132** (Scheme 101).

5.7. 1,5-Ditelluracyclooctane and 5*H*,7*H*-dibenzo[*b*,*g*]-[1,5]tellurothiocin

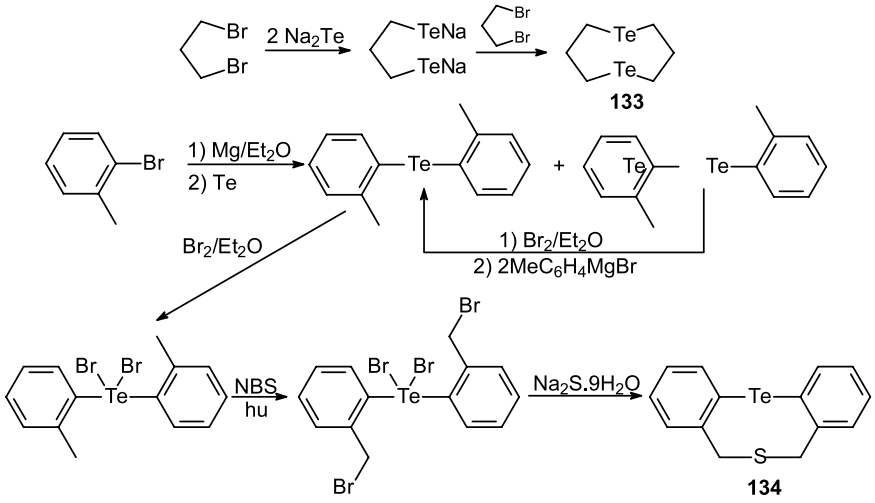
The title compounds **133** and **134** are synthesized in accordance with the self-explicative Scheme 102.[131,132]

The transannular bond formation between Te–Te and Te–S bond giving the dications **135** and **136** is afforded by treatment of compounds **133** and **134** with the oxidizing agents nitrosyl tetrafluoroborate and hexafluorophosphate or with D_2SO_4 (Scheme 103).

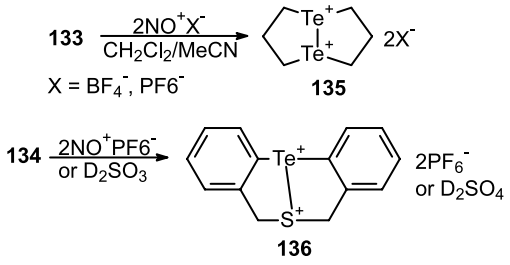
The dications, characterized by spectroscopic means, are



Scheme 101.



Scheme 102.



Scheme 103.

useful oxidizing agents as shown by the oxidation of thiophenol to diphenyl disulfide by dication **135** and **136** as well as of diphenyl hydrazine to azobenzene by dication **136**.

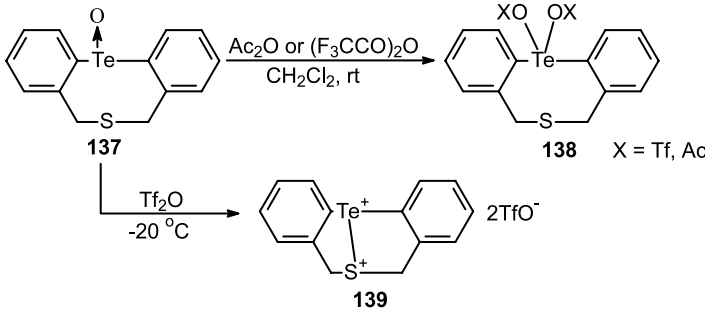
In addition, the telluroxide **137**, prepared by hydrolysis of the dibromide derived from **134** reacts with acetic anhydride and trifluoroacetic anhydride to give the tellurane **138**. The tellurothio dication **139** is formed by treatment of **137** with triflate anhydride[133] (Scheme 104).

5.8. Ditellurane derivatives

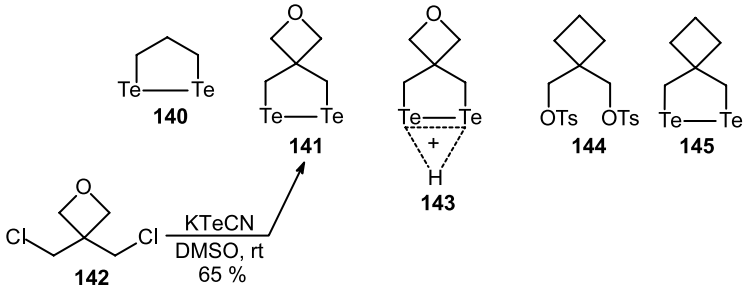
1,2-Ditellurane **140** is an elusive compound which has been detected only in organic solvent solution.

The spiro ditellurolane **141** was obtained by the reaction of 3,3-bis(dichloromethyl)oxetane **142** with potassium tellurocyanide (KTeCN) in DMSO[134] (Scheme 105).

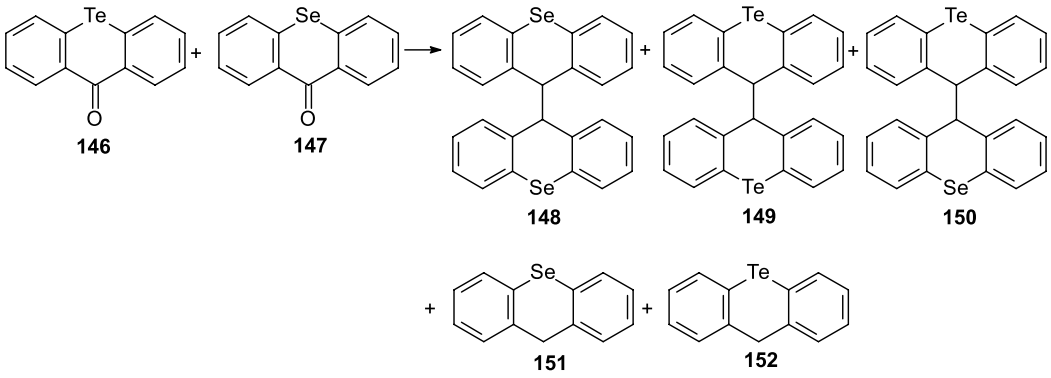
Unequivocal confirmation of its structure was furnished by



Scheme 104.



Scheme 105.



Scheme 106.

X-ray crystallography analysis. Compound **141** forms a blue solution in a variety of solvents. Its solution in benzene shows ESR signal.

An unusual feature of **141** is a π-type conjugation between the two Te atoms, in accordance with the observation that the blue solution of the compound in MeCN becomes orange upon addition of a strong acid. These observations are consistent with protonation of the Te–Te bond to form the new symmetrical π-complex **143**.

The protonation is reversible, the blue ditelluride color reappearing by the addition of pyridine. The carbocyclic analog **145** was synthesized in low yield, by analogous method starting from **144**.

5.9. Reductive dimerization of telluro- and selenoxanthone

By treating an equimolar mixture of telluroxanthone **146** and selenoxanthone **147** with Zn powder in boiling HOAc and concentrated HCl (100:1.25) for 1 h, a reductive dimerization takes rise giving the dimerized products **148**, **149** and **150** in the ratio 21(**148**):35(**149**):44(**150**) in addition to telluroxanthone **151** and selenoxanthone[135] **152** (Scheme 106).

The observed distribution of the products, compared with the statistical distribution 25:25:50, clearly indicates that the Te/Te bridged **149** is preferred over the Se/Te bridged **150** and Se/Se bridged **148**, while **150** is preferred over **148**.

5.10. Tellurosteroids

The tellurolactone of estrone series **154** was synthesized, starting from the estratien-17-one **153**[136] in accordance with Scheme 106 (Scheme 107).

6. Free radical chemistry

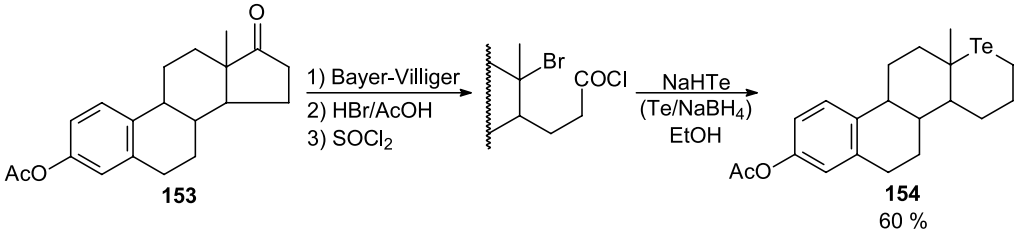
Increasing interest has been directed over the last years to organic radical reactions as a method for organic synthesis.[137]

Special attention was focused on organotellurium compounds as precursors for carbon cantered radicals.

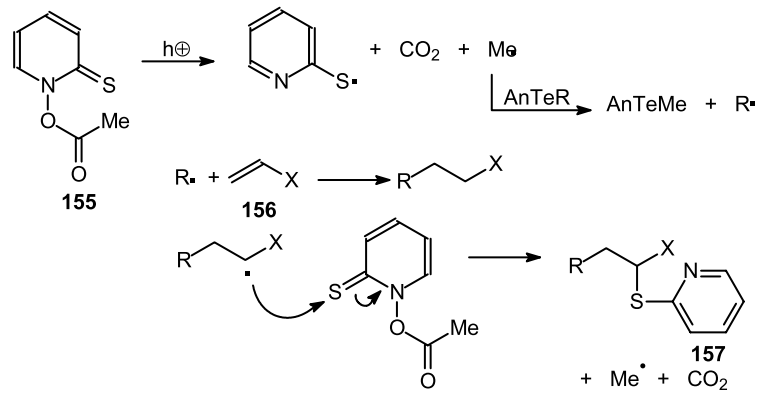
6.1. Organyl tellurides as exchangers of carbon radicals

Organic tellurides recently attained an important role in free radical chemistry.

If *N*-hydroxy-2-thiopyridone **155**, a suitable source of methyl radical, is irradiated with a simple tungsten lamp in the presence of an alkyl anisyl telluride, a radical exchange takes place, giving methyl anisyl telluride and a new alkyl radical. In the presence of an electrophilic olefin **156** a tandem addition occurs with the participation of the thiocarbonyl function of the starting reagent giving the pyridine derivative **157**. A methyl radical is regenerated and a new cycle begins giving the pyridine derivative[138] **157** (Scheme 108).



Scheme 107.



Scheme 108.

This type of radical chemistry is a useful tool for the synthesis or manipulation of complex natural products.

6.2. Tellurium mediated addition of carbohydrates to olefins

Scheme 109 illustrates the application of the just described approach to a carbohydrate anisyl telluride **157** (easily prepared from the corresponding mesylate or tosylate and anisyl tellurolate anion).

The oxidative elimination of the thiopyridine moiety from the product **158** leads to olefinic derivative[138b] **159**.

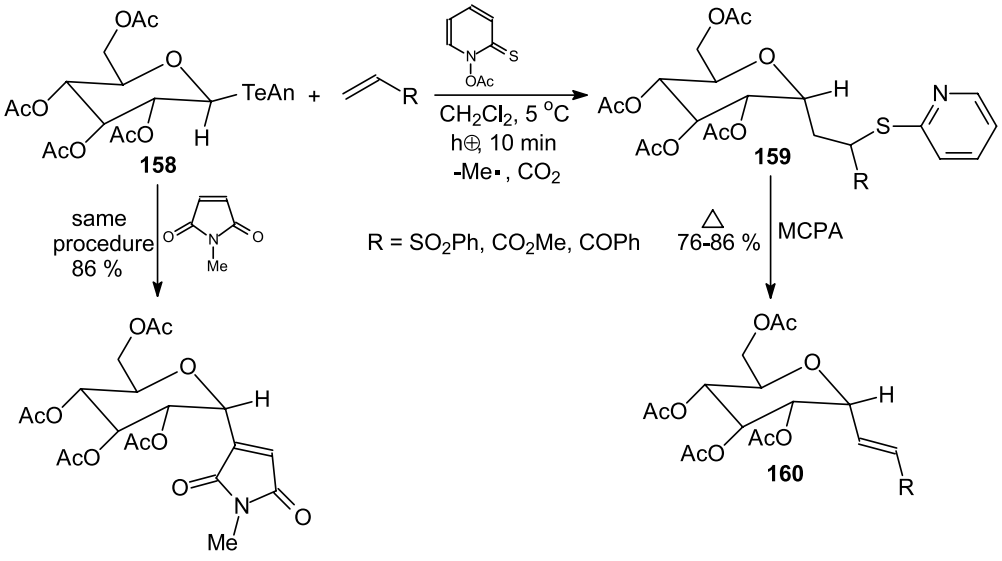
The synthesis of the antibiotic showdomicin **162** starts from a ribose anisyl telluride[138b] **161** (Scheme 110).

6.3. Intramolecular radical cyclization

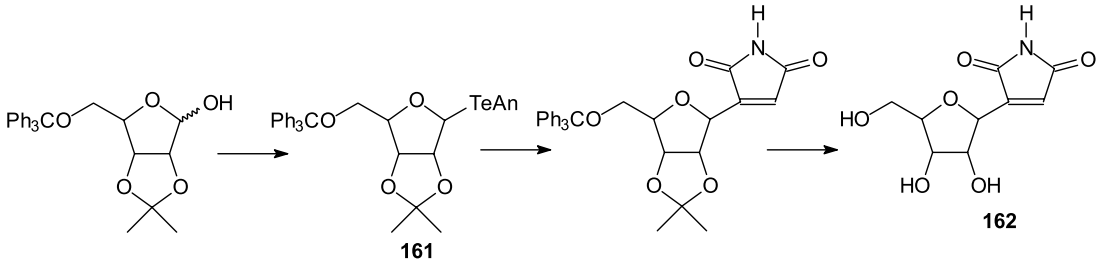
The intramolecular version of the described radical exchangers furnishes an easy approach to the synthesis of six membered carbocycles[139] **163** (Scheme 111).

6.4. Synthesis of cyclo-nucleosides

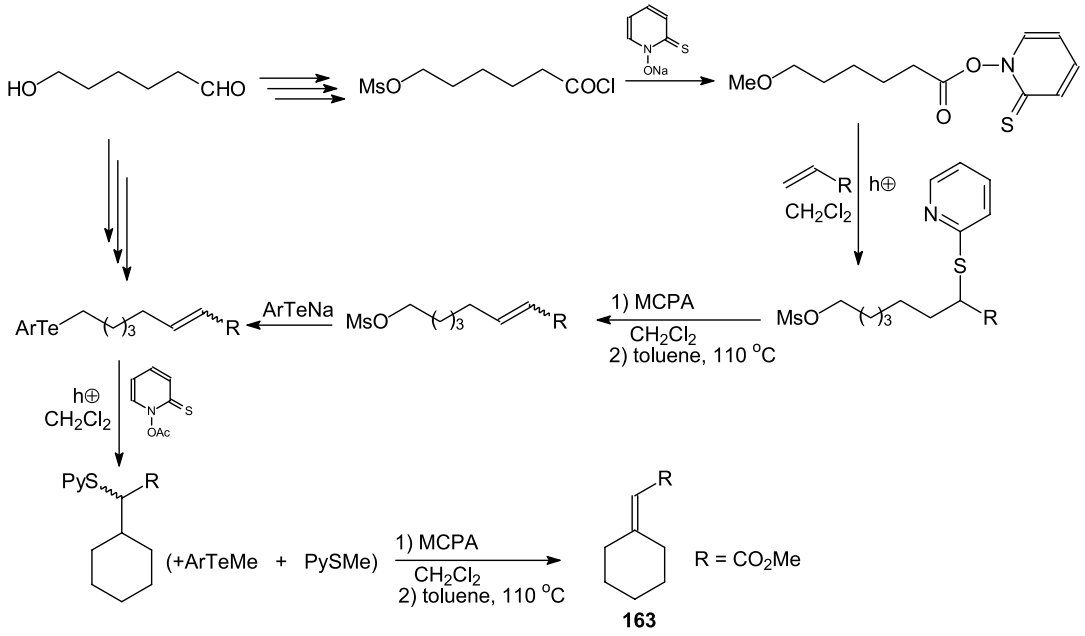
Scheme 112 illustrates the synthesis of cyclo-5,6-dihydro-uridine[140] **164**.



Scheme 109.



Scheme 110.

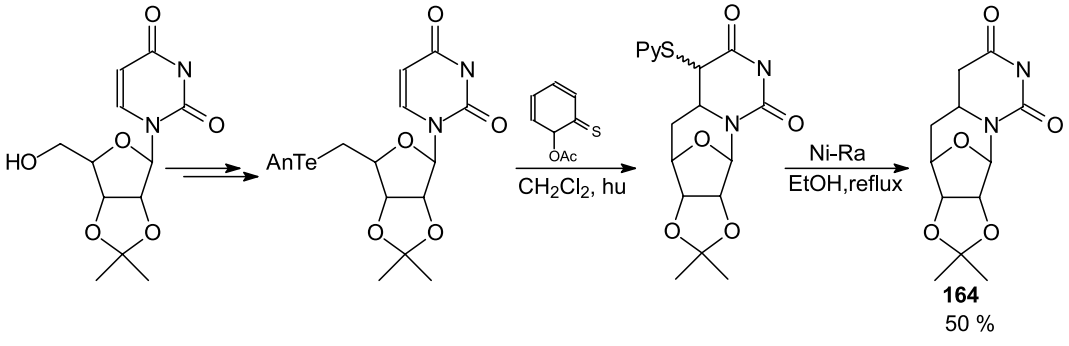


Scheme 111.

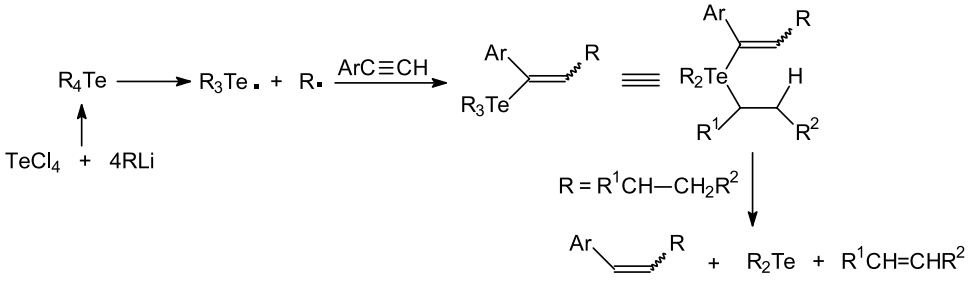
6.5. Reactions of tetraorganyl telluriums with acetylenes

Tetralkyltelluriums, prepared in situ by the reaction of tellurium tetrachloride with 4 equiv of alkyllithiums react with arylacetylenes to afford alkylation products, dialkyltellurides and an alkene[141] (Scheme 113). The alkylation is rationalized as involving the radical addition of R_4Te to the acetylene and the decomposition of the formed adduct to afford the dialkyltelluride and the olefin, originated from the displaced alkyl moiety via transfer of an hydrogen to the vinyl cation.

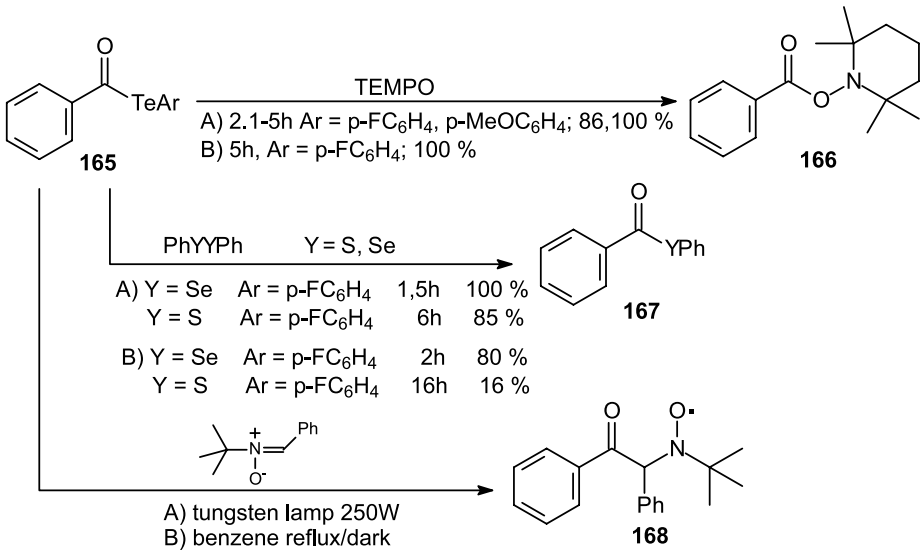
The alkylation proceeds mainly via a *trans* mode giving *cis* 1,2-disubstituted adducts. When an excess of phenylacetylene is used, the yield of the alkylation product is raised (98% *E*/*Z*=9/91), indicating that the alkylation competes with the self-degradation of *n*-Bu_4Te (to *n*-Bu_2Te, butane and octane).



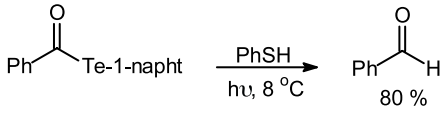
Scheme 112.



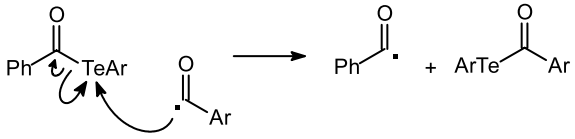
Scheme 113.



Scheme 114.



Scheme 115.



Scheme 116.

An electron-donating (MeO) or an electron withdrawing (F) substituent linked to the benzene ring is without effect in the reaction.

Alkylacetylenes, such as 1-octyne are unreactive at all. The reaction of tetradecyltellurium with 2 equiv of phenylacetylene gives rise to PhCH=CHDec-*n* (86%, *E*/*Z*= 14/86), *n*-Dec_2Te (92%) and 1-decene (91%).

The reaction of dibutyldidecyl tellurium with phenylacetylenes yields nearly statistical ratios of products. PhCH=CHBu-*n* (41%, *E*/*Z*=10/90), PhCH=CHDec (35%, *E*/*Z*=11/89), Bu_2Te (20%), *n*-BuTeDec (41%) and Dec_2Te (18%) as a result of a random transfer of primary alkyl substituents.

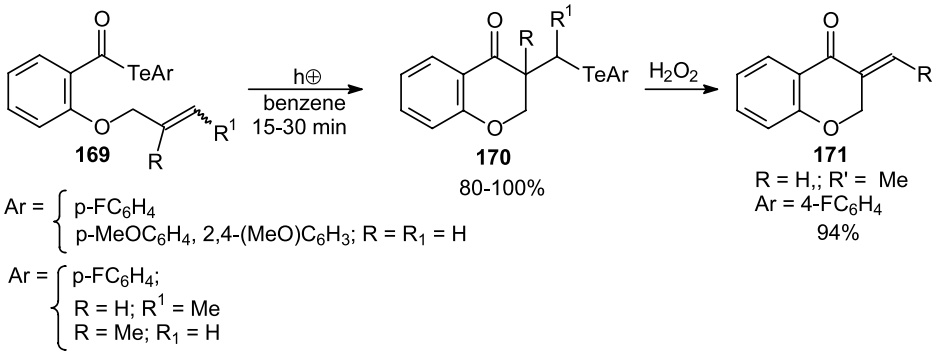
In contrast, di-*n*-butyl-di-*i*-propyl tellurium reacts faster than *n*-tetrabutyl tellurium giving only PhCH=CH*i*-pr, tetraphenyl tellurium does not react at all and *n*-Dec_2TePh_2 decomposes to *n*-DecTePh (95%), 1-decene (93%) and benzene (89%).

6.6. Telluroesters as source of acyl radicals

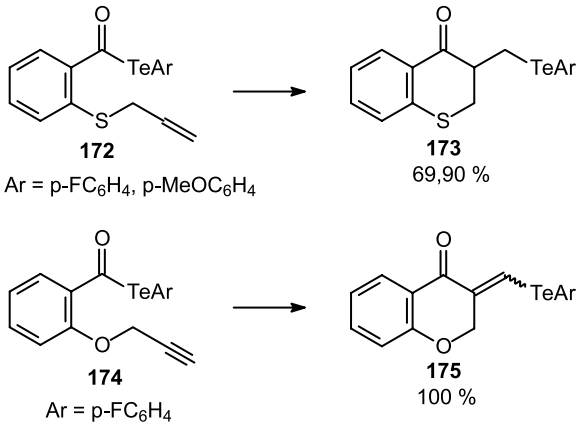
Telluroesters (acyl tellurides) **165** have been recognized as excellent sources of acyl radicals upon photolysis with a 250 W tungsten lamp, or thermal process (benzene at reflux) in the dark.

The formed acyl radicals are reactive toward efficient radical trapping reagents such as 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO), diphenyl diselenide, diphenyl disulfide, *N*-*tert*-butyl-α-phenylnitrone[142–144] giving, respectively, the adducts **166–168** (Scheme 114).

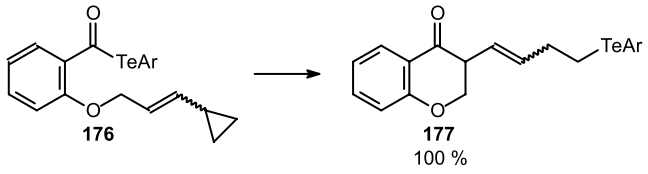
A further evidence fot the generation of acyl radicals is the formation of benzaldehyde on photolysis of benzoyl-1-



Scheme 117.



Scheme 118.



Scheme 119.

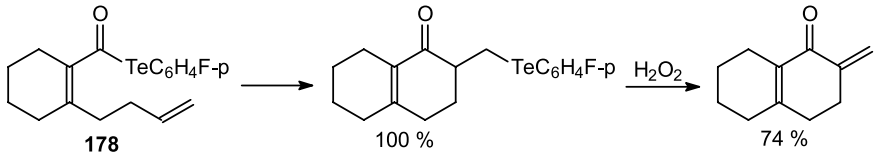
naphtyl telluride in the presence of thiophenol (Scheme 115).

These results, which could be supported in terms of homolysis of the Ac–Te bond with capture of the acyl radical by the trapping reagents, have been rationalized, however, on the basis of further experiments, as a degenerated background reaction in which an acyl radical abstracts an aryltelluro group from an additional molecular of acyl telluride (Scheme 116).

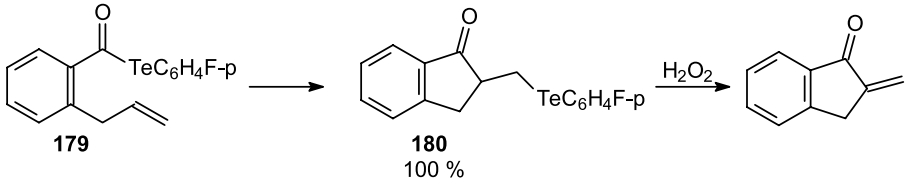
Telluroesters **169** have been employed in highly efficient radical cyclizations with transfer of the arylTe group.[144] Scheme 117 illustrates the formation of 3-(aryltelluro)-methyl or ethyl chromanones **170** via an *exo* mode cyclization.

Compounds **170** are relatively unstable, and treatment with hydrogen peroxide promotes telluroxide elimination to give the corresponding α-methylene ketones **171**.

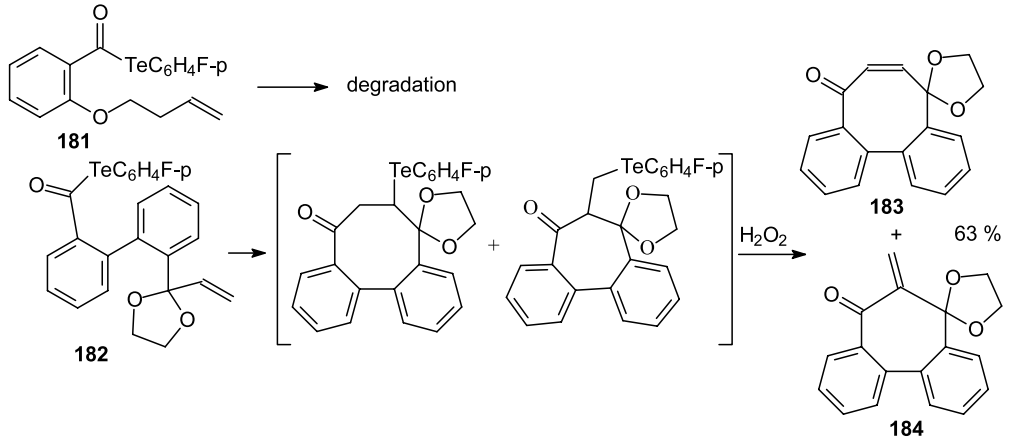
The thio analogue **172** behaves similarly, giving compound **173**, whereas the propargylic derivative **174** is converted to the stable vinylic telluride **175** (Scheme 118).



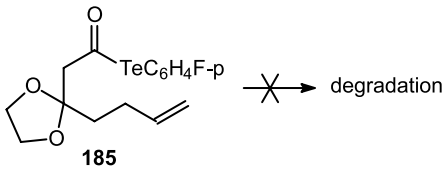
Scheme 120.



Scheme 121.



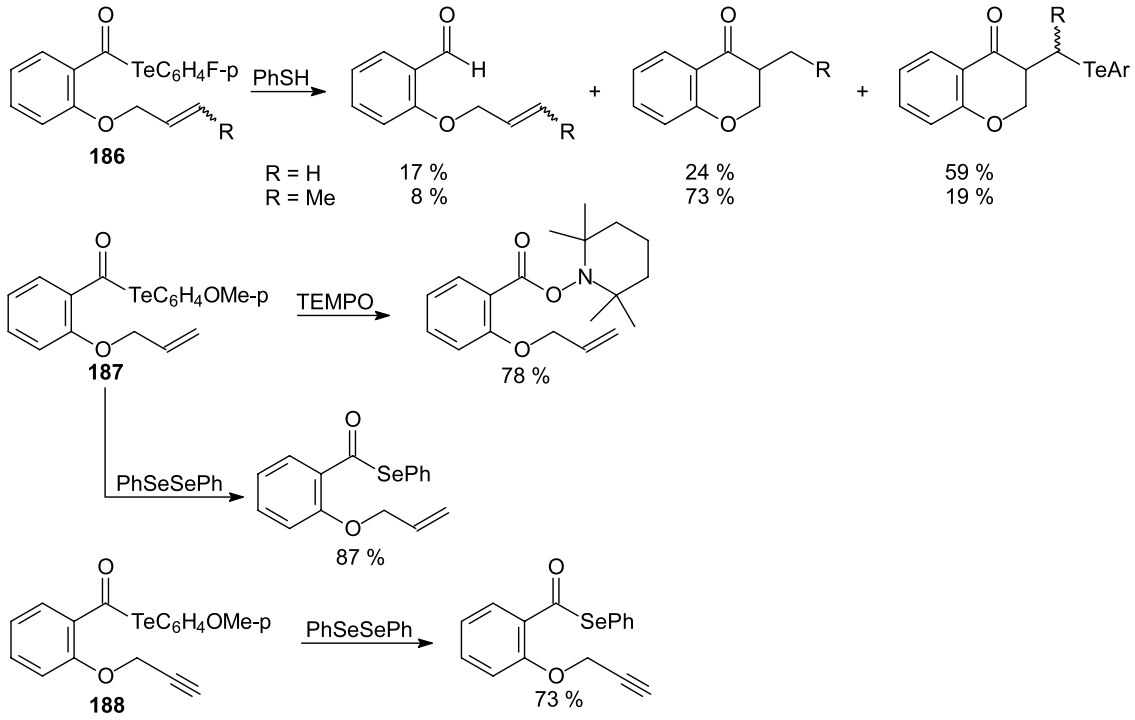
Scheme 122.



Scheme 123.

A series of experiments were effected carrying out the photolysis of substrates **186–188** in the presence of thiophenol, TEMPO, PhSeSePh, PhSSPh where the radical captors compete with the 6-*exo* cyclization in trapping the acyl radical[144] (Scheme 124).

Diphenyl disulfide has shown to be a poor radical captor.



Scheme 124.

Cyclization of substrate **176** proceeds with concomitant cleavage of the cyclopropyl ring giving **177** (Scheme 119).

The α,β-unsaturated acyltelluride **178** also takes part in the photolitic cyclization (Scheme 120).

Each of the above cyclizations proceeds upon a 6-*exo*-trig mode process promoting the formation of six-membered rings as opposed to the more common five-membered ring formation.

A 5-*exo* trig cyclization takes rise by irradiation of substrate **179** giving the five-membered ring **180** (Scheme 121).

Eight-membered ring was not achieved by photolysis of substrate **181** but the more conformationally unstrained substrate **182** undergoes a 8-*endo* cyclization giving a 3.7:1 mixture of compounds **183** and **184** after a treatment with H_2O_2 (Scheme 122).

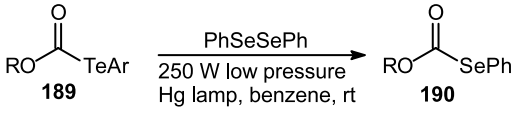
As shown, each of the above described cyclizations involves an acyltelluride group directly conjugated with an aromatic ring or with an alkene. Noteworthy non-conjugated aliphatic acyl tellurides such as **185** are unable to be cyclized (Scheme 123).

6.7. Aryl telluroformates as precursors of oxyacyl and alkyl radicals

Photolysis at room temperature of aryl telluroformates **189** gives rise to oxoacyl radicals which can be trapped with diphenyl diselenides giving the corresponding phenyl selenoformates[35] **190** (Scheme 125).

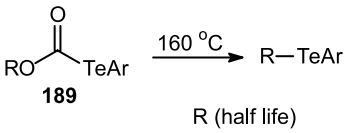
Each of the reactions were performed in NMR tubes and a half-life of 15 h, 11 and 14 h, 10 h, 6 h was found for methyl, primary alkyl, *c*-hexyl, and benzyl (phenyltelluro)formates.

On the other hand, thermolysis of the telluroformates at 160 °C in the dark leads to the formation of alkyl aryl



Ar = Ph, p-FC_6H_4, p-$MeOC_6H_4$; R = Me
Ar = Ph, p-FC_6H_4; R = *i*-Bu, c-hex, 3″-cholestanyl
Ar = Ph ; R = *n*-C_8H_{17}; $C_6H_5CH_2$, 3″-cholesteryl

Scheme 125.



Ar	R (half life)
Ph	Me (33 d), *i*-Bu (19 d), $C_6H_5CH_2$ (8 h), c-hex (6 d)
p-FC_6H_4	*i*-Bu (12 d), c-hex (6 d)
Ph, p-FC_6H_4	β-cholestanyl (10, 11 d)

Scheme 126.

tellurides in good yields, presumably through the transient oxyacyl radicals which undergo thermal decarboxylation to afford alkyl radicals (Scheme 126).

Some runs have been carried out in preparation scale.

Ar=Ph; R=*c*-hex (71%). Ar=Ph; R=α and β-cholestanyl (85%).

Finally, thermolysis of the telluroformate **191** gave benzylphenyl telluride and the methyl selenane **192** (Scheme 127).

6.8. Aryltelluroformates as precursors of selenium containing heterocycles

The seleno substituted telluroformates **193**, synthesized according to the sequence depicted in Scheme 128, are converted to selenium containing heterocycles **195** and **196** by photolitic or thermal process[145] (Scheme 128).

The conversion of the oxyacyl radical **194** into cyclic compound **195** can be considered as the first example of intramolecular homolitic substitution at selenium, whereas the formation of the compounds **196** must likely involve a nucleophilic attack by the selenium moiety with decarboxylative removal of phenyltellurolate.

6.9. 2-Allyloxy and 2-propargyloxy alkyl tellurides as precursors of tetrahydrofuran derivatives

Compounds **197–202** easily prepared by the opening of monosubstituted epoxides with sodium aryl tellurolates, followed by allylation and propargylation of the obtained β-hydroxytellurides, submitted to irradiation with a sun lamp in the presence of hexabutylditin, suffer group transfer cyclization under 5-*exo* mode to give the 2,4-disubstituted tetrahydrofuran[146] **203–208** (Scheme 129).

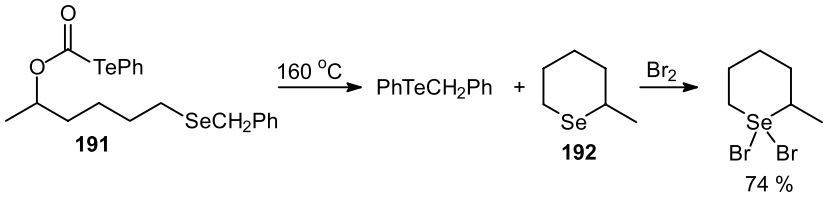
6.10. Telluroglycosides as source of glycosyl radicals

Telluroglycosides **209** generate glucosyl radicals by homolitic C–Te bond cleavage promoted by photolysis with a UV lamp, or by thermolysis at 140 °C in the dark.[147]

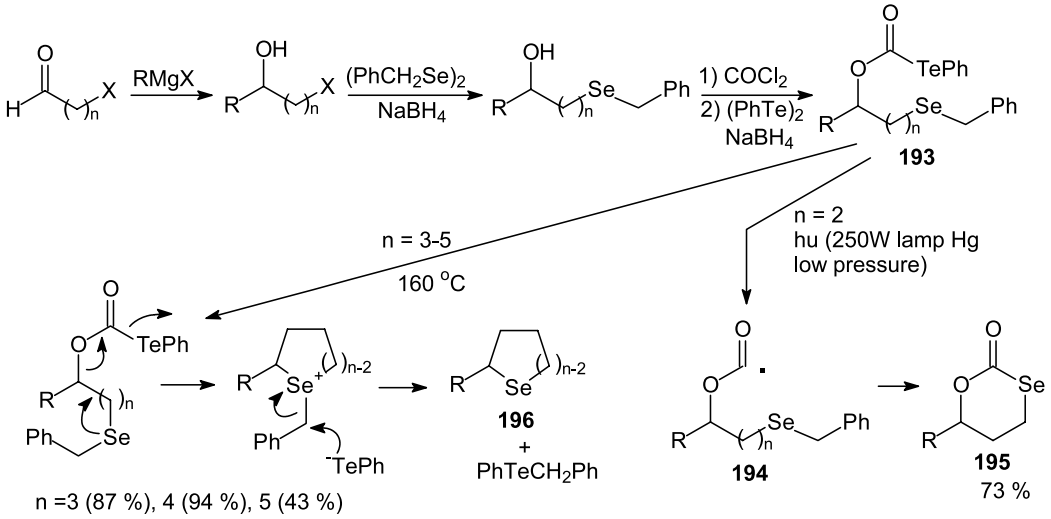
A rapid equilibration of the β-isomer (substrate **209**) into the α-isomer **210** takes rise by a unimolecular radical mechanism, giving a 83:17 α,β-mixture. The same mixture is formed by irradiation of the pure α-isomer.

These results reveal that the α-isomer is thermodynamically more stable than the β-isomer.

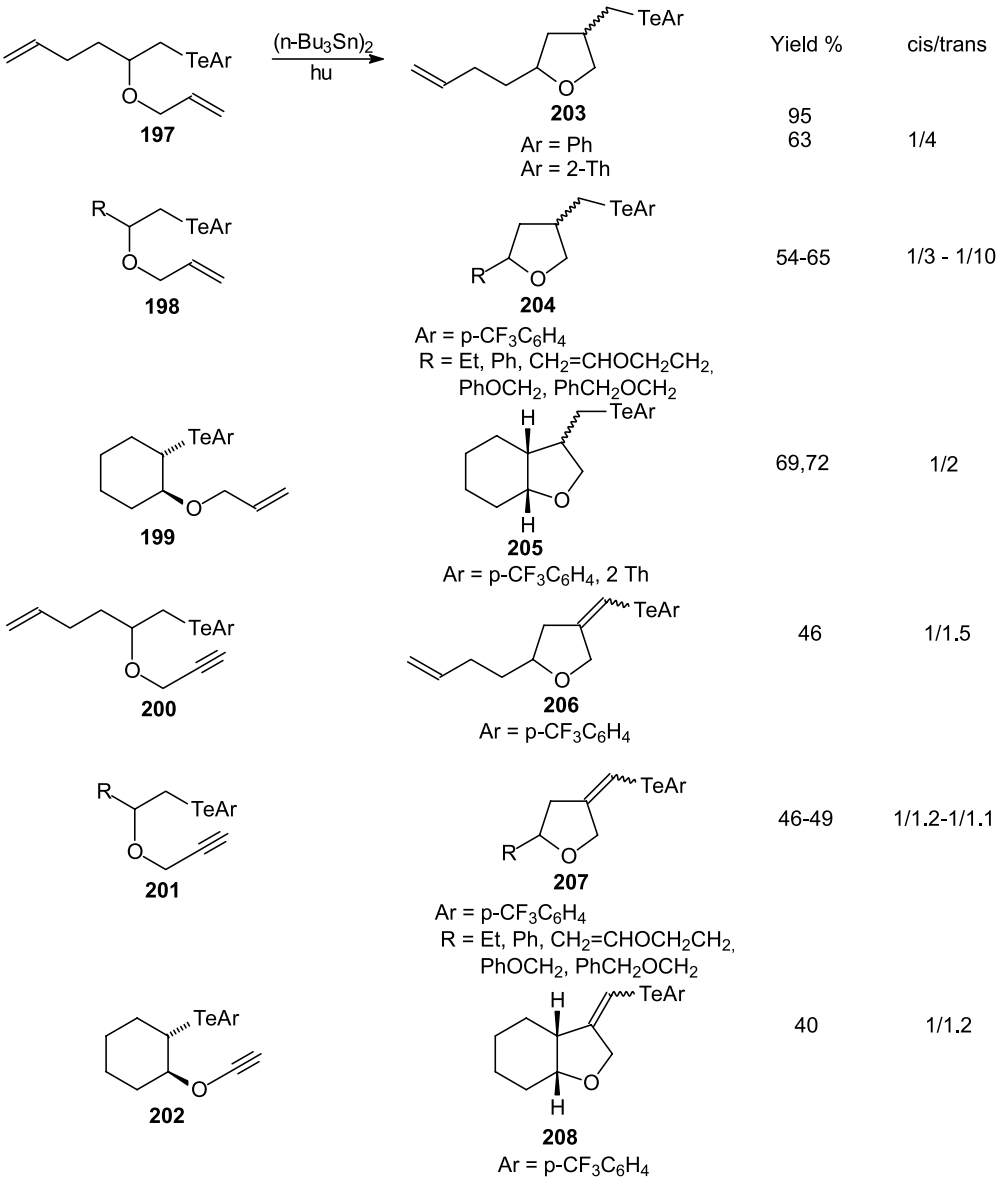
In the presence of a radical scavenger (TEMPO) and



Scheme 127.



Scheme 128.



Scheme 129.

alkynes, the glycosil radicals are trapped to afford compounds **211** and the vinylic tellurides **212**.

In the last case, the α-isomers are the main products and the reactivity is practically insensitive to the nature of the substituents of the alkynes (Scheme 130).

6.11. Radical mediated group transfer imidoylation with isonitriles

Intensive investigations have been directed recently to group-transfer imidoylation of organotellurium compounds with isonitriles[148] (Scheme 131).

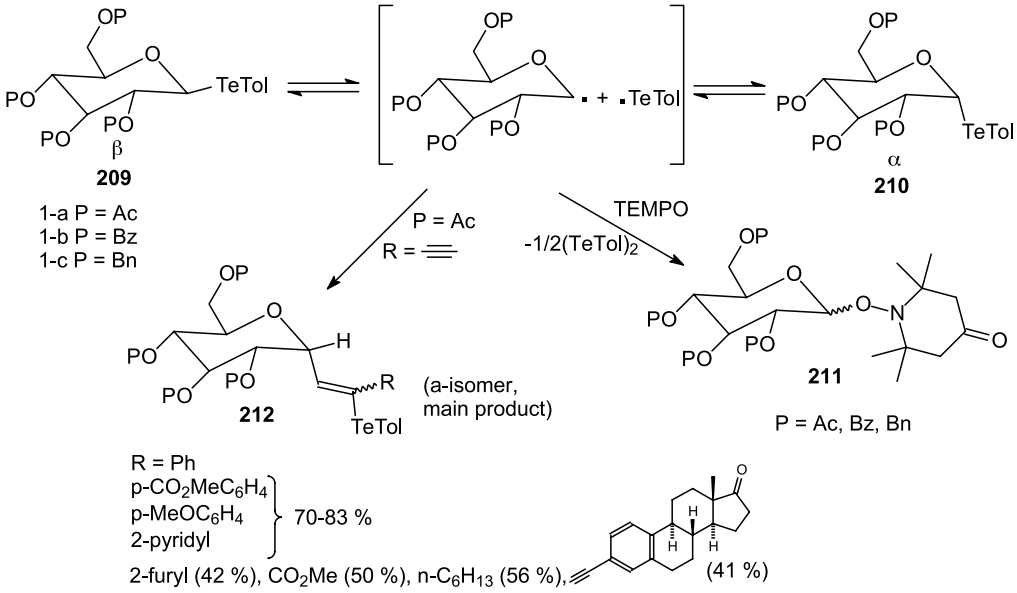
It was found that a variety of stabilized carbon-cantered radicals such as glycosyl, benzyl, α-amino, α-alcoxy, α-carbalcoxy and aryl derivatives, generated from the corresponding organotellurium compounds, are effectively trapped by the isonitriles (Scheme 132).

The reactions are normally carried out at 100 °C with 2 equiv of isonitrile (2,6-xylylisonitrile) in C_6H_6 or benzene in a Pyrex vessel with UV irradiation (250 W high pressure Hg lamp). The reactions work also in the dark, but higher temperature and larger reaction times are required (substrates **218** and **220**).

The described imidoylation of α-acyl radicals deserves a great interest since α-acyl compounds are not only versatile building blocks but also exhibit several biological activities.[149]

In the case of acyltellurides **220c** and **220e** bearing *sec*- and *tert*-alkyl substituents, the decarboxylation of CO from the acyl radical competes with the imidoylation. Such a drawback is avoided by conducting the reaction under CO pressure (50 atm).

The imidoylation of non-stabilized radicals (substrates **219**) also takes rise, but the reaction is slow and requires larger



Scheme 130.

reaction time, the efficiency being increased by the addition of a radical initiator [1,1-azobis(cyclohexane-1-carbonitrile)].

The effect of solvents was also examined and it was observed that on the change of solvent from non-polar to polar ones has only a small effect on the yields and rates of the reactions. Such a result suggests that the imidoylation reactions operate under a radical mechanism.

Since isonitriles are isoelectronic with CO, the competition between these two species in radical mediated reactions was investigated.

The following experiences revealed the advantage of isonitriles over CO:

(a) compounds **213** and **214** failed to react under high CO pressure to generate the corresponding carbonylated products
(b) submitting *t*-butylphenyl telluride **221** to a competitive reaction with CO (50 atm) in the presence of 1.2 equiv of 2,6-xylylisonitrile and a radical initiator, α-acyl- and the single α-imidoyltelluride **222** and **223** are formed in 19 and 36% (Scheme 133).

The synthetic potential of the imidoylated product is noteworthy since some manipulations of the C–Te bond are useful for synthetic transformation (Scheme 134).

6.12. Three component coupling of silyltellurides, carbonyl compounds and isocyanides

The title three component coupling proceeds under mild conditions giving the group-transfer product **224**[150] as depicted in Scheme 135.

The competitive formation of the silyloxytelluride **225**, detected during the progress of the reaction, and of the silylated TEMPO **226** formed by adding the radical scavenger TEMPO, suggest the following reaction pathway (Scheme 136).

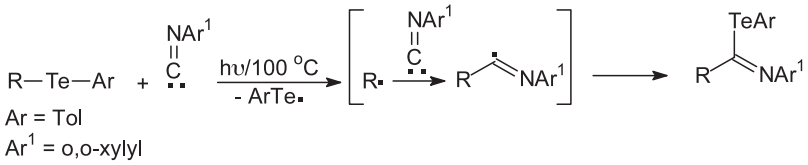
The reaction is of general character, applicable to a variety of aldehydes and ketones. Aromatic ketones give the highest yields.

The synthetic utility of the reaction is demonstrated by the oxidative hydrolysis of the products, giving silyloxy amides **227** (Scheme 137).

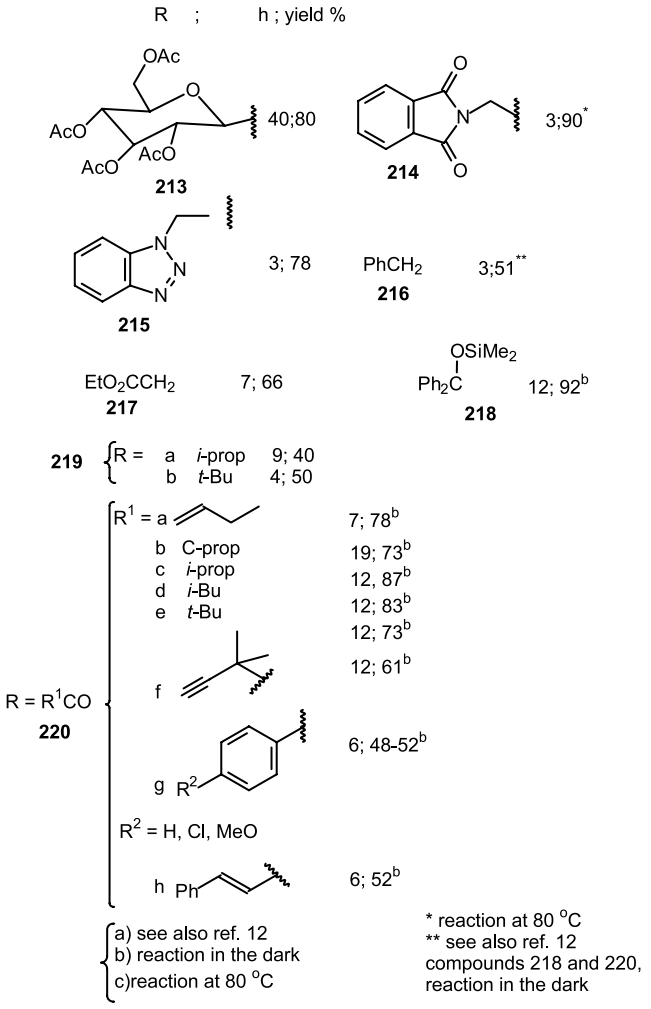
Alkynes have also been employed as a third coupling partner to afford silylated allylic derivatives[151] **229** (Scheme 138).

The reaction shows high *E*-selectivity.

The coupled product **229** is a radical precursor of the vinylic radical **228** which can be generated by treatment of **229** with



Scheme 131.



Scheme 132.

tri-*n*-butyltin hydride (*n*-Bu_3SnH) in the presence of AIBN and submitted to several manipulations (Scheme 139).

6.13. Synthesis of substituted quinones via organotellurium compounds

Carbon centred radicals, generated under photo-thermal conditions from organotellurium compounds, react with a variety of quinones to afford the mono addition products **230**–**233** in good yields[152,153] (Scheme 140).

The reaction in the dark is slow, but eventually gives the same product by heating at 100 °C. The effect of the solvent is marginal.

The reaction has been applied for the synthesis of polyprenyl quinol natural product **234** and **235** (Scheme 141).

The photolytic reaction of acyltellurides with quinones surprisingly takes rise at the oxygen moiety (Scheme 142).

The reductive chemoselective bis-silylation of quinones giving hydroquinone derivatives **236** was afforded by thermal reaction with silyl tellurides[154] (Scheme 143).

Quinones with higher reduction potential react faster that those with lower reduction potential. 1,2-Benzoquinones are also reduced to the corresponding bis silylated hydroquinones.

6.14. Thiotelluration of vinyl cyclopropanes

As part of a systematic study concerning the reaction of chalcogen radicals, generated by irradiation of the corresponding chalcogenides, with carbon–carbon multiple bonds, the highly selective and efficient thiotelluration of vinyl cyclopropanes to give allylic sulfides bearing a phenyl telluroethyl group at the terminal carbon as well the thio- and selenotelluration of acetylene to give *vic* thio- and selenotellurolkenes have been afforded successfully upon visible light irradiation in the presence of the systems $(PhS)_2/(PhTe)_2$ and $(PhSe)_2/(PhTe)_2$.[155] It must be emphasized that radical addition of seleno and telluro moiety to acetylenes are unprecedented.

The following features are noteworthy.

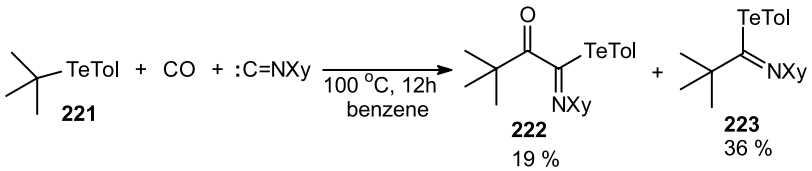
The thiotelluration of a variety of olefins by visible light irradiation does not proceed at all (except for the special case of norbornene), probably due to a reverse photoinduced regeneration of the starting materials (Scheme 144).

The thiotelluration of vinylcyclopropane proceeds efficiently since the intermediate radical (R=C-prop) can be converted to the acyclic primary radical avoiding the reverse process (Scheme 145).

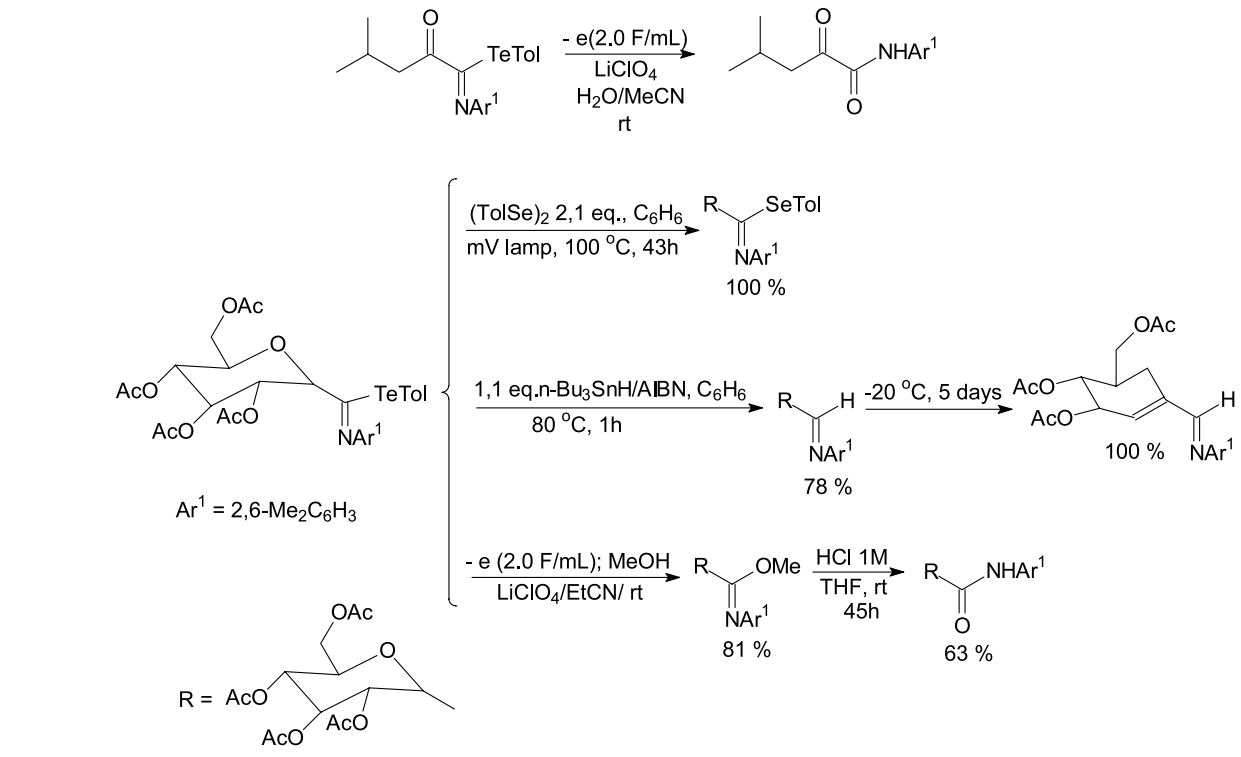
The thio-telluration of acetylenes works well due the higher kinetical stability of the thio vinyl radical  , in comparison with the thioalkyl radical, therefore suppressing the reverse process (Scheme 146).

The thiotelluration of 1-octyne requires prolonged photo-irradiation giving rise to a isomeric mixture of products in moderate yields. This results depends on the different stability of the two vinylic radicals.

The selenotelluration of acetylenes works well in the case of



Scheme 133.



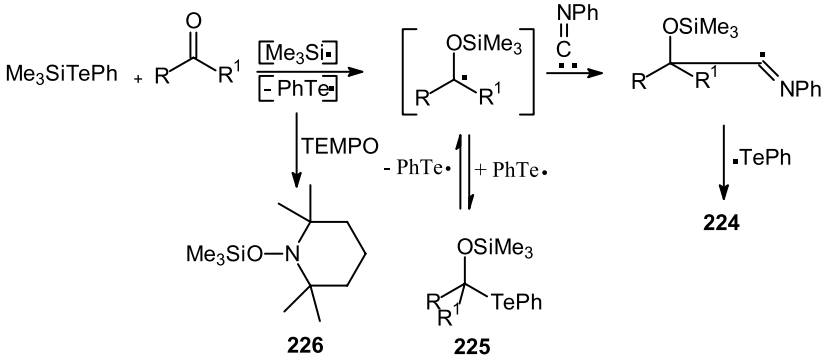
Scheme 134.

Scheme 135.

aromatic acetylenes, whereas aliphatic acetylenes provide a mixture of the expected selenotelluro adducts and the diselenation product (Scheme 147).

6.15. Organotellurium compounds as initiators for controlled living radical polymerization

The use of several diorganyl tellurides as initiators for controlled 'living' radical polymerization of styrenes has been investigated[156] (Scheme 148).



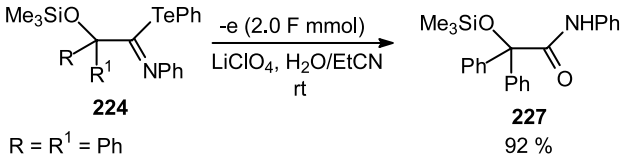
RR^1 (yields %)

R = Ph; R^1 = Ph (82), p-$MeOC_6H_4$ (73), p-$Me_2NC_6H_4$ (84), p-ClC_6H_4 (63), p-pyridyl (81), Ph(MeO)CH (73), c-propyl (93)

RR^1 = $(CH_2)_5$ (61)

R = H; R^1 = C_6H_{13} (55), Ph (46)

Scheme 136.



Scheme 137.

The efficiency of the polymerization was discussed[157] on the basis of the bond dissociation energy (BDEn) and the reactivity of the initiating radical toward styrenes (Scheme 149).

6.16. Perfluoroalkyltelluration of terminal olefins and alkynes

The title reaction has been achieved by the treatment with sodium phenyltellurolate in the presence of perfluoroalkyl halides[158] (Scheme 150).

The reaction proceeds via a single electron transfer (SET) from sodium tellurolate to perfluoroalkyl halides followed by a radical chain reaction of SRN[1] mechanism.

6.17. Synthesis of indole derivatives via radical cyclization of *N*-(*ortho* ethynylbenzene), phenyltelluro trifluoro acetimidates

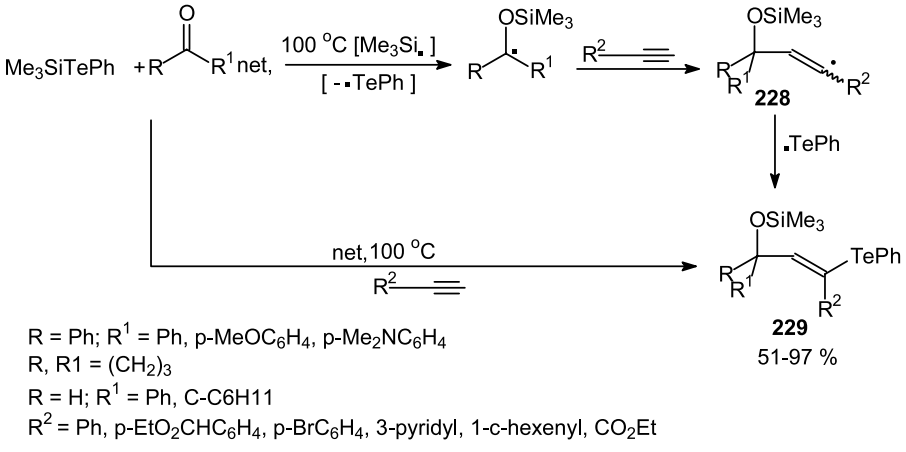
Compound **238**, prepared from *N*-aryl trifluoroacetimidoyl halides **237**, by irradiation with UV lamp gives the indole derivative **239** in moderate yield, via the mechanism proposed[159] in Scheme 151.

Trifluoromethylated organic compounds play an important role in medicinal and agricultural chemistry.[160]

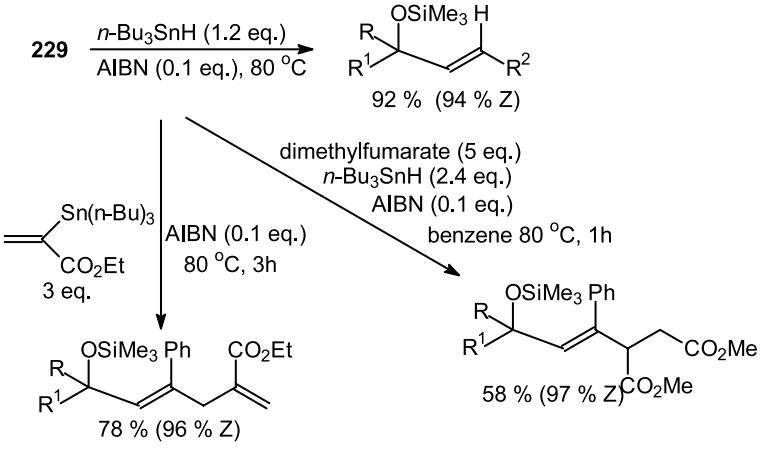
7. Vinylic tellurides

The special reactivity of tellurium associated with the reactivity of carbon–carbon double bonds, confers vinylic tellurides an exceptional synthetic interest. These compounds are extremely able for participating in highly stereoselective carbon–carbon bond formation.

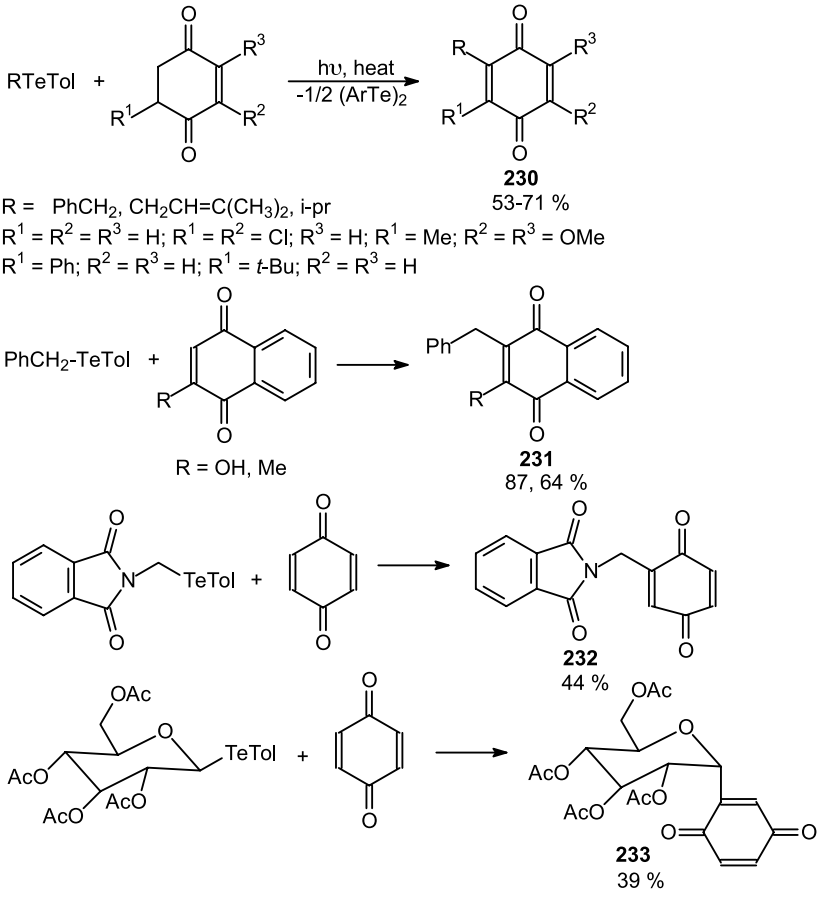
Leading examples of such performance are the tellurium–heteroatom exchange reactions of *Z*-vinylic tellurides



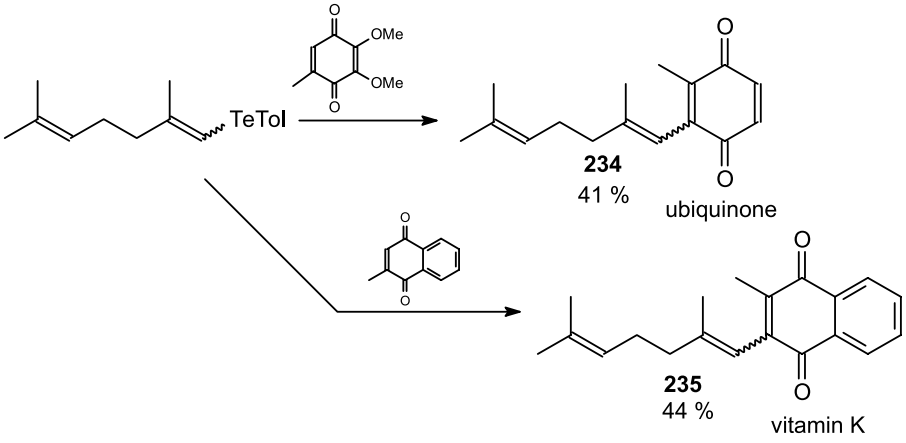
Scheme 138.



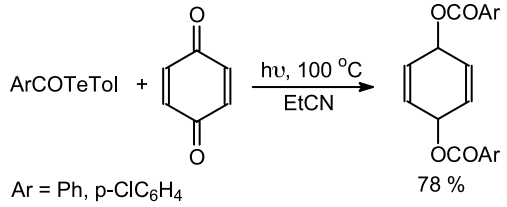
Scheme 139.



Scheme 140.



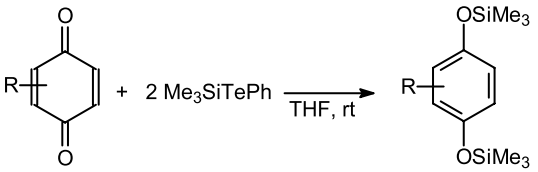
Scheme 141.



Scheme 142.

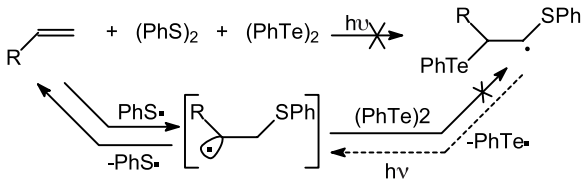
(easily generated by the hydrotelluration of alkynes) associated with appropriate manipulations of the produced *Z*-vinylic organometallic reagents, and the coupling reactions of vinylic tellurides with organometallic reagents.

As a supplement of previous reviews,[3,161] recent progress in the preparation and reactivity of vinylic tellurides will be examined in the forthcoming sections.

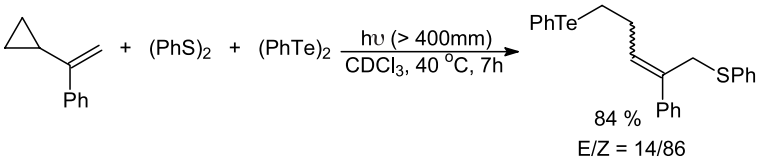


2,3-dichloro-4,5-dicyano-1,4-benzoquinone
2,3,5,6-tetrachloro-1,4-benzoquinone
2,6-dichloro-1,4-benzoquinone
2,3-dimethoxy-5-methyl-1,4-benzoquinone
1,4-naftoquinone, duroquinone, antraquinone

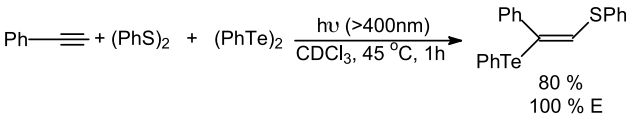
Scheme 143.



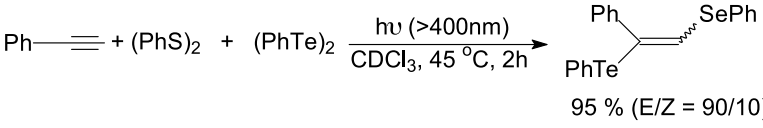
Scheme 144.

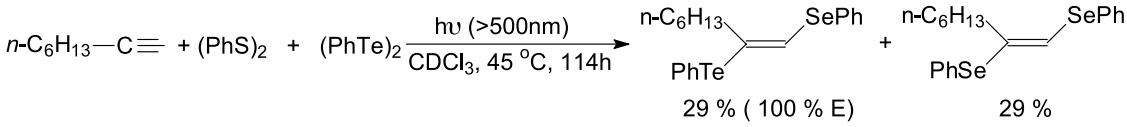


Scheme 145.

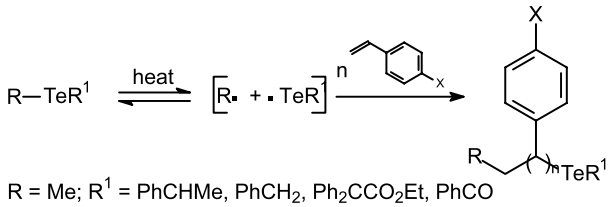


Scheme 146.





Scheme 147.



R = Me; R^1 = PhCHMe, $PhCH_2$, Ph_2CCO_2Et, PhCO
R = Ph; R_1 = PhCHMe, $PhCOSiMe_3$

Scheme 148.

7.1. Preparation

7.1.1. Addition of tellurium IV halides to acetylenes. After the long time described addition of tellurium tetrachloride, aryltellurium trichlorides and other Te electrophiles to terminal acetylenes,[162] some new related reactions have been reported.

Tellurium tetrabomide ($TeBu_4$-*n*), aryl- and alkyl tellurium tribromides $ArTeBu_3$-*n*) add to terminal acetylenes to give, respectively, bis(β-bromovinyltellurium) dibromides and (β-bromovinyl) organyl tellurium dibromides, which can be easily reduced with $NaBH_4$ to the corresponding tellurides[163] **240** and **241** (Scheme 152).

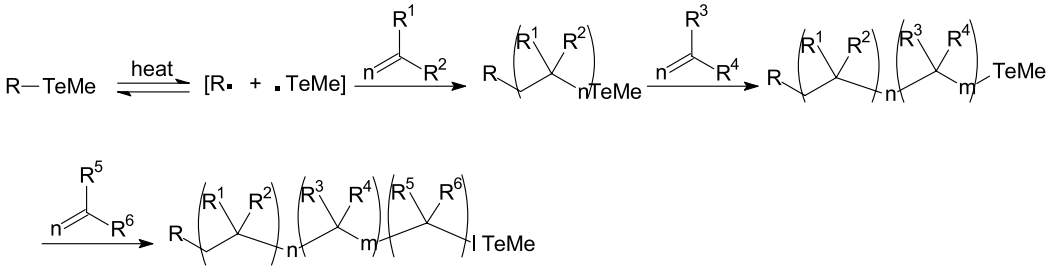
The addition of $TeBr_4$ and aryl $ArTeBr_3$, performed in benzene, gives *Z* products, via a *syn* addition, whereas the addition of $ArTeBr_3$ in methanol exhibits *E* stereochemistry.

In the case of 3-hydroxyalkynes, the OH group promotes *anti* addition. Depending on the steric hindrance at the propargylic position, four or five membered cyclic tellurium oxychlorides **242** and **243** are formed resulting from the opposite regiochemistry of the addition[164] (Scheme 153).

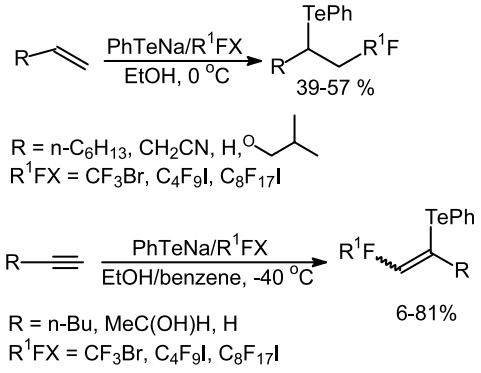
A recent report describes that aryl tellurenyl iodides (prepared in situ from the corresponding diaryl tellurides and iodine) add to alkynes in THF, in a regio- and stereoselective manner to afford *E*-1-iodo-2-aryltelluro-1-alkenes which, by treatment with bromine, give the corresponding dibromides[165] **244** (Scheme 154).

7.1.2. Hydrotelluration of alkynes. The well-established title reaction[166] has been widely employed for the preparation of several types of *Z*-vinylic tellurides.

In this context, a valuable improvement has been introduced in the preparation of *n*-butylvinyl tellurides, the usual precursors of different *Z*-vinylorganometallics, by



Scheme 149.



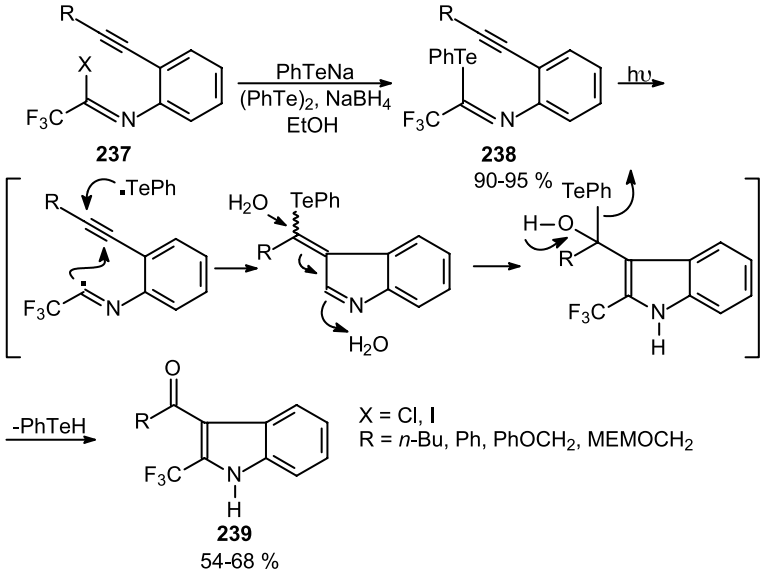
Scheme 150.

substituting the tedious generation of sodium butyl tellurolate, from the non-commercially available *n*-dibutyl ditelluride, for *n*-butyllithium tellurolate, easily generated in situ from *n*-butylLi and elemental Te[167] (Scheme 155).

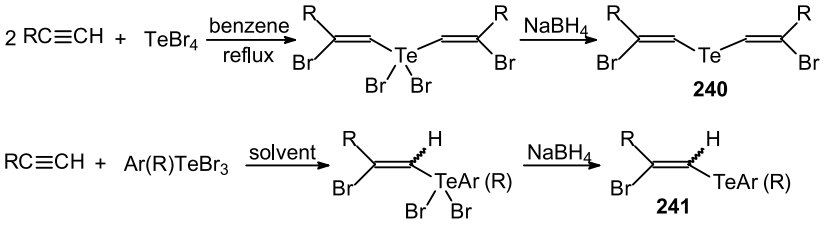
New applications of hydrotelluration of functionalized alkynes, enynes and diynes are illustrated in Scheme 156.[170,171]

By treating tellurothioalkene **245** with *n*-BuLi, the phenylthio group remains untouched, and after treatment with water, thioalkene is obtained, showing the higher reactivity of vinyl tellurides toward vinyl selenide.

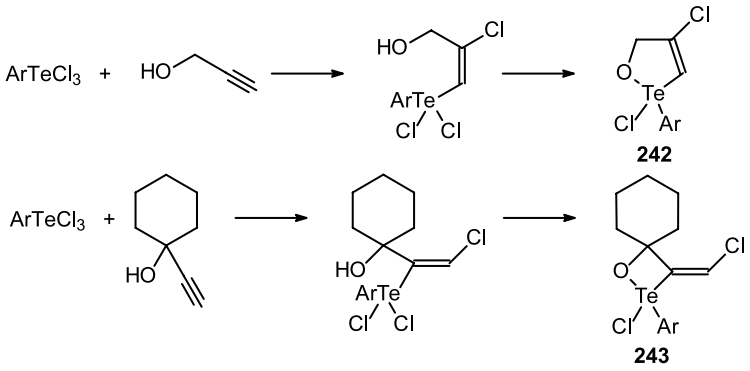
The silyl substituted acetylene **246** gives only the tellurothioethene **247** resulting from a desilylation–hydrotelluration sequence.



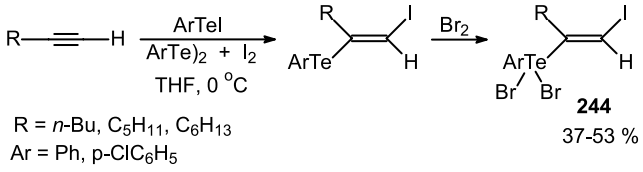
Scheme 151.



Scheme 152.



Scheme 153.



Scheme 154.

Scheme 155.

Aryl telluroesters **248**, prepared from acyl chlorides and bromomagnesium aryl tellurolates, react with aryl propiolate in the presence of K_2CO_3, giving (*Z*)-β-aryl tellurocynnamates **249** in high yield[172] (Scheme 157).

The above procedure involves the addition of a potassium aryl tellurolate anion, derived from telluroesters, thus avoiding the preparation of diaryl ditellurides as a source of the telluroesters employed in previously described methods.[173]

7.1.3. Addition of organotellurolates to activated alkynes. The well known addition of organotellurolate anions to activated alkynes giving functionalized *Z*-vinylic tellurides[174] **250** has been recently enriched with further examples (Scheme 158).[177]

The obtained telluroacroleines (EWG=CHO) have been submitted to a Wittig methylenation, giving the expected tellurodienes **251** (Scheme 159).

The anti-tellurosulfonation of alkynes has been achieved by reacting alkynes with diaryl ditellurides and sodium arylsulfonates in $AcOH/H_2O$. A mechanism involving a sulfonyl radical was proposed. Some of the vinylic tellurosulfones have been converted to the corresponding dibromides **252** by addition of bromine (Scheme 160).

In the case of $R'=Me_3Si$ a desilylated product **253** is obtained.[165]

7.1.4. Tandem vicinal difunctionalization of alkynes. A tandem anti-vicinal difunctionalization of alkynes, involving the addition of a lithium organotellurolate to an activated alkyne, with subsequent trapping of the resulting vinyllithium intermediate **254** with electrophiles, was recently reported with the name 'electrotelluration'[178–180] (Scheme 161).

Terminal alkynyl sulfides also underwent the described reaction at higher temperatures.

An intramolecular version of electrotelluration was carried out employing alkynlesters bearing an aldehyde group with different carbon chain lengths, furnishing five to eight-membered ring systems **255** (Scheme 162).

7.1.5. Telluroacylation of terminal alkynes. *Z*-(β-Aryl telluro)-α,β-enones **256** are prepared by treatment of terminal alkynes with telluroesters in DMF at 50 °C in the presence of CuI and triethylamine, followed by the addition of $Me_3N\cdot HCl$ and heating[181] (Scheme 163).

A mechanism was suggested involving the addition of an aryl tellurol to an acetylenic ketone promoted by CuI.

7.1.6. Vinylic substitution by organotellurolate anions on activated vinylic halides. The first study on the title reaction describes the synthesis of β-aryl tellurovinyl aldehydes and ketones **258** by treating β-chlorovinyl carbonyl compounds or β-acylvinyltriethylammonium chlorides **257** with arene tellurolate anions[182] (Scheme 164).

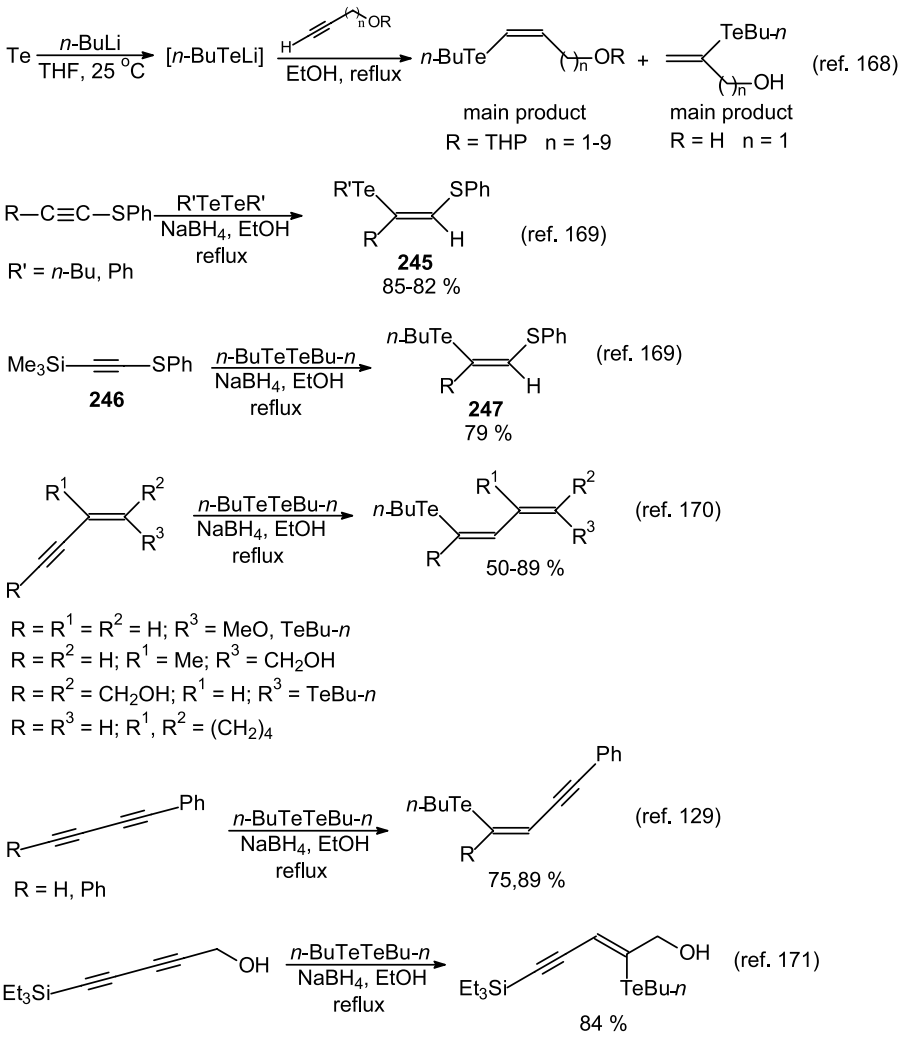
Bis(β-acyl vinyl) tellurides **259** have been prepared by the same protocol using $TeLi_2$ (Scheme 165).

The *Z* geometry of the products was proved by X-ray investigations and NMR spectra.

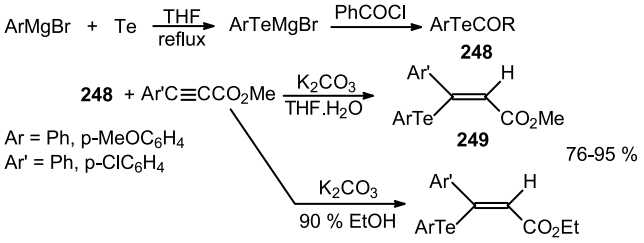
The aldehyde **260** is a precursor of β-formyl tellurenylhalide **261**, a previously unknown type of compound, which is formed by refluxing an acetic acid solution of the corresponding dihalides (Scheme 166).

Similar substitutions at activated vinylchlorides have been carried out employing aluminum tellurolates[183] (Scheme 167).

This protocol has been applied to the coupling of arene tellurolates with *E*-2-iodo-1-alkenylsulfones **262**,



Scheme 156.



Scheme 157.

enolphosphates, acetates, tosylates and triflates **263a–d** of β-dicarbonyl compounds (Scheme 168).

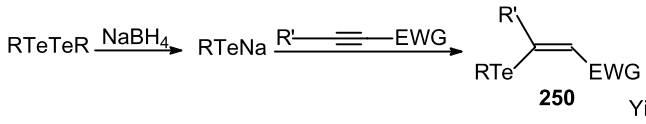
Important remarks are that starting from mixtures of *E*/*Z* enol derivatives, only the *Z*-vinylic tellurides are obtained, and comparative experiments demonstrate that alkyl tellurolates (*n*-BuLi, *s*-BuLi, *t*-BuLi) react faster than the aromatic (PhMgBr, 2-ThLi), and that the reaction time is not influenced by the nature of the leaving group (phosphate, acetate, tosylate, triflate).

7.1.7. Telluro(seleno)ketene acetals, 1-seleno-2-telluroethenes, telluro ketene acetals and telluro (stannyl)-ketene acetals. Vinylic tellurides linking another chalcogeno group at the α- or β- position deserve special synthetic interest since the tellurium moiety can be removed selectively by means of several methods, furnishing new reactive vinylic intermediates.

Although some representative compounds of this type are known,[185] recent investigations have been directed for achieving this purpose.

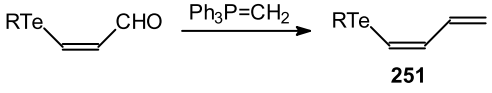
The easily available 1-bromo-1-seleno alkene[185c] **264**, by treatment with sodium phenyl tellurolate under bis-(bipyridine)nickel (II) bromide catalysis, furnishes the corresponding telluro (seleno)ketene acetal[186] **265** (Scheme 169).

The same compound has been obtained with retention of configuration by subsequent treatment of (*E*)-1-bromo-1-seleno alkene[185c] **266** with *n*-BuLi and diphenyl ditelluride, resulting from the preferential Br/Li exchange over Te/Li exchange[187] (Scheme 170).



EWG = $P(O)(OEt)_2$	R = *n*-Bu, Ph	R' = *n*-Bu, Ph, 	42-69	(ref. 175)
		R' = H, *n*-Bu, Ph	72-95	(ref. 176)
	R = Ph, p-ClC_6H_4, p-FC_6H_4, p-Tol	R' = Ph, C_5H_{11}	57-67	(ref. 165)
EWG = $PhSO_2$	R, R' = Ph, *n*-Bu		93-94	(ref. 176)
EWG = p-$TolSO_2$	R = Ph, p-FC_6H_4 R' = H, Ph, n-C_6H_{13}		71-82	(ref. 165)
EWG = -CHO	R = *n*-Bu, Ph R' = H		80-84	(ref. 177)

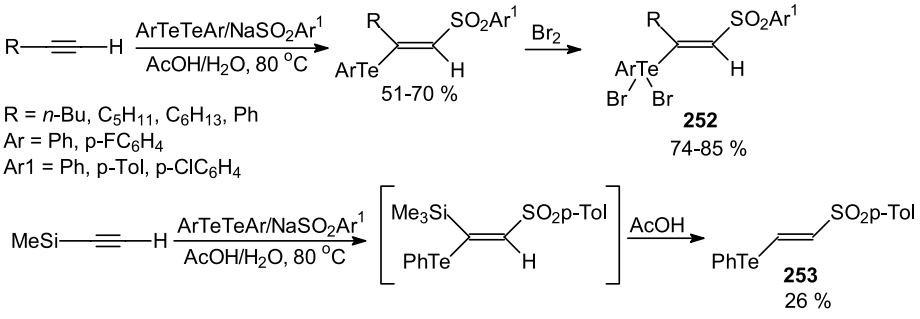
Scheme 158.



Scheme 159.

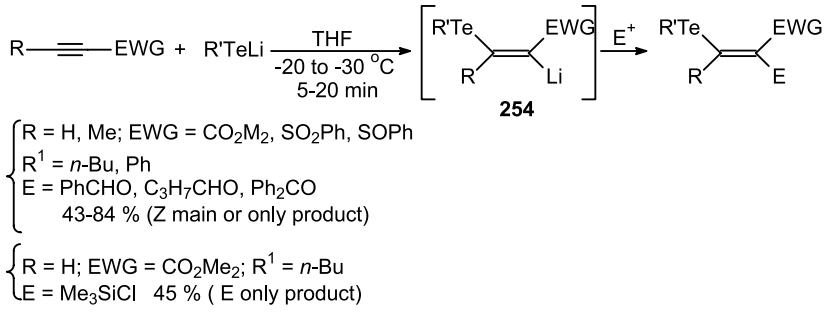
Te–Se ketene acetals with the same[185d] and opposite[185c] stereochemistry have been prepared before.

The previously reported[185d] synthesis of telluro(seleno)-ketene acetals by the Al/Te exchange reaction, which



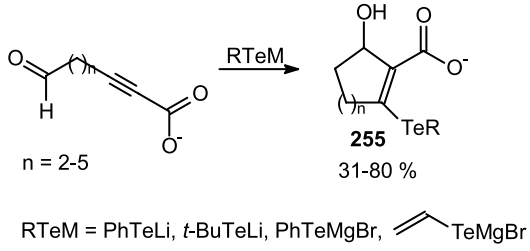
Scheme 160.

furnishes low yield (due to the slow Al/Te exchange in the Al vinyl intermediate and the formation of *Z*-vinyl selenides as a by-product) found a valuable alternative based on hydrozirconation protocols.

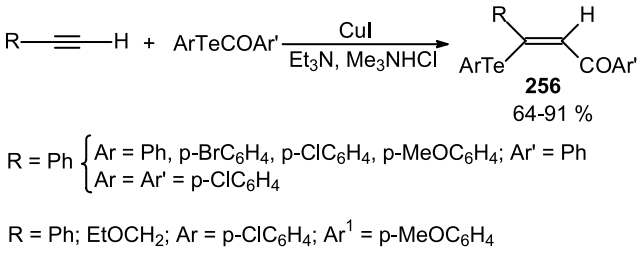


Scheme 161.

In a first reported procedure,[188] alkynyl selenides (freshly prepared and isolated) are treated in sequence with $Cp_2Zr(H)Cl$ (Schwartz reagent) and butyl tellurenyl bromide, giving different regio- and stereochemistry products (Scheme 171).



Scheme 162.

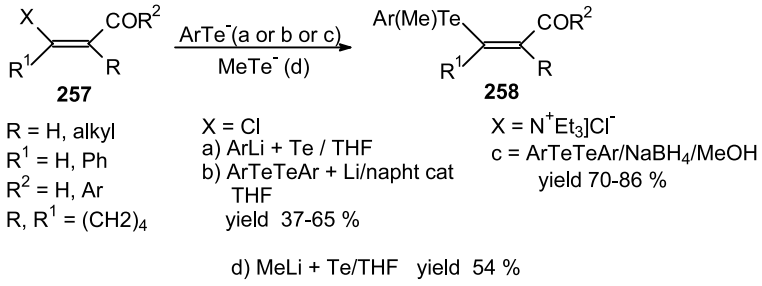


Scheme 163.

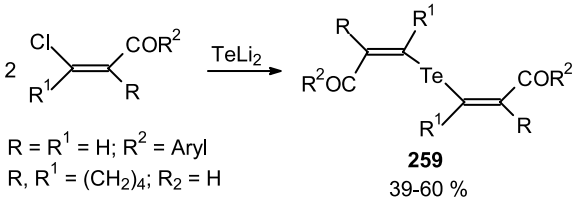
selenides **275** in high yields. This transformation therefore constitutes a convenient alternative to the known methods to prepare vinyl selenides.[189]

The stereochemistry of the obtained products was determined by NMR spectra.

In a further line of experiments[190] lithium alkynyl selenolates **276**, instead of acetylenic selenides, were employed in the hydrozirconation reaction to generate the



Scheme 164.

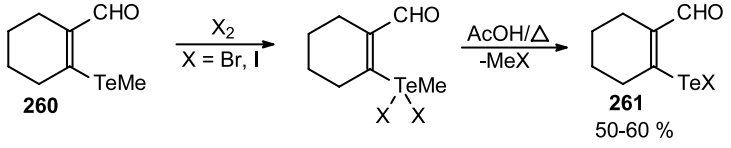


Scheme 165.

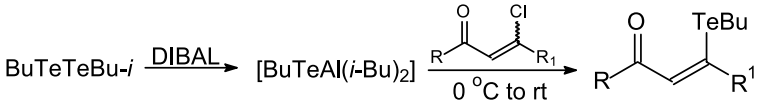
zirconated vinyl selenides **277** precursors of (*E*)-telluro-(seleno)ketene acetals **278** (Scheme 172).

The stereochemistry of the obtained Te–Se ketene acetals was confirmed by NOESY measurement in ^{1}H NMR spectra. No other regio- and stereoisomers were detected by analytical methods.

The above described procedure is advantageous toward the precedent method since: (a) the starting lithium alkynyl



Scheme 166.

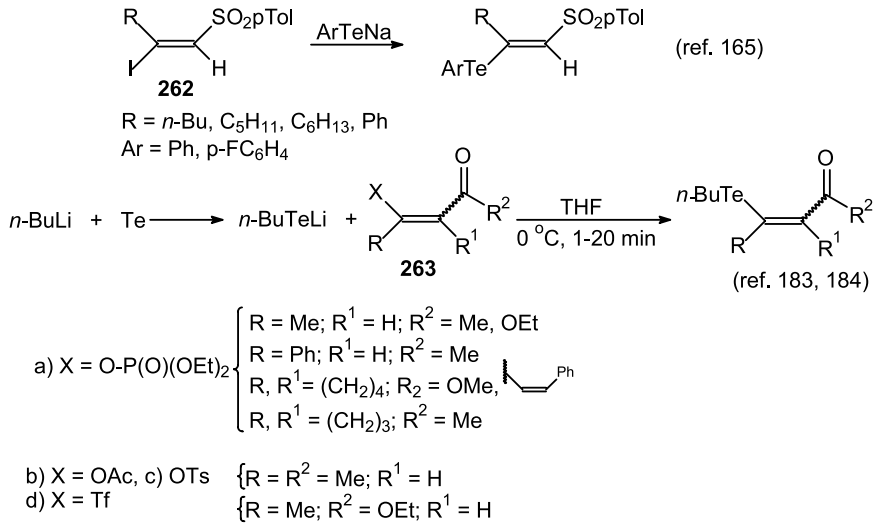


Scheme 167.

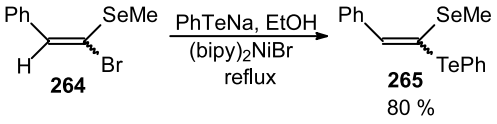
As shown in Scheme 170, with R= H or Ph, an unique product **269** and **265**, is formed, with opposite regiochemistry, whereas selenoalkylethynes (R=alkyl) give rise to a mixture of regioisomers **273** and **274**, the isomer of type **273** being the main product. With all the acetylenic selenides, 2 equiv of the Zr reagent is required to promote the total conversion of the starting materials.

The zirconated vinyl selenide intermediates **268**, **270**–**272** by treatment with water, are converted into *Z*-vinylic selenolate is prepared in situ, avoiding the laborious preparation of the acetylenic selenides; (b) the hydrozirconation step is regio- and stereoselctive, in contrast with the hydrozirconation of acetylenic selenides resulting in a mixture of the regioisomers, (Scheme 170), and requires only 1 equiv of the Schwartz reagent instead of 2 equiv of the precedent procedure.

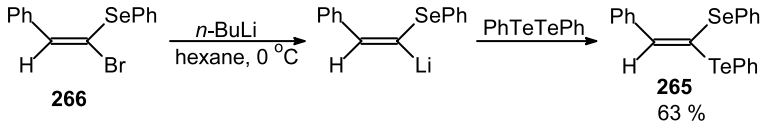
The alkyne hydrozirconation protocol was also applied to acetylenic tellurides **279** furnishing the zirconated vinyl



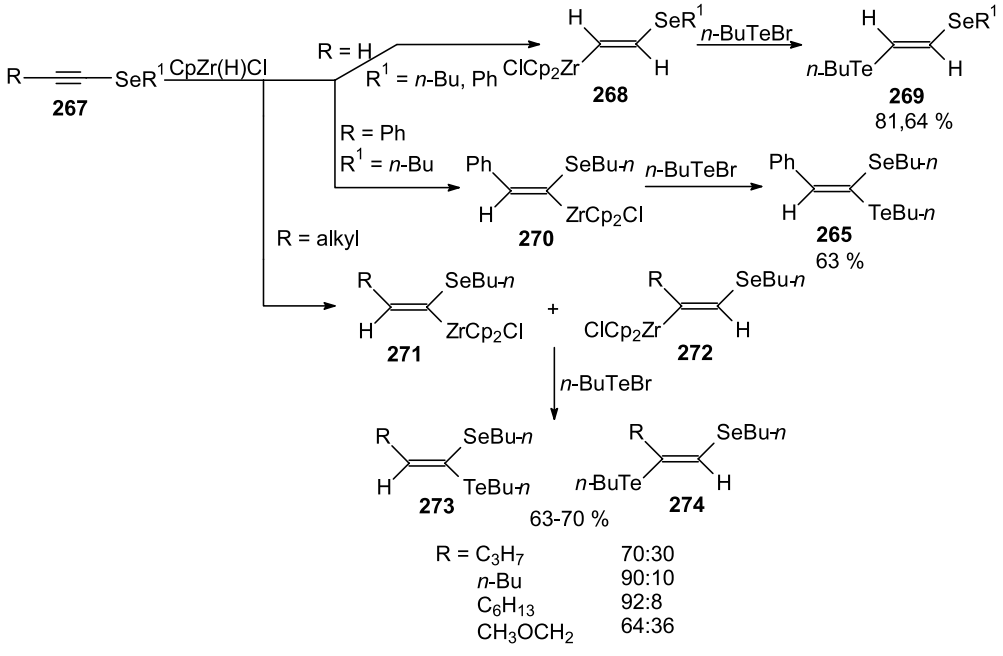
Scheme 168.



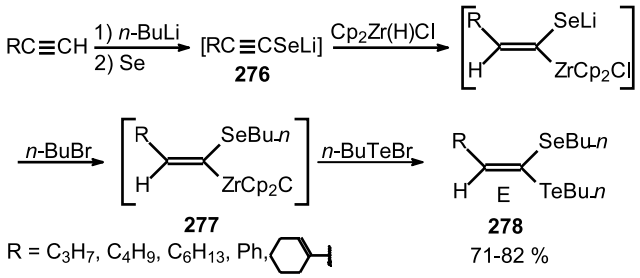
Scheme 169.



Scheme 170.



Scheme 171.

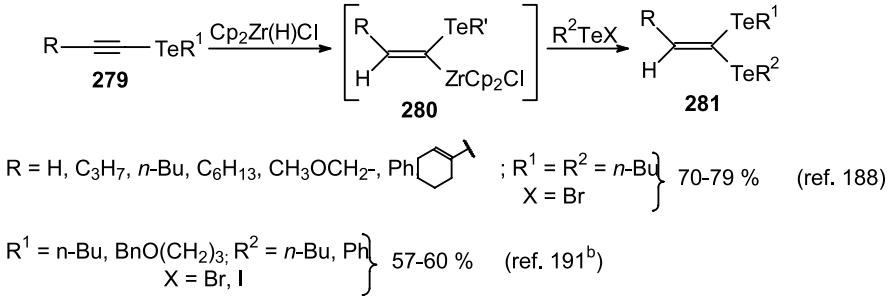


Scheme 172.

reaction of the selenium acetylides as assessed in separate comparable experiments.

The α-zirconated vinyl tellurides **280** have also been used as intermediates of several valuable synthetic manipulations[188] depicted in Scheme 174.

Treatment of **280** with water gives the corresponding *Z*-tellurides **281**. The reaction with *n*-BuSeBr gives Te–Se ketene acetals as unique regioisomer, but as two stereoisomers, *E* **282** and *Z* **278**, showing that, in contrast to the



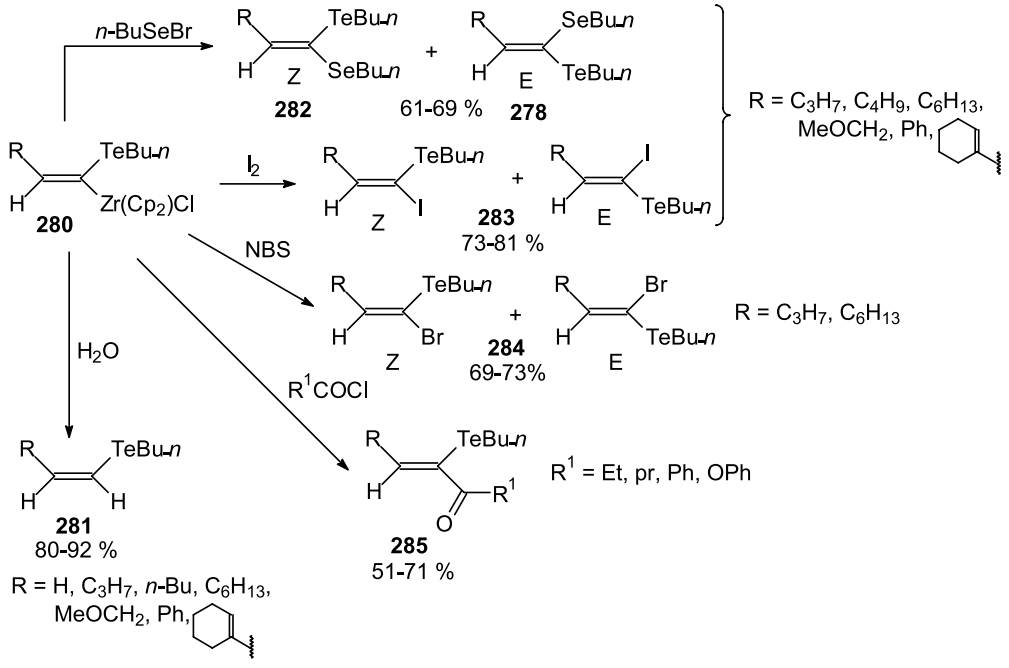
Scheme 173.

tellurides **280** in *cis* fashion and high regioselectivity. Subsequent treatment with tellurenyl halides affords telluroketene acetals **281** with total retention of configuration[188] (Scheme 173).

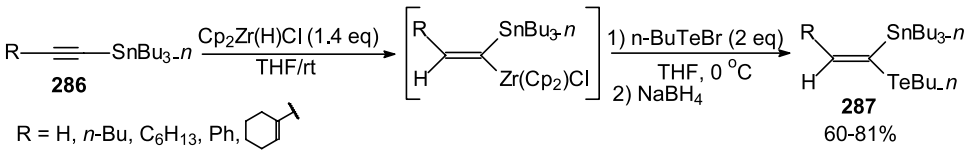
The use of 2 equiv of the reagent is required (in analogy to the selenium route) to achieve the complete conversion of the reagents in contrast with previous reports,[191] where only 1.1 equiv of the reagent was used.

The reactions of acetylenic tellurides are faster than the above discussed Zr/Te exchange reaction, which proceeds with total retention of configuration, the retention of configuration in the Zr/Se exchange is only partial, the major product exhibiting the *E* geometry. The iodinolysis of the Csp^2-Zr bond gives the α-iodo vinyl tellurides **283** as a mixture of *E*/*Z* isomers where the *Z* isomer is the main product with retained geometry.

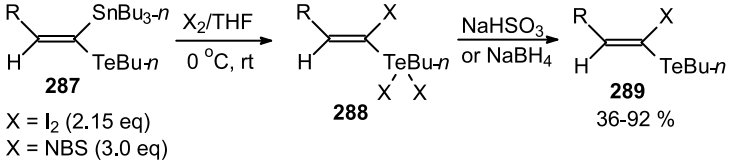
The brominolysis was performed with NBS giving **284** as a mixture of *Z*/*E* isomers. The acylation, giving **285**, was effected with acylchlorides in the presence of CuI.[191a]



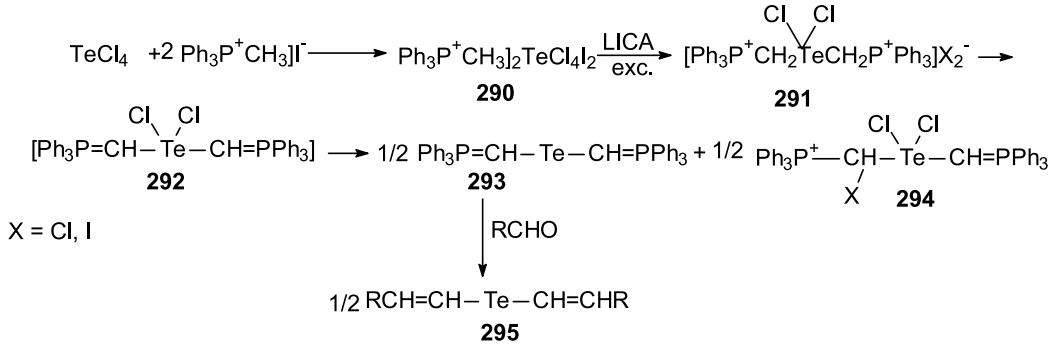
Scheme 174.



Scheme 175.



Scheme 176.



Scheme 177.

Following the precedent methodologies, telluro (stannyl)-ketene acetals **287** are achieved by the hydrozirconation of stannyl acetylenes **286** and successive reactions with butyl tellurenyl bromide and $NaBH_4$[192] (Scheme 175).

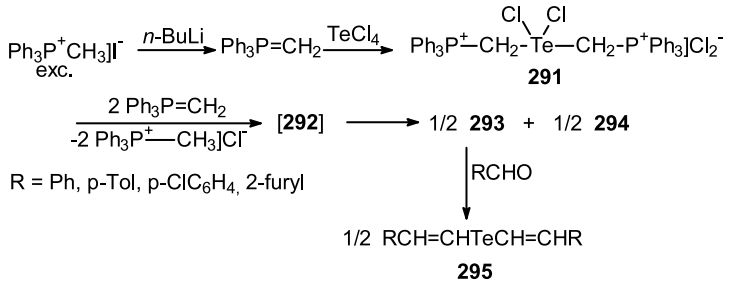
The *E* configuration of the products, assessed by NOE experiments, is a consequence of the known 100% regio- and *E*-stereoselectivity of the hydrozirconation of acetylenic stannanes, and the retained configuration in the Zr/Te exchange.

The treatment with $NaBH_4$ is required to reduce the corresponding tellurodibromide formed at the expense of the excess (2 equiv) of *n*-BuTeBr used, which behaves as brominating agent.

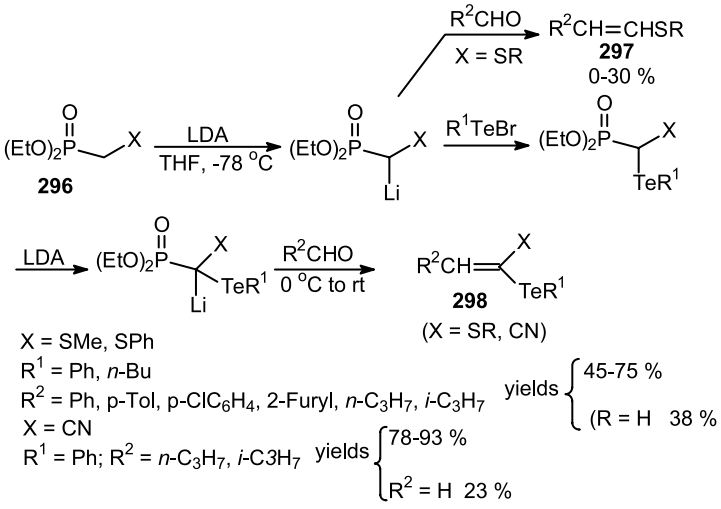
The treatment of the obtained ketene acetals **287** with iodine or NBS in excess promotes exclusively Sn/halogen exchange giving the α-halogen vinyl dihalogeno tellurides **288** which are dehalogenated to the corresponding telluride **289** by treatment with $NaHSO_3$ or $NaBH_4$. This process occurs with total retention of the configuration as confirmed by NOE/^{1}H NMR measurements (Scheme 176).

7.1.8. Vinylic tellurides via Wittig and Horner–Emmons route. Symmetrical divinyl tellurides **295** have been prepared via a ylidation reaction involving the treatment of bis-phosphonium halotellurate **290**[193] with excess base and then with aldehydes in THF at −78 °C[194] (Scheme 177).

The desproportionation of **292** into **293** and **294** can be rationalized on the basis of the known reaction of phosphoranes with halogen sources giving α-haloalkyl-phosphonium salts.[195]



Scheme 178.



Scheme 179.

In an alternative methodology, the bis-tellurophosphorane **293** is prepared in situ by means of a transylidation reaction between **291** and excess of methylene triphenylphosphorane (generated from the corresponding phosphonium salt and *n*-BuLi) (Scheme 178).

The reaction with aromatic aldehydes (R=Ph, *p*-Tol, *p*-ClC_6H_4, 2-furyl) is not strongly stereoselective, the *E* geometry being preferred. In the presence of HMPA (30%) the *Z*-isomers become predominant. In the case of aliphatic aldehydes (R=Me_2CH, C_3H_7) the *Z* geometry is preferred in both solvent systems.

The yields are in the same medium range for both systems (15–48%).

Considering that the described reaction is feasible for both aromatic and aliphatic aldehydes, that the experimental procedure is very easy, that the yields, in spite of moderate, are not far from the theoretical, the described method is certainly a useful contribution for the synthesis of symmetrical divinyl tellurides.

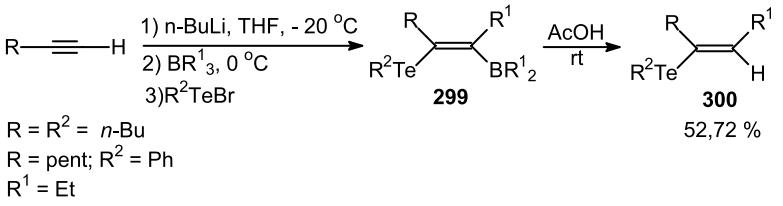
α-Thiovinyltellurides [telluro (thio) ketene acetals] and α-cyanovinyltellurides (telluroacrylonitriles) **298** have been synthesized via Hornner reaction by similar protocols, by treating, respectively, thiomethyl or cianomethyl diethylphosphonates **296** (easily accessible by Arbusov reactions of triethyl phosphonate with chloromethyl sulfides or chloromethyl acrylonitrile) with LDA, organotellurenyl bromides and aldehydes[196,197] (Scheme 179).

In the case of thiotelluro acetals (X=SR), excess thiophosphonate is required to achieve good yields, and therefore vinyl sulfides **297** are formed as by-products. By contrast, in the case of telluro acrylonitriles (X=CN), the reaction works well only by employing PhTeBr in excess.

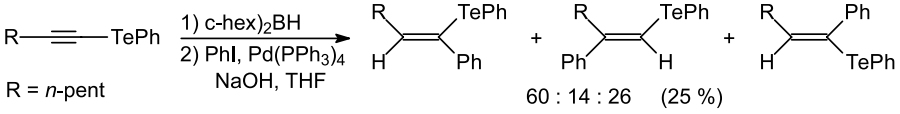
In the two cases, the olefination reaction is not stereoselective, giving mixtures of *Z* and *E* isomers.

7.1.9. Vinyl tellurides via borane chemistry. Internal vinyl tellurides **300**, which are not accessible via hydrotelluration of alkynes, have been prepared from alkynes through a vinyl borane route.

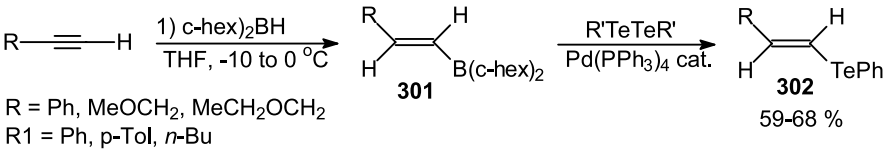
The sequential treatment of 1-alkynes with *n*-BuLi, trialkyl borane and a tellurenyl bromide reaches the *Z*-boro-substituted vinyl telluride **299** which are easily hydrolyzed to the disubstituted vinyl tellurides **300** (Scheme 180). The reaction proceeds with high regio- and stereocontrol.[198]



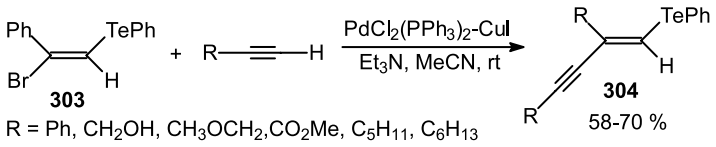
Scheme 180.



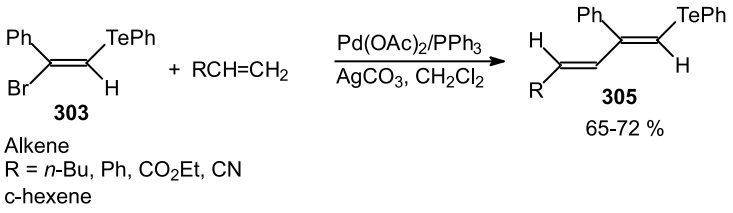
Scheme 181.



Scheme 182.



Scheme 183.



Scheme 184.

It was observed that the telluroborane **299** fails to react under the Suzuki coupling (PhI/Pd(PPh$_3$)$_4$/Na$_3$PO$_4$/DMF) to give trisubstituted vinyl tellurides.

The following scheme illustrates the potential of the acetylenic tellurides hydroboration (Scheme 181).

E-Vinylic tellurides **302** are formed by the coupling reaction of *E*-vinyl borane **301** with diaryl telluride, in the presence of Pd catalysts[199,200] (Scheme 182).

7.1.10. Vinyl tellurides via cross-coupling reactions. 1,3-Eninyl tellurides **304** and (*E*,*E*)-1,3-dienyl tellurides **305** are afforded by the cross-coupling reaction of (*E*)-β-bromovinyl telluride **303**[163a], respectively, with terminal alkynes[201] or alkenes[202] under catalytic conditions (Schemes 183 and 184).

7.2. Reactivity and synthetic applications

7.2.1. The behavior of vinylic tellurides toward several reagents and reaction conditions used in organic synthesis. A systematic study was undertaken to ascertain the behavior of functionalized vinylic tellurides, such those depicted in the following figure toward several reagents and reaction conditions (Fig. 1).[203]

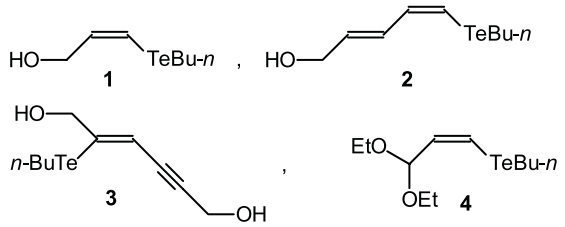


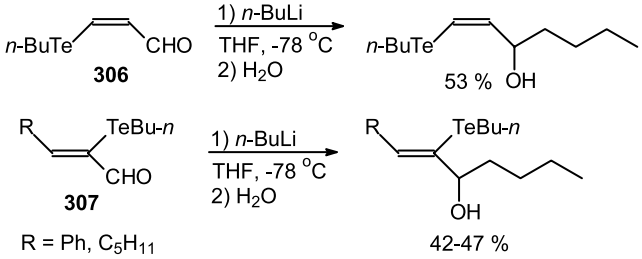
Figure 1.

Protection of hydroxy groups as the THP and *tert*-butyldimethyl silyl ethers and, conversely, deprotection of these derivatives to the original alcohols;
Acetylation of the hydroxy group and hydrolysis of the acetoxy group;
Oxidation of the hydroxy group by MnO_2 in ether or alternatively by Dess–Martin periodinane, and the reduction of the obtained aldehyde by $NaBH_4$;
Hydrolysis of the diethylacetal function employing *p*-toluenesulfonic acid in acetone, pyridinium *p*-toluenesulfonate in EtOH, and a suspension of SiO_2 in hexane.
In all cases the corresponding aldehyde is obtained in high yield as a *Z*/*E* isomeric mixture.

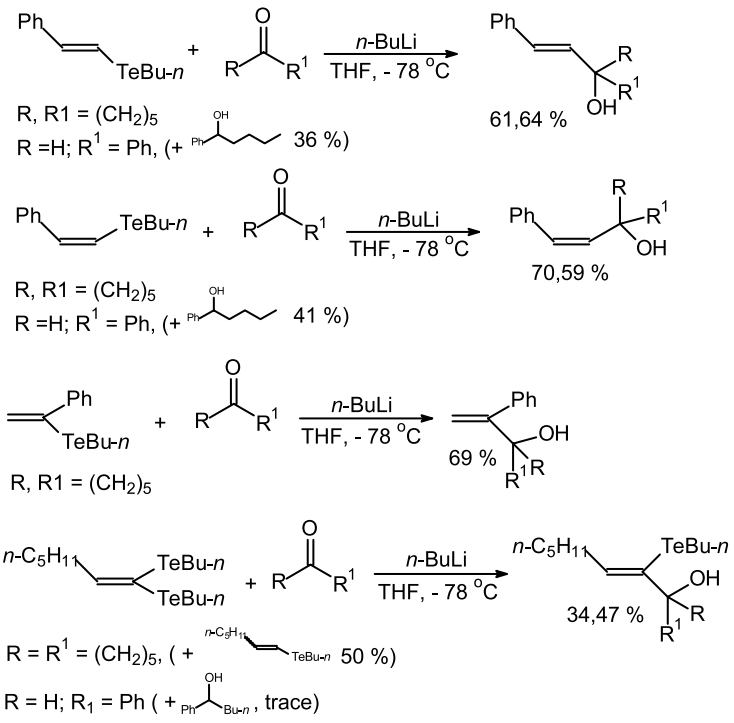
Transmetallation of acetal 4 with $Me_2Cu(CN)Li_2$ followed by treatment with *c*-hexenones giving the 1,4-addition product. Alternatively, transmetallation with *n*-BuLi and reaction with benzaldehyde gives the expected alcohol.

The reaction of 3-butyltelluro and 2-butyltelluro aldehydes **306–307** with *n*-BuLi gives the corresponding allylic alcohols showing the preferential attack to the carbonyl group[204] (Scheme 185).

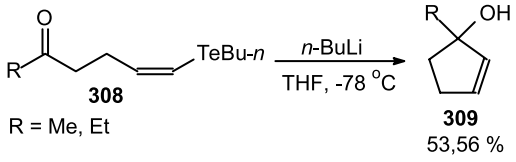
In contrast, when the *n*-butyltellurium moiety and the



Scheme 185.



Scheme 186.

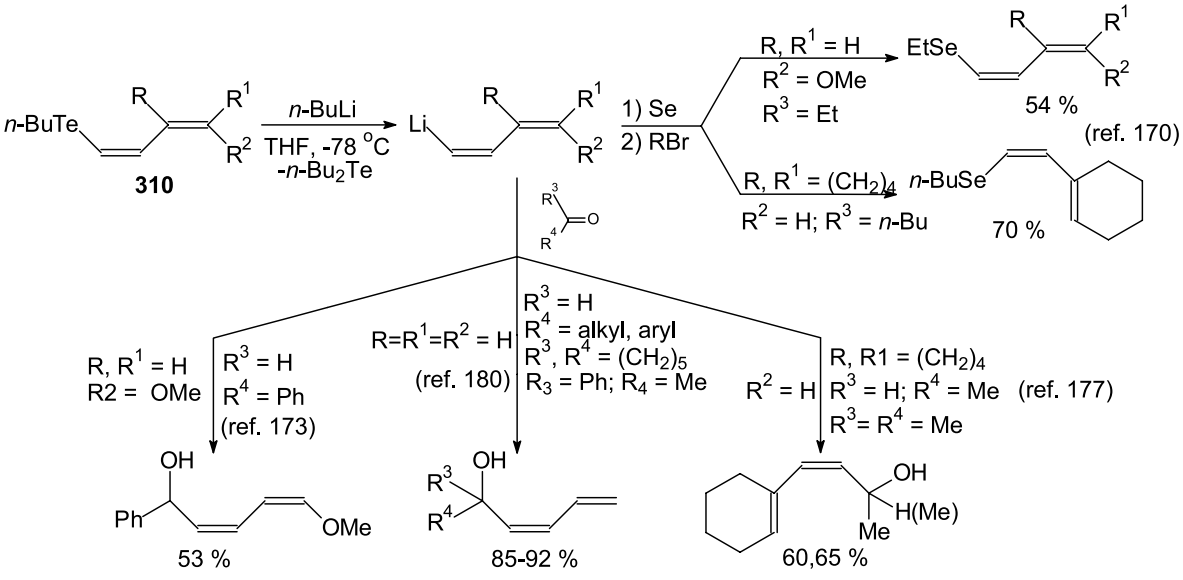


Scheme 187.

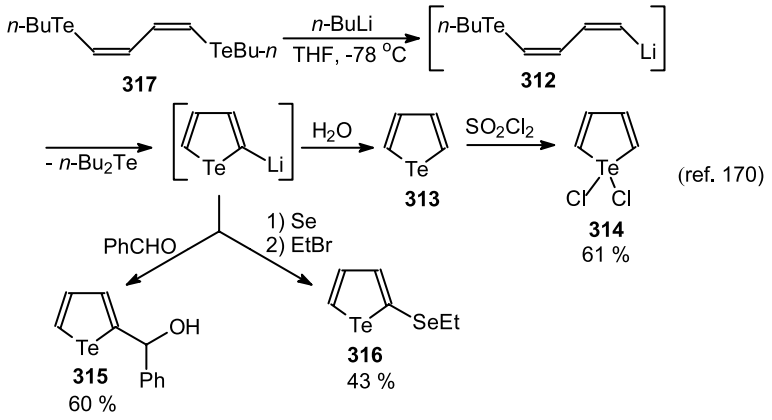
carbonyl group are attached to different substrates, the Te atom exhibits high selectivity for the *n*-BuLi attack, as observed when a 1:1 mixture of a vinyl telluride and a carbonyl compound is reacted with 1.0 equiv of *n*-BuLi (Scheme 186).

Non-conjugated substrates, such as 5-oxocarbonyl vinyl tellurides **308** undergo an intramolecular version of the above described protocol, achieving the synthesis of cycloalkenols **309** (Scheme 187).

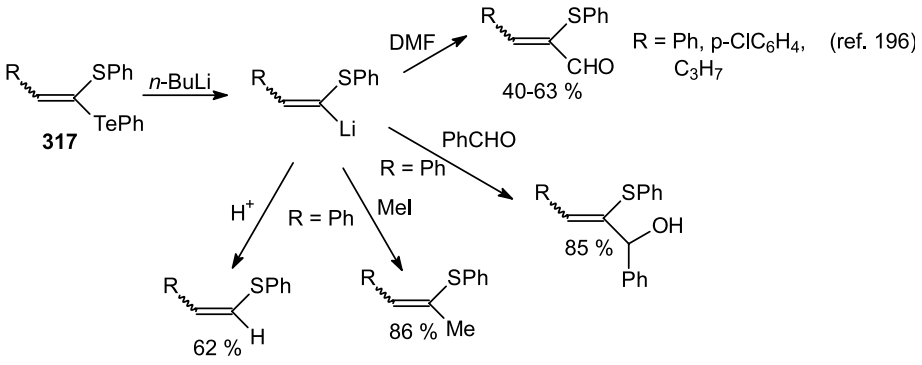
7.2.2. Tellurium/lithium exchange. The synthetic potential of the Te/Li exchange in the Te/Csp[2] bond, followed by trapping of the formed vinyl lithium derivative with electrophile[205] has been widely explored and applied to telluro- **310** and bis(telluro)butadienes **311** (Schemes 188 and 189), telluro (thio)ketene acetals **317** (Scheme 190), telluro (seleno)ketene acetals **318** (Scheme 191), divinyl tellurides **319** (Scheme 192), disubstituted vinyl tellurides



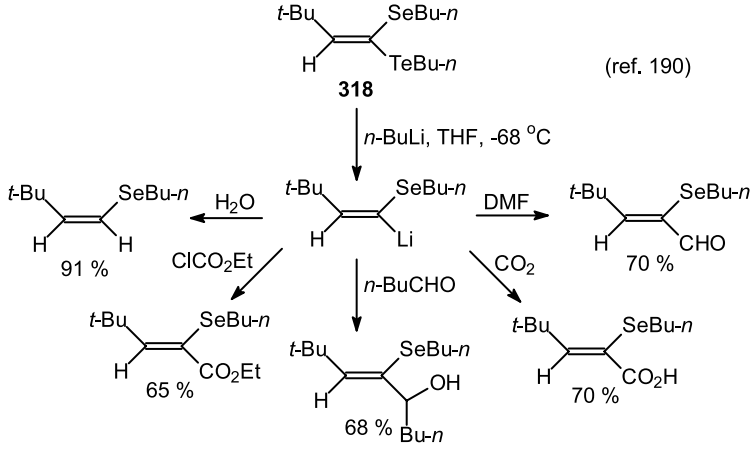
Scheme 188.



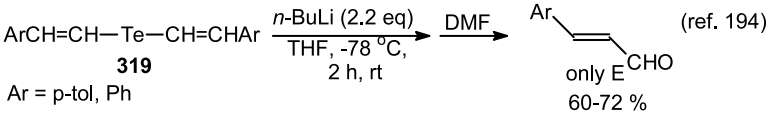
Scheme 189.



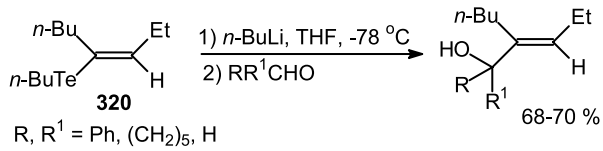
Scheme 190.



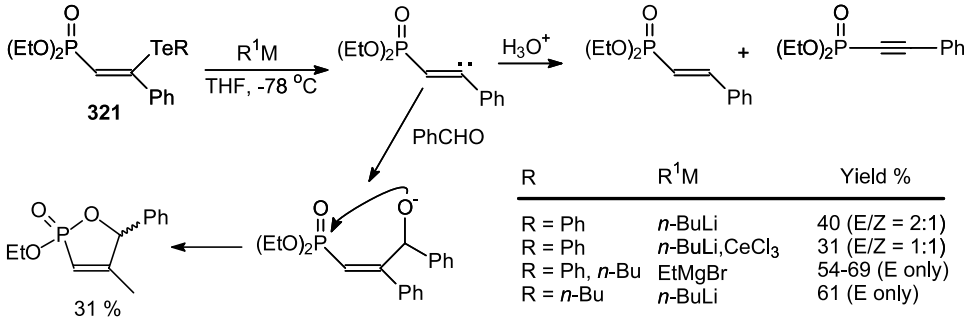
Scheme 191.



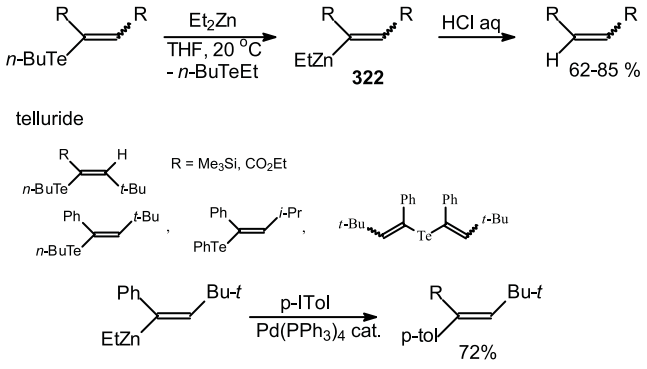
Scheme 192.



Scheme 193.



Scheme 194.



Scheme 195.

320 (Scheme 193) and β-phosphorovinyl tellurides **321** (Scheme 194).

All the reactions proceed with total retention of the configuration.

The treatment of bis(tellurobutadiene) **311** with 1 equiv of *n*-BuLi and quenching with water gives rise to tellurophene **313** which, due to operational facilities was isolated as the corresponding dichloride **314**. The tellurophene is formed via a first Te-Csp^2 cleavage giving **312** followed by an unusual Te-Csp^3 cleavage. The treatment of the reaction mixture with benzaldehyde or with elemental selenium followed by ethyl bromide affords the 2-substituted tellurophenes **315** and **316** (Scheme 189).

The selective Te/Li transmetallation and the subsequent functionalization reactions occur with total retention of the double bond configuration.

Disubstituted vinyl tellurides **321** (prepared via borane route) are converted in to trisubstituted olefins[198] (Scheme 193).

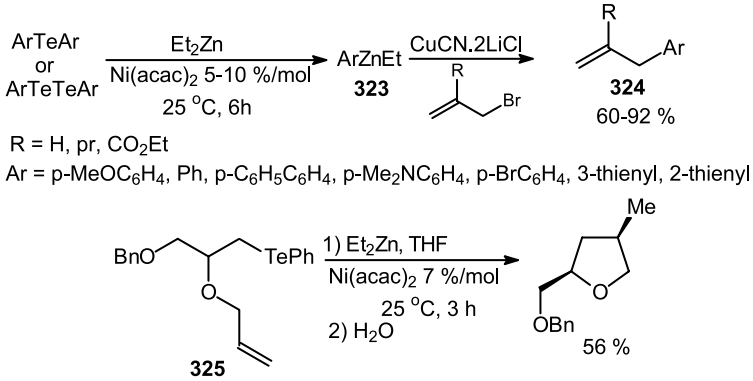
β-Phosphonovinyl tellurides undergo Te-transmetallation with several organometallic reagents.[176]

7.2.3. Tellurium/zinc exchange. Alkenylzinc compounds **322** have been prepared by a Te/Zn exchange reaction on vinylic tellurides under halide-free conditions, with retention of the geometry of the starting telluride[206] (Scheme 195).

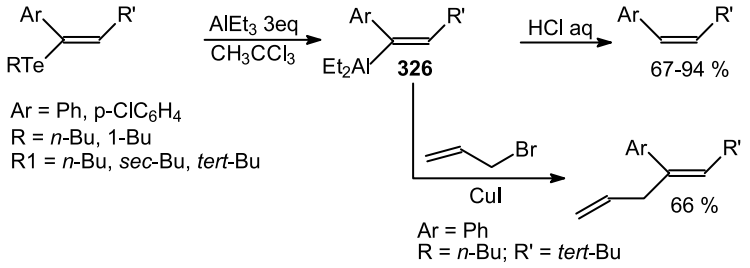
Quenching of the reaction mixture with aq. HCl yields the Te-free alkenes with retained geometry of the C–C double bond.

A Pd cross-coupling reaction takes rise upon treatment of the formed alkenylzinc with *p*-iodotoluene giving.

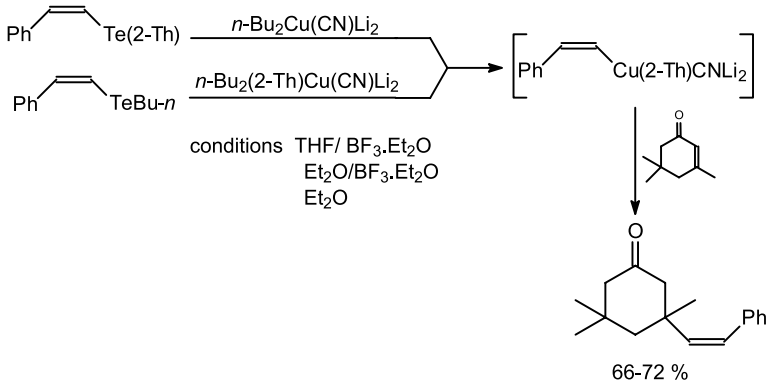
It was later observed[207] that the above Te–Zn exchange reaction is not a general method to prepare alkenyl Zn



Scheme 196.



Scheme 197.



Scheme 198.

reagents, but is restricted to vinylic tellurides bearing Ph, ester, or Me_3Si groups at the α-position, able to stabilize the formed vinyl zinc.

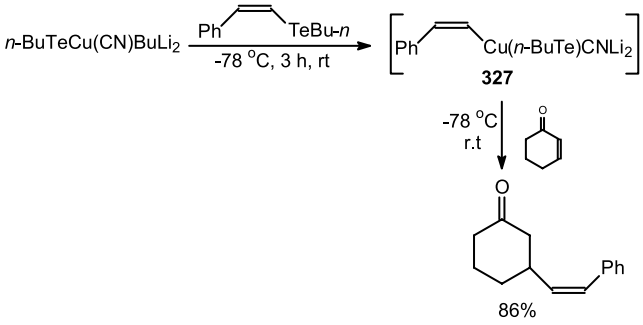
An additional report describes the Te/Zn exchange of diaryl tellurides and diaryl ditellurides by treatment with Et_2Zn under Ni catalysis.[208] The resulting Zn derivatives **323**, submitted to transmetallation with CuCN·2LiCl and subsequent allylation with an allylic bromide, furnishes the expected product **324** in high yield (Scheme 196).

Similar reactions were also performed with alkylphenyl and dialkyl tellurides. A cyclization process was also afforded with compound **325**, probably proceeding via a radical intermediate.

7.2.4. Tellurium/alumminum exchange. Vinylic tellurides undergo Te/Al exchange with trietylalumminun giving the corresponding alkenylalumminun derivative **326** with retention of the original stereochemistry. Successive quenching with aqueous HCl or reaction with allylbromide in the presence of CuI gives, respectively, the corresponding alkenes or a cross-coupling product[209] (Scheme 197).

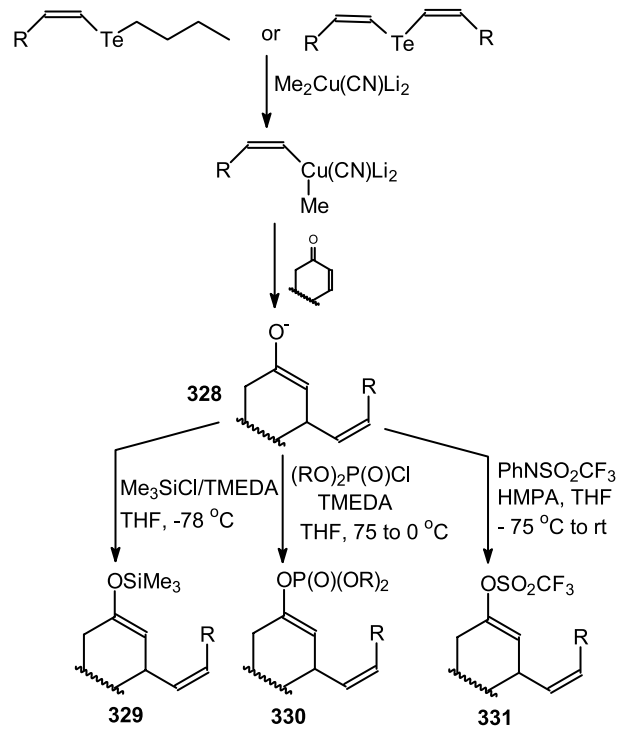
7.2.5. Tellurium/copper exchange. The well-established conjugate addition of higher-order *Z*-vinylic cyanocuprates, generated from the corresponding vinyl tellurides by Te/Cu exchange,[2–5] to enones,[210] has been recently submitted to further useful modifications. Thus it was shown that the serious drawback of this methodology, which is the inertness of hindered enones to the mentioned reagents when THF is used as solvent, can be overcome by the addition of BF_3·etherate to the reaction mixture, or simply by carrying out the reaction in ether in the presence or absence of BF_3·etherate[211] (Scheme 198).

Another highlight concerning these additions was a systematic investigation[212] regarding the use of alkylseleno- and alkyltelluro groups as non-transferable ligands in the 1,4-addition of alkyl higher order cyanocuprates to enones. The following example employing the tellurocuprate **327** is illustrative (Scheme 199).



Scheme 199.

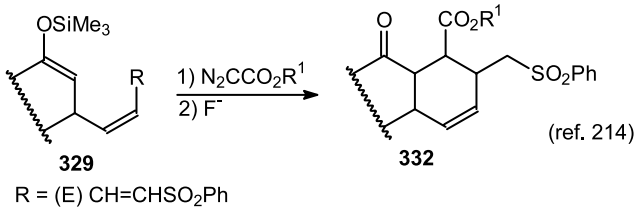
7.2.6. Conjugate addition of higher order cyanocuprates to enones, followed by *o*-functionalization. The enolate intermediate **328**, generated by the addition of higher order cyanocuprates to enones, has been trapped with several electrophiles. Thus the addition of trimethylsilyl chloride, diethyl or diphenyl phosphorochloridate and *N*-phenyl trifluoro methanesulfonate affords the corresponding vinyl sylilethers **329**, vinyl phosphates **330** and vinyltriflates[213] **331** (Scheme 200).



Scheme 200.

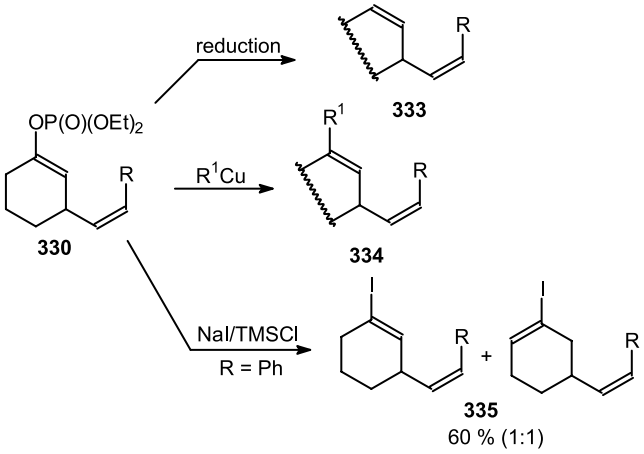
Several synthetic transformations have been performed with the O-functionalized systems **329**–**331**.

Enolsilylethers **329**, submitted to cyclopropanation and followed by F-promoted annulation, give compounds **332**[214] (Scheme 201).



Scheme 201.

Vinylphosphates **330** are converted into dienes **333** and **334** by reduction[215] or organometallic coupling, respectively,[216] and into the corresponding iodides **335** by treatment with TMSCl/NaI in MeCN[217] (Scheme 202).



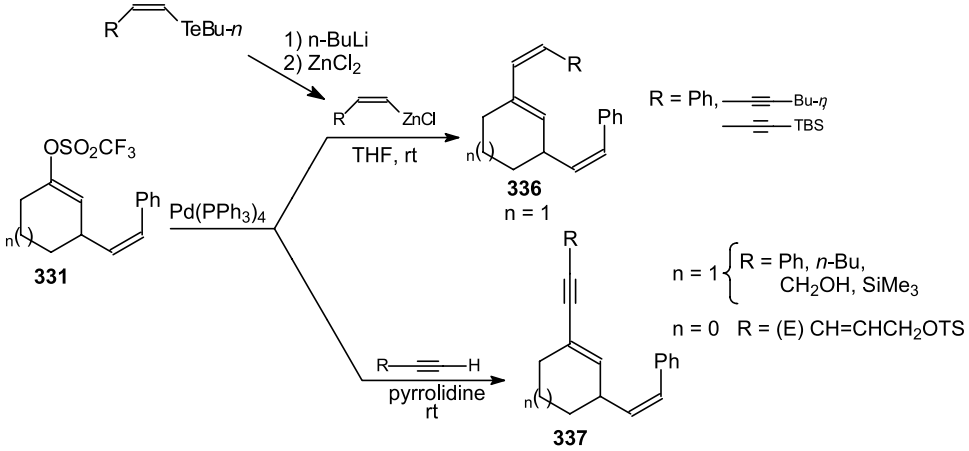
Scheme 202.

As described in Section 7.1.6, vinylphosphates **330** and trifaltes **331** are converted into functionalized tetrasubstituted vinylic tellurides[183,184] (see Scheme 167) by coupling with butyllithium tellurolate.

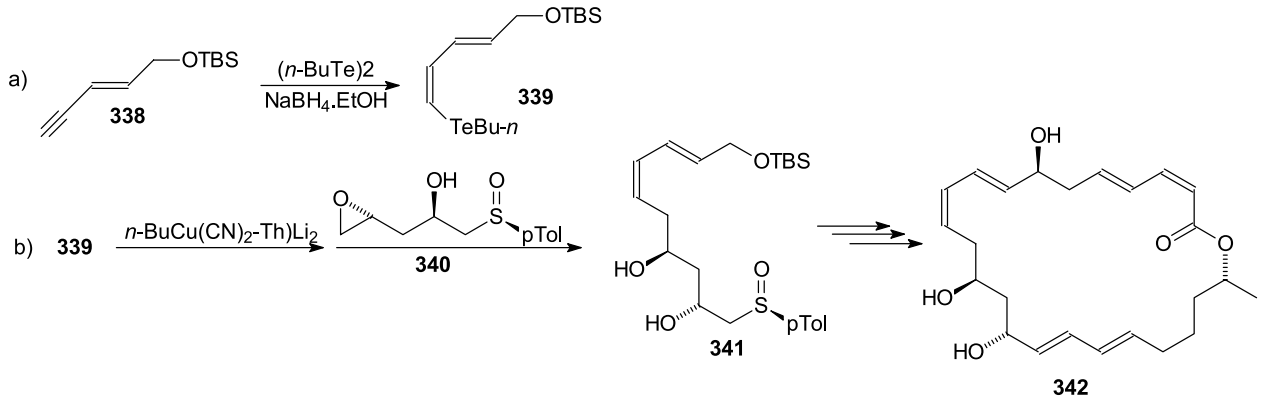
Finally, triflates **331** react with *Z*-vinyl zinc chloride (prepared by treating *Z*-butylvinyl telluride with *n*-BuLi and then with $ZnCl_2$) and with terminal alkynes under $Pd(PPh_3)_4$ catalysis to afford, respectively, the coupled products[213,218] **336** and **337** (Scheme 203).

7.2.7. Synthesis of (−)-macrolactin A. Compound **341** one of the subunits of the natural product (−)-macrolactin A **342**, a strong antiviral agent, has been synthesized as shown in Scheme 204:[219]

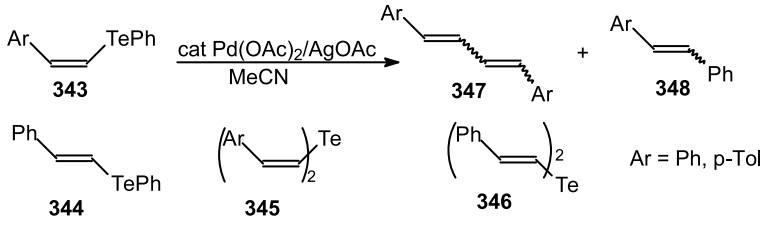
(a) hydrotelluration of the enine **338** giving the *Z*/*E* dienyl telluride **339**.
(b) transmetallation of the **339** with a mixed higher-order cyanocuprate and subsequent reaction with the epoxide **340**.



Scheme 203.



Scheme 204.



Scheme 205.

7.2.8. Coupling reactions. Vinyl tellurides bearing a stiryl moiety **343**–**346** give the corresponding 1,3-dienes **347** homocoupling products with moderate to good yields, by treatment with a catalytic amount of $Pd(OAc)_2$ in the presence of AgOAc as reoxidant[220] (Scheme 205).

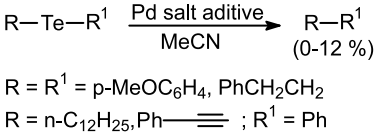
The characteristic feature of this catalytic reaction is the preferential formation of a *Z*,*Z*-diene, the *Z* stereochemistry of the starting telluride being largely retained.

The formation of the stylbenes **348** only in low yield, clearly shows that the fission of a vinyl tellurium bond is favorable toward the Ph–Te bond.

Each of the above tellurides reacts smoothly to give the corresponding dienes **347** where the selectivity to *Z*,*Z* and *E*,*E* isomers in the product is high from **343** and **345** (*Z* isomer) and from **344** and **346** (*E* isomer).

Cross-over experiments suggest that the homocoupling reaction occurs between an alkenyl telluride and an alkenyl Pd species, which is formed via the migration of an alkenyl moiety from Te to Pd.

In addition to the just described reactions with vinylic tellurides, this palladium-catalyzed homocoupling protocol was attempted with a variety of organyl tellurides. This reaction, however, did not take place satisfactorily in disagreement with previous reported results[221] (Scheme 206).

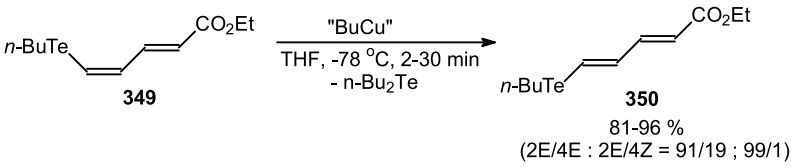


Scheme 206.

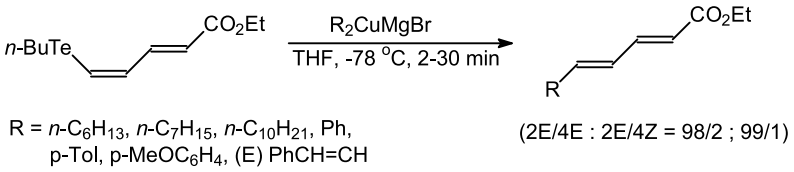
Ethyl 5-telluro-(2*E*,4*Z*)pentanedienoate **349** reacts with different copper reagents $Bu_2Cu(CN)Li_2$, $Bu_2Cu(CN)(MgBr)_2$ and $Bu_2CuMgBr$ to give the cross-coupled Te free dienes **350** with high *E*,*E* stereoselectivity[222] (Scheme 207).

Lower *E*,*E* selectivity is observed with the reagent Bu_2CuLi.

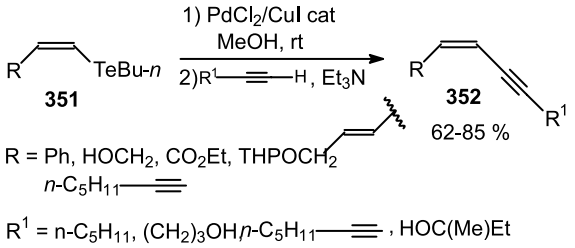
The stereochemistry outcome of the above reaction, proceeding with inversion of the C3–C4 double bond geometry, is anomalous since it differs from the well-established retention of the geometry in the coupling reaction of *Z*-vinylic tellurides with organocopper higher and lower order cyanocuprates.[223]



Scheme 207.



Scheme 208.

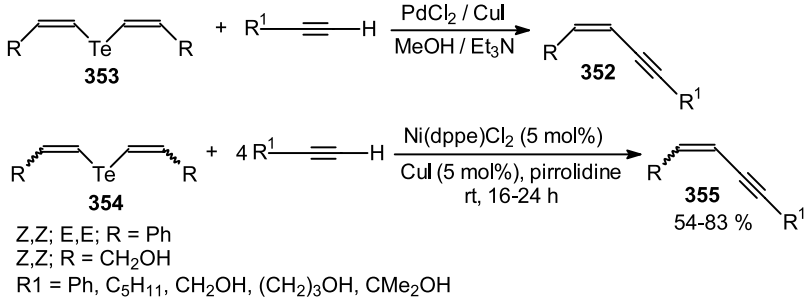


Scheme 209.

Optimum reaction conditions were achieved with the bromomagnesium cuprate, and explored in several examples (Scheme 208).

Cross coupling reactions of alkynes with (*Z*)-vinylic tellurides **351** under $PdCl_2$/CuI catalysis gives rise to the corresponding enynes **352** with retention of the configuration[224] (Scheme 209).

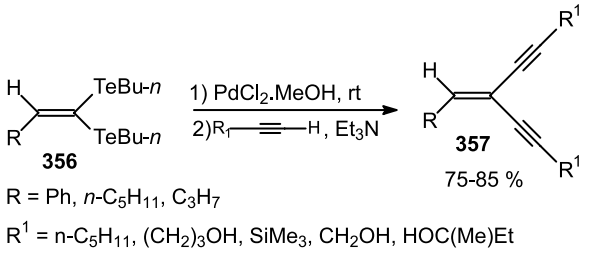
The *Z*-enynes **352** are also obtained in good yields applying the above Pd catalyzed process to *Z*-divinyl tellurides **353**.



Scheme 210.

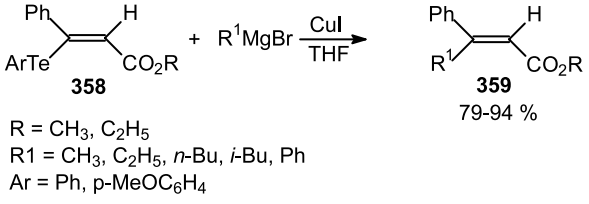
In spite of the excess of alkyne used, the transfer of only one vinylic group was observed. A more general approach of this method involves the reaction of *Z*,*Z*- and *E*,*E*-divinylic tellurides **354** with alkynes under nickel catalysis, to give *Z*- and *E*-enynes **355** with complete retention of configuration[225] (Scheme 210).

It must be emphasized that the enyne units are present in several antitumor and antibiotics.



Scheme 211.

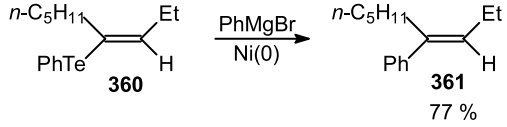
Similar couplings have been performed with telluroketene acetals **356** yielding geminal enediynes **357**. $PdCl_2$ is used instead of the $PdCl_2 \cdot CuI$ system[226] (Scheme 211).



Scheme 212.

(*Z*)-β-Substituted cynnamic esters **359** are formed with retention of the configuration, by the coupling reaction of *Z*-β-aryltelluro cynnamic esters **358** with Grignard reagent in the presence of CuI[227] (Scheme 212).

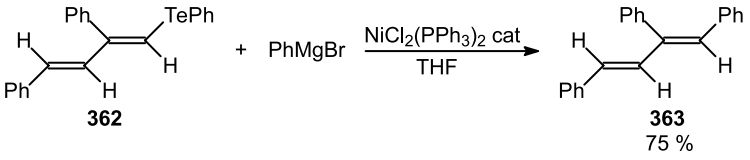
Disubstituted vinylic tellurides **360** are converted to trisubstituted olefins **361** by a similar reaction catalyzed by Ni(0)[198] (Scheme 213).



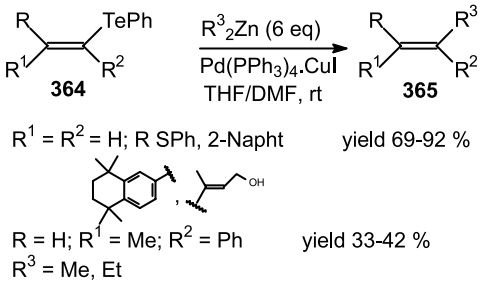
Scheme 213.

Trisubstituted 1,3-butadienes **363** are afforded by Ni-phosphine catalyzed coupling of the corresponding telluro-butadienes **362** with Grignard reagents[202] (Scheme 214).

The cross-coupling reaction of vinylic tellurides **364–366** with diethylzinc or alkylzinc reagents under $Pd(PPh_3)_4$CuI



Scheme 214.

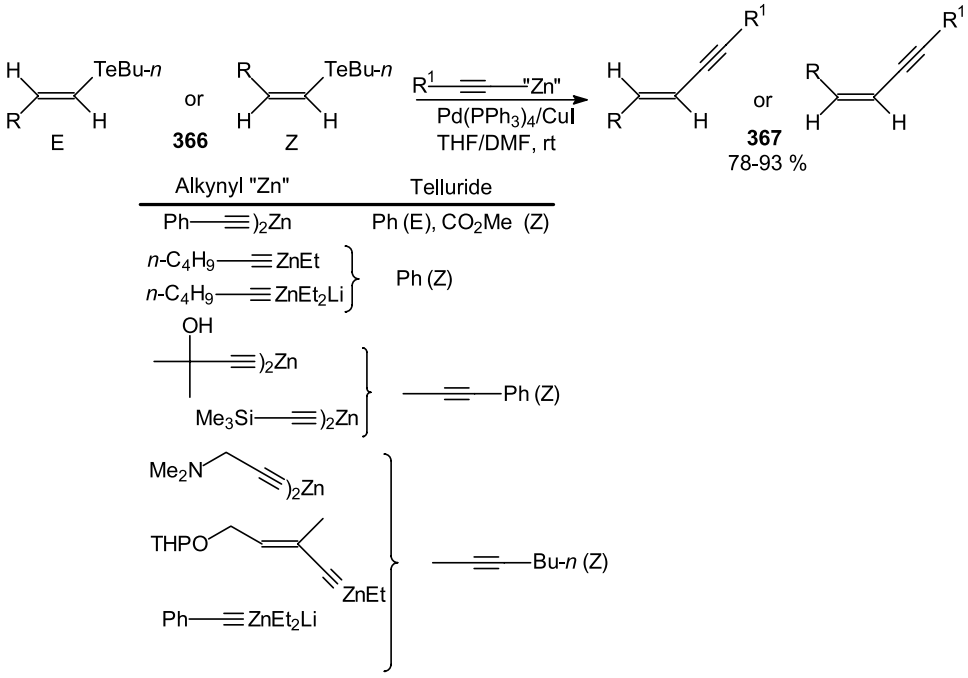


Scheme 215.

catalyst was established as a useful method to synthesize different types of dienes[207] **365**, enynes or enediynes[228] **367** (Schemes 215 and 216).

In addition to vinylic tellurides, phenylbutyltellurides and an aryliodide have been employed to afford the arylation of alkynil Zn reagents[228] **368** and **369** giving the coupled products **370–372** (Scheme 217).

Ethylalkynyl Zn reagents of RC≡CZnEt type were prepared by adding Et_2Zn (4.5 mmol) to acetylenic telluride (3.0 mmol) in THF, reagents of RC≡CZnEt_2Li type by addition of Et_2Zn (3.0 mmol) to a solution of LiC≡CH

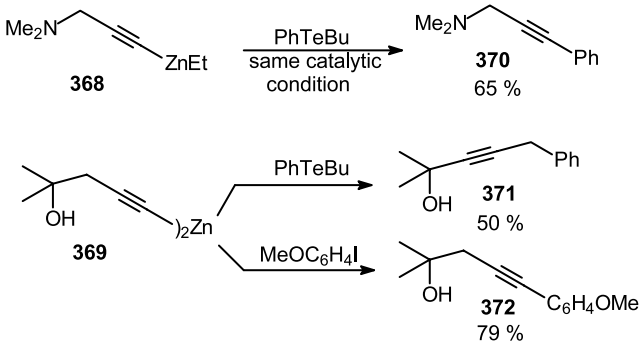


Scheme 216.

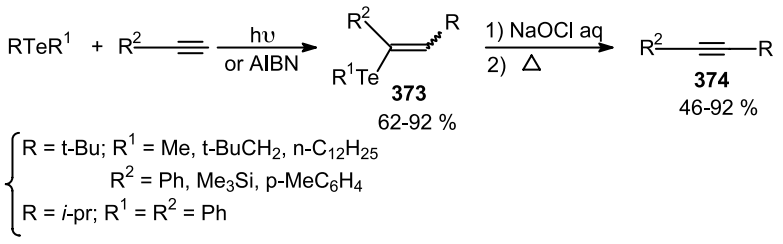
(3.0 mmol) in THF, and reagents of RC≡C)$_2$Zn type by addition of $ZnCl_2$ (3.0 mmol) to a solution of LiC≡CH (6.0 mmol) in THF.

7.2.9. Synthesis of internal acetylenes from vinylic tellurides. Treatment of vinylic tellurides **373**, prepared by photopromoted carbotelluration of terminal acetylenes[229] with aqueous NaOCl, followed by pyrolysis, affords internal acetylenes **374** in good yields[230] (Scheme 218).

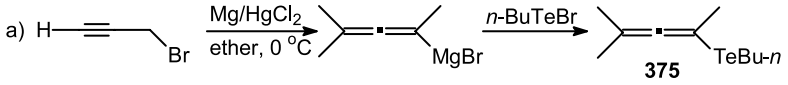
The combination of the photopromoted carbotelluration with the elimination reaction, provides a useful method for the introduction of alkyl groups to terminal acetylenes.



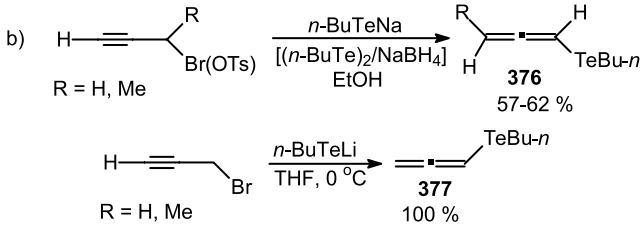
Scheme 217.



Scheme 218.



Scheme 219.

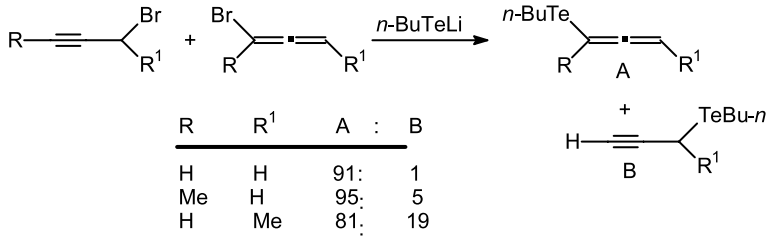


Scheme 220.

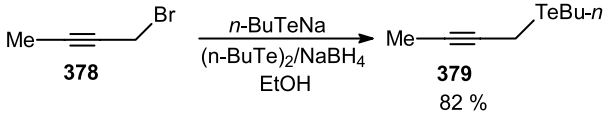
8. Allenic and propargylic tellurides

Allenic butyl tellurides **375–377** have been prepared by two methods:

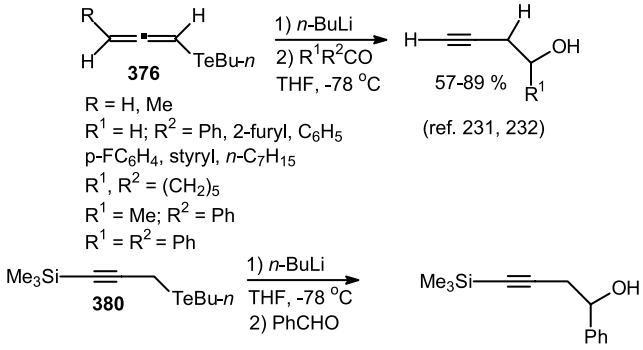
(a) reaction of butyltellurenyl bromide with the allenyl magnesium bromide generated from propargyl bromide and Mg in the presence of $HgCl_2$[231] (Scheme 219).
(b) SN^2 type reaction of propargylic bromides or tosylates with butyltellurolate anions[231,232] (Scheme 220).



Scheme 221.



Scheme 222.



Scheme 223.

Treatment of mixtures of propargyl and allenyl bromides with *n*-BuTeLi affords allenyl tellurides as main product[232] (Scheme 221).

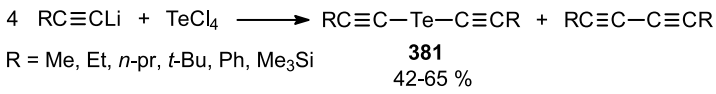
An exception is the trimethylsilyl derivative (R = Me_3Si; R^1 = H), which furnishes only the propargyl telluride.

In disagreement with the above results, the propargyl-bromide of non-terminal acetylene **378** gives only the corresponding propargyl telluride **379** (B)[231] (Scheme 222).

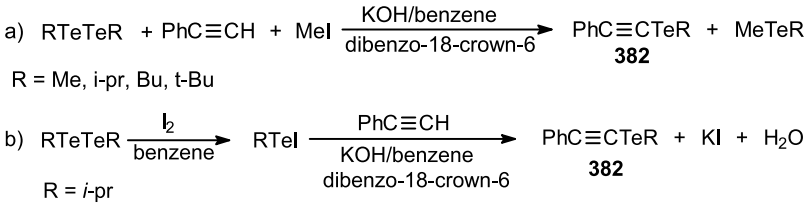
Allenyl tellurides **376** and the propargyl telluride **380** can be submitted to Te/Li exchange and subsequent functionalization[231,232] (Scheme 223).

9. Acetylenic tellurides

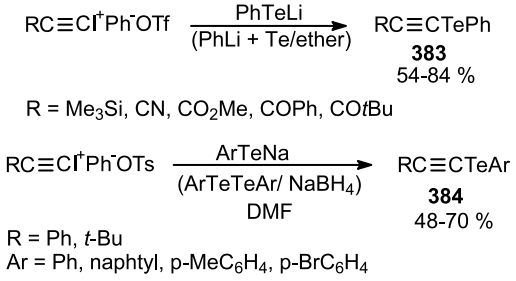
Only few new procedures for the preparation of acetylenic tellurides have been reported in the last decade.



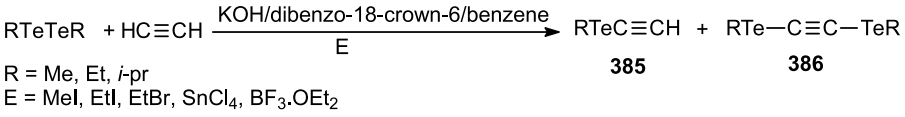
Scheme 224.



Scheme 225.



Scheme 226.



Scheme 227.

9.1. Dialkynyl tellurides

The four-decade old reaction of $TeCl_4$ with 4 equiv Grignard reagents giving diaryl tellurides and biaryls,[233] later extended to alkynyl Grignard reagents,[234] have been revived using 1-alkynyllithiums[235] to give dialkynyl tellurides **381** (Scheme 224).

The by-produced diynes are hardly obtained as pure compounds.

9.2. Alkyl ethynyl and aryl ethynyl tellurides

Some new procedures have been reported to prepare the title compounds: **382–384**.

One-pot reaction of phenylacetylene with a dialkyl ditelluride and an alkyl iodide in the system KOH/crown ether/benzene (method a). The same products can be obtained by using the tellurenyl iodide prepared in situ (method b)[236] (Scheme 225).

Reaction of lithium or sodium aryltellurolate with alkynyl phenyl iodonium triflates[237] or tosylates[238] (Scheme 226).

The reaction of dialkylditellurides with pressurized acetylenes in the presence of an electrophilic reagent, (alkyl halide, Lewis acid), in the system KOH/crown ether/benzene, gives rise to alkylethynyl tellurides **385** and 1,2-bis-alkyltelluroacetylenes **386** in high yields[239] (Scheme 227).

The preferential formation of **385** or **386** is determined by a minor or major molar ratio KOH/RTeTeR, respectively.

The reaction was rationalized assuming the intermediacy of the high electrophilic species $[RTeTe(R^1)R]X^-$ (R^1 = Alkyl and X = Br, I).

10. Addendum

Some references omitted in the text and others published after the completion of the manuscript are referred in sequence:

Synthesis and absolute configuration of optically active telluronium salts[240]
Synthesis and peculiar behavior in solution of optically active telluronium salts[241]
Crystal structure of optically active diasteromeric telluronium and selenonium salts[242]
Distereoselective synthesis and stereochemical research of optically pure telluronium salts[243]
Stereoselctive synthesis of α-phenylchalcogeno-α,β-unsaturated esters[244] (Chapter 7-1)
Sonogashira cross-coupling reaction of organotellurium dichlorides with terminal alkynes[245] (Chapter 7.2.8)
Selenium and tellurium-substituted cyclopropanones and their facile ring-opening with methanol[246] (Chapter 9)
A diversity-oriented synthesis of α-aminoacids derivatives by a silyltelluride-mediated radical coupling reaction of amines and isonitriles[247] (Chapter 6.12)
Acyclic selenoiminium salts: isolation, first structural characterization and reactions (synthesis of telluromides)[248]
Enantioselective synthesis of vinylciclopropanes via chiral telluronium ylides[249] (Chapter 3.2.2)

A convenient preparation of organotellurophosphates using a polimer-supported hypervalent iodine (III) reagent[250]
Stereoselective sp^2–sp^2 bond formation via Negishi cross-coupling of vinyl tellurides and 2-heteroarylzinc chlorides[251] (Chapter 7.2.8)
Palladium-catalyzed Mizoroki–Heck-type reaction using telluronium salts[252]
A telluride-triggered nucleophilic ring opening of monoactivated cyclopropanes[253] (Chapter 3.2)
Telluroporphirines.3—Synthesis, structure, and spectral properties of 21,21-dihalo-21-telluraporphirines[254] (Chapter 5)
Microwave-assisted group-transfer cyclization of organotellurium compounds[255] (Chapter 6)
Optical resolution and racemization mechanism of a tellurinic acid[256]
Tellurium-based cysteine protease inhibition: evaluation of novel organotellurium (IV) compounds as inhibitors of human Cathepsin B[257]
The following reviews are valuable sources of general and specific topics information:
New aspects of old reaction in organotellurium chemistry[258]
Specific features of the reactivity of organotellurium compounds[259]
New routes to unsaturated organoselenium and organotellurium compounds[260]
Optically active selenium and tellurium compounds. Synthesis and application for asymmetric synthesis[261]
Organic derivatives of monocoordinated tellurium[262]
Synthesis, reaction and structure of organic tellurenyl derivatives[263]
Tellurium β-aryl interactions: a new bonding motif for molecular self-assembly and crystal engineering[264]
Derivatives of tellurocarboxylic acids[265]
Synthesis and reaction of organic compounds containing bonds of Te to group 14 elementes[266]
β-Telluroacroleins and tellurovinyl ketones: synthesis, reactions and structures[267]
Biomethylation of selenium and tellurium: microorganism and plants[268]
Palladium-catalyzed coupling of sp^2 hybridized tellurides[269].
The following references concern also with selenium chemistry 3, 11, 12, 16, 17, 21, 33, 36–38, 52–54, 66, 108, 109, 122–124, 135, 136, 146b, 155, 158b, 169, 175, 185a,c, 186–188, 197, 198, 225, 237, 242, 244.

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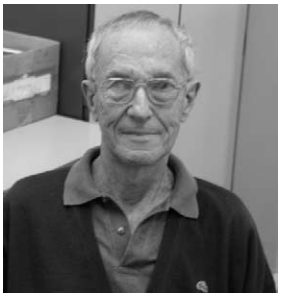
Biographical sketch



Nicola Petragnani was born in Rome, Italy in 1929. In 1947 he moved to Brazil where he studied chemistry at the University of São Paulo. After receiving his B.Sc. in 1951 he began work under the supervision of Professor H. Reinboldt in the field of organic tellurium chemistry, finishing his Ph.D. in 1957. Since then, his major contribution has continued in the field of the organic compounds of tellurium and selenium. In 1960 he reported the first examples of seleno- and telluro-cyclofunctionalization. He spent a year (1962) at the Chemistry Institute of the University of Freiburg, Germany, working with Professor A. Luttringhaus. From 1970–1977 he was the Brazilian coordinator of the NAS-CNPq (National Academy of Sciences/Conselho Nacional de Pesquisa) binational program on Organic Synthesis, a program coordinated by Professor C. Djerassi aiming to introduce new branches of chemistry to Brazilian chemists. Since 1978 he has been full Professor of Organic Chemistry at the Chemistry Institute of The University of São Paulo.

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New benzopyranocarbazoles: synthesis and photochromic behaviour

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Abstract—The synthesis of three new benzopyranocarbazoles (=[indole]naphthopyrans) from hydroxybenzo[*a*]carbazoles is described. The photochromic properties of these novel compounds were investigated under flash photolysis and continuous irradiation. Compared to known [indole]benzopyrans these new compounds showed a significant bathochromic shift in the spectra of the open forms, an increase in colourabilities and slower ring closure kinetics. The photochromic behaviour of compound **4** has been further investigated. Continuous near-UV irradiation led to the formation of one photoisomer (TC) that was subsequently partially converted, to the other (TT). Thermal reversion of the preirradiated system to the original form was only partial and followed a monoexponential decay involving the back-conversion of the TC-isomer to the uncoloured closed form (CF). The thermally stable TT-isomer could only be photobleached with visible light. This process was shown to proceed through a fast photoconversion TT→TC followed by the thermal path TC→CF. Thermal relaxation of the activated system was also studied at various temperatures.

1. Introduction

Benzo- and naphthopyrans derivatives are one of the most studied and important class of photochromic molecules.[1,2] They were originally studied for their potential in offering complementary colours (yellow to orange) to the well known (blue) indolinospironaphthoxazines.[3] Nowadays, it is possible to obtain any colour using only naphthopyrans.[4] Owing to their good photochromic properties, associated with high fatigue resistance, this family of compounds has been used in recent years in the manufacture of photochromic lenses that darken in sunlight.[5]

Under UV irradiation these molecules, in solution or incorporated in polymer matrices, undergo a pyran-ring opening due to the breaking of the $C_{(sp}3)$–O bond leading to an equilibrium between the uncoloured closed form (CF) and a set of coloured stereoisomers of the open form (OF), having different stabilities (Scheme 1).[6] Usually the phenomenon is thermally reversible, although it is well known that in some cases it can be also photoinduced with visible light.

Typically, UV–Vis spectroscopy has been used to study this phenomenon and has resulted in the determination of intrinsic properties of the process which is responsible for the reversible change.[7–9] Normally, however, the UV spectroscopy only gives global information about the photochromic system and does not give individual information about each of the various forms obtained under irradiation.

Recently, the photochromic process has been deeply studied by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy. This technique allowed the elucidation of important mechanistic and structural features along with the calculation of kinetic and thermodynamic parameters. From these studies, it is apparent that benzo- and naphthopyrans, under continuous UV irradiation, usually generate two major photoproducts, namely the *trans–cis* (TC) and the *trans–trans* (TT) forms. Both are responsible for the colour obtained after irradiation; however, usually, the latter isomer was found to be the most thermally stable.[10–12]

Benzo- and naphthopyrans containing a fused carbazolo or indolo group exhibit interesting photochromic properties and have been patented.[13–16] In previous works, we described the photochromic properties of indolo-fused benzopyrans.[17,18] These compounds showed some interesting properties such as a high photocolouration efficiency in the near-UV and two absorption bands in the visible range. Since naphthopyrans are more photochromic and less fatigue prone than benzopyrans (because they are activated

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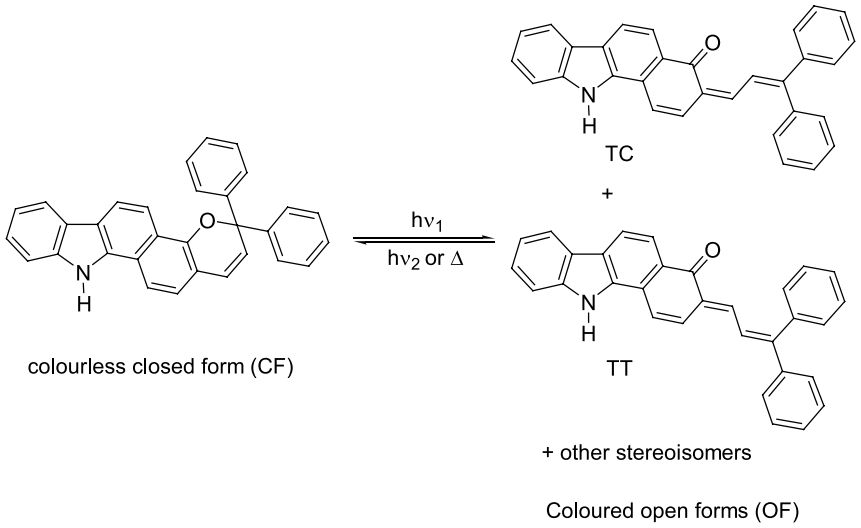


Scheme 1.

with less energetic light) and the photochromic properties can be dramatically changed by structural features[1,4,19] we decided to synthesise and study new indolo-fused naphthopyrans.

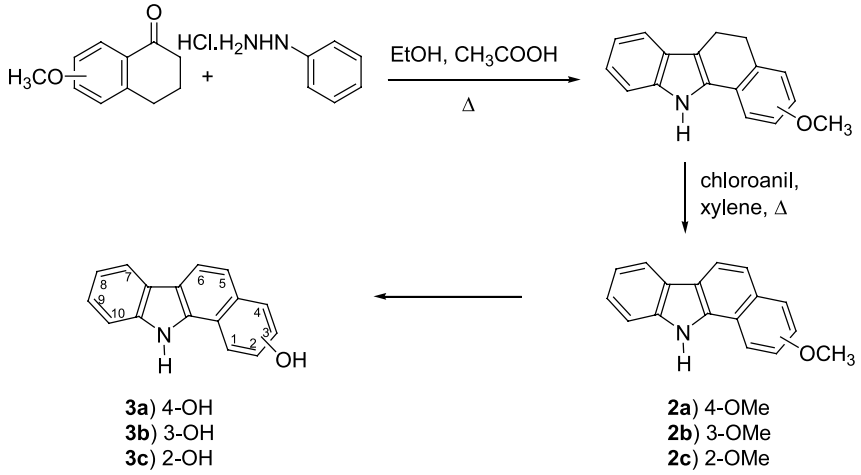
During the evaluation of spectrokinetic parameters, we have found that one of the compounds was particularly suitable to make further studies that allowed to elucidate some interesting features about the photochromic mechanism in the naphthopyrans family.

2. Results and discussion

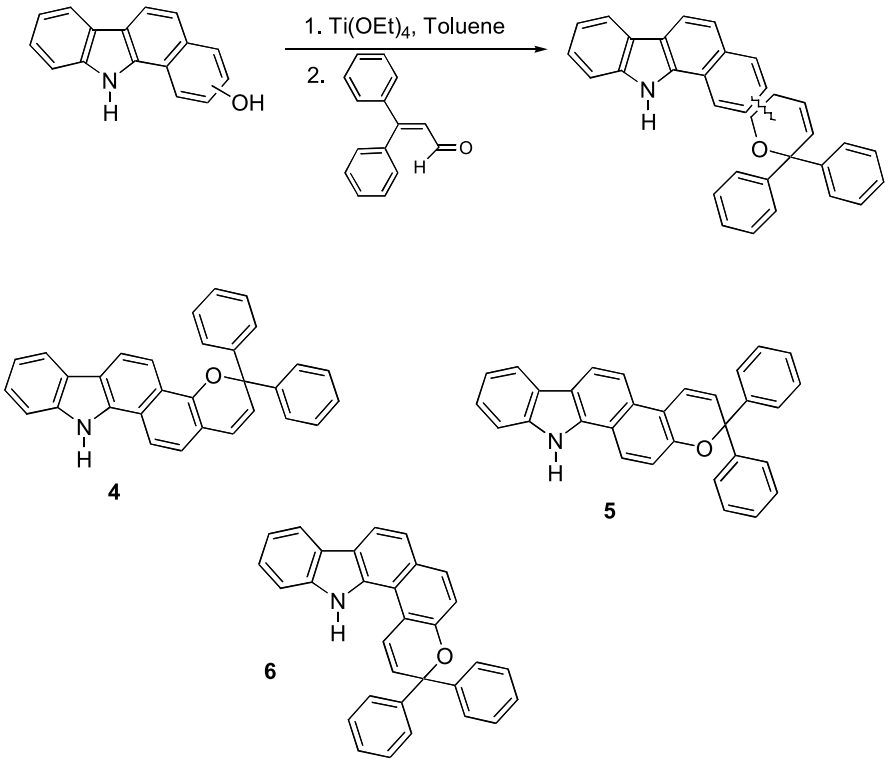
2.1. Synthesis

The new benzopyranocarbazoles **4–6** were prepared in four steps from methoxytetralones **1a–c** as outlined in Schemes 2 and 3. The 5-, 6- and 7-methoxytetralones **1a–c** were refluxed 1 h with phenylhydrazinium chloride in ethanol, in the presence of a few drops of acetic acid[20] and were then dehydrogenated with tetrachloro-1,4-benzoquinone (*p*-chloroanil) in xylene[21,22] affording methoxybenzo[*a*]-carbazoles **2a–c** in very good yields (80–96%). This two step procedure represents an easier route to prepare methoxybenzo[*a*]carbazoles over the Fischer–Borsche[16] method because it avoids bubbling the hydrazone intermediate with gaseous HCl. Demethylation of methoxyl groups using pyridine hydrochloride[21–23] afforded the hydroxybenzo[*a*]carbazoles **3a–c** in good yields (63–85%).

Naphthopyrans are usually prepared through reaction of naphthols with 1,1-diarylprop-2-yn-1-ol under acid catalysis. For basic naphthols, such as hydroxybenzo[*a*]-carbazoles **3a–c**, an alternative method involving the organotitanium mediated condensation with an α,β-unsaturated aldehyde is more adequate. The reaction of α-phenylcinnamaldehyde with a Ti^{IV} 'phenolate', obtained by adding $Ti(OEt)_4$ to the hydroxybenzo[*a*]carbazoles **3a–c** and separating the ethanol formed by azeotropic distillation, leads to C-alkylation in *ortho*-position that through a subsequent electrocyclisation yielded the naphthopyrans **4** (63%), **5** (24%) and **6** (77%) (Scheme 3).[24]



Scheme 2.



Scheme 3.

2.2. Photochromic properties

Although benzopyranocarbazoles with an indole moiety fused to the *f*-face (5,6-positions) of a 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran nucleus were already described in prior art,[16] the compounds **4**–**6**, 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran fused to the *i*-face and 3,3-diphenyl-3*H*-naphtho[2,1-*b*]pyran fused to the *i*- and *k*- faces are now described for the first time. The new naphthopyrans exhibit photochromic behaviour at room temperature in toluene solutions. The relevant spectrokinetic parameters (activation wavelengths of closed forms, maxima wavelengths of the coloured forms, colourability and thermal bleaching rates) were evaluated under flash photolysis and continuous near-UV irradiation. Both methods are extensively used to quantify spectrokinetic parameters of organic photochromes, but the information obtained by the two methods can be very distinct because time scales of observation and light flux intensities applied are completely different. Methods employing continuous irradiation use a longer irradiation time and a lower intensity light flux and are usually well suited to the study of slow systems. Moreover they operate in experimental conditions quite comparable to those that are found in applications where sunlight activation is intended. The data obtained are summarized in Table 1 together with data obtained with the corresponding pyranocarbazoles (**Ref1**, **Ref3** and **Ref4**)[18] and the reference naphthopyrans (**Ref2** and **Ref5**)[25,26] for comparative purposes.

2.2.1. Activation wavelengths of uncoloured forms. Compared to the reference pyranocarbazoles, the introduction of an additional benzene ring, in the *f*- and *h*-faces (5,6- and 7,8-positions) of the 2*H*-1-benzopyran ring system, led to the apparition, in the closed forms, of strong UV absorption bands shifted further towards the visible (see Figure 1 for comparison of **Ref1** and compound **4**). This feature is important as the activation with less energetic radiation improves both the sensitiveness to solar light and also the fatigue resistance.[2]

2.2.2. Maxima wavelengths of coloured forms. Compared to the corresponding 2*H*- and 3*H*-naphthopyrans, the fusion of an indole ring to naphthopyrans led to a global bathochromic shift in the spectra of the open forms. This effect was already observed for 2*H*-1-benzopyrans fused to an indole moiety.[17,18] From a general point of view comparing the two sets of compounds with a fused indole moiety, both under flash photolysis and continuous irradiation, the introduction of an additional benzene ring led to the loss of the two band profile in the visible absorption spectra of the coloured forms. One exception was observed, under continuous irradiation, for the open form of compound **4** (2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran with the indole fused to 7,8 positions) that displays two significant absorption bands in the visible range (Fig. 1). The same was observed for 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran with the indole group fused to the 5,6 positions.[24] No clear electronic effect could be readily observed due to the presence of the indole nitrogen atom. Electron-donating substituents at the 7-position of diphenylnaphthopyrans have little effect on the maxima absorption wavelength of the open form and at the 10-position have not been reported.[2,4]

2.2.3. Colourability and thermal bleaching rate. All the new described compounds exhibit better colourabilities than the corresponding 2*H*-1-benzopyrans fused to an indole

Table 1. Maxima wavelengths of the coloured forms (λ_{max}, nm), colourability (A_0 and A_{eq}), fading rate (k_Δ,s^{-1}) of compounds **4–6** and five reference compounds in toluene solutions under flash photolysis (2.5×10^{-5} M at 25 °C) and continuous irradiation (1×10^{-4} M at 20 °C)

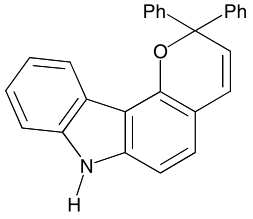
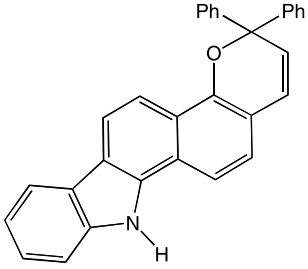
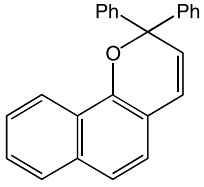
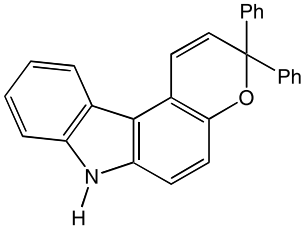
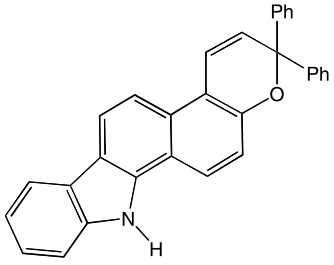
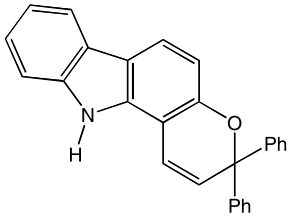
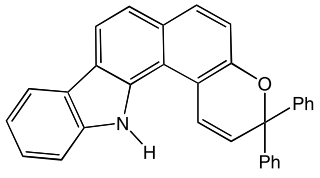
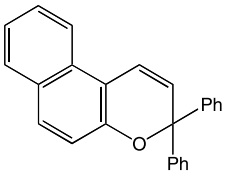
Compound		Flash photolysis open form			Continuous irradiation open form		
		λ_{max}	A_0	k_Δ (%)	λ_{max}	A_{eq}	k_Δ (%)
Ref1		415 542	1.8 0.26	1×10^{-2} (38) 4×10^{-3} (62)	415	2.22	4×10^{-3} (71) 2×10^{-3} (29)
4		531	1.1	1×10^{-3} (100)	414 517	1.34 1.38	1×10^{-3} (100) (414 and 517 nm)
Ref2		403 481	1.08 1.62	<0.01	469	0.72	6×10^{-4} (98) 3×10^{-4} (2)
Ref3		460 549	0.68 0.61	4×10^{-2} (100)	460	0.28	0.04 (100)
5		490	3.2	3×10^{-2} (100)	485	0.37	0.13 (100)
Ref4		443 590	1.1 0.29	0.17 (94) 2×10^{-2} (6)	443	0.15	0.10 (80) 6×10^{-3} (20)
6		474	1.9	4×10^{-2} (84) 9×10^{-3} (16)	467	0.61	3×10^{-2} (100)

Table 1 (*continued*)

Compound		Flash photolysis open form			Continuous irradiation open form		
		λ_{max}	A_0	k_Δ (%)	λ_{max}	A_{eq}	k_Δ (%)
Ref5		432	0.84	0.09	432	0.21	7×10^{-2} (80) 3×10^{-3} (20)

Ref1=2,2-diphenyl-2*H*-pyran[3,2-*c*]carbazole,[18] **Ref2**=2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran,[25] **Ref3**=2,2-diphenyl-2*H*-pyran[6,5-*c*]carbazole,[18] **Ref4**=2,2-diphenyl-2*H*-pyran[5,6-*a*]carbazole[18] and **Ref5**=3,3-diphenyl-3*H*-naphtho[2,1-*b*]pyran.[26]

moiety, but slower thermal bleaching kinetics. This points to an increase in the thermal stability of the open forms, due to the extension of π-conjugation, and results in higher concentrations of coloured forms in the mixture obtained upon irradiation. The effect can be explained by the decrease of nonbonding interactions in the open forms, promoted by the spacing of the indole moiety imposed by the additional benzene ring.

As generally observed for photochromic naphthopyrans, compounds **5** and **6** (5,6 annellation) are less thermally stable than compound **4** (7,8 annellation). Compared to compounds **4** and **5**, under flash photolysis compound **6** exhibits a different bi-exponential bleaching kinetic. Observing the structures of the TT and TC open forms for compound **6** it is apparent, particularly for the TT-isomer, the possible existence of steric interactions, between the NH function and one ethylenic H-atom, that can affect the pyran ring opening/closing process, leading to two thermally unstable isomers with two observable kinetic constants.

After continuous irradiation, all the new compounds exhibited thermal bleaching kinetics that follow the monoexponential law $A=A_0e^{-kt}+R$ (R is the residual absorption of the solution) from which the kinetic constants were determined. Consequently, after the UV irradiation has ceased all the solutions were only partially bleached and, in the dark, a significant residual colour remained for a long time. This behaviour indicates the formation of two photoproducts that possess very similar absorption spectra, but one is thermally unstable and the other has a high thermal stability.[8] According to recent studies these photoproducts can be identified, as the *trans–cis* (TC) and *trans–trans* (TT) isomers (Scheme 1) and the fast fading phase, of higher amplitude, can usually be attributed to the TC-isomer.[11]

2.3. Mechanistic studies

2.3.1. The effect of different times of irradiation. The most interesting observed feature is that compounds **4** and **5**, under flash photolysis or continuous irradiation, follow a bleaching monoexponential model. Compound **6** exhibits a biexponential bleaching kinetic under flash photolysis, but follows a monoexponential model under continuous irradiation. This is indicative that, for this compound, there is a significant difference in the relative amounts of photoisomers in the mixture obtained after irradiation in both methods.

For compound **4** it was observed a noteworthy agreement between the bleaching kinetic obtained in both under flash photolysis and continuous irradiation. This may indicate a close similarity between the photoproducts formed in the two methods. A series of experiments was performed with compound **4**, in the dark at 293 K, evaluating the bleaching kinetics after different times of continuous irradiation

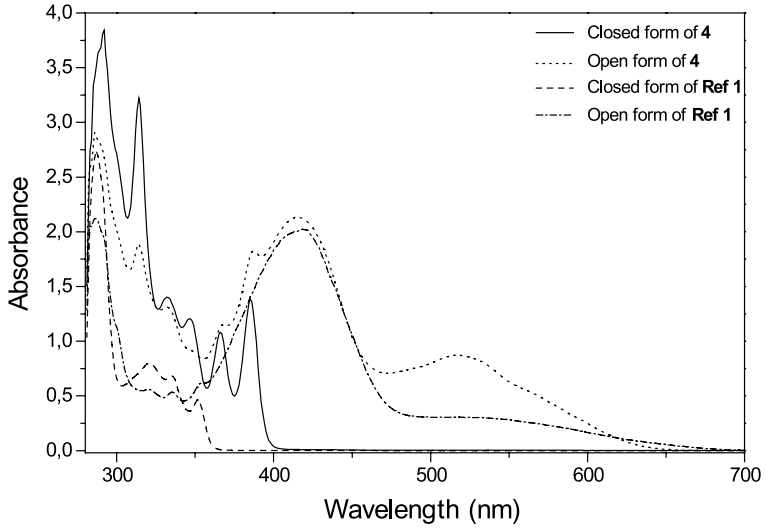


Figure 1. Absorbance spectra of compound **4** and **Ref1** before and after UV–Vis irradiation.

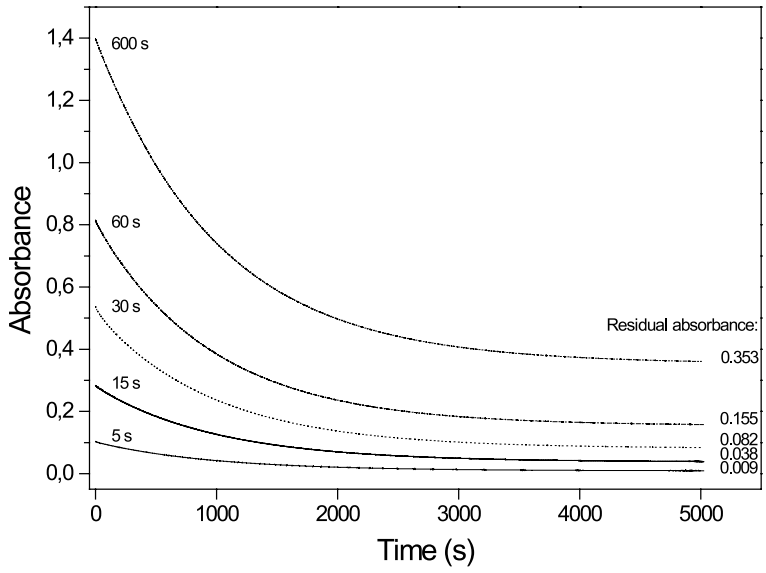


Figure 2. Absorbance decrease at 517 nm after different times of irradiation (toluene solution 1×10^{-4} M of compound **4** at 293 K). Residual absorbances were measured after the system has reached an apparent constant value.

during the colouration process. The results are depicted in Figure 2.

In all experiments the system exhibited the same kinetic behaviour. However, as the time of irradiation became longer, the residual colour of the solution increased. The residual colour can be attributed to the presence of slow decaying coloured species and/or to the formation of coloured photodegradation products. The last assumption was not considered because degradation was estimated to be less than 3%, based on the colourabilities obtained in successive colouration/decolouration cycles. The residual coloured system, on irradiating with visible light (>420 nm), returned to the uncoloured state and recovered almost the same photochromic behaviour as before. From these observations, it is apparent that the residual colour should be attributed to the presence of a thermally stable isomer.

These results suggest that, in this system, the faster decaying isomer (TC) is first produced and, subsequently, partially converted, through light absorption, to the slower decaying isomer (TT). This is in accordance with the expected different energies required to produce each isomer. After the C–O cleavage, promoted by UV irradiation, a one-bond rotation is required to produce the TC-isomer, whereas the TT-isomer requires a subsequent *E*–*Z* isomerisation of a double bond also induced by light. The same was already observed for photochromic 2*H*-chromenes investigated by spectrophotometric methods[8] and ^{19}F NMR spectroscopy.[10]

2.3.2. Visible irradiation and temperature effects. The bleaching was complete only by irradiating with visible light (>420 nm). A series of experiments was performed in order to study the effect of visible light irradiation on the kinetic behaviour of the system at different temperatures. The results are summarized in Table 2.

A monoexponential model could be considered for all the bleaching processes, and examination of the results in Table 2 shows that all the bleaching processes were significantly accelerated by temperature increase (this acceleration was accompanied by an expected decrease in the colourability) (Fig. 3).

A remarkable feature in the results is that, for the same temperature, the observed kinetic constants remained at the same order of magnitude whether or not visible light was on. The visible light, although promoting the complete bleaching of solutions, has a minor effect on the values of kinetic constants whatever the path considered: photostationary state→residual colour, photostationary state→uncoloured state or residual colour→uncoloured state. These results suggest that, for this particular system, the return to the closed uncoloured form (CF) is essentially thermal and corresponds predominantly with a TC→CF pathway. The TT-isomer does not proceed directly to CF but undergoes a

Table 2. Bleaching rate constants for compound **4** at different temperatures considering various paths

Path	Temperature (K)	Visible light (>420 nm)	k (s^{-1})
Photostationary state→residual colour	283	Off	2.6×10^{-4}
Residual colour→uncoloured state	283	On	2.5×10^{-4}
Photostationary state→uncoloured state	283	On	2.6×10^{-4}
Photostationary state→residual colour	293	Off	1.0×10^{-3}
Residual colour→uncoloured state	293	On	8.1×10^{-4}
Photostationary state→uncoloured state	293	On	7.9×10^{-4}
Photostationary state→residual colour	313	Off	8.6×10^{-3}
Photostationary state→residual colour	323	Off	2.3×10^{-2}

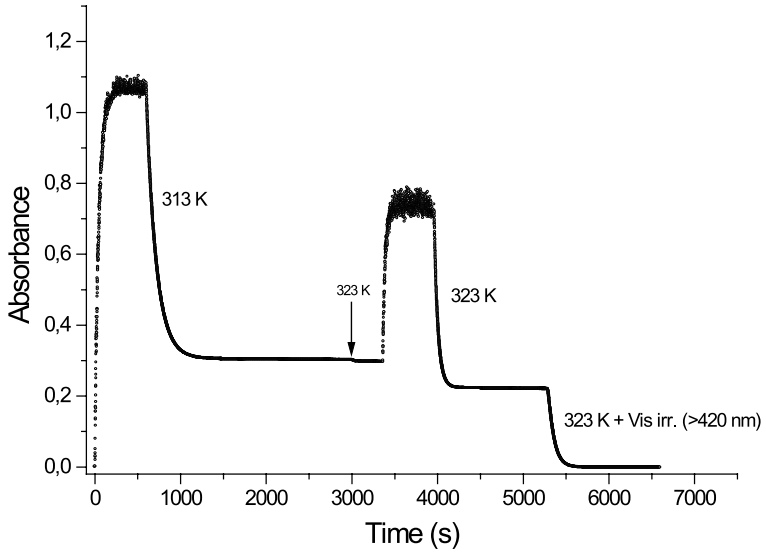


Figure 3. Kinetic behaviour of compound **4** at two different temperatures.

fast photoisomerization TT→TC, induced by visible irradiation. Complete bleaching is then achieved through the slow rate determining thermal process TC→CF. This suggestion is further confirmed with additional experiments irradiating the system with visible light for short time periods, after the first thermal fading. It was observed that it was unnecessary to irradiate with visible light during the whole decolouration process to decolourize the solution completely. With our irradiating device, 180 s of visible irradiation was enough for the system to proceed to the complete bleaching in the dark (Fig. 4).

Based on these informations, the major processes occurring during a photocolouration/decolouration cycle are depicted in Figure 5.

2.3.3. Activation energies. The experiments carried out at different temperatures allowed us to evaluate the standard entropy and enthalpy of activation, for the TC→CF process, using a Eyring plot (Fig. 6): $\Delta H^{\ddagger}=82.2\pm 3.4$ kJ mol^{-1} and $\Delta S^{\ddagger}=-22.3\pm 5.6$ J mol^{-1} K^{-1}. The enthalpy of activation value agrees with those referred for photochromic compounds (40–120 kJ mol^{-1}).[11] The negative value obtained for $\Delta S^{\ddagger}$ points to an expected loss of freedom in the recyclization into the original closed form but is difficult to interpret as it includes an unknown contribution from the rearrangement of the solvent (toluene).

3. Conclusion

The inclusion of an additional benzene ring in pyranocarbazoles yielded three new photochromic benzopyranocarbazoles. All the compounds described exhibited strong absorption bands in the range 370–390 nm which made them readily activated with solar light and potentially less prone to photodegradation. The fusion of an indole moiety

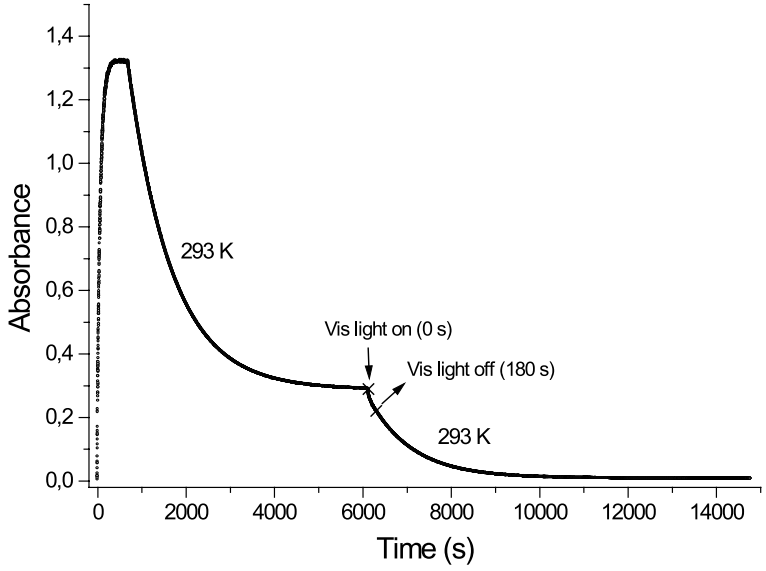


Figure 4. Thermal and photochemical bleaching for compound **4** at 293 K (toluene solution 1×10^{-4} M; visible light >420 nm).

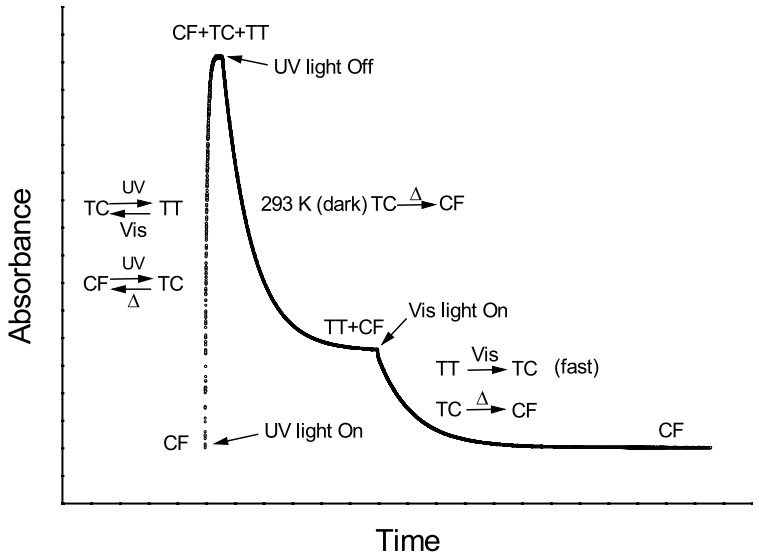


Figure 5. Isomerization processes occurring during a photocolouration/decolouration cycle for compound **4**.

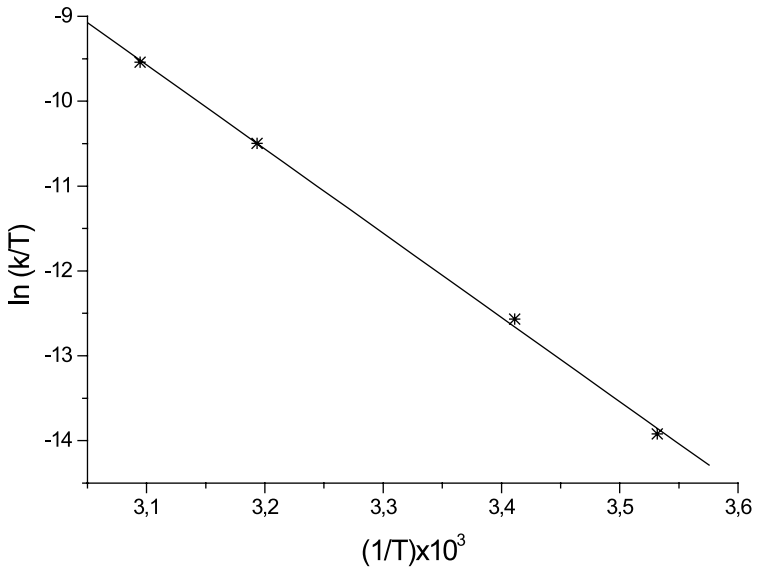
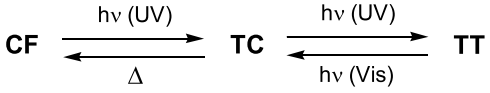


Figure 6. Eyring plot for the thermal relaxation process TC→CF.

at the *i*-face of 2,2-diphenyl-2*H*-naphtho[1,2-*b*]pyran or *i*- and *k*- faces of 3,3-diphenyl-3*H*-naphtho[2,1-*b*]pyran induced some thermal instability to the open forms. However, it is apparent that electronic effects are modest and no relevant additional steric strain is promoted in open forms. Compared to pyranocarbazoles, no relevant enhancement in the colourabilities was observed, and the effects seem to be related to the increase in the thermal stabilities of the open forms due to the extension of conjugation. In the dark, all the UV-irradiated solutions exhibited a partial monoexponential thermal bleaching and a persistent relevant residual colour, which could be removed only through the irradiation with visible light. This points to a three-component system with an original uncoloured compound (CF) giving, upon UV-irradiation, two coloured photoisomers (TC and TT) with very different thermal stabilities.

The photochromic mechanism was investigated for compound **4** and, based on the results, the following plausible reaction mechanism could be proposed (Scheme 4).

In solution, UV irradiation induces the opening of the pyran ring through the C–O bond breakage followed by a one-bond rotation leading to the TC-isomer. Subsequently, this isomer is partially converted to the TT-isomer through a *E–Z* isomerisation of a double bond, also induced by UV light. At the photostationary state, the coloured mixture includes CF, TC and TT and, when the light was turned off,



Scheme 4.

the thermal bleaching observed is mainly due to the process TC→CF, and a thermal process TT→CF can be excluded. Irradiation with visible light promotes the disappearance of the persistent residual colour through the fast back-conversion TT→TC followed by the thermal conversion TC→CF.

4. Experimental

4.1. General remarks

Solvents (Riedel–Haën and Merck) were used without further purification other than drying over sodium (Et_2O) or anhydrous calcium chloride (CH_2Cl_2). Column chromatography (CC) was performed on silica gel Merck 60 (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX (400 and 100.5 MHz, respectively) using tetramethylsilane as internal standard in acetone-d_6 or DMSO-d_6, respectively. Chemical shifts are given in ppm and coupling constants in Hz. IR spectra were recorded on a Perkin–Elmer-FTIR-1600 spectrophotometer using KBr disks and wavenumbers are given in cm^{-1}. UV–Vis spectra were recorded on a CARY 50 Varian spectrophotometer using 1×10^{-4} M toluene solutions. Maxima wavelengths (λ_{max}) are given in nm and molar absorption coefficients of closed forms (ε) in $L\,mol^{-1}\,cm^{-1}$. Mass spectra were obtained under electronic impact (EI=70 eV) on a AutoSpecE spectrometer. Melting points (°C), measured in capillary tubes on a Büchi 535 apparatus, are uncorrected. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy. ta=apparent triplet; sl=large singlet; dl=large duplet.

4.2. Spectrokinetic measurements

4.2.1. Spectrokinetic studies under flash photolysis. For the determination of λ_{max}, A_0, and k_Δ, 5×10^{-5} mol dm^{-3} toluene solutions were used. The flash photolysis experiments were monitored by a Warner and Swasey rapid spectrometer, allowing to record visible absorption spectra of coloured forms in the 400–700 nm range (acquisition time 1 ms, repetitivity 1.25 ms).[27,28] Flashes (duration 50 μs) were generated by two xenon tubes with a quartz envelope. The energy of the flashes was 60 J for the whole polychromatic emission spectrum. For measurements, thermostated (25 °C) 100 mm cells were used. The light from the analysis lamp (50 W, quartz–iodide) was filtered using a Schott GC 400 high-pass filter.

4.2.2. Spectrokinetic studies under continuous irradiation. For measurements of λ_{max}, A_{eq} and k_Δ under continuous irradiation, 1×10^{-4} M toluene solutions were used. Irradiation experiments were made using a CARY 50 Varian spectrometer coupled to a 150 W ozone free xenon lamp (6255 Oriel Instruments). The light from the UV lamp was filtered using a water filter (61945 Oriel Instruments) and then carried to the spectrophotometer holder at the right angle to the monitoring beam using a fiber-optic system (77654 Oriel Instruments). A light flux of 40 W m^{-2}, measured with a Goldilux Photometer with a UV-A probe was used. Visible irradiation experiments were performed using a long-pass filter, Schott GG 420 (Oriel 59480). A thermostated (10, 20, 40 and 50 °C) 10 mm quartz cell, containing the sample solution (3.5 mL), equipped with magnetic stirring was used. In a preliminary experiment, the visible absorption spectrum of the closed form and the λ_{max} of the open form were determined. In a second experiment the absorbance at photostationary equilibrium, A_{eq}, was measured at λ_{max} and then the decrease in the absorbance with the time was monitored. The rate constants were calculated using mono and multiexponential models.

4.3. General method for the synthesis of compounds 2a–c

A mixture of the appropriate methoxytetralone **1a–c** (1.8 g, 10 mmol), phenylhydrazinium chloride (1.1 g, 7.6 mmol) and a few drops of acetic acid was refluxed in ethanol (15 mL) for 1 h. After cooling, the solid formed was filtered, washed with water (2×20 mL) and dissolved with dichloromethane (10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. To the crude (dihydrobenzocarbazoles), chloroanil (tetrachloro-1,4-benzoquinone) (1.4 equiv) and dry xylene (50 mL) were added and the mixture was refluxed for 2 h, under Ar. After cooling the tetrachlorohydroquinone was filtered off by suction and washed with Et_2O. The filtrate was washed with NaOH (10%), water and dried (Na_2SO_4). After solvent evaporation Et_2O was added and a precipitate was formed that corresponded to 5-methoxy-, 6-methoxy- and 7-methoxybenzo[*a*]carbazole in each case.

4.3.1. 4-Methoxybenzo[*a*]carbazole 2a. Light brown powder. Yield 90%. Mp 166–168 (lit[20] 168). ^1H NMR (acetone-d_6): 4.11 (3H, s, –OC*H*$_3$), 7.08 (1H, dl, *J*=8.4 Hz, H-3), 7.29 (1H, dt, *J*=7.6, 1.2 Hz, H-8), 7.44 (1H, dt, *J*=7.6, 1.2 Hz, H-9), 7.58 (1H, t, *J*=8.4 Hz, H-2), 7.66 (1H, dd, *J*=7.6, 1.2 Hz, H-10), 8.06–8.09 (m, 2H), 8.22–8.25 (m, 2H), 10.25 (1H, sl, –N*H*).

4.3.2. 3-Methoxybenzo[*a*]carbazole 2b. Light brown powder. Yield 80%. Mp 243–244 (lit[23] 245).^1H NMR (acetone-d_6): 4.00 (3H, s, –OC*H*$_3$), 7.24–7.31 (2H, m, H-2 and H-8), 7.40 (1H, dt, *J*=8.0, 1.0 Hz, H-9), 7.52 (1H, d, *J*=2.0 Hz, H-4), 7.62–7.64 (2H, m, H-5 and H-10), 8.17 (1H, dd, *J*=8.0 Hz, 1.0, H-7), 8.20 (1H, d, *J*=8.7 Hz, H-6), 8.42 (1H, d, *J*=9.0 Hz, H-2), 11.20 (1H, sl, –N*H*).

4.3.3. 2-Methoxybenzo[*a*]carbazole 2c. Brown powder. Yield 96%. Mp 186–187 (lit[23] 190).^1H NMR (acetone-d_6): 4.03 (3H, s, –OC*H*$_3$), 7.22 (1H, dd, *J*=9.0, 2.4 Hz, H-3), 7.27 (1H, dt, *J*=7.5, 1.0 Hz, H-8), 7.43 (1H, dt, *J*=7.5, 1.0 Hz, H-9), 7.63–7.67 (2H, m, H-5 and H-10), 7.95 (1H, d, *J*=2.4 Hz, H-1), 7.99 (1H, d, *J*=9.0 Hz, H-4), 8.10 (1H, d, *J*=8.4 Hz, H-6), 8.20 (1H, dd, *J*=7.5 Hz, 1.0, H-7), 11.25 (1H, sl, –N*H*).

4.4. General method for the synthesis of compounds 3a–c

A mixture of methoxybenzo[*a*]carbazole 2a–c (1.24 g, 5 mmol) and pyridine hydrochloride (3.47 g, 30 mmol) was gently boiled for 30–40 min. After cooling, water (120 mL) was added, and the precipitate thus obtained was filtered off. The solid was redissolved in acetone and evaporated to dryness affording the hydroxybenzo-[*a*]carbazoles.

4.4.1. 4-Hydroxybenzo[*a*]carbazole 3a. Light brown powder. Yield 94%. Mp >250 (lit[20] 266). ^{1}H NMR (acetone-d_6): 6.92 (1H, dd, J=7.5, 2.3 Hz), 7.13–7.17 (1H, m), 7.28–7.35 (2H, m), 7.52 (1H, d, J=7.8 Hz, 7.86 (1H, d, J=8.2 Hz), 7.96 (1H, d, J=9.0 Hz), 8.06–8.09 (2H, m), 9.00 (1H, s, –O*H*), 11.00 (1H, sl, –N*H*).

4.4.2. 3-Hydroxybenzo[*a*]carbazole 3b. Light brown powder. Yield 94%. Mp >250 (lit[23] 265).^{1}H NMR (acetone-d_6): 7.22–7.29 (2H, m, H-2 and H-8), 7.38 (1H, dt, J=7.5, 1.2 Hz, H-9), 7.42 (1H, d, J=2.4 Hz, H-4), 7.51 (1H, d, J=8.7 Hz, H-5), 7.62 (1H, dl, J=8.1 Hz, H-10), 8.13–8.16 (2H, m, H-6 and H-7), 8.38 (1H, d, J=9.0 Hz, H-1), 8.67 (1H, s, –O*H*).

4.4.3. 2-Hydroxybenzo[*a*]carbazole 3c. Light brown powder. Yield 65%. Mp 237–239 (lit[23] 246). ^{1}H NMR (acetone-d_6): 7.10–7.17 (2H, m), 7.30 (1H, ta, J=7.7 Hz, H-9), 7.49–7.53 (2H, m), 7.71 (1H, sl, H-1), 7.84 (1H, dd, J=7.7 Hz, 1.1), 7.92 (1H, dd, J=8.5 Hz, 1.3), 8.06 (1H, d, J=7.9 Hz), 8.68 (1H, s, –O*H*).

4.5. General method for the synthesis of compounds 4–6

A suspension of hydroxybenzo[*a*]carbazole **3a–c**, (2.33 g, 10 mmol) in dry toluene (50 ml), under Ar, was stirred until all the hydroxybenzocarbazole was dissolved. A solution of titanium (IV) ethoxide (2.28 g, 10 mmol) in dry toluene (40 ml) was added over a period of 10 min. The mixture was refluxed for 30 min, and the ethanol formed was slowly distilled (up to 1/3 of the initial volume). The mixture was cooled to r.t. and a solution of β-phenylcinnamaldehyde (2.08 g, 10 mmol) in 40 ml of dry toluene was added dropwise. The mixture was refluxed for a period of 2–6 h, cooled to r.t., quenched with NaOH (2M aq, 40 mL), and extracted with CH_2Cl_2 (3×40 ml). The combined organic extracts were dried ($MgSO_4$), evaporated to dryness and the residue was purified by CC on silica gel.

4.5.1. 5,13-Dihydro-5,5-diphenyl-1-benzopyran[7,8-*a*]carbazole 4. Light brown solid. Yield 63%. Mp 230.5–231.5. IR: 3424 (NH), 3056, 1517, 1490,1457, 1398, 1232, 821, 746, 700. UV–Vis (closed form): 314 (32210), 332 (14020), 347 (12040), 366 (10810), 385 (13860). ^{1}H NMR: 6.46 (1H, d, J=9.7 Hz, H-4), 6.91 (1H, d, J=9.7 Hz, H-3), 7.22–7.27 (3H, m, H-4′, 4″ and H-12), 7.32–7.42 (6H, m, H-3′, 3′, 5′, 5″, H-10 and H-11), 7.61–7.63 (4H, m, H-2′, 2″, 6′ and 6″), 7.66 (1H, d, J=8.3 Hz, H-1), 8.03 (1H, d, J=8.3 Hz, H-2), 8.18 (1H, d, J=7.8 Hz, H-9), 8.22 (1H, d, J=8.8 Hz, H-7) and 8.27 (1H, d, J=8.8 Hz, H-8) AB system, 11.30 (1H, sl, N–H). ^{13}C NMR: 83.8 (C-5), 112.2 (d), 113.9 (d), 115.4 (d), 116.9 (d), 119.4 (s), 120.0(d), 120.3 (d), 120.5 (d), 123.5 (s), 123.8 (s), 124.6 (s), 124.9 (d), 125.6 (d), 127.4 (4C, C-2′, 2″, 6′ and 6″), 128.3 (2C, C-4′ and 4″), 128.5 (d), 129.4 (4C, C-3′, 3″, 5′ and 5″), 136.4 (s), 140.3 (s), 146.3 (2C, C-1′ and 1″), 149.4 (s). MS: *m*/*z* (%): 423 (100), 346 (43), 317 (6), 212 (7), 191 (7), 165 (6). Exact mass for $C_{31}H_{21}NO$: 423.1623. Found 423.1635.

4.5.2. 4,13-Dihydro-4,4-diphenyl-1-benzopyran[6,5-*a*]carbazole 5. White solid. Yield 24%. Mp > 250. IR: 3429 (NH), 1633, 1448, 1384, 1259, 1209, 1058, 809, 750, 698. UV–Vis (closed form): 333.0 (6180), 350.0 (5770), 368.0 (6270), 386.0 (7090). ^{1}H NMR: 6.53 (1H, d J=10.0 Hz, H-3), 7.07 (1H, t, J=7,5 Hz), 7.11–7.14 (m, 2H), 7.20–7.26 (m, 5H), 7.30 (1H, d, J=8.9 Hz), 7.39–7.41 (4H, m, H-2′, 2″, 6′ and 6″), 7.45 (1H, d J=10.0 Hz, H-4), 7.46 (1H, d, J=8.0 Hz), 7.69 (1H, d, J=8.9 Hz), 8.00 (1H, d, J=7.8 Hz), 8.07 (1H, d, J=8.8 Hz), 8.26 (1H, d, J=8.9 Hz), 11.2 (1H, sl, NH). ^{13}C NMR: 82.3 (C-4), 111.7 (d), 113.4 (d), 115.6 (s), 116.8 (s), 117.2 (d), 117.4 (s), 119.6 (d), 119.9 (d), 120.4 (d), 120.9 (d), 123.9 (s), 124.2 (d), 124.7 (d), 126.9 (4C, C-2′, 2″, 6′ and 6″), 127.8 (2C, C-4′ and 4″), 128.6 (4C, C-3′, 3″, 5′ and 5″), 128.8 (s), 128.9 (d), 136.7 (s), 139.5 (s), 145.4 (2C, C-1′ and 1″), 150.4 (s). MS: *m*/*z* (%): 423 (100), 346 (81), 315 (5), 257 (6), 211 (7), 173 (15), 165 (9). Exact mass for $C_{31}H_{21}NO$: 423.1623. Found 423.1639.

4.5.3. 3,13-Dihydro-3,3-diphenyl-1-benzopyran[5,6-*a*]carbazole 6. White solid. Yield 77%. Mp 217.3–218.4. IR: 3425 (NH), 3056, 1450, 1390, 1240, 809, 746, 699. UV–Vis (closed form): 335.0 (7540), 351.1 (6950), 371.0 (5750), 390.1 (6350). ^{1}H NMR: 6.51 (1H, d, J=9.8 Hz, H-2), 7.23–7.30 (3H, m, H-10 or H-11, H-4′ and 4″), 7.32–7.36 (5H, m, H-3′, 3″, 5′, 5″ and H-7), 7.43 (1H, dt, J=8.0, 1.2 Hz, H-11 or H-10), 7.59 (1H, d, J=8.5 Hz, H-5), 7.61–7.64 (4H, m, H-2′, 2″, 6′, 6″), 7.71 (1H, d, J=8.0 Hz, H-12), 7.91 (1H, d, J=8.8 Hz, H-8), 7.99 (1H, d, J=9.8 Hz, H-1), 8.09 (1H, d, J=8.5 Hz, H-6), 8.18 (1H d, J=8.0 Hz, H-9), 10.82 (1H, sl, N–H). ^{13}C NMR: 82.2 (C-3), 112.6 (d), 115.3 (s), 117.6 (d), 118.0 (d), 119.8 (s), 120.4 (d), 120.5 (d), 121.5 (s), 121.7 (d), 123.7 (d), 124.1 (s), 125.7 (d), 127.7 (4C, C-2′, 2″, 6′ and 6″), 128.3 (2C, C-4′ and 4″), 128.9 (4C, C-3′, 3″, 5′, 5″), 129.0 (d), 129.9 (s), 132.1 (d), 135.1 (d), 140.8 (d), 145.7 (2C, C-1′ and 1″), 151.9 (s). MS: *m*/*z* (%): 423 (100), 346 (40), 315 (5), 257 (9), 228 (6), 212 (7), 191 (6), 173 (8), 165 (11), 77 (5). Exact mass for $C_{31}H_{21}NO$: 423.1623. Found 423.1610.

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One pot synthesis of fused [1,2-*a*]pyrrole from 1,6-dioxo-2,4-diene and haloalkyl primary amine

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Abstract—The one pot synthesis of fused 2,3-dihydropyrrolizine **4a** and 6,7-dihydro-5*H*-indolizine **4b** involving the intermolecular dehydrative condensation of 1-phenyl-1,6-dioxo-hepta-2,4-diene **1** with 2-chloroethylamine and 3-chloropropylamine followed by the intramolecular cyclization of the intermediary products 2-(1-chloroalkyl-5-methylpyrrol-2-yl)-1-phenylethanones **3a**,**b** in the presence of a base such as Na_2CO_3 and $NaHCO_3$ is described. These also led to the concurrent formation of the oxidatively dimerized product 2,3-bis-[1,5-(2-chloroalkyl)-1-*H*-pyrrol-2-yl]-1,4-diphenylbutane-1,4-dione **5a**,**b** whereby the structure was further confirmed by X-ray analysis.

1. Introduction

The fused [1,2-*a*]pyrroles are important scaffold of alkaloids widely isolated from plants, insects, animals, oceanic lives and secondary metabolites of microbes and have potent biological activities.[1–3] The synthesis of pyrrolizines and indolizines continues to attract the attention of organic chemist and numerous synthetic routes have been reported.[4–14] Our previous study demonstrated 1,6-dioxo-2,4-diene to a versatile intermediate in the synthesis of pyrrole derivatives.[15] The important feature of the pyrrole derivates formed is that the hydrogen atom at the carbon atom attached to the 2-position can be readily deprotonated for reaction with an electrophilic center at the *N*-tether to give fused [1,2-*a*]pyrroles. Based on this methodology, we have recently developed a new pathway for the synthesis of pyrrolizines and indolizines.[16] The moderate yield of the pyrrolizine and indolizine derivatives with this approach may be attributed to the reversible condensation reaction (Dieckmann/Thrope) used for the intramolecular ring closure reaction. We felt that greater potential utility for the construction of fused [1,2-*a*]pyrroles could be realized were we to achieve intramolecular cyclization by an irreversible alkylation reaction. Herein, we report our further investigations on the use of an irreversible alkylation reaction for the intramolecular ring closure reaction with the hope of improving the yield. To affect an intramolecular alkylative cyclization, we required the construction of *N*-tether haloalkylpyrrole derivatives. Furthermore the appropriate choice of base might led to the development of a one-pot procedure to prepare pyrrolizine and indolizine derivatives from the reaction of 1-phenyl-1,6-dioxo-hepta-2,4-diene **1** with chloroethylamine and chloropropylamine, respectively (Scheme 1).

2. Results and discussion

Our starting point was the 1-phenyl-1,6-dioxo-hepta-2,4-diene, **1**, which we have previously prepared from the reaction of 2-methylfuran with α-diazoacetophenone according to the method of Wenkert.[17] It has been demonstrated earlier that compound **1** reacted with alkylamines to give *N*-tether alkylpyrrole derivatives. Originally, it was thought that the preparation of *N*-tether haloalkylpyrroles from **1** and aminoalkyl halide under the same condition would be met with competing reaction arising from the self-condensation of the aminoalkyl halide. Therefore, our initial strategy for the synthesis of *N*-tether haloalkylpyrrole involved the reaction of **1** with amino alcohol to form *N*-tether hydroxyalkylpyrrole, followed by a subsequent conversion of the alcohol to the corresponding halide. Compound **1** react with 1-aminoethanol and 1-aminopropanol to give *N*-tether hydroxyalkylpyrrole derivatives **2a** and **2b**, respectively, but in a moderate yield (40–50%). The alcohol functionality in **2a** and **2b** can be converted to the chloride **3a** and **3b** in a near quantitative yield. The overall yields from the two steps were only

Keywords: One-pot synthesis; Intramolecular alkylation; N-fused pyrrolo ring.
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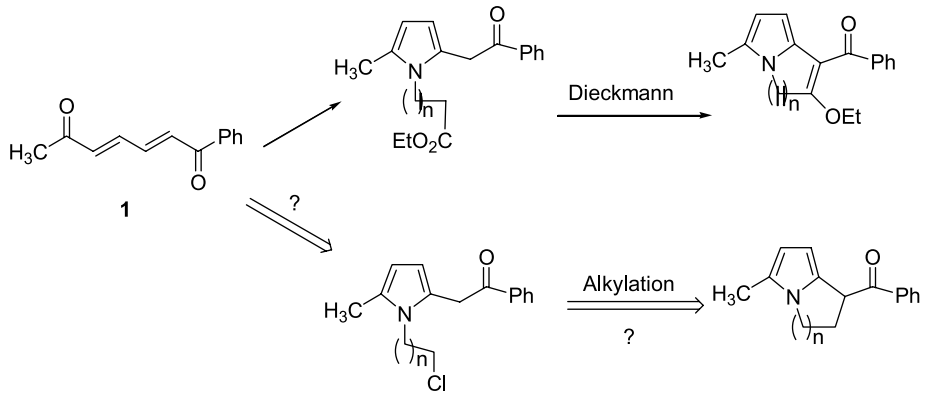
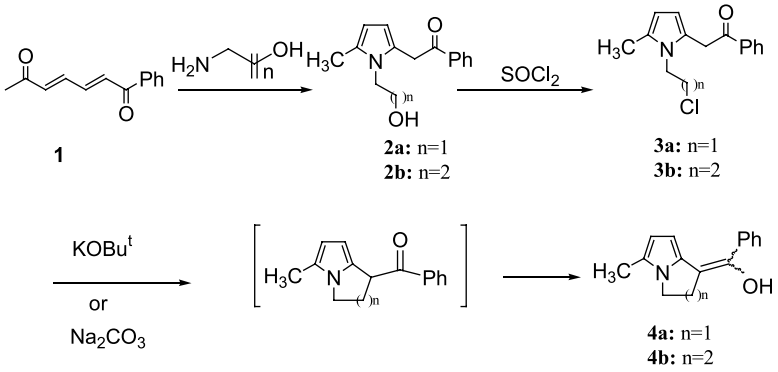


Scheme 1. Synthetic approach towards pyrrolizine and indolizine.

moderate. Next, the intramolecular cyclization of **3a** and **3b** was attempted using potassium *t*-butoxide.[16] Although, submission of **3a** and **3b** under this intramolecular alkylative cyclization condition gave the pyrrolidine **4a** and indolizine **4b** respectively, the yield was rather low (20–25%) (Scheme 2). The ^{1}H and ^{13}C NMR spectra of **4a** and **4b** revealed the absence of an α-methine hydrogen between the pyrrole and the carbonyl group, and this was attributed to the formation of the more stable enol-form due to resonance delocalization. The ketone–enol tautomerizaton of indolizone derivatives has been reported.[9]

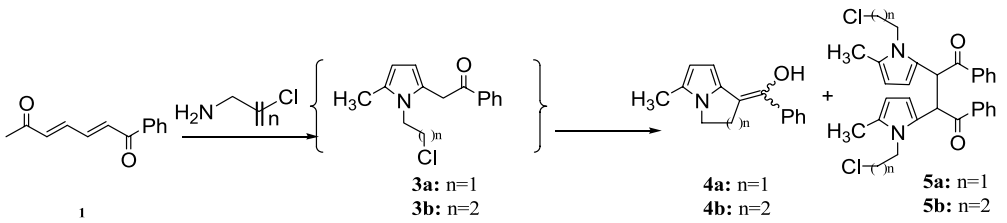
Although the synthesis of pyrrolidine and indolizine were realized, the poor overall yield hampered its practicality. A trial experiment for the reaction of **1** with chloroethylamine was carried out and fortuitously gave **3a** in a ca. 90–95% yield. Similarly, reaction of **1** with chloropropylamine gave **3b** in similar yield. Clearly, the chloroalkylamine did not proceed to give self-polyalkylation products. A greater challenge was to improve the yield during the intramolecular alkylative cyclization step. Several different bases can be called into play and we choose to use sodium carbonate in methanol for its mild condition. Reaction of **3a** and **3b** with sodium carbonate in methanol successfully gave **4a** and **4b** in a dramatically improved yield (55–65%), together with an isolable minor product (5–10%) in each case that was not identified at this stage.

An important requirement for the successful one pot reaction is the non-participation of the base prior to alkylation reaction, allowing the smooth formation of pyrrole intermediate from the reaction of **1** with aminoalkyl halide. The discovery of the sodium carbonate promoted cyclization reaction above point the way for a facile design of a fast one-pot synthesis of fused [1,2-*a*]pyrroles. It was reasoned that sodium carbonate in methanol would not exacerbate the problem of self-condensation of the aminoalkyl halide during its reaction with **1** to form the pyrrole intermediate at the onset of the reaction. In a typical experiment, **1** was reacted with chloroethylamine in the presence of sodium carbonate and the reaction mixture stirred under a nitrogen atmosphere at room temperature in methanol. TLC was used to monitor the progress of the reaction. The TLC showed a complete disappearance of the starting material **1** after 2 h at room temperature, the major product was found to be the pyrrole derivative **3a**. Next, the reaction was carried out for a longer reaction time (72 h) until TLC indicated the total consumption of **1** and the disappearance of intermediate **3a**. This resulted in the formation of two new products **4a** and **5a** in a 3:1 ratio. The major product was the required pyrrolizine derivative **4a**. The minor product **5a** showed a parent peak in the mass spectrum at *m*/*z* 520, 522, 524 (approx. 10:6:1 ratio), an equivalent to 2 units less than that for two molecules of **3a** and a pattern indicating the presence of two chlorine atoms. From this data we tentatively assigned **5a** as 2,3-bis(1*H*-pyrol-2yl)-1,4-diphenyl-1,4-dione, the oxidatively dimerized product of the intermediate **3a**. Oxidative coupling of enolates, especially phenylacetic acid ester, through a variety of methods have been widely reported.[18] At this



Scheme 2.

Table 1. Product distribution for the reaction of **1** with aminoalkyl halide and Na_2CO_3/$NaHCO_3$



Entry	Reaction time (h)	Na_2CO_3/MeOH (ratio)	Entry	Reaction time (h)	$NaHCO_3$/MeOH (ratio)
1	2	**3a** only 85–90%	5	2	**3a** only 85–90%
2	72	**4a/5a** (3:1) 65%	6	72	**4a/5a** (1:4) 77%
3	2	**3b** only 85–90%	7	2	**3b** only 85–90%
4	72	**4b/5b** (3:1) 70%	8	72	**4b/5b** (1:4) 80%

point, we were uncertain of the stereoisomers of the dimer, *dl*- or *meso*-**5a**. The formation of products **4a** and **5** reflect two competing reactions pathway for the intermediate **3a**, one leading to an intramolecular alkylation and the other oxidative coupling.

This one pot strategy can be applied to the synthesis of indolizine derivative **4b** by treatment of 1-phenyl-1,6-dioxo-hepta-2,4-diene **1** with 3-chloropropylamine and sodium carbonate in methanol for 72 h. In this case we also obtained two products, the indolizine derivative **4b** and **5b** in a 3:1 ratio (70% overall yield). The results are summarized in Table 1. A one pot synthesis of indolizines from the reaction of acyl bromide, pyridine and acetylene mediated by microwave has been reported.[19] The mass spectrum of **5b** again correlates to 2 units less than for two molecules of **3b**. We were able to obtain a crystal of **5b** suitable for X-ray crystallographic analysis[20] (Fig. 1) and this unambiguously supported the oxidative coupling product of the intermediate **3b**. The oxidative coupling reaction proceeds to give the *dl* **5b** stereoisomer. Similar high selectivity of *dl* isomer over *meso* isomer has also been reported for the oxidative coupling of phenylacetic acid ester by treating the ester with titanium chloride and then adding triethylamine to the resulting solution.[18h]

Since pyrrolidine **4a** and indolizine **4b** were form in good yield using sodium carbonate in methanol, we assumed that the use of an even milder base such as sodium bicarbonate for the one pot synthesis might further improved the yield. Contrary to expectation, the reaction of **1** with 2-chloroethylamine with sodium bicarbonate in methanol for 72 h was found to give a reverse preponderance of products **4a** and **5a** in a 1:4 ratio (77% overall yield). Similarly, the reaction of **1** with chloropropylamine gave **4b** and **5b** in a ratio of 1:4. The formation of the dimer in these reactions might be explained in consideration of the redox reaction occurring between the generated carbanion of the intermediate **3** and the free **3** or the product **5** which play the role as a single electron acceptor, leading to the formation of the benzoylmethyl radical and the anion radical of **3** or **5**. Accordingly, in the one pot reaction, the use of sodium bicarbonate will give a greater preponderance of the dimeric product **5**.

3. Conclusion

In summary, this paper presents a simple and convenient one pot synthesis of pyrrolizine and indolizine skeletons from the reaction of 1,6-dioxo-2,4-diene and chloroalkylamine in methanol with sodium carbonate in high yield, and under mild condition. Furthermore, the results in this paper clearly show that the use of sodium bicarbonate gave mainly the oxidative coupling product and this has not been reported.

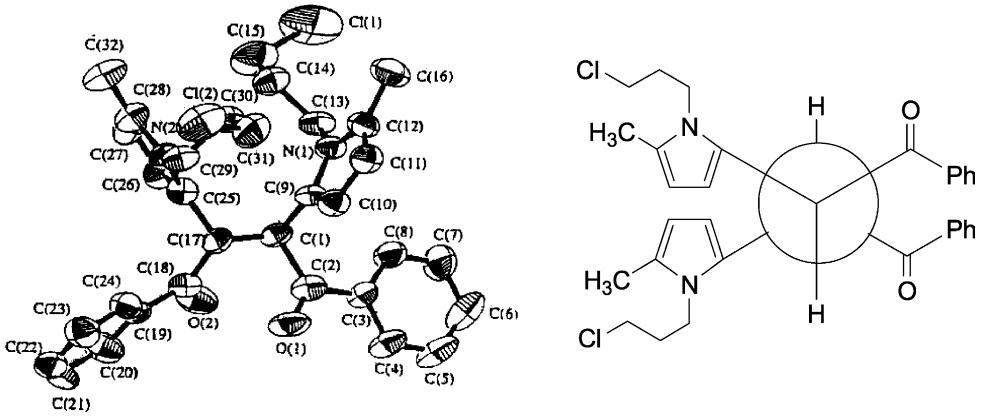


Figure 1. X-ray structure of compound **5b** showing the most stable Newman conformation.

4. Experimental

4.1. General experimental conditions

Compound **1** was prepared according to previously reported method.[16] Commercially available reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard.

4.2. General procedure of pyrrole ring formation 2 and 3 from the reaction of 1 with aminoalkyl alcohol and chloroalkylamine

To a stirred solution of aminoalkyl alcohol (1.30 mmol) in MeOH (20 mL) at 0 °C was added **1**. The reaction was stirred at 0 °C for 2 h and left at room temperature overnight. The MeOH was removed under reduce pressure and the crude product extracted by CH_2Cl_2. The crude product obtain was purified by preparative TLC to provide the corresponding product.

The chloroethyl- or chloropropylamine hydrochloride salt (1.10 mmol) was used and have to be neutralized with an equivalent of Na_2CO_3.

4.2.1. [*N*-(2-Hydroxyethyl)-5-methylpyrrol-1-yl]phenylethanone (2a). Obtained as yellow oil in 45% yield (EtOAc/hexane, 1:5). ν_{max}: 3416, 1685 cm^{-1}. ^{1}H NMR (200 MHz): δ 8.03 (m, 2H), 7.56 (m, 3H), 5.96 (d, J=3.6 Hz, 1H), 5.86 (d, J=3.6 Hz, 1H), 4.25 (s, 2H), 3.98 (t, J=7.2 Hz, 2H), 3.78 (t, J=7.2 Hz, 2H), 2.24 (s, 3H), 1.61 (brd, 1H); MS (EI) *m/z* 243(37). HRMS *m/z* calcd for $C_{15}H_{17}NO_2$, 243.1259; found, 243.1257.

4.2.2. [*N*-(2-Hydroxypropyl)-5-methylpyrrol-1-yl]phenylethanone (2b). Obtained as yellow oil in 40% yield (EtOAc/hexane, 1:5). ν_{max}: 3400, 1681 cm^{-1}. ^{1}H NMR (200 MHz): δ 8.04 (m, 2H), 7.58 (m, 3H), 5.93 (d, J=3.6 Hz, 1H), 5.82 (d, J=3.6 Hz, 1H), 4.26 (s, 2H), 3.81 (t, J=7.1 Hz, 2H), 3.68 (t, J=7.1 Hz, 2H), 2.22 (s, 3H), 2.04 (brd, 1H), 1.68 (m, 2H); MS (EI) *m/z* 257(26). HRMS *m/z* calcd for $C_{16}H_{19}NO_2$, 257.1416; found, 257.1415.

4.2.3. [*N*-(2-Chloroethyl)-5-methylpyrrol-1-yl]phenylethanone (3a). Obtained as yellow oil in 90% yield (EtOAc/hexane, 1:5). ν_{max}: 1685 cm^{-1}. ^{1}H NMR (200 MHz): δ 8.06 (m, 2H), 7.58 (m, 3H), 5.91 (d, J=3.4 Hz, 1H), 5.88 (d, J=3.4 Hz, 1H), 4.29 (s, 2H), 4.12 (t, J=7.3 Hz, 2H), 3.63 (t, J=7.3 Hz, 2H), 2.25 (s, 3H); MS (EI) *m/z* 261(12), 263(36). Anal. Calcd for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.38. Found C, 68.55; H, 6.15; N, 5.26.

4.2.4. [*N*-(2-Chloropropyl)-5-methylpyrrol-1-yl]phenylethanone (3b). Obtained as yellow solid in 95% yield (EtOAc/hexane, 1:5), mp 75–58 °C. ν_{max}: 1685 cm^{-1}. ^{1}H NMR (200 MHz): δ 8.05 (m, 2H), 7.54 (m, 3H), 5.91 (d, J=3.6 Hz, 1H), 5.89 (d, J=3.6 Hz, 1H), 4.28 (s, 2H), 3.97 (t, J=7.0 Hz, 2H), 3.54 (t, J=7.0 Hz, 2H), 2.25 (s, 3H), 2.08 (m, 2H); MS (EI) *m/z* 275(13), 277(39). Anal. Calcd for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58; N, 5.08. Found C, 69.65; H, 6.55; N, 5.11.

4.3. KOBu^t as base for alkylative cyclization

To a solution of KOBu^t (0.65 mmol) in anhydrous THF (20 mL) under N_2 at 0 °C was added **3a/b** (0.65 mmol). The reaction was allowed to warm to ambient temperature and stirred for 6 h. The reaction was quenched with water and the THF removed under reduced pressure, and then extracted with CH_2Cl_2. The crude product obtained was purified by preparative TLC to give **4a/b**, respectively.

4.3.1. 1-((*E*)-1-Hydroxybenz-1-ylidene)-5-methyl-2,3-dihydro-1*H*-pyrrolizine (4a). Obtained as yellow oil in 20% yield (ether/hexane, 1:3). ν_{max}: 3400, 1615 cm^{-1}. ^{1}H NMR (200 MHz): δ 7.98 (d, 2H), 7.60 (m, 1H), 7.52 (m, 2H), 6.89 (d, J=3.9 Hz, 1H), 6.05 (d, J=3.9 Hz, 1H), 4.69 (t, J=6.0 Hz, 2H), 3.95 (t, J=6.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (50 MHz) δ 193.35, 183.21, 142.17, 134.21, 133.53, 130.00, 128.82, 128.75, 126.94, 125.66, 110.87, 43.38, 42.12, 33.61, 12.50; MS (EI) *m/z* 225(16). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found C, 79.78; H, 6.67; N, 6.17.

4.3.2. 8-((*E*)-1-Hydroxybenz-1-ylidene)-3-methyl-5,6-dihydro-8*H*-indolizine (4b). Obtained as yellow oil in 25% yield (ether/hexane, 1:3). ν_{max}: 3400, 1615 cm^{-1}. ^{1}H NMR (200 MHz): δ 8.00 (d, 2H), 7.64 (m, 1H), 6.85 (d, J=4.0 Hz, 1H), 6.03 (d, J=4.0 Hz, 1H), 4.56 (t, J=5.8 Hz, 2H), 3.64 (t, J=5.8 Hz, 2H), 2.38 (s, 3H), 2.30 (m, 2H); ^{13}C NMR (50 MHz) δ 193.35, 182.21, 142.17, 134.21, 133.53, 130.00, 128.82, 128.75, 126.94, 125.66, 110.87, 43.38, 42.12, 33.61, 12.50; MS (EI) *m/z* 239(25). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found C, 80.16; H, 7.07; N, 5.84.

4.4. One pot procedure using sodium carbonate and sodium bicarbonate

The chloroethyl- or chloropropylamine hydrochloride salt (1.10 mmol) was first neutralized with Na_2CO_3 or bicarbonate (2 equiv) in MeOH solution. To the solution was added **1** (1.00 mmol) at 0 °C and than at room temperature for 72 h under N_2 (TLC analysis indicate the disappearance of the **1** and **3**). The MeOH was removed under reduce pressure, water added, and extracted with CH_2Cl_2. Purification of the crude mixture by preparative TLC provided the corresponding product (see Table 1).

4.4.1. 2,3-Di-[*N*-(2-chloroethyl)-5-methylpyrrol-1-yl]-1,4-diphenylbutane-1,4-dione (5a). Obtained as an orange gum. ν_{max}: 1675 cm^{-1}. δ 7.84 (d, J=6.9 Hz, 4H), 7.44 (m, 2H), 7.35 (m, 4H), 6.03 (d, J=3.6 Hz, 2H), 5.84 (d, J=3.6 Hz, 2H), 5.32 (s, 2H), 3.65 (m, 4H), 3.21 (m, 2H), 2.92 (m, 2H), 2.15 (s, 6H); ^{13}C NMR (50 MHz) δ 198.21, 137.06, 132.53, 130.19, 128.46, 128.23, 125.49, 109.71, 108.02, 50.60, 43.91, 41.49, 12.50; MS (EI) *m/z* 524 (2), 522 (10), 520 (16), 260 (100). HRMS *m/z* calcd for $C_{30}H_{30}Cl_2N_2O_2$, 520.1684; found, 520.1686.

4.4.2. 2,3-Di-[*N*-(2-chloropropyl)-5-methylpyrrol-1-yl]-1,4-diphenylbutane-1,4dione (5b). Obtained as an orange crystal, mp 128 °C. ν_{max}: 1670 cm^{-1}. ^{1}H NMR (200 MHz): δ 7.85 (d, J=6.9 Hz, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 5.98 (d, J=3.6 Hz, 2H), 5.78 (d, J=3.6 Hz, 2H), 5.33 (s, 2H)

3.45 (t, $J=7.8$ Hz, 4H), 3.38 (m, 2H), 2.14 (s, 6H), 1.85 (m, 2H), 1.36 (m, 2H); ^{13}C NMR (50 MHz) δ 198.56, 137.28, 132.40, 129.84, 128.41, 128.29, 125.29, 109.17, 107.38, 50.69, 42.15, 40.12, 33.13, 12.74; MS (EI) *m/z* 552 (0.5), 550 (4), 548 (6), 447 (1), 445 (6), 443 (10), 274 (100), 105 (50). HRMS *m/z* calcd for $C_{32}H_{34}Cl_2N_2O_2$, 548.1997; found, 548.2111.

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20. Crystal data for **5b**: orange prism crystal of $C_{32}H_{34}Cl_2N_2O_2$, $M_W=549.54$, triclinic, space group *P*-1 (#2), $a=10.15$ (1) Å, $b=11.59$ (1) Å, $c=14.06$ (2) Å, $\alpha=98.1$ (1)°, $\beta=93.50$ (10)°, $\gamma=113.99$ (8)°, $V=1483$ (3) Å^3, $Z=2$, $D_c=1.230$ g/cm^3, $R=0.063$, $R_w=0.055$, GOF=4.01 for 2358 reflections with $I>3.00\ \sigma(1)$. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Center under the following numbers: CCDC-165004.

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Tandem intramolecular carbolithiation–transmetallation: from lithium to copper or boron chemistry

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Abstract—Lithium/copper transmetallation from the organolithium intermediate **3** (obtained via intramolecular carbolithiation of the acyclic organolithium **2**, generated by a chlorine–lithium exchange) gives the corresponding organocopper intermediate **5**. This intermediate reacts with eletrophiles, such as allylic or propargylic halides, acyl chlorides or α,β-unsaturated carbonyl compounds giving the expected compounds **6**–**10**, which are not possible to be obtained directly from the organolithium **3**. On the other hand, lithium/boron transmetallation affords the corresponding alkylboronic acid **11** which, after palladium-catalysed Suzuki–Miyaura cross-coupling reaction with different aryl bromides gives the expected products **12** with modest yields, the corresponding Ullman biarylic homocoupling products being the major by-products.

1. Introduction

The use of organolithium compounds[1] in synthetic organic chemistry has acquired the label of routine, so it is common to find an organolithium intermediate in some of the steps of a total synthesis of a complex molecule.[2] The main reason for this fact is the high reactivity of organolithium compounds even under mild reaction conditions due to the polarity of the carbon–lithium bond, which confers to these species a significant reactivity as carbanions, specially in carbon–carbon bond forming processes. An interesting case appears when the organolithium compound bears a functional group,[3] because in this case the functionality is transferred to the electrophile giving polyfunctionalised organic molecules in one only synthetic operation. These intermediates are usually not stable at room temperature and therefore their generation should be done at low temperatures. For this reason, and in order to perform lithiation processes under mild reaction conditions, we have been developing in the last few years a lithiation methodology consisting in using an arene [mainly naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB)] as electron transfer catalyst,[4–6] which allows to perform a series of new lithiation-based reactions.[7–11] Among them, we recently found that the DTBB-catalysed lithiation of 6-chlorohex-1-ene (**1**) (and related systems) at −30 °C produced the formation of the corresponding open-chain lithium derivative **2**, that under these reaction conditions cyclised to give cyclopentylmethyllithium (**3**) through an intramolecular carbolithiation process.[12] The intermediate **3** reacted with typical electrophiles, mainly carbonyl compounds, to give the expected products **4** (Scheme 1).[13] In addition, and in order to amplify its synthetic applications, we studied recently its lithium–zinc transmetallation and the further reaction with other different electrophiles, under transition metal catalysis.[14] In this paper we explore two new transmetallation reactions from compound **3**, namely lithium–copper and lithium–boron exchange, in order to get new processes not possible neither with lithium derivatives nor with zinc intermediates without transition metal catalysis.

2. Results and discussion

Once cyclopentylmethyllithium (**3**) was generated by DTBB-catalysed lithiation of 6-chlorohex-1-ene in THF at −30 °C (see above),[13] the excess of lithium was filtered off and the resulting THF solution was added to a solution containing an equimolecular amount of the complex CuCN·2LiCl in THF at 0 °C. The formed organocopper intermediate **5** reacted then with different allylic chlorides to give, after acidic hydrolysis, the corresponding products **6** resulting from a clean S_N2' process (Scheme 2, Chart 1 and Table 1, entries 1–3). The reaction of intermediate **5** with

Keywords: Lithium–copper transmetallation; S_N2' Reaction; Acylation; Michael addition; Lithium–boron transmetallation; Suzuki–Miyaura coupling.
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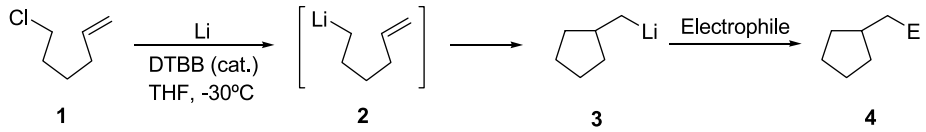
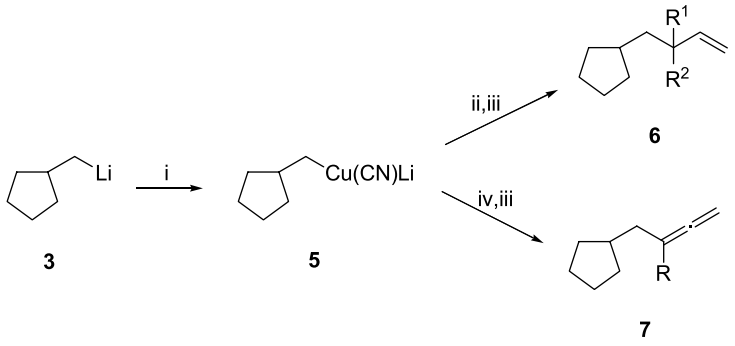


Scheme 1.



Scheme 2. Reagents and conditions: (i) CuCN·2LiCl, THF, 0 °C; (ii) E=(*E*)-PhCH=CHCH$_2$Cl, geranyl chloride, (*E*)-BrCH$_2$CH=CHCH$_2$Br, 0 °C; (iii) 2 M HCl, 0 °C to rt; (iv) E=HC≡CCH$_2$Hal (Hal=Cl, Br), EtC≡CCH$_2$Br, *n*-C$_5$H$_{11}$C≡CCH$_2$Cl, ClCH$_2$C≡CCH$_2$Cl, 0 °C.

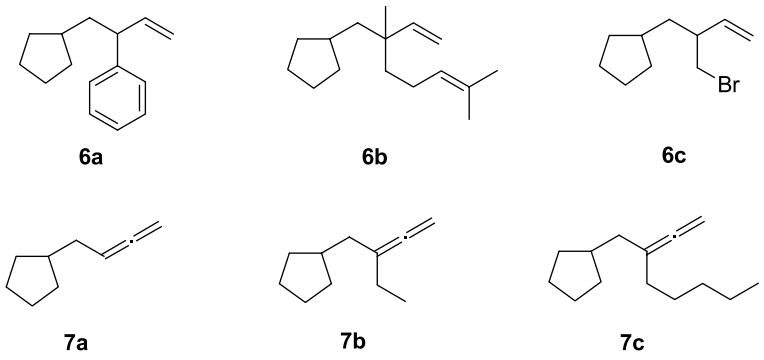


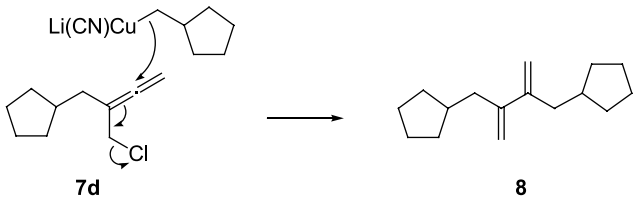
Chart 1.

propargyl halides (chlorides or bromides) under the same reaction conditions gave the corresponding products **7**, also resulting from a S_N2' process (Scheme 2, Chart 1 and Table 1, entries 5–7). In the case of using 1,4-dichlorobut-2-yne as electrophile (0.5 equiv), the corresponding compound **7d** initially formed reacted with a second molecule of the intermediate **5** to yield the isolated product **8** (Scheme 3 and Table 1, entry 8).[15]

Table 1. Preparation of compounds **6–8**

Entry	Electrophile (E)	Product[a]	
		No.	Yield (%)[b]
1	(*E*)-PhCH=CHCH$_2$Cl	**6a**	56
2	Geranyl chloride	**6b**	64
3	(*E*)-BrCH$_2$CH=CHCH$_2$Br	**6c**	63
4	HC≡CCH$_2$Cl	**7a**	33
5	HC≡CCH$_2$Br	**7a**	34
6	EtC≡CCH$_2$Br	**7b**	49
7	*n*-C$_5$H$_{11}$C≡CCH$_2$Cl	**7c**	78
8	ClCH$_2$C≡CCH$_2$Cl	**8**	77[c]

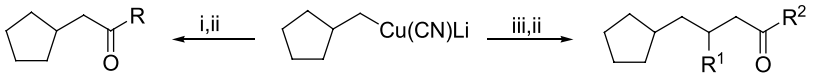
[a] All products were >95% pure (300 MHz ^{1}H NMR and/or GC).
[b] Yields of pure compounds **6–8** after column chromatography purification (silica gel, hexane) based on 6-chlorohex-1-ene (**1**), the precursor of intermediate **3**.
[c] Only 0.5 equiv of the electrophile were used.



Scheme 3.

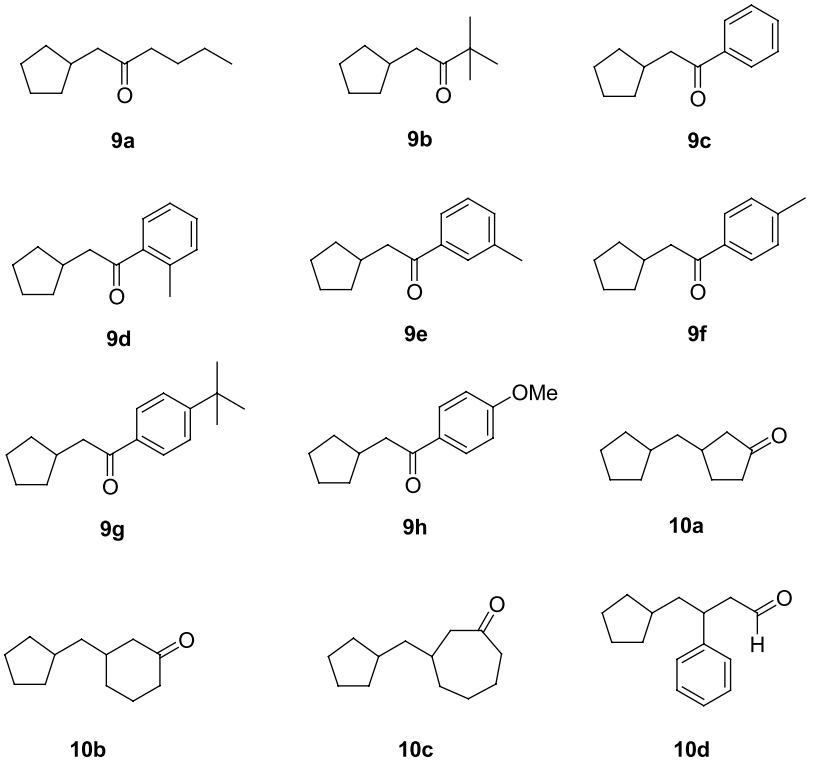
The acylation of the organocopper intermediate **5** with different alkylic or arylic acyl chlorides worked nicely at 0 °C giving, after acidic hydrolysis, the expected ketones **9** (Scheme 4, Chart 2 and Table 2, entries 1–8). A different type of carbonyl compounds **10** were generated by a Michael-type addition of the same intermediate **5** to α,β-unsaturated carbonyl compounds, for this process to occur being necessary to use one equivalent of the complex $BF_3{\cdot}OEt_2$ in order to activate the carbonyl compound (Scheme 4, Chart 2 and Table 2, entries 9–12).

In the last part of this study we considered a lithium–boron transmetallation from cyclopentylmethyllithium (**3**) with triisopropyl borate at −78 °C to give, after basic hydrolysis, the cyclopentylmethylboronic acid **11**.[16] The



9 5 10

Scheme 4. Reagents and conditions: (i) E=Bu^{n}COCl, Bu^{t}COCl, PhCOCl, 2-MeC$_6$H$_4$COCl, 3-MeC$_6$H$_4$COCl, 4-MeC$_6$H$_4$COCl, 4-Bu^{t}C$_6$H$_4$COCl, 4-MeOC$_6$H$_4$COCl, THF, 0 °C; (ii) 2 M HCl, 0 °C to rt; (iii) E=2-cyclopenten-1-one, 2-cyclohexen-1-one, 2-cyclohepten-1-one, (*E*)-PhCH=CHCHO, $BF_3 \cdot OEt_2$, 0 °C.



9a 9b 9c 9d 9e 9f 9g 9h 10a 10b 10c 10d

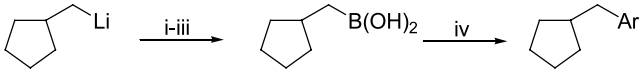
Chart 2.

Suzuki–Miyaura-type reaction of this compound with different aryl bromides under palladium catalysis gave the expected coupling products **12** in modest yields (Scheme 5, Chart 3 and Table 3). As the catalyst the palladacycle **13**[17] gave the best results (100% conversion in all cases) compared to other classical palladium compounds [e.g. $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$], which gave poorer results (<60% conversion) under the same reaction conditions.

Table 2. Preparation of compounds **9** and **10**

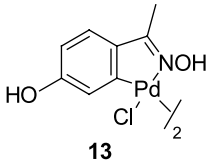
Entry	Electrophile (E)	Product[a]	
		No.	Yield (%)[b]
1	Bu^{n}COCl	**9a**	61
2	Bu^{t}COCl	**9b**	65
3	PhCOCl	**9c**	70
4	2-MeC$_6$H$_4$COCl	**9d**	74
5	3-MeC$_6$H$_4$COCl	**9e**	86
6	4-MeC$_6$H$_4$COCl	**9f**	80
7	4-Bu^{t}C$_6$H$_4$COCl	**9g**	66
8	4-MeOC$_6$H$_4$COCl	**9h**	50
9	2-Cyclopenten-1-one	**10a**	50
10	2-Cyclohexen-1-one	**10b**	46
11	2-Cyclohepten-1-one	**10c**	51
12	(*E*)-Cinnamaldehyde	**10d**	48

[a] All products were >95% pure (300 MHz ^{1}H NMR and/or GC).
[b] Yields of pure compounds **9** or **10** after column chromatography purification (silica gel, hexane/ethyl acetate) based on 6-chlorohex-1-ene (**1**), the precursor of intermediate **3**.

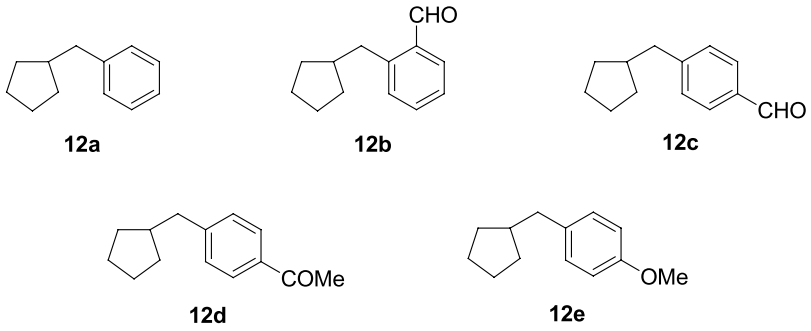


3 11 12

Scheme 5. Reagents and conditions: (i) B(OPr^i)$_3$, THF, −78 to −50 °C; (ii) 2 M NaOH; (iii) conc. HCl; (iv) ArBr=PhBr, 2-HCOC$_6$H$_4$Br, 4-HCOC$_6$H$_4$Br, 4-MeCOC$_6$H$_4$Br, 4-MeOC$_6$H$_4$Br, **13** (1 mol %), K_2CO_3, H_2O reflux.



13



12a 12b 12c 12d 12e

Chart 3.

Table 3. Preparation of compounds **12**

Entry	ArBr	*t* (h)	Product[a]	
			No.	Yield (%)[b]
1	PhBr	24	**12a**	40
2	2-$HCOC_6H_4Br$	19	**12b**	23
3	4-$HCOC_6H_4Br$	19	**12c**	51
4	4-$MeCOC_6H_4Br$	24	**12d**	50 (37)[c]
5	4-$MeOC_6H_4Br$	19	**12e**	33

[a] All products were >95% pure (300 MHz ^{1}H NMR and/or GC)
[b] Yields of pure compounds **12** after column chromatography purification (silica gel, hexane/ethyl acetate) based on the starting aryl bromide.
[c] 1.5 equiv (instead of 3 equiv; see Section 4) of compound **11** were used.

A couple of relevant comments should be made concerning the coupling reaction shown in Scheme 5: (a) the reaction with aryl iodides (for instance phenyl iodide) failed, only homocoupling products (biphenyl) have been isolated, together with some starting aryl iodide; (b) yields are in all cases modest (either with activated or deactivated aryl bromides), homocoupling (biaryl compounds) or reduced (arenes resulting from a bromo-hydrogen exchange) products being the main by-products obtained, together with the desired coupling compound **12**. These modest results are in agreement with those of other Suzuki–Miyaura reactions involving sp^3-hybridised boronic acids reported in the literature.[18]

3. Conclusion

From the results obtained in this paper, we conclude that the lithium–copper transmetallation from intermediate **3** allows to perform new reactions, such as allylic or propargylic S_N2', acylation or Michael addition, which are not possible using the corresponding lithium derivative, because a S_N2, over addition or 1,2-addition take place instead. These results, even being similar to those obtained using a lithium–zinc transmetallation, avoid here the use of a transition metal to activate the corresponding organometallic intermediate. On the other hand, a lithium–boron transmetallation allows a sp^3–sp^2 carbon–carbon coupling with aryl bromides under palladium catalysis, this process (even working with modest yields) being generally very difficult for alkylboronic acids.

4. Experimental

4.1. General

All lithiation reactions were carried out under argon. FT-IR spectra were obtained with a Nicolet Impact 400D spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with a Bruker AC 300 with $CDCl_3$ as solvent and TMS as internal standard; chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. Low-resolution mass spectra (EI) were obtained at 70 eV with an Agilent 5973 Network spectrometer, fragment ions in m/z with relative intensities (%) in parentheses. High-resolution mass spectra were obtained by the corresponding service at the University of Alicante on a Finnigan MAT 95 S apparatus. The purities of volatile products and chromatographic analyses (GLC) were determined with an Agilent 6890 Series instrument equipped with a flame ionisation detector and a 30 m capillary column (0.32 mm diam., 0.25 μm film thickness), with 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). Thin layer chromatography (TLC) was carried out on Merck plastic sheets coated with 60 F_{254} silica gel. Column chromatography was carried out over Merck 63–200 μm silica gel. All starting materials and solvents were commercially available (Acros, Aldrich, Fluka) and were used as the best grade without further purification. Lithium powder was prepared from commercially available lithium granules (99%, high sodium content, Aldrich) as already reported by us.[19]

4.2. S_N2' Reaction of intermediate 5 with allylic and propargylic halides. Isolation of compounds 6–8. General procedure

To a stirred green suspension of lithium powder (40 mg, 5.8 mmol) and DTBB (13.3 mg, 0.05 mmol) in THF (4 mL) at −30 °C was added 6-chlorohex-1-ene (0.138 mL, 1.0 mmol) under an argon atmosphere. The colour disappeared after the substrate addition, the reaction mixture was stirred until the green colour was recovered (40 min) and then, the lithium excess was filtered off using inert conditions. The resulting solution was added to a solution of CuCN·2LiCl [prepared by dissolving copper(I) cyanide (100 mg, 1.1 mmol) and lithium chloride (93 mg, 2.2 mmol) in THF (5 mL)] and the mixture changed to black colour. The solution was stirred 10 min at 0 °C and the corresponding allylic or propargylic halide (1.1 mmol) was added. After 3 h stirring the reaction was hydrolysed with water (10 mL), acidified (10 mL of HCl 2 M) and extracted with ethyl acetate (3×20 mL). The organic layer was washed with NaCl saturated solution (2×15 mL), dried over $MgSO_4$ and the solvents were evaporated (15 Torr) to yield a residue which was purified by column chromatography (silica gel, hexane) to give compounds **6–8**. Structures and yields are given in Scheme 3, Chart 1 and Table 1; physical, spectroscopic and analytical data follow.

4.2.1. 4-Cyclopentyl-3-phenyl-1-butene (6a). R_f 0.7 (hexane); ν (film) 3080, 3061, 3026 (C=CH), 1636, 1600, 1492 cm^{-1} (C=C); δ_H 1.31 (m, 11H, 5×CH_2, CH), 3.29 (m, 1H, C*H*CH=), 5.01 (m, 2H, CH_2=), 5.95 (ddd, J=7.7, 10.2, 17.1 Hz, 1H, CH=), 7.23 (m, 5H, ArH); δ_C 25.1, 25.2, 32.6, 32.7 (4×CH_2), 37.6 (CH), 42.1 (CHCH_2CH), 49.0 (*C*HCH=), 113.6 (CH_2=), 126.0, 127.6, 128.4, 144.8 (6×ArC), 142.7 (CH=); *m/z* 201 (M^++1, 1.0%), 200 (M^+, 6.0%), 118 (36), 117 (100), 115 (29), 104 (14), 91 (16), 55 (14). HRMS: found M^+, 200.1574. $C_{15}H_{20}$ requires 200.1565.

4.2.2. 3-(Cyclopentylmethyl)-3,7-dimethylocta-1,6-diene (6b). R_f 0.8 (hexane); ν (film) 3080, 3056 (C=CH), 1636 cm^{-1} (C=C); δ_H 0.98 (s, 3H, CH_2CCH_3), 1.02 (m, 2H, CH_2), 1.29 (m, 2H, CH_2), 1.49 (m with a s at 1.58, 9H, CH_3CCH_3 and 3×CH_2), 1.85 (m with a s at 1.67, 8H, CH_3CCH_3, 2×CH_2 and CH), 4.88 (dd, J=1.4, 17.5 Hz, 1H, C*H*H=), 4.95 (dd, J=1.4, 10.8 Hz, 1H, CH*H*=), 5.08 [def t, J=7.1 Hz, 1H, $(CH_3)_2C$=C*H*], 5.73 (dd, J=10.8, 17.5 Hz, 1H, CH_2=C*H*); δ_C 17.6, 22.7 [(*C*H_3)$_2$C=], 22.9, 25.1 (3×CH_2), 25.7 (*C*H_3CHCH_2), 35.0, 35.1 (2×CH_2), 36.5 (CH_2*C*HCH_2), 40.1 (CH_2*C*CH_3), 41.6, 47.8 (2×CH_2), 111.1 (=CH_2), 125.2 [$(CH_3)_2$C=*C*H], 130.9 [$(CH_3)_2$*C*=CH], 148.0 (CH_2=*C*H); *m/z* 220 (M^+, 3.0%), 138 (13), 137 (12), 109 (70), 96 (13), 95 (83), 83 (43), 82 (61), 81 (69), 79 (10), 70 (12), 69 (100), 68 (21), 67 (52), 55 (78), 53 (16). HRMS: found M^+, 220.2199. $C_{16}H_{28}$ requires 220.2191.

4.2.3. 3-(Cyclopentylmethyl)-4-bromo-1-butene (6c). R_f 0.7 (hexane); ν (film) 3076 (C=CH), 1641 cm^{-1} (C=C); δ_H 1.46 (m, 11H, 5×CH_2 and CH_2C*H*CH_2), 2.41 (m, 1H, C*H*CH_2Br), 3.35 (d, J=2.8 Hz, 1H, BrC*H*H), 3.37 (d, J=2.3 Hz, 1H, BrCH*H*), 5.10 (m, 2H, CH_2=), 5.62 (m, 1H, CH=); δ_C 25.06, 25.09, 32.1, 33.1 (4×CH_2), 37.3 (CH_2*C*HCH_2), 38.6, 39.5 (2×CH_2), 44.9 (*C*HCH_2Br), 116.5 (CH_2=), 139.8 (CH=); *m/z* 189 (M^+−27, 1.3%), 137 (12), 123 (19), 109 (11), 95 (33), 83 (55), 82 (68), 81 (68), 79 (15), 69 (28), 68 (19), 67 (87), 55 (100), 54 (46), 53 (37). HRMS: found M^+−[CH=CH_2], 189.0067. $C_8H_{12}Br$ requires 189.0279.

4.2.4. 4-Cyclopentyl-1,2-butadiene (7a). R_f 0.9 (hexane); ν (film) 3076, 3063 (C=C=C–H), 1956, 840 cm^{-1} (C=C=C); δ_H 1.16 (m, 2H, CH_2), 1.54 (m, 4H, 2×CH_2), 1.77 (m, 2H, CH_2), 1.89 (m, 1H, CH), 2.01 (m, 2H, CHC*H*$_2$CH), 4.63 (m, 2H, =CH_2), 5.08 (quint, J=6.9 Hz, 1H, CH=); δ_H 25.2, 32.2, 34.9 (5×CH_2), 39.9 (CH), 74.0 (CH=C=*C*H_2), 89.4 (*C*H=C=CH_2), 208.9 (CH=*C*=CH_2); *m/z* 122 (M^+, 0.52%), 107 (11), 93 (33), 91 (12), 81 (20), 80 (20), 79 (39), 77 (16), 69 (29), 68 (78), 67 (100), 66 (13), 65 (10), 55 (15), 54 (39), 53 (26), 51 (11). HRMS: found M^+, 122.1089. C_9H_{14} requires 122.1096.

4.2.5. 3-(Cyclopentylmethyl)-1,2-pentadiene (7b). R_f 0.7 (hexane); ν (film) 3045 (C=C=C–H), 1956, 850 cm^{-1} (C=C=C); δ_H 1.00 (t, J=7.4 Hz, 3H, CH_3), 1.13, (m, 2H, CH_2), 1.54 (m, 4H, 2×CH_2), 1.76 (m, 2H, CH_2), 1.96 (m, 5H, CH and CH_2CCH_2), 4.65 (m, 2H, =CH_2); δ_C 12.2 (CH_3), 25.1, 25.2, 32.7 (4×CH_2), 38.1 (CH), 39.1 (2×CH_2), 75.4 (C=C=*C*H_2), 104.6 (*C*=C=CH_2), 206.0 (C=*C*=CH_2); *m/z* 150 (M^+, 1.31%), 121 (32), 93 (24), 91 (13), 82 (38), 81 (12), 79 (33), 77 (12), 68 (14), 67 (100), 55 (18), 53 (15). HRMS: found M^+, 150.1412. $C_{11}H_{18}$ requires 150.1409.

4.2.6. 3-(Cyclopentylmethyl)-1,2-octadiene (7c). R_f 0.9 (hexane); ν (film) 3046 (C=C=C–H), 1957 cm^{-1} (C=C=C); δ_H 0.89 (t, J=6.6 Hz, 3H, CH_3), 1.56 (m, 19H, 9×CH_2 and CH), 4.62 (m, 2H, =CH_2); δ_C 14.1 (CH_3), 22.6, 25.3, 27.3, 31.6, 32.2, 32.7, 39.1 (9×CH_2), 38.1 (CH), 74.8 (C=C=*C*H_2), 102.9 (*C*=C=CH_2), 206.3 (C=*C*=*C*H_2); *m/z* 192 (M^+, 0.7%), 121 (43), 109 (15), 107 (24), 95 (42), 94 (18), 93 (35), 91 (18), 82 (12), 81 (34), 80 (14), 79 (39), 77 (16), 69 (31), 68 (100), 67 (69), 55 (23), 53 (14). HRMS: found M^+, 192.1860. $C_{14}H_{24}$ requires 192.1878.

4.2.7. 2,3-Di(cyclopentylmethyl)-1,3-butadiene (8).[20] R_f 0.9 (hexane); ν (film) 3088 (C=CH), 1629, 1592 cm^{-1} (C=C); δ_H 1.13, 1.60, 1.98 (3m, 18H, 8×CH_2 and 2×CH), 2.22 (d, J=7.3 Hz, 4H, 2×CH_2C=), 4.88 (s, 2H, =CH_2), 5.03 (s, 2H, =CH_2); δ_C 25.1, 32.5, 40.9 (10×CH_2), 38.4 (2×CH), 112.0 (2×=CH_2), 147.7 (2×*C*=CH_2); *m/z* 219 (M^++1, 1.2%), 218 (M^+, 0.5%), 150 (30), 149 (44), 136 (28), 135 (83), 121 (48), 109 (16), 108 (53), 107 (91), 104 (13), 95 (33), 94 (23), 93 (55), 91 (38), 84 (30), 83 (35), 82 (99), 81 (43), 80 (19), 79 (54), 77 (26), 69 (54), 68 (28), 67 (100), 66 (20), 65 (15), 55 (31), 53 (25). HRMS: found M^+, 218.2035. $C_{16}H_{26}$ requires 218.2035.

4.3. Acylation of intermediate 5. Isolation of ketones 9. General procedure

To a stirred green suspension of lithium powder (40 mg, 5.8 mmol) and DTBB (13.3 mg, 0.05 mmol) in THF (4 mL) at −30 °C was added 6-chlorohex-1-ene (0.138 mL, 1.0 mmol) under argon atmosphere. The colour disappeared

after the substrate addition, the reaction mixture was stirred until the green colour was recovered (ca. 40 min) and then, the lithium excess was filtered off using inert conditions. The resulting solution was added to a solution of CuCN·2LiCl [prepared by dissolving copper(I) cyanide (100 mg, 1.1 mmol) and lithium chloride (93 mg, 2.2 mmol) in THF (5 mL)] and the mixture changed to black colour. The solution was stirred 10 min at 0 °C and the corresponding acid chloride (1.1 mmol) was added. After 3 h stirring, the reaction was hydrolysed with water (10 mL), acidified (10 mL of HCl 2 M) and extracted with ethyl acetate (3× 20 mL). The organic layer was washed with NaCl saturated solution (2×15 mL) and dried over $MgSO_4$, and the solvents were evaporated (15 Torr) to yield a residue which was purified by column chromatography (silica gel, hexane/ethyl acetate) to give compounds **9**. Structures and yields are given in Chart 2 and Table 2; physical, spectroscopic and analytical data follow.

4.3.1. 1-Cyclopentyl-2-pentanone (9a). R_f 0.6 (hexane/ethyl acetate, 9/1); ν (film) 1713 cm^{-1} (C=O); δ_H 0.90 (t, J=7.3 Hz, 3H, CH_3), 1.07 (m, 2H, CH_2), 1.30 (sext, J=7.4 Hz, 2H, CH_3CH_2), 1.57 (m, 4H, 2×CH_2), 1.81 (m, 2H, CH_2), 2.22 (sept, J=7.7 Hz, 1H, CH), 2.40 (m, 4H, CH_2COCH_2); δ_C 13.8 (CH_3), 22.3, 24.9, 25.9, 25.8, 32.6 (5×CH_2), 35.6 (CH), 42.7, 49.1 (CH_2COCH_2), 211.5 (C=O); *m/z* 169 (M^++1, 2.3%), 168 (M^+, 17.4%), 111 (45), 101 (47), 100 (11), 85 (51), 83 (100), 67 (11), 59 (39), 58 (86), 57 (63), 55 (70). HRMS: found M^+, 168.1499. $C_{11}H_{20}O$ requires 168.1514.

4.3.2. 1-Cyclopentyl-3,3-dimethyl-2-butanone (9b).[21] R_f 0.7 (hexane/ethyl acetate, 9/1); ν (film) 1076 cm^{-1} (C=O); δ_H 1.03 (m, 2H, CH_2), 1.12 (s, 9H, 3×CH_3), 1.58 (m, 4H, 2×CH_2), 1.82 (m, 2H, CH_2), 2.26 (def sept, J=7.7 Hz, 1H, CH), 2.51 (d, J=6.9 Hz, 2H, CH_2CO); δ_C 25.0 (2×CH_2), 26.3 (3×CH_3), 32.6 (2×CH_2), 35.2 (CH), 42.7 (CH_2C=O), 43.9 [$C(CH_3)_3$], 215.9 (C=O); *m/z* 168 (M^+, 6.6%), 111 (59), 83 (100), 57 (57), 55 (39). HRMS: found M^+, 168.1507. $C_{11}H_{20}O$ requires 168.1514.

4.3.3. α-Cyclopentylacetophenone (9c).[22] R_f 0.7 (hexane/ethyl acetate, 9/1); ν (film) 3063, 3027 (C=CH), 1599, (C=C), 1688 cm^{-1} (C=O); δ_H 1.18 (m, 2H, CH_2), 1.60 (m, 4H, 2×CH_2), 1.88 (m, 2H, CH_2), 2.39 (def sept, J=7.6 Hz, 1H, CH), 2.99 (d, J=7.0 Hz, 2H, CH_2CO), 7.45, 7.55, 7.96 (3m, 2H, 1H and 2H respectively, 5×ArH); δ_C 24.9, 32.7 (4×CH_2), 36.0 (CH), 44.8 (CH_2C=O), 128.1, 128.5, 132.8, 137.2 (6×ArC), 200.4 (C=O); *m/z* 189 (M^++1, 1.0%), 188 (M^+, 6.2%), 121 (17), 120 (87), 105 (100), 77 (45), 51 (11).

4.3.4. 2′-Methyl-α-cyclopentylacetophenone (9d). R_f 0.4 (hexane/ethyl acetate, 9/1); ν (film) 3062, 3021, 1600 (C=C), 1686 cm^{-1} (C=O); δ_H 1.15 (m, 2H, CH_2), 1.59 (m, 4H, 2×CH_2), 1.85 (m, 2H, CH_2), 2.33 (sept, J=7.7 Hz, 1H, CH), 2.48 (s, 3H, CH_3), 2.90 (d, J=7.2 Hz, 2H, $COCH_2$), 7.23 (def t, J=6.8 Hz, 2H, 2×ArH), 7.75 (m, 2H, 2×ArH); δ_C 21.2 (CH_3), 24.9, 32.6 (4×CH_2), 36.0 (CH), 44.7 ($COCH_2$), 125.2, 128.3, 128.5, 133.5, 137.2, 138.2 (6×ArC), 200.5 (C=O); *m/z* 202 (M^+, 1.98%), 134 (14), 119 (100), 91 (33). HRMS: found M^+, 202.1368. $C_{14}H_{18}O$ requires 202.1358.

4.3.5. 3′-Methyl-α-cyclopentylacetophenone (9e). R_f 0.5 (hexane/ethyl acetate, 9/1); ν (film) 3060, 3046, 3027, 1604 (C=C), 1684 cm^{-1} (C=O); δ_H 1.18 (m, 2H, CH_2), 1.59 (m, 4H, 2×CH_2), 1.87 (m, 2H, CH_2), 2.38 (m with a s at 2.40, 4H, CH and CH_3), 2.96 (d, J=7.0 Hz, 2H, $COCH_2$), 7.33 (m, 2H, 2×ArH), 7.75 (m, 2H, 2×ArH); δ_C 21.2 (CH_3), 24.9, 32.6 (4×CH_2), 36.0 (CH), 44.7 ($COCH_2$), 125.2, 128.3, 128.5, 133.5, 137.2, 138.2 (6×ArC), 200.5 (C=O); *m/z* 202 (M^+, 11.58%), 135 (12), 134 (82), 119 (100), 92 (12), 91 (50), 65 (15). HRMS: found M^+, 202.1354. $C_{14}H_{18}O$ requires 202.1358.

4.3.6. 4′-Methyl-α-cyclopentylacetophenone (9f). R_f 0.5 (hexane/ethyl acetate, 9/1); ν (film) 3086, 3054, 3030, 1607 (C=C), 1683 cm^{-1} (C=O); δ_H 1.18 (m, 2H, CH_2), 1.59 (m, 4H, 2×CH_2), 1.87 (m, 2H, CH_2), 2.37 (m with a s at 2.39, 4H, CH and CH_3), 2.94 (d, J=7.0 Hz, 2H, $COCH_2$), 7.23 (d, J=8.0 Hz, 2H, 2×ArH), 7.85 (d, J=8.1 Hz, 2H, 2×ArH); δ_C 21.4 (CH_3), 24.8, 32.6 (4×CH_2), 36.0 (CH), 44.5 ($COCH_2$), 128.1, 129.1, 134.5, 143.4 (6×ArC), 199.9 (C=O); *m/z* 202 (M^+, 4.90%), 134 (78), 119 (100), 91 (39), 65 (13). HRMS: found M^+, 202.1362. $C_{14}H_{18}O$ requires 202.1358.

4.3.7. 4′-*tert*-Butyl-α-cyclopentylacetophenone (9g). R_f 0.6 (hexane/etil acetate, 9/1); ν (film) 3088, 3056, 3034 (C=CH), 1717, 1681 (C=O), 1606 cm^{-1} (C=C); δ_H 1.19 (m, 2H, CH_2), 1.33 (s, 9H, 3×CH_3), 1.59 (m, 4H, 2×CH_2), 1.85 (m, 2H, CH_2), 2.37 (def sept, J=7.7 Hz, 1H, CH), 2.96 (d, J=7.0 Hz, 2H, $ArCOCH_2$), 7.46 (m, 2H, 2×ArH), 7.90 (m, 2H, 2×ArH); δ_C 24.9 (2×CH_2), 31.0 (3×CH_3), 32.6 (2×CH_2), 36.0 (CH_2CH), 44.6 ($ArCOCH_2$), 125.1, 128.0, 134.6, 166.6 (6×ArC), 199.8 (C=O); *m/z* 245 (M^++1, 0.2%), 244 (M^+, 0.1%), 187 (18), 176 (44), 162 (12), 161 (100), 118 (11). HRMS: found M^+-CH_3, 229.1558. $C_{16}H_{21}O$ requires 229.1592.

4.3.8. α-Cyclopentyl-4′-methoxyacetophenone (9h).[23] R_f 0.3 (hexane/ethyl acetate, 9/1); ν (film) 3074, 3053 (C=CH), 1711, 1676 (C=O), 1258, 1031 cm^{-1} (ArC–O–C); δ_H 1.17 (m, 2H, CH_2), 1.58 (m, 4H, 2×CH_2), 1.86 (m, 2H, CH_2), 2.37 (def sept, J=7.7 Hz, 1H, CH), 2.93 (d, J=7.2 Hz, 2H, CH_2CO), 3.85 (s, 3H, OCH_3), 6.92 (d, J=8.9 Hz, 2H, 2×ArH), 7.94 (d, J=8.9 Hz, 2H, 2×ArH); δ_C 24.8, 32.6 (4×CH_2), 36.2 (CH), 44.3 (CH_2), 55.3 (OCH_3), 113.5, 130.2, 131.4, 163.1 (6C×ArC), 198.9 (C=O); *m/z* 218 (M^+, 1.0%), 150 (78), 135 (100), 92 (14), 77 (18). HRMS: found M^+, 218.1325. $C_{14}H_{18}O_2$ requires 218.1307.

4.4. Conjugate addition of intermediate 5 to α,β-unsaturated ketones and aldehydes. Isolation of compounds 10. General procedure

To a stirred green suspension of lithium powder (40 mg, 5.8 mmol) and DTBB (13.3 mg, 0.05 mmol) in THF (4 mL) at −30 °C was added 6-chlorohex-1-ene (0.138 mL, 1.0 mmol) under argon atmosphere. The colour disappeared after the substrate addition, the reaction mixture was stirred until the green colour was recovered (ca. 40 min) and the lithium excess was filtered off using inert conditions. The resulting solution was added to a solution of CuCN·2LiCl [prepared by dissolving copper(I) cyanide (100 mg, 1.1 mmol) and lithium chloride (93 mg, 2.2 mmol) in THF (5 mL)] and the resulting mixture changed to black colour.

The solution was stirred 10 min at 0 °C and a mixture of the electrophile (1.1 mmol) and $BF_3 \cdot Et_2O$ (1.1 mmol) was added. After 2 h stirring the reaction was hydrolysed with water (10 mL), acidified (10 mL of HCl 2 M) and extracted with ethyl acetate (3×20 mL). The organic layer was washed with NaCl saturated solution (2×15 mL) and dried over $MgSO_4$. The solvents were evaporated (15 Torr) to yield a residue which was purified by column chromatography (silica gel, hexane) to give compounds **10**. Structures and yields are given in Chart 2 and Table 2; physical, spectroscopic and analytical data follow.

4.4.1. 3-(Cyclopentylmethyl)-1-cyclopentanone (10a).[24] R_f 0.3 (hexane/ethyl acetate, 9/1); ν (film) 1740 cm^{-1} (C=O); δ_H 1.09 (m, 2H, CH_2), 1.54 (m, 8H, 4×CH_2), 1.80 (m, 4H, 2×CH_2), 2.20 (m, 4H, 2×CH and CH_2); δ_C 25.01, 25.04 (2×*C*H_2CH_2CH), 29.8 (CH_2), 32.8, 32.9 (2×CH_2-*C*H_2CH), 36.4, 38.5 (2×CH), 38.6, 42.2, 45.6 (3×CH_2), 220.1 (C=O); *m/z* 167 (M^++1, 1.6%), 166 (M^+, 13.3%), 137 (11), 125 (30), 122 (11), 83 (100), 81 (15), 69 (27), 68 (16), 67 (33), 56 (13), 55 (44). HRMS: found M^+, 166.1356. $C_{11}H_{18}O$ requires 166.1358.

4.4.2. 3-(Cyclopentylmethyl)-1-cyclohexanone (10b). R_f 0.3 (hexane/ethyl acetate, 9/1); ν (film) 1713 cm^{-1} (C=O); δ_H 1.07 (2H, m, CH_2), 1.22–2.09 (16H, m, 7×CH_2 and 2×CH), 2.34 (2H, m, CH_2); δ_C 25.0 (2×CH_2), 25.3 (CH_2), 31.5, 32.7, 32.8 (3×CH_2), 37.0 (CH), 38.2 (*C*HCH_2C=O), 41.5 (CH*C*H_2CH), 43.2 (CH_2*C*H_2C=O), 48.4 (CH*C*H_2-C=O), 212.3 (C=O); *m/z* 180 (M^+, 2.6%), 98 (10), 97 (100), 69 (14), 67 (16), 55 (26). HRMS: found M^+, 180.1509. $C_{12}H_{20}O$ requires 180.1514.

4.4.3. 3-(Cyclopentylmethyl)-1-cycloheptanone (10c). R_f 0.4 (hexane/ethyl acetate, 9/1); ν (film) 1701 cm^{-1} (C=O); δ_H 1.04 (m, 2H, CH_2), 1.29 (t, J=7.0 Hz, 2H, CHCH_2CH), 1.35–1.92 (m, 14H, 2×CH and 6×CH_2), 2.42 (m, 4H, CH_2COCH_2); δ_C 24.3, 24.9, 28.3, 32.6, 32.7, 36.9, 43.5, 43.8, 50.0 (10×CH_2), 34.9, 37.2 (2×CH), 214.5 (C=O); *m/z* 194 (M^+, 2.89%), 112 (13), 111 (100), 98 (21), 95 (14), 94 (11), 83 (10), 81 (11), 69 (13), 67 (26), 55 (50). HRMS: found M^+, 194.1668. $C_{13}H_{22}O$ requires 194.1671.

4.4.4. 4-Cyclopentyl-3-phenylbutanal (10d). R_f 0.4 (hexane/ethyl acetate, 9/1); ν (film) 3060, 3026, 1601 (C=C), 2715 (H–CO), 1725 cm^{-1} (C=O); δ_H 1.12 (m, 4H, 2×CH_2), 2.93 (m, 6H, 3×CH_2), 1 (m, 1H, CH), 2.69 (dd, J=7.3, 2.0 Hz, CH_2CHO), 3.21 (m, 1H, CHPh), 7.26 (m, 5H, 5×ArH), 9.65 (t, J=2.0 Hz, 1H, CHO); δ_C 25.0, 25.1, 32.1, 33.1 (4×CH_2), 37.4, 39.2 (2×CH), 43.2, 51.0 (2×CH_2), 126.5, 127.5, 128.6, 144.0 (6×ArC), 202.1 (CHO); *m/z* 217 (M^++1, 4.2%), 216 (M^+, 25.5%), 148 (15), 134 (16), 133 (100), 130 (14), 129 (11), 115 (13), 106 (12), 105 (93), 104 (30), 103 (18), 92 (38), 91 (71), 79 (18), 78 (15), 77 (23), 55 (28). HRMS: found M^+, 216.1518. $C_{15}H_{20}O$ requires 216.1514.

4.5. Suzuki–Miyaura coupling reaction of the boronic acid 11 with aryl bromides. Isolation of compounds 12. Preparation of the cyclopentylmethylboronic acid (11)

To a stirred green suspension of lithium powder (0.4 g, 58 mmol) and DTBB (133 mg, 0.5 mmol) in THF (40 mL) at −30 °C was added 6-chlorohex-1-ene (1.38 mL, 10 mmol) under argon atmosphere. The colour disappeared after the substrate addition, the reaction mixture was stirred until the green colour was recovered (ca. 40 min) and the lithium excess was filtered off using inert conditions. The resulting solution was added to a Schlenk tube at −78 °C and $B(OPr^i)_3$ (6 mL, 25 mmol) was added dropwise to the solution. The reaction mixture was keep cold (ca. −50 °C) overnight, then quenched with 11 mL of NH_4Cl saturated solution, allowing the reaction to warm to room temperature. To the mixture was added an aqueous solution of 0.5 M HCl (55 mL, saturated with NaCl), and stirred for 30 min more. The solution was extracted with hexane (3×40 mL), the combining organics being extracted with 2 M NaOH (3×40 mL). These extracts were combined and acidified (pH∼1) with concentrated HCl, and extracted again with Et_2O (3×40 mL). The final combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure (15 Torr) to give the boronic acid **11** (86% yield) pure enough (91%) to be used in the next reactions without further purification.

4.5.1. Cyclopentylmethylboronic acid (11). M.p. 59 °C (hexane/ethyl acetate); ν (KBr) 3264 cm^{-1} (OH); δ_H (CD_3OD) 0.77 (d, J=7.2 Hz, 2H, CH_2B), 0.98 (m, 2H, CH_2), 1.50 (m, 4H, 2×CH_2), 1.72 (m, 2H, CH_2), 1.88 (def sept, J=7.5 Hz, 1H, CH); δ_C (CD_3OD) 26.0, 36.2 (4×CH_2), 37.3 (CH); *m/z* 330 [3×(M^+-H_2O), 100%], 329 (70), 328 (19), 315 (17), 314 (12), 302 (19), 301 (22), 300 (10), 288 (22), 287 (24), 286 (10), 262 (11), 247 (11), 81 (52), 69 (20), 67 (45), 55 (19); Calc. $C_6H_{13}BO_2$: C, 56.31; H, 10.24; Found: C, 56.16; H, 10.08.

4.6. Suzuki–Miyaura cross-coupling reaction of 11 with aryl bromides. General procedure

In a round-bottom flask were mixed the boronic acid (**11**; 0.194 g, 1.5 mmol), the catalyst **13**[25] (1.5 mg, 1% molar), K_2CO_3 (0.207 g, 1.5 mmol), the corresponding aryl bromide (0.5 mmol) and 2 mL of H_2O. Then the reaction was refluxed during nearly 24 h. The reaction was extracted with ethyl acetate (3×10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure (15 Torr), to yield a residue which was purified by column chromatography (silica gel, hexane/ethyl acetate) to give the expected coupling products **12**. Structures and yields are given in Chart 3 and Table 3; physical, spectroscopic and analytical data follow.

4.6.1. (Cyclopentylmethyl)benzene (12a).[26] R_f 0.6 (hexane); ν (film) 3084, 3062, 3026 (ArC-H), 1603, 1495 cm^{-1} (ArC-C); δ_H 1.19 (m, 2H, CH_2), 1.60 (m, 6H, 3×CH_2), 2.08 (sept def, J=7.6 Hz, 1H, CH), 2.60 (d, J=7.3 Hz, 2H, ArCH_2), 7.21 (m, 5H, ArH); δ_C 24.9, 32.4 (4×CH_2), 42.0 (CH), 42.1 (CH_2), 125.5, 128.1, 128.8, 142.4 (ArC); *m/z* 161 (M^++1, 2.9%), 160 (M^+, 20.2%), 92 (100), 91 (52), 69 (19), 65 (10). HRMS: found M^+, 160.1260. $C_{12}H_{16}$ requires 160.1252.

4.6.2. 2-(Cyclopentylmethyl)benzaldehyde (12b). R_f 0.4 (hexane/ethyl acetate, 9/1); ν (film) 3064, 3019, 1599 (C=C), 2750, 2726 (H-CO, Fermi resonance), 1698 cm^{-1} (C=O); δ_H 1.45 (m, 2H, CH_2), 1.57 (m, 6H, 3×CH_2), 1.98 (def sept, J=7.6 Hz, 1H, CH), 2.97 (d, J=7.5 Hz, 2H,

$ArCH_2$), 7.19 (d, $J=7.2$ Hz, 1H, ArH), 7.28 (t, $J=7.6$ Hz, 1H, ArH), 7.42 (dt, $J=7.5$, 1.5 Hz, 1H, ArH), 7.77 (dd, $J=7.6$, 1.5 Hz, 1H, ArH), 10.33 (s, 1H, CHO); δ_C 24.7, 32.4, 37.9 ($5\times CH_2$), 42.8 (CH), 126.4, 131.0, 131.4, 133.6, 145.2 ($6\times$ArC), 192.3 (C=O); *m/z* 188 (M^+, 10.55%), 187 (11), 171 (12), 170 (83), 169 (17), 155 (11), 145 (10), 142 (61), 141 (63), 131 (13), 129 (16), 128 (14), 120 (66), 119 (100), 115 (19), 91 (46), 77 (10), 65 (15). HRMS: found M^+, 182.1189. $C_{13}H_{16}O$ requires 188.1201.

4.6.3. 4-(Cyclopentylmethyl)benzaldehyde (12c). R_f 0.4 (hexane/ethyl acetate, 9/1); ν (film) 3070, 3045, 1605 (C=C), 2731 (H-CO), 1694 cm^{-1} (C=O); δ_H 1.18 (m, 2H, CH_2), 1.63 (m, 6H, $3\times CH_2$), 2.11 (sept def, $J=7.6$ Hz, 1H, CH), 2.69 (d, $J=7.5$ Hz, 2H, $ArCH_2$), 7.33 (d, $J=8.0$ Hz, 2H, $2\times$ArH), 7.80 (d, $J=8.1$ Hz, 2H, $2\times$ArH), 9.97 (s, 1H, CHO); δ_C 24.8, 32.4, ($4\times CH_2$), 41.7 (CH), 42.2 ($ArCH_2$), 129.4, 129.8, 134.3, 149.9 ($6\times$ArC), 192.0 (CHO); *m/z* 188 (M^+, 28.35%), 121 (18), 120 (100), 91 (32), 69 (13). HRMS: found M^+, 188.1198. $C_{13}H_{16}O$ requires 188.1201.

4.6.4. 4′-(Cyclopentylmethyl)acetophenone (12d). R_f 0.7 (hexane/ethyl acetate, 9/1); ν (film) 3085, 3029, 3000, 1606 (C=C), 1682 cm^{-1} (C=O); δ_H 1.18 (m, 2H, CH_2), 1.62 (m, 6H, $3\times CH_2$), 2.10 (sept, $J=7.6$ Hz, 1H, CH), 2.58 (s, 3H, CH_3), 2.66 (d, $J=7.5$ Hz, 2H, $ArCH_2$), 7.25 (d, $J=8.3$ Hz, 2H, $2\times$ArH), 7.87 (d, $J=8.3$ Hz, 2H, $2\times$ArH); δ_C 24.8, 32.4, ($4\times CH_2$), 26.4 (CH_3), 41.6 (CH), 42.0 ($ArCH_2$), 128.3, 128.9, 134.8, 148.2 ($6\times$ArC), 197.8 (C=O); *m/z* 202 (M^+, 30.68%), 188 (14), 187 (86), 135 (19), 134 (100), 119 (32), 115 (12), 105 (13), 91 (34), 90 (14), 69 (19). HRMS: found M^+, 202.1364. $C_{14}H_{18}O$ requires 202.1358.

4.6.5. *p*-(Cyclopentylmethyl)anisole (12e).[27] R_f 0.3 (hexane); ν (film) 3060, 3030 (ArC-H), 1612, 1583, 1512 (ArC-C), 1246, 1040 cm^{-1} (C–O); δ_H 1.17 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 1.67 (m, 4H, $2\times CH_2$), 2.04 (def sept, $J=7.5$ Hz, 1H, CH_2CH), 2.54 (d, $J=7.5$ Hz, 2H, $ArCH_2$), 3.78 (s, 3H, OCH_3), 6.81 (d, $J=8.6$ Hz, 2H, $2\times$ArH), 7.08 (d, $J=8.4$ Hz, 2H, $2\times$ArH); δ_C 24.9, 32.4 ($4\times CH_2$), 41.1 ($ArCH_2$), 42.2 (CH), 55.2 (CH_3), 113.5, 129.6, 134.5, 157.5 ($6\times$ArC); *m/z* 191 ($M^+ + 1$, 1.2%), 190 (M^+, 8.6%), 122 (13), 121 (100).

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Product selectivity in the electroreduction of thioesters

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Abstract—The electroreduction of differently substituted aromatic and aliphatic thioesters (RCOSR′) led to regioselective reactions depending on the nature of the substituents. Thus, the cleavage between the carbonyl group and the SR′ group afforded α-diketones and the cleavage between the RCOS group and the alkyl R′ group afforded thiocarboxylic acids selectively.

1. Introduction

Reductive coupling of carboxylic acid derivatives constitutes a powerful method of C–C bond formation. In this context, the chemical reductive coupling of acid chlorides and acid cyanides (RCOCl, RCOCN) mediated by SmI_2 has been reported to selectively promote α-diketone formation in good yields.[1,2] For less activated esters, the use of alkali metals for their reductive coupling is well known and leads mainly to the acyloin condensation.[3]

Electrochemistry has been reported as an interesting alternative for the synthesis of α-diketones in good yields from the samarium-catalysed reductive coupling involving aromatic esters.[4] This methodology avoids the use of dangerous alkali metals and of other stoichiometric reducing agents. However, aliphatic esters remain very difficult to reduce either by chemical or by electrochemical methods because of their low reduction potentials (around −3.0 V vs SCE).[5] Their reduction generally affords an unselective reaction providing a variety of products such as carboxylic acids, aldehydes, alcohols or ethers.[5] An electrochemical system based on the use of magnesium as anode and cathode in THF with lithium perchlorate as the supporting electrolyte has been reported to promote aliphatic α-diketone formation from aliphatic esters in moderate to good yields but with low faradic efficiencies (<40%).[6]

The thioester functionality, as compared to esters, is more easily reduced and can be considered as a good alternative to examine the reductive coupling of such carboxylic acid derivatives. A few studies report on the electroreduction of thioesters with a carbonyl-sulfur cleavage reaction of the RCOSR′ group to afford a thiolate anion and an acyl radical.[7–10] The aromatic acyl radical could be further trapped intramolecularly by a reaction on a double bond in a nickel-catalysed reaction,[8] or couple to afford diarylacetylene[11] or rearranged compounds.[12] To our knowledge, no study involving the electroreductive homocoupling of thioesters has yet been reported. We present here our results on the electrochemical reduction of a series of aliphatic and aromatic thioesters and on the influence of the thioester substitution on the observed reactivity and on the product selectivity.

2. Results and discussion

2.1. Cyclic voltammetry studies

Different aliphatic and aromatic thioesters **1a–1k** were prepared in 74–86% yields from the corresponding carboxylic acids and the thiols using the Steglich method (DCC/DMAP).[13] The different thioesters were chosen in order to get all the possible combinations of alkyl and aryl substituents (ArCOSAlk, ArCOSAr′, AlkCOSAr, AlkCOSAlk′). Two bis-thioesters **1d** and **1k** were also considered in order to better examine the possibilities of an intramolecular reductive cyclisation.

The reduction potentials of four selected thioesters **1b**, **1g**, **1h** and **1i** are summarised in Table 1. Irreversible reduction peaks were obtained by cyclic voltammetry, as presented in Figure 1. Important variations in the reduction potentials,

Keywords: Thioesters; Electroreductive homocoupling; α-Diketone; Thioacids.
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Table 1. Reduction potentials of different thioesters in DMF, n-Bu_4NBF_4 (0.1 M) at 25 °C

	Thioesters	E (V) versus Ag/AgCl
1b	n-PrCOSMe	−2.7
1g	n-BuCOSPh	−2.3
1h	PhCOSEt	−1.9
1i	PhCOSTol	−1.8

from −1.8 to −2.7 V versus Ag/AgCl were observed, according to the nature of the substituents.

In the case of thioesters **1g**, **1h** and **1i**, an oxidation peak was observed at around −0.5 V versus Ag/AgCl. This oxidation peak could be attributed to the oxidation of the RS^- moieties, formed from the reductive cleavage of the thioester groups, according to the reported thiolate oxidation by Sawyer.[14]

2.2. Preparative-scale electrolyses

Preparative-scale electroreductions were carried out with compounds **1a–k** (0.08 M) in freshly distilled DMF solution, in a single-compartment cell in the presence of a magnesium anode and a carbon fibre cathode, under a nitrogen atmosphere. Lithium perchlorate ($LiClO_4$, 0.04 M) was used as the supporting electrolyte. Different C–C coupling products such as α-diketones **2** and α-ketols **3** were obtained, as well as cleavage compounds such as thioacids **4**, amides **5** and carboxylic acids **6** (Scheme 1).

α-Diketones **2** and α-ketols **3** are issued from the reductive coupling of the acyl moiety of the reduced thioesters, with loss of the thiolate groups (RS^-). Since α-diketones are more easily reduced than the starting thioesters, compounds **2** can be reduced to the corresponding α-ketols **3** in situ.

The reduction of **1** can also occur with the cleavage of the S–R′ bond to afford the thioacids **4** after hydrolysis. The thioacids were analysed as their corresponding methyl esters after in situ esterification of the crude reaction mixtures with methyl iodide for ease of analysis. The thiolates (RS^-) present in the reaction medium were also converted into the corresponding methyl sulfides by this treatment.

The amides **5** were formed as the major products in some electrolyses. The formation of **5** can be issued from a coupling reaction involving the solvent, DMF.

In some reactions we could also identify the presence of carboxylic acids **6** in low ratios. The presence of carboxylic acids from the electroreduction of aryl thioesters has already been reported,[7] the authors claiming their formation by the presence of dioxygen. The formation of carboxylic acids was a non-expected process in our case because the electrolyses were run under a nitrogen atmosphere and with a degassed DMF solution, in order to avoid the presence of dioxygen.

Table 2 summarises the results obtained in the electroreduction of thioesters **1a–1i**.

We first examined the reactivity of aliphatic thioesters AlkCOSAlk′ such as **1a–1d**. The electroreduction of ethyl thioheptanoate **1a** led after 2.2 F to a complete conversion with the formation of the thioacid **4a** as the main compound in 78% yield (isolated as methyl thioheptanoate after methylation with MeI), together with minor amounts of α-diketone **2a** (5%) and α-ketol **3a** (4%). The S–Et cleavage reaction leading to **4a** was very selectively favoured when compared with the CO–S cleavage leading to the C–C coupling reaction of the acyl moiety to afford **2a** or **3a**. The ratio between S–Alk′ cleavage versus C–C coupling was of 90/10.

The reactivity of methyl thiobutyrate **1b** and ethyl 10-thioundecenoate **1c** was similar to that observed for **1a** and afforded also selectively the thiocarboxylic acids **4b** and **4c**

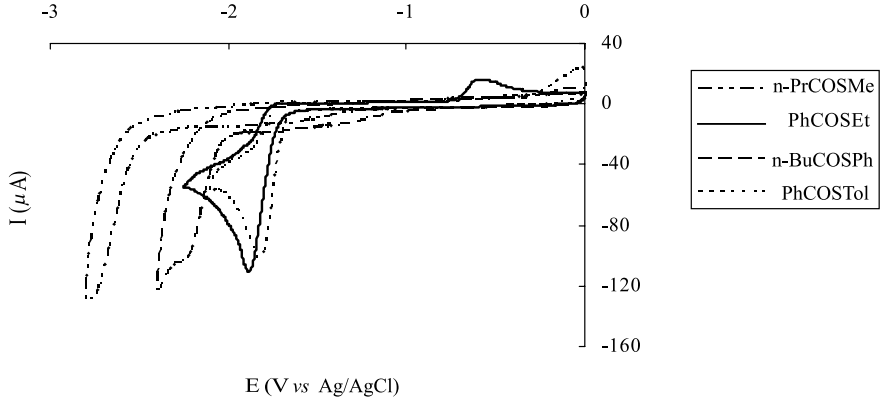
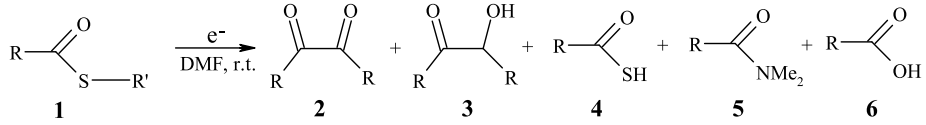


Figure 1. Cyclic voltammograms of different thioesters (5 mM) at a glassy carbon electrode in DMF (n-Bu_4NBF_4 0.1 M) at 25 °C, scan rate = 100 mV s^{-1}.



Scheme 1.

Table 2. Electroreduction of thioesters **1a–i** in DMF/$LiClO_4$ solutions[a]

	Thioester	F	Diketone **2** (%)	Ketol **3** (%)	Thioacid **4** (%)	Amide **5** (%)	Carboxylic acid **6** (%)
1a	*n*-HexCOSEt	2.2	5	4	78	4	—
1b	*n*-PrCOSMe	2.2	5	Trace	53	—	9
1c	CH_2:$CH(CH_2)_8$COSEt	2.7	3	—	74	5	10
1d	EtSCO$(CH_2)_3$COSEt	4.2	—	Trace	71	5	8
1e	*n*-HexCOSTol[b]	2.3	—	—	—	32	—
1f	C_9H_{19}COSPh[b]	2.3	—	—	—	32	—
1g	*n*-BuCOSPh[b]	2.1	—	—	—	28	—
1h	PhCOSEt	2.1	63	20	—	—	5
1i	PhCOSTol[b]	2.1	59	20	—	—	3

[a] Yields determined by ^1H NMR and by the mass balance of the extracted crude mixtures.
[b] Quantitative formation of TolSMe or PhSMe was observed after electrolysis and methylation (K_2CO_3/MeI, DMF) of the reaction medium.

in 53 and 74% yields, respectively issued from the S–Alk′ cleavage process. In the case of **1c**, the presence of a terminal double bond on the aliphatic chain did not allow the formation of any intramolecular radical cyclisation products or intermolecular reaction indicating that an anionic intermediate $AlkCOS^-$ was most possibly formed.

In order to favour the possibility of an acyl C–C homocoupling with aliphatic AlkCOSAlk′ type thioesters by an intramolecular reaction, the electroreduction of the bis-thioester **1d** was examined. This compound was expected to form the 5-membered ring cyclopentane-1,2-diketone **2d** or the corresponding ketol **3d**. However, the electrolysis of **1d** led, after 4.2 F, mainly to the bis-thioacid **4d** in 71% yield. No formation of the α-diketone or of the α-ketol could be observed.

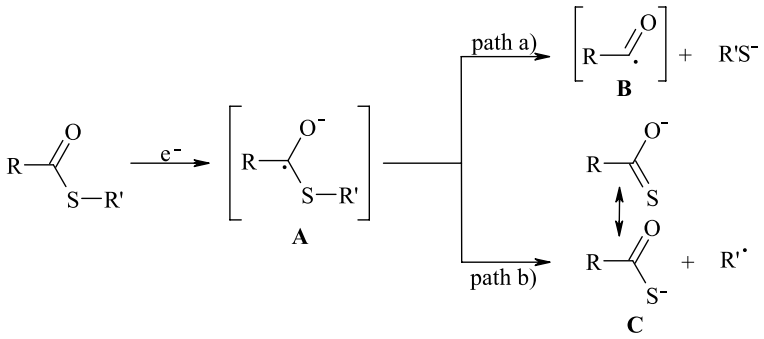
In order to evaluate if these thioacids could be isolated in good yields as such without further methylation, 10-undecenoic thioacid **4c** was extracted after the electrolysis of **1c** using degassed diethyl ether and it could be isolated in 61% yield. Therefore, the electrochemical transformation of aliphatic thioesters into their corresponding thioacid analogues can constitute a novel alternative method of deprotection. In conventional chemistry, strong acidic (fluorhydric acid, triflic acid),[15] basic[16] or reductive (Na, K)[17] media are usually required for this deprotection.

We then carried out the electroreduction of aryl aliphatic thioesters of type AlkCOSAr such as **1e**, **1f** and **1g**, bearing an aromatic group linked to the S atom in order to disfavour the S–R cleavage process. The electoreduction of these thioesters did not lead to the S–Ar cleavage compounds nor to the coupling products of type **2** and **3**. The only isolated compounds were amides **5e**, **5f** and **5g**, in 32, 32 and 28% yields, respectively. The thiolate moieties that were formed during the electrolysis of **1e**, **1f** and **1g** ($TolS^-$ and PhS^-, respectively) were isolated as methyl aryl sulfides ArSMe after methylation of the crude reaction mixtures in almost quantitative yields. In contrast with the behaviour observed for the aliphatic thioesters **1a–1d**, a chemoselective CO–S cleavage occurred with these AlkCOSAr thioesters **1e–1g**.

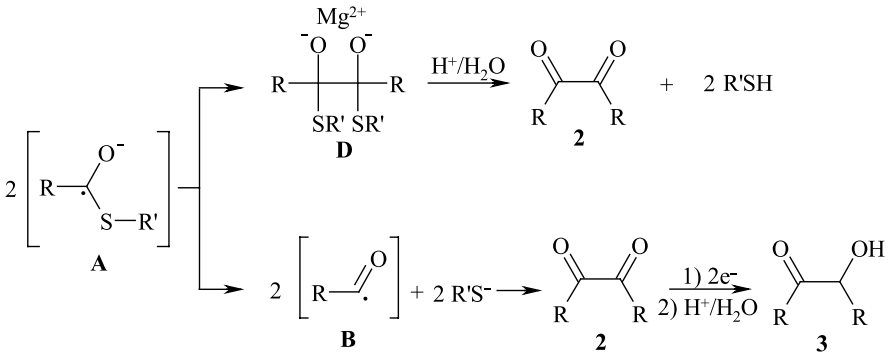
To increase the possibilities of C–C coupling reaction of the acyl moieties, the electrolysis of **1e** was run at a higher concentration (0.32 M instead of 0.08 M). However, the amide **5e** was again obtained in a similar yield.

We further studied the reactivity of aromatic thioesters of type ArCOSAlk and ArCOSAr, such as **1h** and **1i**, respectively. A selective C–C reductive homocoupling of the acyl moieties leading to α-diketones **2h** and **2i** occurred in 63 and 59% yields, respectively. The corresponding α-ketols **3h** and **3i** (20%) were also obtained. In these cases, the reduction selectively involved the CO–S cleavage. No S–Alk or S–Ar cleavage leading to the formation of thioacids **4h** or **4i** was observed.

From a preparative point of view, we can conclude that the products obtained in the electroreduction of thioesters RCOSR′ strongly depend on the aromatic or aliphatic nature of the two substituents R and R′. Upon reduction, the all-aliphatic thioesters AlkCOSAlk′ led selectively to the formation of thioacids involving a S–R′ cleavage reaction. The all-aromatic thioesters ArCOSAr′ led selectively to the formation of α-diketones and α-ketols resulting from the cleavage of the CO–S bond with a further C–C coupling of the acyl moieties. Thioesters of type ArCOSAlk led also to the selective formation of α-diketones and α-ketols by the same process. Thioesters of type AlkCOSAr led to the



Scheme 2.



Scheme 3.

formation of amides resulting from a reaction with DMF and involving the CO–S selective reductive cleavage.

2.3. Mechanistic considerations

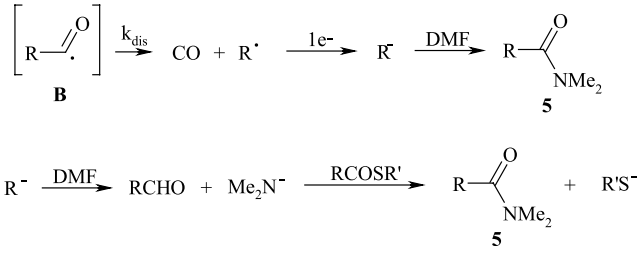
The study of the reactivity of the differently substituted thioesters RCOSR′ indicated that the first one-electron reduction of the thioester group was followed by two different main pathways. Both CO–S and S–R′ cleavage processes should be considered from a first common radical anion intermediate **A** (Scheme 2). Following path (a), the cleavage between the carbonyl moiety and the SR′ group takes place, to form an acyl radical **B** and a thiolate anion. Such a process has already been described by Webster et al. in the case of aromatic thioesters.[7]

Following path (b), the cleavage of the radical anion **A** occurs between the RCOS moiety and the R′ group. The generated R′ radicals can be further reduced and protonated to R′H, or dimerised. The thionocarboxylate and the thiocarboxylate species **C** are in equilibrium. After hydrolysis, the thiocarboxylic acids **4** are formed. In order to indirectly confirm the formation of R′ species, the electroreduction of dodecyl thioacetate **1j** ($CH_3COSC_{12}H_{25}$) was carried out. At the end of the electrolysis, dodecane as well as a low amounts of tetracosane ($C_{24}H_{50}$) were obtained in 80% yield. This result confirmed that AlkCOSAlk′ type thioesters were reduced following path (b) in Scheme 2.

Considering the formation of the different products **2**–**6**, the formation of C–C coupling compounds **2** and **3** should follow pathway (a) of Scheme 2. The formation of α-diketones **2** can be explained from the homocoupling of two acyl units **B**. If α-diketones **2** are formed in the electrolysis medium, they should be rapidly reduced, because of their low reduction potentials,[18] and ketols **3** should be obtained after hydrolysis (Scheme 3). Alternatively, the direct homocoupling of the radical anion **A** should also lead to **2**. In this last case, as shown in Scheme 3, a dithio dialcoolate **D** can be formed and trapped as a magnesium diolate in the presence of Mg^{2+} ions issued from the consumable Mg anode. In the hydrolysis step, the α-diketones **2** and the corresponding thiols are formed.

The formation of thioacids **4** can be explained by path (b) in Scheme 2. The hydrolysis of **C** affords directly thioacids **4** and the treatment of the crude electrolysis mixture with MeI yields the corresponding methyl thioesters.

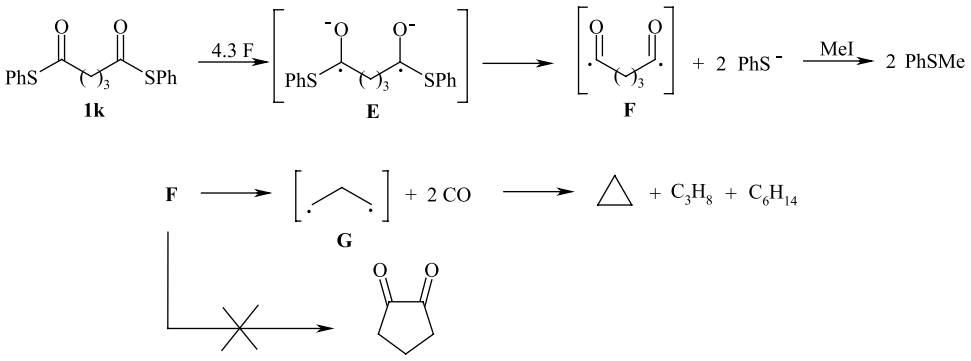
To explain the formation of amides **5** obtained in particular for RCOSAr type thioesters, the reaction with the DMF solvent has to be considered. When R is an aliphatic group, the acyl radicals **B** are highly unstable. These aliphatic acyl radicals have been reported to have half-lifes of about 10^{-5}–10^{-6} s at 298 K,[19] and to decompose thermally with loss of carbon monoxide to form an alkyl radical R˙. In the electrolytic medium, the R˙ radicals or the R^- anion issued from the reduction of R˙ could react with DMF or its reduced species to afford, the corresponding amides **5**, according to Scheme 4. There is some literature evidence that amides can be formed from DMF in the presence of R^- nucleophiles, in a redox process.[20] Alternatively, the reaction of R^- with DMF can lead to the aldehyde and Me_2N^-, which could form the corresponding amide **5** with the starting thioester (Scheme 4).



Scheme 4.

To get some more insight into the reactivity of RCOSAr type thioesters, the electroreduction of the bis-thioester **1k** was carried out (Scheme 5). Complete conversion of **1k** was attained after 4.3 F. The treatment of the crude reaction mixture with MeI led to the isolation of only methyl phenyl sulfide. No cyclic α-diketone **2j** issued from intermediates **E** or **F** was obtained. A rapid decarbonylation of **F** leading to a propyl diradical **G** and further cyclisation, dimerisation, reduction and/or protonation affording volatile hydrocarbons could explain the observed results. No amide function was identified in ^1H or ^{13}C NMR experiments and thus the formation of hydrocarbons issued from **G** seems to be favoured.

The carboxylic acid **6** was obtained as a minor by-product in 3–10% yields in some reactions. Its formation probably



Scheme 5.

involves the reaction of the intermediate acyl radical **B** with dioxygen or with $O_2^{\cdot -}$ as it has already been proposed.[7,21]

For AlkCOSAlk′ type thioesters **1a–d** and **1j**, thioacids were selectively obtained by the cleavage of the S–Alk′ bond following path (b) of Scheme 2. AlkCOSAr type thioesters such as **1e**, **1f** and **1g** presented a different reactivity, which could be explained by a first AlkCO–SAr cleavage according to path (a) in Scheme 2 and further decarbonylation and reaction with DMF (Scheme 4). A selective CO–S cleavage occured also with ArCOSAlk and ArCOSAr′ type thioesters such as **1h** and **1i**. However, in these cases, the aromatic acyl radical of type **B** is stable enough to undergo dimerisation to **2** and/or **3**. The decarbonylation and further reaction with DMF did not occur. Table 3 summarises the results obtained in the different electrolyses, from the point of view of the selectivity of the CO–S versus S–R′ cleavage, for example, path (a) or b) followed by the first formed radical anion **A** in Scheme 2.

Table 3. Cleavage between the carbonyl group and the SR′ group versus cleavage between the RCOS group and the R′ group in the electroreduction of different RCOSR′ thioesters[a]

	Thioester	Cleavage RCO-SR′ versus RCOS-R′	Main product type
1a	*n*-HexCOSEt	22:78	RCOSH
1b	*n*-PrCOSMe	26:74	
1c	CH_2:$CH(CH_2)_8COSEt$	22:78	
1d	$EtSCO(CH_2)_3COSEt$	15:85	
1j	$CH_3COSC_{12}H_{25}$	15:85	
1e	*n*-HexCOSTol	100:—	$RCONMe_2$
1f	$C_9H_{19}COSPh$	100:—	
1g	*n*-BuCOSPh	100:—	
1k	$PhSCO(CH_2)_3COSPh$	100:—	
1h	PhCOSEt	100:—	RCOCOR
1i	PhCOSTol	100:—	

[a] The ratio of cleavage between the carbonyl group and the SR′ group was obtained by adding the yields of diketone **2**, ketol **3**, amide **5** and carboxylic acid **6** or by using R′SMe yields. The ratio of cleavage between the RCOS group and the R′ group was obtained according to the yields of thioacid **4**.

Table 3 clearly indicates that 'all-aliphatic' thioesters of type AlkCOSAlk′ (**1a–d** and **1j**) undergo a selective S–Alk′ cleavage reaction, with selectivities of around 80%. In contrast, all the other thioesters possessing one or two aryl groups such as **1e–1i** and **1k** react exclusively through the cleavage of the CO–S bond, following path (a) in Scheme 2. The intermediates formed (**B**, **D**, **E** or **F**) can then evoluate depending on their stability and on the reaction conditions, affording either an amide (**1e–g**) or an α-diketone (**1h–i**).

3. Conclusion

In conclusion, the electroreduction of thioesters may lead to highly regioselective cleavages depending on the nature of the different substituents. In the case of ArCOSAlk substrates, their electroreduction can constitute an alternative method of C–C bond formation to provide aromatic α-diketones and α-ketols. The electrochemical method can also selectively afford aliphatic thioacids from aliphatic thioesters in good yields. Finally, upon electroreduction in DMF, thioesters of type AlkCOSAr undergo chemoselective process affording the corresponding $AlkCONMe_2$ amides.

4. Experimental

4.1. Cyclic voltammetry

Cyclic voltammetry measurements were conducted with a potentiostat/galvanostat EG&G model 273A using a three electrode arrangement at room temperature. The auxiliary electrode consisted of a Pt wire and the working electrode was a glassy carbon disc. Ag/AgCl was used as the reference electrode. Freshly distilled DMF was used as the solvent and tetrabutyl ammonium tetrafluoroborate *n*-Bu_4NBF_4 (0.1 M) as the supporting electrolyte.

4.2. Typical procedure for the electroreduction of thioesters

In a typical procedure, a single-compartment cell containing carbon fiber as the circular cathode and magnesium rod as the sacrificial anode was purged with nitrogen. $LiClO_4$ (1 mmol), freshly distilled DMF (25 mL) and the thioester (2 mmol) were added. The mixture was then degassed with nitrogen. The electrolysis was run at 60 mA under constant intensity (current density of 0.3 A/dm^2) and was followed by gas chromatography. After the total conversion of the starting thioester, usually around 2.2 F, the crude mixture was transferred under nitrogen to a Schlenk containing potassium carbonate (2 mmol). Methyl iodide (4 mmol) was added and the mixture was heated at 40 °C overnight. The reaction mixture was quenched with HCl 1 M and extracted

with diethyl ether. The organic layers were washed with water, dried with $MgSO_4$ and the solvent was evaporated. The products were analysed by GC, mass spectrometry and NMR and the data were compared with authentic samples.

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Incorporation of an indole-containing diarylbutylamine pharmacophore into furo[2,3-*a*]carbazole ring systems

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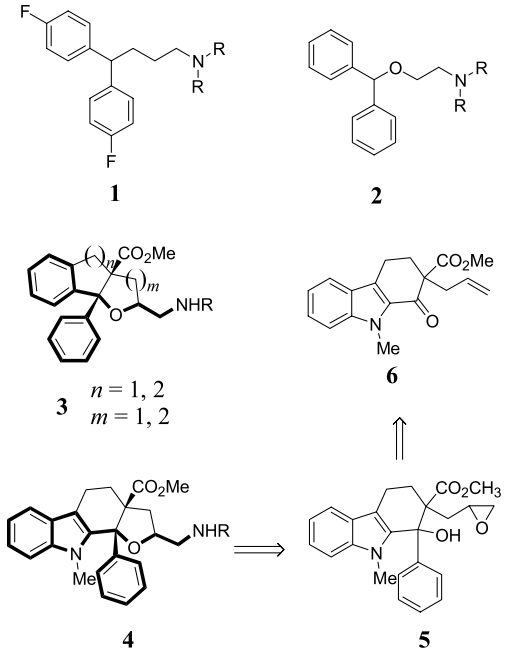
Abstract—Due to concurrent oxidation of the indole moiety in the starting carbazole alkenol, an epoxidation route aiming at incorporation of a conformationally constrained diarylbutylamine failed to give the desired furo[2,3-*a*]carbazole ring system. Instead, an indole epoxide intermediate was generated, which underwent rearrangement involving participation of a vicinal OH group. The required furo[2,3-*a*]-carbazole could, however, be accessed via a Hg^{2+}-induced cyclisation of a carbazole alkynol.

1. Introduction

Recently, we reported the synthesis of various indeno-[1,2-*b*]furan, indeno[1,2-*b*]pyran, naphtho[1,2-*b*]furan and benzo[*h*]chromene ring systems **3** encompassing a conformationally constrained diarylbutylamine pharmacophore.[1] This is a general approach for improving the binding affinity and selectivity of neurotransmitter ligands to receptor molecules. Specifically, these compounds can be viewed as constrained analogues of dopamine receptor ligands **1** and the antihistamine difenhydramine **2**.[2–4]

Since the indole moiety is an essential feature of many bioactive molecules, we conceived target structures of furo[2,3-*a*]carbazole[5] type **4** as constrained analogues of 2-indolylbutylamines. Similar to the strategy used for the synthesis of tricycic compounds **3**, our present approach (Scheme 1) involves regioselective opening of the epoxide ring in precursor **5** by the tertiary alcohol centre. This precursor in its turn may be derived from the 2-alkenyl substituted β-keto-ester **6** via sequential Grignard reaction and epoxidation.



Scheme 1.

2. Results and discussion

Our synthetic approach required the preparation of the carbazole alkenol precursor **12** (Scheme 2). An acid-catalysed ring closure of 3-indolebutyric acid afforded the six-membered ring ketone **8**,[6] which was *N*-methylated to give compound **9**.[7,8] β-Keto ester **10** was prepared by treatment of **9** with potassium hydride and dimethyl carbonate.[9] Subsequent allylation gave the 2-allyl-1-oxo-1*H*-carbazole-2-carboxylate **11**, which was submitted to a Grignard reaction with freshly prepared PhMgBr. Following chromatographic purification alcohol **12** was isolated as the major diastereoisomer with a d.e. of 46%.

Keywords: Heterocyclic compounds; Epoxidation; Indole; Bromocyclisation.
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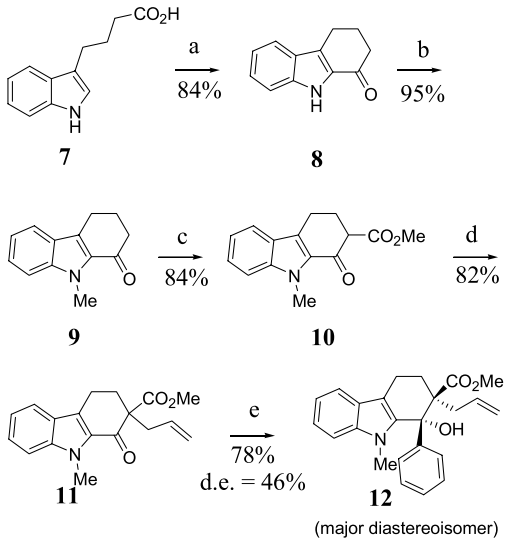


Scheme 2. Reagents and conditions: (a) PPA, toluene, 110 °C; (b) KOH, MeI, acetone; (c) KH, $(CH_3O)_2CO$, reflux; (d) NaH, allyl bromide, DMF; (e) PhMgBr, THF, −78 °C.

A NOESY analysis of **12** reveals a *trans*-diaxial orientation of the phenyl and allyl groups. NOEs are observed between H-2′ of the allyl group and both H-3eq and H-4ax. Proton H-1′b shows a NOE with H-4ax, while H-1′a correlates with the tertiary alcohol proton (see geometrically optimised conformation, Fig. 1). These findings confirm the (Ph, allyl) *trans*-diaxial relation of the major product, in agreement with our previous report regarding the diastereoselectivity of the Grignard reaction in similar systems.[10]

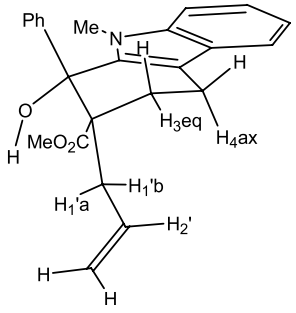
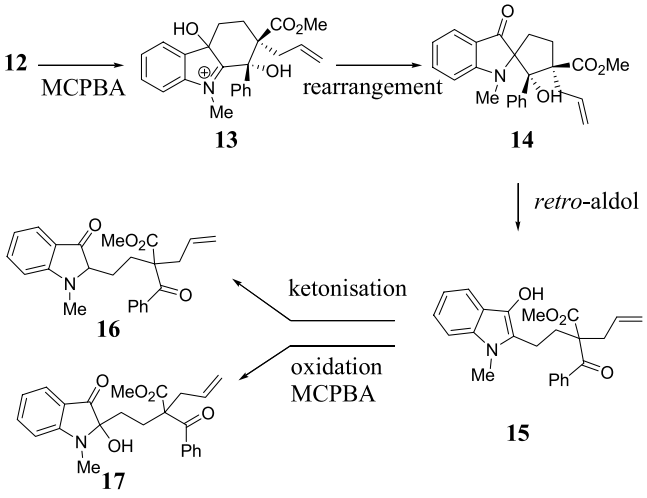


Figure 1. Geometrically optimised conformation of **12**.

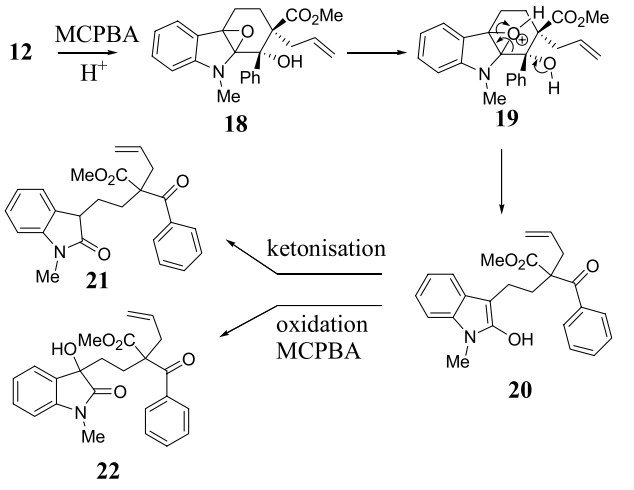
Alkenol **12** was submitted to reaction with *m*-chloroperbenzoic acid (MCPBA) but the two major products isolated from the reaction mixture clearly were not the expected epoxide or ring-closed product. Indeed, tetrahydrocarbazole derivatives have been reported to give 2,2-spiro-annulated 3-indolone products upon oxidation with MCPBA. Apparently, these 3-indolones are generated via a pinacol-type rearrangement, which involves a ring contraction of the 3-hydroxyindolium intermediate.[11]

Initially, we assumed that hydroxylation at the 3-position of the indole moiety of **12** would trigger a similar rearrangement of the cation intermediate **13** to form the spiro product **14** (Scheme 3). For both compounds the presumed spiro structure, however, was refuted based on the observation of three carbonyl signals in each of the ^{13}C NMR spectra. This finding suggested the existence of the ring-opened indolone structures **16** and **17**, which could be formed via an acid-catalysed *retro*-aldol reaction of β-hydroxy ketone **14**. The resulting enol intermediate **15** then would be converted into the corresponding ketone **16** or oxidized to yield the 2-OH product **17**.



Scheme 3. Initially suggested course of MCPBA oxidation.

Surprisingly, the HMBC spectra of the two indolone products revealed a correlation between the *N*-methyl protons ($\delta = 3.17$) and one of the carbonyl groups ($\delta = 176.9$). This finding clearly is not consistent with 3-indolone structures **16** and **17**, but rather with the analogous 2-indolone products **21** and **22**. Actually these 2-indolones also may be generated via initial epoxidation of the indole moiety to form epoxide **18** (Scheme 4).



Scheme 4. Actual course of MCPBA oxidation.

A further literature search indeed revealed that both 2- and 3-indolones can be generated upon epoxidation of 2,3-disubstituted indoles.[12–15] Instead of being converted to the stabilised 3-hydroxyindolium ion **13** (see Scheme 3 before), the protonated epoxide intermediate **19** is subject to an alternative ring cleavage process, which is assisted by the vicinal OH group. The resulting enol intermediate **20** is then

converted into the corresponding lactam carbonyl product **21** or can be further oxidized to give the 3-OH product **22**.

At this point we wanted to examine further the mechanistic course of this rearrangement reaction including the role of the vicinal hydroxyl group and the ring size of the ring annulated onto the indole moiety. To this end, cyclopentaindoles **25** and **28** were prepared and submitted to reaction with MCPBA. For compound **25**, one expects a similar OH-assisted epoxide cleavage process as observed for tetrahydrocarbazole **12** (see Scheme 4 before). With the latter compound **28**, however, any assistance by the (non-existent) neighbouring OH-group is precluded, while the rearrangement proceeding by ring contraction of an indolium ion intermediate appears unlikely since this now would produce a highly strained 4-membered spirocycle (Fig. 2).

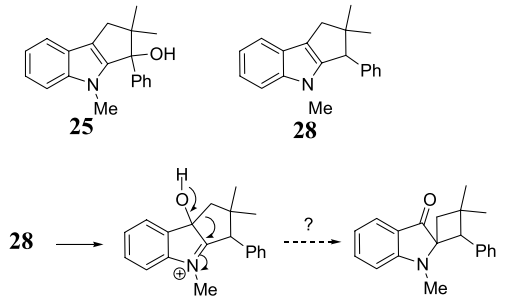
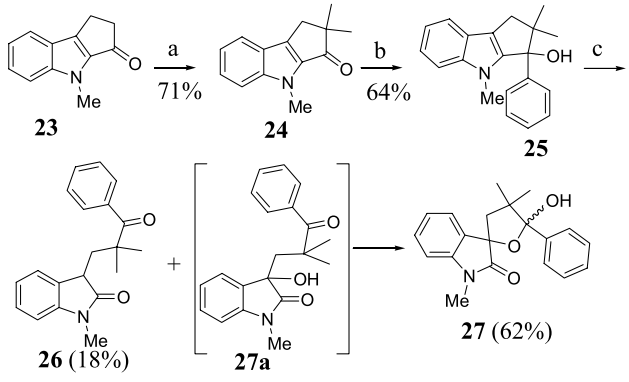


Figure 2. Tetrahydrocyclopentaindole derivatives **25** and **28** and possible outcome of MCPBA oxidation of **28**.

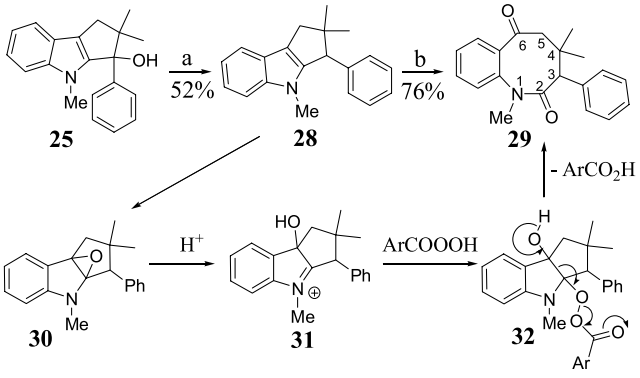
The required tertiary alcohol **25** was synthesised (Scheme 5) by double α-methylation of cyclopentaindolone **23** followed by Grignard reaction on ketone **24**.[9] Subsequent oxidation with MCPBA afforded the 2-indolone product **26** and the spiro-annulated 2-indolone **27**. The 2-indolone structures were confirmed by their HMBC spectra, which again revealed a correlation between the *N*-Me protons and the lactam carbonyl group. This result provides further support to the vicinal OH-assisted epoxide cleavage process depicted in Scheme 4. In this case, further oxidation proceeding at the 3-position of the enolic intermediate intially yields the 3-hydroxy-2-indolone product **27a**, but the γ-hydroxy ketone moiety of **27a** transforms into a five-membered spirocycle to yield two epimeric hemiacetals **27**.



Scheme 5. Reagents and conditions: (a) KH, MeI, DMF, 70 °C; (b) PhMgBr, THF, −78 °C; (c) MCPBA, CH_2Cl_2.

Cyclopentaindole **28** was generated from alcohol **25** by an acid-catalysed dismutation reaction: the benzylic cation produced from **25** (molecular mass 291) is subject to an intermolecular hydride transfer to form the reduced product **28** (CIMS: MH^+ 276) together with an unstable oxidation product (CIMS: MH^+ 290) that was not further characterized.

Compound **28** also was made to react with MCPBA but this reaction resulted in yet another rearrangement affording an 8-membered ring keto lactam, dihydrobenzo[*b*]azocine-2,6-dione **29** (Scheme 6). The latter may be formed by addition of MCPBA to the 3-hydroxyindolium intermediate **31** generated from epoxide **30**, followed by expulsion of *m*-chlorobenzoic acid from adduct **32**. Hence the 3-hydroxyindolium ion **31** generated from cyclopentaindole **28** is unable to form a strained 4-membered spirocycle, in contrast to the carbazole 3-hydroxyindolium ion, which rearranges into a less strained 5-membered spirocycle.[11]



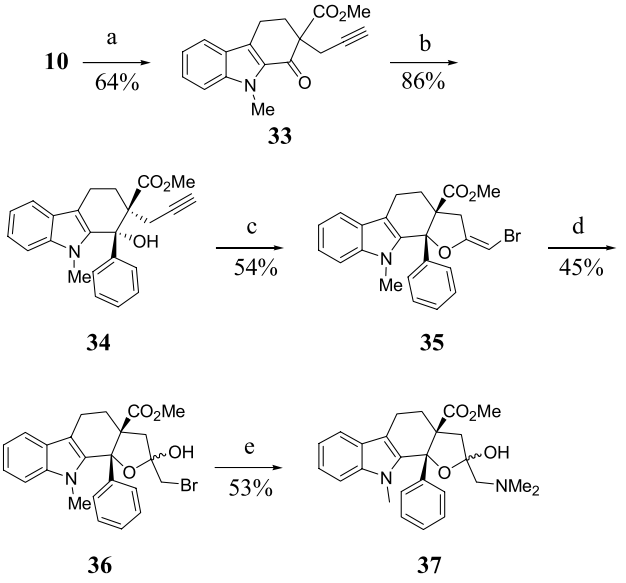
Scheme 6. Reagents and conditions: (a) PTSA, toluene, reflux; (b) MCPBA, CH_2Cl_2.

There is ample precedent for the oxidative cleavage of the indole ring system to form the corresponding keto amide, for example, tryptophan has been converted into a mixture of products which included *N*-formylkynurenine,[16] whereas tetrahydrocarbazole and the octahydroindolo[2,3-*a*]quinolizine ring system afforded the corresponding nine-membered ring keto-lactams.[17,18]

The keto lactam structure of **29** is indicated by two relevant carbonyl signals in the IR (1666, 1596 cm^{-1}) and ^{13}C NMR spectra (δ 198.4, 172.2). The correlations found in the HMBC spectrum confirm the proposed 8-membered keto lactam ring. Thus, amide carbon C-2 (δ=172.2) couples with the protons of the *N*-Me group (δ=3.34) and with H-3 (δ=3.95), while H-3 in its turn correlates with the two Me carbon atoms located on C-4 (δ=25.9 and 26.4) and with C-5 (δ=57.2). Finally, the ketone carbon atom C-6 (δ=198.4) couples with both methylene protons H-5 (δ=3.11 and 2.62).

Turning back to the synthesis of the required furo[2,3-*a*]-carbazole ring system we submitted alkenol **12** to reaction with iodine and $NaHCO_3$ in dichloromethane, but this attempted halocyclisation method also failed. Therefore, a new approach was investigated (Scheme 7), which involved the Hg^{2+}-induced cyclisation[19,20] of the 1-phenyl,

2-propynyl substituted carbazolol **34**. This alkynol starting material was prepared by alkylation of β-keto ester **10** with 3-bromo-1-propyne, followed by a Grignard reaction of **33** with PhMgBr.



Scheme 7. Reagents and conditions: (a) NaH, 3-bromo-1-propyne, HMPA, THF, −10 °C; (b) PhMgBr, THF, −78 °C, d.e.=98%; (c) $HgCl_2$, NBS, DMAP, CH_2Cl_2; (d) PTSA, H_2O, THF, 80 °C; (e) Et_3N, $Me_2NH{\cdot}HCl$, THF/MeOH (2:1).

Alkynol **34** was formed with a very high diastereoisomeric excess (d.e.=98%) and was submitted to reaction with $HgCl_2$, NBS, and DMAP in dichloromethane affording the 2-(bromomethylene) substituted hexahydro-3a*H*-furo[2,3-*a*]-carbazole **35**. In the next step, an acid-catalysed hydration was effected on the enol–ether moiety of hydrofuran compound **35** to give the epimeric cyclic hemiacetals **36**. Final substitution of the hidden α-bromo ketone group with dimethylamine furnished the corresponding epimeric amines **37**.

A NOESY analysis of the epimeric mixture of compounds **36** confirmed their common *cis*-fusion to be expected from the structure of the starting alkynol **34**. The NOESY spectrum indeed revealed a correlation between the protons of the methyl ester and the *ortho*-protons of the phenyl group. This is consistent with a pseudo-equatorial ester and a pseudo-axial phenyl group, in accordance with a geometrically optimised model of **36** (Fig. 3).

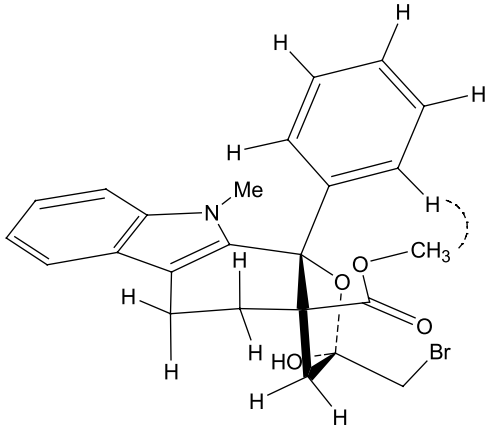


Figure 3. Conformational structure calculated for one epimer of **36** and corresponding NOE interactions.

3. Conclusions

The indole moiety of 2-allyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol **12** appears to be more reactive towards oxidation with *m*-chloroperbenzoic acid than the sidechain allyl group. Consequently, an attempted epoxidation of alkenol **12** was found to result in the formation of an indole epoxide intermediate, which is subject to a further vicinal OH-assisted rearrangement to form the corresponding ring-opened 2-indolone products. The mechanistic course of this rearrangement was checked by studying the MCPBA oxidation of two analogous alkenyl substituted cyclopentaindoles, with and without the neighbouring OH-group.

Finally, we did succeed in the synthesis of the desired furo[2,3-*a*]carbazole ring system encompassing a conformationally constrained diarylalkylamine. This was accomplished by applying a Hg^{2+}-induced cyclisation to alkynol **34**, and by further manipulation of the resulting bromo alkene **35**.

4. Experimental

4.1. General

Infrared spectra were recorded on a Perkin–Elmer 1600 Fourier transform spectrometer. Mass spectra were run using a Hewlett–Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the NMR spectra (δ, ppm) a Bruker AMX 400 and a Bruker Avance 300 spectrometer were used. For column chromatography 70–230 mesh silica 60 (E.M. Merck) was used as the stationary phase. For the synthesis of 2,3,4,9-tetrahydro-1*H*-carbazol-1-one **8**: see Ref. 5, for the synthesis of 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one **9**, methyl 9-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate **10** and 4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one **23** see Ref. 8. Chemicals received from commercial sources were used without further purification. THF was dried with sodium and distilled before use.

4.2. Synthesis of 11 and 12

4.2.1. Methyl 2-allyl-9-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (11). A solution of **10** (1.0 g, 3.4 mmol) in DMF (40 mL) was added to a mixture of sodium hydride (0.32 g, 8 mmol, 60% dispersion in mineral oil) in DMF (30 mL). After stirring at room temperature for 15 min, allyl bromide (0.44 mL, 5 mmol) was added. The reaction mixture was stirred for 3 h, and then water (50 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and

evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 23/2). Yield: 82%; oil; IR (NaCl, cm^{-1}): 1732 (C=O), 1659 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 2.26 (m, 1H, $CH_2CH=CH_2$), 2.95–2.68 (m, 3H, two $H^3+CH_2CH=CH_2$), 3.07 (m, 2H, H^4), 3.72 (s, 3H, OCH_3), 4.08 (s, 3H, NCH_3), 5.16 (d, $J=10$, 1 Hz, 1H, $CH=CH_2$), 5.20 (dd, $J=17$, 1 Hz, 1H, $CH=CH_2$), 5.90 (m, 1H, $CH=CH_2$), 7.16 (t, $J=8$ Hz, 1H, H-arom.), 7.36 (d, $J=8$ Hz, 1H, H-arom.), 7.41 (t, $J=8$ Hz, 1H, H-arom.), 7.64 (d, $J=8$ Hz, 1H, H-arom.); ^{13}C NMR (75 MHz, $CDCl_3$): 19.2, 32.0, 23.7, 39.2, 52.9, 59.1, 110.8, 119.2, 120.7, 121.8, 124.9, 127.4, 127.4, 128.8, 130.0, 134.2, 172.6, 189.0; *m/z* (E.I., %): 297 (22, $M^{\cdot+}$), 226 (5, $M^{\cdot+}-OCH_3$), 256 (98, $M^{\cdot+}-CH_2CH=CH_2$), 224 (100, $M^{\cdot+}-CH_2CH=CH_2$–MeOH); exact mass calculated for $C_{18}H_{19}NO_3$: 297.1365, found: 297.1360.

4.2.2. Methyl 2-allyl-1-hydroxy-9-methyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (12). Bromobenzene (0.64 mL, 6 mmol) was added dropwise to magnesium turnings (0.16 g, 5 mmol) and a crystal of iodine in dry THF (30 mL) under argon. After being refuxed for 60 min, the mixture was cooled down to −78 °C. Then a solution of **11** (0.79 g, 3 mmol) in dry THF (50 mL) was added. After stirring at room temperature for 16 h, NH_4Cl (sat. aq. solution, 50 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 23/2). Yield: 78%, d.e.=46%.

Major isomer methyl (1R,2R*)-2-allyl-1-hydroxy-9-methyl-1-phenyl-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate.* Mp 144–146 °C; IR (KBr, cm^{-1}): 3492 (OH), 1713 (C=O); ^1H NMR (400 MHz, $CDCl_3$): 2.09 (ddd, $J=15$, 6, 2 Hz, 1H, H^3), 2.22 (dddd, $J=15$, 12, 6, 1 Hz, 1H, H^3), 2.58 (dd, $J=14$, 8 Hz, 1H, $CH_2CH=CH_2$), 2.85 (ddd, $J=17$, 12, 6 Hz, 1H, H^4), 2.92 (ddd, $J=17$, 6, 2 Hz, 1H, H^4), 3.11 (ddd, $J=14$, 6, 1 Hz, 1H, $CH_2CH=CH_2$), 3.42 (s, 6H, OCH_3+NCH_3), 4.42 (s, 1H, OH), 5.09 (d, $J=10$ Hz, 1H, $CH=CH_2$), 5.15 (d, $J=16$ Hz, 1H, $CH=CH_2$), 5.68 (m, 1H, $CH=CH_2$), 7.07 (m, 2H, H-arom.), 7.13 (m, 1H, H-arom.), 7.22 (m, 5H, H-arom.), 7.58 (d, $J=8$ Hz, 1H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 16.9, 23.6, 31.2, 36.0, 51.7, 56.6, 77.9, 109.2, 110.4, 118.5, 118.7, 118.9, 121.9, 125.7, 127.2, 127.5, 127.6, 134.3, 134.6, 138.3, 142.3, 175; *m/z* (E.I., %): 375 (100, $M^{\cdot+}$), 343 (13, $M^{\cdot+}-MeOH$), 298 (5, $M^{\cdot+}-H_2O-CO_2CH_3$), 249 (84, $M^{\cdot+}-H_2O-MeOH-HOCO_2CH_3$).

4.3. Synthesis of 21 and 22

MCPBA (0.6 g, 3.47 mmol) was added to a solution of **12** (0.44 g, 1.17 mmol) in dichloromethane (40 mL). After stirring at room temperature for 20 min, Na_2CO_3 (sat. aq. solution, 50 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 1/1) to give 0.10 g of **21** and 0.31 g of **22**.

4.3.1. Methyl 2-benzoyl-2-[2-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)ethyl]-4-pentenoate (21). Mixture of isomers (50/50); yield: 20%; oil; IR (NaCl, cm^{-1}): 1732 (C=O), 1713 (C=O), 1679 (C=O); ^1H NMR (400 MHz, $CDCl_3$): 1.68 (m, 1H, –CH_2–), 2.16–1.81 (m, 3H, –CH_2–), 2.79 (m, 2H, $CH_2CH=CH_2$), 3.16 (s, 1.5H, NCH_3), 3.17 (s, 1.5H, NCH_3), 3.38 (m, 1H, H^3), 3.59 (s, 1.5H, OCH_3), 3.61 (s, 1.5H, OCH_3), 4.99 (m, 2H, $CH=CH_2$), 5.52 (m, 1H, $CH=CH_2$), 6.78 (m, 2H, H-arom.), 7.21 (m, 2H, H-arom.), 7.35 (m, 2H, H-arom.), 7.51 (m, 1H, H-arom.), 7.71 (dd, $J=7$, 1 Hz, 1H, H-arom.), 7.77 (dd, $J=7$, 1 Hz, 1H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 24.3, 26.0, 26.1, 27.7, 28.4, 36.8, 36.9, 44.9, 45.0, 52.3, 60.4, 107.8, 107.9, 119.2, 119.3, 122.2, 123.2, 123.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.5, 131.6, 131.8, 132.6, 132.7, 135.6, 135.7, 144.4, 173.1, 173.2, 176.8, 176.9, 196.1, 196.2; *m/z* (E.I., %): 391 (18, $M^{\cdot+}$), 360 (2, $M^{\cdot+}-OCH_3$), 105 (100, C_6H_5CO), 77 (44, $C_6H_5^+$); exact mass calculated for $C_{24}H_{25}NO_4$: 391.1784, found: 391.1780.

4.3.2. Methyl 2-benzoyl-2-[2-(3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)ethyl]-4-pentenoate (22). Yield: 64%; oil; IR (NaCl, cm^{-1}): 3331 (OH), 1739 (C=O), 1698 (C=O), 1672 (C=O); ^1H NMR (400 MHz, $CDCl_3$): 1.70 (m, 1H, –CH_2–), 2.01–1.78 (m, 3H, –CH_2–), 2.74 (d, $J=7$ Hz, 2H, $CH_2CH=CH_2$), 3.14 (s, 3H, OCH_3), 3.57 (s, 3H, NCH_3), 4.90 (d, $J=17$ Hz, 1H, $CH=CH_2$), 4.95 (d, $J=10$ Hz, 1H, $CH=CH_2$), 5.39 (m, 1H, $CH=CH_2$), 6.81 (d, $J=7$ Hz, 1H, H-arom.), 7.06 (t, $J=7$ Hz, 1H, H-arom.), 7.32 (m, 4H, H-arom.), 7.48 (t, $J=7$ Hz, 1H, H-arom.), 7.71 (dd, $J=7$, 1 Hz, 2H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 25.8, 26.2, 32.2, 36.9, 52.3, 60.1, 76.1, 108.6, 119.4, 123.1, 123.7, 128.1, 128.5, 129.4, 129.7, 130.1, 131.4, 132.8, 133.2, 135.6, 143.3, 173.0, 177.8, 195.9; *m/z* (E.I., %): 407 (17, $M^{\cdot+}$), 389 (1, $M^{\cdot+}-H_2O$), 159 (43, $C_{12}H_{15}^+$), 105 (100, $C_6H_5CO^+$), 77 ($C_6H_5^+$); exact mass calculated for $C_{24}H_{15}NO_5$: 407.1733, found: 407.1730.

4.4. Synthesis of 24 and 25

4.4.1. 2,2,4-Trimethyl-1,4-dihydro-2*H*-cyclopenta[*b*]-indol-3-one (24). A solution of **23** (3 g, 16.2 mmol) in DMF (30 mL) was added to a mixture of potassium hydride (35% dispersion in mineral oil, 5.6 g, 48.6 mmol) in DMF (20 mL) at 0 °C. After stirring at room temperature for 15 min, MeI (3.0 mL, 48.6 mmol) was added dropwise. The reaction mixture was stirred at 70 °C for 2 h, then ice water (50 mL) was added. The aqueous layer was extracted three times with diethyl ether. The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 23/2). Yield: 71%; mp 64–65 °C; IR (KBr, cm^{-1}): 1676 (CO); ^1H NMR (400 MHz, $CDCl_3$): 1.33 (s, 6H, $2\times CH_3$), 2.96 (s, 2H, H^1), 3.94 (s, 3H, NCH_3), 7.19 (ddd, $J=8$, 7, 1 Hz, 1H, H-arom.), 7.05 (m, 2H, H-arom.), 7.68 (dd, $J=8$, 1 Hz, 1H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 26.2, 30.5, 36.9, 52.0, 110.4, 111.3, 120.5, 122.2, 123.6, 125.7, 127.1, 137.3, 141.6, 145.6, 200.6; *m/z* (E.I., %): 213 (100, $M^{\cdot+}$), 198 (72, $M^{\cdot+}-CH_3$), 184 (18, $M^{\cdot+}-CHO$), 181 (14, $M^{\cdot+}-CH_3O$), 170 (16, $M^{\cdot+}-CH_3$–CO), 144 (22, $C_{10}H_{10}N^+$); exact mass calculated for $C_{14}H_{15}NO$: 213.1154, found: 213.1163.

4.4.2. 2,2,4-Trimethyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol (25). Bromobenzene (0.52 mL, 4.9 mmol) was added dropwise to magnesium turnings (0.15 g, 4.4 mmol) and a crystal of iodine in dry THF (10 mL) under argon. After being refluxed for 60 min, the mixture was cooled down to −78 °C. Then a solution of **24** (0.6 g, 2.8 mmol) in dry THF (20 mL) was added. After stirring at room temperature for 16 h, NH_4Cl (sat. aq. solution, 50 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 23/2). Yield: 64%; mp 121–129 °C; IR (KBr, cm^{-1}): 3521 (OH), 2659 (CH_2); ^1H NMR (300 MHz, $CDCl_3$): 0.90 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.30 (s, 1H, OH), 2.84 (d, $J=15$ Hz, 1H, H^1), 2.94 (d, $J=15$ Hz, 1H, H^1), 3.58 (s, 3H, NCH_3), 7.49–7.24 (m, 8H, H-arom.), 7.70 (d, $J=8$ Hz, 1H, H-arom.); ^{13}C NMR (75 MHz, $CDCl_3$): 25.1, 28.3, 31.0, 39.3, 54.2, 85.3, 110.4, 118.8, 119.8, 120.2, 122.1, 124.5, 127.0, 127.7, 128.4, 142.1, 142.5, 146.2; *m/z* (E.I., %): 291 (65, $M^{\cdot+}$), 273 (21, $M^{\cdot+}-H_2O$), 258 (11, $M^{\cdot+}-H_2O$–CH_3), 248 (100, $M^{\cdot+}-C_3H_7$), 231 (17, $M^{\cdot+}-C_3H_8O$), 77 (13, $C_6H_5^+$); exact mass calculated for $C_{20}H_{21}NO$: 291.1623, found: 291.1656.

4.5. Synthesis of 26 and 27

MCPBA (0.18 g, 1.02 mmol) was added to a solution of **25** (0.10 g, 0.34 mmol) in dichloromethane (10 mL). After stirring at room temperature for 20 min, Na_2CO_3 (sat. aq. solution, 10 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 3/22) to give 0.019 g of **26** and 0.068 g of **27**.

4.5.1. 3-(2,2-Dimethyl-3-oxo-3-phenylpropyl)-1-methyl-1,3-dihydroindol-2-one (26). Yield: 18%; mp 95–97 °C; IR (KBr, cm^{-1}): 2987 (CH_2), 1715 (CO), 1613 (CO); ^1H NMR (400 MHz, $CDCl_3$): 1.49 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.28 (dd, $J=19$, 6 Hz, 1H, CH_2), 2.51 (dd, $J=19$, 9 Hz, 1H, CH_2), 3.19 (s, 3H, NCH_3), 3.48 (dd, $J=9$, 6 Hz, 1H, H^3), 6.80 (d, $J=10$ Hz, 1H, H-arom.), 7.03 (t, $J=10$ Hz, 1H, H-arom.), 7.25 (m, 2H, H-arom.), 7.42 (m, 3H, H-arom.), 7.66 (2×d, $J=9$ Hz, 2H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 26.6, 26.7, 27.8, 41.6, 43.0, 47.8, 108.2, 122.8, 124.9, 128.2, 128.3, 128.4, 130.2, 131.1, 139.5, 144.5, 178.5, 209.4; *m/z* (E.I., %): 307 (8, $M^{\cdot+}$), 267 (16, $M^{\cdot+}-C_2O$), 201 (23, $M^{\cdot+}-C_6H_5COH$), 160 (91, $M^{\cdot+}-H_2CO$–C_6H_5CO), 105 (100, $C_6H_5CO^+$), 77 (56, $C_6H_5^+$).

4.5.2. Spiro compound 27. Mixure of isomers (60/40); yield: 62%; mp 136–140 °C; IR (KBr, cm^{-1}): 3398 (OH), 2960 (CH_2), 1703 (CO); ^1H NMR (400 MHz, $CDCl_3$): 0.99 (s, 1.2H, CH_3), 1.08 (s, 1.8H, CH_3), 1.34 (s, 1.8H, CH_3), 1.38 (s, 1.2H, CH_3), 2.20 (d, $J=13$ Hz, 0.4H, CH_2), 2.38 (d, $J=13$ Hz, 0.6H, CH_2), 2.67 (d, $J=13$ Hz, 0.6H, CH_2), 2.71 (d, $J=13$ Hz, 0.4H, CH_2), 2.22 (s, 1.8H, NCH_3), 3.23 (s, 1.2H, NCH_3), 6.80 (d, $J=8$ Hz, 0.6H, H-arom.), 6.88 (d, $J=8$ Hz, 0.4 H, H-arom.), 7.09 (t, $J=7$ Hz, 0.6H, H-arom.), 7.19 (t, $J=7$ Hz, 0.4H, H-arom.), 7.32–7.43 (m, 4H, H-arom.), 7.54–7.76 (m, 3H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 23.3, 23.4, 26.7, 27.0, 27.4, 28.9, 48.5, 49.1, 49.4, 50.0, 82.4, 83.4, 108.4, 109.4, 110.8, 111.1, 123.7, 124.3, 125.2, 125.8, 126.4, 127.2, 127.7, 127.9, 128.0, 128.1, 128.2, 128.7, 129.8, 130.4, 130.6, 132.7, 139.9, 140.7, 144.0, 144.1, 172.3, 177.1, 180.5; *m/z* (E.I., %): 323 (13, $M^{\cdot+}$), 267 (58, $M^{\cdot+}-2\times CO$), 201 (61, $M^{\cdot+}-C_6H_5CO_2$), 105 (100, $C_6H_5CO^+$), 77 (50, $C_6H_5^+$).

4.6. Synthesis of 28 and 29

4.6.1. 2,2,4-Trimethyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole (28). PTSA (0.6 g, 0.3 mmol) was added to a solution of **25** (0.19 g, 0.7 mmol) in toluene (10 mL). The reaction mixture was refluxed for 1 h and was worked up by addition of water (10 mL). The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 19/1). Yield: 52%; oil; IR (NaCl, cm^{-1}): 2954 (CH_2); ^1H NMR (300 MHz, $CDCl_3$): 0.85 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.75 (d, $J=15$ Hz, H^1), 2.86 (d, $J=15$ Hz, H^1), 3.43 (s, 3H, NCH_3), 4.00 (s, 1H, H^3), 7.36–6.87 (m, 8H, H-arom.), 7.57 (d, $J=7$ Hz, 1H, H-arom.); ^{13}C NMR (75 MHz, $CDCl_3$): 27.3, 31.0, 32.7, 40.4, 50.3, 56.8, 109.9, 117.1, 119.3, 120.6, 150.0, 127.0, 128.7, 129.0, 132.8, 141.2, 141.7, 146.6; *m/z* (E.I., %): 275 (100, $M^{\cdot+}$), 260 (11, $M^{\cdot+}-CH_3$), 232 (56, $M^{\cdot+}-C_3H_7$), 217 (16, $M^{\cdot+}-C_4H_{10}$), 184 (22, $C_{14}H_{14}N$); exact mass calc. for $C_{20}H_{21}N$: 275.1674, found: 275.1680.

4.6.2. 1,4,4-Trimethyl-3-phenyl-4,5-dihydro-1*H*,3*H*-benzo[*b*]azocine-2,6-dione (29). MCPBA (0.047 g, 0.27 mmol) was added to a solution of **28** (0.025 g, 0.09 mmol) in dichloromethane (10 mL). After stirring at room temperature for 20 min, Na_2CO_3 (sat. aq. solution, 10 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate,1/4). Yield: 76%; mp 40–42 °C; IR (KBr, cm^{-1}): 2931 (CH_2), 1666 (CO), 1596 (CO); ^1H NMR (400 MHz, $CDCl_3$): 0.74 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.62 (d, $J=14$ Hz, 1H, CH_2), 3.11 (d, $J=14$ Hz, 1H, CH_2), 3.34 (s, 3H, NCH_3), 3.95 (s, 1H, C*H*Ph), 7.15 (m, 3H, H-arom.), 7.19 (dt, $J=7$, 2 Hz, 1H, H-arom.), 7.36 (dt, $J=7$, 1 Hz, 1H, H-arom.), 7.44 (m, 2H, H-arom.), 7.53 (dt, $J=8$, 2 Hz, 1H, H-arom.), 8.08 (dd, $J=8$, 1 Hz, 1H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 25.9, 26.4, 37.5, 38.9, 53.7, 57.2, 77.9, 127.4, 127.7, 127.9, 128.0, 131.3, 131.8, 134.7, 135.3, 144.7, 172.2, 198.4; *m/z* (E.I., %): 307 (56, $M^{\cdot+}$), 267 (29, $M^{\cdot+}-C_2O$), 201 (32, $M^{\cdot+}-C_6H_5COH$), 189 (89, $M^{\cdot+}-C_6H_5CH_2CO$), 105 (100, $C_6H_5CO^+$), 77 (65, $C_6H_5^+$).

4.7. Synthesis of furo[2,3-*a*]carbazole compounds

4.7.1. Methyl 9-methyl-1-oxo-2-(2-propynyl)-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (33). A solution of **10** (1.3 g, 5 mmol) in THF (30 mL) was added dropwise to a mixture of sodium hydride (60% dispersion in mineral oil, 0.27 g, 6.5 mmol) in THF (30 mL) at −10 °C. After stirring at room temperature for 1 h, HMPA (0.89 mL, 5 mmol) and propargyl bromide (80 wt%, 0.74 mL,

6.5 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, then NH_4Cl (sat. aq. solution, 20 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 22/3). Yield: 98%; mp 88–91 °C; IR (KBr, cm^{-1}): 3270 (C≡CH), 1735.5 (C=O), 1660 (C=O); ^1H NMR (300 MHz, $CDCl_3$): 2.07 (t, $J=3$ Hz, 1H, C≡C*H*), 2.60 (ddd, $J=14$, 10, 6 Hz, 1H, H^3), 2.76 (ddd, $J=14$, 10, 5 Hz, 1H, H^3), 2.96 (d, $J=3$ Hz, 2H, CH_2C≡CH), 3.16 (m, 2H, H^4), 3.72 (s, 3H, OCH_3), 4.09 (s, 3H, NCH_3), 7.18 (dt, $J=7$, 1 Hz, 1H, H-arom.), 7.31 (d, $J=8$ Hz, 1H, H-arom.), 7.44 (dt, $J=7$, 1 Hz, 1H, H-arom.), 7.65 (d, $J=8$ Hz, 1H, H-arom.); ^{13}C NMR (75 MHz, $CDCl_3$): 19.3, 24.9, 32.0, 32.8, 53.2, 58.4, 71.7, 70.4, 110.8, 120.7, 121.9, 124.9, 127.7, 129.4, 129.8, 140.8, 171.8, 187.4; *m/z* (E.I., %): 295 (43, $M^{\cdot+}$), 256 (100, $M^{\cdot+}-C_3H_3$), 236 (12, $M^{\cdot+}-CO_2CH_3$), 224 (88, $M^{\cdot+}-C_3H_3$–MeOH), 197 (21, $M^{\cdot+}-C_3H_3$–CO_2CH_3); exact mass calculated for $C_{18}H_{17}NO_3$: 295.1208, found: 295.1203.

4.7.2. Methyl (1*R,2*R**)-1-hydroxy-9-methyl-1-phenyl-2-(2-propynyl)-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (34).** Bromobenzene (1.77 mL, 17 mmol) was added dropwise to magnesium turnings (0.52 g, 15 mmol) and a crystal of iodine in dry THF (40 mL) under argon. After being refluxed for 60 min, the mixture was cooled down to −78 °C. Then **33** (1.5 g, 5 mmol) in dry THF (40 mL) was added. After stirring at room temperature for 16 h, NH_4Cl (sat. aq. solution, 50 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 23/2). Yield: 86%; mp 36–38 °C; IR (KBr, cm^{-1}): 2943 (OH), 1712 (CO); ^1H NMR (400 MHz, $CDCl_3$): 2.04 (t, $J=3$ Hz, 1H, C≡CH), 2.32 (m, 1H, H^3), 2.50 (ddd, $J=15$, 6, 2 Hz, 1H, H^3), 2.76 (dd, $J=17$, 3 Hz, 1H, CH_2C≡CH), 2.93 (ddd, $J=17$, 11, 6 Hz, 1H, H^4), 3.01 (ddd, $J=17$, 7, 2 Hz, 1H, H^4), 3.34 (ddd, $J=17$, 7, 3 Hz, 1H, CH_2C≡CH), 3.41 (s, 3H, NCH_3), 3.48 (s, 3H, OCH_3), 4.40 (s, 1H, OH), 7.43–7.06 (m, 8H, H-arom.), 7.60 (d, $J=8$ Hz, 1H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 17.1, 22.4, 24.2, 31.2, 52.1, 56.5, 71.0, 77.6, 80.8, 118.8, 119.0, 122.1, 126.9, 127.5, 127.7, 128.3, 128.4, 128.5, 129.7, 132.3, 133.9, 138.3, 141.9; *m/z* (E.I., %): 373 (47, $M^{\cdot+}$), 341 (3, $M^{\cdot+}-MeOH$), 296 (7, $M^{\cdot+}-C_6H_5$), 268 (24, $M^{\cdot+}-C_7H_5O$), 250 (100, $C_{17}H_{16}NO^+$), 249 (99, $C_{17}H_{15}NO^+$), 105 (34, $C_7H_5O^+$); exact mass calculated for $C_{24}H_{23}NO_3$: 373.1678, found: 373.1679.

4.7.3. Methyl (3a*S,10b*R**)-2-(bromomethylene)-10-methyl-10b-phenyl-2,3,4,5,10,10b-hexahydro-3a*H*-furo[2,3-*a*]carbazole-3a-carboxylate (35).** $HgCl_2$ (0.15 g, 0.55 mmol), NBS (0.20 g, 1.1 mmol) and DMAP (0.27 g, 2.2 mmol) were added to a solution of **34** (0.41 g, 1.1 mmol) in dichloromethane (40 mL). After being stirred at room temperature for 13 h, the mixture was filtered. The solids were washed three times with dichloromethane. The filtrate was evaporated and the residue purified by column chromatography (silica gel, heptane/CH_2Cl_2, 3/7). Yield: 54%; mp 37–39 °C; IR (KBr, cm^{-1}): 2942 (CH_2), 1729 (CO); ^1H NMR (400 MHz, $CDCl_3$): 2.08 (ddd, $J=15$, 5, 2 Hz, 1H, H^4), 2.57 (ddd, $J=15$, 12, 6 Hz, 1H, H^4), 2.79 (ddd, $J=17$, 12, 5 Hz, 1H, H^5), 2.90 (dd, $J=16$, 2 Hz, 1H, H^3), 3.07 (d, $J=16$ Hz, 1H, H^3), 3.16 (ddd, $J=17$, 6, 2 Hz, 1H, H^5), 3.25 (s, 3H, OCH_3), 3.35 (s, 3H, NCH_3), 4.97 (s, 1H, =C*H*Br), 7.60–7.09 (m, 9H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 17.3, 25.4, 30.6, 35.2, 51.8, 56.9, 88.7, 109.1, 109.3, 111.1, 119.0, 119.1, 122.4, 122.7, 125.2, 127.9, 128.1, 128.3, 133.2, 138.3, 138.7, 156.0, 172.7; *m/z* (E.I., %): 451+453 (8, $M^{\cdot+}$), 372 (4, $M^{\cdot+}-HBr$), 340 (13, $M^{\cdot+}-HBr-MeOH$), 312 (12, $M^{\cdot+}-HBr-HCO_2CH_3$); exact mass calculated for $C_{24}H_{22}O_3NBr$: 451.0783 and 453.0763, found: 451.0793 and 453.0760.

4.7.4. Methyl (3a*S,10b*R**)-2-(bromomethyl)-2-hydroxy-10-methyl-10b-phenyl-2,3,4,5,10,10b-hexahydro-3a*H*-furo[2,3-*a*]carbazole-3a-carboxylate (36).** To a solution of **35** (0.30 g, 0.66 mmol) in THF (20 mL) was added PTSA (0.019 g, 0.10 mmol) and a few drops of water. After stirring at 80 °C for 12 h, the solvent was evaporated and the residue purified by column chromatography (silica gel, heptane/CH_2Cl_2, 3/7). Yield: 45%, mp 81–82 °C; IR (KBr, cm^{-1}): 2946 (OH), 1703 (CO); ^1H NMR (400 MHz, $CDCl_3$): 2.03 (ddd, $J=15$, 6, 1 Hz, 1H, H^4), 2.52 (ddd, $J=15$, 12, 6 Hz, 1H, H^4), 2.55 (d, $J=14$ Hz, 1H, H^3), 2.67 (d, $J=14$ Hz, 1H, H^3), 2.81 (ddd, $J=17$, 12, 6 Hz, 1H, H^5), 2.88 (d, $J=10$ Hz, 1H, CH_2Br), 3.07 (ddd, $J=17$, 6, 1 Hz, 1H, H^5), 3.13 (s, 3H, OCH_3), 3.29 (s, 3H, NCH_3), 3.32 (d, $J=10$ Hz, 1H, CH_2Br), 6.40 (d, $J=1$ Hz, 1H, OH), 6.70 (d, $J=7$ Hz, 1H, H-arom.), 7.29–7.11 (m, 5H, H-arom.), 7.40 (t, $J=7$ Hz, 1H, H-arom.), 7.59 (d, $J=8$ Hz, 1H, H-arom.), 7.81 (d, $J=8$ Hz, 1H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 17.2, 24.8, 30.6, 38.6, 41.9, 52.5, 60.6, 87.5, 104.4, 109.3, 110.5, 119.0, 122.6, 125.3, 127.2, 128.1, 138.2, 139.7, 176.6; *m/z* (E.I.,%): 471 (63, $M^{\cdot+}$), 469 (63, $M^{\cdot+}$), 389 (20, $M^{\cdot+}-HBr$), 376 (15, $M^{\cdot+}-CH_2Br$), 371 (7, $M^{\cdot+}-HBr-H_2O$), 257 (100, $C_{19}H_{15}N^+$), 105 (54, $C_6H_5CO^+$); exact mass calculated for $C_{24}H_{24}O_4NBr$: 471.0868 and 469.0889, found: 471.0869 and 469.0913.

4.7.5. Methyl (3a*S,10b*R**)-2-[(dimethylamino)methyl]-2-hydroxy-10-methyl-10b-phenyl-2,3,4,5,10,10b-hexahydro-3a*H*-furo[2,3-*a*]carbazole-3a-carboxylate (37).** To a solution of **36** (0.064 g, 1.14 mmol) in THF/MeOH (2:1, 10 mL) was added $Me_2NH\cdot HCl$ salt (0.088 g, 1.1 mmol) and Et_3N (0.19 mL, 1.4 mmol). The mixture was stirred at room temperature for 2 days. Then Na_2CO_3 (sat. aq. solution, 15 mL) was added. The aqueous layer was extracted three times with dichloromethane. The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 1/9). Yield: 53%; mixture of isomers (50/50); oil; IR (NaCl, cm^{-1}): 2946 (OH), 1727 (CO); ^1H NMR (400 MHz, $CDCl_3$): 2.02 (m, 2H, H^4), 2.21 (s, 3H, NCH_3), 2.46 (dd, $J=14$, 2 Hz, 1H, H^3), 2.50 (s, 3H, NCH_3), 2.59 (2×d, $J=8$ Hz, 1H, H^3), 2.80 (d, $J=13$ Hz, 1H, CH_2N$(CH_3)_2$), 2.90 (m, 1H, H^5), 3.04 (2× dd, $J=4$, 2 Hz, 1H, H^5), 3.10 (s, 1.5H, OCH_3), 3.11 (s, 1.5H, OCH_3), 3.24 (d, $J=13$ Hz, 1H, CH_2N$(CH_3)_2$), 3.26 (s, 1.5H, NCH_3), 3.28 (s, 1.5H, NCH_3), 6.71 (d, $J=8$ Hz, 1H, H-arom.), 7.26–7.04 (m, 5H, H-arom.), 7.38 (t, $J=7$ Hz, 1H, H-arom.), 7.58 (dd, $J=8$, 1 Hz, 1H, H-arom.), 7.84 (d,

$J=8$ Hz, 1H, H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): 17.2, 17.5, 25.1, 25.8, 30.5, 30.6, 41.9, 42.8, 46.8, 47.1, 51.4, 52.3, 60.0, 60.9, 66.9, 67.6, 86.7, 86.9, 103.9, 106.1, 108.9, 109.1, 110.2, 110.4, 118.6, 118.9, 119.0, 121.8, 122.2, 125.3, 125.4, 125.8, 127.2, 127.6, 127.8, 127.9, 128.1, 134.6, 135.5, 138.1, 140.4, 141.0, 174.6, 176.6; *m/z* (E.I., %): 434 (3, $M^{\cdot+}$), 416 (2, $M^{\cdot+}-H_2O$), 376 (9, $M^{\cdot+}-CH_2N(CH_3)_2$), 316 (4, $M^{\cdot+}-CH_2N(CH_3)_2$–HCO_2CH_3), 58 (100, $CH_2N(CH_3)_2^+$); exact mass calculated for $C_{23}H_{30}O_4N_2$: 434.2206, found: 434.2217.

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Synthesis and redox-active base-pairing properties of DNA incorporating mercapto C-nucleosides

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Abstract—Here, we describe the synthesis and incorporation of the nucleoside base analogue C-deoxyribonucleoside **3** carrying thiophenol into DNA. The 1′-β compound **3** was synthesized by Friedel–Crafts alkylation, followed by deprotection. The coupling reaction with 3,5-ditoluoyl-1-α/β-methoxy-2-deoxy-D-ribose and diphenyldisulfide in the presence of $SnCl_4$ afforded the α/β mixture **2** (β/α=2.8), and the β-form was separated by silica gel chromatography. After formation of the phosphoramidite derivative, the C-nucleoside **3** was incorporated into DNA. When the mercapto-bases were incorporated into complementary singled-stranded (ss) DNAs, the resulting duplex displayed high thermal stabilization on treatment with bubbling O_2 (T_m 73 °C), but was destabilized in the presence of mercaptoethanol (T_m 33 °C). CD spectra showed that the duplex had a right-handed double-stranded structure. Imino proton NMR studies of temperature stability suggested that the strength of hydrogen bonding around the mercapto C-nucleoside was larger when treated with bubbling O_2 than when in treated with reducing agent. Thus, formation of the base-to-base disulfide bond increased the stability of the duplex; correspondingly, reduction of the disulfide to two thiol bases destabilized the DNA reversibly. The duplex-forming disulfide base pair showed resistance to exonulease **III**. The present strategy could be used to introduce new functionalities into cells and novel biomaterials.

1. Introduction

Selective Watson–Crick hydrogen bonding between the natural base pairs dA:dT and dC:dG is the key element for information storage and retrieval in DNA. The strategy of replacing DNA natural bases with analogues has paved the way to add new functions to the biopolymers.[1–3] Using this strategy, workers have recently examined different unnatural base pairs formed by new hydrogen bonding,[4–8] metal coordination,[9,10] hydrophobic interaction[11,12] or molecular shape fitting into duplexes.[13,14] These unnatural nucleic acids can provide functions towards expansion of the genetic alphabet and can be used to align metal ions along the helical axis inside the duplex. In those studies, however, few duplexes have been generated in which the base pairs are linked by covalent bonding. If the base pair of DNA could be formed by such a reversible covalent bond, the duplex would be very stable in terms of both temperature and controlling the process between single strand and duplex formation.

A few examples of DNA with base pairs linked by covalent bonding have been reported.[15,16] These studies were concerned with DNA the base pair formed by irreversible covalent bonding. Although the disulfide bond is covalent, this bond can be easily converted to two SH groups with reducing reagents. In addition, the two SH groups can reversibly form an –S–S– bond with the use of redox reagents. Most studies of disulfide cross-linking in DNA have not concerned the formation of a base-to-base disulfide bond between two complementary positions in DNA.[17,18] Rather, the aim of those studies was to connect ss DNA by a spacer. Studies of a disulfide duplex formed by base-to-base cross-linking via 4-thio-2′-deoxyuridine and 6-thio-2′-deoxyinosine have been also described by Colemann and co-workers (Chart 1).[19]

In the present report, the synthesis and base-pairing properties of new mercapto C-nucleoside *p*-thiophenol nucleobases are described. In addition, we have examined the disulfide base-pairing for base-to-base formation during the incorporation of these synthetic mercapto C-nucleosides into DNA. Our results show that redox agents can control the melting temperature of the resulting duplexes and can aid in the resistance of duplexes to digestion by nuclease. Our results underscore the importance of reversible covalent

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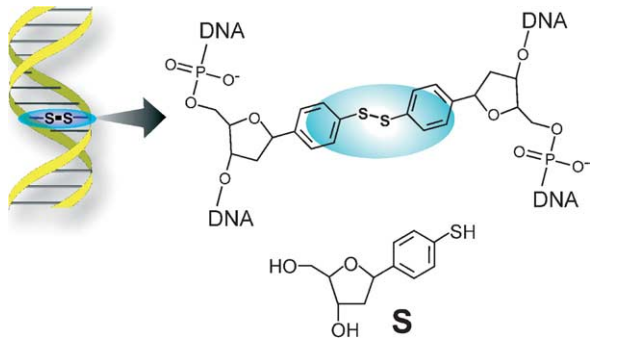


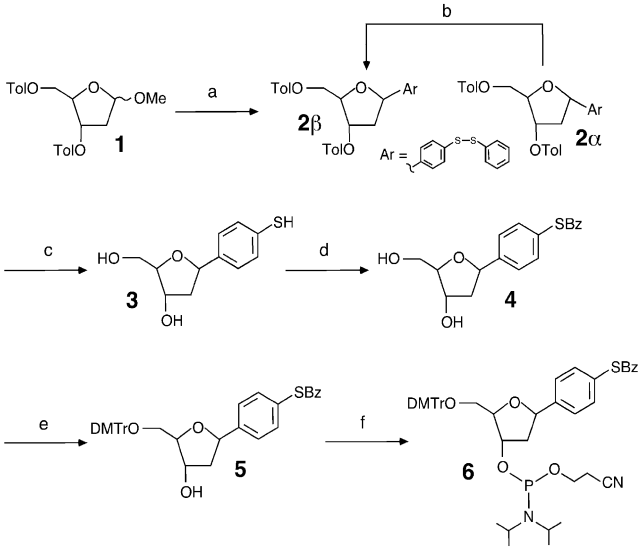
Chart 1.

bonding in base-pair structure and function for stability of the double helix.

2. Results and discussion

2.1. Synthesis

Synthesis of the mercapto C-nucleoside **3** is given in Scheme 1. Initially, the coupling reaction between the protected thiophenol and the 3,5-ditoluoyl-1-α/β-methoxy-2-deoxy-D-ribose **1**[20] was carried out in the presence of Lewis acid in CH_2Cl_2 at −15 °C.[21] The Friedel–Crafts approach via electrophilic aromatic substitution was chosen to build up the C-nucleoside. As the starting material for the coupling reaction of compound **3**, diphenyldisulfide was used. This coupling reaction afforded the base-coupled nucleosides as a mixture of α- and β-anomers (β/α=2.8) in 24% yield. The recovery of the diphenyldisulfide was 70%. However, the reported yields from protective groups other than thiophenol, various temperature and Lewis acids are lower than this.[21] For example, it has been found that 2α is converted to 2β in the presence of 10%-TsOH in THF and CH_2Cl_2 (1:4) at 0 °C to afford the β-isomer (2β) in 21% yield and the α-isomer (2α) in 6.4% yield.[11b,22]



Scheme 1. Reagents and conditions. (a) Diphenyldisulfide, $SnCl_2$ (2 equiv), in CH_2Cl_2 at −15 °C; yield: α, 6.4%; β, 18%. (b) 10%-TsOH, TFA in CH_2Cl_2 at 0 °C; yield, 21%. (c) $LiAlH_4$ in THF at 4 °C; yield, 37%. (d) BzCl, DIPEA in CH_2Cl_2 at 4 °C; yield, 71%. (e) DMTrCl in pyridine at rt; yield, 96%. (f) 2-Cyanoethyl-*N*, *N*′-diisopropyl-chlorophosphoramidite in CH_2Cl_2 at rt; yield, 93%.

The removal of the three protection groups, two toluoyl and a mercaptophenyl, was carried out in one step by using $LiAlH_4$. The anomeric configuration for **3** was determined by ^{1}H NOE experiments and by ^{1}H NMR examination of coupling constants for the 1′- and 2′-protons. The β-anomer had a 1′ resonance that appeared as a nearly evenly spaced doublet of doublets (J=5.4, 10.7 Hz). This trend in 1′-2′ coupling constants is similar to that reported for related β-C-nucleosides.[9a,11b] Irradiation of the 1′H in **3** gave a NOE on 4′H (5.1%) and 2′Hα (3.0%). Similarly, irradiation of 2′Hβ gave a NOE on 3′H (7.1%), and irradiation of 2′Hα yielded enhancements on 1′H (9.1%).

The mercaptophenyl β-C-nucleoside **3** was further *S*-benzoylated (71%), 5′-dimethoxytritylated (96%) and 3′-*O*-phosphitylated (93%) to give 2-cyanoethyl phosphoramidite **6**. Having obtained compound **6**, oligonucleotides containing the mercaptophenyl β-C-nucleoside were readily prepared by standard automated DNA synthetic methods. The *S*-benzoyl group was cleaved by a 27% ammonia solution at 55 °C for 8 h during which the oligonucleotide was also cleaved from the solid phase.

2.2. Thermal denaturation analysis

We studied the stability of the duplex and the pairing ability of the non-natural nucleoside **3** (**S**) in a variety of complementary DNAs by thermal denaturation experiments. Each duplex was characterized by UV melting curves obtained by monitoring the absorbance value at 260 nm, and the corresponding T_m data are summarized in Table 1. The T_m of duplex **I**·**II** was 44 °C in the presence of oxygen and 43 °C in the presence of mercaptoethanol. By contrast, duplex **III**·**IV**, which contained thiol groups at complementary positions in each DNA sequence, showed high stability with a T_m of 73 °C on the treatment with bubbling oxygen for 1 h. The stability of this duplex in bubbling oxygen was significantly greater than that of the natural duplex **I**·**II** (ΔT_m 29 °C).[21] This result suggests that a matching disulfide base pair was formed by oxidation, and that this bond was stronger than the base pair formed by hydrogen bonding in natural DNA. MALDI-TOF mass spectrometry demonstrated that each complementary ss DNA in the duplex had incorporated the non-natural mercapto C-nucleotide, in addition, we also observed formation of the duplex through disulfide bonding of the **S**–**S** base pair by MALDI-TOF.

In the presence of reducing agent, however, the T_m of **III**·**IV** was similar to that of the mismatch sequence **I**·**IV** (33 and 32 °C, respectively). This low T_m was due to the formation of two thiol groups by the addition of reducing agent. Thus, under reducing conditions, the presence of the two base analogues in **III**·**IV** destabilizes the duplex structure to approximately the same extent does as a mismatch base pair in natural DNA.

Duplex **V**·**VI** contains the mercapto C-nucleoside **S** at the penultimate base position in the complementary strands. This duplex also displayed a high T_m on the treatment with

Table 1. Sequence information and effects of T_m of DNA including mercapto-nucleoside **3** (**S**)

	Sequences		T_m (°C)	
	A	B	Oxidation	Reduction
I·II	5′-CAC ATT AAT GTT GTA	3′-GTG TAA TTA CAA CAT	44	43
I·IV	5′-CAC ATT AAT GTT GTA	3′-GTG TAA T**S**A CAA CAT	32	32
I·VI	5′-CAC ATT AAT GTT GTA	3′-G**S**G TAA TTA CAA CAT	37	38
III·IV	5′-CAC ATT A**S**T GTT GTA	3′-GTG TAA T**S**A CAA CAT	73	33
V·VI	5′-C**S**C ATT AAT GTT GTA	3′-G**S**G TAA TTA CAA CAT	70	39
VII·VIII	5′-AAA AAA AAA AAA AAA	3′-TTT TTT TTT TTT TTT	23	24
IX·X	5′-AAA AAA A**S**A AAA AAA	3′-TTT TTT T**S**T TTT TTT	64	18
XI·XII	5′-CGC AAT TGC G	3′-GCG TTA ACG C	67	66
XIII·XIV	5′-CGC AA**S** TTG CG	3′-GCG TT**S** AAC GC	72	58

The duplexes (15 μM/bp) were analyzed in 10 mM Na–phosphate buffer, 100 mM NaCl (**XI·XII** and **XIII·XIV**: 1 M NaCl), pH 7.0, 1 °C/min. Oxidation, bubbling O_2 for 1 h; reduction, 100 μM mercaptoethanol.

bubbling oxygen (70 °C). This means that duplex **V·VI** was stabilized by the disulfide base pair, as well as by hydrogen-bonded base pairs located in the neighborhood of the disulfide base pair. However, the mismatch sequence **I·VI** had a similar T_m to that of **V·VI** in the presence of mercaptoethanol (37 and 39 °C, respectively). Other duplex sequences (**IX·X** and **XIII·XIV**) also showed the same tendency towards different stability in oxygen and mercaptoethanol (Fig. 1).

2.3. Thermodynamic parameters

Thermodynamic parameters for formation of the duplex were determined from melting curves, obtained in 10 mM sodium phosphate buffer and 100 mM NaCl (pH 7.0), which were used to obtain the slope and intercept of a $1/T_m$ versus $C_T/4$ plot. Table 2 shows the parameters evaluated for each duplex. Treatment of duplex **III·IV**, which contained the mercapto C-nucleosides at a central position, with O_2 bubbling had a profound effect on the ΔH value. The formation of a disulfide-linked base pair in the DNA resulted in a gain in enthalpy ($\Delta\Delta H = -35.0$ kcal mol^{-1}) but a drop in entropy owing to structural restriction ($\Delta\Delta S = -86.0$ cal mol^{-1} K^{-1}). The high ΔH value was derived from the strong interaction due to covalent disulfide bonding and was in considerable excess of the drop in ΔS due to structural restriction. Therefore, in the presence of oxidizing agent, the ΔG_{37} value of **III·IV** was highest among the DNAs, and the duplex was stabilized in general ($\Delta\Delta G_{37} = -8.4$ kcal mol^{-1}). Table 2 shows that the enthalpy value of duplex **III·IV** in the presence of a reducing agent also increased slightly towards that of the natural DNA **I·II** ($\Delta\Delta H = -5.6$ kcal mol^{-1}). However, the destabilizing effect of the entropy factor for duplex **III·IV**

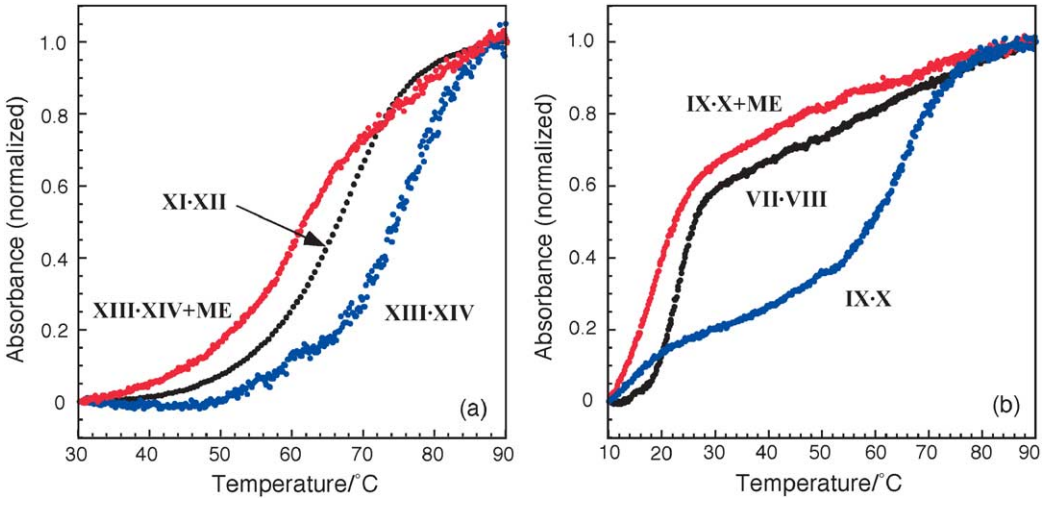


Figure 1. Melting curves for duplexes induced by the formation of disulfide bonding (monitored at 260 nm). Shown are curves for duplexes with the **S** nucleoside located at the center position into Dickerson sequences (a) or the center position into dT_7SdT_7-dA_7SdA_7. (b) See conditions in Table 1.

Table 2. Thermodynamic parameters for the formation of a DNA 15-mer complex

Sequences	ΔS (cal mol^{-1} K^{-1})	ΔH (kcal mol^{-1})	ΔG_{37} (kcal mol^{-1})
I·II	−181.8	−67.2	−10.8
III·IV[a]	−208.9	−72.8	−8.0
III·IV	−267.8	−102.2	−19.2

van't Hoff thermodynamic parameters derived from linear plots of $1/T_m$ vs. $\ln(C_T/4)$ by measuring T_m at various concentrations. The values were obtained in 10 mM sodium phosphate, pH 7.0, 100 mM NaCl.

[a] Plus 75 μM mercaptoethanol.

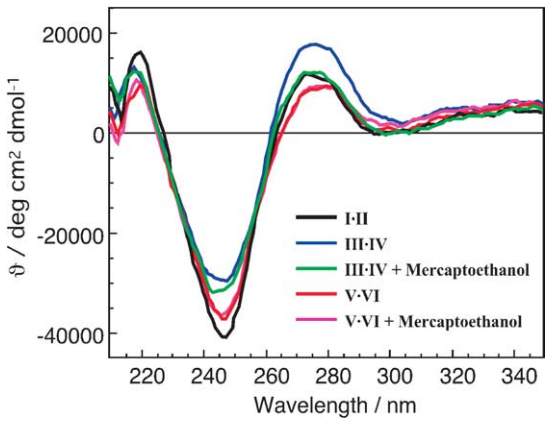


Figure 2. Circular dichroism spectra of selected duplexes from Table 1. The DNA (15 μM/bp) was analyzed in 10 mM phosphate buffer, 100 mM NaCl, pH 7.0, at 20 °C. Mercaptoethanol was used at a concentration of 75 μM.

($\Delta\Delta S = -27.1$ cal mol^{-1} K^{-1}) in the presence of a reducing agent was larger than the effect of the enthalpy factor. This means that the duplex structure was destabilized by the mismatch base pair of the unnatural mercapto C-nucleoside ($\Delta\Delta G_{37} = 2.8$ kcal mol^{-1}).

2.4. Structural analysis with circular dichroism (CD)

Circular dichroism spectroscopy was used to study the macroscopic helical geometry of the DNA duplexes containing mercapto C-nucleosides (Fig. 2). Under all conditions, the CD spectra of duplexes **III·IV** and **V·VI**, which contain disulfide bonds, revealed spectral features of B-DNA similar to those of the control A–T duplex **I·II**. However, duplex **III·IV**, which possesses a central mercapto C-nucleoside, displayed a slight increase in positive Cotton effect at 275 nm and a corresponding decrease at 247 nm relative to the control duplex **I·II** in the absence of mercaptoethanol. The slight divergence of these CD spectra is due to differences in the stacking ability of the duplexes containing the unnatural nucleoside **S**. Thus, disulfide base-pairing did not significantly alter the overall DNA structure.

2.5. Structural analysis with imino proton NMR

The ^{1}H NMR spectra of imino protons gave further insight into several structural features of the DNA duplexes. The presence of the imino protons in the low-temperature spectra confirmed that the duplex containing the disulfide base-pair formed a stable Watson–Crick base-paired duplex (Fig. 3). Dissociation of the base pair was observed as the disappearance of the imino proton in that base pair. Figure 3(a) shows that on treatment with bubbling O_2, duplex **XIII·XIV** displayed a high dissociation temperature (55 °C). Although the imino proton 5 derived from A–T base pair gave a low-magnification signal, this signal was also observed until 55 °C. The A–T base pair 5 was located in the neighborhood of the disulfide base pair, which was located at the center of sequence and differed structurally from the natural base pair. Although the imino proton 5 was affected by the unnatural base pair, its NMR peak changed only a little and its hydrogen bonding was stabilized in terms of temperature. In the presence of 10 mM of mercaptoethanol (Fig. 3(b), **XIII·XIV**+ME), the imino proton peaks observed were broad at 40 °C, and the imino proton 5 peak disappeared at 30 °C. This means that the disulfide base pair in the DNA duplex sequence was reduced to two thiol groups, thereby forming a mismatch base pair, by the reducing reagent. The imino proton 5 could not be observed to form a complementary hydrogen bond at 30 °C. Thus the stability of the duplex was lower in the presence of reducing reagent than in presence of bubbling O_2. These results clearly support the results of the studies described above.

2.6. Nuclease digestion

We measured the resistance of the 15 mer oligonucleotides containing the mercapto C-nucleoside to digestion by two

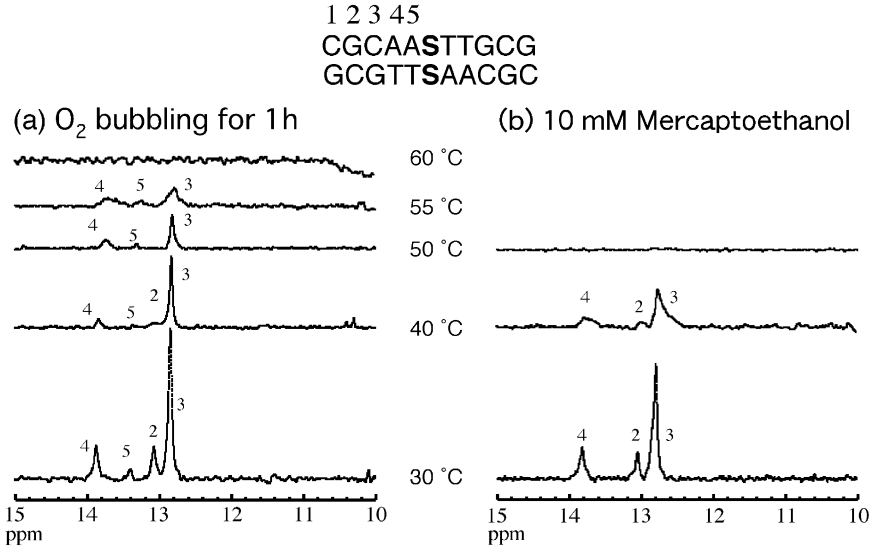


Figure 3. Imino proton spectra of the Dickerson 11 mer (5′-CGCAA**S**TTGCG) containing the mercapto C-nucleoside at the center position. Shown are spectra obtained on treatment with O_2 bubbling for 1 h (a) or with 10 mM mercaptoethanol (b). The DNA (2 mM) was analyzed in 10 mM Na–phosphate buffer, 1 M NaCl, pH 7.0.

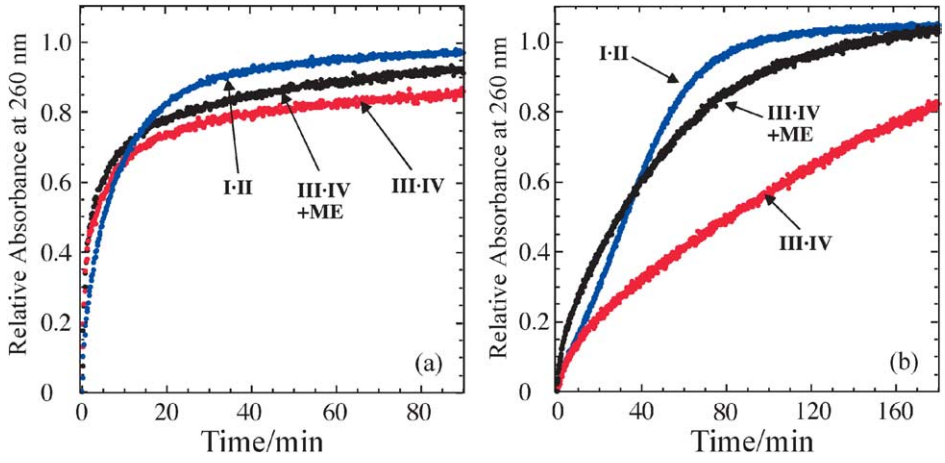


Figure 4. Enzymatic digestion of three types of DNA (blue, duplex **I**·**II**; black, duplex **III**·**IV**+mercaptoethanol; red, duplex **III**·**IV**) by DNase **I** (a) and exonuclease **III** (b). In (a), each duplex (30 μM/bp) was incubated at 25 °C with DNase **I** from bovine pancreas (50 units, 12.5 units/mL) in 4.0 mL of 10 mM phosphate buffer, pH 7, containing 1 mM $MgSO_4$, 100 mM NaCl. In (b), each duplex (30 μM/bp) was incubated at 25 °C with exonuclease **III** from *Escherichia coli* (100 units, 25.0 units/mL) in 4.0 mL of 10 mM phosphate buffer, pH 7, containing 1 mM $MgCl_2$, 100 mM NaCl.

different species of nucleases. Figure 4 shows that nuclease digestion, as calculated by variations in the hypochromicity of the melting curve at 260 nm, was inhibited by the DNA oligonucleotides. To determine the activity, the assay was repeated at least twice for each enzyme and each DNA.[23] The effect of DNase **I**, which is a non-specific endonuclease, showed no marked differences in digestion of the three types of DNA (Fig. 4(a)). In all samples, the reaction of DNase **I** was saturated within 20 min. However, resistance of the oligomers to digestion by exonuclease **III** was much stronger than their resistance to DNase **I** (Fig. 4(b)). Degradation by exonuclease **III** from the 5′-end of DNA chain was resisted by duplex **III**·**IV**, which contained a disulfide base pair. In the presence of mercaptoethanol, however, the digestion of oligonucleotides **I**·**II** and **III**·**IV** by exonuclease **III** was saturated within 120 min. On treatment with O_2 bubbling, by contrast, oligonucleotide **III**·**IV** was not saturated within the same time period. This result suggests that a duplex containing a disulfide base pair at the center of its sequence is more resistant to digestion by exonuclease than are duplexes containing either natural base-pairs or a mismatch base pair consisting of two thiol groups in the presence of reducing reagent.

3. Conclusion

We have described the synthesis of the mercapto C-nucleoside **S** and the properties of disulfide base-pairing in DNA. T_m measurements and imino proton NMR studies indicated that duplexes containing the oxidized form of the disulfide base pair showed temperature stabilization. These results indicate that it is possible to control the melting temperature of duplexes including mercapto C-nucleosides by redox reagents. The van't Hoff plots indicated an entropy loss and a large gain in enthalpy depending on the formation of disulfide base pair. Furthermore, our results indicate that the duplex containing a disulfide base pair was resistant to digestion by exonulease **III**. However, the disulfide bond had no influence on digestion of the duplex by the non-specific endonuclease DNase **I**, because both natural duplexes and duplexes containing the thiol/disulfide modification were digested equally. Our findings may be useful for increasing the functionality of DNA in order to generate a new functional materials, a new genetic code, or novel antisense nucleotides.

4. Experimental

4.1. General methods

All solvents and reagents were of reagent-grade quality, and used without further purification. The TLC analysis was carried out on silica gel 60 F_{254} 1.05554 (Merck). Column chromatography was performed using Wakogel C-300 (silica gel, Wako) or Silica gel 60 N (Kanto Chemical Co.). The ^1H, ^{13}C, COSY and NOE NMR spectra were recorded on a JEOL EX 400 (400.0 MHz for ^1H; 100.4 MHz for ^{13}C) spectrometer. The spectra were referenced to TMS in chloroform-d_3 or CD_3OD-d_4, and to TSP in D_2O. The chemical shifts (δ) are reported in ppm; multiplicity is indicated by: s (singlet), d (doublet), t (triplet), q (quintet), m (multiplet), and br (broad). The coupling constants, J, are reported in Hz. EIMS, FABMS and MALDI-TOFMS were recorded on a Shimadzu KRATOS CONCEPT IS, an JEOL JMS-700V, and Applied Biosystems Voyager DE-STR, respectively. The UV spectra were measured on a Shimadzu UV 2100 spectrometer in a 1 cm quartz cell. The CD spectra were measured on a JASCO J-725 spectropolarimeter in a 1 cm strain-free quartz cell.

4.1.1. Compound 2β. A mixture of diphenyldisulfide (4.26 g, 19.5 mmol) and 3,5-ditoluoyl-1-α/β-methoxy-2-deoxy-D-ribose **1** (5.0 g, 13 mmol) was stirred in 10 mL of anhydrous CH_2Cl_2 at −15 °C under argon atmosphere. 1 M-$SnCl_4$ (26 mL, 26 mmol) was then added to the reaction mixture for 30 min. The solution was stirred at −15 °C for 8 h, and then was quenched by 50 mL of saturated $NaHCO_3$ in H_2O and extracted twice with 100 mL of CH_2Cl_2. The organic layers were combined and washed twice with brine, and dried over anhydrous $MgSO_4$. The solution was filtered, concentrated, and purified by silica gel chromatography, eluting with hexane–diethylether (5:1).

The major β-anomer product was recrystallized from MeOH to afford **2**β as colorless needles (1.36 g, 18%). ^{1}H NMR ($CDCl_3$): δ 2.20 (1H, m), 2.39 (3H, s), 2.43 (3H, s), 2.49 (1H, J=9.3, 14.1 Hz, dd), 4.52 (1H, m), 4.63 (2H, m), 5.21 (1H, J=5.1, 11.2 Hz, dd), 5.59 (1H, J=6.4 Hz, d), 7.27 (9H, m), 7.46 (4H, m), 7.91 (2H, J=8.3 Hz, d), 7.97 (2H, J=8.3 Hz, d); ^{13}C NMR ($CDCl_3$): δ 21.7, 21.7, 41.7, 64.7, 80.3, 83.0, 126.7, 126.9, 127.0, 127.2, 127.5, 127.6, 127.7, 127.8, 129.2, 129.5, 129.7, 129.7, 136.6, 136.9, 143.9, 144.2, 166.1, 166.4. FABMS *m/e* 571 $[M+H]^+$. Anal. Calcd for $C_{33}H_{30}O_5S_2$: C, 69.45; H, 5.30; N, 0.00; S, 11.24. Found: C, 69.37; H, 5.26; N, 0.00; S, 11.18.

4.1.2. Compound 2α. (0.47 g, 6.4%) ^{1}H NMR ($CDCl_3$): δ 2.27 (1H, m), 2.39 (3H, s), 2.40 (3H, s), 2.91 (1H, m), 4.55 (2H, m), 4.66 (1H, m), 5.34 (1H, J=6.6 Hz, t), 5.58 (1H, m), 7.24–8.00 (17 H, m); ^{13}C NMR ($CDCl_3$): δ 21.6, 40.2, 64.4, 76.1, 79.6, 82.1, 126.1, 126.4, 126.8, 126.9, 127.3, 127.5, 128.7, 128.8, 128.8, 129.3, 129.4, 135.7, 136.7, 141.5, 143.5, 143.6, 165.6, 165.9. FABMS *m/e* 571 $[M+H]^+$.

4.1.3. Compound 3. $LiAlH_4$ (0.524 g, 13.8 mmol) was carefully added to a solution of the bis-toluoylester **2** (1.58 g, 2.76 mmol) in dry THF (50 mL). The reaction mixture was stirred at 4 °C for 1 h and then quenched by a 1 N-H_2SO_4 aqueous solution (3 mL). The residue was poured into 50 mL of 1 N-HCl, and then extracted with 50 mL of CH_2Cl_2 (8 times), dried over anhydrous $MgSO_4$, and evaporated. The crude product was chromatographed with $CHCl_3$–MeOH (9:1) and then recrystallized from MeOH to afford mercaptophenyl nucleoside (**3**) as colorless needles (0.231 g, 37%). ^{1}H NMR (CD_3OD): δ 1.90 (1H, m), 2.15 (1H, J=2.4, 5.1, 5.1 Hz, ddd), 3.65 (2H, m), 3.91 (1H, J=3.9, 10.7 Hz, td), 4.29 (1H, br), 5.05 (1H, J=5.4, 10.7 Hz, dd), 7.23 (1H, J=12.2 Hz, d), 7.25 (1H, J=11.8 Hz, d); ^{13}C NMR (CD_3OD): δ 44.9, 64.1, 74.5, 81.3, 89.2, 128.0, 130.5 132.2, 140.4. EIMS *m/e* 226 $[M]^+$. Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24; N, 0.00; S, 14.17. Found: C, 58.25; H, 6.18; N, 0.00; S, 14.18. ε_{260}: 7080 $cm^{-1}\,M^{-1}$ in 10 mM Na–phosphate buffer, 100 mM NaCl at pH 7.0.

4.1.4. Compound 4. To a solution of **3** (118 mg, 0.520 mmol) and diisopropylethylamine (134 mg, 1.04 mmol) in THF (3 mL) was added a solution of benzoyl chloride (80.4 mg, 0.572 mol) dropwise over 10 min with a nitrogen inlet in an iced water bath The reaction mixture was stirred for 1 h at room temperature, and then the reaction solution was quenched by 1 mL of MeOH. The mixture was added to 30 mL of CH_2Cl_2, and washed twice with 30 mL of H_2O, and dried over anhydrous $MgSO_4$. The solution was filtered, concentrated, and purified by silica gel chromatography eluting with $CHCl_3$–MeOH (9:1). The major product was recrystallized from MeOH to afford **4** as colorless needles (122 mg, 71%). ^{1}H NMR ($CDCl_3$): δ 1.94 (2H, br), 2.06 (1H, J=4.6, 6.3, 19.5 Hz, ddd), 2.37 (1H, J=1.5, 5.9, 13.2 Hz, ddd), 3.82 (2H, m), 4.02 (1H, m), 4.42 (1H, br), 5.22 (1H, J=5.6, 10.3 Hz, dd), 7.47 (6H, m), 7.62 (1H, J=7.3, 7.3 Hz, t), 8.03 (2H, J=7.3 Hz, d); ^{13}C NMR ($CDCl_3$): δ 44.1, 63.4, 73.8, 79.6, 87.4, 126.5, 126.8, 127.5, 128.8, 133.7, 135.2, 136.6, 143.2, 190.3. EIMS *m/e* 330 $[M]^+$. Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49; N, 0.00; S, 9.71. Found: C, 65.28; H, 5.44; N, 0.00; S, 9.87.

4.1.5. Compound 5. Compound **4** (50.0 mg, 0.154 mmol) was co-evaporated 3 times in 3 mL of dry pyridine. The solid was dissolved in 1 mL of dry pyridine. DMTrCl (97.3 mg, 0.287 mmol) was added as a solid in one portion to the stirred solution under Ar and the mixture was stirred at room temperature. After 1 h, the reaction was quenched by the addition of EtOH (0.5 mL). The mixture was poured into 10 mL of ice water and extracted 3 times with 15 mL of CH_2Cl_2. The combined organic phase were dried over $MgSO_4$ and concentrated. A silica gel column with hexane–EtOAc (3:1) afforded 5 as a yellow foam (93.2 mg, 96%). ^{1}H NMR ($CDCl_3$): δ 2.01 (2H, br), 2.22 (1H, J=1.8, 7.4, 14.7 Hz, ddd), 3.27 (1H, J=5.4, 9.8 Hz, dd), 3.35 (1H, J=4.0, 8.0 Hz, dd), 4.08 (1H, br), 4.40 (1H, br), 5.21 (1H, J=5.6, 10.2 Hz, dd), 6.81 (4H, J=8.8 Hz, d), 7.19–7.60 (16H, m), 8.01 (2H, J=7.4 Hz, d); ^{13}C NMR ($CDCl_3$): δ 43.9, 55.2, 64.4, 74.6, 79.5, 86.3, 86.4, 113.1, 126.1, 126.8, 127.5, 127.9, 128.2, 128.7, 130.1, 133.6, 135.0, 136.0, 136.6, 143.6, 144.8, 158.5, 190.2. FABMS *m/e* 633 $[M+H]^+$; HRMS calcd for $C_{39}H_{36}N_{11}O_6S$ 633.2311, found 633.2347.

4.1.6. Compound 6. Compound **5** (92 mg, 0.145 mmol) was dissolved in 2 mL of dry CH_2Cl_2 and purged with Ar for 2 min To the stirred solution was added *N*,*N*′-diisopropylrthylamine (37.5 mg, 0.290 mmol) and 2-cyanoethyl-*N*,*N*′-diisopropylchlorophosphoramidite (44.7 mg, 0.189 mmol). The reaction mixture was stirred under Ar at room temperature while protected from light for 1 h. The reaction mixture was added to 30 mL of CH_2Cl_2 and washed twice with 30 mL of H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude compound was chromatographed with 1% trimethylamine in hexane–EtOAc (3:1) to obtain **6** as a colorless solid (98 mg, 93%). ^{1}H NMR ($CDCl_3$): δ 1.12–1.31 (14H, m), 1.65 (1H, br), 2.04 (1H, m), 2.38 (1H, m), 2.46 (1H, J=6.3 Hz, t), 2.62 (1H, J=6.5 Hz, t), 3.31 (2H, m), 3.78 (6H, s), 4.27 (1H, br), 4.53 (1H, br), 5.22 (1H, J=4.6, 9.6 Hz, dd), 6.84 (4H, J=5.0, 9.0 Hz, dd), 7.19–7.66 (16H, m), 8.04 (2H, J=8.3 Hz, d). FABMS *m/e* 833 $[M+H]^+$. HRMS calcd for $C_{48}H_{54}N_2O_7PS$ 833.3389, found 833.3376.

4.2. Oligonucleotide synthesis

The DNA oligomers were synthesized on a DNA synthesizer by phosphoramidite chemistry, with a coupling time for a unnatural monomer of 3 min Syntheses were performed using a 1-μmol-scale trityl-on mode, according to the manufacturer's protocol. The full protected oligonucleotides were cleaved from the controlled pore-glass (CPG) support with 27% aqueous NH_3 solution at 55 °C for 8 h. The *S*-benzoyl group was cleaved at the same time by ammonia solution. The crude DMTr-DNA was purified and detritylated by an OPC protocol, and then freeze-dried immediately. The yields of the oligonucleotides were determined by a comparison of UV absorption at 260 nm with nearest-neighbor parameters and the molar extinction coefficient of the core sequence. Purity was analyzed by reversed-phase HPLC (C18, 0–10% MeCN in 0.1 M-TEAA buffer pH 7.4, at 260 nm).

4.3. Oxidation and reduction of duplexes containing S nucleoside

Duplexes containing a disulfide base pair were incubated in bubbling O_2 for 1 h at room temperature in a buffer containing 100 mM NaCl and 10 mM sodium phosphate, pH 7.0 Reduction was carried out by adding 100 μM of mercaptoethanol at 20 °C. The solution was heated to 90 °C to denature the duplex and cooled slowly to 10 °C at a rate of 1 °C/min.

4.4. Thermal denaturation analysis

Melting studies were performed in Teflon-stoppered 1 cm pathlength quartz cells under a nitrogen atmosphere using a Shimadzu UV 2100 UV–vis recording spectrophotometer equipped with a thermoprogrammer. Absorbance was monitored at 260 nm. The temperature was raised from 10 to 90 °C at a rate of 1.0 °C/min. The solution for the thermal denaturation studies was prepared at an oligomer concentration of 15 μM for the base-pairing studies (1:1 ratio of two complementary oligomers) in a buffer containing 100 mM NaCl (Dickerson sequences **XI**·**XII** and **XIII**·**XIV** was 1 M NaCl) and 10 mM sodium phosphate, pH 7.0.

4.5. Thermodynamic analysis of the melting data

The UV melting curves were analyzed to obtain van't Hoff transition enthalpies (by measuring T_m as a function of concentration, $1/T_m$ vs $\ln(C_T/4)$.

4.6. CD experiments

Circular dichroism spectra were measured on a JASCO J-725 spectropolarimeter between 350 and 200 nm in standard buffer containing 100 mM NaCl, 10 mM sodium phosphate, pH 7.0, at 10 °C. The duplex concentrations were 15 μM per base pair. Spectra were acquired every 1 nm with a bandwidth setting of 1 nm at a speed of 50 nm/min, averaging over 5 scans.

4.7. Imino proton NMR spectroscopy

Oligonucleotide samples were dissolved in 0.18 mL of 10 mM Na–Phosphate, 1 M NaCl, pH 7.0, and 0.02 mL of D_2O The final concentration of the oligonucleotides was 2.0 mM. All spectra were recorded on a JEOL EX 400 spectrometer. The samples were denatured by heating and slowly renatured prior to analysis. The carrier frequency was centered on the water resonance, which was suppressed by using a HMG program for spectra. All spectra were referenced to the 3-(trimethylsilyl)propionic acid sodium salt (TSP).

4.8. Nuclease resistance experiments

Oligonucleotide samples (30 μM/bp) were incubated in buffer (DNase **I**: 10 mM sodium phosphate, 100 mM NaCl, 1 mM $MgCl_2$, pH 7.0; exonulease **III**: 10 mM Na phosphate, 100 mM NaCl, 1 mM $MgSO_4$, pH 7.0) containing nuclease (bovine pancrease DNase **I**, 50 units, 12.5 units/mL; *Escherichia coli* exonuclease **III**, 100 units, 25 units/mL) at 25 °C Nuclease digestion was determined by measuring the absorbance of the reacting solution at 260 nm over time.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.12.038

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Diastereoselective addition of organolithiums to 1,3-oxazolidines complexed with aluminum tris(2,6-diphenylphenoxide) (ATPH)

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Abstract—1,3-Oxazolidines were easily obtained by condensation of N-substituted (*R*)-phenylglycinol with aldehydes. Addition of organolithium reagents to 1,3-oxazolidines by complexation with the bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH) readily produced the corresponding chiral amines with good yield and high diastereoselectivity. The configuration of the new stereogenic center was shown to be opposite to that of adducts obtained for the same 1,3-oxazolidines using Grignard reagents. The best diastereoselectivity was achieved using *N*-isopropyl-1,3-oxazolidines. The mechanism of addition was deduced by determining the stereochemistry of the iminium–aluminum complex by NOE experiments.

1. Introduction

The diastereoselective addition of organometallic reagents to the C═N bond of chiral imines and their derivatives is useful for the asymmetric synthesis of chiral amines.[1] We have previously described a synthetic method for stereoselective preparation of both enantiomers of chiral amines from a single-enantiomer source, (*R*)-phenylglycinol, proceeding via the diastereoselective addition of Grignard reagents to 1,3-oxazolidines with excellent yield and diastereoselectivity.[2] It was previously alleged that addition of Grignard reagents occurred after formation of the ring-opened iminium intermediate, but addition of an organolithium reagent to 1,3-oxazolidine did not proceed for the unopened ring. It was considered that the reaction required activation to open the 1,3-oxazolidine ring. We tried to react 1,3-oxazolidines with organolithium reagents using various Lewis acids. Aluminum compounds might be effective additives to facilitate the reaction. One additive, bulky C_3 symmetrical ATPH, has been shown to have unique properties in various reactions by Yamamoto.[3] ATPH has a small opening in the ligand sphere and is known to give stable complexes with carbonyl compounds. Herein we report the diastereoselective addition of organolithium to 1,3-oxazolidine via activation with ATPH. Interestingly, the absolute configuration of the adducts obtained in the presence of ATPH was the opposite to that obtained by addition of Grignard reagents (Scheme 1). Other groups have also reported that some reactions with ATPH resulted in the reversal events of diastereoselectivity.[4]

2. Results and discussion

2.1. Addition of MeLi to 1a using various Lewis acids

For the addition of MeLi to 1,3-oxazolidines, an activator such as a Lewis acid is needed for cleavage of the 1,3-oxazolidine ring. To activate a diastereomer mixture of 1,3-oxazolidine **1a**,[2a] prepared easily from (*R*)-phenylglycinol, we tried various Lewis acids as additives (Scheme 2, Table 1). As expected, addition of MeLi to **1a** did not proceed without a Lewis acid (run 1). Some Lewis acids provided methylation to the 1,3-oxazolidine but with low yields and diastereoselectivity (runs 2, 3, and 8). Diastereoselective addition of MeLi was possible in the presence of $MgBr_2$ and Me_3Al (runs 9 and 12). Interestingly, the major adduct of methyl addition using ATPH, (*R*,*R*)-**2a**, differed from that obtained using the other Lewis acids (runs 13–16). This result also differed from previous research in which addition of MeMgBr to **1a** gave (*S*,*R*) **2a** in 94% yield and 68% de.[2a] It was assumed that the change in diastereoselectivity was caused by a virtually blocking of the reaction site due to the bulky structure of ATPH. After a series of activating experiments, the optimum activation time of **1a** with ATPH was found to be 2 h at rt. When the reaction time was prolonged, it resulted in a decreased yield (runs 13–15). As ATPH showed encouraging activity,

Keywords: Lewis acid; Phenylglycinol; NOE experiment; Iminium–aluminum complex; Allylic strain.
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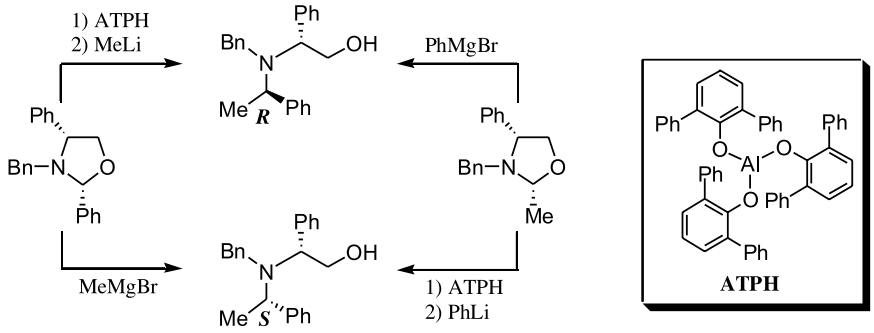
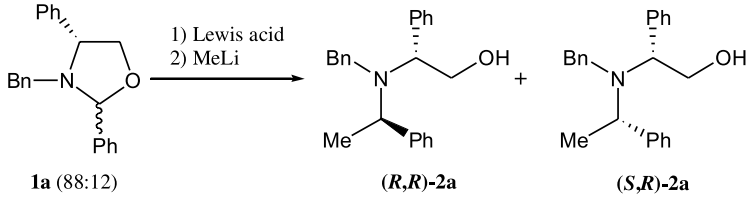


Scheme 1.



Scheme 2.

Table 1. Addition of MeLi to **1a** with Lewis acid

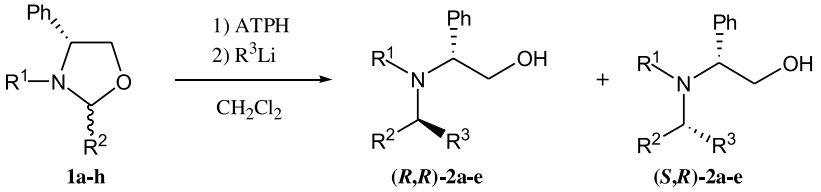
Run	Lewis acid	Activation time (h)	Reaction temperature (°C)	Reaction time (h)	Yield (%)	Ratio (*R*,*R*/*S*,*R*)[a]
1	—	—	rt	20	NR	—
2[b]	BF_3OEt_2	1	rt	20	34	43:57
3[b]	BCl_3	1	rt	20	17	38:62
4	$SnCl_2$	2	−50	20	NR	—
5	$MnBr_2$	2	−50	20	NR	—
6	Et_2Zn	2	−50	20	NR	—
7	$Ln(Otf)_3$	2	−50	20	NR	—
8	$Yb(Otf)_3$	2	−50	20	41	37:63
9	$MgBr_2$	2	−50	20	68	15:85
10	YCl_3	2	−50	20	NR	—
11[b]	Me_3Al	1	rt	20	Trace	—
12[b]	Me_3Al	2	−50	20	72	20:80
13	ATPH	1	−50	20	62	79:21
14	ATPH	1	−50	72	56	67:33
15	ATPH	1	−50	168	19	80:20
16	ATPH	2	−50	20	86	78:22

[a] Estimated by ^{1}H NMR spectrum.
[b] This reaction was carried in THF solvent.

further research looked into the effect of the *N*-substituent of 1,3-oxazolidines at −50 °C.

2.2. Diastereoselective additions of organolithium reagents to N-substituted 1,3-oxazolidines complexed with ATPH

To probe the influence of the *N*-substituent of 1,3-oxazolidine, organolithium reagents were added to various 1,3-oxazolidines complexed with ATPH (Scheme 3, Table 2). N-Substituted 1,3-oxazolidines (**1a–c**,[2a] **1d**,[2b,c] **1f–h**[2a]) were prepared from (*R*)-phenylglycinol in three steps as noted in the literature. **1e** was also prepared from (*R*)-phenylglycinol in the same manner. The diastereomers of **1a–h** were confirmed to be inseparable mixtures in thermodynamic equilibrium differing at the 2 position of the 1,3-oxazolidine ring, and their ratios in $CDCl_3$ were determined from the ^{1}H NMR peak intensities of the 2-H of 1,3-oxazolidine. Addition of organolithium reagents to **1a–h** with ATPH as the Lewis acid gave **2a–e** in 62–98% yield with 78:22 ∼ >99:1 diastereoselectivity. The adducts obtained with ATPH, with the exception of substrate **1b**, showed opposite diastereoselectivities to the adducts obtained with Grignard reactions. The isomer ratios of the adducts were determined from the ^{1}H NMR peak intensity of the 2-Me. The absolute configurations of **2a–c**,[2a] **2d**[2b,c] were previously reported. Treatment of the single isomers (*R*,*R*)-**2e** and (*S*,*R*)-**2e** with TFA gave (*R*,*R*)-**3** in 77% yield



1a-h (*R*,*R*)-2a-e (*S*,*R*)-2a-e

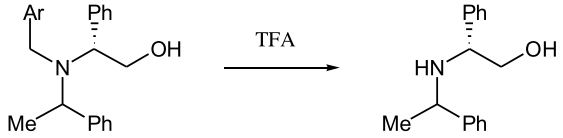
Scheme 3.

Table 2. Addition of R^3Li to **1a–h** with ATPH (cf. Grignard reaction)[a]

Run	Substrate	R^1	R^2	R^3	Yield (%)	Ratio (*R*,*R*/*S*,*R*)[b]	Ratio (*R*,*R*/*S*,*R*)[b]
1	**1a** (88:12)	Bn	Ph	Me	86	78:22	16:84[c]
2	**1b** (97:3)	Me	Ph	Me	98	19:81	34:66[c]
3	**1c** (95:5)	*i*-Pr	Ph	Me	86	97:3	3:97[c]
4	**1d** (89:11)	Diphenylmethyl	Ph	Me	62	84:16	6:94[d]
5	**1e** (90:10)	2,4,6-Trimethylbenzyl	Ph	Me	94	97:3	6:94
6	**1f** (90:10)	Bn	Me	Ph	90	3:97	77:23[c]
7	**1g** (98:2)	Me	Me	Ph	83	27:73	78:22[c]
8	**1h** (98:2)	*i*-Pr	Me	Ph	80	1:>99	88:11[c]

[a] Reaction with R^3MgBr in THF.
[b] Estimated by ^1H NMR spectrum.
[c] See Ref. 2a.
[d] See Ref. 2c.

and (*S*,*R*)-**3** in 84% yield, respectively. The stereochemistry of **3** was established by comparing ^1H NMR spectra with published data[2a–d] (Scheme 4).



2e **3**

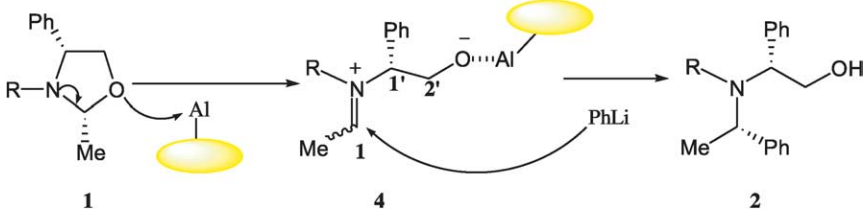
Ar; 2,4,6-trimethylphenyl

Scheme 4.

2.3. Discussion about the diastereoselective addition of organolithium reagents to 1,3-oxazolidines with ATPH based on the geometry of the iminium–aluminum complex

The mechanism of the ring opening of chiral 1,3-oxazolidines has been previously described.[5] First, the metal coordinates to oxygen, and then the C–O bond of the oxazolidine ring is cleaved. As a result, an iminium–metal complex intermediate is formed, with addition of the organometallic reagent giving the chiral amine. We considered the mechanism of addition of organolithium reagents to 1,3-oxazolidines with ATPH to be similar (Scheme 5). However, the geometry of the iminium–aluminum complex (**4**) at the 1 position is not certain, and the diastereoselective process as a whole has not yet been elucidated. To examine the mechanism of addition we determined the geometry of the iminium–aluminum complex by NOE experiment.

A model compound, *N*-isopropyl-2-methyl-1,3-oxazolidine (**1h**), was preferred to the comparative intelligible chart. The ^1H NMR spectra of iminium–aluminum complex (**4h**) prepared from **1h** under usual conditions was assigned by comparison of the decoupling spectra (Fig. 1) with an equivalent C2′ deuterated compound additionally prepared.[6] Trace a shows the high-field region of the spectra of non-deuterated **4h**. Traces b–d show the spin decoupling spectrum acquired by irradiating H2′a, H2′b, and H1″, respectively. In traces b and c, irradiation at H2′a and H2′b was reflected by a change in the H1′ peak from a doublet–doublet to a doublet. Trace d shows that irradiation at H1″ converted the doublet at H2″ into a singlet. Based on these experiments, assignment of the ^1H NMR spectra of **4h** was judged to be consistent. Both NOE difference experiments identified correlation between H2 and H1′ at rt (Fig. 2). The iminium–aluminum complex with an *N*-isopropyl group (**4h**) was found to adopt the *Z* form in $CDCl_3$ (Fig. 3). This result was unexpected because the geometry seemed to be more unstable, as the steric repulsion of the phenethyl group with ATPH would be expected to be greater than that with the isopropyl group. The stereochemistry at the 2 and 3



1 **4** **2**

Scheme 5.

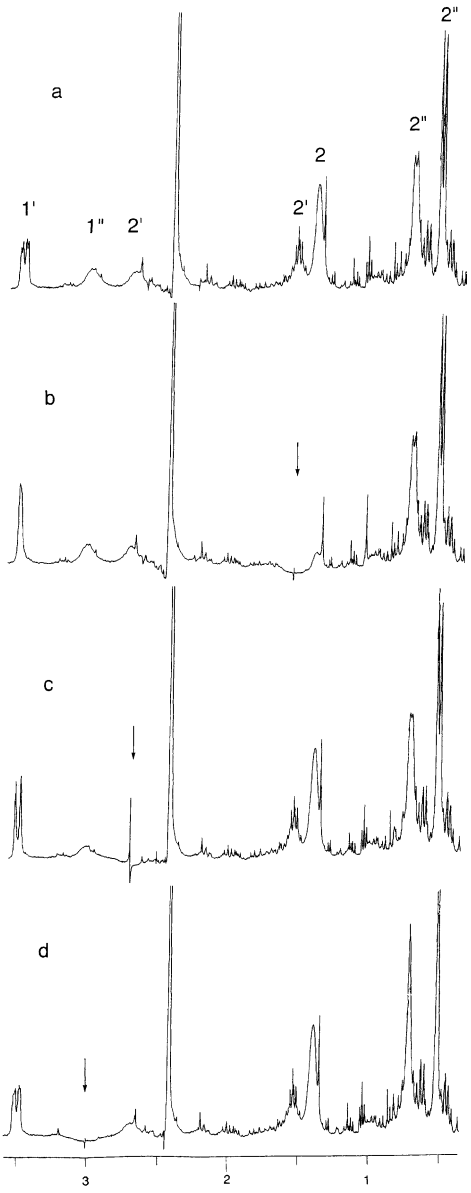


Figure 1. Partial 270 MHz ^{1}H NMR spectrum of **4h** in $CDCl_3$ at 22 °C. (a) Original. (b) Decoupling at 1.6 ppm. (c) Decoupling at 2.7 ppm. (d) Decoupling at 3.0 ppm.

positions of 1,3-oxazolidine might have been important in setting the geometry of the iminium–metal complex. Further, due to the effect of the 1,3-allylic strain, the conformation at C1′ of **4h** is fixed. As a result, the bulky ATPH would situate on the *si* face and the organolithium reagent would attack the iminium–aluminum complex from the *re* face, avoiding ATPH to give (*S*,*R*)-**2c** (Scheme 6). We are still unsure of the exact reason why only ATPH produced this effect when other bulky Lewis acids did not. It may be a result of the remarkable properties of the C_3 symmetrical ATPH, an aluminum center surrounded by bulky ligands in which the aluminum 'peeks out' from a small opening in the ligand sphere. Supposing the mechanism by the observations, the geometry of **4h** related with the configuration at 2 position of oxazolidine (**1h**) and diastereoselectivity of the addition could be a clear explanation. However, in the reactions of **1a**-**1g**, the cause

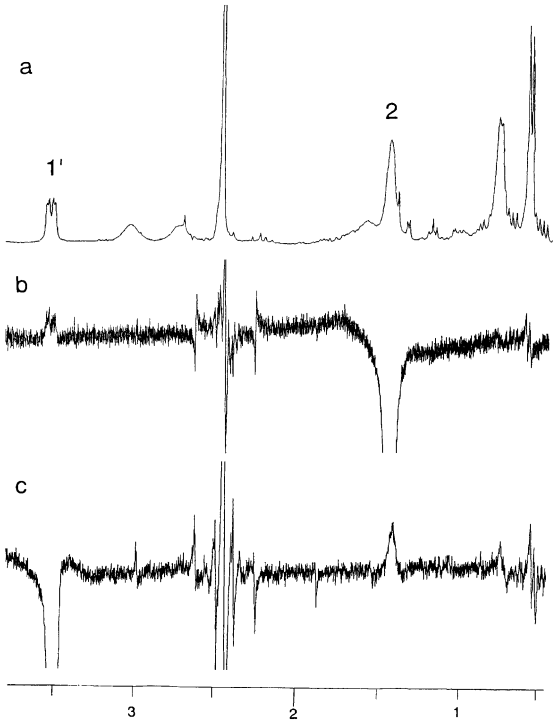


Figure 2. Trace a shows the partial one-dimensional 270 MHz ^{1}H NMR spectrum of **4h** in $CDCl_3$ at 22 °C. Traces b and c are the steady-state NOE difference spectra obtained, when H2 and H1′ are saturated.

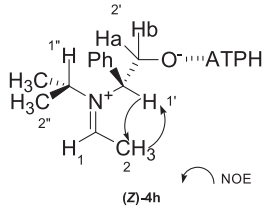
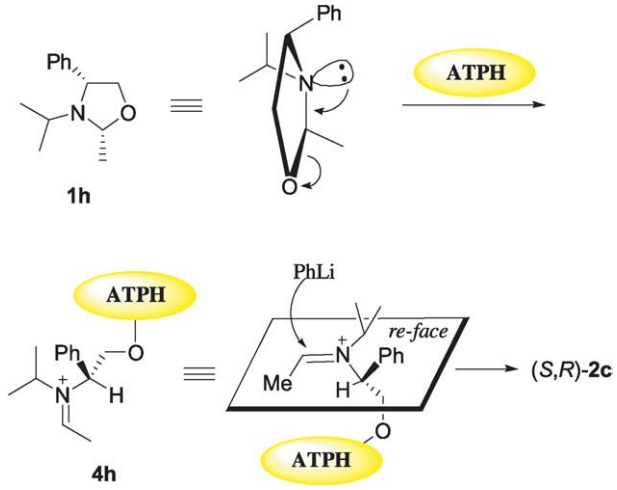


Figure 3.



Scheme 6.

of diastereoselectivity is imprecise, because we were unable to characterize their complexes.

3. Conclusion

1,3-Oxazolidines were reacted with organolithium reagents using the bulky Lewis acid ATPH. The reactions were achieved with high yield and high diastereoselectivity, and the products showed opposite diastereoselectivity to products of Grignard reaction. The best diastereoselectivities were obtained for addition of 1,3-oxazolidines having *N*-isopropyl and 2,4,6-trimethylbenzyl groups. Chiral amines could be synthesized with opposite diastereoselectivity from a chiral 1,3-oxazolidine depending on whether Grignard reagents or ATPH-organolithium reagents were used. ATPH was shown to have activating ability due to effective coordination of the iminium–aluminum complex with the *N*,*O*-acetal. A variation of this method may be useful for the asymmetric synthesis of compounds with medical applications, including physiologically active natural products.

4. Experimental

4.1. General

Melting points were measured with a Yanagimoto Micro melting Point apparatus without collection. IR spectra were recorded on a 215 Hitachi Granting IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL GSX 270 instrument, and chemical sifts are reported in ppm on the δ-scale from internal Me_4Si. MS spectra were measured with a JEOL JMS D-300 spectrometer by using the chemical ionization (CI) with isobutene and the electron impact (EI) methods. Elemental analyses were performed on a Perkin–Elmer 240-B instrument. Optical rotation were taken with a JASCO-DIP-370 polarimeter at rt. Sibata Glass Tube Oven GTO-350RD was used as distillation apparatus. Column chromatography was performed on silica gel (45–75 μm, Wakogel C-300). The reaction solvents were prepared as the following. THF was distilled over potassium metal. Dichloromethane was distilled over phosphorus pentoxide. Ether and toluene were distilled over sodium metal.

4.1.1. (2*R*,4*R*)-*N*-(2,4,6-Trimethylbenzyl)-2,4-diphenyl-1,3-oxazolidine (1e). A mixture of (*R*)-phenylglycinol (6.85 g, 50 mmol) and 2,4,6-trimethylbenzylaldehyde (7.41 g, 50 mmol) in benzene (100 mL) was refluxed for 1 h with a Dean–Stark trap. After being cooled, the mixture was concentrated under reduced pressure, and the residue was dissolved in methanol (100 mL). To this solution was added portionwise $NaBH_4$ (4.73 g, 125 mmol) at rt. After the reaction mixture was stirred for 40 min, it was added with water (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized (EtOAc–hexane) to afford (*R*)-*N*-2,4,6-trimethylbenzylphenylglycinol (89%) as colorless needles. Mp 98–99 °C. $[\alpha]_D^{22}=-72.5$ (*c* 1.00, $CHCl_3$). MS *m*/*z*: CI, 270 ($M^+ +1$, base peak); EI, 269 (M^+), 238 ($M^+ - CH_2OH$), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3440 (O–H, N–H). ^{1}H NMR ($CDCl_3$) δ: 1.42 (1H, br), 2.25 (9H, s), 2.69 (1H, br), 3.47–3.76 (4H, m), 3.83 (1H, dd, $J=9.2$, 4.8 Hz), 6.84 (2H, s), 7.29–7.42 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 19.39q, 20.95q, 45.53t, 65.40d, 66.56t, 127.30d, 127.66d, 128.62d, 129.06d, 133.33s, 136.59s, 137.00s, 140.71s. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.01; H, 8.95; N, 4.96. A mixture of above compound (5.38 g, 20 mmol) and benzaldehyde (6.36 g, 60 mmol) in benzene (100 mL) was refluxed for 20 h with a Dean–Stark trap. After being cooled, the mixture was concentrated under reduced pressure. The residue was distilled (231 °C, 4 mm Hg) to afford **1e** (88%, 90:10 mixture) as colorless oil. $[\alpha]_D^{20}=-7.40$ (*c* 1.00, $CHCl_3$). MS *m*/*z*: CI, 358 ($M^+ +1$, base peak); EI, 357 (M^+), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3030, 2950, 2860 (C–H). ^{1}H NMR ($CDCl_3$) δ: major component; 2.03 (3H, s), 2.09 (6H, s), 3.64 (1H, d, $J=$ 12.4 Hz), 3.68 (1H, d, $J=12.4$ Hz), 3.97 (2H, m), 4.32 (1H, m), 5.12 (1H, s), 6.41 (2H, s), 7.12–7.41 (10H, m). ^{13}C NMR ($CDCl_3$) δ: major component; 20.33q, 20.66q, 49.59t, 69.05d, 74.52t, 98.66d, 127.15d, 127.35d, 127.73d, 127.77d, 127.88d, 128.44d, 128.48d, 130.77s, 136.21s, 137.20s, 139.98s, 140.11s. HRMS calcd for $C_{25}H_{27}NO$: 357.2093. Found: 357.2071.

4.2. General procedure for the addition of organolithium reagent to 1a–h with ATPH

A mixture of 2,6-diphenylphenol (0.55 g, 2.25 mmol) and Me_3Al (1.75 mL, 0.75 mmol; 1 M in hexane) in dry CH_2Cl_2 (2 mL) was stirred at rt under nitrogen for 30 min to afford the solution of ATPH.[6] To this solution was added the solution of oxazolidine (**1a–h**) (0.5 mmol) in dry CH_2Cl_2 (3 mL) and stirred at rt for 2 h. The solution was cooled to −50 °C, and organolithium (1.5 mL, 1.5 mmol, 1 M solution) was added dropwise to it. After being stirred at −50 °C for 20 h, the reaction mixture was treated with a small amount of water, and the resulting white precipitate was filtered off. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane–ether (2:1) to give a diastereomeric mixture of amine (**2a–e**).

4.2.1. (1*R*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-*N*-2,4,6-trimethylbenzyl-1-phenylethylamine (*R*,*R*-2e). Yield 86% (97:3 mixture). Diastereomers were separated by column chromatography on silica gel with hexane–ether (3:1) to give pure (*R*,*R*)-**2e** as colorless oil. $[\alpha]_D^{22}=-115.5$ (*c* 1.27, $CHCl_3$). MS *m*/*z*: CI, 374 ($M^+ +1$, base peak); EI, 373 (M^+), 342 ($M^+ - CH_2OH$), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3500 (O–H). ^{1}H NMR ($CDCl_3$) δ: 1.28 (3H, d, $J=$ 7.1 Hz), 1.82 (1H, br), 2.24 (3H, s), 2.28 (6H, s), 3.39 (1H, m), 3.85 (4H, m), 4.01 (1H, q, $J=7.1$ Hz), 6.84 (2H, s), 7.20–7.46 (10H, m). ^{13}C NMR ($CDCl_3$) δ: 13.64q, 20.15q, 20.82q, 45.44t, 54.96d, 62.39t, 62.94d, 126.95d, 127.60d, 128.34d, 128.36d, 2×129.54d, 132.13s, 136.62s, 138.03s, 139.06s, 144.42s. Anal. Calcd for $C_{26}H_{31}NO$: C, 83.60; H, 8.37; N, 3.75. Found: C, 83.64; H, 8.32; N, 3.64.

4.2.2. (1*S*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-*N*−2,4,6-trimethylbenzyl-1-phenylethylamine (*S*,*R*-2e). Methylmagnesium bromide (0.5 mL, 1.5 mmol, 3 M in ether) was

added dropwise to a stirred solution of oxazolidine (**1e**) (0.5 mmol) in dry THF (5 mL) at rt under nitrogen over 10 min period. After the reaction mixture was stirred for 20 h, it was quenched with a small amount of water and diluted with ether (10 mL). The resulting white precipitate was filtered off, and the filtrate was washed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with ether (2×10 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a oily residue, which was subjected to column chromatography on silica gel with hexane–ether (2:1) to give a diastereomeric mixture of amine (**2e**) (85% yield, 94:6 mixture). Diastereomers were separated by column chromatography on silica gel with hexane–ether (3:1) to give pure (*S*,*R*)-**2e** as colorless oil. $[\alpha]_D^{24} = -68.0$ (*c* 1.40, $CHCl_3$). MS *m/z*: CI, 374 ($M^+ + 1$, base peak); EI, 373 (M^+), 342 ($M^+ - CH_2OH$), 133 (base peak). IR ($CHCl_3$, cm^{-1}): 3440 (O–H). ^1H NMR ($CDCl_3$) δ: 1.51 (3H, d, $J=7.1$ Hz), 1.55 (1H, br), 2.05 (6H, s), 2.22 (3H, s), 3.66 (1H, d, $J=12.7$ Hz), 3.86 (1H, dd, $J=9.4$, 4.9 Hz), 4.01 (1H, d, $J=12.7$ Hz), 4.02 (1H, q, $J=7.1$ Hz), 4.15 (1H, dd, $J=10.7$, 4.9 Hz), 4.26 (1H, dd, $J=10.7$, 9.4 Hz), 6.77 (2H, s), 6.87–7.01 (4H, m), 7.13–7.29 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 16.03q, 19.75q, 20.78q, 43.82t, 54.71d, 61.10t, 61.65d, 126.49d, 126.99d, 127.57d, 128.08d, 128.25d, 128.78d, 129.23d, 132.45s, 136.27s, 138.21s, 139.96s, 143.97s. Anal. Calcd for $C_{26}H_{31}NO$: C, 83.60; H, 8.37; N, 3.75. Found: C, 83.79; H, 8.51; N, 3.72.

4.3. General procedure for removal of the *N*-2,4,6-trimethylbenzyl group from (*R*,*R*)- and (*S*,*R*)-2e

A single diastereomer of (*R*,*R*)- and (*S*,*R*)-**2e** (0.134 mmol) and trifluoroacetic acid (5 mL) was stirred at 50 °C for 3 days, and then diluted with water (20 mL). The resulting aqueous phase was basified with 10% NaOH solution and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave a oily residue, which was subjected to column chromatography on silica gel with ethyl acetate–hexane (1:2) to give (*R*,*R*)- and (*S*,*R*)-**3**, respectively.

4.3.1. Synthesis of (*Z*,*R*)-*N*-isopropyliminium–aluminum complex (4h) for NOE experiment. A mixture of 2,6-diphenylphenol (0.148 g, 0.6 mmol) and Me_3Al (0.1 mL, 0.2 mmol; 2 M in toluene) in dry CH_2Cl_2 was stirred at rt under nitrogen for 30 min to afford the solution of ATPH.[6] Then the solution was concentrated under reduced pressure and residue was solved in $CDCl_3$ (0.5 mL). To this solution was added the solution of oxazolidine (**1c**) (0.1 mmol) in $CDCl_3$ (0.5 mL) and stirred at rt for 2 h to obtain the $CDCl_3$ solution of iminium–aluminum complex (**4h**). The solution was used for NOE experiment without purification and the data was showed some peak for complicated chart: ^1H NMR ($CDCl_3$) δ: 0.55 (3H, brd), 0.75 (3H, brd), 1.41 (3H, br), 1.54 (1H, br), 2.67 (1H, br), 2.99 (1H, br), 3.50 (1H, brdd), 6.52 (2H, brd).

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6. The assignment of ^1H NMR spectrum on 1′ and 2′ position of **4h** determined as follows. 2′-Dideuteriumed iminium–aluminum complex (**4h′**) was obtained from (*R*)-phenylglycine with $LiAlD_4$ for 5 steps by the similar procedure.[4] In **4h′**, the signals of ^1H NMR spectrum on 2′ position (δ: 1.54, 2.67 ppm) were not observed, and the signal on 1′ position (δ: 3.50 ppm) was observed. Therefore, the assignment of ^1H NMR spectrum on 1′ and 2′ position of **4h** was determined.

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Chemical and enzymatic synthesis of glycocluster having seven sialyl lewis X arrays using β-cyclodextrin as a key scaffold material

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Abstract—An efficient and practical method for the large-scale synthesis of an anti-inflammatory glycocluster having seven sialyl Lewis X (SLeX) residues was established on the basis of chemical and enzymatic strategy from β-cyclodextrin (β-CD) as a key starting scaffold material. A key intermediate, β-CD derivative having seven *N*-acetyl-D-glucosamine (GlcNAc) residues [$(GlcNAc)_7CD$], was prepared by a coupling reaction with heptakis 6-deoxy-6-iodo-β-cyclodextrin and sodium thiolate containing a GlcNAc residue. Subsequent sugar elongation reactions of $(GlcNAc)_7CD$ proceeded smoothly by means of β-1,4-galactosyltransferase, α-2,3-sialyltransferase, and α-1,3-fucosyltransferase V in the presence of the corresponding sugar nucleotides (UDP-Gal, CMP-Neu5Ac, and GDP-Fuc) and allowed to give a mono-dispersed glycodendrimer ($M_w = 7924.5$, calcd for $C_{301}H_{490}N_{21}O_{196}S_7Na_7$; MALDI-TOF MS, *m/z* 7946 $[M+Na]^+$) that completely substituted with seven SLeX branches at C-6 positions in excellent overall yield (74%, 3 steps). Hyper-branched glycodendrimer, $(SLeX)_7CD$, exhibited highly amplified inhibitory effect on the interaction of E-selectin with SLeXn-BSA immobilized on the sensor chip by means of surface plasmon resonance method.

1. Introduction

L, P and S-selectins are a family of transmenbrane glycoproteins responsible for the adhesion of leukocytes to the vascular endothelium cells in the early cascade of events leading to inflammation.[1] The tethering and rolling of leukocytes on endothelial cells of blood vessels are the initial stage in the recruitment of leukocytes to inflamed tissue.[2] Sialylated and fucosylated oligosaccharides related to sialyl Lewis X tetrasaccharide [Neu5Acα2,3-D-Galβ1,4-(L-Fucα1,3)-D-GlcNAcβ1-OR, SLeX] are the minimal carbohydrate structural motif expressed on leukocytes and on endothelial cell surfaces that is required for the initial recognition by L-selectin on leukocytes. Conventional structure activity relationship studies have led to the development of numerous SLeX related analogs in the research for potential anti-inflammatory agents.[3] However, it is well documented that the binding affinity of low-molecular weight of SLeX derivatives with selectins is generally weak under equilibrium conditions.[4] At present, there is no ideal candidate for further clinical trials on the basis of small SLeX derivatives. The glycoside cluster effect proposed by Lee[5] has attracted considerable attention for amplified interaction with selectins and promoted extensive efforts by synthetic chemists to design a variety of multivalent glycoligands. Recent efforts have been focused on the increase of the affinity by designing mimics of SLeX and through multivalent interaction based on the general glycoside cluster effect.[6] In addition, Kunz et al. reported that chemically synthesized rigid cyclic peptides carrying trivalent SLeX showed improved inhibitory effect on the interaction between recombinant E-selectin-IgG fusion protein and tumor cells carrying SLeX ligands (HL_{60}).[7] We also demonstrated that the effect of cyclic glycopeptides having triantennary sialooligosaccharides, glycotentacles, on anti-influenza virus infection through the binding with hemagglutinin is greatly influenced by the amino acid sequences of the cyclic peptides as a scaffold molecule.[8] Considering that clustered arrangements of biological forms

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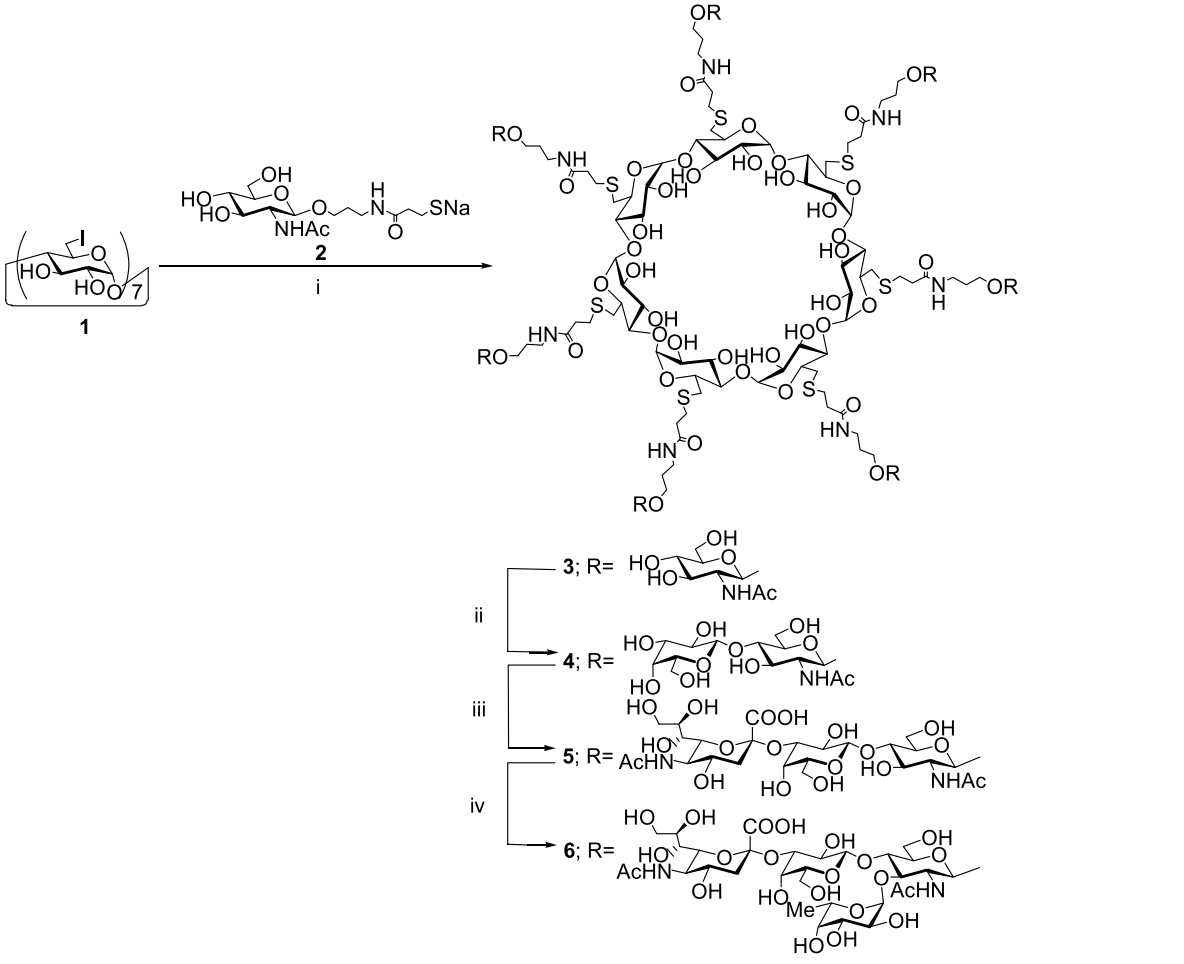
both in proteins (selectins) and in their natural ligands (SLeX), these results may suggest the importance of the functional role of the scaffolds for displaying sugar chains arrays with an appropriate form in the successful binding with multiple selectin lattices on the cell surfaces.[9] Although polyvalency using synthetic polymers is of growing interest from a view point of functional materials in biotechnology,[10] it should also be noted that heterogeneity due to the molecular weight distribution of the polymer-based multivalent reagents may often become critical problem to the clinical trial stages. Therefore, advent of the efficient and practical synthetic strategy of chemically and structurally well-defined multivalent SLeX molecules is now strongly required.

Cyclodextrins are potent scaffolds for the synthesis of structurally well-characterized glycoclusters termed as glycoCDs. They are useful tools to discuss the effects of topology and direction as well as flexibility of substituted sugars on multivalency and cluster effects.[11,12] We have established a facile method for the chemical synthesis of a versatile per-glycosylated cyclodextrins though nucleophilic substitution reaction of heptakis 6-deoxy-6-iodo-β-cyclodextrin (**1**) with simple sodium thiolates derived from 3-(3-thioacetyl propionamido)propyl glycosides.[13] It was also demonstrated that persubstituted cyclodextrin-based glycoclusters having Gal, Galβ1,4Glc, and Galβ1,4GlcNAc become powerful inhibitors of protein-carbohydrate recognition using purified plant and mammalian lectins, and wild-type and galectin-gene-transfected tumor cells as targets.[14] To expand the potential of cyclodextrin-based glycoclusters as practical therapeutic reagents, our attention is now focused on the highly efficient and practical synthesis of the glycodendrimer bearing seven SLeX arrays (**6**) based on the combined chemical and enzymatic modifications of β-cyclodextrin. In the present communication, we would like to report the feasibility of the precise synthesis of cyclodextrin-scaffolded glycodendrimer showing highly amplified inhibitory effect on the interaction of recombinant E-selectin with immobilized multiple SLeX-BSA conjugates as a model of the cell surface ligands lattices.

2. Results and discussion

Scheme 1 indicates the synthetic route of the target glycodendrimer, $SLeX_7CD$ (**6**), using heptakis{6-deoxy-6-S-[7-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-4-aza-3-oxo-heptano-1-yl]-6-thio}-cyclomaltoheptaose, $(GlcNAc)_7$-CD (**3**), prepared from the nucleophilic substitution reaction between β-cyclodextrin derivative **1** and thiolate **2**.[13] Compound **3** was employed for the subsequent stepwise



Scheme 1. *Reagents and conditions*: (i) DMF, 70 °C, 24 h, 88%; (ii) UDP-Galactose, β1,4-GalT, $MnCl_2$, 50 mM HEPES buffer (pH 6.0), 37 °C, 48 h, 87%; (iii) CMP-NeuAc, α2,3-SiaT, calf intestine alkaline phosphatase, $MnCl_2$, BSA, Triton CF-54, 50 mM sodium cacodylate buffer (pH 7.4), 37 °C, 48 h, 92%; (iv) GDP-Fuc, α1,3-FucT V, calf intestine alkaline phosphatase, $MnCl_2$, 50 mM sodium cacodylate buffer (pH 6.5), 37 °C, 72 h, 95%.

modification study by three glycosyltransfarases in the presence of each sugar nucleotide as sugar donor substrate. Incubation of $(GlcNAc)_7CD$ **3** with UDP-galactose (UDP-Gal) and bovine milk β-1,4 galactosyltransferase (β-1,4-GalT) in 50 mM HEPES buffer (pH 6.0, containing 10 mM $MnCl_2$) gave $(LacNAc)_7CD$ **4** in 87% yield. It was found that there is no contamination due to by-products in the major fraction after simple size exclusion chromatography on Sephadex G-25 column using water as eluant, suggesting that galactosylation proceeded smoothly and topology of seven GlcNAc residues on the dendritic substrate seemed to serve an appropriate accessibility to the enzyme active site. Similarly, $(LacNAc)_7CD$ **4** was treated with CMP-*N*-acetylneuraminic acid (CMP-Neu5Ac), rat recombinant α-2,3 sialyltransferase (α-2,3-SiaT) and alkaline phosphatase in 50 mM sodium cacodylate buffer (pH 7.4, containing 5 mM $MnCl_2$) and gave (Sialyl $LacNAc)_7CD$ **5** with seven α-2,3-linked NeuAc residues in 92% yield after the same purification process. Finally, treatment of (Sialyl $LacNAc)_7$-CD **5** with GDP-fucose (GDP-Fuc), human recombinant α-1,3-fucosyltransferase V (α-1,3-FucT V) and alkaline phosphatase in 50 mM sodium cacodylate buffer (pH 6.5, containing 10 mM $MnCl_2$) afforded $SLeX_7CD$ **6** having seven SLeX residues in 95% yield.

As shown in Figure 1, the appearance of the new signals due to H-1 of the Gal residue (4.48 ppm), H-3eq of the Neu5Ac residue (2.75 ppm) and H-1 of the Fuc residue (5.10 ppm) were observed in the ^{1}H-NMR spectra of the compounds **4**, **5** and **6**, respectively. It was clearly suggested from the relative integration values of these spectra that each enzymatic modification proceeded completely and provided fully-substituted new glycodendrimers bearing seven sialo-oligosaccharides **5** and **6**. All the signals of the ^{13}C-NMR spectrum were determined as sharp and simple singlets, representing the seven-fold symmetric branched structures (Supporting information). As a result, all sugar elongation reactions of $(GlcNAc)_7CD$ proceeded in satisfactory efficacy by means of three enzymes and allowed to give a mono-dispersed glycodendrimer (M_w=7924.5, calcd for $C_{301}H_{490}N_{21}O_{196}S_7Na_7$; MALDI-TOF MS, *m/z*: 7946 $[M+Na]^+$) that completely substituted with seven SLeX branches at C-6 positions in excellent overall yield (74%, 3 steps). Although the mechanism of the mode of action in the extremely improved sugar elongation reactions by enzymes to the cyclodextrin-based acceptor substrates, it was demonstrated that seven GlcNAc residues displayed on the C-6 positions of β-cyclodextrin through the flexible spacer moiety can be applied for further precise and large-scale modifications by glycosyltransferase families.[15] Merit of the present synthetic strategy is evident because precisely incorporated multivalent oligosaccharides onto the structurally well-defined macrocyclic scaffolds will provide fundamental insights into the significance of the topologies of sugar ligands in carbohydrate recognitions.[8,9]

Inhibitory effect of glycodendrimers on the interaction between E-selectin and neoglycoprotein having multiple SLeX residues (SLeXn-BSA) as a suited model of the intact biological forms related to the tethering and rolling of leukocytes on endothelial cells of blood vessels was preliminarily investigated on the basis of surface plasmon resonance (SPR) method. Compounds **5**, **6**, and SLeX as a

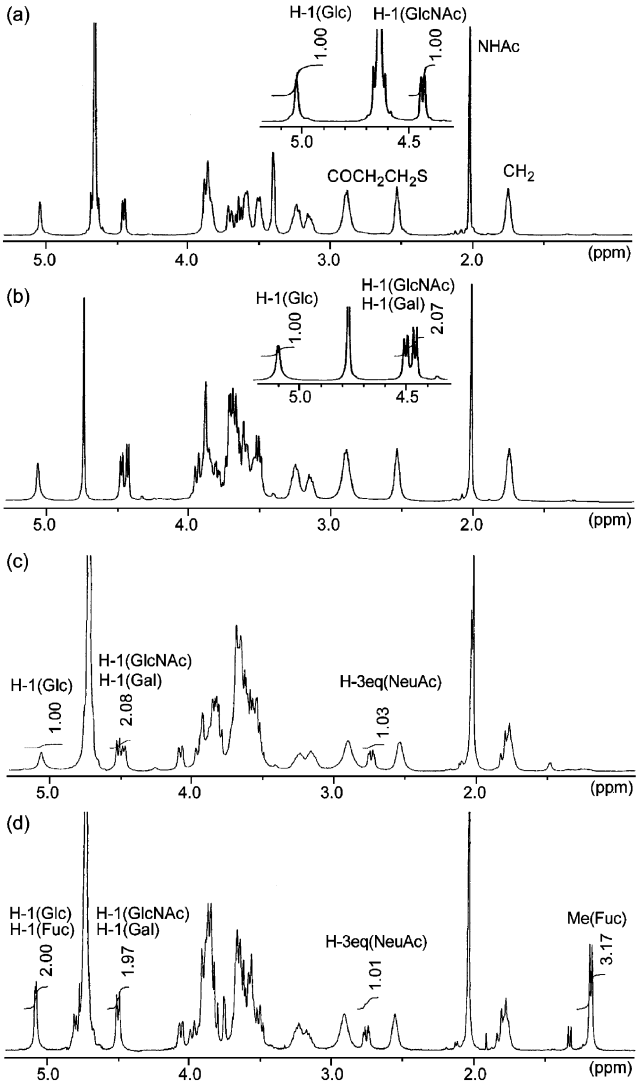


Fig. 1. ^{1}H-NMR spectra of glycoclusters **3** (a), **4** (b), **5** (c) and **6** (d).

control were tested for the inhibition assay and the results were indicated in Figure 2(a). It was suggested that compound **6**, $SLeX_7CD$, showed highly enhanced inhibitory effect (IC_{50}=1.5 mM as normalized concentration) toward the tight binding of E-selectin with immobilized SLeXn-BSA chip, while both SLeX and (Sialyl $LacNAc)_7CD$ **5** did not show any significant inhibition under the same condition. SLeXn-BSA complex has about 10 SLex moieties per single BSA. Due to its glycocluster effect, the complex on the sensor chip binds to E-selectin with an enhanced affinity as detected in case of solution. Thus, the apparent IC_{50} seems much greater than real K_d value between E-selectin and injected inhibitors. It is noteworthy that CD-based compounds **5**, **6** and SLeX did not exhibit any non-specific adsorption onto the surface of SPR sensor chip displaying SLeXn-BSA. The results clearly demonstrate that the enhanced inhibitory effect by $SLeX_7CD$ was due to the clustered SLeX arrays displayed on β-CD. This means that SLeX arrays on the CD-based glycocluster **6** could bind efficiently with selectins even in the presence of two-dimensional and multiple SLeX lattices as a model of natural competitor (Fig. 2(b)).

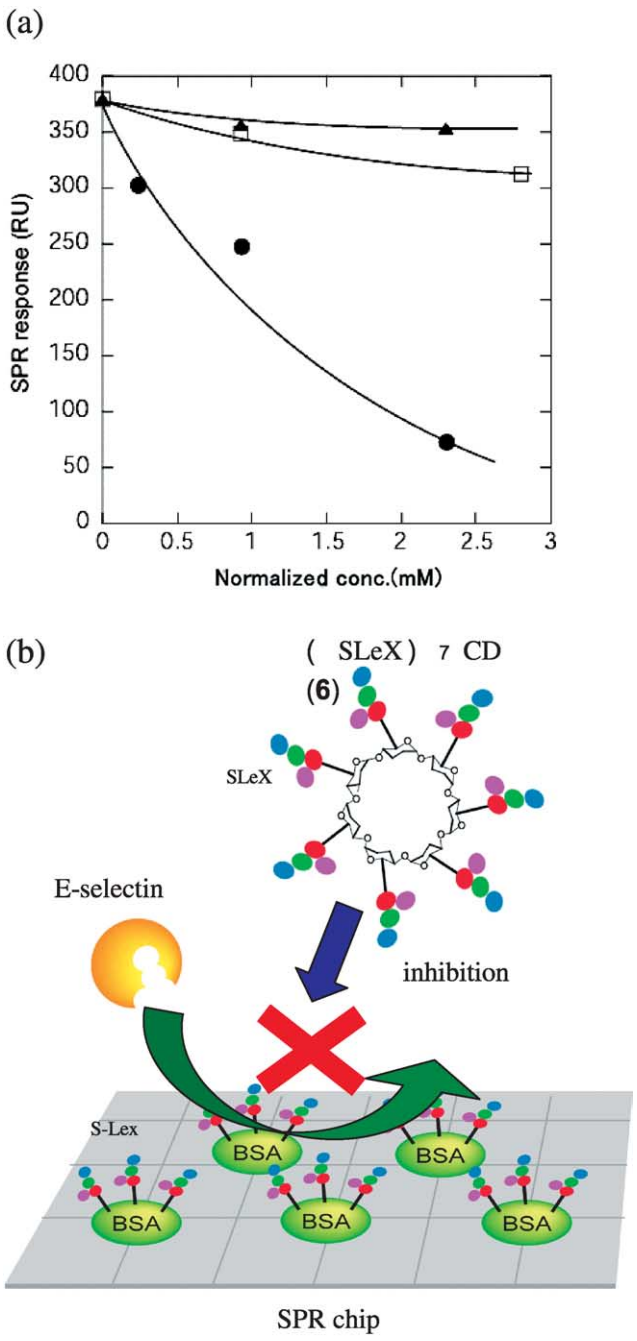


Fig. 2. (a) Inhibitory effect of glycoclusters **5** (▲), **6** (●), and SLeX (□) on the interaction of E-selectin with immobilized SLeXn-BSA. (b) Plausible mechanism of the inhibition by glycocluster **6**.

In conclusion, we have established an efficient and practical method for the large-scale synthesis of an anti-inflammatory glycocluster having seven sialyl Lewis X (SLeX) residues on the basis of chemical and enzymatic strategy. Hyperbranched glycocluster, $(SLeX)_7CD$, exhibited highly amplified inhibitory effect on the interaction of E-selectin with SLeXn-BSA immobilized on the sensor chip by means of surface plasmon resonance method. Versatility of our synthetic strategy of glycoclusters and glycoamphiphiles[16] using CD as a key starting material is under investigation and the results will be reported as soon as possible.

3. Materials and methods

3.1. General procedures

Proton (^{1}H-) and ^{13}C-NMR spectra were recorded at 400 MHz and 100 MHz on a JEOL lambda-400 spectrometer. Elemental analyses were performed with a Yanako CHN corder MT-6. Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) Mass Spectrometry was carried out on a Shimazu/KRATOS AXIMA-CFR instruments using 2,5-dihydroxy benzoic acid as a matrix. The instrument was operated in the positive ion linear mode with an accelerating potential of 20 kV. Optical rotations were determined with a Perkin–Elmer 241 polarimeter for samples in a 10 cm cell at ambient temperature (22±2 °C). β-1,4-Galactosyltransferase from bovine milk was purchased from Sigma Co. Ltd. α-2,3-Sialyltransferase from rat recombinant and α-1,3-fucosyltransferase V from human recombinant were purchased from Calbiochem Co. Ltd. GlycoCD having GlcNAc residues **3** was prepared according to the procedure described in the previous paper.[13]

3.2. Synthesis

3.2.1. Heptakis{6-deoxy-6-S-[7-(2-acetamido-4-O-(β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranosyl-oxyl)-4-aza-3-oxo-heptano-1-yl]-6-thio}-cyclomaltoheptaose (4). To a solution of **3** (60.0 mg, 16.8 μmol) in 50 mM HEPES buffer pH 6.0 (1.0 mL), containing 10 mM $MnCl_2$, and 1 mM NaN_3, were added UDP-galactose (96.8 mg, 158.6 μmol) and bovine milk β-1,4-galactosyltransferase (1 U). The mixture was incubated for 48 h at 37 °C and ultrafiltrated with a membrane having a molecular weight cut-off of 300 kDa. The obtained residue was concentrated and applied to a Sephadex G-25 column (4×60 cm) eluted with water. The appropriate fractions were freeze-dried to give **4** (69.0 mg, 87%); $[\alpha]_D=+23.5°$ (*c* 0.553, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 5.07(brs, 7H, H-1 of Glc), 4.48 (d, 7H, $J_{1,2}=7.5$ Hz, H-1 of Gal), 4.44 (d, 7H, $J_{1,2}=7.9$ Hz, H-1 of GlcNAc), 2.89 (brs, 14H, CH_2S), 2.53 (brs, 2H, $COCH_2$), 2.01 (s, 21H, $NHCOCH_3$) and 1.74 (brs, 14H, CH_2); ^{13}C NMR (D_2O, 100 MHz) δ 176.34, 175.75 (C=O), 105.15 (C-1 of Gal), 104.01 (C-1 of Glc), 103.24, (C-1 of GlcNAc), 86.63 (C-4 of Glc), 81.12, 77.50, 76.96, 75.01, 74.82, 74.66, 74.49, 74.37, 73.17, 70.75, 69.87, 63.12, 62.48, 57.32 (C-2 of GlcNAc), 38.45, 38.25, 35.30 (C-6 of Glc), 30.99, 30.84 and 24.51; Anal. calcd for $C_{182}H_{308}N_{14}O_{112}S_7\cdot 10H_2O$: C, 44.22; H, 6.69; N, 3.97; S, 4.54. found: C, 44.20; H, 6.62; N, 3.71; S, 4.69; MALDI-TOF MS: *m/z*: calcd for $C_{182}H_{308}N_{14}O_{112}S_7$ 4709.0. found: 4731.4 $[M+Na]^+$.

3.2.2. Heptakis{6-deoxy-6-*S*-[7-(2-acetamido-4-*O*-(3-*O*-(5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonic acid)-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranosyl-oxyl)-4-aza-3-oxo-heptano-1-yl]-6-thio}-cyclomaltoheptaose (5). To a solution of **4** (25.0 mg, 5.31 μmol) in 50 mM sodium cacodylate buffer pH 7.4 (1.0 mL), containing 5 mM $MnCl_2$, bovine serum albumin (1.0 mg), 1 mM NaN_3 and Triton CF-54 (0.05 v/v%), were added CMP-*N*-acetyl-neuraminic acid (33.0 mg, 50.2 μmol), calf intestine alkaline phosphatase (20 U) and

rat recombinant α-2,3-sialyltransferase (100 mU). The mixture was incubated for 48 h at 37 °C and ultrafiltrated with a membrane having a molecular weight cut-off of 300 kDa. The filtrate was subjected to a Dowex 50W-X8 (Na^+) column with water as eluent. The obtained eluate was concentrated and the residue was applied to a Sephadex G-50 column (3.5×45 cm) eluted with water. The appropriate fractions were freeze-dried to give **5** (33.0 mg, 92%); $[\alpha]_D = +7.4°$ (*c* 0.236, H_2O); ^{1}H-NMR (D_2O, 400 MHz) δ 5.10 (brs, 7H, H-1 of Glc), 4.55 (d, 7H, H-1 of Gal), 4.51 (d, 7H, H-1 of GlcNAc), 4.12 (brd, 7H, H-3 of Gal), 2.92 (brs, 14H, CH_2S), 2.75 (brd, 7H, H-3eq of NeuAc), 2.55 (brs, 14H, COCH_2), 2.04 (s, 21H, NHCOCH_3), 2.03 (s, 21H, NHCOCH_3) and 1.84-1.72 (m, 21H, CH_2 and H-3ax of NeuAc); ^{13}C-NMR (D_2O, 100 MHz) δ 177.72, 176.92, 176.40, 176.29 (C=O), 105.46 (C-1 of Glc), 104.70 (C-1 of Gal), 103.76 (C-1 of GlcNAc), 102.59 (C-2 of NeuAc), 87.46 (C-4 of Glc), 81.48, 78.22, 77.78, 77.44, 75.57, 75.57, 75.09, 74.81, 74.38, 72.22, 72.22, 72.03, 70.93, 70.93, 70.36, 70.22, 65.36, 63.62, 62.92, 57.78 (C-2 of GlcNAc), 54.43 (C-5 of NeuAc), 42.35 (C-3 of NeuAc), 38.92, 38.72, 35.76 (C-6 of Glc), 31.54, 31.30, 24.98 and 24.71; MALDI-TOF MS: *m/z*: calcd for $C_{259}H_{420}N_{21}O_{168}S_7Na_7$ 6901.5. Found: 6922.0 $[M+Na]^+$.

3.2.3. Heptakis{6-deoxy-6-*S*-[7-(2-acetamido-4-*O*-(3-*O*-(5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-non-2-ulopyranosylonic acid)-2-*O*-(α-D-fucopyranosyl)-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranosyl-oxyl)-4-aza-3-oxo-heptano-1-yl]-6-thio}-cyclomaltoheptaose (6). To a solution of **5** (15.0 mg, 2.22 μmol) in 50 mM sodium cacodylate buffer pH 6.5 (500 μL) containing 10 mM $MnCl_2$ were added GDP-fucose (13.3 mg, 21.0 μmol), calf intestine alkaline phosphatase (20 U) and human recombinant α-1,3-fucosyltransferase V (100 mU). The mixture was incubated for 72 h at 37 °C and ultrafiltrated with a membrane having a molecular weight cut-off of 300 kDa. The filtrate was subjected to a Dowex 50W-X8 (Na^+) column with water as eluent. The solution containing product was concentrated and the residue was applied to a Sephadex G-50 column (3.5×45 cm, eluent: water). The appropriate fractions were collected and freeze-dried to give **6** (16.4 mg, 95%); $[\alpha]_D = -23.9°$ (*c* 0.248, H_2O); ^{1}H-NMR (D_2O, 400 MHz) δ 5.11–5.08 (brd, 14H, H-1 of Glc and Fuc), 4.82 (brd, 7H, H-5 of Fuc), 4.52 (brd, 14H, H-1 of GlcNAc and Gal), 4.09 (d, 7H, H-3 of Gal), 2.91 (brs, 14H, CH_2S), 2.76 (dd, 7H, H-3eq of NeuAc), 2.55 (brs, 14H, COCH_2), 2.03 (2 s, 42H, NHCOCH_3), 1.84–1.72 (m, 21H, CH_2 and H-3ax of NeuAc) and 1.16 (d, 21H, Me of Fuc); ^{13}C-NMR (D_2O, 100 MHz) δ 177.69, 176.62, 176.37, 176.25 (C=O), 104.50 (C-1 of Glc), 104.37 (C-1 of Gal), 103.53 (C-1 of GlcNAc), 102.41 (C-2 of NeuAc), 101.08 (C-1 of Fuc), 87.07 (C-4 of Glc), 78.36, 78.02, 77.44, 77.44, 76.20, 75.58, 74.83 (C-2, 3, 5 of Glc), 74.59, 74.45, 71.93, 71.93, 70.88, 70.88, 70.44, 70.44, 70.09, 69.25, 65.36, 64.00, 64.48, 58.48 (C-2 of GlcNAc), 54.43 (C-5 of NeuAc), 42.44 (C-3 of NeuAc), 38.95, 38.70, 35.76 (C-6 of Glc), 31.36, 31.34, 25.01, 24.69 and 17.92 (Me of Fuc); MALDI-TOF MS: *m/z*: calcd for $C_{301}H_{490}N_{21}O_{196}S_7Na_7$ 7924.5. Found: 7945.7 $[M+Na]^+$.

3.3. Biological assay

The inhibitory effects of glycodendrimers were performed by means of surface plasmon resonance (SPR) method, Biacore-2000, Biacore Co. Ltd using HBS-N buffer as a running buffer. SLeXn-BSA (14-atom spacer) was obtained from Calbiochem Co. Ltd. Recombinant human E-selectin was purchased from R&D Systems, Inc. SLeXn-BSA was immobilized by amine-coupling method with CM5 sensor chip in acetate buffer (10 mM, pH4.5). When 5 μL of E-selectin solution (0.9 μM in 10 mM HEPES buffer, pH7.4, 150 mM NaCl) was injected (flow rate 10 μl/min), increase of the signal (380 RU) was observed in the binding profile due to the binding of E-selectin with immobilized SLeX residues. Compounds **5**, **6**, and SLeX were incubated with E-selectin prior to the injection to the Biacore apparatus and the inhibitory effect on the binding was monitored as the decrease of the sensor signals.

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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.2004.12.035

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Sassafrins A–D, new antimicrobial azaphilones from the fungus *Creosphaeria sassafras*

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Abstract—Four new azaphilones named sassafrins A–D (**1**–**4**) were isolated from the methanol extract of the stromata of the fungus *Creosphaeria sassafras* (Xylariaceae, Ascomycetes). Their structures were elucidated by 2D NMR, HR-MS, IR, UV and CD spectroscopy. Sassafrin D (**4**) possesses a novel skeleton and its biosynthetic pathway is also discussed. In addition, all compounds showed broad-spectrum antimicrobial activity. Their apparently unique occurrence in *C. sassafras* supports the status of this fungus as a member of a distinct genus within the Xylariaceae, coinciding with molecular and morphological traits.

1. Introduction

Creosphaeria sassafras is widespread and reported from Brazil, Canada, Chile, France, Italy, Taiwan, and America.[1,2] Previously, it was classified as *Hypoxylon sassafras* by Miller[1] due to closed distinctive features with *Hypoxylon* genera. Recently, Ju et al.,[2] revised it as *Creosphaeria sassafras* without any chemical evidence. In the course of our chemosystematic study on Xylariaceae family, we have reported the chemical constituents of *Daldinia* sp.,[3,4] entonaemins from *Entonaema splendens*,[5] daldinins E–F from *Hypoxylon fuscum*,[6] rubiginosins A–C from *H. rubiginosum*,[7] cohaerins A–B from *H. cohaerens*.[8] Furthermore, the chemotypes of several *Hypoxylon* species in section *Hypoxylon* and section *Annulata* have been successfully discussed by using HPLC-based metabolite profiles.[8–10] With the purpose of obtaining more evidence for classification of *C. sassafras* and seeking biologically active substances from fungi, we studied the chemical constituents of this fungus and isolated four new azaphilones named sassafrins A–D (**1**–**4**). This paper describes their isolation, structural elucidation and antimicrobial activity.

2. Results and discussion

The methanolic extract of *C. sassafras* was subjected to reversed-phase HPLC, followed by silica gel column chromatography to obtain four compounds sassafrins A–D (**1**–**4**) (Fig. 1).

Sassafrin A (**1**) was isolated as oil. EIMS of **1** showed a molecular ion peak at *m/z* 468 $[M]^+$ and its molecular formula was found to be $C_{27}H_{32}O_7$ by HREIMS indicating the presence of twelve degrees of unsaturation in the molecule. The ^1H and ^{13}C NMR spectra of **1** (Tables 1 and 2) showed seven olefinic protons, five methyls, two conjugated carbonyl (δ_C 190.7, 191.6) and one ester (δ_C 169.4). The structure could then be elucidated as azaphilone partly by analysis of the data obtained in 2D NMR experiments and partly by comparison with those of previously characterized azaphilones.[5–7] The presence of 2-hydroxypropyl was established by ^1H–^1H coupling between H-11/H-10 and H-12. The positioning of this on C-3 was shown by HMBC correlations from H-10 to C-3 and C-4. Investigation of ^1H ^1H COSY and HMBC spectra of **1** (Fig. 2) revealed the presence of 3-hydroxy-

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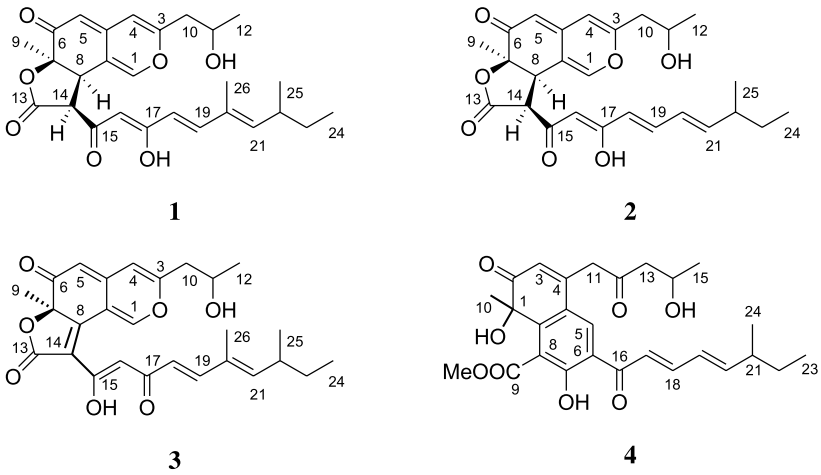

Figure 1. Structures of sassafrins A–D (**1**–**4**).

Table 1. ^{1}H NMR data for sassafrins A–C (**1**–**3**) ($CDCl_3$)

Position	1	2	3
1	7.43 (s)	7.42 (s)	8.81 (s)
4	6.11 (s)	6.11 (s)	6.20 (s)
5	5.40 (s)	5.39 (s)	5.31 (s)
8	3.92 (d, 12.4)	3.92 (d, 12.4)	
9	1.60 (s)	1.59 (s)	1.70 (s)
10	2.55 (dd, 4.4, 14.8)	2.55 (dd, 4.4, 14.8)	2.59 (m)
	2.51 (dd, 8.2, 14.8)	2.51 (dd, 8.0, 14.8)	
11	4.18 (m)	4.17 (m)	4.23 (m)
12	1.31 (d, 6.0)	1.30 (d, 6.0)	1.34 (d, 6.0)
14	3.67 (d, 12.4)	3.68 (d, 12.4)	
16	5.83 (s)	5.79 (s)	6.68 (s)
18	5.86 (d, 15.4)	5.87 (d, 15.4)	6.51 (d, 15.7)
19	7.29 (d, 15.4)	7.24 (dd, 11.4, 15.9)	7.34 (d, 15.7)
20		6.17 (dd, 11.8, 15.9)	
21	5.72 (d, 15.4)	6.05 (dd, 8.0, 15.1)	5.77 (d, 9.9)
22	2.46 (m)	2.19 (m)	2.48 (m)
23	1.41 (m)	1.38 (m)	1.42 (dd, 5.8, 7.4)
	1.25 (m)		1.32 (m)
24	0.85 (t, 7.4)	0.87 (t, 7.4)	0.86 (t, 7.4)
25	0.99 (d, 6.6)	1.03 (d, 6.6)	1.00 (d, 6.6)
26	1.80 (d, 1.1)		1.82 (d, 0.8)

6,8-dimethyl-2,4,6-triene-decan-1-one, which was located at C-14 due to the long-range correlation between H-14 and C-15. The C-7 methyl group (C-9), which showed HMBC correlations to C-6, C-7 and C-8, must be located at C-7. Furthermore, H-8 gave the HMBC correlation with C-7, C-14 and C-8a, as well as the HMBC correlations between H-14/ C-8 and C-13 indicating the presence of a five membered-lactone ring from O-7 to C-8. The relative stereochemistry of **1** was determined by creation of a three-dimensional model and by means of a NOESY experiment, H-8 showed correlations with H-1, H-9 and H-14 indicating that H-8 and 7-methyl (H-9) locate the same side. Three double bonds C_{16-17}, C_{18-19} and C_{20-21} were established to be *E*-form by the coupling constants (Table 1) and the NOE correlations between H-16 and H-18, H-18 and H-26, H-19 and H-21. The absolute configuration at C-7 was established to be *R* by CD spectrum, which showed the positive (367 nm and 274 nm) and negative (321 nm) Cotton effects.[11,12] From the above spectral evidence, sassafrin A (**1**) was determined to be 3-(2-hydroxypropyl)-14-(3-hydroxy-6,8-dimethyldeca-2,4,6-trienoyl)-(7*R*)-7-methyl-8,14-dihydro-7*H*-furo[2,3-*h*]isochromene-6,13-dione as shown in Figure 1.

The molecular formula of sassafrin B (**2**) was determined as $C_{26}H_{30}O_7$ by HREIMS. Investigation of 2D NMR spectral data of **2** (Tables 1 and 2) revealed that **2** was very similar to **1** except for the presence of one olefinic proton H-20 (δ_H 6.17) in the place of the vinylic methyl. Therefore, sassafrin B (**2**) was determined as 3-(2-hydroxypropyl)-14-(3-hydroxy-8-methylnona-2,4,6-trienoyl)-7(*R*)-7-methyl-8,14-dihydro-7*H*-furo[2,3-*h*]isochromene-6,13-dione.

The HREIMS of **3** indicated the molecular formula of $C_{27}H_{30}O_7$. In comparison with the spectral data of **1** pointed out that **3** resembled **1**, but it differs in the following points. The presence of an α,β-unsaturated lactone was detected by down-field shift of C-8 and C-14 and the up-field shift of C-13 (Table 2).[13] The side-chain at C-14 possessed the same carbon skeleton as that of **1** except that the hydroxyl and the ketone groups were located at C-15 and C-17, respectively due to the HMBC correlations between C-15 and H-16;

Table 2. ^{13}C NMR data for sassafrins A–C (**1**–**3**) ($CDCl_3$)

Position	1	2	3
1	147.8	147.7	154.3
3	159.8	159.9	159.0
4	108.6	108.6	109.7
5	105.9	105.9	105.2
6	191.6	191.6	190.5
7	82.8	82.8	87.5
8	43.2	43.2	163.8
9	23.3	23.3	26.2
10	42.9	42.9	42.7
11	65.6	65.5	65.3
12	23.6	23.6	23.7
13	169.4	169.3	167.9
14	54.2	54.3	121.0
15	190.7	191.1	179.6
16	101.3	101.4	101.0
17	177.3	176.6	183.1
18	119.1	122.9	120.7
19	146.9	142.3	147.6
20	132.1	127.5	132.3
21	149.6	150.9	150.3
22	35.1	38.9	35.1
23	30.0	29.3	30.0
24	11.9	11.7	12.0
25	20.1	19.5	20.9
26	12.3		12.4
4a	144.4	144.4	144.2
8a	114.7	114.7	111.5

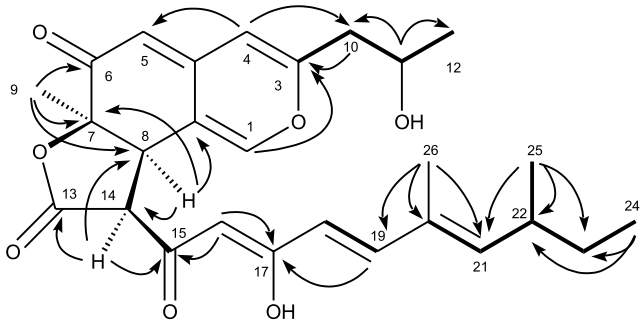

Figure 2. ^{1}H-^{1}H COSY (bold lines) and HMBC correlations (arrows) of **1**.

C-17 and H-16, H-18, H-19.[14] The absolute configuration at C-7 was determined to be *R* by comparing CD spectrum with **1** and **2**. From the above discussed data, sassafrin C (**3**) was found to be 3-(2-hydroxypropyl)-14-(1-hydroxy-6,8-dimethyl-3-oxodeca-1,4,6-trienyl)-7(*R*)-7-methyl-7*H*-furo[2,3-*h*]isochromene-6,13-dione as shown in Figure 1.

Sassafrin D (**4**) was obtained as oil. Its EIMS indicated the molecular peak at *m*/*z* 484 and the molecular formula was determined to be $C_{27}H_{32}O_8$ by HREIMS. The number of unsaturations in **4** is consequently 12. Its ^{1}H NMR data (Table 3) showed the presence of six olefinic protons, four methyls, one methoxyl and one phenolic hydroxyl group. The ^{13}C NMR spectrum exhibited the resonances of 27 carbon signals (Table 3), including the presence of three ketones and one ester. The structure of **4** could then be determined by analysis of 2D NMR data, of which all HMBC correlations are presented in Table 3. The presence of 4-hydroxy-2-oxopentyl was established by ^{1}H–^{1}H COSY correlations between H-14 and H-13, H-15 as well as long-range correlations between C-12 and H-11, H-13. This side-

Table 3. ^{1}H and ^{13}C NMR data for sassafrin D (**4**) ($CDCl_3$)

Position	δ_H (multiplicity, *J* in Hz)	δ_C	HMBC
1		78.1	H-3, H-10
2		202.0	H-10
3	6.13 (s)	122.3	H-11
4		148.9	H-11
5	7.91 (s)	128.8	
6		118.5	7-OH
7		162.6	H-5, 7-OH
8		124.0	7-OH
9		176.1	9-OMe
10	1.74 (s)	31.8	
11	4.00 (d, 16.5) 3.74 (d, 16.5)	49.9	H-3
12		206.3	H-11, H-13
13	2.72 (dd, 9.2, 16.5) 2.65 (dd, 3.3, 16.5)	50.3	H-15
14	4.29 (m)	64.6	H-13, H-15
15	1.26 (d, 6.2)	23.1	
16		193.2	H-5, H-17, H-18
17	6.99 (d, 14.7)	120.5	
18	7.57 (dd, 10.6, 14.7)	148.2	H-20
19	6.38 (dd, 10.6, 15.4)	127.3	H-17, H-20
20	6.30 (dd, 7.7, 15.4)	155.0	H-18, H-22, H-24
21	2.27 (m)	39.2	H-20, H-22, H-24
22	1.43 (m)	29.2	H-23, H-24
23	0.91 (t, 7.3)	11.7	H-22
24	1.09 (d, 7.0)	19.3	
4a		120.0	H-3, H-11
8a		148.8	H-5, H-10, H-11
7-OH	13.8 (s)		
9-OCH_3	3.97 (s)	52.7	

chain was located at C-4 due to the HMBC correlation from H-11 to C-4. H-10 (1-methy) also correlated with C-1, C-2 (a keto carbon), and C-8a in the HMBC spectrum, indicating that it is attached to C-1 (oxygenated carbon). H-5 gave HMBC correlations to C-4a and C-7. The phenolic hydroxy group also showed HMBC correlations to C-6, C-7 and C-8. One more side-chain was elucidated as 6-methyl-octa-2,4-dienoyl by 2D NMR spectra (Table 3 and Fig. 3), which is located at C-6 by the HMBC correlation from H-5 and C-16. Strong NOE correlations between H-5 and H-17, H-11 (Fig. 3) were detected in NOESY spectrum confirming the proposed structure. The absolute configurations at C-1, C-14 and C-21 remained to be clarified. Consequently, sassafrin D (**4**) was elucidated as 1,7-dihydroxy-1-methyl-4-(4-hydroxy-2-oxo-pentyl)-6-(6-methylocta-2,4-dienoyl)-2-oxo-1,2-dihydronaphthalene-8-carboxylic acid methyl ester.

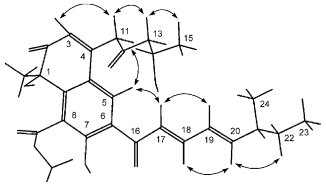

Figure 3. NOE correlations of sassafrin D (**4**).

Previously, the biosynthetic pathway of several azaphilones have been elucidated by ^{13}C labeling studies and revealed that they were formed by the polyketide pathway.[15] Here,

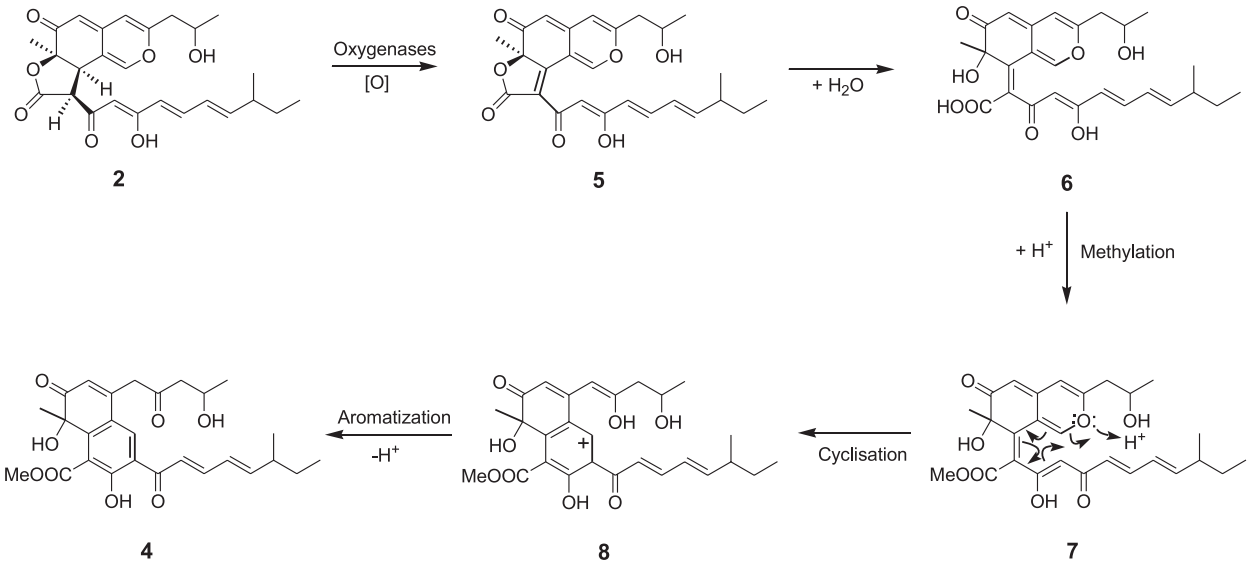

Figure 4. Possible biosynthetic pathway for sassafrin D (**4**).

we propose the possible biosynthesis pathway for novel sassafrin D (**4**) as shown in Figure 4. Starting from an azaphilone-sassafrin B (**2**) which was also isolated from *C. sassafras* as precursor by oxidization to form an α,β-unsaturated lactone (**5**), followed by hydrolysis to open the lactone ring and furnish **6** and then methylation to obtain **7**. The nucleophile center at oxygen of ether ring was attacked by proton and the rearrangements occur to form a cation intermediate (**8**). Finally, the elimination of a proton and aromatization would result in the formation of sassafrin D (**4**).

Azaphilones have been repeatedly shown to exhibit strong antimicrobial activities.[13,14,16] Sassafrins A–D (**1**–**4**) showed moderate antibacterial activity and strong antifungal activity (Table 4). Sassafrin C (**3**) indicated the largest inhibition zones of 22 mm against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* 95, while sassafrins A and B (**1**,**2**) showed relatively strong antifungal activity with inhibition zones of 20 and 19 mm against *Aspergillus niger* and *Candida albicans*, respectively. These effects, however, appear to be non-selective if seen in concert, since neither fungi nor bacteria remained unaffected by any of the sassafrins. They are in agreement with previously reported bioactivities for other azaphilones[14,16] and point toward the role of azaphilones as defense metabolites that may protect the stromata of Xylariaceae against feeding enemies or colonizing microbes.[10]

A HPLC profiling study, comparing the extracts of *C. sassafras* with those of ca. 1000 specimens of Xylariaceae,[8–10,17] preferably of the genera *Hypoxylon* and *Daldinia*, was also carried out. According to preliminary results, the sassafrins were not located in any of the other species of the family. On the other hand, various azaphilones and other metabolites which were identified from *Hypoxylon* and allied genera in the past years all proved absent in the extract of *C. sassafras*. These results support the taxonomic view of Ju et al.[2] that *Creosphaeria* is not a close ally of *Hypoxylon*. Furthermore, the results of the current paper provide another good example that chemotaxonomic data are well in agreement with recently established molecular phylogeny of this family, since they coincide with two recent independent PCR-based studies on the ITS nrDNA gene[18,19] that also revealed the status of *Creosphaeria* as a rather isolated genus within the family.

3. Experimental

3.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 600 NMR spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C), using $CDCl_3$ as solvent. Chemical shifts are given relative to TMS (δ 0.00) as internal standard (^{1}H) and δ 77.0 (ppm) from $CDCl_3$ as standard (^{13}C). Mass spectra including high-resolution mass spectra were

Table 4. Antimicrobial activity of sassafrins A–D (**1**–**4**) (diameter of the zone of growth inhibition, bactericidal or fungicidal zone in mm, including the diameter of disc, 12.7 mm)

Microorganism	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*	S. *enteritidis*	*E. coli*	*A. niger*	*C. albicans*
Sample							
Sassafrin A (**1**)	19	18	20	20	20	20	19
Sassafrin B (**2**)	18	19	20	21	14	20	19
Sassafrin C (**3**)	22	22	22	20	22	19	18
Sassafrin D (**4**)	17	19	17	17	19	18	17
Tetraciclin (Standard)	25	24	26	24	23	18	19

recorded on a JEOL JMS AX-500 spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter with $CHCl_3$ as solvent. UV spectra were obtained on a Shimadzu UV-1650PC instrument in MeOH. CD spectra were measured on a JASCO J-725 spectrometer in MeOH. IR spectra were measured on a PerkinElmer Spectrum One FT-IR spectrometer. Column chromatography was carried out on silica gel 60 (0.2–0.5 mm, 0.04–0.063 mm, Merck) and Sephadex LH-20 (Amersham Pharmacia Biotech). Preparative medium-pressure liquid chromatography (MPLC) was performed with Work-21 pump (Lab-Quatec Co., Ltd, Japan) and a Lobar Rp-18 column (Merck). HPLC was performed on Shimadzu Liquid chromatograph LC-10AS with RID-6A and SPD-10A detectors using a Waters 5C 18-AR-II column.

3.2. Fungus materials

Stromata of *Creosphaeria sassafras* (Schwein.: Fr.) Y.-M. Ju, F. San Martin & J. D. Rogers were collected and identified by J. Fournier. Two specimens collected from Rimont (Ariége, France), were used for extraction and isolation of bioactive compounds, showing essentially the same metabolite compositions: JF 03202 (collected from *Ficus carica*, 16 October 2003) and JF04009 (collected from *Laurus nobilis*, 20 January 2004). Voucher specimens of both materials are deposited at the mycological herbarium of the Fuhlrott-Museum, Wuppertal, Germany, and in the personal herbarium of Jacques Fournier.

3.3. Extraction and isolation

1.3 g MeOH extract of *C. sassafras* was subjected to Sephadex LH-20 column chromatography using $CHCl_3$–MeOH (1:1) as solvent system to afford four fractions. Fraction 2 (146.8 mg) was separated by reversed-phase MPLC (70% CH_3CN), followed by reversed-phase HPLC (95% CH_3CN) to give sassafrin C (**3**) (11.3 mg). Fraction 3 (68.8 mg) was separated by reversed-phase MPLC (60% CH_3CN) to give **3** (7.2 mg) and a mixture, which was further purified by reversed-phase HPLC (80% CH_3CN) to yield sassafrin D (**4**) (2.8 mg). Fraction 4 (112.4 mg) was chromatographed on silica gel column using hexane-EtOAc (gradient) and then reversed-phase MPLC (75% CH_3CN) to obtain sassafrin A (**1**) (8.2 mg) and sassafrin B (**2**) (10.7 mg).

3.3.1. Sassafrin A (1). $[\alpha]_D^{20} = +277.3$ (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 3330, 1779, 1675, 1602, 1554, 1455, 1179, 1088, 981; UV λ_{max} nm (log ε): 349 (4.6), 237 (4.1); CD (MeOH) λ_{ext} nm ($\Delta\varepsilon$) 367 (+7.1), 321 (−4.0), 274 (+0.2); EIMS *m/z* 468 $(M)^+$; HREIMS *m/z* 468.2150 [Calcd for $C_{27}H_{32}O_7$ $(M)^+$, 468.2148); ^1H NMR and ^{13}C NMR are listed in Tables 1 and 2.

3.3.2. Sassafrin B (2). $[\alpha]_D^{20} = +310.8$ (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) ν_{max} cm^{-1}: 3354, 1779, 1675, 1585, 1456, 1373, 1249, 1088; UV λ_{max} nm (log ε): 346 (4.7), 230 (4.5); CD (MeOH) λ_{ext} nm ($\Delta\varepsilon$) 373 (+7.5), 322 (−6.0), 263 (+0.2); EIMS *m/z* 454 $(M)^+$; HREIMS *m/z* 454.2007 [Calcd for $C_{26}H_{30}O_7$ $(M)^+$, 454.1992);^1H NMR and ^{13}C NMR are listed in Tables 1 and 2.

3.3.3. Sassafrin C (3). $[\alpha]_D^{20} = +878.6$ (*c* 0.95, $CHCl_3$); UV λ_{max} nm (log ε): 360 (4.2), 273 (4.1); CD (MeOH) λ_{ext} nm ($\Delta\varepsilon$) 436 (+32.7), 368 (−40.0), 277 (+22.1), 244 (−3.7), 216 (+7.3); IR ($CHCl_3$) ν_{max} cm^{-1}: 3466, 1761, 1606, 1539, 1454, 1249, 1175, 1119, 1040, 882; EIMS *m/z* 466 $(M)^+$; HREIMS *m/z* 466.1996 [Calcd for $C_{27}H_{30}O_7$ $(M)^+$, 466.1992); ^1H NMR and ^{13}C NMR are listed in Tables 1 and 2.

3.3.4. Sassafrin D (4). $[\alpha]_D^{20} = -6.9$ (c 0.84, $CHCl_3$); UV λ_{max} nm (log ε): 324 (4.3), 221 (4.0); CD (MeOH) λ_{ext} nm ($\Delta\varepsilon$) 373 (−12.4), 328 (+6.5), 227 (−17.0); IR ($CHCl_3$) ν_{max} cm^{-1}: 3464, 1746, 1694, 1640, 1611, 1568, 1368, 1073, 995; EIMS *m/z* 484 $(M)^+$; HREIMS *m/z* 484.2126 [Calcd for $C_{27}H_{32}O_8$ $(M)^+$, 484.2097); ^1H NMR and ^{13}C NMR are listed in Table 3.

3.4. Antimicrobial activity

3.4.1. Test microorganisms. The in vitro antimicrobial activities of sassafrins A–D (**1**–**4**) were tested against a panel of laboratory control strains belonging to the American Type Culture Collection Maryland, USA: Gram-positive: *Staphylococcus aureus* (ATCC 6538), Gram-negative: *Klebsiella pneumoniae* (ATCC 10031), *Pseudomonas aeruginosa* (ATCC 9027), *Salmonella enteritidis* (ATCC 13076), and fungal organisms *Aspergillus niger* (ATCC 16404) and *Candida albicans* (ATCC 10231) except for the Gram-negative bacteria *Escherichia coli* 95 which was obtained from the Institute of Immunology and Virology 'Torlak', Belgrade, Serbia and Montenegro.

3.4.2. Evaluation of antimicrobial activity. Disc diffusion method according to the NCCLS[20] was employed for determination of antimicrobial activity of the compounds. The following nutritive media were used: Antibiotic Medium 1 (Difco Laboratories, Detroit, MI, USA) for growing Gram-positive and Gram-negative bacteria and Tripton soy agar (TSA-Torlak, Belgrade) for *Candida albicans* and *Aspergillus niger*. Nutritive media have been prepared according to the instructions of the manufacturer. All agar plates were prepared in 90 mm Petri dishes with 22 ml of agar giving the final depth of 4 mm. 0.1 ml of a suspension of the tested microorganisms (10^8 cells per ml) was spread on the solid media plates. Sterile filter paper disks ('Antibiotika Test Blättchen', Schleicher & Schüll, Dassel, Germany, 12.7 mm in diameter) were impregnated with 50 µl of the sample solutions in dimethylsulphoxide (DMSO), 1 mg per 1 ml of DMSO (all solutions were filter-sterilized using a 0.45 µm membrane filter) and placed on inoculated plates. These plates, after standing at 4 °C for 2 h, were incubated at 37 °C for 24 h for bacteria and at 30 °C for 48 h for the fungi. Standard disks of Doxiveto, Neomycin Meticilin, Tetraciclin and Tiamulin (origin—Institute of Immunology and Virology 'Torlak', diameter 10 mm) were individually used as positive controls, while the disks imbued with 50 µl of pure DMSO as a negative control. The diameters of the inhibition zones were measured in millimeters using a 'Fisher-Lilly Antibiotic Zone Reader' (Fisher Scientific Co. USA). Each test was performed in triplicate and repeated three times and results analyzed for statistical significance. Mean values were selected.

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3,8,11,16-Tetrakis(aminomethyl)-1,2,9,10-tetrathia-cyclohexadecane tetra-trifluoroacetic acid: synthetic precursor to a novel thio-substituted diamine

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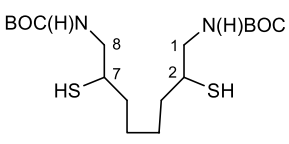
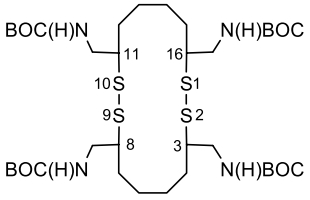
Abstract—Diamines have proven to be versatile intermediates in organic chemistry. Few diamines, however, can be appended to organic and inorganic supports without modification of the diamine functionality. We report the synthesis of 3,8,11,16-tetrakis-(*N*-BOC-aminomethyl)-1,2,9,10-tetrathia-cyclohexadecane (**2**) and 3,8,11,16-tetrakis(aminomethyl)-1,2,9,10-tetrathia-cyclohexadecane tetra-trifluoroacetic acid (**3**), potential precursors to 1,8-diamino-2,7-octanedithiol (**4**). Incorporation of the thiol units within the diamine backbone of **4** permits this compound to attach to organic and inorganic scaffolds. Spectral and chemical data showed that base hydrolysis of 1,8-bis(*N*-BOC-amino)-2,7-bis(acetylthio)octane (**16**) produced the 16-membered bis-disulfide **2** rather than the 8-membered ring dithiocane **17**.

1. Introduction

Diamines have received considerable interest as scaffolds for the synthesis of novel pharmaceutical compounds and as catalysts for asymmetric synthesis.[1] Their importance has led to the development of new synthetic routes from readily accessible starting materials.[2] Few of these syntheses permit subsequent diamine attachment to organic or inorganic materials without modification of the amino units. Among organic functional groups, thiols are unique for the ease with which they react with organic electrophiles[3] and metals.[4] Thiols are readily prepared from disulfides by reduction (catalytic, chemical) and by nucleophilic substitution reactions.[3] Here, we report the synthesis of the *N*-protected disulfide **2** upon oxidation of 1,8-bis(*N*-BOC-amino)-2,7-octanedithiol (**1**) and show that acid deprotection provides the cyclic diamine **3**. Compound **3** is the oxidized precursor of the thio-substituted diamine **4**.



1



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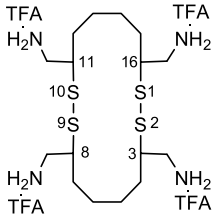

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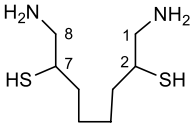

4

2. Results and discussion

2.1. Synthesis

Recent investigations on the design and evaluation of novel porfiromycins and mitomycins required that we synthesize **5**[5] and **6**.[6] Both these diamines, like **3**, can be appended to organic and inorganic scaffolds after the disulfide unit is converted to the corresponding thiols. Diamines **5** and **6** were obtained by oxidizing the intermediate acyclic dithiols

Keywords: Thio-substituted diamines; Tetrathiacyclohexadecanes; Synthesis.
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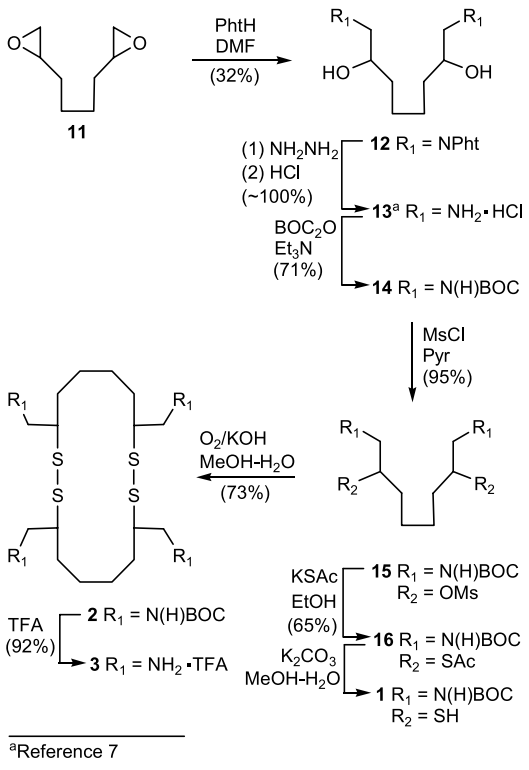
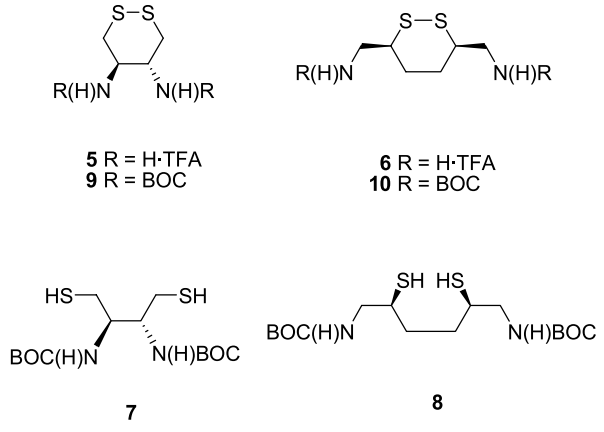
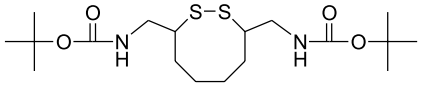


Scheme 1.

7 and **8** to give **9** and **10**, respectively, followed by acid removal of the *N*-BOC protecting groups.[5,6] We patterned our synthesis of **2** after the route used for **6** (Scheme 1).



Treatment of 1,7-octadiene diepoxide (**11**, a mixture of diastereomers (1.1:1, ^{13}C NMR analysis)) with phthalimide in DMF gave **12**. Deprotection ($NH_2NH_2 \cdot H_2O$) of the phthalimide groups in **12** provided **13**[7] in near quantitative yields after acid work-up. Subsequent protection of the amino groups in **13** with BOC_2O and Et_3N afforded **14** as a mixture of diastereomers (1.1:1 mixture, ^{13}C NMR analysis) in moderate yield (71%). The ^{13}C NMR (75 MHz) for **14** showed signals of near equal heights for the C(2) and C(3) resonances, indicating that the isolated product was a 1.1:1 diastereomeric mixture and further suggesting a similar stereochemical composition for **12** and **13**. Interestingly, we observed only a single set of ^{13}C NMR resonances for **12** and **13**. This phenomenon has been attributed to the spatial distance and stereochemical relationship of the two chiral centers within these compounds. Thus, we suspect that the four carbon spacer in **12** and **13** does not permit the differentiation of the carbons by 75 MHz ^{13}C NMR spectroscopy. Further proof that **13** existed as a diastereomeric mixture was obtained by converting **13** to a diastereomeric mitomycin mixture readily distinguishable by HPLC and ^{13}C NMR (see Section 2.3). Compound **14** (1.1:1 diastereomeric mixture) was treated with MsCl in pyridine to give **15** in high yield (95%). Displacing the mesylate units in **15** with KSAc in EtOH led to **16** in 65% yield. Hydrolysis of the thioacetate groups in **16** with aqueous methanolic K_2CO_3 gave dithiol **1**, which was directly oxidized in basic methanol with O_2 to yield cyclic **2** as the major adduct (73% yield from **16**) and not the 8-membered ring dithiocane **17**. There is precedent for the formation of the bis-disulfide **2**. Kato and co-workers report that treatment of a dichloromethane solution of 1,6-hexanedithiol with triethylamine in the presence of diethyl bromomalonate gave the 8-membered ring 1,2-dithiocane and the corresponding 16-membered dimeric disulfide in 10 and 26% yields, respectively.[8] The BOC groups in **2** were removed in 92% yield by trifluoroacetic acid (TFA) to give the 16-membered bis-disulfide **3** as the principal product.



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2.2. Spectroscopic structural characterization of 2 and 3

Mass spectral data showed that oxidative treatment of thiol **1** gave the 16-membered ring adduct **2** rather than the expected dithiocane **17**. We found that in the low-resolution +ESI MS the major peak appeared at *m/z* 835.6 (calcd for $[C_{36}H_{68}N_4O_8S_4+Na]^+$, 835.4) in agreement with the sodium adduct of **2** (Fig. 1). Additional peaks that likely corresponded to higher oligomers of **1** were observed at *m/z* 1241.5 (trimer) and 1650.5 (tetramer). The spectrum remains essentially unchanged when the concentration of the sample is varied, indicating that these are covalent species in solution and not formed as adducts of a monomer (e.g., $[2M+Na]^+$, $[3M+Na]^+$, and $[4M+Na]^+$) during ionization. Similarly, +ESI MS analysis of **3** gave a prominent peak for monoprotonated **3** at *m/z* 413.1 (calcd for $[C_{16}H_{36}N_4S_4+H]^+$, 413.2) (Fig. 2). A very small signal was observed that matched the monomer (not labeled in Fig. 2) and additional peaks that can be attributed to higher oligomers of **4** were observed at *m/z* 619.2 and 824.7. Again,

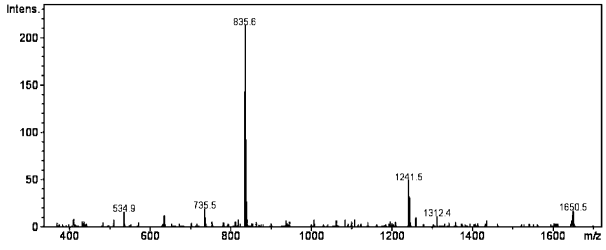


Figure 1. +ESI mass spectrum for **2**.

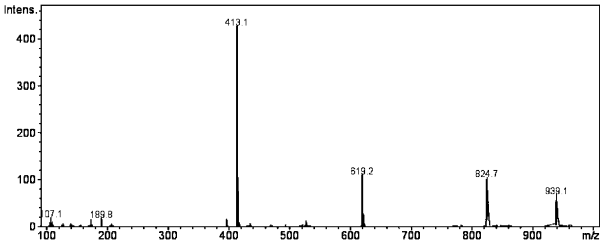


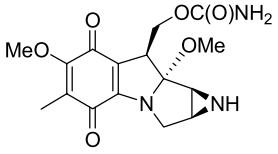
Figure 2. +ESI mass spectrum for **3**.

varying the concentration of the sample had little affect on the appearance of the spectrum. Confirmation of the exact masses for **2** and **3** were obtained by high-resolution MS (+CI). Thus, we concluded that the product after oxidative work-up of **1** was a mixture in which the 16-membered ring adduct **2** was the major constituent but also with minor amounts of smaller and larger disulfides. The composition of cyclic disulfides was not altered after acid deprotection of the BOC units in **2**.

The ^{13}C NMR for **2** exhibited only seven signals. The simplicity of this spectrum was surprising. Dimerization of **1** is expected to give three diastereomers and two pairs of enantiomers due to the different stereochemical permutations of the appended *N*-BOC-aminomethylene units. A similar, unexpected equivalence of NMR signals was observed for the acylic adducts **12** and **13**, and, again, we have attributed this to the spatial differences between the chiral centers and the conformational ability within the 16-membered ring system **2**. The ^{13}C NMR for **3** exhibited one set of broad signals.

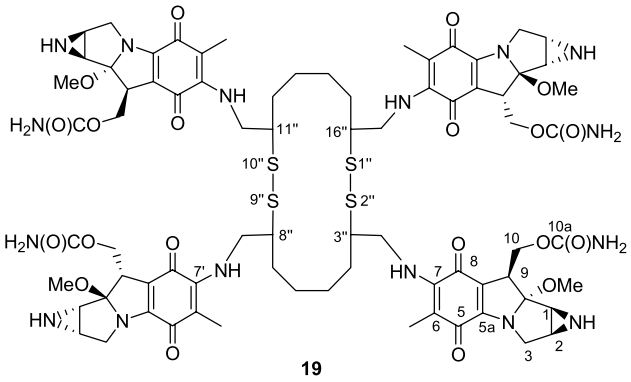
2.3. Chemical derivatization of 3

We sought independent evidence for the 16-membered ring tetra-amine **3**. Previously, we have coupled diamines **5** and **6** with mitomycin A[9] (**18**) to provide novel mitomycins that can efficiently cross-link DNA when treated with nucleophiles.[5,6] We chose to modify **3** with **18**, to take advantage of the distinctive UV–vis chromophore of the appended mitomycin units for product identification and isolation.

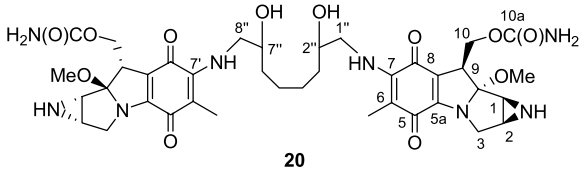


18

Treating a methanolic solution of **3** with **18** in the presence of Et_3N gave **19** in 52% yield. Under similar reaction conditions, treatment of **13** with **18** gave dimeric mitomycin **20** (44% yield). ^{13}C NMR analysis of **20** showed that this dimer existed as a mixture of diastereomers (1.1:1 mixture) where two peaks in an approximate 1.1:1 ratio were observed for five signals (C(2), C(5), C(4a), C(9), C(10a)), thus confirming that **13** consisted of a diastereomeric mixture.



19



20

The HPLC chromatogram for **19** showed 6 peaks between 32.9–35.2 min in an approximate 1:5:6:5:2:2 ratio (Fig. 3(a)). All 6 peaks had the same UV–vis profile (Fig. 3(b)). Attaching four mitomycin units to **3** yields 7 possible diastereomers. By comparison, we would have expected only 3 diastereomers ((2″*S*,7″*R*), (2″*R*,7″*R*), (2″*S*,7″*S*)) from coupling the deprotected diamine of dithiocane **17** with **18**. Thus, the appearance of at least 6 distinct peaks for **19** is consistent with the 16-membered adduct. The ^{1}H and ^{13}C NMR chemical shift resonances observed for **19** were similar to those obtained separately for mitomycin C (**21**)[10] and the linking diamine unit **3**. Compound **19** showed UV maxima at ~222 and ~374 nm, similar to those found for **21**.[11] The low-resolution +ESI MS for **19** is shown in Figure 4. Major peaks were observed at *m/z* 1703.4 and 1363.6 that matched the **19** $[M+Na]^+$ peak and the loss of one mitomycin unit from **19**, respectively. A smaller signal was also observed at *m/z* 863.4. This peak corresponded with the $[M+Na]^+$ signal for the dimeric mitomycin

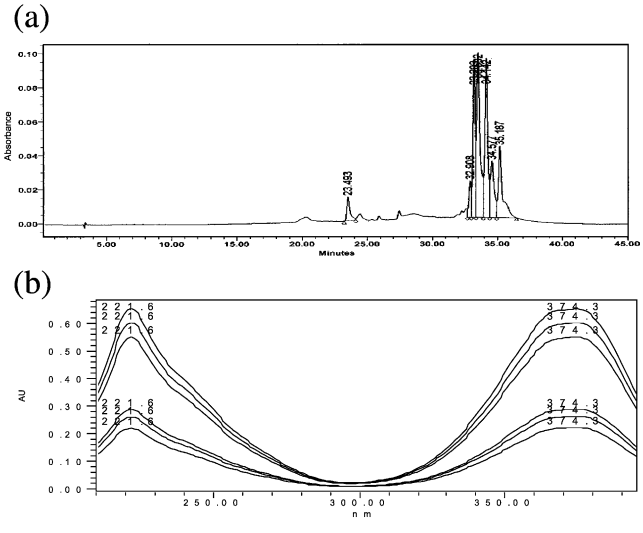


Figure 3. Compound **19**: (a) HPLC and (b) UV–vis profile.

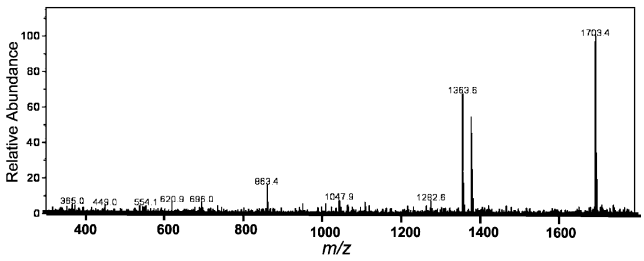
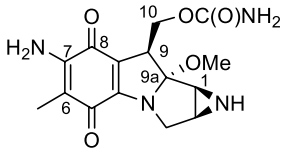


Figure 4. +ESI mass spectrum for **19**.

produced from **17**. MS–MS analysis of the *m/z* 1703.4 signal did not give significant levels of the *m/z* 863.4 peak (data not shown). Lack of significant formation of *m/z* 863.4 strongly suggests that *m/z* 1703.4 is predominantly, if not exclusively, $[M+Na]^+$ where M is **19**, rather than $[2M+Na]^+$ where M is the dimeric mitomycin from **17**. These findings provide additional evidence that the predominant product generated after oxidation of dithiol **1** was the dimeric 16-membered ring adduct **2**.



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3. Conclusions

A straightforward procedure has been developed for the synthesis for the 16-membered cyclic adduct **3**, the dimeric bis-disulfide of 1,8-diamino-2,7-octanedithiol (**4**). We anticipate reduction of **3** (e.g., Et_3P,[12] TCEP·HCl[13]) will provide the novel, diamine **4**. Correspondingly, conversion of the disulfide units in the *N*-BOC derivative **2** to **1** would allow, prior to diamine generation (TFA), thiol adduction of the protected diamine onto organic and inorganic supports without risk of competing reactions from the diamine. We expect that such disulfide diamines **3**, **5**, and **6** will serve as useful synthetic intermediates.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer. Mass spectral (MS) data were obtained by Dr. Mehdi Moini at the University of Texas at Austin. The low-resolution MS studies were run on a Finnegan TSQ-70 triple quadruple mass spectrometer, and the high-resolution MS studies were conducted on a Micromass ZAB-E mass spectrometer. ESI MS for **2**, **3**, **19**, and **20** were obtained on a Bruker Esquire Ion Trap instrument. LC-MS analyses were conducted with Agilent 1100 LC/MSD by Dr. Voyksner (LCMS Limited, Raleigh, NC). The products were analyzed with a Zorbak C_{18} SB column (2.1×50 mm, 3.5 μm particles) using the following linear gradient condition: 80% A (0.025 M ammonium acetate in H_2O–CH_3CN (95:5), pH 6.5), 20% B (0.025 M ammonium acetate in H_2O–CH_3CN (5:95), pH 6.5) isocratic for 1 min, and then from 80% A, 20% B to 20% A, 80% B for 30 min. The flow rate was 0.3 mL/min, and the eluent was monitored at 365 and 313 nm. The mass spectral mode of operation was positive ion electrospray (+ESI) and scan range was 300–1900 daltons with 45 psi of nebulization pressure. FT-IR spectra were run on a Mattson Galaxy Series FT-IR 5000 spectrometer. Melting points were determined in open capillary tubes using a Thomas–Hoover melting point apparatus and are uncorrected.

HPLC analyses were conducted with the following Waters Associate Units: 515 A pump, 515 B pump, Millennium chromatography manager, Waters 996 photodiode array detector, Rheodyne 7725i manual injector. The column was fitted with a μbondapak guardpak pre-column. The product analyses were conducted with a C_{18} μBondapak (stainless steel) column (3.9×300 mm) using the following linear gradient condition: 90% A (aqueous 0.025 M triethylammonium acetate, pH 6.5), 10% B (acetonitrile) isocratic for 5 min, then from 90% A, 10% B to 45% A, 55% B in 30 min. The flow rate was 1 mL/min, and the eluent was monitored from 200 to 400 nm. The HPLC solvents were filtered (aqueous solution with Millipore HVLP, 0.45 mm; acetonitrile with Millipore HV, 0.45 mm) and degassed before utilization. Thin layer chromatography was run on general purpose silica gel plates (20×20 cm^2; Aldrich No. Z12272-6). Deionized water was obtained with a Milli-Q (18 MΩ s) water system (Millipore). The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. UV–vis spectra were obtained using a Cary-3Bio UV–vis spectrophotometer.

4.1.1. 1,8-Bis(phthalimido)-2,7-octanediol (12). To a DMF solution (11 mL) of phthalimide (6.60 g, 44 mmol) maintained at 135 °C was added dropwise **11** (a mixture of diastereomers (1.1:1, ^{13}C NMR analysis), 2.56 g, 18 mmol) with vigorous stirring. The reaction mixture was heated (1 h, 135 °C) and then cooled. The precipitate was filtered and successively washed with aqueous 1.0 N NaOH (50 mL), H_2O (100 mL), EtOH (20 mL), and Et_2O (20 mL) to give **12** as a white solid: yield, 2.51 g (32%); mp 204–207 °C; R_f 0.34 (2:1 EtOAc/hexanes); IR (KBr) 3383, 2931, 1772 (sh), 1716, 1430, 1394, 1356, 1085, 994, 718 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.25–1.50 (m, 8H, CH_2CH_2CH), 3.40–3.60 (m, 4H, CH_2N), 3.76 (br s, 2H, CHOH), 4.85 (d, J=5.4 Hz, 2H, CHO*H*), 7.82–7.95 (m, 8H, Pht); ^{13}C NMR (DMSO-d_6) δ 25.1 (CH_2CH_2CH), 34.4 (CH_2CH_2CH), 44.1 (CH_2N), 67.1 (CHOH), 122.8 (Pht, *C*HCHC), 131.7 (Pht, C), 134.2 (Pht, *C*HC), 168.0 (NCO), the ^{13}C NMR data were in agreement with the DEPT spectrum; MS (+CI) *m/z* 437 $[M+1]^+$; M_r (+CI) 437.171 13 $[M+1]^+$ (calcd for $C_{24}H_{25}N_2O_6$ 437.171 26).

4.1.2. 1,8-Diamino-2,7-octanediol dihydrochloride (13).[7] A mixture of 1,8-bis(phthalimido)-2,7-octanediol **12** (2.00 g, 4.6 mmol), EtOH (37 mL) and $NH_2NH_2\cdot H_2O$ (0.55 mL, 11.5 mmol) was heated under reflux (3.5 h). After cooling to room temperature, the solvent was removed in vacuo. H_2O (44 mL) and concentrated aqueous HCl (22 mL) were added to the residue and the mixture was

heated under reflux (1 h). After cooling to 0 °C, the precipitate was removed by filtration and the filtrate was then concentrated under reduced pressure. The remaining wet residue was dissolved in H_2O (50 mL) and then a small amount of insoluble matter was removed by filtration. The clear filtrate was concentrated under reduced pressure to afford **13** as a yellow solid: yield, 1.15 g (~100%); mp 175–180 °C; IR (KBr) 3272, 3021, 2913, 1618, 1486, 1285, 1115, 1007, 947, 650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15–1.47 (m, 8H, CH_2CH_2CH), 2.50–2.70 (m, 2H, $CHH'N$), 2.71–2.93 (m, 2H, $CHH'N$), 3.60–3.77 (m, 2H, $CHOH$), 5.58 (br s, 2H, $CHOH$), 7.90–8.17 (s, 6H, $NH_2 \cdot HCl$); ^{13}C NMR (DMSO-d_6) δ 24.6 (CH_2CH_2CH), 34.1 (CH_2CH_2CH), 44.4 (CH_2N), 66.6 (CHOH); MS (+CI) m/z 177 $[M+1]^+$; M_r (+CI) 177.159 84 $[M+1]^+$ (calcd for $C_8H_{21}N_2O_2$ 177.160 30).

4.1.3. 1,8-Bis(*N*-BOC-amino)-2,7-octanediol (14). To a stirred H_2O–DMF solution (1:1, 84 mL) of **13** (1.04 g, 4.2 mmol) and Et_3N (3.5 mL, 25 mmol) was added a solution of BOC_2O (2.27 g, 10.4 mmol) in DMF (10 mL). After warming to 50 °C, stirring was continued (6 h) and then the solvent was removed in vacuo. H_2O (80 mL) was added to the residue and then the mixture was extracted with EtOAc (2×80 mL). The combined organic layers were successively washed with aqueous 0.1 N HCl (80 mL), saturated aqueous $NaHCO_3$ (80 mL) and H_2O (80 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Recrystallization (2:3 EtOAc/hexanes, 50 mL) followed by filtration afforded **14** (white solid) as a mixture of diastereomers (1.1:1, ^{13}C NMR analysis): yield, 1.11 g (71%); mp 123–125 °C; R_f 0.20 (2:1 EtOAc/hexanes); IR (KBr) 3405, 2978, 2934, 2865, 1668, 1531, 1259, 1173, 1097, 864, 599 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.30–1.58 (m, 26H, CH_2CH_2CH, $OC(CH_3)_3$), 2.84 (d, J=9.9 Hz, 2H, $CHOH$), 2.91–3.05 (m, 2H, $CHH'N$), 3.09–3.23 (m, 2H, $CHH'N$), 3.61 (br s, 2H, $CHOH$), 5.89 (br s, 2H, NHCO), the ^1H NMR data were in agreement with the COSY spectrum; ^{13}C NMR (acetone-d_6) for the major diastereomer, δ 26.2 (CH_2CH_2CH), 28.5 ($OC(CH_3)_3$), 35.6 (CH_2CH_2CH), 47.4 (CH_2N), 71.1 (CHOH), 78.6 ($OC(CH_3)_3$), 157.1 (NHCO); ^{13}C NMR (acetone-d_6) for the minor diastereomer, δ 35.5 (CH_2CH_2CH), 71.2 (CHOH), the other signals were not detected and are believed to overlap with the observed peaks; MS (+CI) m/z 377 $[M+1]^+$; M_r (+CI) 377.264 45 $[M+1]^+$ (calcd for $C_{18}H_{37}N_2O_6$ 377.265 16).

4.1.4. 1,8-Bis(*N*-BOC-amino)-2,7-octanediol dimethanesulfonate (15). To a cooled (0 °C) solution of **14** (0.91 g, 2.4 mmol) in pyridine (4.8 mL) was slowly added (20 min) MsCl (0.64 mL, 8.2 mmol). After warming to room temperature, stirring was continued (4 h) and then the mixture was poured into a cooled aqueous 2 N HCl solution (90 mL) leading to the precipitation of a white solid. After stirring at 0 °C (1 h), the reaction mixture was filtered and successively washed with H_2O (50 mL) and EtOH (10 mL) to afford **15** as a white solid: yield, 1.22 g (95%); mp 145–146 °C; R_f 0.60 (2:1 EtOAc/hexanes); IR (KBr) 3375, 1690, 1522, 1340, 1169, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 18H, $OC(CH_3)_3$), 1.60–1.80 (m, 8H, CH_2CH_2CH), 3.05 (s, 6H, OMs), 3.20–3.35 (m, 2H, $CHH'N$), 3.38–3.52 (m, 2H, $CHH'N$), 4.69–4.78 (m, 2H, CHOMs), 4.93–5.01 (m, 2H, NHCO), the ^1H NMR data were in agreement with the COSY spectrum; ^{13}C NMR ($CDCl_3$) δ 24.4 (CH_2CH_2CH), 28.3 ($OC(CH_3)_3$), 32.0 (CH_2CH_2CH), 38.5 (OMs), 44.0 (CH_2N), 79.9 ($OC(CH_3)_3$), 81.7 (CHOMs), 155.9 (NHCO); MS (+CI) m/z 533 $[M+1]^+$; M_r (+CI) 533.220 65 $[M+1]^+$ (calcd for $C_{20}H_{41}N_2O_{10}S_2$ 533.220 27).

4.1.5. 1,8-Bis(*N*-BOC-amino)-2,7-bis(acetylthio)octane (16). To a stirred solution of **15** (0.85 g, 1.6 mmol) in DMF (22 mL) was added KSAc (0.42 g, 3.6 mmol). After warming to 60 °C, stirring was continued (3 h) and then the solvent was removed in vacuo. H_2O (80 mL) was added to the residue and then the mixture was extracted with EtOAc (2×80 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Recrystallization (2:3 EtOAc/hexanes, 40 mL) of the residue followed by filtration afforded **16** as a white solid: yield, 0.50 g (65%); mp 113–115 °C; R_f 0.48 (1:2 EtOAc/hexanes); IR (KBr) 1690, 1521, 1269, 1168, 952, 641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–1.72 (m, 26H, CH_2CH_2CH, $OC(CH_3)_3$), 2.34 (s, 6H, SAc), 3.15–3.45 (m, 4H, CH_2N), 3.47–3.61 (m, 2H, CHSAc), 4.78 (br s, 2H, NHCO); ^{13}C NMR ($CDCl_3$) δ 26.5 (CH_2CH_2CH), 28.3 ($OC(CH_3)_3$), 30.8 ($COCH_3$), 31.6 (CH_2CH_2CH), 44.4 (CH_2N), 45.0 (CHSAc), 79.4 ($OC(CH_3)_3$), 155.9 (NHCO), 195.6 ($COCH_3$), the ^{13}C NMR data were in agreement with the DEPT spectrum; MS (+CI) m/z 493 $[M+1]^+$; M_r (+CI) 493.239 24 $[M+1]^+$ (calcd for $C_{22}H_{41}N_2O_6S_2$ 493.240 61).

4.1.6. 3,8,11,16-Tetrakis(*N*-BOC-aminomethyl)-1,2,9,10-tetrathia-cyclohexadecane (2). To a stirred solution of **16** (0.33 g, 0.66 mmol) in MeOH–H_2O (5:1, 36 mL) was added K_2CO_3 (0.55 g, 4.0 mmol). After stirring at room temperature (30 min), KOH (78 mg, 1.38 mmol) was added and O_2 was bubbled through the solution (3 d). The solvent was removed in vacuo and H_2O (50 mL) was added to the residue. The mixture was extracted with EtOAc (2×50 mL) and then the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by PTLC (1:2 EtOAc/hexanes) afforded **2** as a white solid: yield, 0.20 g (73%); mp 65–75 °C; R_f 0.45 (1:2 EtOAc/hexanes); IR (KBr) 3357, 2974, 2929, 1701, 1515, 1254, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 36H, $OC(CH_3)_3$), 1.55–1.77 (m, 16H, CH_2CH_2CH), 2.74 (br s, 4H, CHS), 3.14–3.26 (m, 4H, $CHH'N$), 3.37–3.53 (m, 4H, $CHH'N$), 4.96 (br s, 4H, NHCO), the ^1H NMR data were in agreement with the COSY spectrum; ^{13}C NMR ($CDCl_3$) δ 26.7 (CH_2CH_2CH), 28.4 ($OC(CH_3)_3$), 31.5 (CH_2CH_2CH), 44.0 (CH_2N), 52.7 (CHS), 79.5 ($OC(CH_3)_3$), 155.9 (NHCO); MS (+CI) m/z 407 $[0.5M+1]^+$, 813 $[M+1]^+$; MS (+ESI) m/z 1241.5 (26%), 835.8 ($[M+Na]^+$, 100%); M_r (+CI) 407.204 88 $[0.5M+1]^+$ (calcd for $C_{18}H_{35}N_2O_4S_2$ 407.203 83), 813.397 88 $[M+1]^+$ (calcd for $C_{36}H_{69}N_4O_8S_4$ 813.399 83).

4.1.7. 3,8,11,16-Tetrakis(aminomethyl)-1,2,9,10-tetrathia-cyclohexadecane tetra-trifluoroacetic acid (3). Compound **2** (12.3 mg, 0.03 mmol) was dissolved in TFA (1.2 mL) and stirring was continued at room temperature (30 min). The reaction was concentrated in vacuo to afford **3** as a viscous oil: yield, 12 mg (92%); IR (neat) 2911, 1680, 1195, 835, 721 cm^{-1}; ^1H NMR (D_2O) δ 1.31–1.79 (m, 16H, CH_2CH_2CH), 2.92–3.09 (m, 4H, CHS), 3.10–3.38 (m, 8H, NCH_2); ^{13}C NMR (D_2O) δ 25.7 (CH_2CH_2CH), 30.8

(CH_2CH_2CH), 42.0 (CH_2N), 48.9 (CHS); MS (+ESI) 413.1 ($[M-4TFA+1]^+$, 100%), 619.2 (28%), 824.7 (22%); M_r (+CI) 207.098 53 $[0.5\ M-2TFA+1]^+$ (calcd for $C_8H_{19}N_2S_2$ 207.098 97), 413.189 28 $[M-4TFA+1]^+$ (calcd for $C_{16}H_{37}N_4S_4$ 413.190 11).

4.1.8. 7-*N*,7′-*N*′-(1″,2″,9″,10″-Tetrathia-cyclohexadecanyl-3″,8″,11″,16″-tetramethylenyl)tetrakismitomycin C (19). To an anhydrous methanolic solution (1 mL) of **3** (6.2 mg, 0.014 mmol) and Et_3N (12 μL, 0.09 mmol) was added **18** (10 mg, 0.057 mmol). The reaction solution was stirred at room temperature (1 d) and then the solvent was removed in vacuo. Purification of the reaction mixture by PTLC (20% MeOH–$CHCl_3$) afforded **19**: yield, 6.2 mg (52%); HPLC t_R 32.9–35.2 min (6 peaks); R_f 0.15 (20% MeOH–$CHCl_3$); UV–vis (CH_3CN–H_2O) λ_{max} 222, 374 nm; ^1H NMR (pyridine-d_5, 300 MHz) δ 1.55–1.98 (m, 16H, C(3′)H_2, C(4′)H_2), 2.24 (s, 12H, C(6)CH_3), 2.76 (br s, 4H, C(2)H), 3.14 (br s, 4H, C(1)H), 3.23 (s, 12H, C(9a)OCH_3), 3.58 (br d, J=12.6 Hz, 4H, C(3)*H*H′), 3.75–3.96 (m, 8H, C(1′)H_2), 3.98–4.05 (m, 4H, C(9)H), 4.54 (d, J=12.6 Hz, 4H, C(3)H*H*′), 4.98–5.11 (m, 4H, C(10)*H*H′), 5.34–5.44 (m, 4H, C(10)H*H*′), 7.32 (br s, 4H, C(7)NH), the signals for the C(10)OC(O)NH_2, N(1a)H and C(2′)H protons were not detected and are believed to overlap with the observed peaks, the ^1H NMR data were in agreement with the COSY spectrum; ^{13}C NMR (pyridine-d_5, 75 MHz) δ 10.4 (C(6)*C*H_3), 27.8 (C(4′)), 29.9 (C(3′)), 32.7 (C(2)), 36.8 (C(1)), 44.4 (C(9)), 48.5 (C(1′)), 49.7 (C(9a)O*C*H_3), 50.6 (C(3)), 54.3 (C(2′)), 62.5 (C(10)), 105.0 (C(6)), 106.9 (C(9a)), 111.0 (C(8a)), 148.3 (C(7)), 155.5 (C(4a)), 158.1 (C(10a)), 176.7 (C(8)), 178.5 (C(5)); MS (+ESI) *m*/*z* 1703.4 ($[M+Na]^+$, 100%), 1363.6 (68%), 863 ($[0.5M+Na]^+$, 16%); LC-MS *m*/*z* 1703 $[M+Na]^+$, 863 $[0.5M+Na]^+$ (t_R 17.1–18.1 min).

4.1.9. 7-*N*,7′-*N*′-(2″,7″-Dihydroxy-1″,8″-octanediyl)bismitomycin C (20). To an anhydrous methanolic solution (1.5 mL) of **13** (5.4 mg, 0.022 mmol) and Et_3N (18 μL, 0.13 mmol) was added **18** (15 mg, 0.043 mmol). The reaction solution was stirred at room temperature (1 d) and then the solvent was removed in vacuo. Purification of the reaction mixture by PTLC (30% MeOH–$CHCl_3$) afforded **20** as a mixture of diastereomers (1.1:1, ^{13}C NMR analysis): yield, 7.7 mg (44%); HPLC t_R 24.9 min (br); R_f 0.46 (30% MeOH–$CHCl_3$); UV–vis (CH_3CN–H_2O) λ_{max} 222, 368 nm; ^1H NMR (pyridine-d_5, 300 MHz) δ 1.53–1.88 (m, 8H, C(3′)H_2, C(4′)H_2), 2.21 (s, 6H, C(6)CH_3), 2.75 (d, J=3.9 Hz, 2H, C(2)H), 3.14 (d, J=3.9 Hz, 2H, C(1)H), 3.21 (s, 6H, C(9a)OCH_3), 3.62 (d, J=12.6 Hz, 2H, C(3)*H*H′), 3.63–3.77 (m, 2H, C(1′)*H*H′), 3.78–3.91 (m, 2H, C(1′)H*H*′), 3.95–4.07 (m, 4H, C(9)H, C(2′)H), 4.57 (d, J=12.6 Hz, 2H, C(3)H*H*′), 5.06 (dd, J=10.5, 10.2 Hz, 2H, C(10)*H*H′), 5.36–5.43 (m, 2H, C(10)H*H*′), 7.51 (br d, J=6.0 Hz, 2H, C(7)NH), the signals for the C(10)OC(O)NH_2 and N(1a)H protons were not detected and are believed to overlap with the observed peaks, the ^1H NMR data were in agreement with the COSY spectrum; ^{13}C NMR (pyridine-d_5, 75 MHz) for the major diastereomer, δ 10.3 (C(6)*C*H_3), 26.2 (C(4′)), 32.8 (C(2)), 35.9 (C(3′)), 36.7 (C(1)), 44.4 (C(9)), 49.6 (C(9a)O*C*H_3), 50.7 (C(3)), 51.3 (C(1′)), 62.5 (C(10)), 70.2 (C(2′)), 103.6 (C(6)), 107.0 (C(9a)), 110.6 (C(8a)), 147.9 (C(7)), 156.4 (C(4a)), 158.2 (C(10a)), 176.8 (C(8)), 179.0 (C(5)); ^{13}C NMR (pyridine-d_5, 75 MHz) for the minor diastereomer, δ 32.7 (C(2)), 44.5 (C(9)), 156.3 (C(5a)), 158.1 (C(10a)), 178.9 (C(5)), the other signals were not detected and are believed to overlap with the observed peaks, the ^{13}C NMR data were in agreement with the DEPT spectrum; MS (+ESI) *m*/*z* 833 $[M+Na]^+$.

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Synthesis of poly(pyridylthioether) dendrimers incorporating a $Fe_2(CO)_6$ cluster core

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Abstract—New pyridylthioether-based dendrons bearing a thiol moiety at their focal point have been prepared by a convergent synthetic approach. These dendrons were readily attached to a $Fe_2(CO)_6$ core to generate two-directional dendritic molecules incorporating an iron-carbonyl cluster.

1. Introduction

Organic–inorganic composites deriving from the encapsulation of metal clusters within dendrimer molecules are emerging as a new class of nanosized materials that are expected to have applications in many areas including catalysis,[1] molecular recognition,[2] and photoactive device engineering.[3] In these materials, the chemical interaction between an organic array and the inorganic counterpart can be either covalent or noncovalent. The noncovalent method of incorporation, which uses dendrimers as both nanoreactor that sequesters metal ions and stabilizer, leads to dendrimer-encapsulated metal nanoclusters. Moreover, the size of such metallic nanoparticles can be controlled by the size of the dendrimer template.[4] Typically, the synthetic strategy to achieve encapsulation relies on complexation of metal ions into the dendrimer interior and their subsequent chemical reduction to zero-valent form. Most syntheses of these nanocomposites concern noble metals[1,4–7] but dendrimers incorporating copper[8] have also been reported. Recently, Fréchet-type dendritic wedges[9] focally functionalized with a metal-coordinating group, such as a thiol[10] or 4-pyridone[11] moiety, were assembled around gold clusters affording dendron-stabilized gold nanoparticles in which the average size of the metallic nanoparticles seems to be correlated to the generation number of the dendritic wedges.

The covalent encapsulation of a metal cluster inside dendritic architectures was first reported by Gorman and co-workers who prepared metallodendrimers containing a $[Fe_4S_4]^{2+}$ cluster core unit via replacement of bulky aliphatic thiols at the four vertices of this cluster by dendron-functionalized aromatic thiols.[12] The main object of Gorman's research group, however, was to understand the relationship between dendritic structure and electrochemical properties of encapsulated iron–sulfur clusters.[13]

Because dendritic wedges bearing a thiol functionality at their focal point play a key role in the chemistry of both noncovalent and covalent dendrimer-encapsulated metal clusters we decided to explore the synthesis of a new series of thiol-functionalized pyridylthioether-based dendrons.

There are two features of our dendrons that make them appealing as precursors of dendron-functionalized inorganic clusters. First, the S–N–S terdentate ligands constituting the dendritic framework are potential binding sites of transition metals.[14] This, therefore, may enable the preparation of heterometallic dendritic assemblies. Second, the pyridylthioether-based repeating units are directly connected through phenyl groups affording a scaffold that could facilitate the electron transfer between dendron units and a focal point.

A prerequisite to successfully achieve the covalent encapsulation of transition-metal clusters using these types of focally-functionalized dendrons, is an efficient synthetic methodology that provides easy access to products of high purity.

To accomplish such a task we have chosen to investigate the chemistry of the dinuclear hexacarbonyls of formula $[Fe_2(CO)_6(SR)_2]$. It has been previously shown that the

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reactions between $Fe_3(CO)_{12}$ and bulky aromatic thiols afford compounds of the type $[Fe_2(CO)_6(\mu\text{-}SR)_2]$ in good yields.[15]

We focused our efforts on the preparation of analogous systems with dendritic topologies. The results of the synthetic studies which allowed us to assembly novel pyridyl thioether dendrons around an iron-carbonyl core are presented here.

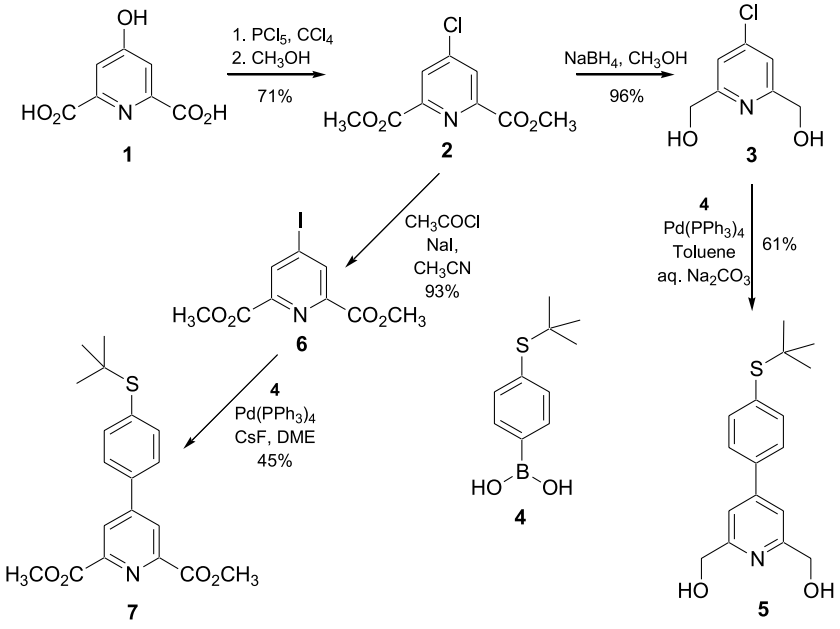
2. Results and discussion

The synthetic route we have adopted to prepare a dendrimer-encapsulated $Fe_2(CO)_6$ core unit consists of treating commercially available $Fe_3(CO)_{12}$ with a dendron-functionalized aromatic thiol which was synthesized via convergent methodology.[9] The building block designed for the synthesis of all dendron generations, namely compound **12**, is depicted in Scheme 2, along with the synthetic approach we have developed for its preparation.

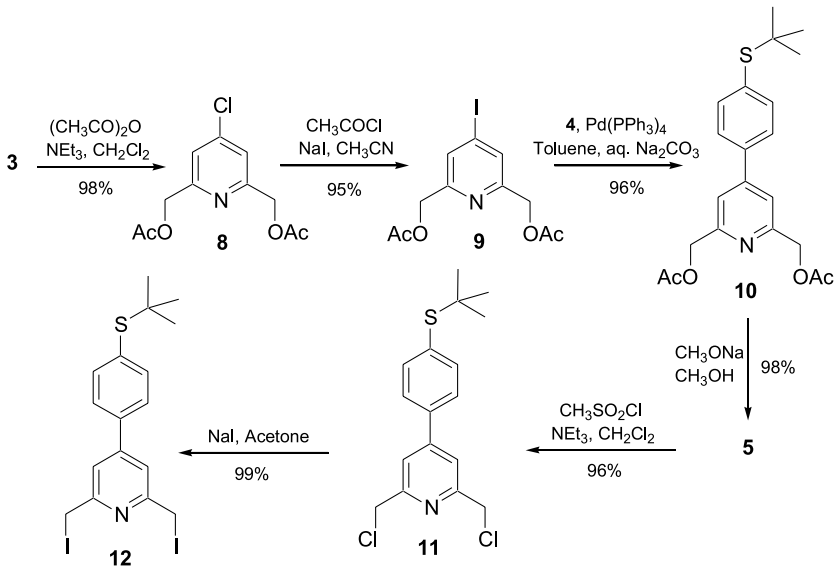
The synthesis of **12** was initiated from the commercial diacid **1**, (Scheme 1) which was converted to dimethyl 4-chloropyridine-2,6-dicarboxylate **2** in 71% yield according to suitably modified literature procedures.[16] Subsequent reduction of the ester functionalities to alcohols, using $NaBH_4$ in methanol,[17] afforded diol **3** in 96% yield. Halopyridine **3** was then treated with boronic acid **4**, prepared[18] in high yield and purity from 4-bromobenzenethiol, employing the Suzuki cross-coupling conditions (toluene/H_2O, Na_2CO_3, $Pd(PPh_3)_4$) to give the aryl-substituted pyridine derivative **5** in 61% yield after chromatographic purification. Although we have obtained the desired compound **5** in reasonable yield, the purification step was arduous because of the difficulty in separating **5** from the starting materials. To overcome this problem and to improve the yield of cross-coupling product an alternative approach to **5** was explored.

Since the order of reactivity of the aryl halides towards oxidative addition to a Pd(0) complex suggests that iodopyridines are much more effective substrates than the corresponding chloropyridines, the chloro-substituted pyridine **2** was converted to the corresponding iodo derivative **6** in 93% yield by sonochemical reaction with acetyl chloride, and NaI in dry CH_3CN.[19] Unfortunately, the coupling reaction of **6** with boronic acid **4** under anhydrous conditions in the presence of CsF as base[20] only afforded **7** in moderate yield (40–60%). However, the yields compare well with those reported by Lohse,[21] who investigated the reactivity of methyl 4-chloropyridine-2-carboxylate in a Suzuki reaction. These relatively low yields, presumably due to the sensitivity to base of the esters functions, prompted us to pursue the preparation of **5** from diol **3** by a four-step procedure that proved to give superior results regarding achievable yield of compound **5**.

Thus, as outlined in Scheme 2, the hydroxyl functions of **3** were acylated with Ac_2O and trietylamine to afford the corresponding acetate **8** in essentially quantitative yield. To increase the reactivity of **8** in cross-coupling reactions the chloro group of this compound was replaced by iodo employing *trans*-halogenation conditions (AcCl/NaI, CH_3CN, room temperature, ultrasonic irradiation) to produce compound **9** in 95% yield. As expected, halopyridine **9** furnished the arylpyridine **10** in excellent yield (96%) by a Suzuki reaction using boronic acid **4** as coupling partner of **9**, $Pd(PPh_3)_4$ as catalyst, $NaHCO_3$ as base, and toluene/H_2O as solvent system. Due to the acetyl groups protecting the hydroxyl moieties, the solubility of **10** in organic solvents was significantly enhanced relative to the unprotected derivative allowing easy separation and purification by silica gel chromatography of this material after reaction. Furthermore, the acetate moiety can be selectively and cleanly removed under mild basic conditions. Accordingly, deacetylation of compound **10** by alkaline methanolysis generated the diol **5**, as formed by Suzuki coupling of **3** with **4**, in 98% yield (88% overall yield from **3**).



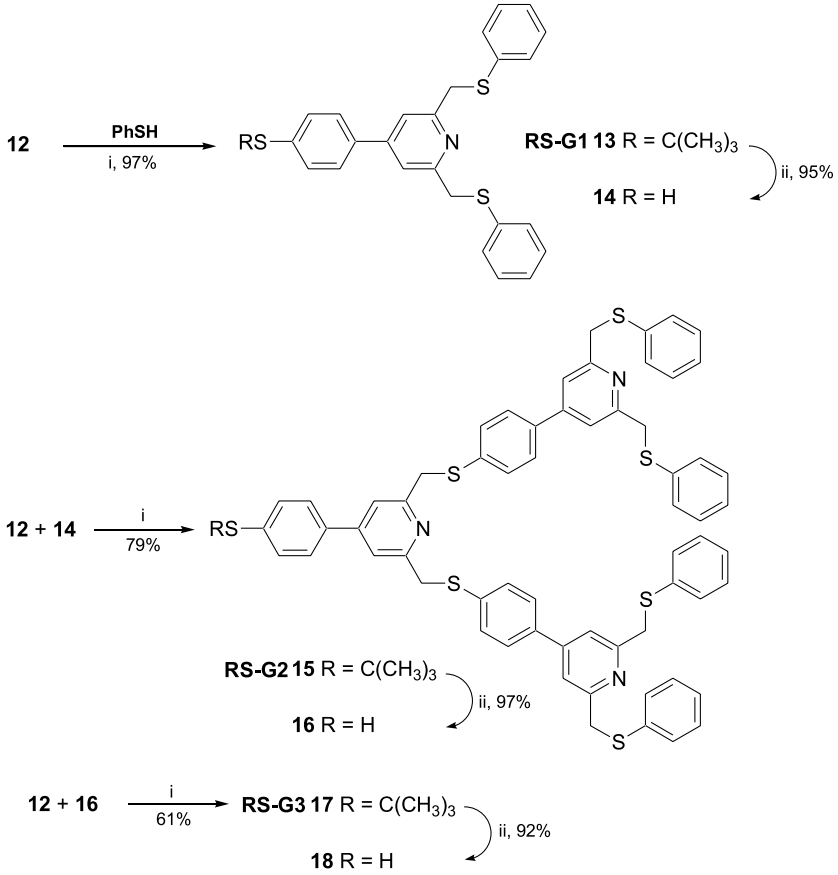
Scheme 1. Synthesis of the intermediates **5** and **7**.



Scheme 2. Synthesis of the building block **12**.

Reaction of **5** with methanesulfonyl chloride and triethylamine furnished the corresponding chloride **11** in 96% yield, which was subsequently converted into its iodo analogue **12** in 99% yield by reaction with NaI in acetone because iodides easily undergo a nucleophilic substitution. On the contrary, direct conversion of diol **5** to diiodide **12** by I_2/imidazole/PPh_3[22] gave poor yields.

The reactivity of the pyridine-based building block **12** evidently emerges in the synthesis of the first-generation dendron. As a matter of fact, coupling diiodide **12** with slightly over 2 equiv of thiophenol under standard etherification conditions (DMF/K_2CO_3) proceeded quickly (2 h, room temperature) to give the protected first-generation dendron **13** in 97% yield (Scheme 3).



Scheme 3. Synthesis of dendrons: (i) DMF/K_2CO_3, rt; (ii) thioanisole, TFA, CF_3SO_3H, rt.

It is well-known that some *S*-thiophenol protecting groups, such as thioethers, are particularly stable and their selective removal may be difficult to accomplish in high yield.[23] Nevertheless, the *tert*-butyl moiety in compound **13** could be easily removed using the thioanisole-trifluoromethanesulfonic acid (TFMSA)-trifluoroacetic acid system[24] to produce the desired thiol-funtionalized dendron **14** in 95% yield. In accordance with a convergent growth strategy thiol **14** was then reacted with diiodide **12**, under conditions similar to those used for **13**, to give the second-generation dendron **15** (79%), which was deprotected to the corresponding thiol **16** in 97% yield by reacting with thioanisole-trifluoromethanesulfonic acid (TFMSA)-TFA at room temperature for 4 h (Scheme 3). While the deprotection proceeds smoothly, the purification of the crude product of this reaction by silica gel chromatography proved to be unsuitable affording the thione form of **16** (Chart 1), as confirmed by NMR and mass spectrometry analysis. Thus to circumvent this problem, the thiol **16** was purified by repeated precipitation from dichloromethane–hexane mixtures.

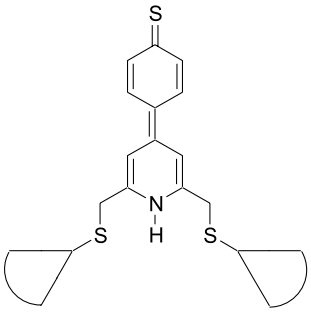


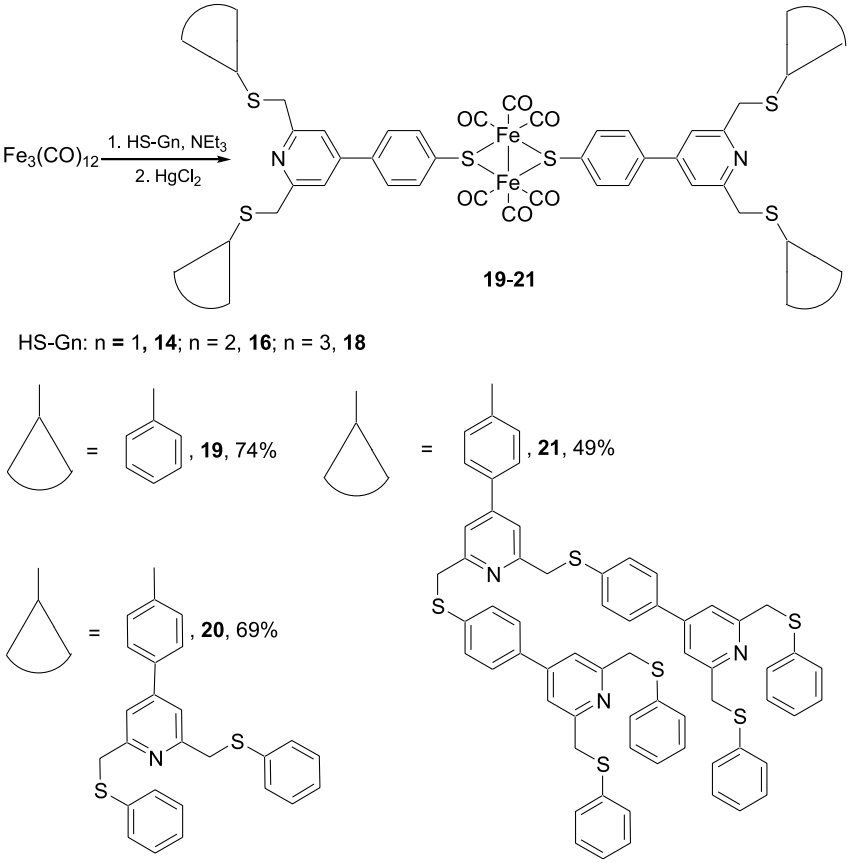
Chart 1. Thione form of pyridylthioether-based dendrons focally functionalized with a thiol unit.

The third-generation dendritic wedge **17** was prepared in a similar way to its earlier generation analogue. However, the coupling of **12** with thiol **16** gives **17** in moderate yields (61%), presumably due both to steric problems and the inherent low stability of the thiol moiety. Following the same procedure that gave compounds **14** and **16**, dendron **17** was deprotected to furnish the corresponding thiol derivative **18** in 92% yield.

All dendrons display NMR spectra consistent with their structures. The aliphatic regions in the ^{1}H NMR spectra provide the most important information since the aliphatic protons give well-resolved signals. The number of singlets at around 4.25–4.36 ppm due to CH_2S protons clearly corresponds with the generation of the dendron involved. Moreover, the relative integrations for these signals and the aromatic proton signals match perfectly with the proposed structures.

Finally, the conversion from *tert*-butyl protected dendron to the corresponding thiol derivative was easily confirmed by the complete absence of the signal associated with the *tert*-butyl moiety coupled with the presence of a new resonance at 3.52–3.55 ppm for the SH group.

The last step of our approach involved the assembly of the



Scheme 4. Synthesis of dendrimers with $Fe_2(CO)_6$ as core.

synthesized dendrons around a transition-metal cluster. To this end we initially reacted $Fe_3(CO)_{12}$ with thiol **14** in THF, using triethylamine as a base, followed by treatment with $HgCl_2$ in a one-pot procedure (Scheme 4), which has been suggested from the communication describing the reactions of alkyl- and arylmercuric halides with $[Et_3NH][((-CO)-((-RS)Fe_2(CO)_6]$ complexes.[25] According to the above procedure, the desired cluster compound **19** was obtained in 74% yield after chromatographic purification. The analogous reaction of $Fe_3(CO)_{12}$ with dendron-functionalized thiols **16** and **18** afforded the iron cluster dendrimers **20** and **21** in 69 and 49% yield, respectively (Scheme 4).

The formation of metallodendrimers **19–21** was confirmed by disappearance of the thiol signal in their ^1H NMR spectra. The ^1H NMR spectrum of the third generation dendrimer **21** in $CDCl_3$ was broad and structureless, probably as a consequence of restricted movement of the attached dendrons, but consistent with the proposed structure in DMSO-d6 at 50 °C. However, the structure of **21** could be established unambiguously by ^{13}C NMR that showed the expected resonances for the aliphatic and aromatic carbons of the dendritic building block as well as the signal for the carbonyl groups of the cluster core. Further evidence for the formation of **19–21** was provided by their IR spectra that showed in the carbonyl region the expected absorbances for complexes of this type.[15] To confirm the molecular masses of the synthesized metallodendrimers, the MALDI-TOF technique was applied. Unfortunately, MALDI-TOF mass spectra of molecules **19–21** did not show the expected molecular ion peaks, but instead signals corresponding to the mass of the starting dendron were observed. Therefore these results indicate that the structure of the iron-carbonyl core dendrimers is too weak to withstand the conditions of the MALDI-TOF analysis.

Electrospray ionization technique was also used as an alternative mass analysis in an attempt to provide characterization of the dendritic complexes. However, these attempts were unsuccessful.

Though the mass spectrometric studies did not provide straightforward evidence for the formation of **19–21**, the elemental analysis data coupled with the NMR and IR spectra offered clear indication that the desired compounds had been successfully obtained.

3. Conclusions

Following a convergent strategy a series of novel pyridylthioether dendrimers that incorporate a $Fe_2(CO)_6$ unit in the core have been assembled by coupling commercially available triiron dodecacarbonyl with synthetic monodendrons. These dendrons have been constructed by employing the activated and protected building block 4-[4-*tert*-butylthio(phenyl)]-2,6-bis(iodomethyl)pyridine (**12**) which has been efficiently generated by a multistep sequence. The key dendron growth steps involved coupling via Williamson reaction conditions followed by deprotection of the thiol function. The formation of the novel metallodendrimers is supported by ^1H, ^{13}C, and FT-IR spectroscopy, and elemental analyses.

Preliminary experiments confirm that these metal cluster core dendrimers are capable of binding the same number of palladium atoms as the tridentate SNS units affording a metallodendrimer that incorporates two kinds of transition metal centres in its structure. The preparation and investigation of these complexes are currently underway. We are also investigating the electrochemical properties of these dendritic systems to gain insight into structure-property relationships.

4. Experimental

4.1. General comments

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. Methanol and acetone were dried and stored over 3 and 4 Å molecular sieves, respectively. *N*,*N*-Dimethylformamide (DMF), dichloromethane, acetonitrile and triethylamine were distilled from calcium hydride. Other solvents and reagents were used as received. Flash chromatography was performed on 230–400 mesh silica gel (Macherey–Nagel). ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions, unless otherwise indicated, on a Bruker Avance 300 spectrometer using the solvent signal as internal standard. IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer. Melting points were taken in capillary tubes with a Buchi 535 apparatus and are uncorrected.

Mass spectra of dendrimers were obtained by Matrix Assisted Laser Desorption Ionisation Mass Spectrometry (MALDI-MS), using a Voyager-DE PRO instrument (Applied Biosystems, Foster City, CA, USA), operating in positive linear mode. The instrumental conditions were: acceleration voltage: 20 keV; grid voltage = 93%; guide wire = 0.3%; delay time = 200 ns. The matrix used was (2-(*p*-hydroxy-phenylazo)benzoic acid (HABA), at a concentration of 10 mg/mL in choloroform. 0.5 mg of dendrimer was dissolved in 1 mL of $CHCl_3$ and 5 μL of this solution were added to the same volume of the matrix solution. About 1 μL of the resulting solution was deposited on the stainless steel sample holder and allowed to dry before introduction into the mass spectrometer.

ESI mass spectra were obtained using an LCQ (Finnigan, Palo Alto, CA, USA), operating in positive ion modes. The entrance capillary temperature was 270 °C and the capillary voltage was kept at +3 kV. Sample solutions (at a concentration of about 5×10^{-6} M in $CHCl_3$) were introduced by direct infusion at a flow rate of 8 μL/min. The He pressure inside the trap was kept constant. The pressure directly read by ion gauge (in the absence of the N_2 stream) was 2.8×10^{-5} Torr.

4.1.1. Dimethyl 4-chloropyridine-2,6-dicarboxylate (2). A mixture of anhydrous 4-hydroxypyridine-2,6-dicarboxylic acid (64.45 g, 0.32 mol) and PCl_5 (200.2 g, 0.96 mol) in CCl_4 (300 mL) was heated under reflux for 4 h. Then dry methanol (200 mL) was added dropwise over a period of 40 min, and the resulting mixture was heated under reflux for 1 h. The solvent was evaporated to afford a tan yellow solid which was dissolved in water (500 mL) and

neutralized with Na_2CO_3. The resulting solid was collected by filtration, washed with water and dissolved in $CHCl_3$ (400 mL). The organic solution was washed with saturated aqueous Na_2CO_3 (3×200 mL), brine (200 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure and recrystallization of the residue from methanol gave **2** as white crystals (52.6 g, 71%). Mp 139–140 °C. IR (KBr), ν: 1722, 1710, 1578 cm^{-1}. ^1H NMR: δ 4.02 (s, 6H, CH_3), 8.29 (s, 2H, PyH). ^{13}C NMR: δ 53.9 (CH_3), 128.7 (3,5-PyC), 147.2 (4-PyC), 149.8 (2,6-PyC), 164.5 (CO). Anal. calcd for $C_9H_8ClNO_4$ (229.6): C, 47.08; H, 3.51;Cl, 15.44; N, 6.10. Found: C, 46.85; H, 3.44;Cl, 15.70; N, 6.00.

4.1.2. 4-Chloro-2,6-bis(hydroxymethyl)pyridine (3). This compound was prepared from **2** following a literature procedure[17] in 96% yield.

4.1.3. 4-[4-*tert*-Butylthio(phenyl)]-2,6-bis(hydroxymethyl)pyridine (5). *Method A.* A stirred mixture of diol **3** (1.00 g, 5.76 mmol), 4-(*tert*-butylthio)phenylboronic acid **4** (2.42 g, 11.52 mmol), $Pd(PPh_3)_4$ (1.33 g, 1.52 mmol) in toluene (100 mL) and saturated aqueous Na_2CO_3 (50 mL) was heated under reflux under argon for 64 h. After cooling to room temperature the reaction mixture was extracted with ethyl acetate (3×50 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel eluting with 5–10% methanol in $CHCl_3$. Removal of the solvent followed by precipitation of the residue from CH_2Cl_2/hexane gave **5** as a white solid (1.07 g, 61%).

Method B. A stirred solution of **10** (4.00 g, 10.32 mmol) and CH_3ONa (4.13 mmol, from 94 mg of Na) in dry methanol (50 mL) was heated under reflux under argon for 4 h. Then the reaction mixture was evaporated to dryness and the residue taken up in CH_2Cl_2 (150 mL). The resulting organic solution was washed with water (2×50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was precipitated from CH_2Cl_2/hexane to afford **5** as a white solid (3.08 g, 98%). Mp 119–120 °C. IR (KBr), ν: 1610 cm^{-1}. ^1H NMR (DMSO-d6): δ 1.29 (s, 9H, *t*-Bu) 4.59 (d, 4H, J=5.9 Hz, CH_2), 5.44 (d, 2H, J=5.9 Hz, OH), 7.62 (s, 2H, PyH), 7.65 (d, 2H, J=8.5 Hz, 3PhH), 7.78 (d, 2H, J=8.5 Hz, 2-PhH). ^{13}C NMR (DMSO-d6): δ 31.1 (C(CH_3)$_3$), 46.5 (C(CH_3)$_3$), 64.5 (CH_2), 116.0 (3,5-PyC), 127.4 (2-PhC) 133.6 (4-PhC), 137.9 (3-PhC), 138.7 (1-PhC), 147.6 (4-PyC), 162.3 (2,6-PyC). Anal. calcd for $C_{17}H_{21}NO_2S$ (303.4): C, 67.29; H, 6.98; N, 4.62. Found: C, 67.32; H, 6.81; N, 4.49. ESI/MS *m/z*: 304 $[M+H]^+$ (Rel. Int.=100%).

4.1.4. Dimethyl 4-iodopyridine-2,6-dicarboxylate (6). Acetyl chloride (5.15 g, 65.61 mmol) was added to a mixture of chloropyridine **2** (5.00 g, 21.77 mmol) and NaI (65.28 g, 435.5 mmol) in dry CH_3CN (150 mL) at 0 °C. The reaction mixture was sonicated for 5 h under an argon atmosphere maintaining the bath temperature below 50 °C. After cooling to 0 °C saturated aqueous Na_2CO_3 (75 mL) and CH_2Cl_2 (150 mL) were added. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (100 mL), water (2×100 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure and recrystallization of the residue from methanol gave **6** as a white solid (6.51 g, 93%). Mp 174–175 °C. IR (KBr) ν: 1751, 1558 cm^{-1}. ^1H NMR: δ 4.03 (s, 6H, CH_3), 8.67 (s, 2H, PyH). ^{13}C NMR: δ 53.3 (CH_3), 106.9 (4-PyC), 137.0 (3,5-PyC), 148.2 (2,6-PyC), 163.8 (CO). Anal. calcd for $C_9H_8INO_4$ (321.1): C, 33.67; H, 2.51; N, 4.36. Found: C, 33.72; H, 2.66; N, 4.38.

4.1.5. Dimethyl 4-[4-*tert*-butylthio(phenyl)]pyridine-2,6-dicarboxylate (7). A solution of **6** (500 mg, 1.56 mmol), 4-(*tert*-butylthio)phenylboronic acid **4** (393 mg, 1.87 mmol), CsF (473 mg, 3.12 mmol) and $Pd(PPh_3)_4$ (90 mg, 0.078 mmol) in dry DME (10 mL) was stirred under argon at 60 °C for 18 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with water (2×50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue subjected to flash chromatography on silica gel eluting with CH_2Cl_2/ethyl acetate 4:1. Removal of the solvent followed by precipitation of the residue from CH_2Cl_2/hexane gave **7** as a yellowish solid (251 mg, 45%). Mp 139–140 °C. IR, ν: 1741, 1716, 1603 cm^{-1}. ^1H NMR: δ, 1.34 (s, 9H, *t*-Bu) 4.06 (s, 6H, CH_3), 7.67–7.74 (m, 4H, PhH), 8.55 (s, 2H. PyH). ^{13}C NMR: δ 31.0 (C(CH_3)$_3$), 46.7 (C(CH_3)$_3$), 53.3 (CH_3), 125.6 (3,5-PyC), 127.1 (2-PhC), 135.8 (1-PhC), 136.3 (4-PyC), 138.1 (3-PhC), 148.9 (4-PhC), 150.4 (2,6-PyC), 165.2 (CO). Anal. calcd for $C_{19}H_{21}NO_4S$ (359.44): C, 63.49; H, 5.98; N, 3.90. Found: C, 63.66; H, 5.91; N, 4.05.

4.1.6. 4-Chloro-2,6-bis(acetoxymethyl)pyridine (8). To a stirred solution of **3** (5.00 g, 28.8 mmol) in dry CH_2Cl_2 (150 mL) and dry triethylamine (13.11 g, 129.6 mmol) was added acetic anhydride (11.76 g, 115.21 mmol). The reaction mixture was heated under reflux under argon for 2 h and then cooled to room temperature. CH_2Cl_2 (100 mL) was added, and the resulting solution was washed with saturated aqueous $NaHCO_3$ (50 mL), water (2×50 mL), and dried over $MgSO_4$. After filtration, the solvent was removed from the filtrate and the pure product (7.24 g, 98%) was obtained as a white solid. Mp 50–51 °C. IR (KBr), ν: 1732, 1578 cm^{-1}. ^1H NMR: δ 2.19 (s, 6H, CH_3), 5.20 (s, 4H, CH_2), 7.30 (s, 2H, PyH). ^{13}C NMR: δ, 20.7 (CH_3), 65.9 (CH_2), 120.7 (3-PyC), 145.5 (4-PyC), 157.3 (2-PyC), 170.2 (CO). Anal. calcd for $C_{11}H_{12}ClNO_4$ (257.7): C, 51.27; H, 4.69; N, 5.44. Found: C, 51.46; H, 4.84; N, 5.42.

4.1.7. 4-Iodo-2,6-bis(acetoxymethyl)pyridine (9). This compound was prepared analogously to **6** by reacting **8** (4.45 g, 17.29 mmol), acetyl chloride (4.07 g, 51.87 mmol), and NaI (18.14 g, 121.03 mmol) in dry CH_3CN (90 mL), except the reaction mixture was sonicated for 18 h instead of 5 h while the bath temperature was allowed to warm to 65 °C. After workup, the crude product was purified by precipitation from CH_2Cl_2/hexane to give **9** as a pale yellow solid (5.73 g, 95%). Mp 116–117 °C. IR (KBr), ν: 1751, 1558 cm^{-1}. ^1H NMR: δ 2.18 (s, 6H, CH_3), 5.15 (s, 4H, CH_2), 7.66 (s, 2H, PyH). ^{13}C NMR: δ 20.8 (CH_3), 65.7 (CH_2), 106.7 (4-PyC), 129.7 (3,5-PyC), 156.4 (2,6-PyC), 170.3 (CO). Anal. calcd for $C_{11}H_{12}INO_4$ (349.12): C, 37.84; H, 3.46; N, 4.01. Found: C, 37.95; H, 3.49; N, 4.19.

4.1.8. 4-[4-*tert*-Butylthio(phenyl)]-2,6-bis(acetoxymethyl)pyridine (10). A mixture of boronic-acid **4**

(2.65 g, 12.6 mmol), **9** (4.00 g, 11.46 mmol), $Pd(PPh_3)_4$ (264 mg, 0.229 mmol) in toluene (90 mL) and saturated aqueous $NaHCO_3$ (75 mL) was stirred under argon at 50 °C for 72 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (3×50 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2/ethyl acetate 4:1. Removal of the solvent followed by recrystallization of the residue from methanol gave **10** as a white solid (4.25 g, 96%). Mp 157–158 °C. IR (KBr), *ν*: 1745, 1736, 1610 cm^{-1}. ^1H NMR: *δ*, 1.29 (s, 9H *t*-Bu) 4.59 (s, 4H, CH_2), 7.62 (s, 2H, PyH), 7.65 (d, *J*=8.5 Hz, 2H, 3-PhH), 7.78 (d, *J*=8.5 Hz, 2H, 2-PhH). ^{13}C NMR: *δ*, 20.9 (CH_3), 31.0 (C(*C*H_3)$_3$), 46.4 (*C*(CH_3)$_3$), 66.8 (CH_2), 119.0 (3,5-PyC), 127.1 (3-PhC), 134.5 (1-PhC), 137.9 (2-PhC), 138.1 (4-PyC), 149.5 (4-PhC), 156.3 (2,6-PyC), 170.6 (CO). Anal. calcd for $C_{21}H_{25}NO_4S$ (387.49): C, 65.09; H, 6.50; N, 3.61. Found: C, 65.11; H, 6.48; N, 3.42.

4.1.9. 4-[4-*tert*-Butylthio(phenyl)]-2,6-bis(cloromethyl)-pyridine (11). Methanesulfonyl chloride (8.49 g, 74.15 mmol) was slowly added over 10 min to a cooled solution (0 °C) of **5** (7.50 g, 24.72 mmol) in dry CH_2Cl_2 (100 mL) containing triethylamine (8.0 g, 79.1 mmol) under argon. The mixture was stirred at room temperature for 2 h, then was heated to reflux for 14 h and, after cooling to room temperature, CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) were added. The organic layer was washed with water, dried over $MgSO_4$ and filtered. The filtrate was passed through a silica plug eluting with CH_2Cl_2. Removal of the solvent under reduced pressure gave **11** as a pale brown solid (8.10 g, 96%). Mp 82–83 °C. IR (KBr), *ν* 1605 cm^{-1}. ^1H NMR: *δ*, 1.35 (s, 9H *t*-Bu) 4.74 (s, 4H, CH_2), 7.64 (d, *J*=8.6 Hz, 2H, 2-PhH), 7.67 (s, 2H, PyH), 7.68 (d, *J*=8.6 Hz, 2H, 2-PhC). ^{13}C NMR: *δ* 31.4 (C(*C*H_3)$_3$), 46.9 (*C*(CH_3)$_3$), 46.9 (CH_2), 120.4 (3,5-PyC), 127.5 (2-PhC), 135.2 (4-PhC), 138.1 (1-PhC), 138.4 (3-PhC), 150.5 (4-PyC), 157.4 (2,6-PyC). Anal. calcd for $C_{17}H_{19}Cl_2NS$ (340.31): C, 60.00; H, 5.63; N, 4.12. Found: C, 59.81; H, 5.58; N, 4.26.

4.1.10. 4-[4-*tert*-Butylthio(phenyl)]-2,6-bis(iodomethyl)-pyridine (12). A stirred solution of **11** (3.02 g, 8.86 mmol) and NaI (6.64 g, 44.31 mmol) in dry acetone (50 mL) was heated under reflux under argon for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 mL). The organic solution was washed with saturated aqueous $Na_2S_2O_3$ (100 mL), water and dried over $MgSO_4$. The mixture was filtered and the solvent was removed from the filtrate affording **12** as a pale yellow solid (4.58 g, 99%). Mp 155 °C Dec. IR (KBr), *ν*: 1603 cm^{-1}. ^1H NMR: *δ*, 1.34 (s, 9H, *t*-Bu) 4.56 (s, 4H, CH_2), 7.49 (s, 2H, PyH) 7.59 (d, *J*=8.5 Hz, 2H, 2-PhH), 7.66 (d, *J*=8.5 Hz, 2H, 3-PhH). ^{13}C NMR: *δ* 5.7 (CH_2), 30.9 (C(*C*H_3)$_3$), 46.4 (*C*(CH_3)$_3$), 119.7 (3,5-PyC), 126.9 (2-PhC), 134.6 (4-PhC), 137.5 (1-PhC), 137.9 (3-PhC), 149.7 (4-PyC), 158.8 (2,6-PyC). Anal. calcd for $C_{17}H_{19}I_2NS$ (523.21): C, 39.02; H, 3.66; N, 2.68. Found: C, 39.11; H, 3.61; N, 2.83. ESI/MS *m/z*: 524 $[M+H]^+$ (Rel. Int.=100%).

4.1.11. *tert*-BuS-G1 (13). To a stirred suspension of anhydrous K_2CO_3 (2.19 g, 15.86 mmol) and benzenethiol (1.33 ml, 13.01 mmol) in dry DMF (30 mL) was added **12** (3.32 g, 6.34 mmol) portionwise over 10 min. The resulting mixture was stirred at room temperature under an argon atmosphere for 2 h and then evaporated to dryness. The residue was extracted with CH_2Cl_2 (100 mL) and the organic extract was washed with saturated aqueous Na_2CO_3 (50 mL), water (2×50 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the resulting crude product was recrystallized from methanol to give **13** as a white solid (2.98 g, 97%). Mp 54–55 °C. IR (KBr), *ν*: 1599 cm^{-1}. ^1H NMR: *δ*, 1.33 (s, 9H, *t*-Bu), 4.31 (s, 4H, CH_2), 7.22 (tt, 2H, *J*=7.1, 1.4 Hz, CH_2S-Ph*H*), 7.27 (tt, 4H, *J*=7.3, 1.4 Hz, CH_2S-Ph*H*), 7.37 (dd, 4H, *J*=8.0, 1.5 Hz, CH_2S-PhH), 7.37 (s, 2H, PyH), 7.41 (d, 2H, *J*=8.3 Hz, 2-PhH), 7.59 (d, 2H, *J*=8.3 Hz, 3-PhH). ^{13}C NMR: *δ*, 31.4 (C(*C*H_3)$_3$), 41.0 (CH_2), 46.8 (*C*(CH_3)$_3$), 119.7 (3,5-PyC), 126.8, 127.4, 129.3, 130.3, 134.5, 136.2, 138.2, and 138.6 (PhC), 149.2 (4-PyC), 158.4 (2,6-PyC). MALDI-TOF MS *m/z*: 488 $[M+H]^+$; calcd for $C_{29}H_{30}NS_3$: 488.7.

4.1.12. HS-G1 (14). To a stirred solution of **13** (4.22 g, 8.64 mmol) in thioanisole (20 mL) was slowly added trifluoroacetic acid (2.9 mL, 38.9 mmol) and triflic acid (2.7 mL, 30.25 mmol). The resulting mixture was kept stirring at room temperature under an argon atmosphere for 4 h and then CH_2Cl_2 (100 mL) was added. The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), water (2×50 mL), and dried over $MgSO_4$. After filtration, the organic phase was evaporated to dryness and the residue was purified by repeated precipitation from CH_2Cl_2/hexane to give **14** as a yellow solid (354 g, 95%). Mp 110–110.5 °C. IR (KBr) *ν*: 1605 cm^{-1}. ^1H NMR: *δ*, 3.54 (s, 1H, SH), 4.30 (s, 4H, CH_2), 7.19 (tt, 2H, *J*=7.0, 1.5 Hz, CH_2S-Ph*H*), 7.26 (btt, 4H, *J*=7.5, 1.5 Hz, CH_2S-Ph*H*), 7.33-7.31 (m, 4H, CH_2S-Ph*H*), 7.32 (s, 2H, PyH), 7.34–7.83 (m, 4H, PhH). ^{13}C NMR: *δ*, 40.4 (CH_2), 118.9 (3,5-PyC), 126.4, 127.5, 128.8, 129.4, 129.9, 132.7, 135.1, and 135.6 (PhC), 148.7 (4-PyC), 157.8 (2,6-PyC). MALDI-TOF MS *m/z*: 432 $[M+H]^+$, calcd for $C_{25}H_{22}NS_3$: 432.6.

4.1.13. *tert*-BuS-G2 (15). This compound was prepared analogously to **13** by reacting **14** (1.00 g, 2.32 mmol), K_2CO_3 (396 mg, 2.87 mmol) and **12** (577 mg, 1.10 mmol) in dry DMF (15 mL), except the reaction mixture was stirred at room temperature over a period of 4 h instead of 2 h. After workup, the crude product was purified by flash chromatography on silica gel eluting with 2.5–5% ethyl acetate in CH_2Cl_2 to give **15** as a pale yellow glassy solid (987 mg, 79%). IR (KBr) *ν*: 1601 cm^{-1}. ^1H NMR: *δ*, 1.32 (s, 9H, *t*-Bu), 4.27 (s, 8H, CH_2), 4.36 (s, 4H, CH_2), 7.17 (tt, 4H, *J*=7.2, 1.3 Hz, CH_2S-Ph*H*), 7.24 (tt, 8H, *J*=7.5, 1.4 Hz, CH_2S-Ph*H*), 7.33–7.48 (m, 18H, 2,6-PhH and CH_2S-Ph*H*), 7.29 (s, 4H, Py′H), 7.46 (s, 2H, PyH), 7.59 (d, 2H, *J*=8.3 Hz, 3,5-PhH). ^{13}C NMR: *δ*, 30.9 (C(*C*H_3)$_3$), 39.9 (CH_2), 40.4 (CH_2), 46.3 (*C*(CH_3)$_3$), 118.9 (3,5-Py′C), 119.4 (3,5-PyC), 126.3, 126.9, 127.3, 128.8, 129.2, 129.7, 134.4, 135.6, 135.7, 137.6, 137.8, and 137.9 (PhC), 148.6 (4-Py′C), 149.1 (4-PyC), 157.6 (2,6-PyC), 157.8 (2,6-Py′C). MALDI-TOF MS *m/z*: 1132. $[M+H]^+$, calcd for $C_{67}H_{60}N_3S_7$: 1131.7.

4.1.14. HS-G2 (16). This compound was prepared

analogously to **14** starting from **15** (2.00 g, 1.77 mmol) and purified by repeated precipitation from CH_2Cl_2/hexane to give **16** as a yellow glassy solid (1.85 g, 97%). IR (KBr) ν: 1607 cm^{-1}. ^1H NMR: δ 3.55 (s, 1H, SH), 4.28 (s, 8H, CH_2), 4.34 (s, 4H, CH_2), 7.15–7.45 (m, 38H, PyH, Py′H, PhH and CH_2S-Ph*H*). ^{13}C NMR: δ, 39.9 (CH_2), 40.4 (CH_2), 118.9 (3,5-Py′C), 119.0 (3,5-PyC), 126.3, 127.3, 127.4, 128.8, 129.4, 129.5, 135.5, 135.6, 135.7, 136.6, 137.6, and 138.1 (PhC), 148.7 (4-Py′C), 148.9 (4-PyC), 157.5 (2,6-PyC), 157.7 (2,6-Py′C). MALDI-TOF MS *m/z*: 1075 $[M+H]^+$, calcd for $C_{63}H_{52}N_3S_7$: 1075.6.

4.1.15. *tert*-BuS-G3 (17). This compound was prepared analogously to **13** by reacting **16** (2.00 g, 1.86 mmol), K_2CO_3 (311 mg, 2.25 mmol) and **12** (453 mg, 0.866 mmol) in dry DMF (25 mL), except the reaction mixture was stirred at room temperature for 18 h instead of 2 h. After workup, the crude product was purified by flash chromatography on silica gel eluting with CH_2Cl_2/EtOAc/NEt_3 9:1:0.5 to give **17** as a pale yellow glassy solid (1.27 g, 61%). IR (KBr) ν: 1602 cm^{-1}. ^1H NMR: δ, 1.31 (s, 9H, *t*-Bu), 4.26 (s, 16H, CH_2), 4.30 (s, 8H, CH_2), 4.33 (s, 4H, CH_2) 7.15 (tt, 8H, $J=7.0$, 1.4 Hz, CH_2S-Ph*H*), 7.22 (tt, 16H, $J=7.6$, 1.3 Hz, CH_2S-Ph*H*), 7.27–7.60 (m, 58H, PyH, Py′H, Py″H, PhH and CH_2S-Ph*H*). ^{13}C NMR: δ, 31.0 (C(*C*H_3)$_3$), 39.8 (CH_2), 39.9 (CH_2), 40.5 (CH_2), 46.4 (*C*(CH_3)$_3$), 118.9 (3,5-Py″C), 119.1 (3,5-Py′C), 119.4 (3,5-PyC), 126.4, 126.9, 127.3, 127.4, 128.9, 129.1, 129.2, 129.3, 129.8, 134.5, 135.3, 135.6, 135.8, 137.7, 137.8, and 138.1 (PhC), 148.6 (4-Py″C), 149.0 (4-Py′C), 149.2 (4-PyC), 157.5 (2,6-PyC), 157.6 (2,6-Py′C), 157.8 (2,6-Py″C). MALDI-TOF MS *m/z*: 2418 $[M+H]^+$, calcd for $C_{143}H_{120}N_7S_{15}$: 2417.5.

4.1.16. HS-G3 (18). This compound was prepared analogously to **14** starting from **17** (1.27 g, 0.525 mmol) and purified by repeated precipitation from CH_2Cl_2/hexane to give **18** as a yellow glassy solid (1.18 g, 92%).

IR (KBr) ν: 1603 cm^{-1}. ^1H NMR: δ 3.52 (s, 1H, SH), 4.25 (s, 16H, CH_2), 4.30 (s, 8H, CH_2), 4.34 (s, 4H, CH_2) 7.12–7.38 (m, 82H, PyH, Py′H, Py″H, PhH and CH_2S-Ph*H*). ^{13}C NMR: δ 39.7 (CH_2), 39.8 (CH_2), 40.4 (CH_2), 118.9 (3,5-Py″C), 119.0 (3,5-Py′C), 119.1 (3,5-PyC), 126.3, 127.3, 127.5, 127.6, 128.8, 128.9, 129.1, 129.2, 129.7, 134.9, 135.1, 135.5, 135.7, 137.6, 137.9, and 138.0 (PhC), 148.6 (4-Py″C), 148.8 (4-Py′C), 149.0 (4-PyC), 157.4 (2,6-PyC), 157.5 (2,6-Py′C), 157.8 (2,6-Py″C). MALDI-TOF MS *m/z*: 2362 $[M+H]^+$, calcd for $C_{139}H_{112}N_7S_{15}$: 2361.4.

4.1.17. $[Fe_2(CO)_6]$-[S-G1]$_2$ (19). To a stirred solution of $Fe_3(CO)_{12}$ (1.17 g, 2.32 mmol) and **14** (1.00 g, 2.32 mmol) in dry THF (30 mL) was added triethylamine (235 mg, 2.32 mmol) and, after 30 min, $HgCl_2$ (629 mg, 2.32 mmol). The resulting mixture was stirred under argon for 14 h, filtered through celite, and washed with CH_2Cl_2 (100 mL). After the solvent was removed, the residue was purified by flash chromatography on silica gel eluted with $CHCl_3$ to give **19** as a red glassy solid (980 mg, 74%). IR (KBr) ν: 2073, 2035, 1996, 1598 cm^{-1}. ^1H NMR: δ, 4.30 (s, 8H, CH_2), 7.15 (t, 4H, $J=6.9$ Hz, CH_2S-Ph*H*), 7.26 (t, 8H, $J=$ 7.5 Hz, CH_2S-Ph*H*), 7.39 (d, 8H, $J=7.1$ Hz, CH_2S-Ph*H*), 7.51 (s, 4H, Py), 7.50–7.52 (m, 8H, PhH). ^{13}C NMR: δ 40.0 (CH_2), 119.1 (3,5-PyC), 126.4, 127.2, 129.2, 129.5, 129.6, 133.1, 136.7, and 137.8 (PhC), 148.2 (4-PyC), 158.8 (2,6-PyC), 208.7 (CO). Anal. calcd for $C_{56}H_{40}Fe_2N_2O_6S_6$ (1141.01): C, 58.95; H, 3.53; N, 2.46. Found: C, 58.30; H, 3.58; N, 2.50.

4.1.18. $[Fe_2(CO)_6]$-[S-G2]$_2$ (20). This compound was prepared analogously to **19** starting from **16** (1.00 g, 0.931 mmol) and purified by flash chromatography on silica gel eluted with 7.5–10% ethyl acetate in CH_2Cl_2 to give **20** as a red glassy solid (778 mg, 69%). IR (KBr) ν: 2073, 2037, 1996, 1601 cm^{-1}. ^1H NMR: δ, 4.25 (s, 16H, CH_2), 4.32 (s, 8H, CH_2), 7.12–7.41 (m, 76H, PyH, Py′H, PhH and CH_2S-Ph*H*). ^{13}C NMR: δ, 39.8 (CH_2), 40.5 (CH_2), 118.9 (3,5-Py′C), 119.1 (3,5-PyC), 126.3, 126.6, 126.8, 127.3, 128.8, 129.0, 129.7, 132.5, 134.5, 135.5, 135.7, and 137.6 (PhC), 148.4 (4-Py′C), 148.6 (4-PyC), 157.7 (2,6-PyC), 157.8 (2,6-Py′C), 207.9 (CO). Anal. calcd for $C_{132}H_{100}Fe_2N_6O_6S_{14}$ (2426.86): C, 65.33; H, 4.15; N, 3.46. Found: C, 64.86; H, 3.94; N, 3.57.

4.1.19. $[Fe_2(CO)_6]$-[S-G3]$_2$ (21). This compound was prepared analogously to **19** starting from **18** (1.00 g, 0.423 mmol) and purified by flash chromatography on silica gel eluted with 5% ethyl acetate in $CHCl_3$ to give **21** as a pale red glassy solid (520 mg, 49%). IR (KBr) ν: 2073, 2036, 1995, 1599 cm^{-1}. ^1H NMR (DMSO-d6, 50 °C): 4.25 (bs, 32H, CH_2), 4.26 (bs, 16H, CH_2), 4.32 (bs, 8H, CH_2), 7.10 (bt, 16H, $J=7.2$, CH_2S-Ph*H*), 7.20 (bt, 32H, $J=7.2$, CH_2S-Ph*H*), 7.29–7.47 (m, 116H, PyH, Py′H, Py″H, PhH and CH_2S-Ph*H*). ^{13}C NMR: δ, 39.7 (CH_2), 39.9 (CH_2), 40.5 (CH_2), 118.9 (3,5-Py″C), 119.0 (3,5-Py′C), 119.2 (3,5-PyC), 126.3, 126.7, 126.9, 127.3, 128.8, 129.2, 129.7, 134.5, 135.1, 135.5, 135.7, 137.6, 138.0, and 138.1 (PhC), 148.6 (4-Py″C), 148.8 (4-Py′C), 149.0 (4-PyC), 157.3 (2,6-PyC), 157.5 (2,6-Py′C), 157.8 (2,6-Py″C) 207.8 (CO). Anal. calcd for $C_{284}H_{220}Fe_2N_{14}O_6S_{30}$ (4998.55): C, 68.24; H, 4.44; N, 3.92. Found: C, 68.18; H, 4.25; N, 3.71.

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The regioselective synthesis of monomethoxynaphthylene diacetates

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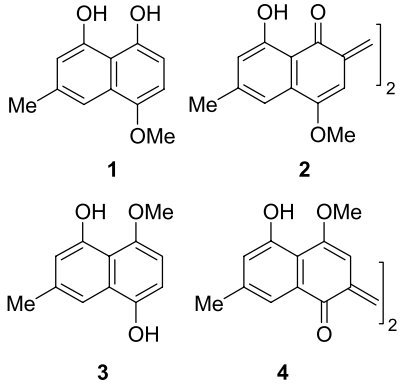
Abstract—Methods for the conversion of 1,4,5-naphthalenetriols into the corresponding monomethoxy diacetates are described. All utilise the formation of *peri*-bridged intermediates.

1. Introduction

The naturally-occurring blue quinone diosindigo A **2** can be prepared[1] by the oxidative coupling of the methoxynaphthylenediol **1**, while the isomeric quinone[2] diosindigo B **4** is formed[3] in a similar manner from the methoxydiol **3**. In this paper we describe syntheses of the acetates of these and related methoxynaphthylenediols, which utilise the ready formation of *peri*-bridged derivatives of 1,8-naphthylenediols.



2. Results and discussion

Our first objective was to develop a procedure for the selective methylation of the isolated hydroxy group of 1,4,5-naphthalenetriol **5**, with the use of ketal formation to protect the *peri*-hydroxy groups appearing attractive. The acid-catalysed reaction of the triol with acetone gave the desired 1,8-bridged naphthol **6**, the structure of which was supported by its ready oxidation in air to form the binaphthylylenediol **7**, in turn oxidised by lead(IV) oxide producing the expected blue quinone **8** (Scheme 1). The treatment of the bridged naphthol **6** with methyl iodide and potassium carbonate produced the desired methyl ether **9**, but the selective removal of the isopropylidene bridge proved not to be possible. Treatment with hydrochloric acid under a range of conditions cleaved not only the ketal but also the methyl ether giving, after aerial oxidation, juglone (5-hydroxy-1,4-naphthaquinone) **10** as the only significant product. We therefore sought a *peri*-bridging group which would be more easily removed.

1,4-Naphthaquinone **11** is known[4] to undergo reduction and mono-methylation on being treated with tin(II) chloride and phosphoryl(V) chloride in methanolic solution, with the formation of 4-methoxy-1-naphthol **12** together with tin(IV) species (Scheme 2). Catechol and related compounds react with tin(IV) chloride to form complexes of the type **13**,[5,6] and we considered it likely that derivatives of 1,8-naphthylenediol would behave in a similar manner. The reaction of juglone **14** with the $SnCl_2/POCl_3$/MeOH mixture, followed by acetylation of the product gave the methoxydiacetate **16** (63%) as the sole product. A possible reaction sequence is shown in Scheme 3. A similar reaction with 7-methyljuglone **15** gave the corresponding 7-methyl-substituted compound **17** (38%) required for the synthesis[1] of diosindigo A. In contrast, the application of the procedure to plumbagin **18**, which has a methyl group in the 2-position of juglone, resulted in little or no methylation, the only product isolated being 1,4,5-triacetoxy-2-methylnaphthalene **20** (13%). The adverse effect of the 2-methyl

Keywords: Boron heterocycles; Naphthols; Quinones; Tin compounds.
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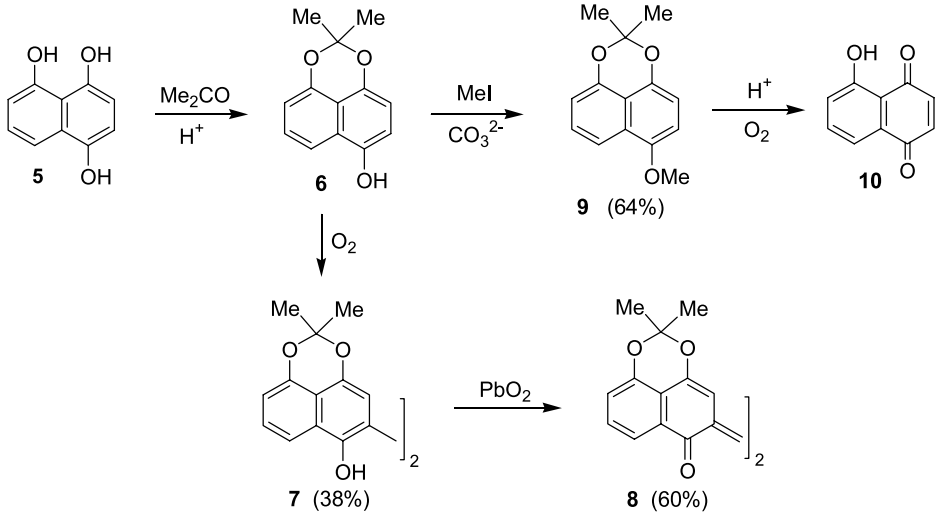
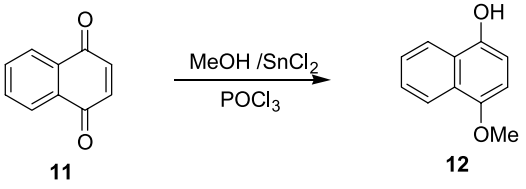
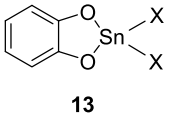


Scheme 1.



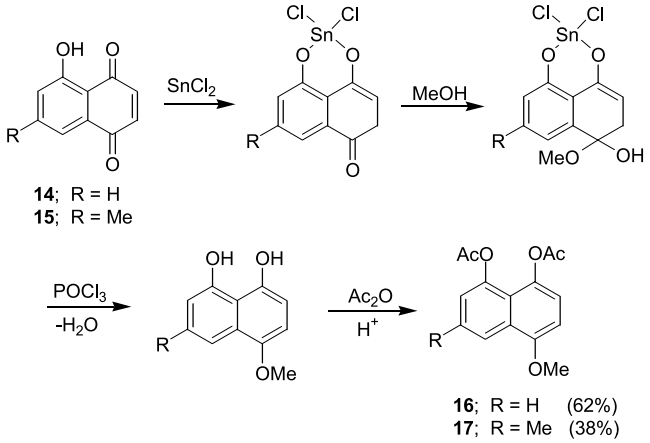
Scheme 2.



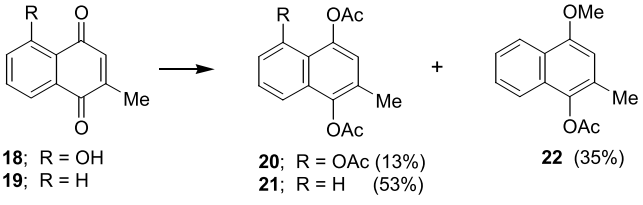
group was also apparent in a similar reaction with 2-methyl-1,4-naphthaquinone **19**, which gave the corresponding leucoacetate **21** (53%) and the methoxyacetate **22** (35%) (Scheme 4). Presumably the hyperconjugative effect of the methyl group stabilises the adjacent enol so inhibiting the formation of the tautomeric carbonyl group, and consequently the introduction of a methoxy group at C-1. (Scheme 4).

The above reactions with plumbagin occur in an acidic environment and we briefly investigated the possibility of a selective methylation procedure under alkaline conditions. Borate can be used to bridge the *peri*-positions of a 1,8-naphthylenediol for example in the formation of the 1:1-chromotropic acid–borate complex in alkaline solution.[7] The treatment of 1,4,5-naphthalenetriol **23** with sodium borate followed by dimethyl sulphate and alkali and subsequent acetylation gave the desired methoxydiacetate **25** (55%) (Scheme 5). The reduction product of plumbagin, the triol **24**, behaved in the same way giving the corresponding 2-methyl derivative **26**.

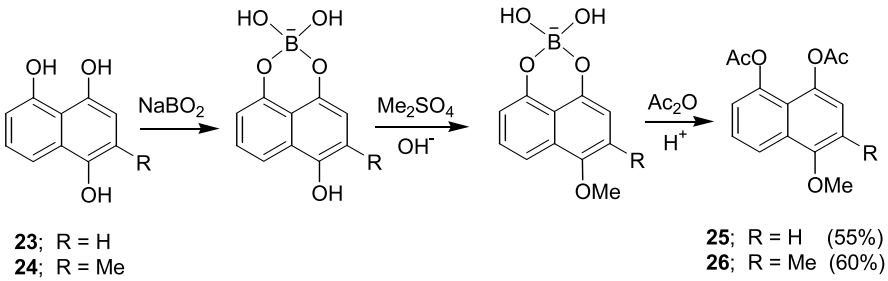
We found that the selective methylation of one of the *peri*-hydroxy groups of a 1,8-naphthylenediol could be achieved by the use of a *peri*-bridging group, this time the phenylboronate. Cyclic phenylboronate esters are easily prepared from diols and phenylboronic anhydride, $(PhBO)_3$ and we had noticed that when they are treated with acetic anhydride and sodium acetate followed by water, the products are acetic and phenylboronic acids together with the hydroxyacetates derived from the parent diols.[3] A feasible mechanism (Scheme 6) for the reaction involves the initial formation of a mixed anhydride **27** which then undergoes ready hydrolysis as would be expected. By this sequence of reactions (Scheme 7) we were able to convert catechol via its phenylboronate **28** into 2-acetoxyphenol **29**, saligenin via **30** into 2-acetoxymethylphenol **31** (together with the corresponding diacetate **32**), and 1,8-naphthylenediol via **33** into 8-acetoxy-1-naphthol **34**. The



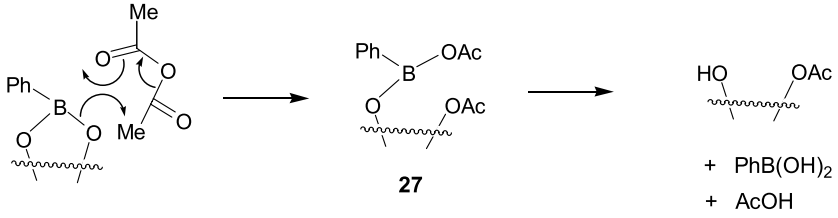
Scheme 3.



Scheme 4.



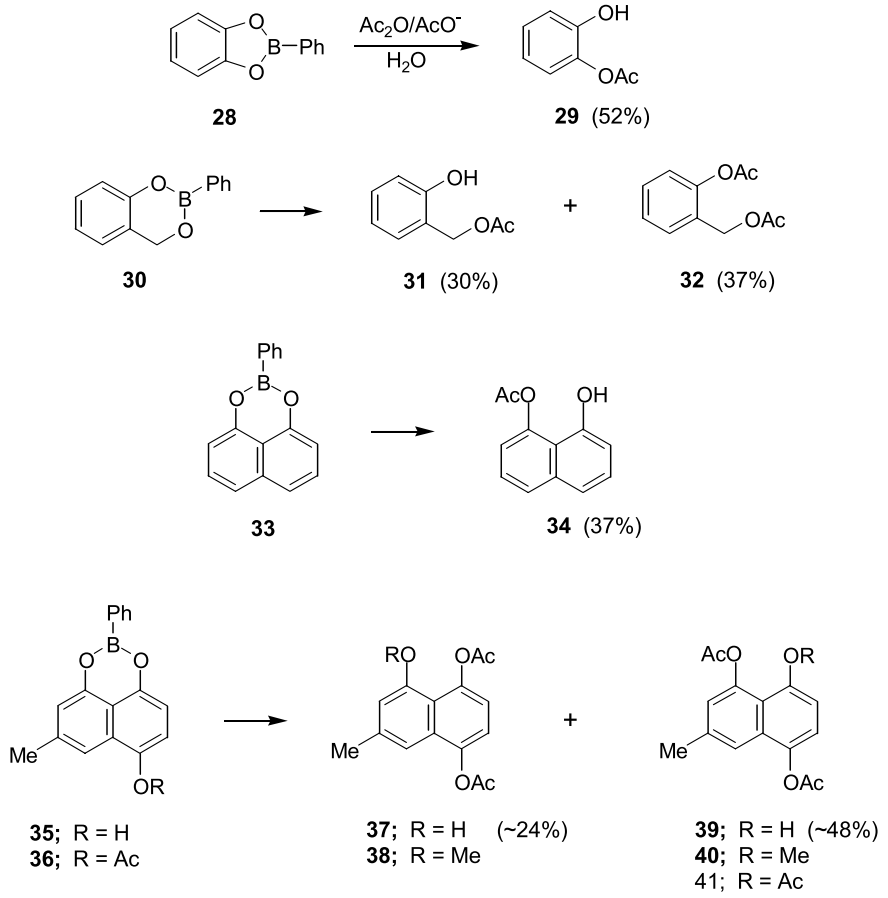
Scheme 5.



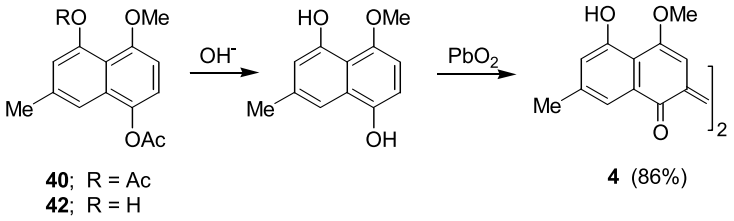
Scheme 6.

phenylboronate **35** derived from 7-methylnaphthalene-1,4,5-triol is unsymmetrical and afforded a mixture (essentially 1:2 by ^{1}H NMR) of the two possible diacetoxynaphthols **37** and **39** together with a little of the acetylated phenylboronate **36**.

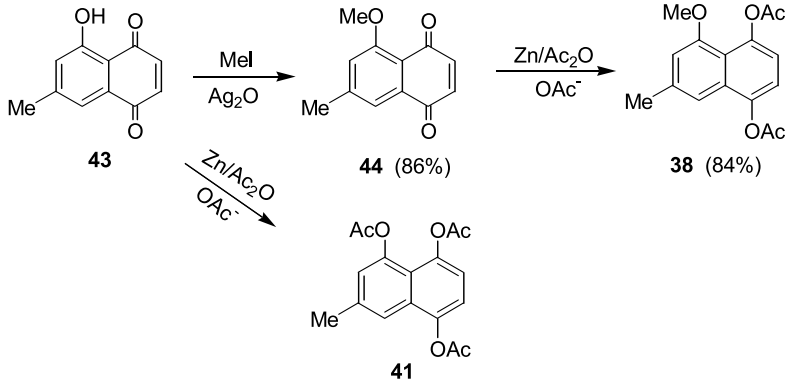
The methylation of the mixture of diacetoxynaphthols using diazomethane yielded a mixture of the corresponding methoxy diacetates which we separated by fractional crystallisation into the major component, the methoxy diacetate **40** (54%) and the isomeric compound **38** (25%).



Scheme 7.



Scheme 8.



Scheme 9.

The mother-liquor afforded small amounts of the triacetoxymethylnaphthalene **41** and the hydroxymethoxy acetate **42**. Both the methoxy diacetate **40** and the hydroxymethoxy acetate **42**, after being hydrolysed with alkali, were efficiently converted by oxidation with lead(IV) oxide into diosindigo B **4** (Scheme 8). The structures of the acetates **38** and **41** were confirmed by their alternative syntheses from 5-hydroxy-7-methyl-1,4-naphthaquinone **43** by methylation and/or reductive acetylation (Scheme 9).

3. Experimental

3.1. General

Operations involving the formation of the free naphthols, particularly those in alkaline solution, were performed under nitrogen. IR spectra were measured for potassium bromide discs and UV–visible spectra were obtained for ethanolic solutions. ^{1}H NMR spectra were measured at 100 MHz for solutions in deuterochloroform with tetramethylsilane as internal standard. Mass spectra were measured using EI at 70 eV. TLC was performed on silica gel (Merck GF_{254}). 'Light petroleum' refers to the fraction with bp 60–80 °C.

3.1.1. 4,5-Isopropylidenedioxy-1-methoxynaphthalene 9. A mixture of naphthalene-1,4,5-triol[8] (500 mg, 2.84 mmol), acetone (75 ml) and concentrated sulphuric acid (1 ml) was shaken for 18 h and then poured into water (750 ml) and extracted with chloroform (4×150 ml). The organic layer was washed with 1 M-sodium hydroxide (4×250 ml) and the alkaline extract was acidified with 2 M-hydrochloric acid. Extraction with chloroform gave the crude monohydric naphthol as a brown oil which was methylated by heating under reflux for 3 h with methyl iodide (2 ml, 4.56 g, 32.1 mmol), potassium carbonate (2 g, 14.5 mmol) and acetone (50 ml). Filtration and evaporation followed by column chromatography of the residue on silica gel using light petroleum–benzene (1:1) gave the methoxynaphthalene **9** (420 mg, 1.83 mmol, 64%) as an oil (found: C, 73.9; H, 5.3; $C_{14}H_{14}O_3$ requires C, 73.7; H, 5.3%); ν_{max}/cm^{-1} 1635, 1615 and 1594 (aromatic C=C); δ_H 1.63 [6H, s, $(CH_3)_2C$], 3.93 (3H, s, CH_3OAr), 6.73 (2H, s, H-2 and -3), 6.87 (1H, dd, $J=1.5$, 8 Hz, H-6), 7.38 (1H, dd, $J=8$, 8 Hz, H-7) and 7.76 (1H, dd, $J=1.5$, 8 Hz, H-8).

3.1.2. 4,5:4′,5′-Bisisopropylidenedioxy-2,2′-binaphthylylene-1,1′-diol 7. The crude monohydric phenol from a similar reaction was subjected to TLC (in the presence of air) using dichloromethane followed by benzene. Crystallisation of the product from light petroleum gave the binaphthylylenediol **7** (230 mg, 0.53 mmol, 38%), mp 238–239 °C (found: M^+, 430. C, 72.5; H, 5.3%. $C_{26}H_{22}O_6$ requires *M*, 430. C, 72.6; H, 3.1%); *m*/*z* 430 (100%, M), 412 (20, M−H_2O), 372 (12, 412-C_3H_4), 371 (12, 412-C_3H_5), 332 (10, 372-C_3H_4), 331 (11, 371-C_3H_4) and 303 (12, 331-CO); ν_{max}/cm^{-1} 3430 (HOAr); λ_{max}/nm 242 (log ε 4.54), 268 (4.57), 315infl (4.06), 333infl (4.08), 341infl (4.12) and 354 (4.18); δ_H [$(CD_3)_2CO$] 1.64 (12H, s, $(CH_3)_2C$), 6.84 (2H, s, H-3 and -3′), 6.93 (2H, dd, $J=1$, 8 Hz, H-6 and -6′), 7.47 (2H, dd, $J=8$, 8 Hz, H-7 and -7′) and 7.90 (2H, dd, $J=1$, 8 Hz, H-8 and -8′).

3.1.3. 4,5:4′,5′-Bisisopropylidenedioxy-2,2′-binaphthyl-1,1′-quinone 8. A mixture of the binaphthylylenediol **7** (10 mg, 0.023 mmol), chloroform (50 ml) and lead (IV) oxide (200 mg, 0.84 mmol) was boiled under reflux for

5 min, filtered and evaporated. After two repetitions of this treatment the residue crystallised from light petroleum to give the binaphthylquinone **8** (6 mg, 0.014 mmol, 60%) as deep blue needles, mp 209–211 °C (found: M^+, 428.1261. $C_{26}H_{20}O_6$ requires *M*, 428.1260); *m*/*z* 430 (72%, M+2H), 428 (100, M), 412 (18, 430-H_2O) and 370 (63, M−Me_2CO); ν_{max}/cm^{-1} 1625 and 1595 (quinone C=O); λ_{max}/nm ($CHCl_3$) 290 (log ε 4.31), 325infl (4.09), 634infl (4.32), 675 (4.40) and 718infl (4.22).

3.1.4. 1-Methoxy-4,5-naphthylene diacetate 16 (using acidic conditions). Phosphoryl(V) chloride (3.25 g, 21.2 mmol) was added slowly to anhydrous methanol (20 ml) and cooled to 20 °C. Tin(II) chloride dihydrate (2.4 g, 10.63 mmol) and juglone (5-hydroxy-1,4-naphthaquinone; 1.74 g, 10.0 mmol) were added and the mixture was boiled and stirred under reflux for 1 h and then poured into 1 M-hydrochloric acid (750 ml). The resulting precipitate (1.9 g) was dried and stirred overnight with acetic anhydride (5 ml) and concentrated sulphuric acid (0.1 ml) and then poured onto ice. Column chromatography on silica gel of the resulting solid using benzene gave the methoxy diacetate **16** which crystallised from ethanol as needles (1.7 g, 6.20 mmol, 62%), mp 135–135.5 °C (lit.,[9] 133 °C) (found: C, 65.4; H, 4.9%, M^+, 274.0846. Calcd for $C_{15}H_{14}O_5$: C, 65.7; H, 5.1%, *M*, 274.0841); *m*/*z* 274 (4%, M), 232 (6, M−CH_2CO) and 190 (100, 232-CH_2CO); ν_{max}/cm^{-1} 1765 and 1747 (aryl acetate C=O); λ_{max}/nm 233infl (log ε 4.35), 295infl (3.77), 303 (3.84), 313infl (3.79) and 327infl (3.62); δ_H 2.36 (6H, s, CH_3CO_2Ar), 3.96 (3H, s, CH_3OAr), 6.76 (1H, d, *J*=8 Hz, H-2), 7.04 (1H, d, *J*=8 Hz, H-3), 7.14 (1H, dd, *J*=1.5, 8 Hz, H-6), 7.46 (1H, dd, *J*=8, 8 Hz, H-7) and 8.21 (1H, dd, *J*=1.5, 8 Hz, H-8).

3.1.5. 1-Methoxy-7-methyl-4,5-naphthylene diacetate 17. A similar reaction with 5-hydroxy-7-methyl-1,4-naphthaquinone[10] gave the methoxy diacetate **17** (38%) as needles from ethanol, mp 123–124 °C (lit.,[1] 122–124 °C) (found: M^+, 288.0999. Calcd for $C_{16}H_{16}O_5$: *M*, 288.0997); *m*/*z* 288 (4%, M), 246 (6, M−CH_2CO), 204 (100, 246-CH_2CO) and 189 (22, 204-Me); ν_{max}/cm^{-1} 1762 (aryl acetate C=O); δ_H 2.34 (6H, s, CH_3CO_2Ar), 2.47 (3H, s, CH_3Ar), 3.94 (3H, s, CH_3OAr), 6.73 (1H, d, *J*=8 Hz, H-2), 6.94 (1H, d, *J*=8 Hz, H-3), 7.00 (1H, br.s, H-6) and 7.99 (1H, br.s, H-8).

3.1.6. Attempted reductive methylation of plumbagin 18. The product from a similar reaction with plumbagin (5-hydroxy-2-methyl-1,4-naphthaquinone; 500 mg, 2.66 mmol) after column chromatography using light petroleum–benzene (1:1) gave 1,4,5-triacetoxy-2-methyl-1,4-naphthalene **20** (110 mg, 0.35 mmol, 13%) as needles, mp 126–127 °C (lit.,[11] 124–126 °C) identical with an authentic specimen prepared by heating plumbagin with zinc dust, anhydrous sodium acetate and acetic anhydride under reflux.

3.1.7. 4-Methoxy-2-methyl-1-naphthyl acetate 22. A similar reaction with 2-methyl-1,4-naphthaquinone **19** (2 g, 11.6 mmol) gave a mixture which was separated by TLC using chloroform. The faster-moving component crystallised from ethanol to give 2-methyl-1,4-naphthylene diacetate **21** (1.59 g, 6.16 mmol, 53%) which crystallised from ethanol in needles, mp 112–114 °C (lit.,[12] 112.5–114 °C) identical with an authentic specimen prepared by the reductive acetylation of 2-methyl-1,4-naphthaquinone using zinc dust, acetic anhydride and anhydrous sodium acetate. The slower-moving component afforded 4-methoxy-2-methyl-1-naphthyl acetate **22** (0.93 g, 4.05 mmol, 35%) which crystallised from ethanol in needles, mp 65–66 °C (found: C, 73.3; H, 6.1. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%); ν_{max}/cm^{-1} 1748 (aryl acetate C=O); λ_{max}/nm 239 (log ε 4.49), 291infl (3.74), 298 (3.78), 311infl (3.64) and 326 (3.45); δ_H 2.30 (3H, s, CH_3Ar), 2.43 (3H, s, CH_3CO_2Ar), 3.95 (3H, s, CH_3OAr), 6.62 (1H, s, H-3), 7.33–7.83 (3H, m, H-6, -7 and -8) and 8.22 (1H, m, H-5).

3.1.8. 1-Methoxy-4,5-naphthylene diacetate 25 (using alkaline conditions). A mixture of 1,4,5-naphthalenetriol[8] **5** (500 mg, 2.84 mmol), sodium metaborate tetrahydrate (392 mg, 2.84 mmol) and 2 M-sodium hydroxide (70 ml) was shaken for 30 min. Dimethyl sulphate (1 ml, 1,33 g, 10.6 mmol) was added and shaking was continued for 2 h. This was repeated with more dimethyl sulphate (1 ml) after which the mixture was added to 1 M-hydrochloric acid (200 ml). The resulting solid was dried and stirred overnight with acetic anhydride (2 ml, 2.16 g, 21.2 mmol) and concentrated sulphuric acid (0.1 ml). The mixture was added to hot water and extracted with chloroform. Column chromatography of the product on silica gel using light petroleum–benzene (1:1) gave the methoxy diacetate **25** (430 mg, 1.57 mmol, 55%) which crystallised from ethanol in needles, mp 135–136 °C identical with the product prepared under acidic conditions.

3.1.9. 1-Methoxy-2-methyl-4,5-naphthylene diacetate 26. A similar reaction with 2-methyl-1,4,5-naphthalenetriol [from plumbagin (890 mg, 4.73 mmol) by reduction with zinc dust and sulphuric acid[8]] gave the methoxy diacetate **26** (815 mg, 2.83 mmol, 60%) which crystallised in needles from ethanol, mp 121–123 °C) (found: C, 66.8; H, 5.7. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6%); ν_{max}/cm^{-1} 1760 (aryl acetate C=O); λ_{max}/nm 286infl (log ε 3.79), 293 (3.83), 311infl (3.53) and 327 (3.28); δ_H 2.37 (6H, s, CH_3CO_2Ar), 2.42 (3H, s, CH_3Ar), 3.88 (3H, s, CH_3OAr), 6.95 (1H, s, H-3), 7.07 (1H, dd, *J*=1.5, 8 Hz, H-6), 7.45 (1H, dd *J*=8, 8 Hz, H-7) and 7.98 (1H, dd, *J*=1.5, 8 Hz, H-8).

3.1.10. 1-Hydroxy-7-methyl-4,5-naphthylene phenylboronate 35. A mixture of 7-methyl-1,4,5-naphthalenetriol [from 5-hydroxy-7-methyl-1,4-naphthaquinone **15** (2 g, 10.6 mmol) by reduction[8] with zinc dust and 1 M-sulphuric acid], phenylboronic anhydride, $(PhBO)_3$, (1.85 g, 5.94 mmol) and benzene (400 ml) was boiled under reflux using a Dean and Stark apparatus until evolution of water was complete. Concentration of the solution to 100 ml and crystallisation of the resulting solid from benzene gave the hydroxy phenylboronate **35** (2.7 g, 9.75 mmol, 92%) as needles, mp 165–166 °C (found: M^+, 276.0956. $C_{17}H_{13}{}^{11}BO_3$ requires *M*, 276.0957); *m*/*z* 276 (100%, M) and 247 (5, M−CHO); ν_{max}/cm^{-1} 3240 (phenolic OH) and 1330 (B–O); δ_H 2.49 (3H, s, CH_3Ar), 4.95 (1H, s, HOAr), 6.73 (2H, s, H-2 and -3), 6.88 (1H, br.s, H-6), 7.42 (1H, br.s, H-8), 7.45–7.56 (3H, m, *m*- and *p*-H's of Ph) and 8.02–8.18 (2H, m, *o*-H's of Ph).

3.2. Reactions of the phenylboronates with acetic anhydride/sodium acetate

3.2.1. 1,2-Phenylene phenylboronate 28. A mixture of the phenylboronate[13] **28** (200 mg, 1.02 mmol), acetic anhydride (3 ml, 3.24 g, 31.7 mmol) and anhydrous sodium acetate (50 mg, 0.61 mmol) was kept at 20 °C for 2 h and then poured into warm water. Extraction with chloroform, which was then shaken with aqueous sodium hydrogen carbonate to remove acidic products, gave 2-acetoxyphenol **29** (80 mg, 0.53 mmol, 52%) which crystallised from benzene in needles, mp 57–58 °C (lit.,[14] 57–58 °C) (found: M^+, 152.0475. Calcd for $C_8H_8O_3$: *M*, 152.0473); *m/z* 152 (28%, M), 110 (100, M−CH_2CO), 92 (36, 110-H_2O) and 81 (27, 110-CHO); ν_{max}/cm^{-1} 3380 (phenolic OH) and 1740 (aryl acetate C=O); δ_H 2.30 (3H, s, CH_3CO_2Ar), 5.80 (1H, br.s, HOAr) and 6.70–7.20 (4H, m, ArH). When a similar reaction mixture was kept for 20 h two products resulted and were separated by TLC using chloroform. The first crystallised from light petroleum–chloroform to give 1,2-phenylene diacetate (22 mg, 0.11 mmol, 11%) as needles, mp 64 °C (lit.,[14] 64 °C) (found: M^+, 194.0581. Calcd for $C_{10}H_{10}O_4$: *M*, 194.0579); *m/z* 194 (1%, M), 152 (6, M−CH_2CO) and 110 (100, 152-CH_2CO); ν_{max}/cm^{-1} 1760 (aryl acetate C=O); δ_H 2.25 (6H, s, CH_3CO_2Ar) and 7.20 (4H, br.s, ArH). The second product was 2-acetoxyphenol (60 mg, 0.39 mmol, 39%).

3.2.2. Toluene-α,2-diyl phenylboronate 30. A similar reaction between the phenylboronate[15] **30** (400 mg, 1.90 mmol), acetic anhydride (6 ml, 6.48 g, 63.5 mmol) and anhydrous sodium acetate (80 mg, 0.97 mmol) at 20 °C for 72 h gave a mixture which was separated by TLC into:

(i) 2-(acetoxymethyl)phenyl acetate **32** (145 mg, 0.70 mmol, 37%), an oil (found: M^+, 208.0732. $C_{11}H_{12}O_4$ requires *M*, 208.0735); *m/z* 208 (2%, M), 166 (28, M−CH_2CO), 106 (100, 166-AcOH) and 78 (50, 106-CO); ν_{max}/cm^{-1} (film) 1775 (aryl acetate C=O) and 1745 (alkyl acetate C=O); δ_H 2.04 (3H, s, CH_3CO_2R), 2.29 (3H, s, CH_3CO_2Ar), 5.08 (2H, s. $ArCH_2OAc$) and 7.04–7.50 (4H, m, ArH);
(ii) 2-(acetoxymethyl)phenol **31** (94 mg, 0.57 mmol, 30%), also an oil (found: M^+, 166.0627. $C_9H_{10}O_3$ requires *M*, 166.0629); *m/z* 166 (28%, M), 106 (100, M−AcOH) and 78 (79%, 106-CO); ν_{max}/cm^{-1} (film) 3385 (phenolic OH) and 1710 (alkyl acetate C=O); δ_H 2.11 (3H, s, CH_3 CO_2R), 5.12 (2H, s, $ArCH_2OAc$), 6.88–7.40 (4H, m, ArH) and 7.69 (1H, s, HOAr);
(iii) unreacted phenylboronate (63 mg).

3.2.3. 1,8-Naphthylene phenylboronate 33. A similar reaction between the phenylboronate[13] **33** (50 mg, 0.20 mmol), acetic anhydride (1.5 ml, 1.62 g, 15.9 mmol) and anhydrous sodium acetate (30 mg, 0.36 mmol) with stirring for 27 h at 20 °C gave 8-acetoxy-1-naphthol **34** (15 mg, 0.074 mmol, 37%) as needles, mp 129–130 °C, from benzene (found: M^+, 202.0626. $C_{12}H_{10}O_3$ requires *M*, 202.0629); *m/z* 202 (5%, M), 160 (100, M−CH_2CO), 131 (3, 160-CHO); ν_{max}/cm^{-1} 3400 (HOAr) and 1736 (hydrogen-bonded aryl acetate C=O); λ_{max}/nm 298.5 (log ε 3.74), 312.5 (3.67) and 327 (3.62); δ_H 2.42 (3H, s, CH_3CO_2Ar) and 6.80–7.80 (7H, m, HOAr and ArH).

3.2.4. 1-Hydroxy-7-methyl-4,5-naphthylene phenylboronate 35. A similar reaction between the phenylboronate **35** (2 g, 7.25 mmol), acetic anhydride (15 ml, 16.2 g, 159 mmol) and anhydrous sodium acetate (300 mg, 3.66 mmol) gave a mixture (essentially 1:2 by NMR) of 5,8-diacetoxy-3-methyl-1-naphthol **37** and 4,8-diacetoxy-6-methyl-1-naphthol **39** (1.4 g, 5.11 mmol, 71%) as needles, mp 144–146 °C, from benzene (found: M^+, 274.0840. Calcd for $C_{15}H_{14}O_5$: *M*, 274.0841); ν_{max}/cm^{-1} 3355 (HOAr), 1757 and 1730 (aryl acetate C=O).

Acidification of the sodium hydrogen carbonate washings gave 1-acetoxy-7-methyl-4,5-naphthylene phenylboronate **36** (50 mg, 0.16 mmol, 2%) which crystallised from benzene as needles, mp 173–174 °C (found: M^+, 318.1065. $C_{19}H_{15}{}^{11}BO_4$ requires *M*, 318.1063); *m/z* 318 (6%, M), 276 (100, M−CH_2CO) and 247 (2, 276-CHO); ν_{max}/cm^{-1} 1765 (aryl acetate C=O) and 1320 (B–O); λ_{max}/nm 301infl (log ε 3.75), 310.5 (3.83), 325 (3.85) and 340 (3.86); δ_H 2.41 (3H, s, CH_3CO_2Ar), 2.46 (3H, s, CH_3Ar), 6.85 (1H, d, *J*=8 Hz, H-3), 6.88 (1H, br.s, H-6), 7.07 (1H, d, *J*=8 Hz, H-2), 7.10 (1H, br.s, H-8), 7.42–7.60 (3H, m, *m*- and *p*-H's of Ph) and 8.04–8.20 (2H, m, *o*-H's of Ph).

3.2.5. Methylation of the mixture of diacetoxynaphthols 37 and 39. A solution of diazomethane [from *N*-methylnitrosourea (12 g, 116 mmol)] in ether (120 ml) was added to a solution of the diacetoxynaphthols (2.1 g, 7.66 mmol) in ether (150 ml) and the mixture was kept for 4 d at 20 °C and then evaporated. Fractional crystallisation of the residue from light petroleum–chloroform gave, as the major component, 4-methoxy-7-methyl-1,5-naphthylene diacetate **40** (1.2 g, 4.17 mmol, 54%) as needles, mp 164 °C (found: M^+, 288. 0994. $C_{16}H_{16}O_5$ requires *M*, 288.0997); *m/z* 288 (7%, M), 246 (16, M−CH_2CO), 204 (100, 246-CH_2CO) and 189 (27, 204-Me); ν_{max}/cm^{-1} 1768 (aryl acetate C=O); λ_{max}/nm 237infl (log ε 3,74), 296 (3.69), 315 (3.86) and 330 (3.58); δ_H 2.35 and 2.42 (each 3H, s, CH_3CO_2Ar), 2.48 (3H, s, CH_3Ar), 3.90 (3H, s, CH_3OAr), 6.72 (1H, d, *J*=8 Hz, H-3), 6.95 (1H, d, *J*=1.5 Hz, H-6), 7.12 (1H, d, *J*=8 Hz, H-2) and 7.45 (1H, d, *J*=1.5 Hz, H-8).

The minor component, 5-methoxy-7-methyl-1,4-naphthylene diacetate **38** crystallised as prisms (0.55 g, 1.93 mmol, 25%), mp 116–117 °C (found: M^+, 288.0994. $C_{16}H_{16}O_5$ requires *M*, 288.0997); *m/z* 288 (40%, M), 246 (8, M−CH_2CO), 204 (100, 246-CH_2CO) and 189 (16, 204-Me); ν_{max}/cm^{-1} 1776 (aryl acetate C=O); λ_{max}/nm 287infl (log ε 3.78), 300 (3.85), 315 (3.68) and 330 (3.53); δ_H 2.35 and 2.43 (each 3H, s, CH_3CO_2Ar), 2.47 (3H, s, CH_3Ar), 3.91 (3H, s, CH_3OAr), 6.70 (1H, br.s, H-6), 6.96 (1H, d, *J*=8 Hz, H-3), 7.18 (1H, d, *J*=8 Hz, H-2) and 7.23 (1H, br.s, H-8). This was identical with a specimen of the leucoacetate prepared from 5-methoxy-7-methyl-1,4-naphthaquinone (see below).

The mother-liquor from the above fractional crystallisation, on being subjected to TLC using chloroform, gave more of the above methoxy diacetates and two other products. The faster-moving of these crystallised from light petroleum to yield 1,4,5-triacetoxy-7-methylnaphthalene **41** (57 mg, 0.18 mmol, 2.5%) as needles, mp 175–176 °C (lit.,[16]

175.5–176.5 °C) (found: M^+, 316.0944. Calcd for $C_{17}H_{16}O_6$: *M*, 316.0946); δ_H 2.37, 2.37 and 2.45 (each 3H, s, CH_3CO_2Ar), 2.49 (3H, s, CH_3Ar), 7.03 (1H, d, J= 1.5 Hz, H-6), 7.04 (1H, d, J=8 Hz, H-3), 7.22 (1H, d, J= 8 Hz, H-2) and 7.57 (1H, d, J=1.5 Hz, H-8). This was identical with an authentic specimen prepared by the reductive acetylation of 5-hydroxy-7-methyl-1,4-naphthaquinone **43** using zinc dust, acetic anhydride and anhydrous sodium acetate.

The slower-moving TLC fraction crystallised from light petroleum to give 5-acetoxy-8-methoxy-3-methyl-1-naphthol **42** (28 mg, 0.11 mmol, 1.5%) as needles, mp 119 °C Found: M^+, 246.0890. $C_{14}H_{14}O_4$ requires *M*, 246.0892); *m/z* 246 (14%, M), 204 (100, M−CH_2CO), 189 (75, 204-Me) and 161 (6, 189-CO); ν_{max}/cm^{-1} 3350 (hydrogen-bonded HOAr) and 1762 (aryl acetate C=O); λ_{max}/nm 292infl (log ε 3.76), 306 (3.85), 321 (3.84) and 336 (3.86); δ_H 2.42 (6H, s, CH_3CO_2Ar and CH_3Ar), 4.00 (3H, s, CH_3OAr), 6.62 (1H, d, J=8 Hz, H-7), 6.76 (1H, d, J= 1.5 Hz, H-2), 7.02 (1H, d, J=8 Hz, H-6), 7.03 (1H, d, J= 1.5 Hz, H-4) and 9.25 (1H, s, hydrogen-bonded HOAr).

3.2.6. 5-Methoxy-7-methyl-1,4-naphthylene diacetate 38. A mixture of 5-hydroxy-7-methyl-1,4-naphthaquinone **43** (50 mg, 0.27 mmol), chloroform (15 ml), methyl iodide (0.5 ml, 1.14 g, 8.0 mmol) and silver oxide (200 mg, 0.85 mmol) was boiled under reflux for 1 h and filtered. The filtrate, after column chromatography on neutral alumina using chloroform, gave 5-methoxy-7-methyl-1,4-naphthaquinone **44** (46 mg, 0.23 mmol, 86%) which crystallised from light petroleum–chloroform as needles, mp 170–171 °C (lit.,[16] 166.5–167.5 °C) (found: M^+, 202.0626. Calcd for $C_{12}H_{10}O_3$: *M*, 202.0629); *m/z* 204 (14%, M+2H), 202 (100, M), 174 (6, M−CO) and 173 (13, M−CHO); ν_{max}/cm^{-1} 1671 and 1656 (quinone C=O); λ_{max}/nm 249 (log ε 4.18), 285infl (3.16) and 400 (3.57); δ_H 2.46 (3H, s, CH_3Ar), 3.98 (3H, s, CH_3OAr), 6.82 (2H, s, H-2 and -3), 7.10 (1H, br.s, H-6) and 7.53 (1H, br.s, H-8).

A mixture of the methoxy quinone **44** (20 mg, 0.1 mmol), zinc dust (20 mg, 0.31 mmol), anhydrous sodium acetate (10 mg, 0.12 mmol) and acetic anhydride (1.5 ml, 1.62 g, 16.0 mmol) was boiled under reflux for 0.5 h, filtered and poured into hot water. Extraction with chloroform gave 5-methoxy-7-methyl-1,4-naphthylene diacetate **38** (24 mg, 0.08 mmol, 84%) as needles, mp 116 °C.

3.2.7. 5,5′-Dihydroxy-4,4′-dimethoxy-7,7′-dimethyl-2,2′-binaphthyl-1,1′-quinone 4 (diosindigo B). A mixture of 4-methoxy-7-methyl-1,5-naphthylene diacetate **40** (100 mg, 0.35 mmol) and 2% methanolic potassiuim hydroxide (5 ml) was boiled under reflux for 0.5 h, poured into 1 M-sulphuric acid (8 ml) and shaken with chloroform. Lead(IV) oxide (300 mg, 1.26 mmol) was added to the dried chloroform solution and the mixture was boiled for 5 min and filtered while hot. The deep blue product crystallised from chloroform to give the quinone **4** (60 mg, 0.15 mmol, 86%), mp 275 °C (dec.) [lit.,[2] 275 °C (dec.)] (found: M^+, 404.1260. $C_{24}H_{20}O_6$ requires *M*, 404.1259) identical with a specimen of diosindigo B isolated from *Diospyros celebica*.

A similar reaction with 5-acetoxy-8-methoxy-3-methyl-1-naphthol **42** gave the same product (81%).

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Regio- and stereospecific [3+2] cycloaddition of an unusual nitrone derived from a *N*-hydroxy-2-pyridone with medium ring enones

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Abstract—Regio- and stereospecific 1,3-dipolar cycloaddition of the nitrone derived from a *N*-hydroxy-2-pyridone **6** with *Z*-2-cyclodecenone **7a** was accomplished, thus substantiating a possible biomimetic route to pyridomacrolidin **2** from pyridovericin **1** and cephalosporolide B **5**. This reaction was further exemplified with different enones (**7a–g**) similar to cephalosporolide B **5**. In all the cases the cycloaddition occurred with high regiochemical control and with high retention of alkene geometry. Both *endo* and *exo* modes of cycloaddition were observed. This process can also be extended to aryl conjugated enones as long as no enolisable hydrogens are present.

1. Introduction

Pericyclic reactions are of particular interest because of their stereospecific course and their broad preparative significance in the chemistry of drugs and natural products.[1–6] Pericyclic reactions also occur in natural biological systems; for example, the formation of vitamin D_3 (cholecalciferol) in the outer skin regions which proceeds from 7-dehydrocholesterol under the influence of sun light,[7,8] and the transformation of chorismic to prephenic acid which occurs in plants and microorganisms in the synthesis of aromatic amino-acids (phenylalanine, tyrosine).[8–10] Furthermore, in the past few years there have been an explosion of reports about numerous inter- and intramolecular Diels–Alder reactions (or apparent Diels–Alder reactions) occurring in plants and microorganisms;[11] for example, the biosynthesis via Diels–Alder reaction of *Iboga* and *Aspidosperma* alkaloids,[12–14] and novel bis-sesquiterpene lactones from *Helenium autumnale* L.[15,16]

Amongst pericyclic reaction [3+2] cycloaddition of nitrones to alkenes has become a method of choice for synthesis of a wide variety of molecules. 1,3-Dipolar cycloaddition reaction between an alkene and a nitrone leading to isoxazolidines is an important reaction in organic chemistry.[17] The isoxazolidines formed by this reaction can easily be converted into a variety of different 'building blocks' such as 3-amino alcohols. The isoxazolidine route has often been used as a key step during the preparation of a variety of different natural products, e.g. DL-supinidine, DL-retronecine (pyrrolizidine alkaloids), DL-lupinine, DL-epilupinine (quinolizidine alkaloid), nupharidine (nuphar alkaloid), elaeocarpine, isoelaeocarpine (indolizidine alkaloids), pseudotropine (tropane alkaloid), DL-luciduline (lycopodium alkaloid).[18] Various cyclic nitrones have been reported as 1,3-dipoles including 5,5-dimethyl pyrroline-*N*-oxide, 4-dihydroisoquinoline-*N*-oxide, pyridine-*N*-oxide and phenanthridine-*N*-oxide.[19]

In course of our ongoing research toward the investigation of biomimetic pericyclic reactions in the synthesis of natural products, we proposed and demonstrated in a model study a possible biomimetic route to pyridomacrolidin **2** involving 1,3-dipolar cycloaddition of the cyclic nitrone **4** derived from pyridovericin **1** with enone **5**.[20–22] The crucial step in our biomimetic proposal is the in situ generation of the nitrone **4** followed by 1,3-dipolar cycloaddition with the enone **5** and subsequent aromatisation to provide the natural product **2** (Scheme 1). Herein, we describe full details of our studies directed towards investigating the scope, regio- and stereochemical outcome of the cycloaddition reaction of the

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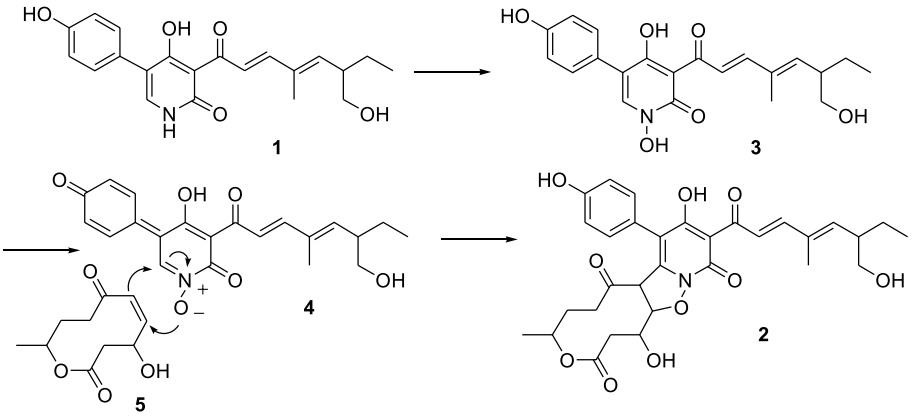


Scheme 1. Proposed biomimetic route to pyridomacrolidin **2**.

cyclic nitrone **8** (analogue of **4**) with various enones similar to cephalosporolide B **5**.

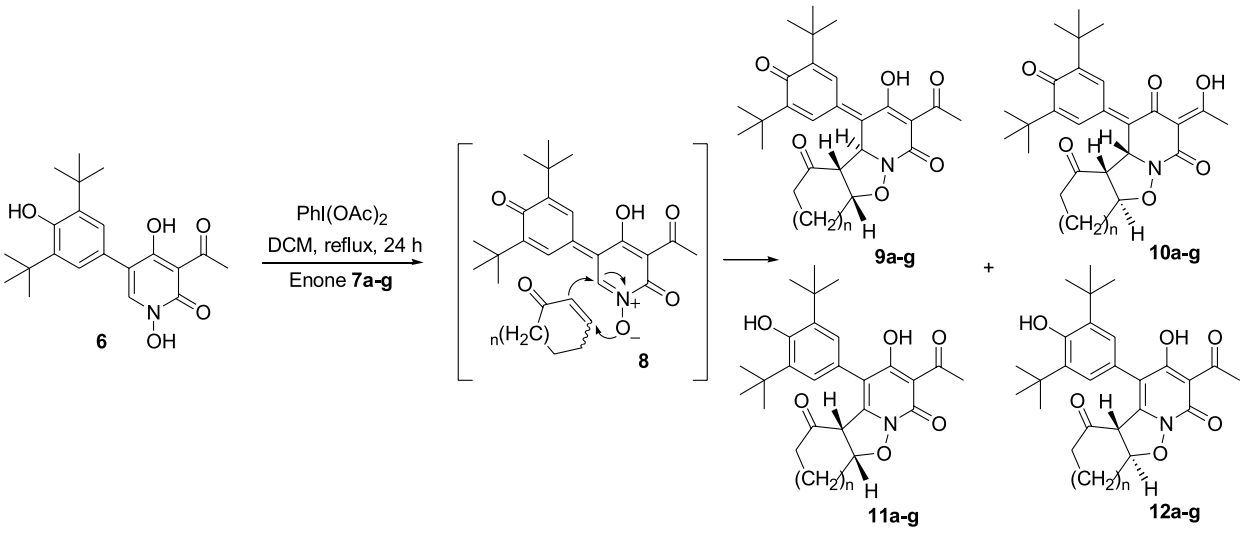
2. Results and discussion

Although 1,3-dipolar cycloadditions of nitrones with enones are well documented,[23] to the best of our knowledge, such reactions have not been demonstrated from a nitrone (such as **4**) derived from the oxidation of a 5-(4-hydroxyphenyl)-*N*-hydroxy-2-pyridone (such as **3**). Since, as expected, our attempts to oxidatively generate and trap unsubstituted quinonoid species similar to **4** were unsuccessful, probably due to competing additions to this highly electron deficient system as well as solubility problems, we chose to block the phenolic *ortho*-positions by sterically hindering groups. Thus we prepared **6**[22] and studied its oxidative cycloaddition with *Z*-2-cyclodecenone **7a**[24] (Scheme 2).

2.1. Oxidative cyclisation with medium ring enones similar to cephalosporolide B 5

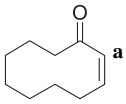
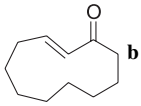
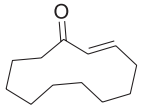
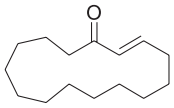
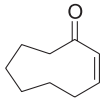
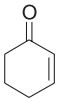
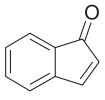
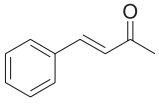
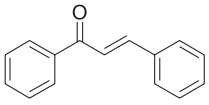
Oxidation of *N*-hydroxy-2-pyridone **6** in presence of *Z*-2-cyclodecenone **7a** with iodobenzene diacetate in DCM at reflux was attempted. Pleasingly, the unstable nitrone **8** generated in situ underwent [3+2] cycloaddition with enone **7a** smoothly to give the cyclised products **9a–12a** in a combined 65% yield with **9a** and **11a** as major products (Table 1, entry 1). We were encouraged by this result and in an attempt to shed some light on this unusual oxidative cyclisation, the reaction with various other assorted enones was investigated. Medium ring enones similar to cephalosporolide B **5** (Table 1, entries 1–5) impressively underwent oxidative cyclisation with nitrone **8** in good to excellent yield. Thus *E*-2-cycloundecenone, **7b** underwent the reaction producing **10b** and **12b** in 75% yield along with **9b** in 5% yield in a combined excellent (80%) yield. Likewise, *E*-2-cyclododecenone, **7c** smoothly afforded the cyclised products **10c** and **12c** in 55% yield along with the minor product **9c** in 2% yield in a combined good (57%) yield. *E*-2-Cyclopentadecenone, **7d** cleanly rendered the cyclised products **10d** and **12d** in 70% yield without formation of *cis*-fused adducts **9d** or **11d**. Furthermore, *Z*-2-cyclonenone, **7e** gave the products **9e** and **11e** in a moderate yield (Scheme 2).

Smaller rings, e.g. 2-cyclopentenone **7f** and 2-cyclohexenone **7g** (Table 1, entries 6 and 7) resulted in only traces of **9f** and **9g**, respectively, despite complete



Scheme 2. Oxidative cyclisation with medium ring enones.

Table 1. Oxidative cyclisation of *N*-hydroxy-2-pyridone **6** with various enones

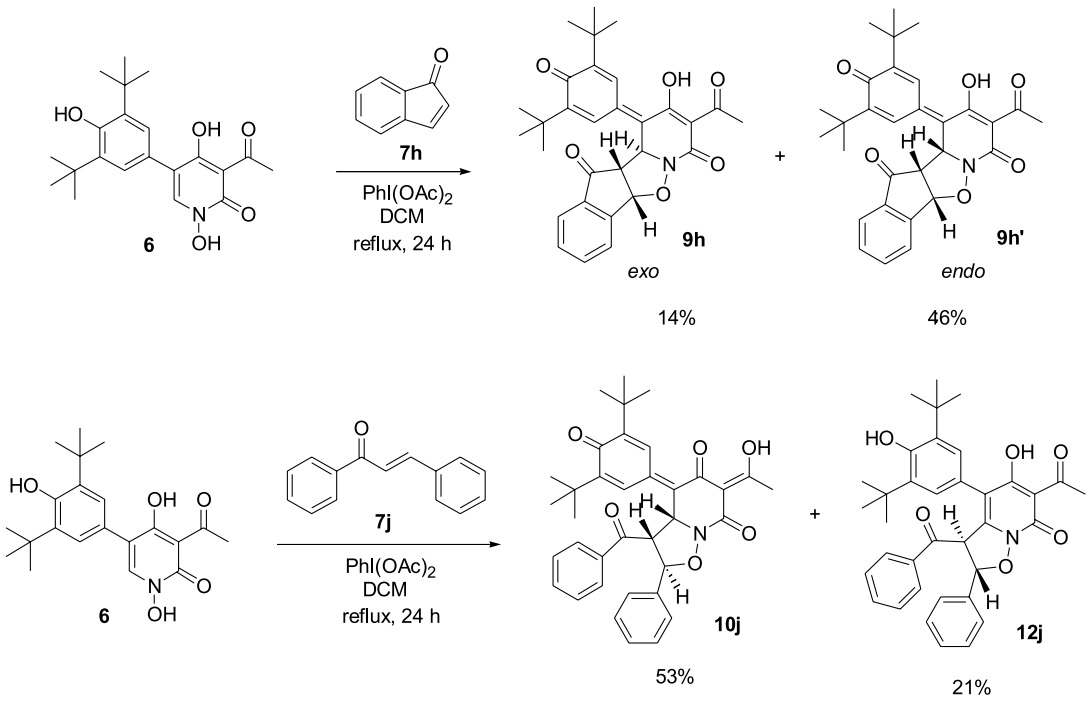
Entry	Enone **7**	**9** (%)	**10** (%)	**11** (%)	**12** (%)	**9′**(%)	Combined yield %
1	 **a**	35[a,b,c]	3[d]	25[a,b]	2[a,b,d]		65
2	 **b**	5[b,d]	55[a,b,e]	—	20[a]		80
3	 **c**	2[b,d]	41[b,e]	—	14[a]		57
4	 **d**	—	45[b,e]	—	25[a]		70
5	 **e**	29[b,c]	—	3	—		32
6	 **f**	Traces	—	—	—		Traces
7	 **g**	Traces	—	—	—		Traces
8	 **h**	14[b]		—	—	46[b,f]	60
9	 **i**	—	—	—	—		—
10	 **j**	—	53[e]	—	21		74

[a] Structure was confirmed by single crystal crystallography.
[b] Structure was confirmed by comparable NOE with the one confirmed by X-ray.
[c] Major product was obtained by an *exo* mode of cycloaddition in case of *Z*-enones.
[d] Small leakage via step-wise pathway.
[e] Major product was obtained by an *endo* mode of cycloaddition in case of *E*-enones.
[f] Formed due to *endo* mode of cycloaddition.

conversion of the starting material **6**. We reasoned that failure in these cases might result from an increased tendency for enone enolisation. With an intent to obtain supporting evidence, we chose to investigate the reactivity of aromatic enones where there is no possibility of enolisation. Interestingly, *Z*-2-indenone **7h** underwent the reaction providing the quinone methides **9h** and **9h′** in a combined 60% yield. In a similar fashion, *trans*-chalcone **7j** underwent oxidative cyclisation affording the cyclised products **10j** and **12j** in a combined 74% yield. However, reaction of benzylideneacetone **7i** failed to give any traces of cyclised product. The failure to undergo cycloaddition in the case of smaller rings and benzylidineacetone and success in the case of *trans*-chalcone and 2-indenone supports the view of failure due to the possibility of enolisation (Scheme 3).

2.2. Regio- and stereochemistry

It is interesting to note that in all cases cycloaddition resulted from the addition of the oxygen of the nitrone to the β-carbon of enones producing complete regiochemical control. The stereochemistry of the major products retained the geometry of the enones. All starting materials (enones) were greater than 98% *E* (or *Z*), and no evidence of isomerisation of starting material under reaction conditions was observed, via the analysis of recovered unreacted enone. This is consistent with the cycloaddition reaction following a concerted mechanism. The formation of minor products with inversion of stereochemistry at the junction might be due to a small leakage via step-wise pathway. Two different modes of cycloaddition of nitrone to enone have also been observed. The quinone methides **9a** and **9e**



Scheme 3. Oxidative cyclisation using aromatic enones with no enolisable hydrogen.

(obtained from *Z*-enones) are classified as resulting from the *exo* mode of cycloaddition, whereas the quinone methides **10b**,**c**,**d**,**j** (resulted from *E*-enones) are classified as resulting from *endo* mode of cycloaddition. Notably, *Z*-2-indenone **7h** (Table 1, entry 8) underwent both *exo* and *endo* modes of cycloaddition (Scheme 3) furnishing two different quinone methides **9h** and **9h′**, respectively, with **9h′** as the major product.

2.3. ^{1}H and ^{13}C NMR assignment

The characteristic ^{1}H NMR and ^{13}C NMR δ values of junction hydrogens (a, b and c) of all the cyclised products (**9**–**12** and **9h′**) are shown in Table 2. The structures of **11a**–**j** and **12a**–**j** can be differentiated by ^{1}H and ^{13}C NMR spectroscopy. For phenol **11a**–**j**, Cb is upfield of Cc. In the case of phenol **12a**–**j**, Hb is upfield of Hc and Cb is upfield of Cc (as in previous case). The compounds **9a**–**j** and **10a**–**j** also can be differentiated by ^{13}C NMR δ values of Ca and Cb. In class **9**, Ca is downfield of Cb, whereas in class **10**, Ca is upfield of Cb.

2.4. Observed NOE corroborations

The structure and stereochemistry of all cyclised products (**9**–**12a**–**j** and **9h′**) were also established by extensive proton coupling experiments and one-dimensional NOE (Table 3). The strong NOE corroborations between Hb and Hc (ca. 11.0%) and weak NOE corroborations between Ha and Hb (ca. 1.7%) and Ha and Hc (ca. 0.4%) confirmed the relative stereochemistry of class **9a**–**j**. The strong NOE corroborations between Ha and Hb (7.6–5.9%) and weak corroborations between Ha and Hc (ca. 0.4%) and Hb and Hc (1.0–2.3%) confirmed the relative stereochemistry of class **10a**–**j**. Likewise, the strong NOE corroborations between Hb and Hc (ca. 11.3%) confirmed *cis* stereochemistry in phenol **11a**–**j**, whereas the weak NOE corroborations between Hb and Hc (ca. 1.2%) confirmed the *trans* stereochemistry in phenol **12a**–**j**. The strong NOE corroboration between Ha and Hb and Hc confirmed the structure and relative stereochemistry of **9h′**.

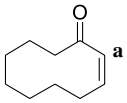
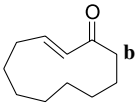
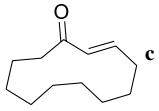
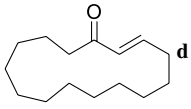
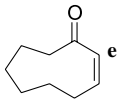
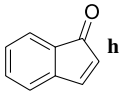
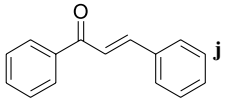
2.5. X-ray crystallographic studies and data

The structure and relative stereochemistry of the cyclised products were further unambiguously confirmed by single crystal crystallography. The stereochemistry of class **9** was established from the crystal structure of the cyclised product **9a** obtained with *Z*-2-cyclodecenone **7a**. The crystal structure showed clearly that Ha is *trans* to Hb and Hc, whereas Hb and Hc are *cis* to each other. The geometry of the nitrogen is pyramidal. Furthermore, there is an intra-molecular hydrogen bond between the hydroxyl group at the C-4 of the pyridone ring and the carbonyl oxygen of the neighbouring acetyl group (Fig. 1).

The structure and stereochemistry of compounds of class **10** were established by single crystal crystallography of **10b**. It is clear from the crystal structure that the pyridone ring is in a different tautomeric form compared with class **9**, there being an intra-molecular hydrogen bond between the carbonyl oxygen at C-4 of the pyridone ring and the adjacent enol ether. It is also evident from the crystal structure that Ha and Hb are *cis* to each other, whereas Hc is *trans* to Ha and Hb. Moreover, the quinone methides of class **10** were resulted by means of *endo* mode of cycloaddition. The geometry of the nitrogen is pyramidal (Fig. 2).

The structure and stereochemistry of compounds of class **11** were unequivocally established by single crystal crystallography of **11a**. The relative stereochemistry of the class **11**

Table 2. ^{1}H and ^{13}C NMR chemical shifts of compounds **9–12a–j** and **9h′**

Entry	Enone **7**	**9**	**10**	**11**	**12**	**9′**
1	 **a**	**a** δ_C 66.0; δ_H 5.35 (d, J=9.0 Hz) **b** δ_C 61.3; δ_H 3.69 (ca. t, J=9.0 Hz) **c**=85.6; δ_H 4.32 (ca. t, J=9.0 Hz)	**a** δ_C 64.0; δ_H 5.34 (d, J=8.5 Hz) **b** δ_C 64.8; δ_H 4.03 (dd, J=8.5, 6.0 Hz) **c**=87.5; δ_H 4.41 (m)	**b** δ_C 55.5; δ_H 4.91 (d, J=7.0 Hz) **c** δ_C 84.0; δ_H 4.79–4.83 (m)	**b** δ_C 64.1; δ_H 4.61(d, J= 10.5 Hz) **c** δ_C 87.6; δ_H 4.74 (dt, J=10.5, 2.5 Hz)	—
2	 **b**	**a** δ_C 66.4; δ_H 5.35 (d, J=10.0 Hz) **b** δ_C 65.1; δ_H 3.17 (dd, J=10.0, 7.5 Hz) **c** δ_C 90.2; δ_H 4.68–4.74 (m)	**a** δ_C 63.6; δ_H 5.27 (d, J=8.5 Hz) **b** δ_C 67.8; δ_H 3.76 (dd, J=8.5, 7.0 Hz) **c** δ_C 86.7; δ_H 4.39 (m)	—	**b** δ_C 62.9; δ_H 4.41 (d, J=10.5 Hz) **c** δ_C 85.9; δ_H 4.88 (m)	—
3	 **c**	**a** δ_C 65.8; δ_H 5.20 (d, J=10.0 Hz) **b** δ_C 65.6; δ_H 3.19 (dd, J=10.0, 7.0 Hz) **c** δ_C 89.3; δ_H 4.76–4.81 (m)	**a** δ_C 63.2; δ_H 5.29 (d, J=8.0 Hz) **b** δ_C 65.2; δ_H 3.76 (dd, J=8.0, 5.5 Hz) **c** δ_C 85.2; 4.59 (m)	—	**b** δ_C 61.7; δ_H 4.48 (d, J=9.5 Hz) **c** δ_C 83.3; δ_H 4.86 (dt, J=9.5, 6.5 Hz)	—
4	 **d**	—	**a** δ_C 62.8; δ_H 5.25 (d, J=8.5 Hz) **b** δ_C 66.1; δ_H 3.74 (dd, J=8.5, 6.5 Hz) **c** δ_C 85.5; δ_H 4.25 (ca. q, J=6.5 Hz)	—	**b** δ_C 62.3; δ_H 4.36 (d, J=9.5 Hz) **c** δ_C 84.8; δ_H 4.61–4.75 (m)	—
5	 **e**	**a** δ_C 63.8; δ_H 5.51 (d, J=9.5 Hz) **b** δ_C 61.2; δ_H 3.58 (ca. t, J=9.5 Hz) **c** δ_C 86.4; δ_H 4.45 (dt, J=9.5, 2.0 Hz)	—	**b** δ_C 57.9; δ_H 4.66 (d, J=7.5 Hz) **c** δ_C 84.0; δ_H 4.78–4.87 (m)		—
6	 **h**	**a** δ_C 62.8; δ_H 5.10 (d, J=9.0 Hz) **b** δ_C 60.4; δ_H 3.52 (dd, J=9.0, 7.0 Hz) **c** δ_C 84.0; δ_H 6.10 (d, J=7.0 Hz)	—	—	—	**a** δ_C 62.3; δ_H 5.34 (d, J=8.5 Hz) **b** δ_C 57.7; δ_H 3.70 (dd, J=8.5, 6.0 Hz) **c** δ_C 82.5; δ_H 6.06 (d, J=6.0 Hz)
7	 **j**	—	**a** δ_C 63.8; δ_H 5.71 (d, J=8.5 Hz) **b** δ_C 64.1; 4.83 (dd, J=8.5, 6.0 Hz) **c** δ_C 86.5; δ_H 5.50 (d, J=6.0 Hz)	—	**b** δ_C 60.0; δ_H 5.47 (d, J= 7.5 Hz) **c** δ_C 86.4; δ_H 5.73 (d, J=7.5 Hz)	—

was established as *cis* (Hb and Hc are *cis* to each other). It also showed that the geometry of the nitrogen is planar. The crystal structure of phenol **11a** revealed the presence of an intra-molecular hydrogen bond between the hydroxyl group at C-4 of the pyridone ring and the carbonyl oxygen of the neighbouring acetyl group. The angle between the best planes of the two six-membered rings is 78.1°, indicating that there is little conjugation of the two six-membered rings. (Fig. 3).

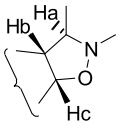
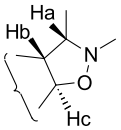
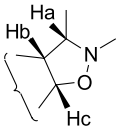
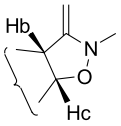
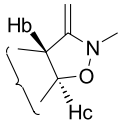
The structure and stereochemistry of class **12** were unambiguously confirmed by single crystal crystallography of compounds **12a–d**. Similar to class **11**, there is an intra-molecular hydrogen bond between the hydroxyl group at C-4 of the pyridone ring and the carbonyl oxygen of the neighbouring acetyl group. It is also clear from the crystal structure that Hb and Hc are *trans* to each other. The angle between the best planes of the two six membered rings is 74.6°, suggesting that there is little conjugation of the two π systems. The geometry of the nitrogen is planar (Fig. 4).

The crystallographic data for compounds (**9a** and **10b**, **11a** and **12a–d**) is displayed in Table 4.

2.6. Equilibration of quinone methides (9 and 10) into phenols (11 and 12)

All the quinone methides **10a–d**,**j** were cleanly transformed into their corresponding phenols **12a–d**,**j**. The quinone methides **10a** and **10b** obtained from *Z*-2-cyclodecenone **7a** and *E*-2-cycloundecenone **7b**, respectively, were equilibrated into phenol **12a** and **12b** by refluxing in *tert*-butanol for 24 h. The quinone methides **10c**, **10d**, and **10j** obtained from *E*-2-cyclododecenone **7c**, *E*-2-cyclopentadodecenone

Table 3. NOE corraborations of compounds **9–12a–j** and **9h′**

Compound	Relative stereo-chemistry	NOE corroborations (%)	
9a–j		a↔b b↔c c↔a	Weak (1.7) Strong (11.0) Weak (0.4)
10a–j		a↔b b↔c c↔a	Strong-medium (7.6–5.9) Weak (2.3–1.0) Weak (0.4)
9h′		a↔b b↔c c↔a	Strong Strong Strong
11a–j		b↔c	Strong (11.3)
12a–j		b↔c	Weak (1.2)

7d and chalcone **7j**, respectively, were easily transformed into the corresponding phenols **12c**, **12d** and **12j** by stirring in ethanol at room temperature. Contrary to the quinone methides of class **10**, the quinone methides **9a** and **9e** obtained as major products from *Z*-2-cyclodecenone **7a** and *Z*-2-cyclononenone **7e** failed to undergo aromatisation in protic solvents (*tert*-butanol) and non-protic solvents (DCE, DCM), or under acidic (trifluoroacetic acid) and basic conditions (Hunig's base). However, conversion to **11a** and **11e** was accomplished by treatment with $AlCl_3$ in DCE at reflux for 24 h. The quinone methides **9h** and **9h′** obtained from *Z*-2-indenone **7h** failed to undergo aromatisation (Scheme 4).

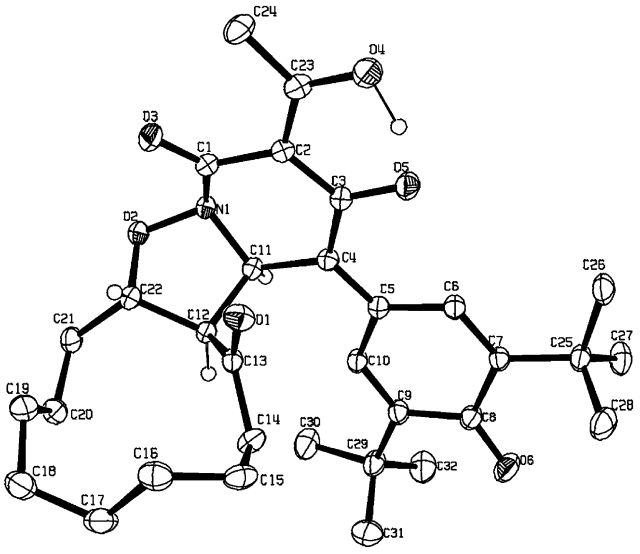


Figure 2. Crystal structure of **10b** obtained from oxidative cyclisation with *E*-2-cycloundecenone **7b** (entry 2, Table 1).

3. Conclusion

An unusual biomimetic oxidative cyclisation of *N*-hydroxy-2-pyridone **6** with various enones was investigated. The regiochemistry of the reaction was controlled; in all cases the oxygen of the nitrone adds to the β-carbon of the enone. Medium ring enones similar to cephalosporolide B gave better cycloaddition yields than small ring enones (Table 1, entries 1–4 > 5 ≫ 6 and 7). High retention of alkene geometry during cycloaddition was observed (Table 1, entries 1–5, 8 and 10) consistent with a concerted mode of cycloaddition with only a small leakage via a step-wise process. The nitrone underwent two different modes of

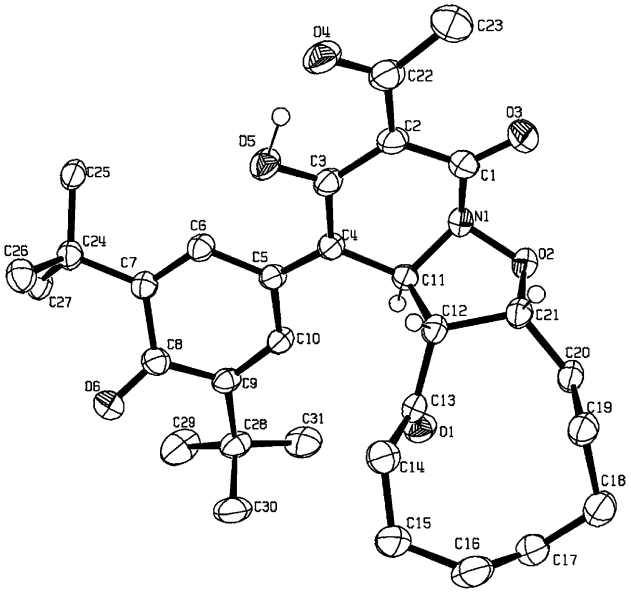


Figure 1. Crystal structure of **9a** obtained from oxidative cyclisation with *Z*-2-cyclodecenone **7a** (Table 1, entry 1).

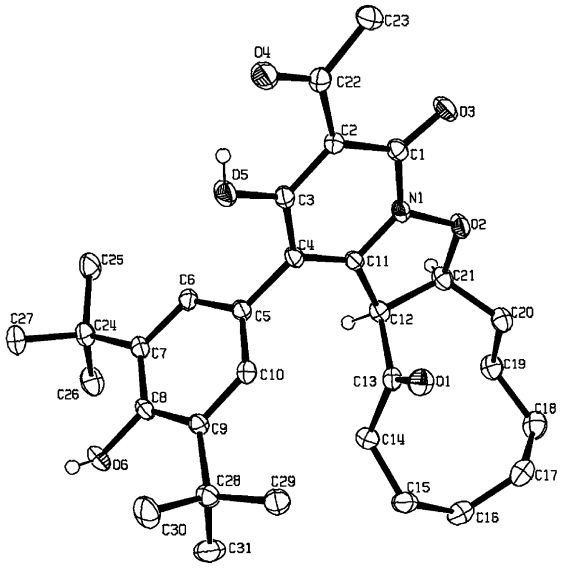


Figure 3. Crystal structure of **11a** obtained from oxidative cyclisation with *Z*-2-cyclodecenone **7a** (Table 1, entry 1).

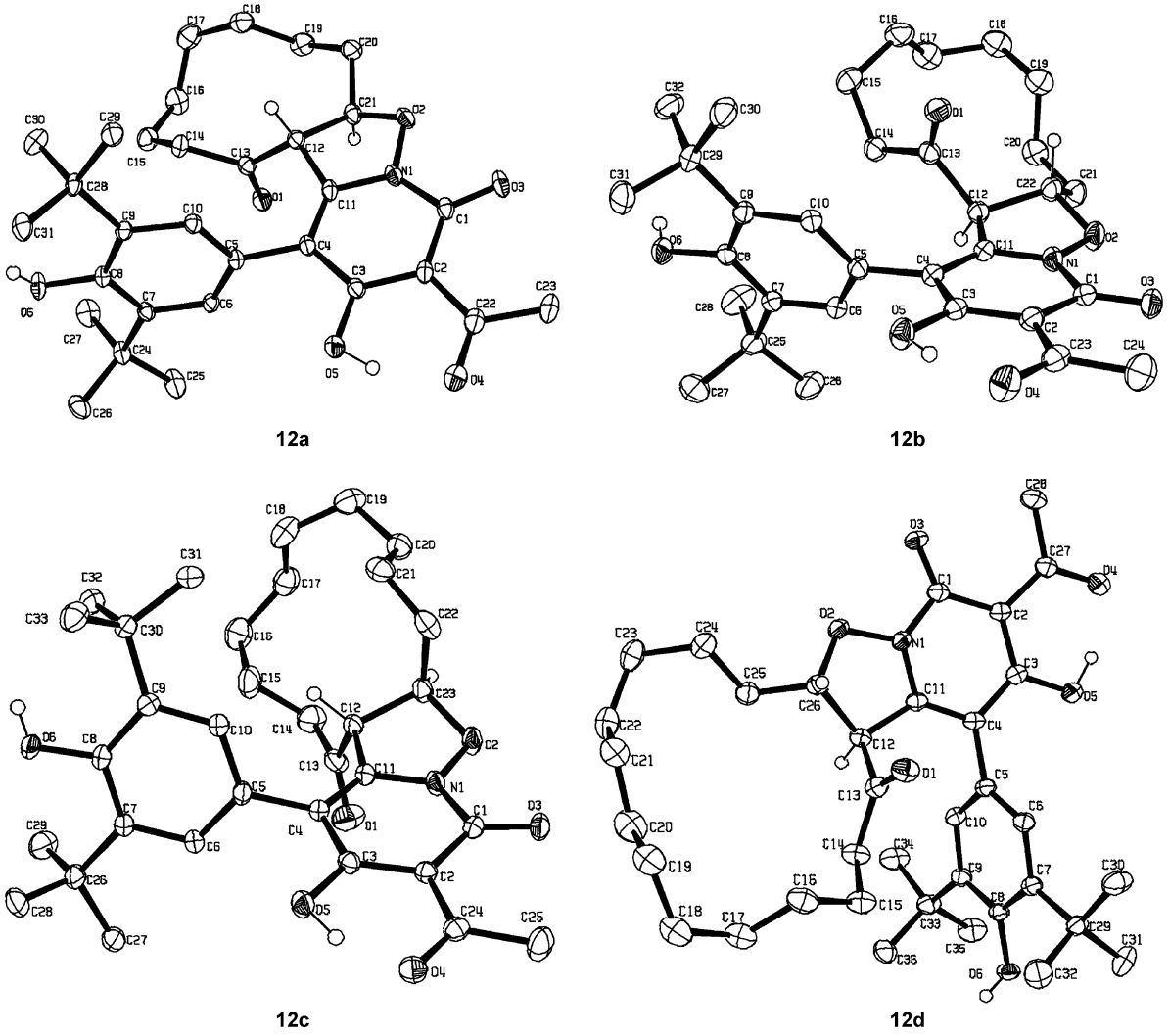
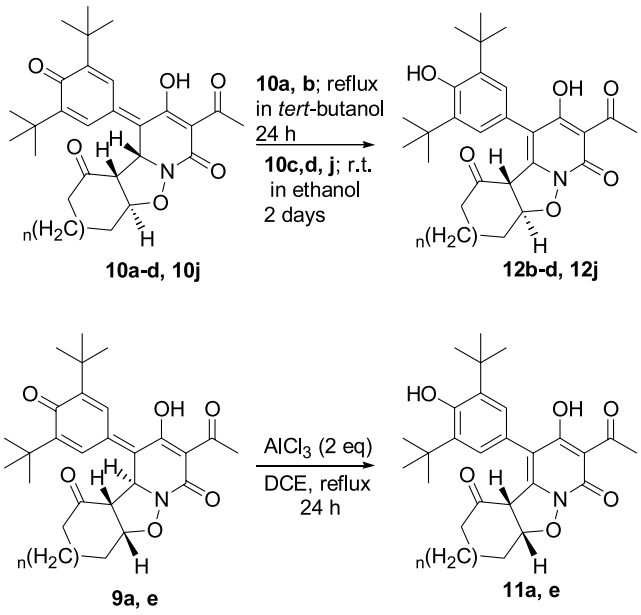


Figure 4. Crystal structures of **12a–d** obtained from oxidative cyclisation with enones **7a–d** (Table 1, entries 1–4).

Table 4. Summary of crystallographic data

Compound	**9a**	**10b**	**11a**	**12a**	**12b**	**12c**	**12d**
Formula	$C_{31}H_{41}NO_6+1/8(H_2O)$	$C_{32}H_{43}NO_6\cdot 1.10$ (MeCN)	$C_{31}H_{41}NO_6$	$C_{31}H_{41}NO_6$	$C_{34}H_{46}N_2O_6$	$C_{33}H_{45}NO_6$	$C_{38}H_{54}N_2O_6$
Formula weight	523.68+18.016/8	582.81	523.67	523.67	578.30	551.72	634.86
Cryst syst	Monoclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	*C* 2/*c*	$P\bar{1}$	$P2_1$	$P2_1/n$	$P2_1/c$	*Pbcn*	$P2_1/n$
a (Å)	26.7051(2)	10.4459(2)	6.0298(2)	10.5172(2)	15.4613(2)	26.5094(3)	10.8850(2)
b (Å)	25.9806(2)	14.2781(2)	19.8766(6)	20.4602(6)	21.7487(3)	9.7639(2)	21.9001(3)
c (Å)	34.1527(2)	23.0270(3)	11.5736(4)	13.1197(4)	19.9989(2)	23.1273(3)	15.7232(2)
α (°)	90	78.7344(6)	90	90	90	90	90
β (°)	104.9299(4)	77.9148(6)	94.4784(15)	90.0512(12)	90.4876(6)	90	108.8713(7)
γ (°)	90	79.2375(5)	90	90	90	90	90
V (Å^3)	22895.7	3255.29(9)	1382.9	2823.1	6724.65(14)	5986.16(16)	3546.67(9)
Reflections measured	118,873	48,748	15,054	18,114	60,251	53,825	35,608
Unique reflections	26,594	14,760	3234	6446	15,674	7529	8275
R_{int}	0.071	0.040	0.044	0.052	0.056	0.072	0.067
Observed reflections ($I>3\sigma(I)$)	12,740	9107	2288	5033	8069	3417	4268
Parameters refined	1390	776	351	352	773	369	423
GOF	1.0527	0.9321	1.0575	1.0478	1.0540	1.0519	1.0477
R	0.0500	0.0522	0.0318	0.0425	0.0417	0.0432	0.0447
wR	0.0579	0.0658	0.0359	0.0468	0.0516	0.0502	0.0525



Scheme 4. Aromatisation of *exo* and *endo* quinone methides into phenols.

cycloaddition, that is, *exo* and *endo* (**9a**, **9e**, **9h**-*exo*, **10b**–**d**,**j**,**9h**′-*endo*). Compounds of class **10a**–**d**,**j** were more easily converted into phenols of type **12a**–**d**,**j** than quinone methides of type **9a**,**e** were converted into **11a**,**e**. The process can also be extended to aryl conjugated enones (Table 1, entries 8 and 10) as long as they do not contain any enolisable hydrogen atoms.

A *cis*-fused ring geometry, e.g. like compound **11a** [$J_{Hb,Hc}=7.0$ Hz (Table 2, entry 1)] rather than a *trans*-fused geometry, e.g. like compound **12a** [$J_{Hb,Hc}=10.5$ Hz (Table 2, entry 1)] matches closer to the corresponding coupling constant $J=5.9$ Hz of pyridomacrolidin **2**.[20b] Thus it is reasonable to assume a *cis*-fused ring junction derived from a concerted suprafacial–suprafacial [3+2] cycloaddition of a functionalised *Z*-2-cyclodecenone and suitable nitrone, for pyridomacrolidin.

4. Experimental

4.1. General methods

Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected NMR spectra were recorded on a Bruker AMX-500, Bruker AV-400, Bruker DPX-400 or Varian Gemini DPX-200 spectrometers. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Proton assignments are supported by ^{1}H–^{1}H COSY when necessary. Data are reported in the following manner.

Chemical shift (multiplicity, coupling constant, integration if appropriate). Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are given in hertz to the nearest 0.5 Hz.

^{13}C NMR spectra were recorded at 50.3, 100.6 and 125.8 MHz using Varian Gemini 200, Bruker AV-400 or Bruker AMX-500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C–^{1}H (HMQC and HMBC) correlations when necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak.

IR-spectra were recorded as a thin film on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Strong (s) medium (m) and weak (w) absorption bands are reported in wavenumbers (cm^{-1}).

High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel 60F_{254}. Column chromatography was carried out on Sorbsil™ C60 (40–63 μm, 230–400 mesh) silica gel.

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 1 mm Hg.

All experiments were carried out under inert atmosphere unless otherwise stated.

4.2. General procedure for the oxidative cyclisation of *N*-hydroxy-2-pyridone with enones (7a–e,h,j)

To a mixture of 3-acetyl-*N*-hydroxy-5-[(3′,5′-di-*tert*-butyl-4′-hydroxy)phenyl]-4-hydroxy-2(1*H*)-pyridone **6**[22] (1.0 equiv) and enone **7a**–**e**,**h**,**j** (1.0 equiv) in DCM (0.026 M) was added iodobenzene diacetate (1.1 equiv) all at once. Immediately the reaction turned to a dark colour. After stirring for 2 h at 25 °C, the reaction was refluxed for 24 h. During the reflux the colour of the reaction turned into reddish yellow. After cooling to 25 °C, water (5 mL) was added to the reaction mixture and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 10–30% EtOAc in 30–40 petroleum ether, followed by second purification with 0– 3% EtOAc in DCM as a gradient elution, silica gel having been pre-washed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C for 24 h).

4.2.1. Oxidative cyclisation with *Z*-2-cyclodecenone 7a (9a–12a). The general procedure, applied to pyridone **6** (100 mg, 0.27 mmol) using *Z*-2-cyclodecenone **7a**, gave

49 mg (35%) of quinone methide **9a**, as a reddish yellow solid, re-crystallised from ethanol, mp 105–107 °C, 4.5 mg (3%) of *trans*-quinone methide **10a** as a reddish yellow solid, 35 mg (25%) of phenol **11a**, as pale yellow solid, re-crystallised from acetonitrile, mp 135–137 °C, and 3 mg (2%) of *trans*-phenol **12a**. *cis*-Quinone methide **9a** was equilibrated into *cis*-phenol **11a** by treating with aluminium chloride (2 equiv) in DCE at reflux for 24 h. *trans*-Quinone methide **10a** was equilibrated into *trans*-phenol **12a** by refluxing in *tert*-butanol for 24 h and it was re-crystallised from acetonitrile to yield a pale yellow crystal, mp 265 °C(d).

cis-Quinone methide (**9a**): IR ν_{max} (film)/cm^{-1} 2954s, 2871m, 1690s, 1620s, 1562m, 1438s, 1366m, 1260m, 1092w, 1040w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96–1.03 (m, 1H), 1.11–1.19 (m, 2H), 1.30–1.42 (m, 3H), 1.34 (s, 9H), 1.36 (s, 9H), 1.46–1.51 (m, 1H), 1.69–1.79 (m, 2H), 1.88–1.97 (m, 1H), 2.03–2.12 (m, 2H), 2.22–2.28 (m, 1H), 2.53 (dd, J=16.5, 10.5 Hz, 1H), 2.81 (s, 3H), 3.69 (ca. t, J=9.0 Hz, 1H), 4.32 (ca. t, J=9.0 Hz, 1H), 5.35 (d, J=9.0 Hz, 1H), 7.04 (d, J=2.5 Hz, 1H), 8.47 (d, J=2.5 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.1, 23.1, 24.2, 24.5, 24.9, 27.3, 28.6, 29.4, 29.5, 35.8, 36.2, 48.1, 61.3, 66.0, 85.6, 106.7, 126.3, 128.6, 129.2, 141.1, 150.7, 152.7, 167.9, 182.3, 187.3, 204.1, 209.4; HRMS: Found 524.3000 (MH^+). $C_{31}H_{42}NO_6$ requires 524.3012.

trans-Quinone methide (**10a**): IR ν_{max} (film)/cm^{-1} 2954s, 2871m, 1690s, 1620s, 1562m, 1438s, 1366m, 1260m, 1092w, 1040w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–1.03 (m, 1H), 1.11–1.19 (m, 2H), 1.30–1.42 (m, 3H), 1.31 (s, 9H), 1.38 (s, 9H), 1.46–1.51 (m, 1H), 1.69–1.79 (m, 2H), 1.88–1.97 (m, 1H), 2.03–2.12 (m, 2H), 2.28–2.32 (m, 1H), 2.81 (s, 3H), 2.81–2.88 (m, 1H), 4.03 (dd, J=8.5, 6.0 Hz, 1H), 4.41 (m, 1H), 5.34 (d, J=8.5 Hz, 1H), 7.17 (d, J=2.5 Hz, 1H), 8.71 (d, J=2.5 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.1, 24.1, 24.8, 25.4, 27.0, 27.9, 29.4, 29.5, 30.1, 35.6, 36.1, 45.5, 64.0, 64.8, 87.5, 107.7, 125.8, 128.4, 129.2, 139.4, 151.0, 152.3, 165.5, 181.5, 186.2, 202.2, 213.6; HRMS: Found 522.2856 $(M-H)^-$. $C_{31}H_{40}NO_6$ requires 522.2856.

cis-Phenol (**11a**): IR ν_{max} (film)/cm^{-1} 3634w, 2953s, 2874m, 1711m, 1659s, 1609m, 1539m, 1434m, 1415m, 1364w, 1278w, 1237w, 1151m, 1121m, 978w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.10 (m, 2H), 1.21–1.30 (m, 4H), 1.42–1.55 (m, 5H), 1.51 (s, 18H), 1.68–1.73 (m, 1H), 2.11–2.15 (m, 2H), 2.85 (s, 3H), 4.79–4.83 (m, 1H), 4.91 (d, J=7.0 Hz, 1H), 5.42 (s, 1H), 7.04–7.15 (brs, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.0, 22.6, 23.0, 24.2, 27.0, 29.4, 30.2, 31.4, 34.3, 45.6, 55.5, 84.0, 107.1, 108.8, 121.9, 126.1, 136.7, 145.0, 154.0, 154.2, 173.1, 204.9, 205.4; HRMS: Found 524.3005 (MH^+). $C_{31}H_{42}NO_6$ requires 524.3012.

trans-Phenol (**12a**): IR ν_{max} (film)/cm^{-1} 3599m, 2953s, 2873m, 1711m, 1659s, 1610m, 1540m, 1432s, 1362m, 1238m, 1152m, 1119m, 975m; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82–0.88 (m, 1H), 0.89–0.97 (m, 1H), 1.21–1.30 (m, 6H), 1.43 (s, 9H), 1.43–1.46 (m, 1H), 1.46 (s, 9H), 1.48–1.55 (m, 2H), 1.81 (dd, J=15.0, 2.0 Hz, 1H), 1.87–1.94 (m, 1H), 2.30–2.34 (m, 1H), 2.80 (s, 3H), 4.61 (d, J=10.5 Hz, 1H), 4.74 (dt, J=10.5, 2.5 Hz, 1H), 5.38 (s, 1H), 6.89 (s, 1H), 6.98 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.4, 23.8, 24.3, 25.4, 25.9, 29.8, 30.6, 30.7, 31.8, 34.7, 34.9, 44.1, 64.1, 87.6, 107.4, 109.4, 122.6, 127.4, 129.7, 136.6, 137.2, 147.0, 154.7, 154.8, 174.1, 205.9, 208.2; HRMS: Found 524.3030 (MH^+). $C_{31}H_{42}NO_6$ requires 524.3012.

4.2.2. Oxidative cyclisation with *E*-2-cycloundecenone, 7b (9b,10b,12b). Following the general procedure, applied to pyridone **6** (75 mg, 0.20 mmol) using *E*-2-cycloundecenone **7b**, 22 mg (20%) of phenol **12b** as a pale yellow solid, re-crystallised from acetonitrile, mp>270 °C and 60 mg (55%) of quinone methide **10b** as a reddish yellow solid, re-crystallised from acetonitrile, mp 125–126 °C along with 5 mg (5%) of *cis*-quinone methide **9b** as a reddish yellow solid, mp 103–105 °C were obtained. The *trans*-quinone methide **10b** was cleanly transformed into the *trans*-phenol **12b** by refluxing in *tert*-butanol for 24 h.

cis-Quinone methide (**9b**): IR ν_{max} (film)/cm^{-1} 2954s, 2871m, 1689s, 1620s, 1438s, 1366m, 1092w, 1040w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03–1.20 (m, 2H), 1.21–1.28 (m, 2H), 1.31 (s, 9H), 1.32 (s, 9H), 1.37–1.51 (m, 7H), 1.68–1.78 (m, 1H), 1.88–2.12 (m, 2H), 2.14–2.28 (m, 1H), 2.78 (s, 3H), 2.95–3.09 (m, 1H), 3.17 (dd, J=10.0, 7.5 Hz, 1H), 4.68–4.74 (m, 1H), 5.35 (d, J=10.0 Hz, 1H), 7.02 (d, J=2.5 Hz, 1H), 8.43 (d, J=2.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.0, 21.4, 21.8, 22.4, 22.7, 26.2, 29.2, 29.9, 30.0, 34.0, 36.4, 36.7, 43.1, 65.1, 66.4, 90.2, 106.6, 126.9, 128.8, 129.2, 141.7, 151.3, 153.2, 168.4, 182.0, 187.7, 204.7, 209.1; HRMS: Found 538.3151 (MH^+). $C_{32}H_{44}NO_6$ requires 538.3169.

trans-Quinone methide (**10b**): IR ν_{max} (film)/cm^{-1} 2953s, 2871m, 1707s, 1619s, 1562m, 1440s, 1365m, 1258m, 1090w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80–0.94 (m, 1H), 1.11–1.21 (m, 3H), 1.22–1.41 (m, 6H), 1.28 (s, 9H), 1.35 (s, 9H), 1.51–1.67 (m, 1H), 1.68–1.91 (m, 3H), 2.11–2.18 (m, 1H), 2.73 (s, 3H), 2.81–2.89 (m, 1H), 3.76 (dd, J=8.5, 7.0 Hz, 1H), 4.39 (m, 1H), 5.27 (d, J=8.5 Hz, 1H), 7.11 (d, J=2.5 Hz, 1H), 8.67 (d, J=2.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.93, 20.98, 21.8, 22.3, 22.7, 25.3, 27.9, 29.6, 29.7, 30.5, 36.0, 36.2, 42.2, 63.6, 67.8, 86.7, 107.7, 126.3, 129.4, 129.43, 138.9, 150.8, 152.1, 165.9, 182.1, 186.3, 202.2, 211.6; HRMS: Found 538.3164 (MH^+). $C_{32}H_{44}NO_6$ requires 538.3169.

trans-Phenol (**12b**): IR ν_{max} (film)/cm^{-1} 3631m, 2952s, 2869m, 1717m, 1659s, 1610m, 1541m, 1432s, 1365m, 1237m, 1156m, 1119m, 975m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–0.87 (m, 1H), 0.92–1.06 (m, 4H), 1.23–1.31 (m, 4H), 1.31–1.48 (m, 3H), 1.43 (s, 9H), 1.46 (s, 9H), 1.58–1.68 (m, 1H), 1.85–1.95 (m, 1H), 2.16–2.30 (m, 1H), 2.45 (dd, J=19.0, 11.0 Hz, 1H), 2.80 (s, 3H), 4.41 (d, J=10.5 Hz, 1H), 4.88 (m, 1H), 5.37 (s, 1H), 6.88 (s, 1H), 6.98 (s, 1H), 15.92 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.1, 21.2, 22.4, 22.57, 22.63, 26.3, 30.1, 30.7 (2C), 31.9, 34.7, 34.9, 41.3, 62.9, 85.9, 107.7, 109.4, 122.5, 127.1, 129.2, 136.6, 137.3, 146.6, 154.6, 154.8, 174.0, 205.8, 205.9; HRMS: Found 560.3002 (MNa^+). $C_{32}H_{43}NO_6Na$ requires 560.2988.

4.2.3. Oxidative cyclisation with *E*-2-cyclododecenone, 7c (9c,10c,12c). The general procedure, applied to pyridone **6** (100 mg, 0.27 mmol) using *E*-2-cyclododecenone **7c**, gave 20 mg (14%) of phenol **12c** as pale yellow solid,

re-crystallised from acetonitrile, mp 123 °C and 60 mg (41%) of quinone methide **10c**, as a reddish yellow solid (aromatised into phenol in an attempt to re-crystallise from ethanol), mp 93–95 °C along with 2.5 mg (2%) of *cis*-quinone methide **9c** as a reddish yellow solid, mp 65–67 °C. The *trans*-quinone methide **10c** was cleanly equilibrated into *trans*-phenol **12c** by stirring in ethanol at room temperature for 2 days.

cis-Quinone methide (**9c**): IR ν_{max} (film)/cm^{-1} 2932s, 2866m, 1691s, 1621s, 1560m, 1438s, 1366m, 1260m, 1091w, 1040w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02–1.39 (m, 27H), 1.39–1.51 (m, 4H), 1.57–1.61 (m, 1H), 1.78–1.91 (m, 1H), 2.13 (ddd, J=17.0, 8.0, 2.5 Hz, 1H), 2.16–2.21 (m, 1H,), 2.63 (ddd, J=17.0, 10.0, 2.0 Hz, 1H), 2.77 (s, 3H), 3.19 (dd, J=10.0, 7.0 Hz, 1H), 4.76–4.81 (m, 1H), 5.20 (d, J=10.0 Hz, 1H), 6.93 (d, J=2.5 Hz, 1H), 8.44 (d, J=2.5 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.2, 24.2, 24.9 (2C), 25.3, 25.5, 26.5, 29.2, 29.9, 30.1, 35.0, 36.4, 36.8, 45.9, 65.6, 65.8, 89.3, 106.7, 126.5, 128.7, 129.1, 141.5, 151.5, 153.4, 167.9, 182.3, 187.5, 204.7, 208.4; HRMS: Found 550.3160 $(M-H)^-$. $C_{33}H_{44}NO_6$ requires 550.3169.

trans-Quinone methide (**10c**): IR ν_{max} (film)/cm^{-1} 2935s, 2871m, 1706s, 1620s, 1563m, 1440s, 1365m, 1258m, 1091w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04–1.09 (m, 2H), 1.09–1.25 (m, 2H), 1.26–1.37 (m, 5H), 1.29 (s, 9H), 1.38 (s, 9H), 1.40–1.54 (m, 4H), 1.67–1.82 (m, 2H), 2.05 (ddd, J=15.5, 9.0, 3.0 Hz, 1H), 2.09–2.19 (m, 1H), 2.38 (ddd, J=15.5, 9.0, 3.0 Hz, 1H), 2.75 (s, 3H), 3.76 (dd, J=8.0, 5.5 Hz, 1H), 4.59 (m, 1H), 5.29 (d, J=8.0 Hz, 1H), 7.16 (d, J=2.5 Hz, 1H), 8.69 (d, J=2.5 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.4, 24.1, 24.5, 25.0, 25.3, 26.2, 26.8, 27.9, 29.5, 29.6, 31.8, 35.9, 36.1, 44.5, 63.2, 65.2, 85.2, 107.7, 126.1, 128.2, 129.1, 139.7, 151.0, 152.4, 165.4, 181.6, 186.2, 202.3, 210.4; HRMS: Found 574.3137(MNa^+). $C_{33}H_{45}NO_6Na$ requires 574.3145.

trans-Phenol (**12c**): IR ν_{max} (film)/cm^{-1} 3632m, 2950s, 2869m, 1715m, 1661s, 1610m, 1541m, 1433s, 1365m, 1237m, 1156m, 1119m, 975m; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05–1.13 (m, 1H), 1.15–1.23 (m, 2H), 1.24–1.40 (m, 10H), 1.44 (s, 18H), 1.41–1.48 (m, 1H), 1.48–1.59 (m, 1H), 1.63–1.81 (m, 1H), 1.82–1.89 (m, 1H), 2.04–2.13 (m, 1H), 2.81 (s, 3H), 4.48 (d, J=9.5 Hz, 1H), 4.86 (dt, J=9.5, 6.5 Hz, 1H), 5.36 (s, 1H), 6.98 (s, 2H), 16.03 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.5, 22.7, 23.8, 24.1, 24.9, 25.3, 29.1, 29.5, 30.1, 31.3, 34.2, 40.6, 61.7, 83.3, 107.0, 109.4, 121.5 (2C), 136.3, 144.0, 154.1, 154.3, 173.4, 203.5, 205.4; HRMS: Found 552.3351(MH^+). $C_{33}H_{46}NO_6$ requires 552.3325.

4.2.4. Oxidative cyclisation with *E*-2-cyclopentadecenone, 7d (10d and 12d). The general procedure, applied to pyridone **6** (50 mg, 0.13 mmol) using *E*-2-cyclopentadecenone **7d**, gave 20 mg (25%) phenol **12d**, as a pale yellow solid, re-crystallised from acetonitrile, mp 125–7 °C and 36 mg (45%) of quinone methide **10d**, as a reddish yellow solid, mp 88–90 °C. The quinone methide **10d** was cleanly aromatised into phenol **12d** by stirring in ethanol at room temperature for 2 days.

trans-Quinone methide (**10d**): IR ν_{max} (film)/cm^{-1} 2931s, 2861m, 1707s, 1693s, 1619s, 1563m, 1441s, 1365m, 1259m, 1091w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17–1.23 (m, 4H), 1.25–1.38 (m, 10H), 1.28 (s, 9H), 1.35 (s, 9H), 1.38–1.43 (m, 3H), 1.49–1.56 (m, 3H), 1.80–1.86 (m, 1H), 1.91–1.98 (m, 1H), 2.09 (ddd, J=16.5, 8.0, 5.5 Hz, 1H), 2.37 (dt, J=16.5, 7.5 Hz, 1H), 2.71 (s, 3H), 3.74 (dd, J=8.5, 6.5 Hz, 1H), 4.25 (ca. q, J=6.5 Hz, 1H), 5.25 (d, J=8.5 Hz, 1H), 7.08 (d, J=2.5 Hz, 1H), 8.67 (d, J=2.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.9, 23.8, 24.9, 25.3, 25.8, 26.1, 26.2, 26.7, 27.0 (2C), 27.8, 29.6, 29.7, 32.1, 36.0, 36.1, 43.9, 62.8, 66.1, 85.5, 106.8, 126.2, 129.4, 129.8, 138.8, 150.7, 152.1, 165.9, 182.4, 186.3, 201.9, 209.3; HRMS: Found 592.3657 $(M-H)^-$. $C_{36}H_{50}NO_6$ requires 592.3638.

trans-Phenol (**12d**): IR ν_{max} (film)/cm^{-1} 3635m, 2932s, 2861m, 1720m, 1659s, 1610m, 1542m, 1433s, 1416m, 1365m, 1237m, 1156m, 1119m, 975m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05–1.40 (m, 20H), 1.44 (s, 18H), 1.50–1.55 (m, 1H), 1.72–1.84 (m, 1H), 1.99–2.10 (m, 2H), 2.81 (s, 3H), 4.36 (d, J=9.5 Hz, 1H), 4.61–4.75 (m, 1H), 5.36 (s, 1H), 6.95 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.3, 23.7, 25.1, 25.3, 25.7, 25.9, 26.0, 26.5, 26.6, 26.7, 30.2, 31.3, 31.5, 34.3, 42.7, 62.3, 84.8, 109.4, 121.8, 131.1 (2C), 136.3, 144.8, 154.6 (2C), 173.6, 204.1, 205.5; HRMS: Found 592.3658 $(M-H)^-$. $C_{36}H_{50}NO_6$ requires 592.3638.

4.2.5. Oxidative cyclisation with *Z*-2-cyclononeone, 7e (9e). The general procedure, applied to pyridone **6** (50 mg, 0.13 mmol) using *Z*-2-cyclononenone **7e**, gave 2 mg (3%) phenol **11e**, as a pale yellow solid, mp 224-5 °C and 20 mg (29%) quinone methide **9e**, as a reddish yellow solid, mp 89–91 °C. *cis*-Quinone methide **9e** was equilibrated into *cis*-phenol **11e** by treating with aluminium chloride (2 equiv) in DCE at reflux for 24 h.

cis-Quinone methide (**9e**): IR ν_{max} (film)/cm^{-1} 2954s, 2871m, 1698s, 1619s, 1560m, 1438s, 1366m, 1260m, 1091w, 1043w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05–1.20 (m, 1H), 1.21–1.40 (m, 1H), 1.28 (s, 9H), 1.33 (s, 9H), 1.42–1.48 (m, 1H), 1.49–1.63 (m, 2H), 1.64–1.75 (m, 2H), 1.76–1.86 (m, 1H), 1.88–1.97 (m, 1H), 2.01–2.08 (m, 1H), 2.29 (ddd, J=14.5, 9.0, 3.0 Hz, 1H), 2.55 (ddd, J=14.5, 10.0, 2.5 Hz, 1H), 2.76 (s, 3H), 3.58 (ca. t, J=9.5 Hz, 1H), 4.45 (dt, J=9.5, 2.0 Hz, 1H), 5.51 (d, J=9.5 Hz, 1H), 7.35 (d, J=2.5 Hz, 1H), 8.35 (d, J=2.5 Hz, 1H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 21.8, 22.8, 25.1, 27.2, 28.7, 29.1, 29.9, 30.0, 36.3, 36.7, 45.8, 61.2, 63.8, 86.4, 107.1, 127.8, 129.2, 129.8, 141.8, 151.1, 153.0, 169.0, 183.3, 187.7, 204.5, 209.5; HRMS: Found 508.2723 $(M-H)^-$. $C_{30}H_{38}NO_6$ requires 508.2699.

cis-Phenol (**11e**): ν_{max} (film)/cm^{-1} 3634w, 2953s, 2874m, 1711m, 1659s, 1609m, 1539m, 1434m, 1415m, 1364w, 1278w, 1237w, 1151m, 1121m, 978w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.10 (m, 4H), 1.21–1.30 (m, 4H), 1.44 (s, 18H), 1.68–1.73 (m, 2H), 2.11–2.15 (m, 2H), 2.81 (s, 3H), 4.66 (d, J=7.5 Hz, 1H), 4.78–4.87 (m, 1H), 5.33 (s, 1H), 6.97 (brs, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 20.9, 22.0, 25.0, 29.0, 29.4, 30.2, 31.3, 34.3, 44.5, 57.9, 84.0, 107.1, 109.0, 122.1, 126.1, 136.4, 145.7, 153.9, 154.2, 173.4, 205.4, 206.1; HRMS: Found 508.2693 $(M-H)^-$. $C_{30}H_{38}NO_6$ requires 508.2699.

4.2.6. Oxidative cyclisation with *Z*-2-indenone, 7h (9h and 9h′). The general procedure, applied to pyridone **6** (100 mg, 0.27 mmol) using *Z*-2-indenone **7h**, gave 62 mg (46%) of *endo*-quinone methide **9h′**, as a reddish yellow solid, mp 145–147 °C and 19 mg (14%) of *exo*-quinone methide **9h** as a reddish yellow solid, mp 114–116 °C.

exo-Quinone methide (**9h**): IR ν_{max} (film)/cm^{-1} 2959s, 2871m, 1719s, 1689s, 1620s, 1560m, 1437s, 1366m, 1284m, 1091w, 1040w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.32 (s, 9H), 2.79 (s, 3H), 3.52 (dd, J=9.0, 7.0 Hz, 1H), 5.10 (d, J=9.0 Hz, 1H), 6.10 (d, J=7.0 Hz, 1H), 7.00 (d, J=2.5 Hz, 1H), 7.63–7.67 (m, 1H), 7.79–7.82 (m, 3H), 8.52 (d, J=2.5 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 29.3, 29.8, 30.1, 36.4, 36.6, 60.4, 62.8, 84.0, 106.7, 125.0, 127.7, 127.8, 129.4, 131.7 (2C), 135.9, 137.0, 142.9, 148.6, 151.5, 152.2, 169.0, 182.7, 187.1, 198.4, 204.7; HRMS: Found 502.2249 (MH^+). $C_{30}H_{32}NO_6$ requires 502.2230.

endo-Quinone methide (**9h′**): IR ν_{max} (film)/cm^{-1} 2959s, 2871m, 1717s, 1687s, 1619s, 1562m, 1438s, 1366m, 1258m, 1091w, 911w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.36 (s, 9H), 2.28 (s, 3H), 3.70 (dd, J=8.5, 6.0 Hz, 1H), 5.34 (d, J=8.5 Hz, 1H), 6.06 (d, J=6.0 Hz, 1H), 7.20 (d, J=2.5 Hz, 1H), 7.53 (t, J=8.0 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.79 (br.t, J=8.0 Hz, 1H), 7.95 (d, J=8.0 Hz, 1H), 8.67 (d, J=2.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.7, 29.6, 29.7, 36.0, 36.2, 57.7, 62.3, 82.5, 105.7, 122.6, 126.1, 128.3, 129.4, 130.9, 126.5, 136.9, 137.7, 141.2, 150.2, 150.8, 152.6, 164.9, 181.1, 186.6, 199.1, 203.5; HRMS: Found 502.2228 (MH^+). $C_{30}H_{32}NO_6$ requires 502.2230.

4.2.7. Oxidative cyclisation with *trans*-chalcone, 7j (10j and 12j). The general procedure, applied to pyridone **6** (50 mg, 0.13 mmol) using *trans*-chalcone **7j**, gave 16 mg (21%) of phenol **12j** as a pale yellow solid, mp 105–6 °C. and 41 mg (53%) of quinone methide **10j** as a reddish yellow solid, mp 87–8 °C. The quinone methide **10j** was cleanly aromatised into phenol **12j** by stirring in ethanol at room temperature for 2 days.

trans-Quinone methide (**10j**): IR ν_{max} (film)/cm^{-1} 2958s, 2871m, 1707s, 1659s, 1610s, 1562m, 1440s, 1365m, 1258m, 1090w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.20 (s, 9H), 2.77 (s, 3H), 4.83 (dd, J=8.5, 6.0 Hz, 1H), 5.50 (d, J=6.0 Hz, 1H), 5.71 (d, J=8.5 Hz, 1H), 7.00 (d, J=2.5 Hz, 1H), 7.24 (ca. t, J=8.0 Hz, 2H), 7.42–7.48 (m, 3H), 7.47 (br.s, 5H), 8.46 (d, J=2.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.9, 29.4, 29.5, 35.8, 35.9, 63.8, 64.1, 86.5, 107.8, 126.0, 126.7, 127.9, 128.7, 128.8, 129.0, 134.0, 129.1, 129.4, 136.98, 137.0, 139.6, 150.4, 151.7, 165.6, 181.9, 186.1, 198.7, 202.1; HRMS: Found 580.2690 (MH^+). $C_{36}H_{38}NO_6$ requires 580.2699.

trans-Phenol (**12j**): IR ν_{max} (film)/cm^{-1} 3630m, 2958s, 2869m, 1657s, 1610m, 1542m, 1433s, 1415m, 1364m, 1236m, 1155m, 1117m, 970m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 18H), 2.86 (s, 3H), 5.08 (s, 1H), 5.47 (d, J=7.5 Hz, 1H), 5.73 (d, J=7.5 Hz, 1H), 6.85 (s, 2H), 7.20–7.30 (m, 4H), 7.40 (br.s, 5H), 7.44–7.49 (m, 1H), 16.21 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 30.0, 31.4, 34.1, 60.0, 86.4, 107.4, 109.8, 121.7, 126.3, 127.0, 127.9, 128.7, 129.2, 129.9, 134.1, 134.5, 135.6, 135.9, 144.6, 153.8, 154.4, 174.1, 193.1, 205.5; HRMS: Found 580.2703 (MH^+). $C_{36}H_{38}NO_6$ requires 580.2699.

4.3. X-ray crystallographic studies

Crystals were grown as described in preparations. A single crystal was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems Cryostream unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated Mo K_α radiation, λ=0.71073 Å). Intensity data were processed using the DENZO-SMN package.

Space groups were assigned by examination of the systematic absence of the intensity data. The structures were solved using the direct-methods program SIR92, which located all non-hydrogen atoms of the organic molecules. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydroxyl hydrogen atoms of the organic molecules were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. CH hydrogen atoms were positioned geometrically after each cycle of refinement. 3-Term Chebychev polynomial weighting schemes were applied. The crystal structures are shown as thermal ellipsoid plots (ORTEP-3[25]) at 40% probability.

Crystallographic data for compounds **9a**, **11a**, **10b**, **12a**, **12b**, **12c** and **12d** have been deposited with Cambridge Crystallographic Data Centre (Deposition numbers CCDC 215236, 215237, 245742–245746, respectively). Copies of this data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam).

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Distinction between stepwise and concerted mechanisms in reductive cleavage reactions—use of voltammetric current function in the analysis of non-linear kinetic laws

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Abstract—A systematic way of distinguishing stepwise and concerted mechanisms in reductive cleavage reactions has been formulated involving current function analysis of the voltammetric data. The electrochemical reductive cleavage of the carbon–iodine bond in 1,3-dichloro-2-iodobenzene has been analyzed from a mechanistic point of view to illustrate the methodology. 1,3-Dichloro-2-iodobenzene undergoes an initial stepwise electron transfer obeying quadratic activation-driving force relationship. The current function analysis yields the reorganization energy for the reduction of 1,3-dichloro-2-iodobenzene and the results have been verified independently using convolution potential sweep voltammetry.

1. Introduction

Electron transfer to an organic molecule with a suitable leaving group (RX) is often accompanied by bond fragmentation that can take place in two possible pathways. When the leaving group is relatively stable to oxidation and/or the bond is weak, the electron transfer and bond cleavage are concerted (reaction (1)). On the other hand, when RX is capable of hosting transitorily the incoming electron, then the product is a frangible radical anion (reaction (2a)), which decomposes to neutral radical ($R^{\cdot}$) and anion (X^{-}) (reaction (2b)) in a subsequent step.

$$RX + e^{-} \rightarrow R^{\cdot} + X^{-} \quad (E^{0}_{RX/R^{\cdot}+X^{-}}) \tag{1}$$

$$RX + e^{-} \rightleftharpoons RX^{\cdot -} \quad (E^{0}_{RX/RX^{\cdot -}}) \tag{2a}$$

$$RX^{\cdot -} \rightarrow R^{\cdot} + X^{-} \tag{2b}$$

The most commonly employed experimental technique for studying heterogeneous electron transfer—bond cleavage reactions is cyclic or linear sweep voltammetry as it yields the kinetic and thermodynamic information for the electron transfer and the follow up chemical reaction.[1] If the first order fragmentation rate constant of the radical anion (reaction (2b)) is less than $10^{4}\ s^{-1}$, then the standard potential of the reaction (2a) ($E^{0}_{RX/RX^{\cdot -}}$) can be determined directly[2] from the reversible reduction of RX. However, if the fragmentation rate constant of the radical anion is very fast and/or the electron transfer itself is rate limiting, then it is seldom possible to determine $E^{0}_{RX/RX^{\cdot -}}$ from the direct voltammetry and the distinction between the stepwise and concerted mechanisms requires a detailed analysis. In our previous study,[3] a systematic way of distinguishing between the stepwise and concerted mechanistic pathways was made using cyclic voltammetry in conjunction with convolution analysis of the voltammetric data.

In this communication, we report a new method of analysis to distinguish between stepwise and concerted mechanisms. The methodology relies upon the extraction of current function from the voltammetric wave which is analyzed using the theoretical expression under the framework of stepwise and concerted mechanisms. The electrochemical reductive cleavage of carbon–iodine bond in 1,3-dichloro-2-iodobenzene at the glassy carbon electrodes is investigated as an illustrative example and the resulting conclusions have been verified independently using convolution potential sweep voltammetry.

2. Experimental

The electrochemical studies were carried out in a single

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compartment electrochemical cell (thermostatted at 298 K) using Bioanalytical Systems (BAS) 100 A Electrochemical workstation. The working electrode was a glassy carbon disc of 3 mm diameter (BAS) and was polished with the alumina slurry (BAS) prior to use. It was observed that the electrochemical pre-treatment[4] rendered the glassy carbon electrode suitable for highly reproducible and quantitative studies, whereas the analysis became poor without the electrochemical pre-treatment. Silver/silver ion (1 mM) electrode (BAS) was used as the quasi-reference electrode (which was calibrated against the ferrocene/ferrocenium couple under identical conditions of solvent and supporting electrolyte), while a platinum foil (2 cm^2) served as the counter electrode. Tetra-*n*-butyl ammonium hexafluorophosphate (Fluka) was the supporting electrolyte (0.1 M) and used as received. The solvent *N*,*N*′-dimethyl formamide (DMF) was distilled initially from anhydrous copper sulfate, then the distillate was again distilled from calcium hydride under reduced pressure and was immediately used for voltammetric studies, since, as noted during the experiment, the presence of traces of water reduces the peak height of the wave. 1,3-dichloro-2-iodobenzene was synthesized according to the literature procedure[5] and the compound was purified by crystallization for the electrochemical studies.

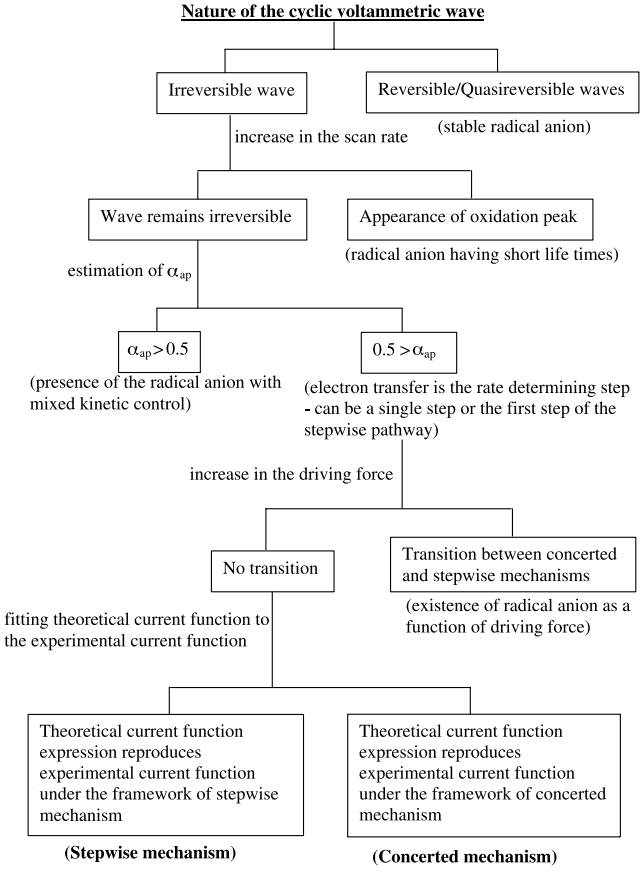
The properties of the interfacial region affect both the magnitude and shape of the current-potential curve and hence quantitative voltammetric studies are rather difficult. The charging current and the uncompensated solution resistance (R_u, which tends to shift the peak potential) have deleterious effects both on the quality and quantity of the voltammogram. The highly reversible reduction of *p*-nitrotoluene[6] was used to evaluate R_u. The cyclic voltammogram of *p*-nitrotoluene was obtained under the identical conditions of electrode, solvent and supporting electrolyte employed in the reduction of 1,3-dichloro-2-iodobenzene. Using scan rates up to 1000 Vs^{-1}, the extent of compensation was increased in BAS 100 A electrochemical workstation until the voltammogram exhibited strict reversible characteristics (the logarithmic analysis of the convolution current yielded a slope of RT/F). This extent of compensation (ca. 200 Ω) was employed in the electrochemical studies of 1,3-dichloro-2-iodobenzene. Without assuming the charging current to be a linear function of potential, the experimental charging current was evaluated from the study involving only the solvent and the supporting electrolyte. The current data so obtained were subtracted from the raw data (voltammogram with the electroactive species) so as to render the voltammogram free of charging current. The experimental and computational details of the convolution analysis of background-subtracted voltammogram have been described earlier.[7]

3. Results and discussion

The reductive cleavage of aromatic carbon–halogen bonds (C–X) are generally considered to follow a stepwise mechanism owing to relatively large bond dissociation energies of C–X bonds. Further, the aromatic molecules are capable of hosting transitorily the incoming electron in their π* orbitals leading to radical anions[8] ($RX^{\cdot -}$) (reaction (2a)) that decompose with a first order rate constant greater than $10^4\ s^{-1}$ (reaction (2b)). A large number of aromatic chlorides and bromides have been shown to follow a stepwise mechanism in electrochemical and homogeneous reductive cleavage reactions. However, an ambiguous situation prevails in the case of aromatic iodides as some of them have been demonstrated to undergo a concerted mechanism at low driving force.[9]

Using cyclic voltammetry, the distinction between stepwise and concerted pathways can be made, in which the presence of reversible/quasireversible wave would indicate the existence of radical anion. However, for most practical purposes (in the explored scan rate domain), this is limited to radical anions with a lifetime greater than 10^{-4} s. In such cases, the value of electrochemical transfer coefficient (α) may allow distinction between the two mechanisms. In general, because of the large activation overpotential suffered by the concerted pathway, the peak potential (E_p) occurs at more negative potentials than the standard potential ($E^0_{RX/R^{\cdot}+X^-}$) and hence α assumes values significantly lower than 0.5. On the other hand, in the case of a stepwise mechanism which undergoes an initial electron transfer, a value of α larger than 0.5 can be anticipated. However, this is not always the case, since, even in the stepwise pathway, the electron transfer rate (reaction (2a)) can be slower than the cleavage rate of the radical anion (reaction (2b)) resulting in an α value lower than 0.5.[10]

Under this circumstance, a change in driving force of the



Scheme 1. Diagnostic criteria for the distinction between stepwise and concerted mechanisms of electrochemical reductive cleavage reactions.

reaction may allow one to observe a transition between the stepwise and concerted mechanistic pathways.[11] The experimental control variables for changing the reaction driving force are scan rate and temperature.[9] In the cases of iodobenzene and 3-methyl-iodobenzene an increase in temperature and/or a decrease in scan rate results in a transition from a stepwise to a concerted pathway. In contrast, 1-iodonapthalene undergoes a stepwise reductive cleavage whatever be the driving force of the reaction.[9] In an ambiguous condition wherein the transfer coefficient is less than 0.5 (which may correspond either to a stepwise pathway with the initial electron transfer as the rate determining step or a concerted mechanism) and no transition between the mechanisms, distinction between the two pathways is rather difficult. Comparison of the experimental standard potential (obtained either from the convolution analysis of the voltammetric data,[7,10] or using standard potentials of the model compounds[12]) with the theoretical predictions for stepwise and concerted mechanisms can help to discriminate the two mechanistic pathways. Equivalently, in our previous study,[3] comparison of the experimental reorganization energy (estimated from the convolution analysis of the voltammetric data) with the theoretical predictions for stepwise and concerted mechanisms led to an unambiguous distinction between the two mechanistic possibilities in the electrochemical reductive cleavage of carbon–iodine bond in 5-bromo-1,3-dichloro-2-iodobenzene. The current function analysis of the voltammetric data under the theoretical framework of stepwise and concerted mechanisms can offer an alternate and more straightforward way of distinguishing the two mechanisms in an unambiguous manner. Scheme 1 illustrates the diagnostic criteria for the distinction between stepwise and concerted mechanisms of electrochemical reductive cleavage reactions.

3.1. Mechanistic diagnosis in 1,3-dichloro-2-iodobenzene

Figure 1 shows the cyclic voltammogram pertaining to the reduction of 1,3-dichloro-2-iodobenzene at the glassy carbon electrode in DMF containing 0.1 M nBu$_4$NPF$_6$ as the supporting electrolyte. The cathodic waves a, b and c represent, respectively, the reduction of carbon–iodine (C–I) and two carbon–chlorine bonds. The voltammogram B shows the reduction waves of 1,3-dichlorobenzene which corresponds to the peaks b and c of voltammogram A. The neutral radical ($R^{\cdot}$) formed during the reduction of the carbon–halogen bond is easier to reduce than the parent polyhalobenzene and immediately undergoes a second electron transfer to form R^-, however, the characteristic features of the wave are solely governed by the kinetics of the first electron transfer. R^- abstracts a proton either from the solvent or the supporting electrolyte to give the hydrocarbon RH and it was observed that several halobenzenes and other aromatic halides upon electrolysis yielded 100% of RH.[13] A recent investigation, involving in situ electrochemical NMR spectroscopy, has revealed that the aryl anion abstracts a proton preferably from the solvent rather than the supporting electrolyte.[14] The hydrocarbon RH is susceptible to reduction, in fact, a second wave is observed[13] in some cases before the background discharge. However, in most cases the reduction wave of RH is suppressed by the background discharge current of the supporting electrolyte. Therefore, the reduction waves a, b and c represent the hydrogenolyses of respective carbon–halogen bonds resulting in the formation of benzene at the end of the wave c and hence an overall consumption of six electrons in a single voltammetric cycle. The π^* level of 1,3-dichloro-2-iodobenzene being comparatively lower than the monosubstituted benzene is indicated by the fact that the

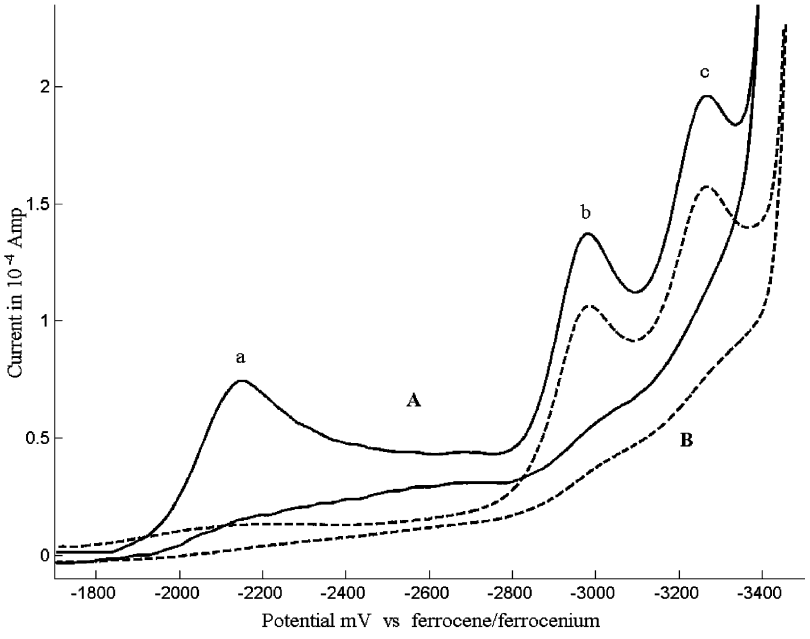


Figure 1. Cyclic voltammograms of (A) 1,3-dichloro-2-iodobenzene and (B) 1,3 dichlorobenzene in DMF/0.1 M nBu$_4$NPF$_6$ at glassy carbon electrode. Scan rate: 200 mV s^{-1}; Temperature: 298 K.

reduction potential of C–I bond (wave a) is ca. 248 mV more positive than that of iodobenzene.

The peak current of the reduction of C–I bond (wave a) is proportional to the square root of the scan rate indicating the diffusional nature of the electrode reaction and the wave remains irreversible even at a scan rate of 2000 V s^{-1}, hence the lifetime of the radical anion, if formed during the reductive cleavage, should be less than 10^{-4} s. The next step in the mechanistic diagnosis (Scheme 1) involves the estimation of apparent transfer coefficient (α_{ap}). From the variation of peak potential (E_p) with scan rate (υ), α_{ap} was determined as 0.301 (Eq. (3)).

$$\alpha_{ap} = \frac{-RT/2F}{\partial E_p/\partial \ln \upsilon} \tag{3}$$

The voltammetric wave of the reduction of C–I bond is relatively broad (Fig. 1) indicating slow electron transfer and the value of α_{ap} points to concerted dissociative reduction (reaction (1)). Further, there was a monotonous change in the α_{ap} with increase in the scan rate at various temperatures (−10 to 50 °C), hence there is no transition between the mechanistic pathways. At this instance, it is worth noting two prevailing contradictory situations, viz. (i) the π* level of the ring in 1,3-dichloro-2-iodobenzene being lower than the monosubstituted halobenzene, accommodating an incoming electron should be facile leading to an enhanced stabilization of the radical anion and (ii) on the other hand, the value of α_{ap} points to a concerted pathway. Under this ambiguous condition, the voltammetric data for the reduction of C–I bond was subjected to current function analysis so as to distinguish between the two possible pathways.

3.2. Current function analysis

Current function may be interpreted as the dimensionless part of the voltammetric wave containing all the mechanistic and thermodynamic information of the electrode reaction.[15] In the case of irreversible electron transfer reactions, current function (χ_{irrev}) is related to the voltammetric current (i) as Eq. (4)

$$i = n\mathrm{FAC_b}\sqrt{\frac{\pi\alpha nF\upsilon D}{RT}}\chi_{irrev} \tag{4}$$

where C_b denotes bulk concentration of the electroactive species and the other symbols have the usual electrochemical significance. We reported a simple analytical expression, a [2/2] Pade' approximant, for the current function,[15] viz. Eq. (5)

$$\chi_{irrev} = \frac{1.7807\theta + 0.3361\theta^2}{1.0000 + 2.0492\theta + 1.2705\theta^2} \tag{5}$$

For the reactions obeying non-linear (quadratic) activation-driving force relationship, θ in the above equation is defined as Eq. (6)[16]

$$\theta = \exp\left(-\frac{F(E-E_p)}{RT}\left[0.5 + \frac{F}{2\lambda}(E - E_p + \eta_{act})\right]\right) \tag{6}$$

where η_{act} represents activation overpotential. η_{act} for the concerted pathway is given as Eq. (7)

$$\eta_{act} = E_p - E^0_{RX/R^{\cdot}+X^-} \tag{7}$$

and for the stepwise mechanism η_{act} is given as Eq. (8)

$$\eta_{act} = E_p - E^0_{RX/RX^{\cdot-}} \tag{8}$$

λ in the Eq. (6) denotes reorganization energy which is contributed by two independent terms, viz. for the concerted pathway λ is given as Eq. (9)

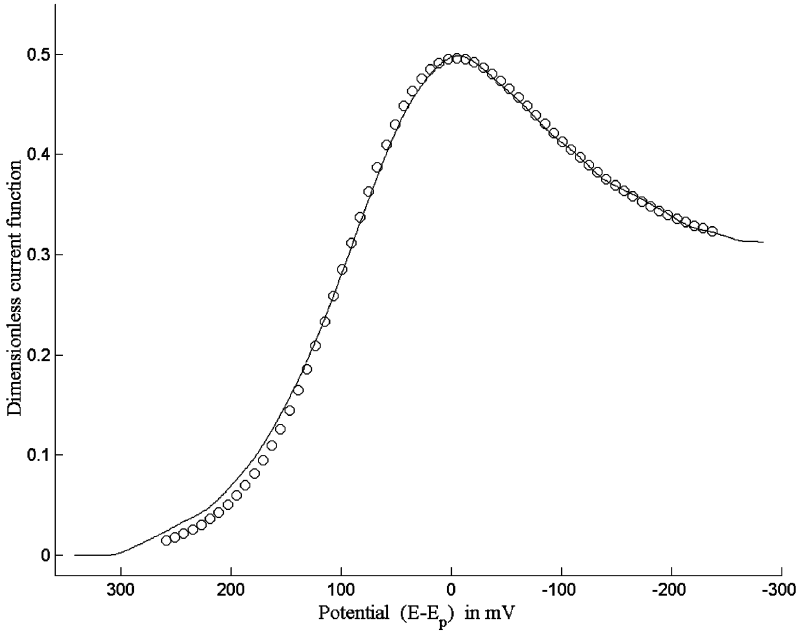


Figure 2. Comparison between the experimental and theoretical current functions. The potential axis is referenced with respect to the peak potential (E_p). The solid line represents the experimental current function pertaining to the reduction of carbon–iodine bond in 1,3-dichloro-2-iodobenzene. Circles denote the expression (5) and (6) in which η_{act} and λ are −235 mV and 0.526 eV, respectively.

$$\lambda = D_{C-I} + \lambda_s \quad (9)$$

and in the case of stepwise pathway λ is given as Eq. (10)

$$\lambda = \lambda_s + \lambda_i \quad (10)$$

D_{C-I} is the bond dissociation energy of the cleaving bond, viz. carbon–iodine bond. λ_s and λ_i represent, respectively, the solvent and inner reorganization energies.[17] In the current function analysis, the potential axis of the voltammogram is referenced with respect to the peak potential,[16] viz. $E-E_p$ in the Eq. (6).

In the current function expression (Eq. (5)) reductive cleavage reactions are characterized by Eqs. (7) and (9) for the concerted pathway and Eqs. (8) and (10) for the stepwise pathway. Because of the large activation overpotential exhibited by the concerted dissociative electron transfer, the potentials at which the voltammetric peak appear are more negative, viz. about one volt more negative than the standard potential[10] ($E^0_{RX/R^{\cdot}+X^-}$) and the expected range of values for η_{act} in the present study is -1.5 to -0.5 V. Further, since D_{C-I} has a value of 2.835 eV,[18] the expected value of λ in the case of concerted mechanism should be greater than 2.835 eV (cf. Eq. (9)). In contrast, the effect of successive bond cleavage in the stepwise mechanism is to make the peak appear close to (or more positive than) the standard potential[10] ($E^0_{RX/RX^{\cdot-}}$) and hence the value of η_{act} can be between -1.0 and 0.5 V. In view of the meagre contribution to λ, λ_i can be neglected in the case of stepwise mechanism,[19] hence, λ_s for the stepwise reduction of C–I bond can be expected to have a value between 0.1 and 1 eV. Based on our above knowledge on reorganization energy and activation overpotential for stepwise and concerted mechanisms, the experimental current function can be simulated using Eqs. (5) and (6). A best fit to the experimental current function was obtained using Matlab under the framework of stepwise mechanism (Fig. 2) employing the values -235 mV and 0.526 eV for η_{act} and λ, respectively, while the experimental current function could not be reproduced under the purview of concerted mechanism. The above analysis points to the operation of a stepwise mechanism in the reductive cleavage of C–I bond in 1,3-dichloro-2-iodobenzene and excludes the possibility of a concerted pathway. Furthermore, the values of η_{act} (-235 mV) and λ (0.526 eV) imply that $E^0_{RX/RX^{\cdot-}}$ for the reduction of C–I bond should be -1916 mV versus ferrocene/ferrocenium couple (cf. Eq. (8); $E_p = -2151$ mV) and λ_s should be ca. 0.526 eV (neglecting the contribution of λ_i to λ; cf. Eq. (10)).

3.3. Convolution analysis

Convolution potential sweep voltammetry was invoked in order to verify the results of current function analysis wherein the voltammetric current (i) was converted to convolution current (I) using the convolution integral[20] given as

$$I = \frac{1}{\sqrt{\pi}} \int_0^t \frac{i(u)}{(t-u)^{1/2}} \mathrm{d}u \quad (11)$$

The plot between the convolution current and the electrode potential (E) is sigmoidal in shape reaching a plateau when the applied potential is sufficiently negative. Figure 3 shows the convolution potential sweep voltammogram of the reduction of 1,3-dichloro-2-iodobenzene at a scan rate of 200 mV s^{-1}. The logarithmic analysis of the convolution current in conjunction with the voltammetric current yields the heterogeneous electron transfer rate constant ($\ln k_{ET}$),[20] viz.

$$\ln k_{ET} = \ln D^{1/2} - \ln \frac{I_L - I(t)}{i(t)} \quad (12)$$

where D is the diffusion coefficient of the electroactive species which can be obtained from the limiting convolution

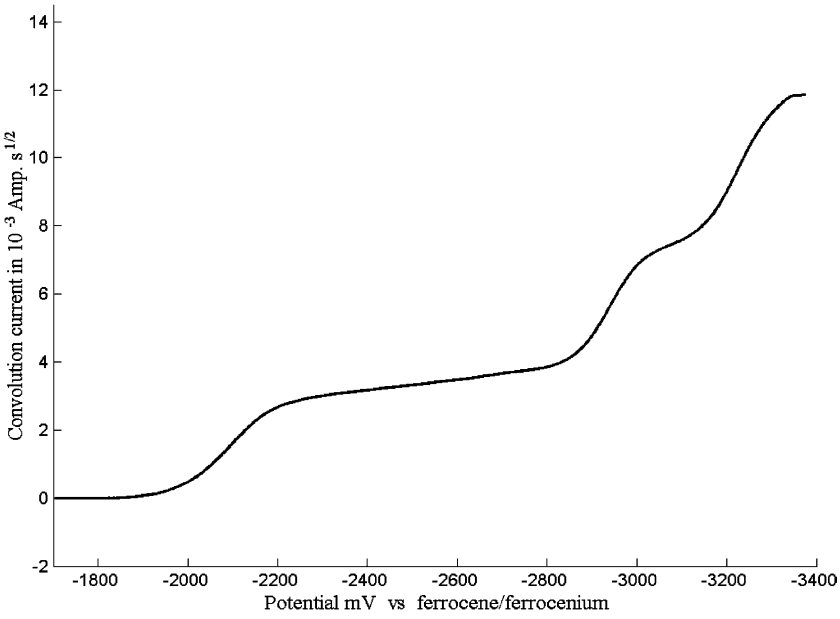


Figure 3. Convolution potential sweep voltammogram of 1,3-dichloro-2-iodobenzene in DMF containing 0.1 M nBu$_4$NPF$_6$ at glassy carbon electrode. Scan rate: 200 mV s^{-1}; temperature: 298 K.

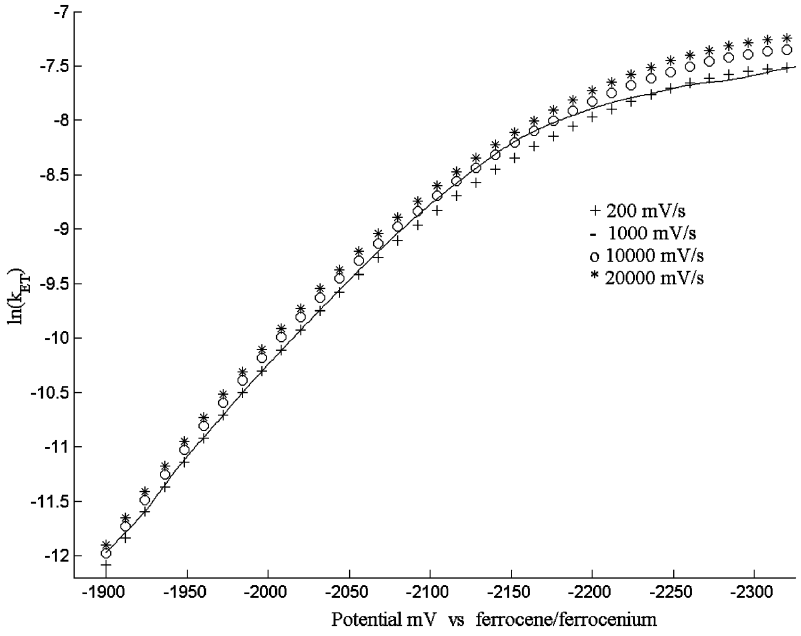


Figure 4. Potential dependence of logarithmic electron transfer rate constant (ln k_{ET}) for the reduction of carbon–iodine bond in 1,3-dichloro-2-iodobenzene at various scan rates.

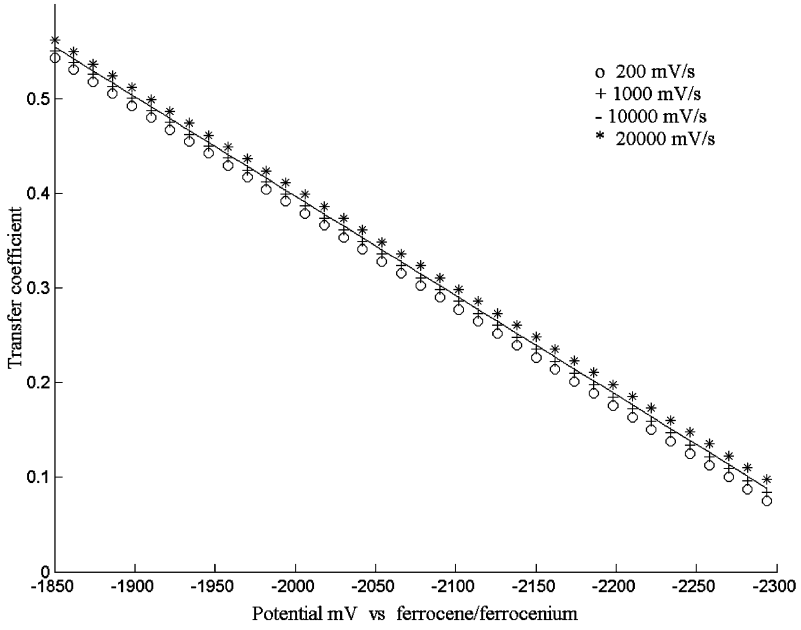


Figure 5. The dependence of the transfer coefficient on electrode potential at various scan rates for the reduction of carbon–iodine bond in 1,3-dichloro-2-iodobenzene.

current, I_L given as

$$I_L = nFAD^{1/2}C_b \tag{13}$$

where C_b denotes the bulk concentration of the electroactive species and A, the surface area of the electrode. I_L was found to vary linearly with the bulk concentration.

Figure 4 depicts the variation of ln k_{ET} with E at various scan rates for the reduction of C–I bond in 1,3-dichloro-2-iodobenzene. The variation is parabolic, obeying the quadratic activation (ΔG^{*})-driving force (ΔG^0) relationship,[21] viz.

$$\Delta G^* = \frac{(\Delta G^0)^2}{16\Delta G_0^*} + \frac{\Delta G^0}{2} + \Delta G_0^* \tag{14}$$

ΔG_0^* in the above equation denotes the intrinsic barrier of the reaction which equals $\lambda/4$. The above relation, neglecting the double layer effects,[22] implies a linear variation of transfer coefficient α with the electrode potential

$$\alpha = \frac{\partial \Delta G^*}{\partial \Delta G^0} = 0.5 + \frac{F(E - E^0)}{2\lambda} \tag{15}$$

From the plot between $\ln k_{ET}$ versus E (Fig. 4), the experimental α can be estimated using the relationship

$$\alpha = -\frac{RT}{F}\frac{\mathrm{d}\ln k_{ET}}{\mathrm{d}E} \quad (16)$$

Since the variation of $\ln k_{ET}$ with E is parabolic, α varies linearly with E thus conforming to Eq. (15) as shown in Figure 5. As inferred from the Eq. (15), most theoretical models for outer sphere or dissociative electron transfer predict that α should be 0.5 at zero driving force[23] ($\Delta G^0 = F(E-E^0)=0$). From the linear α versus E plot (Fig. 5), the experimental standard potential of the reduction of C–I bond can be estimated as the potential at which α becomes 0.5[10] and the value being -1903 mV versus the ferrocene/ferrocenium couple. The slope of α versus E plot yields λ (cf. Eq. (15)) as 0.476 eV. The results of the convolution analysis, viz. E^0 and λ, are according to the predictions of the stepwise mechanism, further, the values are close to that obtained from the current function analysis of the voltammetric wave (the standard potential and the reorganization energy obtained from the current function analysis are 13 mV and 0.05 eV higher than those obtained from the convolution analysis, respectively, however, the double layer effects have not been corrected in both the analyses). Both the current function and convolution analyses point to the stepwise reduction of C–I bond in 1,3-dichloro-2-iodobenzene. The above verification, therefore, confirms the application of the current function method of analysis in delineating between the stepwise and concerted mechanisms in reductive cleavage reactions.

4. Summary

The mechanistic aspects of the reaction where single electron transfer results in the cleavage of a chemical bond form an important issue in the general understanding of chemical reactivity. In this regard, the dichotomy of stepwise and concerted electrochemical reductive cleavage reactions can be analyzed based on the current function of the voltammetric wave. The carbon–iodine bond in 1,3-dichloro-2-iodobenzene undergoes a slow electron transfer leading to an ambiguous condition wherein the electron transfer may correspond either to the dissociative electron transfer of the concerted mechanism or the initial electron transfer of the stepwise mechanism. A best fit of the theoretical current function expression to the experimental current function was obtained under the framework of a stepwise mechanism. The results of the current function analysis were verified independently using convolution potential sweep voltammetry.

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Reaction of 3/2-formylindoles with TOSMIC: formation of indolyloxazoles and stable indolyl primary enamines

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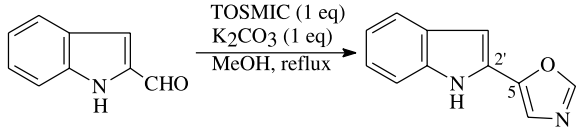
Abstract—3-Formylindole and its 1-substituted and 1,5-disubstituted derivatives react with TOSMIC in presence of potassium carbonate in methanol under reflux to furnish 5-(3′-indolyl)oxazoles, new stable *E*-2-(3′-indolyl)-2-tosylethenamines and two diastereomers of *N*-[2-(3′-indolyl)-1,2-dimethoxy]ethylformamides. In contrast, 2-formylskatole furnishes *N*-(1-tosyl-2-skatolyl)ethenylformamide.

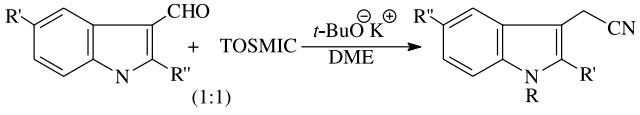
1. Introduction

1,3-Azoles are important heterocycles,[1a–c] of which only oxazoles do not participate in normal biochemical processes. Yet, bioactive secondary metabolites containing the oxazole ring are known, specially from marine organisms.[2] Our continued interest in the synthesis[3] and reactions[4] of condensed nitrogen heterocycles drew our attention to a small group of several 2-alkyl-5-(3′-indolyl)oxazoles of microbial origin. These are pimprinine[5a,b] or WS-30581c,[5c,d] pimprinethine,[5c,6] pimprinaphine,[5c] WS-30581a and b[5d] and labradorins 1 and 2,[7] which display a broad spectrum of biological activities including anticancer properties.[7–9] Some of these metabolites have already been synthesised by three different routes, viz. the cyclisation of 3-acylaminoacetylindoles,[5b,c,10] the oxidative cyclisation of *N*-acetyl/benzoyltryptamine[11a,b] and the cycloaddition of appropriate in situ-derived rhodium carbenoids, with nitriles.[12] A number of analogues have also been synthesised by the base-catalysed reaction of 3-formylindoles with *N*-tosylmethylimino synthons[13] and also by a tandem aza-Wittig/heterocumulene-mediated annulation involving iminophosphoranes.[14] However, all these methods were multi-step syntheses and the overall yields of the indolyloxazoles were as low as 10% in quite a few cases. This motivated us to try to develop an efficient, one-step synthesis of 5-(3′-indolyl)oxazoles. Towards this end, we intended to employ van Leusen's oxazole synthesis,[15a–c] which involves the base-catalysed reaction of tosylmethylisocyanide (TOSMIC) with aldehydes. This method was later applied to several heteroaryl[16a] and azole carbaldehydes,[16b] mostly leading to the corresponding 5-heteroaryl and 5-azolyloxazoles, including 5-(2′-indolyl)-oxazole from 2-formylindole (Scheme 1), which is of relevance to our objective.



Scheme 1.

In this backdrop, our modified objective was to extend this protocol to 3-formylindoles. Such an attempt also appeared to have been undertaken,[17] in which potassium *tert*-butoxide in 1,2-dimethoxyethane (DME) was used as the base. Surprisingly, indole-3-acetonitriles were formed instead of the expected indolyloxazoles (Scheme 2).



R=H, Me, Bn; R'=H, OMe

Scheme 2.

In our view, the use of the strong base, potassium *tert*-butoxide, was responsible for this unexpected outcome, and the use of a milder base, viz. potassium carbonate would

Keywords: 3-Formylindoles; TOSMIC; Base; Indolyloxazoles; Indolyl primary enamines.
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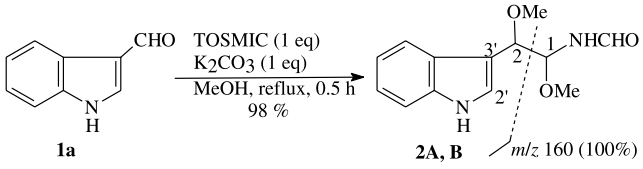
have led these reactions to the desired course. Accordingly, we carried out the reaction of a number of 3-formylindoles with TOSMIC using potassium carbonate in refluxing methanol. As a result, although the target molecules were formed in certain cases, several new structurally interesting and mechanistically significant products, including one type of stable indolyl primary enamines, were formed. The identification of these products, the possible mechanism of their formation, their synthetic potential and the significance of some of their spectral data are presented in this paper.

2. Results and discussion

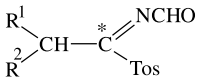
When 3-formylindole (**1a**) was allowed to react with 1 equiv of TOSMIC in the presence of potassium carbonate in methanol under reflux, two products were formed in nearly quantitative overall yield. Each of these products were analysed for $C_{13}H_{16}N_2O_3$, corroborated by mass spectral data (M^+ 248), and showed (^{1}H NMR spectroscopy) the presence of one 3-indolyl moiety, two methoxy groups, one formamido group and two separate aliphatic methine protons—one (δ 4.67–4.80) as a doublet (J=2.5–4 Hz) and the other (δ 4.62–5.52) as a doublet of doublet (J=2.5–4, ~10 Hz). All these data could only be accommodated in the gross structure of *N*-[2-(3′-indolyl)-1,2-dimethoxy]-ethylformamide (**2**), the two products being the diastereomers **2A** and **2B** (Scheme 3). Each of **2A** and **2B** recorded in its EI-MS the base peak at *m/z* 160, formed by cleavage of the *N*-(methoxymethyl)formamide moiety, thus lending additional support to the gross structures of **2A** and **2B**.



Scheme 3.

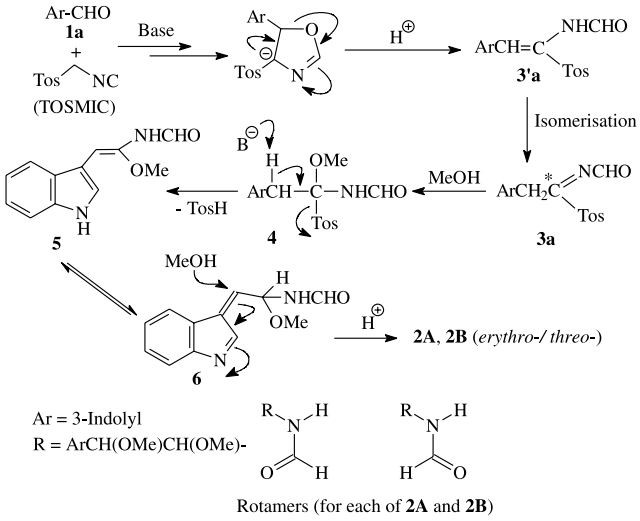
The mechanism of formation of these two products was somewhat intriguing and their NMR spectral behaviour was indeed revealing. As regards the latter, each diastereoisomer recorded two sets of signals with 2:1 ratio. It suggested the presence of each diastereoisomer as an equilibrium mixture (2:1) of two rotamers, resulting from the restricted rotation around the *N*-formyl group. Further, in each of the two diastereoisomers, the ^{1}H NMR signal for the aldehydic proton of the formamido group appeared as a singlet in the major rotamer and as a doublet (J=11.7/11.9 Hz) in the minor rotamer. Clearly, this observation was a reflection of the dihedral angle between the NH and the CHO protons, which must be 90° in the major rotamer and nearly 180° in the minor rotamer.

As to the formation of **2A** and **2B**, the intermediacy of **3a** (cf. a similar species **3b**, postulated as an intermediate in the van Leusen's base-catalysed one-step synthesis of nitriles from ketones and TOSMIC)[18] must be assumed.



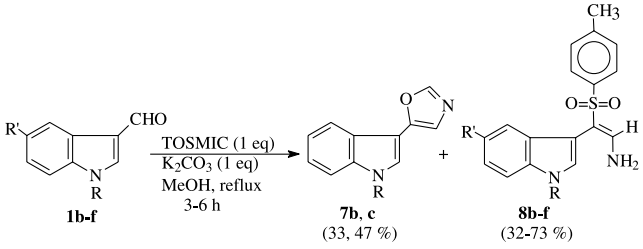
3a : R^1=H; R^2=3-Indolyl
3b : R^1, R^2=Alkyl

This intermediate possesses a carbon center, marked with asterisk, that might well be more electrophilic than the carbonyl carbon.[19] Consequently, a nucleophilic attack at this center by methanol, followed by a base-induced β-elimination of *p*-toluenesulphinic acid from the resulting molecule (**4**), may lead to the formation of the formamido olefin **5**. Thereafter, a Michael-type addition of weakly nucleophilic methanol to the benzylic carbon of the indolenine tautomer (**6**) of **5**, followed by protonation, may result in the formation of the diastereoisomers, **2A** and **2B** (*erythro*- and *threo*-), as shown in Scheme 4.



Scheme 4.

Since the outcome of the reaction with 3-formylindole (**1a**) was different from that with 2-formylindole,[16b] the present protocol was extended to the 3-formyl derivatives of *N*-methyl, *N*-ethyl, 5-methoxy-*N*-methyl, 5-methoxy-*N*-ethyl and 5-methoxy-*N*-isopropylindoles (**1b–f**, respectively). Different results were obtained from **1b** and **1c** on one hand and from **1d–f** on the other hand. Thus, each of **1b** and **1c** furnished two products, viz. **7b** and **8b** from **1b**, and **7c** and **8c** from **1c** in 79% and 75% overall yields, respectively. In contrast, each of **1d–f** furnished only one type of products, **8d–f** in (62–73)% yields (Scheme 5, Table 1).



Scheme 5.

Table 1. Reaction of 3-formylindoles (**1b–f**; 1 mmol) with TOSMIC (1.1 mmol) in presence of potassium carbonate (1.1 mmol) in methanol under reflux

3-Formylindoles (**1**)			Time (h)	Yield[a] (%)		
SM	R	R′		**7**	**8**	Overall
1b	Me	H	6	47	32	79
1c	Et	H	4	33	42	75
1d	Me	OMe	4	—	62	62
1e	Et	OMe	3	—	68	68
1f	^{i}Pr	OMe	3	—	73	73

[a] Refers to isolated pure products.

The less polar products from **1b** and **1c**, that is **7b** and **7c** were identified as the expected 5-(1′-methyl/ethyl-3′-indolyl)oxazoles from their diagnostic ^{1}H (H-2: ∼δ 7.87, s; H-4: δ 7.38/7.46, s; H-2′: δ 7.24, s) and ^{13}C (CH-2: δ 149.1; CH-4: ∼δ 123.0; C-5: δ 148.4) NMR spectral data, typical of 5-substituted oxazolyl moieties, in addition to those expected for the *N*-alkyl-3-indolyl moieties (see Section 4).

The more polar products from **1b** and **1c**, that is **8b** and **8c** and the only products from **1d–1f**, that is **8d–f** recorded similar NMR spectral data. Thus, each of these products showed the presence of a β,β-disubstituted primary enamine moiety (>C=C*H*–NH_2: δ 7.77/7.78, 1H, t, J=10/10.5 Hz and δ 4.31–4.34, 2H, d, J=10/10.5 Hz, D_2O-exchangeable; CH_α: δ 142.6/142.9; C_β: ∼δ 105), a tosyl group (MS: base peaks at M^+-155 m.u.) and a 2-unsubstituted (H-2: δ 7.09–7.23, 1H, s; *C*H-2: δ 129.7–131.4) 3-indolyl residue (see Section 4). The products **8b–f** thus turned out to be the novel stable 2-[3′-(substituted) indolyl]-2-tosylethenamines.

The formation of these primary enamines could not be explained by any straightforward mechanism. Although primary enamines were first implicated as reactive intermediates as early as 1914,[20] the first stable primary enamine was prepared nearly half a century later.[21a,b] Therefore, before discussing the stability of **8b–f** in the light of the available information on primary enamines and their equilibrium with tautomeric imines, most of which is due to the pioneering work of Albrecht et al.,[22a–c] it became all the more desirable to settle the structures of **8b–f** beyond doubt. This was accomplished by analysing the HMQC and HMBC spectra of **8b** (as a representative compound), which established the structure assigned to it. The observed HMBC correlations of **8b** are shown in Figure 1.

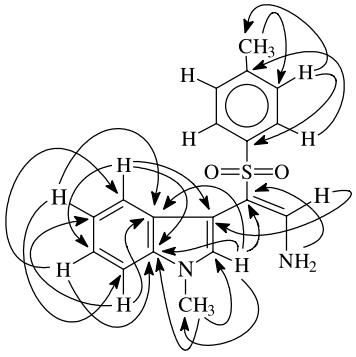


Figure 1. HMBC correlations of **8b**.

Since all the critical ^{1}H and ^{13}C NMR spectroscopic data of **8c–f** paralleled those of **8b** (see Section 4), the correctness of the structures assigned to the former group of compounds was thus established as well.

Two aspects of **8b–f** now needed to be considered—their stability and their mechanism of formation. As regards the former, Albrecht's studies revealed that, inter alia, both an electron-withdrawing group (e.g., tosyl group in **8b–f**) and a π-conjugating hydrocarbyl group (e.g., indolyl moiety in **8b–f**) at the β-carbon of a primary enamine stabilise the enamine structure in preference to its aldimine tautomer. The stability of **8b–f** is thus accounted for. Nevertheless, the structure of **8d**, again as a representative, was finally confirmed by single crystal X-ray crystallographic analysis.[23] The ORTEP diagram of **8d** is shown in Figure 2.

Although the X-ray crystallographic analysis of a few 1,6-diaryl-1,3,5-trienyl-1,6-diamines has previously been documented,[24a–c] this is, to the best of our knowledge, the first X-ray crystallographic analysis of an indolylethenamine. Also, the formation of **8b–f** constitutes the first report of indolylethenamines, although a number of indolic[25] and bisindolic[26] enamides have previously been reported as natural products.

As to the mechanism of the formation of **8b–f**, the *N*-(2-aryl-1-tosylethenyl)formamides (**A**; cf. **3′a** in Scheme 4) are likely to be the crucial intermediates. Compounds of type **A** were also independently suggested by Schöllkopf et al.[27a,b] as intermediates in the formation of carboxylic acids via nitriles from the reaction of aldehydes and ketones with TOSMIC. The lone pair of electrons on the indolic nitrogen of **A** then triggers the protonation (from methanol) of the enamidic double bond, resulting in the indoleninium species **9**. Subsequently, a 1,2-shift of the tosyl group with simultaneous neutralisation of the indoleninium cation, followed by the loss of a proton, gives rise to the intermidiate **10**. Finally, a nucleophilic attack by methanol to the *N*-formyl carbon of **10**, followed by the loss of a molecule of methyl formate and subsequent protonation, gives rise to the enamines **8b–f** (Scheme 6).

The formation of the indoleninium species **9** through the participation of the indole ring seems to be crucial to the formation of the enamines. This explains why increasing electron density at the indolic C-3 either by the presence of an alkyl group at indolic *N*(1) or by the additional presence of an electron-donating methoxyl at C-5 of the indole ring gives rise to the enamines **8b–f** in increasing yields in going from **1b** to **1f** (see Table 1). Indeed, the three

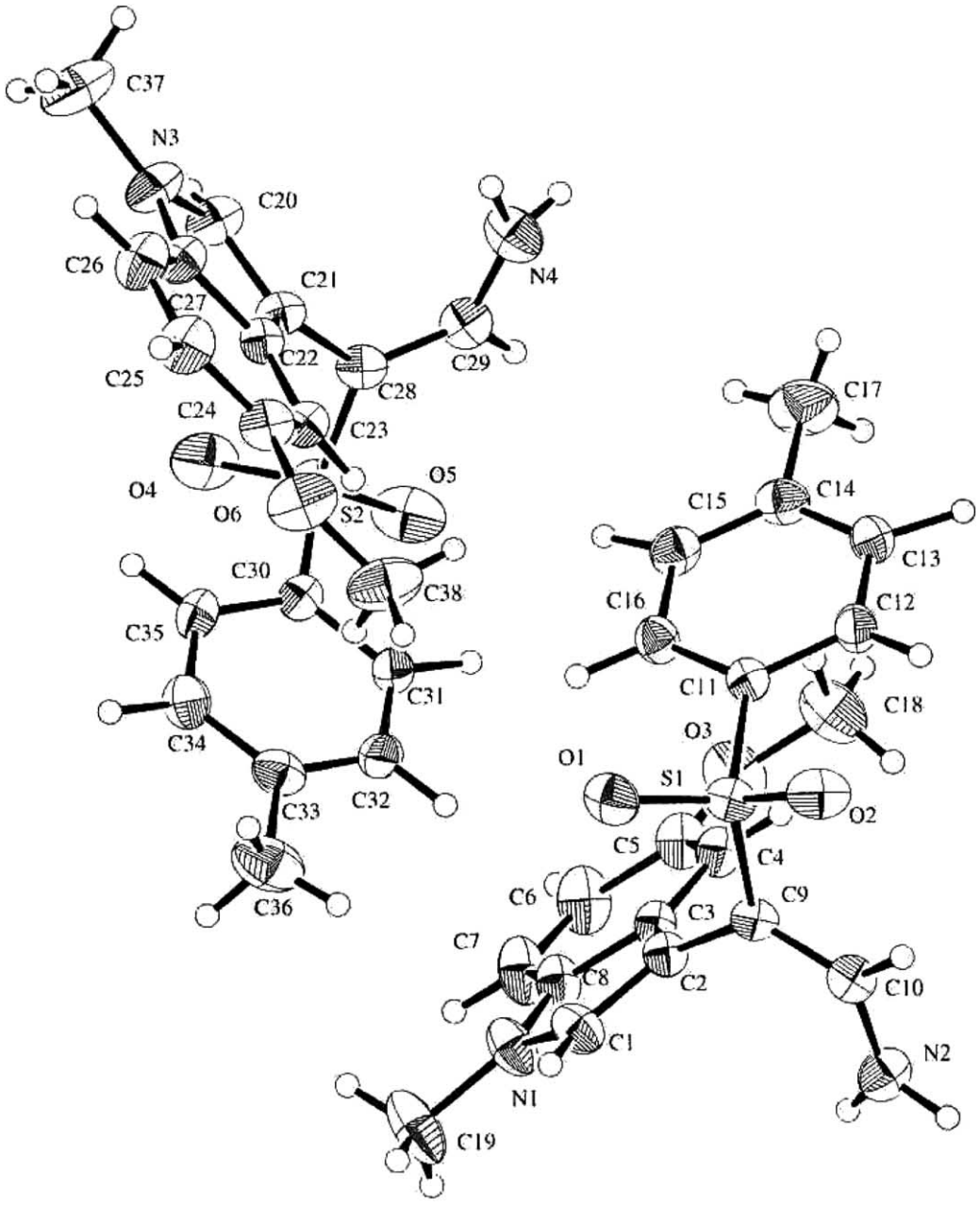
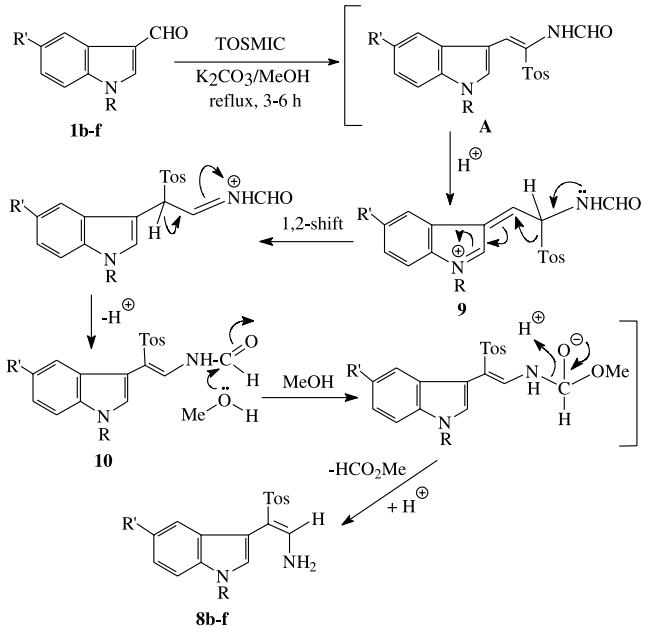


Figure 2. ORTEP diagram of **8d**.

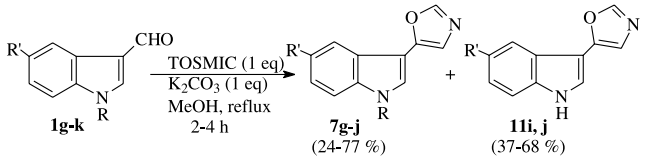
5-methoxyindoles **1d–f** furnished the enamines (**8d–f**) as the only products.

With *N*-benzyl-3-formylindole (**1g**) and 5-bromo-*N*-methyl-3-formylindole (**1h**), only the respective 5-(3′-indolyl)-oxazoles (**7g**,**h**) were formed. But with *N*-tosyl-3-formyl-indole (**1i**) and its 5-methoxy derivative (**1j**), the respective 5-(3′-indolyl)oxazoles (**7i**,**j**) along with their *N*-deprotected analogues (**11i**,**j**) were formed in excellent overall yields. In the case of these two substrates (**1i**,**j**), that the formation of the indolyloxazoles and their *N*-deprotection were taking place simultaneously was evident from a comparison of the relative yields of **7i** and **11i** with those of **7j** and **11j** as against the respective time periods for the completion of the reactions. Thus, the reaction with **1i**, which was complete in 2 h, furnished **7i** and **11i** in nearly 7:5 relative yields. Whereas, the reaction with **1j**, which took twice the time for completion, provided **7j** and **11j** in ca. 5:14 relative yields. When *N*-boc-3-formylindole (**1k**) was used as the substrate, the deprotected indolyloxazole (**11i**) was the only product. Strangely, when *N*-ethoxycarbonyl-3-formylindole (**1l**) was treated with TOSMIC under similar conditions, a mixture of **2A** and **2B** in nearly quantitative yield was obtained as the only products. This observation along with the lack of formation of similar products from **1i–k** pointed out that the cyclisation preceded *N*-deprotection in the case of reactions with **1i–k**, whereas *N*-deprotection preceded subsequent reaction with TOSMIC in the case of reaction with **1l**. The reactions with **1g–k** are shown in Scheme 7 and the results (including that from **1l**) in Table 2.

In this connection, the contrasting behaviour of

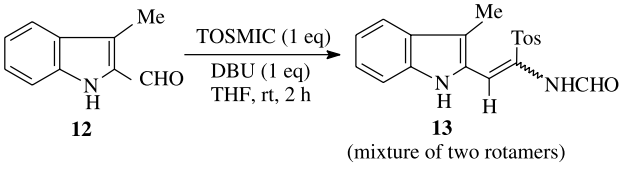


Scheme 6.



Scheme 7.

2-formylindole and 2-formylimidazole towards their base-induced reaction with TOSMIC, referred to earlier, drew our attention. While the former, using potassium carbonate in methanol as the base, furnished 5-(2′-indolyl)oxazole,[16b] the latter, using 1,3-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) as the base, afforded 3-tosyl-imidazo[1,2-*c*]pyrimidine, albeit in low yield (14%). These workers similarly tried to convert 2-formylindole to indolopyrimidine by treatment with TOSMIC using DBU in THF, but only a tarry mass was reported to have been formed.[16b] We felt that this objective could be accomplished by blocking C-3 of 2-formylindole and carrying out the reaction using DBU in THF. Accordingly, 2-formylskatole (**12**) was treated with equimolar amounts of TOSMIC and DBU in THF at room temperature. The reaction was complete in 2 h, but it furnished, contrary to expectation, the *N*-(indolylethenyl)formamide **13** (62%) (Scheme 8), identified spectroscopically.



Scheme 8.

Like **2A** and **2B**, **13** also showed two sets of ^{1}H and ^{13}C NMR signals, thereby demonstrating the presence of two rotamers in nearly 3:2 ratio.

3. Conclusions

The present work demonstrates the versatility of TOSMIC in bringing about a wide variety of unpredictable reactions particularly with indole-3-carbaldehydes. Besides the formation of the expected 5-(3′-indolyl)oxazoles (**7b**,**c**,**g–j**, **11i**,**j**), the formation of the novel, rearranged stable indolyl primary enamines (**8b–f**), the mechanistically conspicuous dimethoxy-*N*′-formyltryptamines (**2A**,**B**) and *N*-(1-tosyl-2-skatolyl)ethenylformamide (**13**) and the interesting spectroscopic behaviour (presence of rotamers) of **2A**, **2B** and **13** highlight the importance of our work. The present work also provides us with a suitable substrate, **13**, for preparing indolo[1,2-*c*]pyrimidines, which is open to exploitation. More importantly, on acylation/aroylation, followed by proteodetosylation, these enamines opens up a new and practicable synthetic route to the analogues of the naturally occurring indolic[25] and bisindolic enamides.[26]

4. Experimental

4.1. General

Solvents were dried and purified using standard techniques. Melting points were determined on a Toshniwal apparatus and are uncorrected. IR spectra were recorded on Nicolet Impact 410 and Magnus 750 Series II spectrophotometers, LR EI-MS in a AEI MS 30 and LR EI-MS as well as HR MS, both EI and FAB (*m*-nitrobenzyl alcohol as liquid matrix) on JEOL JMS-AX505HA and JEOL JMS-700 MStation mass spectrometers and ^{1}H (500 MHz) and ^{13}C

Table 2. Reaction of 3-formylindoles (**1g–l**; 1 mmol) with TOSMIC (1.1 mmol) in presence of potassium carbonate (1.1 mmol) in methanol under reflux

3-Formylindoles (**1**)			Time (h)	Yield[a] (%)		
SM	R	R′		**7**	**11**	Overall
1g	Bn	H	4	72	—	72
1h	Me	Br	3	77	—	77
1i	Tos	H	2	53	37	90
1j	Tos	OMe	4	24	68	92
1k	Boc	H	3	—	38[b]	38
1l[c]	CO_2Et	H	—	—	—	98

[a] Refers to isolated pure products.
[b] This product is the same (**11i**) as that obtained from **1i**.
[c] Furnished **2A**, **2B** as the only products.

(125 MHz) NMR spectra, both 1D and 2D including DEPT-135, on a Bruker DRX 500 NMR spectrometer. Individual ^{1}H and ^{13}C NMR assignments, wherever made, were based on HMQC and HMBC spectral analyses. Silica gel G (Merck, India) was used for TLCs, both analytical and preparative, and silica gel (60–120 mesh; Qualigens, India) was used for column chromatography (CC). Elemental analyses were performed in a Dr. Hans Hoesli Analyser. The 3-formylindoles **1b**,[28] **1c**,[29] **1g**,[30] **1i**,[31] **1j**,[32] **1k**[33] and 2-formylskatole (**12**)[34] were prepared following the literature procedures. For **2A**, **2B** and **13**, the designatory letters mj and mn, used in presenting NMR data, stand for the major and the minor rotamer, respectively.

4.2. General procedure for the preparation of 3-formylindoles (1d–f,h,l)

To a solution of the 3-formylindole (5 mmol) in dry DMSO (5 mL) was added NaH (0.22 g, 5.5 mmol, 60% dispersion in mineral oil) and stirred at room temperature for 30 min. The respective alkyl iodide (MeI for **1d**, **1h**; EtI for **1e**; ^{i}PrBr for **1f**; $ClCO_2Et$ for **1l**) (0.34 mL for MeI, 0.45 mL for EtI and 0.52 mL for ^{i}PrBr, 5.5 mmol in each case) was then added to this suspension, which was then stirred for another 30 min. The reaction mixture was poured into crushed ice and extracted with EtOAc (3×25 mL). The pooled extracts were washed with water, dried (Na_2SO_4), solvent distilled off and the resulting residue crystallised from pet. ether–CH_2Cl_2 to furnish the 3-formylindoles (**1d–f**,**h**,**l**).

4.2.1. 3-Formyl-5-methoxy-1-methylindole (1d). Brown crystals; yield: 0.94 g (100%); mp 128–130 °C; ν_{max} (nujol): 3105, 1645, 1614, 1536, 1265, 1034, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.88 and 3.89 (3H, s each), 6.97 (1H, dd, J=9, 2.5 Hz), 7.22 (1H, d, J=9 Hz), 7.59 (1H, s), 7.78 (1H, d, J=2.5 Hz), 9.92 (1H, s). Anal. calcd for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82; N, 7.40. Found C, 69.78; H, 5.83; N, 7.42.

4.2.2. 1-Ethyl-3-formyl-5-methoxyindole (1e). Reddish brown flakes; yield: 1.0 g (99%); mp 98 °C; ν_{max} (nujol): 1650, 1533, 1255, 1215, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.54 (3H, t, J=7 Hz), 3.89 (3H, s), 4.19 (2H, q, J=7 Hz), 6.97 (1H, d, J=8 Hz), 7.26 (1H, d, J=8 Hz), 7.68, 7.8 and 9.95 (1H, s each). Anal. calcd for $C_{12}H_{13}NO_2$: C, 70.93; H, 6.40; N, 6.89. Found C, 70.98; H, 6.38; N, 6.87.

4.2.3. 3-Formyl-1-isopropyl-5-methoxyindole (1f). Yellow solid; yield: 1.06 g (98%); mp 108–110 °C; ν_{max} (nujol): 1659, 1619, 1261, 1089, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58 (6H, d, J=6.5 Hz), 3.89 (3H, s), 4.64 (1H, septet, J=6.5 Hz), 6.96 (1H, dd, J=9, 2 Hz), 7.29 (1H, d, J=9 Hz), 7.77 (1H, s), 7.80 (1H, d, J=2 Hz), 9.96 (1H, s). Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found C, 71.80; H, 6.93; N, 6.43.

4.2.4. 5-Bromo-3-formyl-1-methylindole (1h). Pale yellow solid; yield: 1.19 g (100%); mp 122–124 °C; ν_{max} (nujol): 1660, 1649, 1535, 1084, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.86 (3H, s), 7.22 (1H, d, J=8.5 Hz), 7.44 (1H, dd, J=8.5, 1.5 Hz), 7.66, 8.46 and 9.9 (1H, s each). Anal. calcd for $C_{10}H_8NOBr$: C, 50.42; H, 3.36.; N, 5.88. Found C, 50.46; H, 3.35; N, 5.86.

4.2.5. 1-Ethoxycarbonyl-3-formylindole (1l).[35] Yellow crystals; yield: 1.04 g (96%); mp 74 °C; ^{1}H NMR ($CDCl_3$): δ 1.51 (3H, t, J=7 Hz), 4.57 (2H, q, J=7.5 Hz), 7.38 and 7.43 (1H, t each, J=7.5 Hz), 8.18 (1H, d, J=7.5 Hz), 8.26 (1H, s), 8.29 (1H, d, J=7.5 Hz), 10.10 (1H, s). Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.45. Found C, 66.28; H, 5.05; N, 6.43.

4.3. General procedure for the reaction of 3-formylindoles (1a–l) with TOSMIC

A solution of the 3-formylindole (**1a–l**, 1 mmol) and TOSMIC (0.22 g, 1.1 mmol) in dry MeOH (10 mL) containing anhydrous K_2CO_3 (0.16 g, 1.1 mmol) was refluxed until the 3-formylindole was consumed completely (see Tables 1 and 2). The solution was then poured into water and extracted with EtOAc (3×25 mL). The pooled extracts were washed with water until free from of alkali, dried (Na_2SO_4), solvent distilled off and the resulting residue purified by prep. TLC [35% EtOAc/pet. ether (double development) for **2**; 35% EtOAc/pet. ether for **7b**,**c**,**j**, **8b**,**c**,**e**,**f**, **11j**; 25% EtOAc/pet. ether for **7g**,**i**, **11i**; EtOAc: pet. ether:benzene (2:4:4) for **8d**] to furnish the products, as shown in Tables 1 and 2.

4.3.1. *N*-[2-(3′-Indolyl)-1,2-dimethoxy]ethylformamide (2A and 2B). Overall yield (**2A**+**2B**) 0.24 g (98%).

2A (*mixture of two rotamers*). Cream yellow solid; mp 144–146 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3327, 3267, 1692, 1665, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.36 and 3.37 (3H, s each, mn), 3.40 and 3.43 (3H, s each, mj), 4.62 (1H, dd, J=10, 2.5 Hz, mn), 4.76 (1H, d, J=2.5 Hz, mj), 4.80 (1H, d, J=2.5 Hz, mn), 5.52 (1H, dd, J=10, 2.5 Hz, mj), 6.29 (1H, dd, J=10, 11.9 Hz, mn), 6.33 (1H, d, J=10 Hz, mj), 7.14 and 7.15 (1H, t each, J=7.5 Hz, mj, mn), 7.15 (1H, s, mn), 7.19 (1H, s, mj), 7.20 (mj) and 7.22 (mn) (1H, t each, J=7.5 Hz), 7.36 (mj) and 7.38 (mn) (1H, d each, J=7.5 Hz), 7.65 (mn) and 7.69 (mj) (1H, d each, J=7.5 Hz), 7.95 (1H, d, J=11.9 Hz, mn), 8.26 (1H, s, mj), 8.44 (mj) and 8.50 (mn) (1H, br s each); ^{13}C NMR: δ 55.5 (mn), 56.8 (mj), 57.6 (mn), 57.8 (mj), 78.3 (mj), 78.8 (mn), 81.4 (mj), 87.4 (mn), 111.8 (mj), 111.9 (mn), 119.2 (mn), 119.5 (mj), 120.50 (mj), 120.54 (mn), 122.8 (mj), 122.9 (mn), 123.8 (mj), 124.1 (mn), 162.0 (mj), 164.2 (mn) (all CH), 111.5 (mn), 111.7 (mj), 127.1 (2×; mj+mn), 136.5 (2×; mj+mn) (all C); EI-MS: *m*/*z* (%) 248 (M^+, 7), 216 (61), 214 (25), 184 (22), 160 (100), 156 (50), 144 (38), 130 (60), 129 (29), 117 (18). HR FAB-MS: M^+, Anal. calcd for $C_{13}H_{16}N_2O_3$ 248.1161. Found 248.1173.

2B (*mixture of two rotamers*). White solid; mp 72–74 °C (pet. ether–CH_2Cl_2); ν_{max} ($CHCl_3$): 3473, 3414, 1691, 1491, 1081 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.32 (3H, s, mn), 3.34 (3H mj +3H mn, s), 3.37 (3H, s, mj), 4.67 (1H, d, J=3.5 Hz, mj), 4.68 (1H, d, J=4 Hz, mn), 4.76 (1H, dd, J=10, 4 Hz, mn), 5.51 (1H, dd, J=10, 3.5 Hz, mj), 6.03 (1H, dd, J=10, 11.7 Hz, mn), 6.29 (1H, d, J=10 Hz, mj), 7.14 (1H mj +1H mn, t, J=7.5 Hz), 7.20 (1H, s, mn), 7.21 (1H mj +1H mn, t, J=7.5 Hz), 7.27 (1H, d, J=2 Hz, mj), 7.38 (mn) and 7.38 (mj) (1H, d each, J=8 Hz), 7.71 (mn) and 7.74 (mj) (1H, d each, J=8 Hz), 8.11 (1H, d, J=11.7 Hz, mn), 8.29 (1H, s, mj), 8.42 (mj) and 8.46 (mn) (1H, br s each); ^{13}C NMR: δ

55.6 (mn), 57.0 (mj), 57.3 (mn), 57.5 (mj), 78.8 (mj), 79.2 (mn), 81.0 (mj), 86.9 (mn), 111.7 (mj), 111.8 (mn), 120.2 (2×; mj+mn), 120.4 (mj), 120.6 (mn), 122.7 (mj), 122.9 (mn), 124.4 (mj), 124.7 (mn), 161.8 (mj), 163.9 (mn) (all CH), 111.0 (2×; mj+mn), 126.8 (mn), 127.2 (mj), 136.6 (mj), 136.8 (mn) (all C); EI-MS: *m/z* (%) 248 (M^+, 11), 216 (50), 214 (19), 184 (14), 160 (100), 156 (40), 144 (30), 130 (51), 129 (22), 117 (17). HR FAB-MS: M^+, Anal. calcd for $C_{13}H_{16}N_2O_3$ 248.1160. Found 248.1152.

4.3.2. 5-(1′-Methyl-3′-indolyl)oxazole (7b). Waxy; yield: 0.091 g (46%); ν_{max} (nujol): 3128, 1632, 1527, 1332, 1089, 970, 741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.81 (3H, s), 7.24 (1H, s), 7.24 (1H, dt, J=7.5, 1 Hz), 7.30 (1H, dt, J=7.5, 1 Hz), 7.35 (1H, d, J=8 Hz), 7.39 (1H, s), 7.83 (1H, d, J=8 Hz), 7.87 (1H, s); ^{13}C NMR: δ 33.4 (N-CH_3), 110.1, 119.5, 120.4, 121.0, 123.0, 127.0, 149.1 (all CH), 104.3, 125.0, 137.5, 148.4 (all C); EI-MS: *m/z* (%) 198 (M^+, 100), 169 (19), 158 (14), 143 (55), 128 (12), 115 (14). Anal. calcd for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.05; N, 14.14. Found C, 72.78; H, 5.03; N, 14.10.

4.3.3. 5-(1′-Ethyl-3′-indolyl)oxazole (7c). Waxy; yield: 0.07 g (33%); ν_{max} (film): 3127, 1631, 1608, 1525, 1208, 1089, 977, 741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (3H, t, J=7.5 Hz), 4.20 (2H, q, J=7.5 Hz), 7.23 (1H, dt, J=7.5, 1 Hz), 7.24 (1H, s), 7.29 (1H, dt, J=7.5, 1 Hz), 7.38 (1H, d, J=8 Hz), 7.47 (1H, s), 7.84 (1H, d, J=8 Hz), 7.87 (1H, s); ^{13}C NMR: δ 15.7 (CH_3), 41.6 (N-CH_2), 110.2, 119.5, 120.5, 121.0, 122.9, 125.28, 149.1 (all CH), 104.4, 125.22, 136.5, 148.4 (all C); EI-MS: *m/z* (%) 212 (M^+, 100), 197 (52). Anal. calcd for $C_{13}H_{12}N_2O$: C, 73.58; H, 5.66; N, 13.20. Found C, 73.43; H, 5.63; N, 13.25.

4.3.4. 5-(1′-Benzyl-3′-indolyl)oxazole (7g). Orange crystals; yield: 0.195 g (71%); mp 106–108 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 1633, 1527, 1182, 970, 751 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.32 (2H, s), 7.14 (2H, d, J=7 Hz), 7.25 (2H, t, J=7 Hz), 7.26 (1H, s), 7.2–7.27 (1H, m), 7.29 (1H, d, J=7.5 Hz), 7.27–7.35 (2H, m), 7.45 (1H, s), 7.85 (1H, s), 7.86 (1H, d, J=7.5 Hz); ^{13}C NMR: δ 50.7 (N-CH_2), 110.7, 119.9, 120.5, 121.3, 123.3, 126.3, 127.3 (2×), 128.3, 129.3 (2×), 148.2/149.2 (all CH), 105.1, 125.3, 137.0, 137.1, 149.2/148.2 (all C); EI-MS: *m/z* (%) 274 (M^+, 100), 234 (13), 183 (11), 120 (7), 91 (40). Anal. calcd for $C_{18}H_{14}N_2O$: C, 78.83; H, 5.10; N, 10.21. Found C, 78.91; H, 5.11; N, 10.18.

4.3.5. 5-(5′-Bromo-1′-methyl-3′-indolyl)oxazole (7h). Orange solid; yield: 0.214 g (77%); mp 88–90 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 1639, 1527, 1109, 903, 777 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.80 (3H, s), 7.20 (1H, s), 7.20 (1H, d, J=8.5 Hz), 7.36 (1H, s), 7.37 (1H, dd, J=8.5, 1.5 Hz), 7.88 (1H, s), 7.96 (1H, d, J=1.5 Hz); ^{13}C NMR: δ 33.6 (N-CH_3), 111.6, 119.8, 123.0, 125.9, 127.9, 149.3 (all CH), 104.0, 114.4, 126.6, 136.1, 147.6 (all C); EI-MS: *m/z* (%) 278 (M^+, 100), 276 (100), 197 (21). Anal. calcd for $C_{12}H_9N_2OBr$: C, 51.98; H, 3.24; N, 10.10. Found C, 51.90; H, 3.22; N, 10.14.

4.3.6. 5-(1′-Tosyl-3′-indolyl)oxazole (7i). Pale yellow solid; yield: 0.18 g (53%); mp 144 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3145, 3118, 1633, 1593, 1176, 1113, 961, 751 cm^{-1}; ^1H NMR (d_6-DMSO): δ 2.27 (3H, s), 7.35 (2H, d, J=8 Hz), 7.36 (1H, t, J=7.5 Hz), 7.43 (1H, t, J=7.5 Hz), 7.75 (1H, s), 7.91 (2H, d, J=8 Hz), 7.93 (1H, d, J=8 Hz), 7.99 (1H, d, J=8 Hz), 8.21 (1H, s), 8.48 (1H, s); ^{13}C NMR: δ 21.8 (CH_3), 114.3, 121.7, 123.6, 124.1, 125.1, 126.6, 127.8 (2×), 131.2 (2×), 145.3/146.7 (all CH), 111.4, 127.1, 134.5, 135.1, 146.7/145.3, 152.2 (all C); EI-MS: *m/z* (%) 338 (M^+, 29), 183 (100), 155 (13), 127 (24), 91 (16). Anal. calcd for $C_{18}H_{14}N_2O_3S$: C, 63.90; H, 4.14; N, 8.28. Found C, 63.95; H, 4.12; N, 8.24.

4.3.7. 5-(5′-Methoxy-1′-tosyl-3′-indolyl)oxazole (7j). White amorphous solid; yield: 0.09 g (24%); mp 160–162 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3130, 1631, 1595, 1230, 1141, 970, 799 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.34 (3H, s), 3.86 (3H, s), 7.0 (1H, dd, J=9, 2 Hz), 7.18 (1H, d, J=2 Hz), 7.23 (2H, d, J=8 Hz), 7.34 (1H, s), 7.78 (2H, d, J=8 Hz), 7.86 (1H, s), 7.93 (1H, d, J=9 Hz), 7.95 (1H, s); ^{13}C NMR: δ 21.9 (CH_3), 56.1 (OCH_3), 103.5, 114.8, 115.1, 122.4, 124.2, 127.2 (2×), 130.4 (2×), 145.7/146.1 (all CH), 111.2, 128.3, 130.2, 135.2, 146.1/145.7, 150.3, 157.3 (all C); EI-MS: *m/z* (%) 368 (M^+, 26), 213 (100), 199 (9), 115 (18). Anal. calcd for $C_{19}H_{16}N_2O_4S$: C, 61.95; H, 4.34; N, 7.60. Found C, 61.90; H, 4.35; N, 7.57.

4.3.8. (*E*)-2-(1′-Methyl-3′-indolyl)-2-tosylethenamine (8b). Reddish brown solid; yield: 0.104 g (32%); mp 92–94 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3463, 3354, 1641, 1536, 1275, 1145, 743 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.31 (3H, s, CH_3), 3.77 (3H, s, N-CH_3), 4.35 (2H, d, J=10.5 Hz; D_2O-exchangeable; NH_2), 6.99 (1H, t, J=7.5 Hz, H-5′), 7.06 (2H, d, J=8 Hz, H-3″, 5″), 7.08 (1H, d, J=7.5 Hz, H-4′), 7.17 (1H, t, J=7.5 Hz, H-6′), 7.18 (1H, s, H-2′), 7.29 (1H, d, J=7.5 Hz, H-7′), 7.55 (2H, d, J=8 Hz, H-2″, 6″), 7.78 (1H, t, J=10.5 Hz, =C*H*NH_2; collapsed to a singlet on addition of D_2O); ^{13}C NMR: δ 21.7 (CH_3), 33.4 (N-CH_3), 102.3 (C-3′), 104.9 [Ar*C*(Tos)=], 110.0 (CH-7′), 119.94 and 119.98 (CH-4′, 5′), 122.1 (CH-6′), 126.7 (C-3′a), 127.3 (2×; CH-2″, 6″), 129.4 (2×; CH-3″, 5″), 131.4 (CH-2′), 137.1 (C-7′a), 140.1 (C-1″), 142.6 (C-4″), 142.9 (=*C*HNH_2); EI-MS: *m/z* (%) 326 (M^+, 56), 171 (100), 156 (11), 144 (21), 130 (10), 91 (11). HR FAB-MS: M^+, Anal. calcd for $C_{18}H_{18}N_2O_2S$ 326.1089. Found 326.1091.

4.3.9. (*E*)-2-(1′-Ethyl-3′-indolyl)-2-tosylethenamine (8c). Brown solid; yield: 0.14 g (41%); mp 70–72 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3471, 3355, 1639, 1271, 1142, 1080, 741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (3H, t, J=6.5 Hz), 2.28 (3H, s), 4.15 (2H, q, J=6.5 Hz), 4.33 (2H, d, J=10 Hz, D_2O-exchangeable; NH_2), 6.98 (1H, t, J=7.5 Hz), 7.05 (2H, d, J=7 Hz), 7.10 (1H, d, J=7.5 Hz), 7.16 (1H, t, J=7.5 Hz), 7.23 (1H, s), 7.31 (1H, d, J=7.5 Hz), 7.54 (2H, d, J=7 Hz), 7.78 (1H, t, J=10 Hz, =C*H*NH_2; collapsed to a singlet on addition of D_2O); ^{13}C NMR: δ 15.8, 21.7 (both CH_3), 41.5 (CH_2), 110.0, 119.9, 120.0, 121.9, 127.4 (2×), 129.4 (2×), 129.7 (all CH), 142.6 (2×; CH+C), 102.4, 105.2, 126.9, 136.2, 140.0 (all C); FAB-MS: *m/z* (%) 340 (M^+, 85), 313 (10), 186 (39), 185 (100), 172 (23), 158 (49), 130 (13). Anal. calcd for $C_{19}H_{20}N_2O_2S$: C, 67.05; H, 5.88; N, 8.23. Found C, 67.11; H, 5.87; N, 8.26.

4.3.10. (*E*)-2-(5′-Methoxy-1′-methyl-3′-indolyl)-2-tosylethenamine (8d). Colourless prisms; yield: 0.22 g (62%);

mp 180–182 °C (pet. ether–EtOAc); ν_{max} (nujol): 3461, 3347, 1639, 1533, 1269, 1215, 1134, 1082, 671 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.29 (3H, s), 3.67 (3H, s), 3.73 (3H, s), 4.32 (2H, d, J=10 Hz), 6.42 (1H, s), 6.81 (1H, d, J=8.5 Hz), 7.08 (2H, d, J=8 Hz), 7.09 (1H, s), 7.16 (1H, d, J=8.5 Hz), 7.55 (2H, d, J=8 Hz), 7.77 (1H, t, J=10 Hz); ^{13}C NMR: δ 21.7, 33.5, 56.0 (all CH_3), 101.4, 110.7, 112.4, 127.5 (2×), 129.4 (2×), 131.8, 142.9 (all CH), 101.7, 105.2, 127.5, 132.5, 140.2, 142.6, 154.6 (all C); EI-MS: *m/z* (%) 356 (M^+, 58), 202 (16), 201 (100), 186 (10), 185 (10), 174 (11). Anal. calcd for $C_{19}H_{20}N_2O_3S$: C, 64.04; H, 5.61; N, 7.86. Found C, 64.15; H, 5.60; N, 7.89.

4.3.11. (*E*)-2-(1′-Ethyl-5′-methoxy-3′-indolyl)-2-tosylethenamine (8e). Reddish brown solid; yield: 0.25 g (68%); mp 142–144 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3502, 3376, 1633, 1533, 1268, 1215, 1129, 1076, 671 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (3H, t, J=7.5 Hz), 2.29 and 3.68 (3H, s each), 4.10 (2H, q, J=7.5 Hz), 4.31 (2H, d, J=10.5 Hz), 6.46 (1H, d, J=2 Hz), 6.80 (1H, dd, J=9, 2 Hz), 7.07 (2H, d, J=8 Hz), 7.14 (1H, s), 7.19 (1H, d, J=9 Hz), 7.55 (2H, d, J=8 Hz), 7.77 (1H, t, J=10.5 Hz); ^{13}C NMR: δ 15.8, 21.7 (both CH_3), 56.1 (OCH_3), 41.6 (N-CH_2), 101.6, 110.7, 112.2, 127.5 (2×), 129.4 (2×), 130.1 (all CH), 142.6 (2×; CH+C), 101.9, 105.5, 127.6, 131.5, 140.1, 154.5 (all C); EI-MS: *m/z* (%) 370 (M^+, 93), 216 (41), 215 (100), 188 (32), 185 (18), 160 (15), 91 (20). Anal. calcd for $C_{20}H_{22}N_2O_3S$: C, 64.86; H, 5.94; N, 7.56. Found C, 64.90; H, 5.95; N, 7.52.

4.3.12. (*E*)-2-(1′-Isopropyl-5′-methoxy-3′-indolyl)-2-tosylethenamine (8f). Ochre yellow solid; yield: 0.28 g (73%); mp 54–56 °C (pet. ether–CH_2Cl_2); ν_{max} (KBr): 3479, 3375, 1637, 1483, 1276, 1218, 1147, 673 cm^{-1}; ^1H NMR ($CDCl_3$): (1.47 (6H, d, J=6.5 Hz), 2.29 and 3.69 (3H, s each), 4.32 (2H, d, J=10.5 Hz), 4.57 (1H, septet, J=6.5 Hz), 6.49 (1H, d, J=2 Hz), 6.80 (1H, dd, J=9, 2 Hz), 7.07 (2H, d, J=8 Hz), 7.17 (1H, s), 7.22 (1H, d, J=9 Hz), 7.54 (2H, d, J=8 Hz), 7.77 (1H, t, J=10.5 Hz); ^{13}C NMR: δ 21.7, 23.1 (2×) (all CH_3), 56.1 (OCH_3), 47.9, 101.5, 110.9, 112.1, 126.9, 127.6 (2×), 129.3 (2×), 142.4/142.6 (all CH), 102.0, 105.6, 127.6, 131.2, 139.9, 142.4/142.6, 154.4 (all C); EI-MS: *m/z* (%) 384 (M^+, 50), 229 (100), 202 (21), 187 (12), 174 (9), 160 (16), 156 (12), 91 (27); Anal. calcd for $C_{21}H_{24}N_2O_3S$: C, 65.62; H, 6.25; N, 7.29. Found C, 65.73; H, 6.27; N, 7.32.

4.3.13. 5-(3′-Indolyl)oxazole (11i). Pale yellow solid; yield: 0.068 g (37%); mp 170–172 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3170, 3143, 1630, 1614, 1089, 979, 738 cm^{-1}; ^1H NMR (d_6-DMSO): δ 7.12 and 7.17 (1H, t each, J=7.5 Hz), 7.41 (1H, s), 7.45 (1H, d, J=7.5 Hz), 7.77 (1H, s), 7.82 (1H, d, J=7.5 Hz), 8.29 (1H, s), 11.68 (1H, br s); ^{13}C NMR ($CDCl_3$): δ 112.0, 119.9, 120.3, 121.4, 122.5, 123.5, 149.3 (all CH), 106.0, 124.5, 136.6, 148.3 (all C); EI-MS: *m/z* (%) 184 (M^+, 100), 157 (10), 141 (18), 130 (35). Anal. calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.34; N, 15.21. Found C, 71.83; H, 4.35; N, 15.19.

4.3.14. 5-(5′-Methoxy-3′-indolyl)oxazole (11j). White solid; yield: 0.146 g (68%); mp 154–156 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3159, 1639, 1633, 1252, 1090, 797 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.90 (3H, s), 6.94 (1H, dd, J=9, 2 Hz), 7.25 (1H, s), 7.29 (1H, d, J=2 Hz), 7.32 (1H, d, J=9 Hz), 7.52 (1H, d, J=2 Hz), 7.91 (1H, s), 8.72 (1H, br s); ^{13}C NMR: δ 56.3 (OCH_3), 102.1, 112.8, 113.6, 119.6, 123.2, 149.2 (all CH), 105.6, 125.0, 131.7, 148.5, 155.4 (all C); EI-MS: *m/z* (%) 214 (M^+, 100), 199 (33), 171 (28). Anal. calcd for $C_{12}H_{10}N_2O_2S$: C, 67.28; H, 4.67; N, 13.08. Found C, 67.35; H, 4.66; N, 13.06.

4.4. Reaction of 2-formyskatole (12) with TOSMIC

To a solution of 2-formylskatole (0.16 g, 1 mmol) in THF (2 mL) was added TOSMIC (0.22 g, 1.1 mmol) and DBU (0.17 mL, 1.1 mmol), the mixture stirred at room temperature for 2 h and then neutralised with acetic acid. The solution was poured into water and extracted with EtOAc (3×20 mL). The pooled extracts were washed with water, dried (Na_2SO_4), solvent distilled off and the resulting residue purified by prep. TLC using 20% EtOAc/pet. ether as the developing system to furnish **13**.

4.4.1. *N*-[1-Tosyl-2-(3′-methyl-2′-indolyl)]ethenylformamide (13; 3:2 mixture of two rotamers). Yellow solid, yield: 0.22 g (62%); mp 74–76 °C (pet. ether–CH_2Cl_2); ν_{max} (nujol): 3362, 1712, 1639, 1225, 1137, 1076, 671 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.70 (mj) and 1.72 (mn) (3H, s each), 2.34 (3H mj +3H mn, s), 7.11 and 7.12 (2H, d each, J=7 Hz, mj, mn), 7.10 (1H, d, J=8 Hz) and 7.14 (1H, d, J=8 Hz) (mj, mn), 7.25 (1H mj+1H mn, t, J=8 Hz), 7.39 (1H mj +1H mn, t, J=8 Hz), 7.44 (mn) and 7.43 (mj) (2H, d each, J=8 Hz), 7.47 (1H mj+1H mn, d, J=8 Hz), ~7.46 (1H, s, mn), 7.65 (1H, d, J=12 Hz, mj), 7.95 (1H, d, J=11 Hz, mn), 8.19 (1H, s, mj), 8.39 (1H, d, J=12 Hz, mj), 8.51 (1H, d, J=8 Hz, mn), 8.67 (mn) and 8.77 (mj) (1H, br s each); ^{13}C NMR: δ 9.0 (mj), 14.5 (mn), 21.9 (mj), 23.0 (mn), 111.8 (mj), 111.9 (mn), 119.5 (mj), 119.6 (mn), 120.1 (2×; mj+mn), 124.1 (mj), 124.2 (mn), 127.7 (2×; mn), 127.8 (2×; mj), 130.0 (2×; mj), 130.1 (2×; mn), 131.4 (mj), 135.0 (mn), 158.8 (mj), 162.8 (mn) (all CH), 114.1 (mj), 114.2 (mn), 116.2 (mn), 117.6 (mj), 120.4 (mn), 121.1 (mj), 128.1 (2×; mj+mn), 136.6 (mn), 136.8 (mj), 137.2 (mn), 137.3 (mj), 144.6 (mj), 144.8 (mn) (all C); EI-MS: *m/z* (%) 354 (M^+, 88), 200 (17), 199 (100), 171 (31), 158 (29), 144 (13), 130 (13). HR FAB-MS: M^+, Anal. calcd for $C_{19}H_{18}N_2O_3S$ 354.1038. Found 354.1059.

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23. Crystal data: crystals from petroleum ether–EtOAc, $C_{19}H_{20}N_2O_3S$, $M=356.44$, monoclinic, $a=18.019(2)$ Å, $b=10.485(1)$ Å, $c=19.661(3)$ Å, $\beta=101.98(1)^\circ$, $V=3633.6(8)$ Å^3, $T=296.2$ K, space group $P2_1/n$, $Z=8$, $D_c=1.303$ g cm^{-3}, μ(Cu-Kα)$=17.51$ cm^{-1}, $F(000)=1504.00$, crystal dimensions: $0.40\times0.40\times0.40$ mm, Rigaku AFC5R diffractometer (rotating anode), Cu-Kα radiation, $\lambda=1.54178$ Å, $\theta_{max}=70.12^\circ$; 7220 reflections measured, 6682 unique ($R_{int}=0.082$), 5092 with $I>2.00\,\sigma(I)$, $2\theta<140.24^\circ$, $wR(F^2)=0.1810$ (all data). Two crystallographically independent molecules exist in an asymmetric unit and are represented by the carbon number C1–C19 and C20–C38. CCDC-244416 contains the supplementary crystallographic data for this paper. These data can be obtained via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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Synthesis and antagonist activities of 4-aryl-substituted conformationally restricted cyclopentenyl and cyclopentanyl-glutamate analogues

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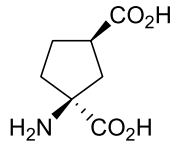
Abstract—The conformationally restricted glutamate analogues, 4-aryl-1-amino-2-cyclopentene-1,3-dicarboxylates and their cyclopentane analogues have been prepared in a diastereoselective manner. Biological studies of **12a** and **12b** indicates that both compounds are modest antagonists at mGluR2.

1. Introduction

Considerable research efforts have been focused upon the development of selective agonists and antagonists for the ionotropic and metabotropic glutamate sub-type receptors.[1] Such selective compounds have potential applications as therapeutic agents for the treatment of a number neurodegenerative diseases. A variety of cyclic, conformationally restricted glutamate analogues have been prepared in laboratories around the world but only a few are highly potent and sub-type selective.[1] One such compound is the conformationally restricted glutamate analogue, (1*S*, 3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (1*S*, 3*R*-ACPD) **1**, which selectively activates metabotropic glutamate receptors (mGluR) over the ionotropic type. This compound, however, is not selective for the individual eight mGluR subtypes that are currently known.[2] We recently reported that (*S*)-**2**, the dehydro-analogue of APCD, was an agonist at mGluR5 (EC_{50} 18 μM) and mGluR2 (EC_{50} 45 μM).[3] (*S*)-4-Carboxyphenylglycine (4CPG) **3** was reported as one of the first potent and selective mGluR2 competitive antagonists that antagonised 1*S*, 3*R*-ACPD (**1**) induced inositol phosphate (IP) formation in cerebral cortical slices.[4] One approach in designing potent and selective antagonists is by the introduction of a bulky and lipophilic group into an agonist. This was clearly demonstrated in the xanthylmethyl substituted compound, LY341495 (**4**), which displays antagonist activity at the mGluR2 in the low nM range ($IC_{50}=0.010\pm0.001$ μM).[5] [H^3]LY341495 was synthesised and employed as a mGluR2 radioligand in receptor mapping studies.[6] This compound and its analogues have also been used to study the effect of mGluR2 antagonists on locomotor activity in mice, with an attempt to probe the function of this receptor.[7] From a consideration of these findings, we have synthesised several 4-aryl substituted derivatives of racemic **1** and 2,3-dehydro **1**. We report here the diastereoselective synthesis of these 4-aryl substituted derivatives and the activities of four of these compounds as agonists and antagonists at mGluR2.



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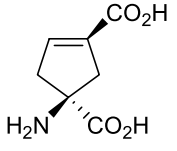
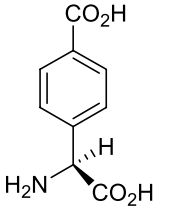
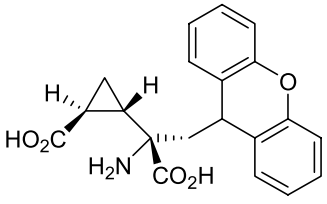


(*S*)-**2**



(*S*)-4CPG (**3**)



LY341495 (**4**)

Keywords: Metabotropic glutamate receptors; Antagonists; Heck reaction.
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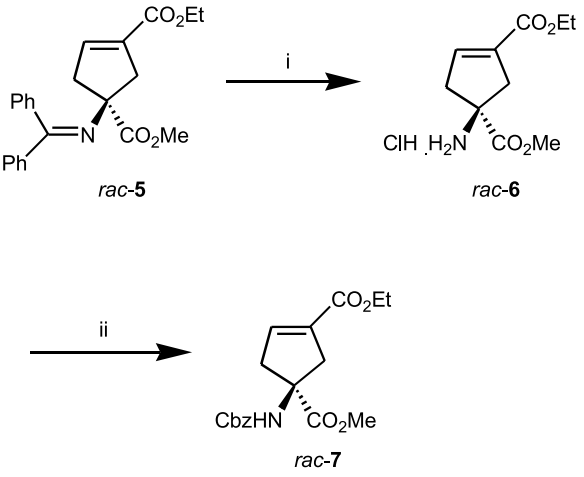
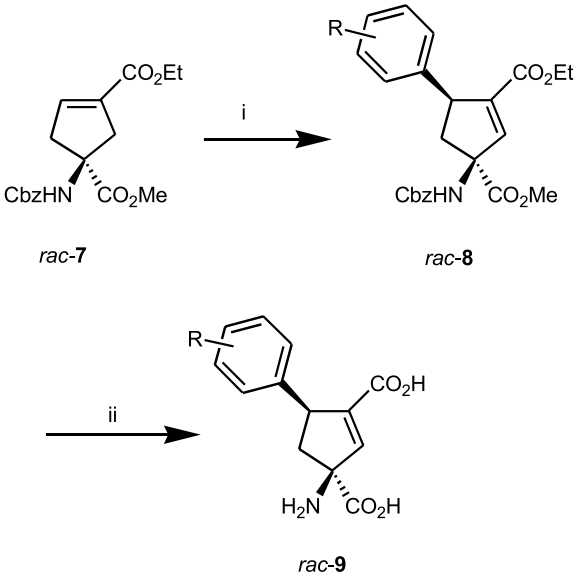
2. Chemistry

The initial methodology used for the synthesis of the potential antagonists (**9** and **12**) was based on the palladium-catalysed Heck coupling reaction of the Cbz-derivative *rac*-**7** with an aryliodide.[8] Compound **7** was obtained from deprotection of the known racemic compound **5**,[3a] followed by reaction of the hydrochloride salt **6** with benzyl chloroformate in the presence of saturated K_2CO_3 to give **7** in 78% (Scheme 1).



Scheme 1. Synthesis of compound **7**. Reagents and yields: (i) 1 M HCl, ether, 0–25 °C, 16 h, 98%; (ii) 4 M Na_2CO_3, benzyl chloroformate, THF, 0 °C, 78%.

Compound **7** was treated with iodobenzene under standard Heck conditions (10 mol% $Pd(OAc)_2$, Ph_3P, Et_3N) in acetonitrile solution at 100 °C in a sealed tube for 38 h (Scheme 2). Purification of the crude reaction mixture by column chromatography gave **8a** as a 94:6 mixture of two diastereomers in 55% yield (Table 1). Under similar conditions 4-iodotoluene gave **8b** in 62% yield as a 95:5 mixture of diastereomers (Table 1). Pure **8a** and **8b** could be obtained by preparative HPLC, using a solvent system of ethyl acetate and hexane (15:85). Using the standard Heck conditions to prepare compounds **8c** and **8d** was less efficient resulting in poor yields of these desired compounds (Table 1). Attempts to prepare compounds **8e–8j** were less successful. However, the reactions of compound **7** with these more hindered aryl halides under the conditions originally developed by Jeffrey,[9] using $Pd(OAc)_2$, $NaHCO_3$ as the base and *n*-Bu_4NCl as a phase-transfer catalyst gave the coupling products **8f–k** in improved yields (Table 1). The selectivity of the major and minor coupling products was determined by ^1H NMR experiments, and found to be in the ratio of approximately 95–90:5–10, in all cases.



Scheme 2. Reagents: (i) ArX (1.3 equiv), $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%), Et_3N (2 equiv), CH_3CN, 100 °C, (ii) 10% aqueous HCl, [*rac*-**8**] = 1.3 M, 100 °C, 16 h.

Table 1. Isolated yields of **8**

Compounds	Method	Yield (%)
8a (R = H)	A	55
8b (R = *p*-CH_3)	A	62
8c (R = *p*-OTBS)	A	20
8d (R = *m*-CH_3)	A	29
8e (R = *m*-CF_3)	B	40
8f (R = *m*-Et)	B	76
8g (R = *o*-CH_3)	B	33
8h (R = 3,4-diMe)	B	52
8i (R = *m*-OCH_3)	B	50
8j (R = 2-napthyl)	B	47

Method A: Heck coupling; ArX (1.3 equiv), $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%), Et_3N (2 equiv), CH_3CN, 100 °C. Method B: Jeffery–Heck coupling condition; ArX (1.3 equiv), $Pd(OAc)_2$ 3% mol, Bu_4NCl (1 equiv), $NaHCO_3$ (2.5 equiv), DMF, 90 °C.

^1H NMR spectroscopic analysis of the two diastereomers of **8a** (R = H) indicated that the major diastereomer exhibited a H-4 resonance (δ 4.20, dd) upfield from the corresponding resonance (δ 4.47, br s) for the minor isomer (Fig. 1). The H-5α resonance at δ 3.10 of the major isomer appeared markedly more downfield than the corresponding resonance (δ 2.73) of the minor isomer. Furthermore, the H-5β of the major isomer exhibited a resonance at δ 2.23, upfield from the corresponding resonance (δ 2.73) of the minor isomer.

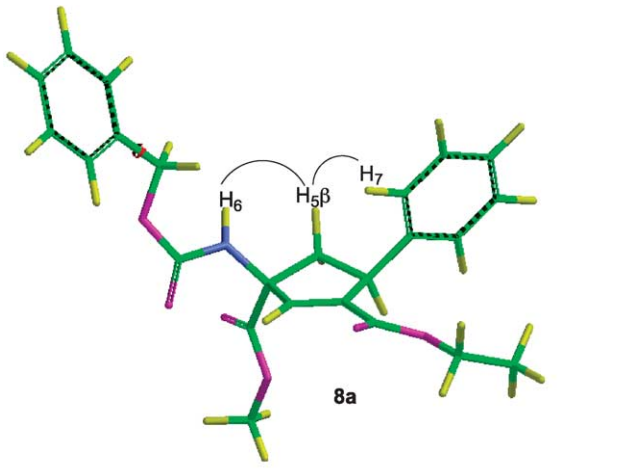


Figure 1. NOESY study of **8a**.

In general, the major diastereomers **8** exhibited a H-4 chemical shift between δ 4.20 and 4.36, however, for compound **8g**, this proton had a chemical shift at δ 4.53. We attribute this downfield chemical shift to the *ortho* methyl-substituent on the aromatic ring. The relative stereochemistry of the major isomer of **8a** (R=H) was determined from NOESY experiments. These NMR experiments showed significant cross-peaks between H-6 and H-5β and H-5β and H-7 on the aryl ring, which is consistent with their relative *syn* stereochemistry (Fig. 1).

The high diastereoselectivity and the stereochemical outcome of these reactions may be due to formation of the aryl-palladium(II) complex **A**; that could be favoured by coordination to the electron pair of the Cbz-nitrogen (Fig. 2). *Syn* β-hydride elimination from **B** then gives compound **8** (Fig. 2).

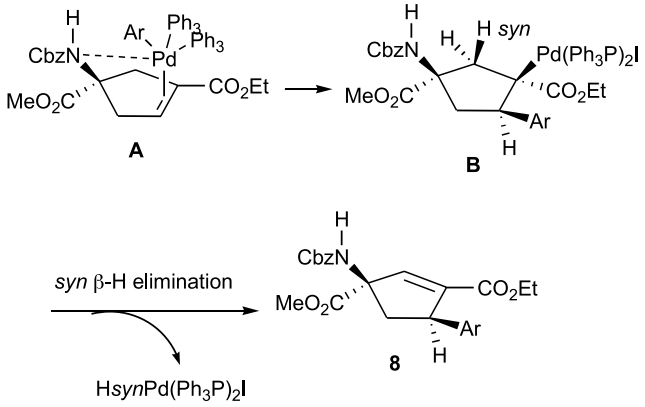


Figure 2. Suggest mechanism for the stereochemistry of compounds **8**.

Acid hydrolysis of compounds **8a–j**, with 10% aqueous HCl at reflux gave the corresponding amino acids **9a–j** as their hydrochloride salts (Scheme 2 and Table 2).

Table 2. Isolated yields (%) of compounds **9**, **10** and **12**

Compounds	9	10	12
a (R=H)	100	73[a]	63[b]
b (R=*p*-CH_3)	97	77[a]	90[b]
c (R=*p*-OTBS)	81	na	na
d (R=*m*-CH_3)	80	43[c]	95[c]
e (R=*m*-CF_3)	78	95[c]	94[c]
f (R=*m*-Et)	59	94[c]	98[c]
g (R=*o*-CH_3)	100	92[c]	100[c]
h (R=3,4-diMe)	56	76[c]	56[c]
i (R=*m*-OCH_3)	89	86[c]	88[c]
j (R=2-napthyl)	58	34[c]	33[c]

[a] Compounds **10** and **11** were separated by HPLC.
[b] Obtained diastereomically pure from **10a** or **10b**.
[c] These samples were ca. 5:1 mixture of diastereomers.

Reduction of α,β-unsaturated esters and other electron deficient alkenes using magnesium in methanol has been described to be a selective and efficient method.[10–12] Compounds **8a–j** were successfully reduced using Mg-turnings in dry methanol to selectively afford the cyclopentane derivatives **10a–j** and **11a–j** as the major and minor diastereomers (d.r.=5:1), respectively (Scheme 3 and Table 2). The selectivity observed in this magnesium–methanol reduction may be due to the formation of the Mg(II) complex **A**, as shown in Figure 3, which upon stereoselective protonation gives compound **10** as the major product. Alternatively, the formation of the more stable 3,4-*anti*-products (**10**) may be due to a based-catalysed epimerisation during the course of the reaction.

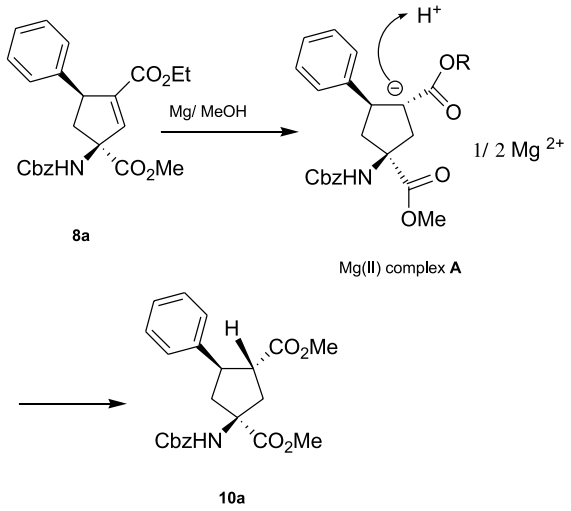


Figure 3. Suggest mechanism for the stereochemistry of compounds **10a**.

Complete transesterification of the ethyl ester group in **10** was observed in most cases from ^{1}H NMR analysis. HPLC separation of a mixture of **10a** and **11a** and **10b** and **11b**, gave pure samples of **10a**, **11a**, **10b** and **11b**, respectively. The relative stereochemistry of **10b** was determined by NOESY experiments that showed significant cross peaks between H-1 and H-5β, H-6 and H-3, H-6 and H-5β, H-3 and H-2, and H-2 and H-1 which confirmed the *syn* orientation of the two carboxyl groups (Fig. 4).

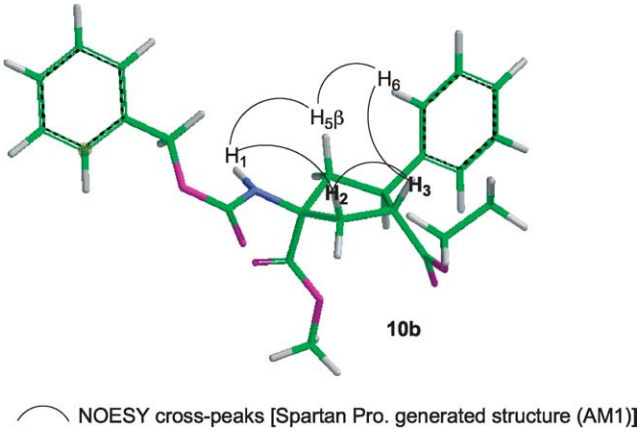
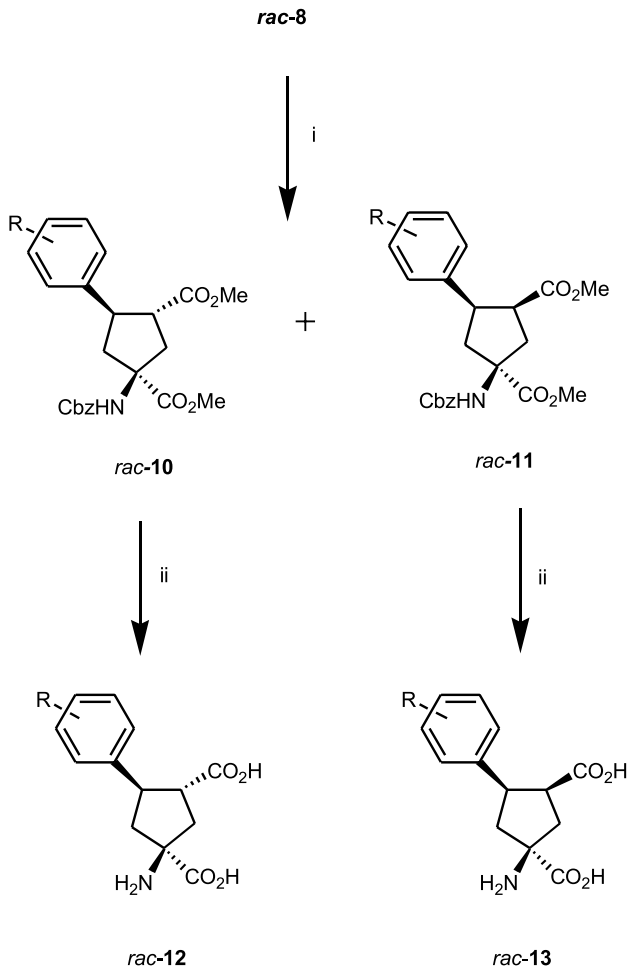


Figure 4. NOESY study of compound **10b** (*p*-CH_3 not shown).

Acid hydrolysis of compounds **10** and **11** proceeded smoothly under the same conditions as previously described for the hydrolysis of compounds **8a–j**, to give the hydrochloride salts **12** and **13**, respectively, in good yields (Scheme 3 and Table 2).



Scheme 3. Reagents: (i) Mg, MeOH, (ii) 10% HCl, reflux.

3. Biological studies

The antagonist and agonist activity of the diastereomerically pure, but racemic compounds **9a**, **9b**, **12a** and **12b**, were investigated. Signal transduction experiments were performed with CHO cells heterologously expressing human mGluR2. Signaling at mGluR2 receptor measured by mean of a [^{35}S]GTPγS binding assay on membranes from these cells.[3] The results for antagonist activity are summarized in Table 3.

Table 3. Antagonist potencies of phenyl substituted analogues for inhibition of glutamate-induced GTPγS binding to human mGluR2

Compounds	Mean $IC_{50}\pm SD$ in μM (E_{max}, %)	Compounds	Mean $IC_{50}\pm SD$ in μM (E_{max}, %)
9a	>100	**12a**	32 (71%)
9b	>100	**12b**	73 (100%)

Unlike racemic **4** and (*S*)-**4** these compounds showed no mGluR2 agonist activity ($EC_{50}>100$ μM). Compounds **12a** and **12b**, however, showed modest antagonist activities with IC_{50} values of 32 and 73 μM, respectively. In contrast, **9a** and **9b** were not antagonists ($IC_{50}>100$ μM). These limited results suggested that an sp^3 hybridized carbon at C-2 and C-3 and an aryl substituent at C-4 is important for anatagonist activity in these types of compounds and that a C-4-aryl substituent has adverse effects on the agonist activity of *rac*-**1**.

In summary, we have developed a diastereoselective method for preparing 4-aryl-1-amino-2-cyclopentene-1,3-dicarboxylates and their cyclopentane analogues. The palladium-catalysed Heck reactions of the Cbz-derivative, *rac*-**7**, with *ortho* and *meta* substituted aryl halides were successfully achieved by using the Jeffrey–Heck coupling reaction conditions. This method provided the desired aryl derivatives in higher yields than the classical Heck coupling reaction conditions. Compounds **12a** and **12b** were found to behave selectively as antagonists at mGluR2 with modest activities.

4. Experimental

4.1. Chemistry

Solvents and reagents were purchased from commercial sources and used without further purification unless otherwise stated. Unless specified, all NMR spectra were recorded at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) in $CDCl_3$ solution. ^{13}C NMR assignments were based on DEPT experiments. Preparative HPLC was performed using a Waters Delta prep 4000 HPLC, on a normal phase Pre Nova-Pak® HR Silica 6 μm 60 (25×10 mm) column. All separations were carried out by isocratic elution, using eluents A and B (A, in petroleum spirit; B, isopropanol) in the ratio 98:2. The flow rate was at 20 ml/min. Compounds were detected using a Waters 486 tunable UV absorbance detector.

4.2. Biological testing

[^{35}S]GTPγS (specific activity 37 MBq/ml) was obtained from Amersham (Little Chalfort, UK). Dulbecco's modified Eagle medium (DMEM) and dialyzed fetal calf serum were from Life technologies (Gaithersburg, MD). Scintillation fluid Ultimaflo AF as well as the Unifilter-96 GF/B plates were from Packard (Meriden, CT). Guanosine-5′-diphosphate dilithium salt (GDP) was from Boehringer Manheim (Basel, Switzerland), Fluo 3-AM was from Molecular Probes (Leiden, The Netherlands). Probenecid was from Sigma (St Louis, MO). Black 96-well plates were from Costar (Merck, Overijse Belgium).

4.2.1. 3-Ethyl 1-methyl 1-amino-3-cyclopentene-1,3-dicarboxylate hydochloride salt (6). To a stirred solution of compound **5** (1.94 g, 5.13 mmol) in diethyl ether (10 mL) at 0 °C, was slowly added a solution of 1 M HCl (6.6 mL). The reaction mixture was stirred at 0 °C for 2 h and then at RT overnight. The layers were separated and the aqueous layer was extracted with diethyl ether. Water was removed to give **6** as a white crystalline solid (1.08 g, 98%). ^{1}H NMR δ: 6.69 (s, 1H), 4.18 (q, 2H), 3.85 (s, 3H), 3.28 (br s, 4H), 1.28 (s, 3H); ^{13}C NMR δ: 172.1 (CO), 164.7 (CO), 139.7 (CH), 134.2 (C), 64.2 (C), 61.9 (CH_2), 54.4 (CH_3), 44.6 (CH_2), 43.1 (CH_2), 14.5 (CH_3). MS (ES) *m*/*z* 214.2 ([M+1], 100%).

4.2.2. 3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-3-cyclopentene-1,3-dicarboxylate (7). To the mixture of

ammonium salt **6** (0.957 g, 3.83 mmol) and an aqueous solution of 4 M Na_2CO_3 (9.6 mL) in THF (2.4 mL) at 0 °C was added benzyl chloroformate (0.6 mL, 4.213 mmol) and a solution of 4 M Na_2CO_3 (4.8 mL). The mixture was left to stir at 0 °C for 2 h. THF was removed and the residue was extracted with $CHCl_3$ (3×20 mL) and the combined extracts were washed with a saturated solution of NaCl and dried over $MgSO_4$. The solvent was removed to give a yellow oil which was purified by column chromatography (35% ethyl acetate/hexane) to give a colourless oil (1.30 g, 97%). ^{1}H NMR δ: 7.40–7.34 (m, 5H), 6.68 (s, 1H), 5.52 (br s, 1H), 5.10 (s, 2H), 4.19 (q, 2H), 3.74 (s, 3H), 3.25 (dd, J= 2.4, 16.8 Hz, 1H), 3.20 (dd, J=1.8, 13.2 Hz, 1H), 2.91 (d, 2H), 1.28 (s, 3H). ^{13}C NMR δ: 173.8 (CO), 163.0 (CO), 155.1 (CO), 139.4 (CH), 135.9 (C), 132.7 (C), 127.8 (2 CH), 127.4 (2 CH), 126.2 (CH), 66.0 (CH_2), 63.8 (C), 59.8 (CH_2), 52.1 (CH_3), 43.9 (CH_2), 42.6 (CH_2), 13.6 (CH_3). MS (ES) m/z 348.3 ([M+1], 100%).

4.3. General procedure for the Heck coupling reaction, method A

A mixture of compound **7** (0.771 g, 2.22 mmol), $Pd(OAc)_2$ (10% mol, 48 mg), Ph_3P (20% mol, 0.12 g), iodobenzene (3.33 mmol, 0.4 mL) and Et_3N (0.6 mL) in dry acetonitrile (2 mL) was heated at 100 °C in a sealed tube for 38 h. After cooling, the reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was washed with a saturated solution of NaCl. The solvent was removed to give dark thick oil, which was purified by column chromatography (25% ethyl acetate/hexane) to give **8a** as a mixture of diastereomers **8a** (0.520 g, 55%) in a ratio of 94:6 as determined by ^{1}H NMR analysis. The two diastreoisomers were separated by HPLC (5% ethyl acetate/petroleum spirit).

4.3.1. 3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-phenyl-2-cyclopentene-1,3-dicarboxylate (8a). (1*S**, 4*R**) Major isomer: a yellow oil, ^{1}H NMR δ: 7.35 (s, 5H), 7.28–7.20 (m, 5H), 6.80 (s, 1H) 5.76 (s, 1H), 5.12 (s, 2H), 4.28 (ddd, J=1.5, 13.2, 13.2 Hz, 1H), 4.04 (m, 2H), 3.79 (s, 3H), 3.10 (dd, J=8.7, 14.1 Hz, 1H), 2.23 (dd, J=6.3, 12.6 Hz, 1H), 1.08 (t, 3H). ^{13}C NMR δ: 172.3 (CO), 163.8 (CO), 154.8 (CO), 143.2 (C), 142.9 (C), 135.9 (C), 128 4 (2CH), 128.1 (2CH), 128.1 (2CH), 128.0 (2CH), 127.4 (2CH), 126.6 (2CH), 69.4 (C), 66.8 (CH_2), 60.5 (CH_2), 53.1 (CH_3), 49.6 (CH), 45.7 (CH_2), 13.7 (CH_3). MS (ES) m/z 424.0 ([M+1], 100%). HRMS calcd for $C_{24}H_{26}O_6N$ (MH^+) 424.1760. Found 424.1767.

(1*S**, 4*S**) Minor isomer: a yellow oil, ^{1}H NMR δ: 7.36 (s, 5H), 7.30–7.20 (m, 5H), 6.78 (s, 1H), 5.73 (s, 1H), 4.47 (br s, 1H), 4.13–3.93 (m, 2H), 3.80 (s, 3H), 2.73 (dd, J=9.0, 13.8 Hz, 1H), 2.49 (dd, J=6.3, 14.4 Hz, 1H), 1.07 (t, 3H). ^{13}C NMR δ: 169.4 (CO), 160.9 (CO), 151.7 (CO), 140.7 (C), 140.0 (C), 136.7 (HC), 132.9 (C), 125.5 (2CH), 125.4 (3CH), 125.2 (CH), 125.0 (CH), 124.4 (3CH), 123.5 (CH), 66.3 (C), 63.9 (CH_2), 57.5 (CH_2), 50.1 (CH_3), 46.9 (CH), 42.5 (CH_2), 10.8 (CH_3).

4.3.2. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(4′-methylphenyl)-2-cyclopentene-1,3-dicarboxylate (8b).** A pale yellow oil (1.123 g, 62%). ^{1}H NMR δ: 7.36 (s, 5H), 7.15–7.09 (m, 4H), 6.79 (s, 1H), 5.73 (br s, 1H), 5.12 (s, 2H), 4.26 (ddd, J=1.8, 6.6, 8.4 Hz, 1H), 4.05 (m, 2H), 3.79 (s, 3H), 3.07 (dd, J=8.1.13.5 Hz, 1H), 2.22–2.18 (m, 1H), 1.12 (t, 3H). ^{13}C NMR δ: 172.3 (CO), 163.8 (CO), 154.8 (CO), 142.9 (C), 140.1 (CH), 135.9 (4C), 129.0 (2 CH), 128.3 (3 CH), 128.0 (CH), 127.9 (CH), 127.2 (2CH), 69.3 (CH_2), 66.7 (C), 60.4 (CH_2), 53.0 (CH_3), 49.2 (CH), 45.7 (CH_2), 20.9 (CH_3), 13.7 (CH_3). MS (ES) m/z 438.1 ([M+1]$^+$, 100%). HRMS calcd for $C_{25}H_{28}O_6N$ (MH^+) 438.1917. Found 438.1904.

4.3.3. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(4′-*tert*-butyldimethylsilyloxyphenyl)-2-cyclopentene-1,3-dicarboxylate (8c).** A dark yellow oil (0.315 g, 20%). ^{1}H NMR δ: 7.35 (s, 5H), 7.11 (br d, J= 6.6 Hz, 2H), 6.75 (br d, J=8.1 Hz, 2H), 5.80 (s, 1H), 5.11 (s, 2H), 4.23 (t, 1H), 4.16–3.95 (m, 2H), 3.77 (s, 3H), 3.09 (dd, J=8.4, 13.8 Hz, 1H), 2.19 (m, 1H), 1.07 (t, 3H), 0.97 (s, 9H), 0.16 (s, 6H). ^{13}C NMR δ: 172.3 (CO), 163.8 (CO), 154.8 (CO), 154.1 (C), 143.1 (C), 139.8 (2C), 135.9 (CH), 128.3 (4CH), 128.0 (2CH), 127.9 (CH), 119.8 (2CH), 69.2 (C), 66.7 (CH_2), 60.3 (CH_2), 52.9 (CH_3), 48.9 (CH), 45.7 (CH_2), 25.5 (3CH_3), 13.7 (CH_3), −4.6 (CH_3). MS (ES) m/z 264.0 ([M+1], 30%).

4.3.4. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(3′-methylphenyl)-2-cyclopentene-1,3-dicarboxylate (8d).** A yellow oil (0.686 g, 29%). ^{1}H NMR δ: 7.35 (s, 5H), 7.26–7.04 (m, 4H), 6.80 (s, 1H), 5.12 (s, 1H), 4.23 (dd, J=8.7, 14.7 Hz, 1H), 4.13 (q, 2H), 3.78 (s, 3H), 3.10 (dd, J= 8.4, 8.4 Hz, 1H), 2.31 (s, 3H), 2.18 (m, 1H), 1.13 (t, 3H). ^{13}C NMR δ: 172.0 (CO), 163.9 (CO), 154.4 (CO), 143.0 (C), 142.5 (C), 140.7 (CH), 140.0 (C), 137.6 (C), 128.31 (2CH), 127.42 (3CH), 127.36 (2CH), 126.43 (CH), 124.96 (CH), 69.1 (CH_2), 66.1 (C), 60.4 (CH_2), 52.9 (CH_3), 49.4 (CH), 45.6 (CH_2), 21.1 (CH_3), 13.5 (CH_3). MS (CI) m/z 438 ([M+1], 46%).

4.4. General procedure for the Jeffery–Heck coupling reaction, method B

A solution of compound **7** (0.2 g, 0.58 mmol), $Pd(OAc)_2$ (3% M equiv, 0.017 mmol, 4.6 mg) and $NaHCO_3$ (0.121 g, 1.44 mmol) in dry DMF (2 mL) were added into a high-pressure tube and the tube was purged with nitrogen. A solution of tetrabutylammonium chloride (0.169 g, 0.576 mmol) in dry DMF (2 mL) was added to the tube followed by 5-iodo-*m*-xylene (0.134 g, 0.58 mmol) and DMF (2 mL). The reaction mixture was purged with argon for 20 min before sealing and was heated with stirring at 90 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 mL). The mixture was washed with half-saturated NaCl (3× 100 mL) and was dried over $MgSO_4$. The solvent was evaporated to give a dark oil, which was purified by column chromatography (flash silica, 15% ethyl acetate/petroleum spirits as eluent) to give **8h** as a light brown oil (136 mg, 52%). ^{1}H NMR δ: 7.24 (s, 5H), 6.73 (s, 4H), 5.68 (bs, 1H), 5.11 (s, 2H), 4.21 (dd, J=15, 8.4 Hz, 1H), 4.09 (q, 2H), 3.77 (s, 3H), 3.09 (dd, J=14.1, 5.4 Hz, 1H), 2.20 (s, 6H), 2.12 (dd, J=14.1, 9.8 Hz, 1H), 1.12 (t, 3H). ^{13}C NMR δ: 172.7 (CO), 164.3 (CO), 155.3 (CO), 143.3 (2C), 140.4 (C), 138.2 (C), 128.8 (3CH), 128.4 (3CH), 125.5 (3CH), 69.7 (C), 67.2 (CH_2), 60.9 (CH_2), 53.4 (CH_3), 49.8 (CH), 46.2 (CH_2), 21.5

($2CH_3$), 14.2 (CH_3). MS (CI) *m/z* 452 ([M+1], 20%); HRMS calcd for $C_{26}H_{30}O_6N$ (MH^+) 452.2073. Found 452.2015.

4.4.1. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(3′-trifluoromethylphenyl)-2-cyclopentene-1,3-dicarboxylate (8e).** A yellow oil (0.94 g, 40%). ^{1}H NMR δ: 7.57–7.40 (m, 4H), 7.35 (s, 5H), 6.81 (s, 1H), 5.94 (s, 1H), 5.11 (s, 2H), 4.34 (ddd, J=2.1, 8.4, 8.4 Hz, 1H), 4.00 (m, 1H), 3.79 (s, 3H), 3.12 (dd, J=8.4, 13.8 Hz, 1H), 2.28 (dd, J=6.3, 13.2 Hz, 1H), 1.06 (t, 3H). ^{13}C NMR δ: 172.5 (CO), 163.9 (CO), 155.4 (CO), 144.3 (C), 142.4 (CH), 141.8 (2C), 136.4 (2C), 131.3 (CH), 129.3 (CH), 128.7 (2CH), 128.4 (CH), 128.3 (CH), 126.3 (CH), 122.6 (CH), 69.7 (CH_2), 67.1 (C), 60.9 (CH_2), 53.4 (CH_3), 49.8 (CH), 45.6 (CH_2), 13.9 (CH_3). MS (CI) *m/z* 492.0 ([M+1], 30%). HRMS calcd for $C_{25}H_{25}O_6NF_3$ (MH^+) 429.1634. Found 492.1636.

4.4.2. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(3′-ethylphenyl)-2-cyclopentene-1,3-dicarboxylate (8f).** A yellow oil (0.415 g, 76%). ^{1}H NMR δ: 7.35 (s, 5H), 7.19 (m, 1H), 7.06 (m, 3H), 6.82 (s, 1H), 5.70 (br s, 1H), 5.11 (s, 1H), 4.27 (ddd, J=2.1, 6.9, 6.9 Hz, 1H), 4.10 (m, 2H), 3.78 (s, 3H), 3.10 (dd, J=9.0, 14.1 Hz, 1H), 2.61 (q, 2H), 2.18 (dd, J=6.3, 14.1 Hz, 1H), 1.21 (t, 3H), 1.09 (t, 3H). ^{13}C NMR δ: 172.2 (CO), 164.3 (CO), 155.5 (CO), 144.5 (C), 143.6 (C), 143.3 (C), 140.7 (CH), 136.5 (C), 128.7 (3CH), 127.4 (2CH), 128.3 (CH), 127.4 (CH), 126.4 (CH), 125.0 (CH), 69.8 (C), 67.0 (CH_2), 60.8 (CH_2), 53.3 (CH_3), 50.0 (CH), 46.1 (CH_2), 29.0 (CH_2), 15.9 (CH_3), 14.1 (CH_3). MS (ES) *m/z* 452.0 ([M+1], 40%). HRMS calcd for $C_{26}H_{30}O_6N$, (MH^+) 452.2073. Found 452.2082.

4.4.3. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(2′-methylphenyl)-2-cyclopentene-1,3-dicarboxylate (8g).** A yellow oil (0.141 g, 33%). ^{1}H NMR δ: 7.34 (s, 5H), 7.12 (d, J=10.5 Hz, 1H), 6.85 (br s, 1H), 5.70 (br s, 1H), 5.10 (s, 2H), 4.53 (ddd, J=1.8, 6.6, 6.6 Hz, 1H), 4.06 (m, 2H), 3.79 (s, 3H), 3.16 (dd, J=8.4, 13.8 Hz, 1H), 2.41 (s, 3H), 2.10 (m, 1H), 108 (t, 3H). ^{13}C NMR δ: 172.8 (CO), 164.3 (CO), 155.5 (CO), 143.4 (C), 142.1 (C), 140.6 (CH), 136.5 (C), 135.7 (C), 130.4 (CH), 128.7 (3CH), 128.4 (CH), 128.3 (CH), 126.7 (CH), 69.9 (C), 67.1 (CH_2), 60.9 (CH_2), 53.3 (CH_3), 45.4 (CH), 45.1 (CH_2), 20.0 (CH_3), 14.1 (CH_3). MS (ES) *m/z* 438.1 ([M+1], 40%). HRMS calcd for $C_{25}H_{28}O_6N$ (MH^+) 438.1917. Found 438.1909.

4.4.4. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(3′-methoxyphenyl)-2-cyclopentene-1,3-dicarboxylate (8i).** A colourless oil (0.486 g, 50%). ^{1}H NMR δ: 7.34 (s, 5H), 7.25 (t, 1H), 6.85 (s, 1H), 6.78 (2, 1H), 6.73 (m, 2H), 5.80 (br s, 1H), 5.10 (s, 2H), 4.20 (t, 1H), 4.10 (m, 2H), 3.77 (s, 3H), 3.10 (dd, J=8.7, 10.8 Hz, 1H), 2.20 (dd, J=9.0, 15.3 Hz, 1H), 1.10 (t, 3H). ^{13}C NMR δ: 172.5 (CO), 164.1 (CO), 159.9 (CO), 155.1 (C), 145.2 (C), 143.1 (C), 140.7 (C), 136.3 (C), 129.7 (CH), 128.8 (2CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 120.1 (CH), 113.3 (CH), 112.5 (CH), 69.8 (C), 67.2 (CH_2), 60.0 (CH_2), 55.4 (CH_3), 53.6 (CH_3), 50.1 (C), 46.0 (C), 14.3 (CH_3). MS (CI) *m/z* 454 ([M+1], 25%). HRMS calcd for $C_{25}H_{28}O_6N$ (MH^+) 454.1866. Found 454.1821.

4.4.5. (1*S, 4*R**)-3-Ethyl 1-methyl 1-(benzyloxycarbonylamino)-4-(1)-naphthalene-2-cyclopentene-1,3-dicarboxylate (8j).** An yellow oil (0.13 g, 47%). ^{1}H NMR δ: 8.2–7.2 (m, 12H), 7.03 (s, 1H), 5.6 (br s, 1H), 5.1 (s, 2H), 4.05 (m, 3H, OCH_2CH_3 and H-5), 3.81 (s, 3H), 3.30 (dd, J=5.1, 9.8 Hz, 1H), 2.20 (m, 1H), 1.10 (t, 3H). ^{13}C NMR δ: 172.5 (CO), 164.1 (CO), 155.0 (CO), 140.5 (C), 136.1 (C), 134.2 (C), 133.1 (C), 131.0 (C), 124–133 (C), 69.0 (C), 66.5 (CH_2), 61.0 (CH_2), 52.8 (CH_3), 45.9 (CH_2), 14.0 (CH_3). MS (CI) *m/z* 474 ([M+1], 100%). HRMS calcd for $C_{28}H_{27}O_6N$ (MH^+) 473.1838. Found 473.1815.

4.5. General hydrolysis procedure for the preparation of *rac*-9

Compound **8a** (0.146 g, 0.345 mmol), was dissolved in 6 M HCl (2 mL) and heated at 100 °C overnight. After cooling, the reaction mixture was diluted with water (2 mL) and washed with diethyl ether (2×4 mL). Water was removed under reduced pressure to give **9a** as a white solid (96 mg, 100%). ^{1}H NMR (D_2O) δ: 7.43 (br s, 5H), 6.96 (br s, 1H), 4.55 (br s, 1H), 3.37 (m, 1H), 2.22 (m, 1H). ^{13}C NMR (D_2O) δ: 166.8 (CO), 162.2 (CO), 141.9 (C), 137.5 (C), 124.8 (2 CH), 123.2 (3 CH), 63.7 (C), 45.4 (CH), 39.6 (CH_2). MS (ES) *m/z* 247.9 ([M+1], 55%). HRMS calcd for $C_{13}H_{14}O_4N$ (MH^+) 248.0923. Found 248.0911.

4.5.1. (1*S, 4*R**)-1-Amino-4-(4′-methylphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9b).** A white solid (0.190 g, 97%). ^{1}H NMR (D_2O) δ 7.15–7.08 (m, 4H), 6.77 (d, J=2.1 Hz, 1H), 4.36 (dd, J=2.4, 8.1 Hz, 1H), 3.17 (dd, J=8.4, 14.1 Hz, 1H), 2.20 (s, 3H), 2.00 (d, J=8.4, 14.1 Hz, 1H). ^{13}C NMR (D_2O) δ: 167.2 (CO), 162.5 (CO), 142.5 (C), 134.7 (C), 133.4 (C), 132.6 (CH), 125.6 (2 CH), 123.5 (2 CH), 64.0 (C), 45.4 (CH), 39.9 (CH_2), 16.4 (CH_3). MS (ES) *m/z* 262.1 ([M+1], 100%). HRMS calcd for $C_{14}H_{16}O_4N$ (MH^+) 262.1079. Found 262.1131.

4.5.2. (1*S, 4*R**)-1-Amino-4-(4′-hydroxyphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9c).** A light grey solid (0.067 g, 81%). ^{1}H NMR (D_2O) δ: 7.05 (d, J=7.5 Hz, 2H), 6.76 (d, J=7.5 Hz, 2H), 6.71 (s, 1H), 4.33 (t, 3H), 3.12 (dd, J=8.1, 14.1 Hz, 1H), 1.94 (dd, J=8.1, 13.5 Hz, 1H). ^{13}C NMR (D_2O) δ: 168.0 (CO), 163.4 (CO), 151.1 (C), 143.1 (C), 133.1 (CH), 130.5 (C), 125.3 (2CH), 112.3 (2CH), 64.4 (C), 45.5 (CH), 40.5 (CH_2). MS (ES) *m/z* 264.0 ([M+1], 30%).

4.5.3. (1*S, 4*R**)-1-Amino-4-(3′-methylphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9d).** A light grey solid (0.067 g, 80%). ^{1}H NMR (D_2O) δ: 7.13–6.89 (m, 4H), 6.66 (s, 1H), 4.28 (dd, J=8.1, 15.6 Hz, 1H), 3.36 (dd, J=7.5, 14.4 Hz, 1H), 3.10 (dd, J=8.4, 14.4 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (D_2O) δ: 173.1 (CO), 168.5 (CO), 148.2 (C), 143.8 (C), 141.0 (C), 138.7 (CH), 130.9 (CH), 129.9 (CH), 126.2 (CH), 69.8 (C), 51.5 (CH), 45.8 (CH_2), 22.4 (CH_3). MS (ES) *m/z* 169 [M− (2×CO_2H+2H)].

4.5.4. (1*S, 4*R**)-1-Amino-4-(3′-trifluoromethylphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9e).** A white solid (0.062 g, 78%). ^{1}H NMR (D_2O) δ: 7.42 (br s, 2H), 7.31 (m, 2H), 6.69 (d, J=2.1 Hz, 1H), 4.38

(dd, J=2.4, 8.1 Hz, 1H), 3.09 (dd, J=8.1, 14.1 Hz, 1H), 1.90 (dd, J=8.1, 14.1 Hz, 1H). ^{13}C (D_2O): 171.5 (CO), 166.1 (CO) 147.7 (C), 145.1 (C), 138.1 (C), 132.7 (CH), 130.6 (CH), 125.4 (CH), 124.9 (CH), 125.4 (CH), 111.1 (C), 69.0 (C), 51.4 (CH), 45.3 (CH_2). MS (ES) m/z 317.9 ([M+1], 100%). HRMS calcd for $C_{14}H_{15}F_3O_4N$ (MH^+) 318.0953. Found 318.0966.

4.5.5. (1*S, 4*R**)-1-Amino-4-(3′-ethoxylphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9f).** A white solid (0.055 g, 59%). ^{1}H NMR (D_2O, 300 MHz) δ: 7.03 (d, J=6.6 Hz, 3H), 6.91 (d, J=6.0 Hz, 1H), 6.67 (s, 1H), 4.54 (m, 1H), 3.14 (dd, J=8.1, 14.1 Hz, 1H), 2.18 (s, 3H), 1.77 (dd, J=7.8, 14.1 Hz, 1H). ^{13}C NMR (CD_3OD) δ: 170.8 (CO), 165.5 (CO), 147.5 (C), 144.8 (C), 142.6 (CH), 135.9 (C), 130.1, 128.6 (CH), 127.0 (CH), 126.4 (CH), 68.0 (C), 50.6 (CH), 44.5 (CH_2), 28.7 (CH_2), 15.1 (CH_3). MS (ES) m/z 262.0 ([M+1], 50%). HRMS Calcd for $C_{14}H_{15}F_3O_4N$ (MH^+) 262.1079. Found 262.1119.

4.5.6. (1*S, 4*R**)-1-Amino-4-(2′-methylphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9g).** A grey solid (56 mg, 100%). ^{1}H NMR (D_2O) δ: 7.19 (t, 1H), 7.06 (d, J=9.9 Hz, 2H), 6.97 (d, J=7.5 Hz, 1H), 6.70 (s, 1H), 4.34 (t, H), 3.09 (dd, J=8.7, 13.8 Hz, 1H), 2.48 (q, 2H), 1.89 (dd, J=8.4, 13.5 Hz, 1H), 1.03 (t, 3H). ^{13}C NMR (CD_3OD) δ: 170.5 (CO), 165.4 (CO), 147.9 (C), 141.1 (C), 135.7 (CH), 135.6 (C), 130.1 (CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 68.0 (C), 46.1 (CH), 43.5 (CH_2), 18.6 (CH_3). MS (ES) m/z 276.0 ([M+1], 10%). HRMS calcd for $C_{15}H_{18}O_4N$ (MH^+) 276.1236. Found 276.1246.

4.5.7. (1*S, 4*R**)-1-Amino-4-(3′,4′-dimethylphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9h).** A white solid (65 mg, 56%). ^{1}H NMR (CD_3OD) δ: 6.87 (s, 3H), 6.66 (s, 1H), 4.35 (m, 1H), 3.17 (dd, J=8.1, 13.2 Hz, 1H), 2.2 (s, 6H), 1.98 (dd, 1H, J=8.7, 12.9 Hz, 1H). ^{13}C NMR (CD_3OD) δ: 173.4 (CO), 168.3 (CO), 149.0 (C), 145.5 (C), 139.2 (2C), 136.8 (CH), 129.3 (CH), 127.5 (2CH), 67.4 (C), 49.8 (CH), 45.4 (CH_2), 21.2 ($2CH_3$). MS (ES) m/z 276.1 ([M+1], 80%).

4.5.8. (1*S, 4*R**)-1-Amino-4-(3′-methoxyphenyl)-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9i).** A white solid (77 mg, 89%). ^{1}H NMR (CD_3OD) δ: 7.25 (m, 1H), 6.70–6.9 (m, 4H), 4.30 (m, 1H), 3.70 (s, 3H), 3.05 (dd, J=8.7, 14.1 Hz, 1H), 1.90 (dd, J=7.5, 13.5 Hz, 1H). ^{13}C NMR (CD_3OD) δ: 170.0 (CO), 156.8 (CO), 156.0 (C), 144.2 (C), 137.7 (C), 130.6 (CH), 120.1 (CH), 119.4 (CH), 114.4 (CH), 113.0 (CH), 68.4 (C), 55.6 (OCH_3), 49.8 (CH), 44.2 (CH_2). MS (ES) m/z 278.0 ([M+1], 100%). HRMS calcd for $C_{14}H_{16}NO_5$, (MH^+) 278.1048. Found 278.1028.

4.5.9. (1*S, 4*R**)-1-Amino-4-(1)-naphthlene-2-cyclopentene-1,3-dicarboxylate hydrochloride salt (9j).** A white solid (27 mg, 58%). ^{1}H NMR (CD_3OD) δ: 8.2 (d, J=5.4 Hz, 1H), 7.9 (d, J=8.1 Hz, 1H), 7.8 (d, J=8.4 Hz, 1H), 7.5 (m, 3H), 6.8 (s, 1H), 5.3 (m, 1H), 3.5 (m, 1H), 2.0 (m, 1H). ^{13}C NMR (CD_3OD) δ: 170.6 (CO), 165.3 (CO), 147.6 (C), 135.9 (CH), 134.0 (C), 131.4 (2C), 128.7 (CH), 128.3 (CH), 127.4 (CH), 126.3 (CH), 125.4 (CH), 123.3 (CH), 122.9 (CH), 68.3 (C), 45.5 (CH), 44.0 (CH_2). MS (ES) m/z 298 ([M+1], 100%). HRMS calcd for $C_{17}H_{16}NO_4$ (MH^+) 298.1079. Found 298.1053.

4.6. General procedure for the preparation of *rac*-10

To a solution of **8a** (0.445 mmol) in dry MeOH (8 mL) under a nitrogen atmosphere at 0 °C was added Mg turnings (4.45 mmol, 0.11 g). The reaction mixture was left to stir at 0 °C for 2 h then at room temperature for 3 h. Ethyl acetate (20 mL) was then added to the reaction mixture and then cooled to 0 °C. An ice-cold solution of 1 M HCl (10 mL) was added to the mixture and the resulting mixture extracted with ethyl acetate. The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed to give an oil, which was purified by column chromatography (ethyl acetate/petroleum spirit, 40:60) to give a mixture of **10a** and **11a**. This mixture was further separated by preparative HPLC.

4.6.1. (1*SR*, 3*RS*, 4*RS*)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-phenyl-cyclopentane-1,3-dicarboxylate (10a). A pale yellow oil (0.23 g, 73%). ^{1}H NMR δ: 7.34 (m, 5H), 7.26 (m, 5H), 5.82 (br s, 1H), 5.11 (dd, J=12.0, 15.3 Hz, 2H), 3.75 (br s, 3H), 3.68–3.58 (m, 1H), 3.55 (s, 3H), 3.37 (m, 1H), 2.76–2.63 (m, 2H), 2.50 (m, 1H), 2.29 (m, 1H). ^{13}C NMR δ: 174.3 (CO), 174.1 (CO), 155.2 (CO), 141.3 (C), 136.1 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 126.8 (CH), 66.8 (CH_2), 64.4 (C), 53.0 (CH_3), 51.7 (CH_3), 50.7 (CH), 48.8 (CH), 45.6 (CH_2), 41.5 (CH_2). MS (CI) m/z 412 ([M+1], 88%).

4.6.2. (1*SR*, 3*SR*, 4*RS*)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-phenyl-cyclopentane-1,3-dicarboxylate (11a). A pale yellow oil (46 mg, 15%). ^{1}H NMR δ: 7.35–7.16 (m, 10H), 5.86 (br s, 1H), 5.12 (s, 2H), 3.75 (br s, 3H), 3.69–3.60 (m, 1H), 3.57 (s, 3H), 3.34 (m, 1H), 2.76 (m, 2H), 2.39 (m, 1H). ^{13}C NMR δ: 174.9 (CO), 174.4 (CO), 156.0 (CO), 139.6 (C), 139.6 (C), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.2 (CH), 67.1 (CH_2), 65.1 (C), 60.6 (CH_2), 53.1 (CH_3), 49.3 (CH), 47.1 (CH), 42.0 (CH), 40.2 (CH_2), 13.8 (CH_3). MS (CI) m/z 426 ([M+1], 67%).

4.6.3. (1*S, 3*R**, 4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(4′-methylphenyl)-cyclopentane-1,3-dicarboxylate (10b).** A pale yellow oil (0.408 g, 77%). ^{1}H NMR δ: 7.36 (s, 5H), 7.18–7.06 (m, 4H), 5.67 (s, 1H), 5.12 (dd, J=12.0, 15 .0 Hz, 1H), 4.03 (q, 2H), 3.78 (s, 3H), 3.60 (dd, J=11.1, 16.5 Hz, 1H), 3.33 (m, 1H), 2.69 (dd, J=7.8, 14.1 Hz, 1H), 2.67 (dd, J=10.8, 13.5 Hz, 1H), 2.52–2.45 (m, 1H), 2.31 (s, 3H), 1.11 (t, 3H). ^{13}C NMR δ: 174.3 (CO), 173.6 (CO), 155.3 (CO), 138.2 (C), 136.2 (C), 127.1 (2×CH), 128.4 (2×CH), 128.0 (CH), 127.6 (CH), 127.1 (2×CH), 66.7 (CH_2), 64.4 (C), 60.4 (CH_2), 52.9 (CH_3), 50.8 (CH), 48.4 (CH), 45.6 (CH_2), 41.4 (CH_2), 20.9 (CH_3), 14.0 (CH_3). MS (ES) m/z 439.6 ([M+1], 100%). HRMS calcd for $C_{25}H_{30}O_6N$ (MH^+) 440.2073. Found 440.2066.

4.6.4. (1*S, 3*R**, 4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(3′-methylphenyl)-cyclopentane-1,3-dicarboxylate (10d).** A light yellow oil (0.46 g, 85%). ^{1}H NMR δ: 7.36 (s, 5H), 7.26–7.04 (m, 4H), 5.62 (br s, 1H), 5.13 (dd, J=12.3, 14.1 Hz, 2H), 4.11 (q, 2H), 3.78 (br s, 3H), 3.65 (dd, J=11.1, 15.9 Hz, 2H), 3.58 (s, 3H), 3.37 (m,

1H), 2.88 (dd, J=9.0, 14.4 Hz, 1H), 2.67 (dd, J=10.5, 13.8 Hz, 1H), 2.54–2.48 (m, 1H), 2.31 (br s, 1H), 1.25 (t, 3H). ^{13}C NMR δ: 174.7 (CO), 174.5 (CO), 155.8 (CO), 141.6 (C), 138.3 (C), 136.5 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.1 (CH), 124.5 (CH), 66.9 (CH_2), 64.7 (C), 53.2 (CH_3), 52.0 (CH_3), 50.8 (CH), 48.9 (CH), 21.7 (CH_3). MS (CI) m/z 426 ([M+1], 24%).

4.6.5. (1*S,3*R**,4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(3′-trifluoromethylphenyl)-cyclopentane-1,3-dicarboxylate (10e).** A light yellow oil (0.139 g, 95%). ^{1}H NMR δ: 7.53–7.39 (m, 4H), 7.35 (s, 5H), 5.81 (s, 1H), 5.12 (s, 2H), 3.73 (br s, 1H), 3.72–3.65 (m, 1H), 3.58 (s, 3H), 2.77–2.63 (m, 2H), 2.54–2.36 (m, 2H). ^{13}C NMR δ: 174.5 (CO), 174.1 (CO), 155.7 (CO), 142.8 (C), 141.0 (C), 136.4 (C), 131.0 (CH), 129.4 (CH), 128.8 (3CH), 128.8 (C), 128.5 (CH), 128.4 (2CH), 128.3 (C), 124.6–124.5 (CH), 124.1–124.0 (CH), 67.1 (CH_2), 64.6 (C), 53.4 (CH_3), 52.1 (CH_3), 51.0 (CH), 48.8 (CH), 45.4 (CH_2), 41.7 (CH_2). MS (ES) m/z 494 ([M+1], 20%). HRMS calcd for $C_{25}H_{27}O_6NF_3$ (MH^+) 494.179048. Found 494.17933.

4.6.6. (1*S,3*R**,4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(3′-ethylphenyl)-cyclopentane-1,3-dicarboxylate (10f).** A light yellow oil (0.22 g, 94%). ^{1}H NMR δ: 7.37 (s, 5H), 7.22 (t, 3H), 7.10–6.99 (m, 3H), 5.62 (s, 1H), 5.13 (s, 2H), 3.80 (br s, 3H), 3.67–3.60 (m, 1H), 3.59 (s, 3H), 3.37 (m, 1H), 2.69 (dd, J=6.3, 8.1 Hz, 2H), 2.61 (q, 2H), 2.53–2.51 (m, 1H), 2.36–2.28 (m, 1H), 1.22 (t, 3H). ^{13}C NMR δ: 174.7 (CO), 174.5 (CO), 155.8 (CO), 144.7 (C), 141.6 (C), 135.3 (C), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (2CH), 127.3 (CH), 126.7 (CH), 124.6 (CH), 67.1 (CH_2), 64.8 (C), 53.3 (CH_3), 52.0 (CH_3), 50.9 (CH), 49.0 (CH), 45.9 (CH_2), 41.8 (CH_2), 29.1 (CH_2), 15.9 (CH_3). MS (ES) m/z 454.1 ([M+1], 80%). HRMS calcd for $C_{26}H_{32}O_6N$ (MH^+) 454.2230. Found 454.2290.

4.6.7. (1*S,3*R**,4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(2′-methylphenyl)-cyclopentane-1,3-dicarboxylate (10g).** A light yellow oil (0.243 g, 92%). ^{1}H NMR δ: 7.35 (s, 5H), 7.2–7.12 (m, 4H), 5.63 (br s, 1H), 5.12 (s, 2H), 3.93 (dd, J=10.2, 18.6 Hz, 1H), 3.79 (br s, 3H), 3.57 (s, 3H), 2.77–2.67 (m, 2H), 2.55 (m, 1H), 2.36 (dd, J=8.4, 16.5 Hz, 1H), 2.36 (s, 3H), 2.08 (m, 1H). ^{13}C NMR δ: 174.7 (CO), 174.5 (CO), 155.7 (CO), 139.8 (C), 136.6 (C), 136.4 (2C), 130.6 (CH), 128.8 (CH), 128.8 (2CH), 128.5 (CH), 128.4 (CH), 127.1 (CH), 126.8 (CH), 125.9 (CH), 67.1 (CH_2), 64.7 (C), 53.3 (CH_3), 52.1 (CH_3), 50.0 (CH), 46.0 (CH_2), 44.5 (CH), 41.65 (CH_2), 19.9 (CH_3). MS (ES) m/z 440.1 ([M+1], 50%). HRMS Calcd for $C_{25}H_{30}O_6N$ (MH^+) 440.2073. Found 440.2065.

4.6.8. (1*S,3*R**,4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(3′,4′-dimethylphenyl)-cyclopentane-1,3-dicarboxylate (10h).** A light yellow oil (92 mg, 76%). ^{1}H NMR δ: 7.39 (s, 1H), 6.86 (s, 3H), 5.11 (s, 2H), 3.76 (s, 3H), 3.58 (s, 3H), 3.61 (m, 1H), 3.30 (m, 1H), 2.65 (dd, J=10.5, 13.8 Hz, 2H), 2.48 (m, 1H), 2.20 (s, 6H), 2.08 (dd, J=12.6, 12.9 Hz, 1H), 1.12 (t, 3H). ^{13}C NMR δ: 174.8 (CO), 155.8 (CO), 141.8 (CO), 138.2 (2C), 137.9 (C), 130.0 (CH), 128.1 (CH), 127.8 (CH), 67.0 (CH_2), 65.0 (C), 53.0 (CH_3), 52.0 (CH_3), 50.8 (C), 49.0 (C), 46.0 (C), 41.8 (C), 21.8 ($2CH_3$).

4.6.9. (1*S,3*R**,4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(3′-methoxyphenyl)-cyclopentane-1,3-dicarboxylate (10i).** A light yellow oil (85 mg, 86%). ^{1}H NMR δ: 7.33 (s, 5H), 7.18 (t, J=6.57 Hz, 1H), 6.82 (s, 1H), 6.73 (dd, J=2.4, 3.3 Hz, 2H) 5.68 (br s, 1H), 5.10 (s, 2H), 3.75 (s, 6H), 3.73 (m, 1H), 3.57 (s, 3H), 3.38 (dd, J=11.0, 19.0 Hz, 1H), 2.69 (dd, J=10.5, 13.8 Hz, 2H), 2.45 (m, 1H), 2.25 (dd, J=9.0, 15.0 Hz, 1H). ^{13}C NMR δ: 174.5 (CO), 159.8 (2CO), 155.5 (C), 143.3 (C), 136.3 (C), 129.8–112.3 (4CH), 67.1 (C), 64.8 (CH_2), 55.5 (2CH3), 53.4 (CH_3), 52.2 (CH), 50.9 (CH), 45.7 (CH_2), 41.8 (CH_2). MS (CI) m/z 442 ([M+1], 100%). HRMS Calcd for $C_{24}H_{28}O_7N$ (MH^+) 442.1866. Found 442.1811.

4.6.10. (1*S, 3*R**, 4*R**)-1,3-Dimethyl 1-(benzyloxycarbonylamino)-4-(1)-naphthlene-cyclopentane-1,3-dicarboxylate (10j).** A light yellow oil (25 mg, 34%). ^{1}H NMR δ: 8.20–7.20 (m, 12H), 5.70 (br s, 1H), 5.10 (s, 2H), 4.50 (dd, J=8.4, 18.9 Hz, 1H), 3.8 (s, 3H), 3.6 (m, 1H), 3.30 (s, 3H), 2.9 (dd, J=5.4, 13.8 Hz, 1H), 2.8 (dd, J=8.4, 18.8 Hz, 1H), 2.6 (dd, J=6.3, 8.2 Hz, 1H), 2.2 (m, 1H). ^{13}C NMR δ: 175.0 (CO), 156.0 (CO), 136–132 (3C), 124–130 (7CH), 68.0 (CH_2), 66.O (C), 50.0 ($2CH_3$), 48.1 (CH), 46.0 (CH_2), 44.2 (CH_2) 42.0 (CH).

4.7. General hydrolysis procedure the preparation of *rac*-12 and *rac*-13

Compound **10b** (0.168 g, 0.38 mmol), was dissolved in 6 M HCl (2 mL) and heated at 100 °C overnight. After cooling, the reaction mixture was diluted with water (2 mL) and washed with ether (2×4 mL). Water was removes under reduced pressure to give **12b** as a white solid (98 mg, 90%). ^{1}H NMR (D_2O) δ: 7.04 (d, J=7.8 Hz, 2H), 6.97 (d, J=7.5 Hz, 2H), 3.44 (ddd, J=6.9, 11.4, 11.4 Hz, 1H), 3.14 (dd, J=10.5, 19.5 Hz, 1H), 2.62 (dd, J=10.8, 12.0 Hz, 1H), 2.57 (dd, J=7.5, 14.1 Hz, 1H), 2.36 (dd, J=8.7, 15.0 Hz, 1H), 2.05 (s, 3H), 2.0 (t, J=6.9 Hz, 1H). ^{13}C NMR (D_2O) δ: 173.6 (CO), 170.9 (CO), 134.6 (C), 133.0 (C), 126.1 (2×CH), 124.3 (2×CH), 59.3 (C), 46.9 (CH), 46.0 (CH), 35.5 (CH), 41.0 (CH_2), 16.9 (CH_3). MS (ES) m/z 264.1 ([M+1], 100%). HRMS calcd for $C_{14}H_{18}O_4N$, (MH^+) 264.1236. Found 264.1261.

4.7.1. (1*SR*, 3*RS*, 4*RS*)-1-Amino-4-phenyl-cyclopentane-1,3-dicarboxylate hydrochloride salt (12a). A white solid (22 mg, 63%). ^{1}H NMR (D_2O) δ: 6.92–6.83 (m, 5H), 3.19 (m, 1H), 2.19 (m, 1H), 2.33 (m, 2H), 2.08 (m, 1H), 1.74 (m, 1H). ^{13}C NMR (D_2O, 75.65 MHz) δ: 176.5 (CO), 173.8 (CO), 139.2 (C), 128.9 (CH), 128.7 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 61.9 (C), 49.5 (CH), 49.0 (CH), 43.7 (CH_2), 38.2 (CH_2).

4.7.2. (1*S, 3*R**, 4*R**)-1-Amino-4-(3-methyl)-phenyl-cyclopentane-1,3-dicarboxylate hydrochloride salt (12d).** A white solid (95 mg, 95%). ^{1}H NMR (D_2O) δ: 7.18–6.93 (m, 4H), 4.50 (dd, J=8.3, 16.0 Hz, 1H), 3.36 (dd, J=8.1, 11.7 Hz, 1H), 2.89 (dd, J=7.5, 12.0 Hz, 1H), 2.54 (dd, J=6.3, 14.1 Hz, 1H), 2.36 (dd, J=10.2, 14.1 Hz, 1H), 2.13 (s, 3H), 1.98 (m, 1H). ^{13}C NMR (D_2O) δ: 168.1 (CO), 166.5 (CO), 141.1 (C), 139.0 (C), 128.9 (CH), 128.1 (CH), 127.4 (CH), 124.3 (CH), 64.5 (C), 53.7 (CH), 50.3 (CH), 44.6 (CH_2), 41.1 (CH_2), 20.6 (CH_3).

4.7.3. (1*S, 3*R**, 4*R**)-1-Amino-4-(3-trifluoromethyl)-phenyl-cyclopentane-1,3-dicarboxylate hydrochloride salt (12e).** A white solid (87 mg, 94%). ^{1}H NMR (D_2O) δ: 7.39 (s, 1H), 7.31–7.19 (m, 3H), 3.48 (dd, J=12.0, 18.3 Hz, 1H), 3.14 (dd, J=8.7, 19.5 Hz, 1H), 2.62–2.50 (m, 2H), 2.33 (dd, J=9.0, 15.0 Hz, 1H), 1.97 (dd, J=12.9, 12.9 Hz, 1H). ^{13}C NMR (D_2O) δ: 176.4 (CO), 174.1 (CO), 140.5 (C), 130.9 (CH), 130.0 (C), 129.5 (2CH), 125.9 (C), 124.2 (2CH), 62.5 (C), 50.0 (CH), 49.0 (CH), 44.0 (CH_2), 38.7 (CH_2). MS (ES) m/z 317.9 ([M+1], 100%). HRMS calcd for $C_{14}H_{15}O_4NF_3$ (MH^+) 318.0953. Found 318.0966.

4.7.4. (1*S, 3*R**, 4*R**)-1-Amino-4-(3-ethyl)-phenyl-cyclopentane-1,3-dicarboxylate hydrochloride salt (12f).** A white solid (82 mg, 98%). ^{1}H NMR (D_2O) δ: 7.17 (dd, J=7.5, 15.0 Hz, 1H), 7.12–7.00 (m, 3H), 3.51 (ddd, J=6.6, 11.7, 11.7 Hz, 1H), 3.22 (dd, J=10.5, 19.8 Hz, 1H), 2.65 (m, 1H), 2.44 (m, 3H), 2.03 (t, J=12.9 Hz, 1H), 1.00 (t, 3H). ^{13}C NMR (D_2O) δ: 175.12 (CO), 173.5 (CO), 144.7 (C), 140.0 (C), 28.5 (CH), 126.9 (CH), 126.6 (CH), 124.5 (CH), 60.0 (C), 50.2 (CH), 50.2 (CH), 45.0 (CH_2), 39.7 (CH_2), 28.7 (CH_2), 15.0 (CH_3). MS (ES) m/z 278 ([M+1], 100%). HRMS calcd for $C_{15}H_{20}O_4N$ (MH^+) 278.1392. Found 278.1394.

4.7.5. (1*S, 3*R**, 4*R**)-1-Amino-4-(2-methyl)-phenyl-cyclopentane-1,3-dicarboxylate hydrochloride salt (12g).** A white solid (98 mg, 100%). ^{1}H NMR (D_2O) δ: 7.27 (d, J=7.5 Hz, 1H), 7.14–7.10 (m, 3H), 3.69 (ddd, J=7.8, 12.0, 16.2 Hz, 1H), 3.06 (ddd, J=7.2, 12.0, 16.8 Hz, 1H), 2.59 (dd, J=7.5, 13.8 Hz, 1H), 2.42 (dd, J=13.8, 13.8 Hz, 1H), 2.23 (dd, J=7.5, 15.3 Hz, 1H), 2.21 (s, 3H), 1.60 (dd, J=12.0, 13.8 Hz, 1H). MS (ES) m/z 264 ([M+1], 100%). HRMS calcd for $C_{14}H_{18}O_4N$ (MH^+) 264.1236. Found 264.1262.

4.7.6. (1*S, 3*R**, 4*R**)-1-Amino-4-(3,4-dimethyl)-phenyl-cyclopentane-1,3-dicarboxylate hydrochloride salt (12h).** A white solid (65 mg, 56%). ^{1}H NMR (CD_3OD) δ: 6.90 (s, 2H), 6.88 (s, 1H), 3.17 (dd, J=10.2, 12.8 Hz, 1H), 2.57 (dd, J=10.2, 20.7 Hz, 2H), 2.3 (m, 1H), 2.2 (s, 6H), 1.98 (dd, J=10.3, 12.9 Hz, 1H). ^{13}C NMR (CD_3OD) δ: 175.1 (CO), 173.0 (CO), 139.7 (C), 138.1 (2C), 128.6 (CH), 125.0 (2CH), 62.6 (C), 50.1 (CH), 47.3 (CH), 45.4 (CH_2), 39.4 (CH_2), 21.2 ($2CH_3$). MS (ES) m/z 264.1 ([M+1], 100%). HRMS calcd for $C_{14}H_{18}O_4N$ (MH^+) 264.1236. Found 264.1261.

4.7.7. (1*S, 3*R**, 4*R**)-1-Amino-4-(3-methoxy)-phenyl-cyclopentane-1,3-dicarboxylate hydrochloride salt (12i).** A white solid (54 mg, 88%). ^{1}H NMR (CD_3OD) δ: 7.20 (t, 1H), 6.78 (s, 1H), 6.90–6.70 (m, 2H), 3.62 (s, 3H), 3.4 (m, 1H), 3.2 (dd, J=9.0, 19.8 Hz, 1H), 3.05 (dd, 1H, J=9.0, 15.3 Hz, 1H), 2.61 (dd, J=6.3, 12.6 Hz, 2H), 1.90 (dd, J=7.2, 11.8 Hz, 1H). ^{13}C NMR (D_2O) δ: 178.0 (CO), 174.4 (CO), 155.6 (C), 141.6 (C), 130.5 (CH), 120.0 (CH), 114.6 (CH), 114.3 (CH), 63.9 (C), 55.6 (CH_3), 49.7 (CH), 44.2 (CH_2), 39.7 (CH_2). MS (ES) m/z 280 ([M+1], 80%).

4.7.8. (1*S, 3*R**, 4*R**)-1-Amino-4-(1)-naphthlene-cyclopentane-1,3-dicarboxylate hydrochloride salt (12j).** A white solid (66 mg, 33%). ^{1}H NMR (CD_3OD) δ: 8.1 (d, J=8.4 Hz, 1H), 7.8 (d, J=9.3 Hz, 1H), 7.7 (d, J=7.2 Hz, 1H), 7.6 (d, J=7.2 Hz, 1H), 7.5 (m, 3H), 4.6 (dd, J=6.3, 8.2 Hz, 1H), 3.7 (dd, J=6.1, 8.4 Hz, 1H), 2.9 (m, 2H), 2.6 (dd, J=6.3, 8.1 Hz, 1H), 2.2 (dd, J=10, 13.5 Hz, 1H), ^{13}C NMR (CD_3OD) δ: 174.7 (CO), 172.9 (CO), 135.7 (C), 134.2 (C), 132.1 (C), 128.7 (CH), 127.6 (CH), 126.1 (CH), 125.6 (CH), 125.4 (CH), 122.6 (CH), 122.5 (CH), 62.3 (C), 47.9 (CH), 45.2 (CH), 45.0 (CH_2), 39.6 (CH_2). MS (ES) m/z 300 ([M+1], 100%).

4.8. Signal transduction at mGlu2 receptors in CHO cells

Human mGluR2 (cloned and expressed in house) were grown in DMEM/Glutamax-I to which 2 mM glutamine, 46 mg/L proline, and 10% dialyzed fetal calf serum were added.

4.9. [^{35}S]GTPγS radioligand binding assay for human mGlu2

Membrane preparation. Cells were grown to confluence. Cells were washed twice with ice-cold PBS without Ca^{2+} and Mg^{2+}, scraped off and homogenized in buffer (EDTA mM, Hepes 20 mM). After centrifugation (18,000 rpm, 15 min, 4 °C), the pellet was washed with 0.1 mM EDTA, 20 mM Hepes, and resuspended in the same buffer for protein determination with the Biorad assay. Membrane aliquots were stored at −70 °C.

[^{35}S]GTPγS radioligand binding. Each incubate contained 10 μg of membrane protein in 250 μL of binding buffer (HEPES 20 mM, NaCl 100 mM, $MgCl_2$ 3 mM, GDP 3 μM, pH 7.4). The incubation was started by addition of an appropriate concentration of agonist and/or antagonist. Compounds were incubated with the membranes at 37 °C for 30 min. Subsequently, 0.1 nM [^{35}S]GTPγS (approximately 2×10^5 DPM) was added in the presence or absence of 30 μM glutamate. The mixture was further incubated for 30 min at 37 °C. The reactions were terminated by separating free and bound radioactivity by rapid vacuum filtration using a Packard filtration manifold through GF/B prewetted glass fiber filters. Filters were rapidly washed two times with cold 10 mM.

NaH_2PO_4/10 mM Na_2HPO_4 buffer, pH 7.4. Filters were transferred to vials for subsequent counting in a scintillation counter. Results are expressed as % of glutamate-induced response, the latter being defined as 100%. Glutamate and amino acids were dissolved and diluted in water. Concentration–response curves were drawn on a logarithmic scale. Sigmoidal curves of best fit were calculated by nonlinear regression analysis using GraphPad software (San Diego, CA). The pIC_{50}-value referred to the concentration of a compound producing half the maximum response.

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Convenient syntheses of 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols and the corresponding trimethylsilyl ethers

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Abstract—A new convenient synthetic procedure to obtain various 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols and the corresponding trimethylsilyl ethers has been worked out starting from anhydrides or activated esters of carboxylic acids and trimethyl(trifluoromethyl)silane in the presence of tetramethylammonium fluoride. Conditions for the selective formation of 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols as well as the trimethylsilyl derivatives have been found.

1. Introduction

A series of 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols was established in 1960.[1] Benzene derivatives with 2-hydroxy-1,1,1,3,3,3-hexafluoropropyl groups have been widely used as polymerisation sources for obtaining epoxy resins and urethane coatings.[2] Some years later it was found that such derivatives can be used for the stabilisation of hypervalent compounds.[3,4] Increased interest in fluorinated alcohols arose when they were used as intermediates for producing biologically active substances. In particular, compounds of different compositions, all containing the hydroxy-hexafluoro-2-propyl group, exhibited regulatory properties for plants growth, fungicidal, and also anti-arhythmic and antithrombotic activities[5] as liver X-receptor (LXR) modulators.[6] The lack of suitable and effective synthetic procedures has prevented the development of this field of organic chemistry so far.

The major number of aliphatic and aromatic 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols have been prepared from the appropriate organomagnesium compounds and hexafluoroacetone.[1,7] Electrophilic reactions of activated aromatic or heterocyclic compounds with hexafluoro-acetone offer an alternative access.[5,8]

During the past 15 years, trimethyl(trifluoromethyl)silane has been widely used for the introduction of trifluoromethyl groups into organic compounds.[9–11] Only few examples of 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols have been prepared from trifluoromethylketones and trimethyl-(trifluoromethyl)silane in the presence of fluoride-ion sources.[9–11]

To our knowledge, reactions of trimethyl(trifluoromethyl)-silane in the presence of fluoride ions with carboxylic acids anhydrides and activated esters have not been mentioned in the literature. It should be noted that commercial accessibility of a number of anhydrides of various carboxylic acids, as well as simple preparation of activated esters make these compounds considerably attractive for nucleophilic trifluoromethylations.

In this paper, we report a new and convenient synthetic method to prepare 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols and the corresponding trimethylsilyl ethers, based on the interaction of carboxylic acids anhydrides and activated esters with trimethyl(trifluoromethyl)silane in the presence of different amounts of fluoride ions.

2. Results and discussion

As a model reactant, we chose benzoic acid anhydride **1a**. In the reaction of 1 equiv of **1a**, 2 equiv of Me_3SiCF_3 and 1 equiv of $[Me_4N]F$ in dimethoxyethane,

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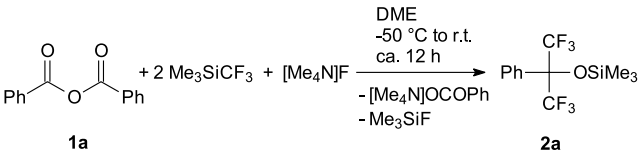
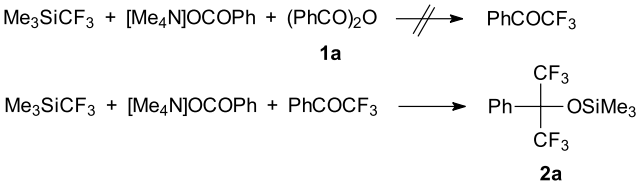
trimethyl[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)-ethoxy]silane **2a** was formed in 82% yield (Scheme 1).



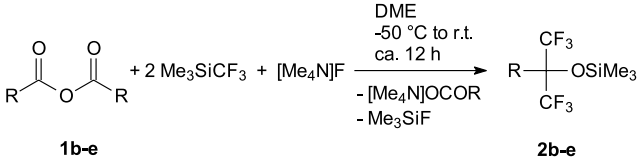
Scheme 1.

$[Me_4N]F$ initiates the reaction of Me_3SiCF_3 with **1a**. Later on, trifluoromethylation is forwarded by the concomitant product, tetramethylammonium benzoate. It must be noted that the nucleophilicity of the benzoate ion as an initiator is sufficiently high for the introduction of the second CF_3-group into the molecule (i.e. in the reaction with α,α,α-trifluoroacetophenone formed in the first step), while substitution of the benzoate moiety would require fluoride ions as activators. In comparative experiments, **1a** and α,α,α-trifluoroacetophenone were reacted with Me_3SiCF_3 and $[Me_4N]OCOPh$ in separate entries. While no reaction was observed with **1a**, α,α,α-trifluoroacetophenone was selectively transferred into **2a** (Scheme 2).



Scheme 2.

On the basis of the results obtained, we extended our attempts onto the anhydrides of aromatic, aliphatic, and heterocyclic acids, as well as *tert*-butyl carbonic anhydride, and succeeded in obtaining the corresponding trimethylsilyl ethers **2b–e** in high yields (Scheme 3, Table 1) proving that, again, the carboxylates formed during these reactions initiate formal addition of Me_3SiCF_3 to the carbonyl function of trifluoromethyl ketones.

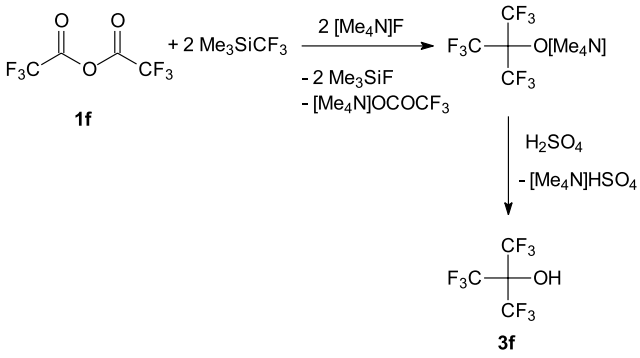


Scheme 3.

Table 1. Conversion of anhydrides **1a–f** into 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols **3** and the corresponding trimethylsilyl ethers **2**

Substrate	R	$[Me_4N]F$ (equiv)	Product	Yield (%)
1a	Ph	1	**2a**	82
1a	Ph	2	**3a**	81
1b	1-Naphthyl	1	**2b**	88
1c	Me	1	**2c**	62
1d	2-Furyl	1	**2d**	75
1e	*t*-BuO	1	**2e**	50
1f	CF_3	2	**3f**	87

From the anhydrides investigated, the reaction with trifluoroacetic acid anhydride **1f** gave a product mixture by ^{19}F NMR. Only after addition of a second equivalent of $[Me_4N]F$, the tetramethylammonium salt of 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-ol was selectively formed. This might be attributed to the low nucleophilicity of the trifluoroacetate anion which unlike the others does not initiate the consecutive reaction with the second equivalent of Me_3SiCF_3. Finally, acidification gave the alcohol **3f** in an overall yield of 87% (Scheme 4).



Scheme 4.

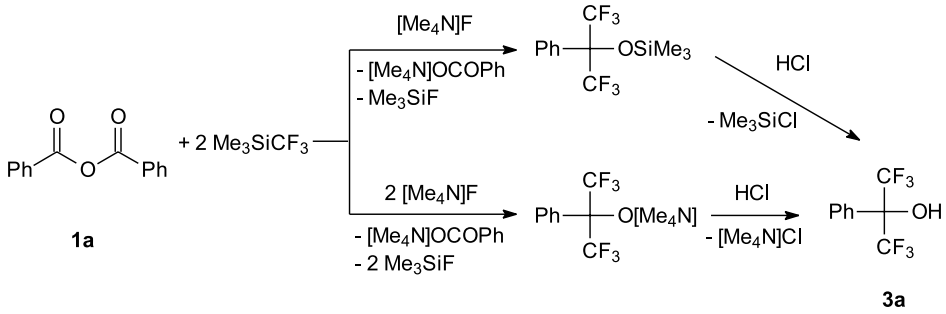
This procedure opens a convenient alternative route to 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-ol starting from relatively inexpensive trifluoroacetic acid anhydride, in contrast to the previously developed method requiring hexafluoroacetone.[12]

Procedures for obtaining 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols are based on treatment of the trimethylsilyl ethers or the tetramethylammonium salts with hydrochloric acid in tetrahydrofuran solution[13] which was exemplary studied in reactions with **1a** yielding the alcohol **3a** (Scheme 5, Table 1).

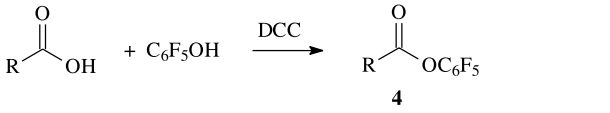
Unfortunately, anhydrides of some carboxylic acids are extremely difficult to synthesise, i.e. pyridine carboxylic acids anhydrides. In these cases, we applied a method nowadays frequently used in peptide synthesis.[14–16] For our purposes, we synthesised a series of highly reactive pentafluorophenyl esters and 1-benzoyl imidazole. These may be regarded as 'mixed' anhydrides of two Brönsted acids, a carboxylic acid and a phenol or imidazole, respectively.

Pentafluorophenyl esters of benzoic **4a**, pyridinecarboxylic **4g–i** and 3-phenyl-acrylic **4j** acids were prepared in high yields by reacting the corresponding carboxylic acids and pentafluorophenol in the presence of 1,3-dicyclohexyl-carbodiimide (DCC) (Scheme 6).[17]

In subsequent reactions, the pentafluorophenyl esters **4a**,**g–j** were treated with Me_3SiCF_3 in the presence of $[Me_4N]F$ under comparable conditions as used for the anhydrides. After adding 2 equiv of trimethyl(trifluoromethyl)silane and 1 equiv of tetramethylammonium fluoride to solutions of the pentafluorophenyl esters, the corresponding trimethylsilyl ethers **2a**,**g–j** were obtained in high yields (Scheme 7, Table 2).

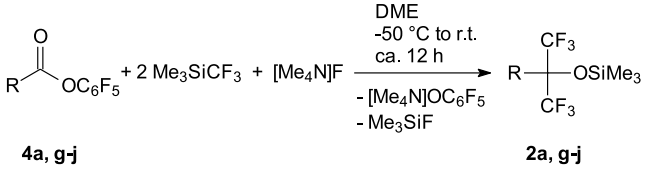


Scheme 5.



R = Ph (**a**), 2-C_5H_4N (**g**), 3-C_5H_4N (**h**), 4-C_5H_4N (**i**), *trans*-PhCH=CH (**j**)

Scheme 6.



Scheme 7.

substituent. As expected, 1-benzoyl imidazole **5** was converted into the trimethylsilyl ether **2a** or the alcohol **3a** under respective conditions in comparable high yields (Scheme 8, Table 2).

Despite of the fact that numerous papers deal with reactions of Me_3SiCF_3 in the presence of nucleophilic initiators with carbonyl group-containing compounds,[9–11] the formation of trimethyl[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)-ethoxy]silane **2a** starting with benzoyl chloride has only been mentioned once.[18] Bis(trifluoromethyl)cadmium complexes react with aromatic acid chlorides in the presence of strong bases to form both trifluoromethylaryl ketones and 1,1,1,3,3,3-hexafluoro-2-aryl-propan-2-ols.[19]

To compare the reaction behaviour of $Cd(CF_3)_2$ complexes and the Me_3SiCF_3/$[Me_4N]F$ system, we studied

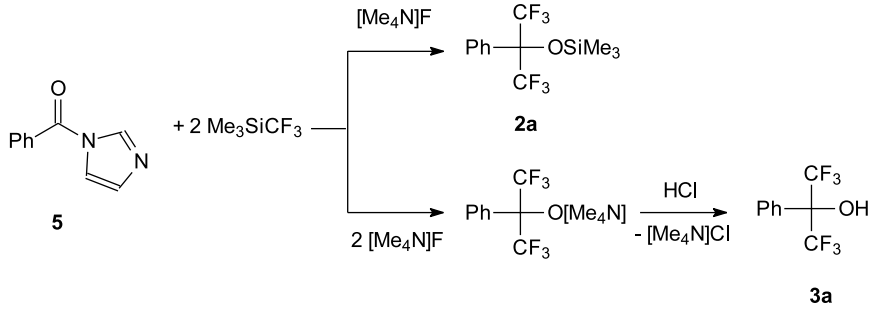
Table 2. Conversion of pentafluorophenyl esters **4** and 1-benzoyl imidazole **5** into 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols **3** and the corresponding trimethylsilyl ethers **2**

Substrate	R	Me_4NF (equiv)	Product	Yield (%)
4a	Ph	1	**2a**	92
4a	Ph	2	**3a**	81
4g	2-C_5H_4N	1	**2g**	52
4h	3-C_5H_4N	1	**2h**	72
4i	4-C_5H_4N	1	**2i**	60
4j	*trans*-PhCH=CH	1	**2j**	81
5	Ph	1	**2a**	94
5	Ph	2	**3a**	87

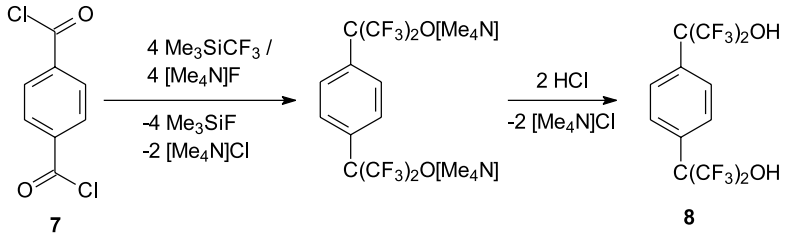
Both **1a** (see above) and **4a** in reactions with 2 equiv of Me_3SiCF_3 and 2 equiv of $[Me_4N]F$ after acidification gave **3a** in very good yield.

Effects on the activation of the carbonyl function are comparable for both the OC_6F_5 group and the imidazole

the reactions with the aroyl chlorides, benzoyl chloride **6** and terephthaloyl chloride **7**. Benzoyl chloride **6**, 2 equiv of Me_3SiCF_3 and 2 equiv of $[Me_4N]F$ in DME selectively gave the tetramethylammonium salt of 1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol which was converted into **3a** by acidification in 77% yield.



Scheme 8.



7 8

Scheme 9.

In a similar manner, terephthaloyl chloride **7** reacts with 4 equiv of trimethyl (trifluoromethyl)silane and 4 equiv of tetramethylammonium fluoride with formation of the bis(tetramethylammonium) salt of 1,1,1,3,3,3-hexafluoro-2-[4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-phenyl]propan-2-ol which upon treatment with hydrochloric acid was transferred into the corresponding alcohol **8** (82% yield) (Scheme 9).

It should be mentioned that benzene derivatives substituted with two hydroxy-hexafluoro-2-propyl groups are of interest as building blocks e.g. in polysiloxane chains.[20] Therefore, the search for selective and efficient synthetic methods for **8** and related compounds can be regarded as one of considerable interest.

3. Conclusion

A new, convenient and efficient synthesis for 1,1,1,3,3,3-hexafluoro-2-organyl-propan-2-ols has been developed starting from carboxylic anhydrides, activated esters, carboxylic acid chlorides and trimethyl(trifluoromethyl)-silane in the presence of tetramethylammonium fluoride. In a two-step reaction-substitution followed by addition to the carbonyl double bond-the title compounds are formed highly selectively in excellent yields.

4. Experimental

4.1. Materials and methods

All reactions were carried out in a dry argon (or nitrogen) atmosphere using Schlenk techniques.

Me_3SiCF_3 was purchased from ABCR, di-*tert*-butyldicarbonate from Fluka, 1,3-dicyclohexyl-carbodiimide (DCC), C_6F_5OH, all anhydrides and carboxylic acids from Aldrich. The following products were synthesised according to literature procedures: $[Me_4N]F$,[21] 2-furan carboxylic acid anhydride,[22] 1-naphthalene carboxylic acid anhydride,[23] 1-benzoyl imidazole.[24] All solvents were purified according to literature procedures.[25]

$^{13}C\{^1H\}$ NMR spectra (50.32 MHz) were recorded on a Bruker AC-200 spectrometer, ^1H (299.95 MHz) and ^{19}F (282.20 MHz) NMR spectra on a Varian VXR-300 spectrometer. Chemical shifts are given in ppm relative to Me_4Si and CCl_3F as external standards. EI mass spectra were run on a Finnigan MAT 95 spectrometer (20 eV). Melting points were measured in one-end open glass capillaries and are uncorrected.

4.2. Pentafluorophenyl esters (4a,g–j); general procedure

To a mixture of the appropriate acid (10 mmol) and pentafluorophenol (2.00 g, 11 mmol) in dioxane (30 mL), 1,3-dicyclohexylcarbodiimide (DCC) (2.27 g, 11 mmol) was added. The mixture was stirred for 1 h at room temperature. Dicyclohexylurea formed was filtered off, the solvent was evaporated under reduced pressure and the residue was purified by crystallisation from hexane.

4.2.1. Benzoic acid pentafluorophenyl ester (4a). Yield: 2.45 g (86%); colourless solid; mp 75–76 °C (lit.[26] mp 74–75 °C); δ_H (299.95 MHz, acetone-d_6) 8.26 (2H, dd, $J=8.6$, 1.6 Hz), 7.87 (1H, tt, $J=7.5$, 1.4 Hz), 7.70 (2H, td, $J=7.9$, 1.6 Hz); δ_F (282.20 MHz, acetone-d_6) −154.1 (2F, d, $J=$ 18.4 Hz), −159.3 (1F, t, $J=21$ Hz), −163.8 (2F, t, $J=$ 20.5 Hz).

4.2.2. Pyridine-2-carboxylic acid pentafluorophenyl ester (4g). Yield: 2.20 g (76%); colourless solid; mp 64–65 °C (lit.[17] mp 62–64 °C; lit.[27] mp 61–63 °C); δ_H (299.95 MHz, $CDCl_3$) 8.87 (1H, dq, $J=4.8$, 0.9 Hz), 8.34 (1H, d, $J=7.8$ Hz), 8.01 (1H, td, $J=7.8$, 1.8 Hz), 7.68 (1H, ddd, $J=7.8$, 4.8, 1.0 Hz); δ_F (282.20 MHz, $CDCl_3$) −152.6 (2F, d, $J=21$ Hz), −157.9 (1F, t, $J=21.5$ Hz), −162.0 (2F, t, $J=20$ Hz).

4.2.3. Pyridine-3-carboxylic acid pentafluorophenyl ester (4h). Yield: 1.94 g (67%); colourless solid; mp 62–63 °C; [Found: C, 49.7; H, 1.5; F, 33.1; N, 4.9. $C_{12}H_4F_5NO_2$ requires C, 49.84; H, 1.39; F, 32.85; N, 4.84%]; δ_H (299.95 MHz, $CDCl_3$) 9.41 (1H, dd, $J=1.8$, 0.8 Hz), 8.93 (1H, dd, $J=5.0$, 1.6 Hz), 8.48 (1H, dt, $J=8.1$, 1.8 Hz), 7.54 (1H, ddd, $J=8.1$, 5.0, 0.8 Hz); δ_F (282.20 MHz, $CDCl_3$) −152.7 (2F, d, $J=20$ Hz), −157.3 (1F, t, $J=21.5$ Hz), −162 (2F, t, $J=21.3$ Hz).

4.2.4. Pyridine-4-carboxylic acid pentafluorophenyl ester (4i). Yield: 2.08 g (72%); colourless solid; mp 53–54 °C (lit.[27] mp 52–54 °C); δ_H (299.95 MHz, $CDCl_3$) 8.91 (2H, dd, $J=4.5$, 1.6 Hz), 8.00 (2H, dd, $J=4.5$, 1.6 Hz); δ_F (282.20 MHz, $CDCl_3$): −152.7 (2F, d, $J=18.5$ Hz), −156.9 (1F, t, $J=21.7$ Hz), −161.8 (2F, t, $J=19.5$ Hz).

4.2.5. 3-Phenyl acrylic acid pentafluorophenyl ester (4j).[14] Yield: 2.86 g (91%); colourless solid; mp 87–88 °C; [Found: C, 57.6; H, 2.3; F, 30.1. $C_{15}H_7F_5O_2$ requires C, 57.33; H, 2.25; F, 30.23%]; δ_H (299.95 MHz, $CDCl_3$)

7.95 (1H, d, $J=16$ Hz), 7.60 (2H, d, $J=5.7$ Hz), 7.46 (2H, s), 7.44 (1H, t, $J=5.7$ Hz), 6.64 (1H, d, $J=16$ Hz); δ_F (282.20 MHz, $CDCl_3$) −153.1 (2F, d, $J=18.5$ Hz), −158.7 (1F, t, $J=21$ Hz), −163.0 (2F, t, $J=20.2$ Hz).

4.3. Trimethyl[2,2,2-trifluoro-1-organyl-1-(trifluoromethyl)ethoxy]silane (2a–j); general procedure

To a solution of the appropriate substrate (5 mmol) in dimethoxyethane (DME) (8 mL) at −50 °C trimethyl(trifluoromethyl)silane (Me_3SiCF_3) (1.50 g, 10.5 mmol) and tetramethylammonium fluoride ([Me_4N]F) (0.47 g, 5.0 mmol) were added. The mixture was stirred for 1 h at −30 °C and then overnight at room temperature. H_2O (25 mL) was added and the product was extracted with Et_2O (2×10 mL). The extract was washed with H_2O (5 mL), dried ($MgSO_4$) and purified by vacuum distillation.

4.3.1. Trimethyl[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy]silane (2a). Yield: 1.30 g (82%) (from **1a**); 1.45 g (92%) (from **4a**); 1.49 g (94%) (from **5**); colourless liquid; bp 80 °C/10 Torr. (lit.[28] bp 29 °C/0.03 Torr); δ_H (299.95 MHz, $CDCl_3$): 7.58–7.73 (2H, m); 7.44 (m, 3H), 0.23 (s, 9H, $Si(CH_3)_3$); δ_F (282.20 MHz, $CDCl_3$) −73.6.

4.3.2. Trimethyl[2,2,2-trifluoro-1-(1-naphtyl)-1-(trifluoromethyl)ethoxy]silane (2b). Yield: 1.61 g (88%); colourless oil; bp 75 °C/0.02 Torr; [Found: C, 52.7; H, 4.5; F, 31.3. $C_{16}H_{16}F_6OSi$ requires C, 52.45; H, 4.40; F, 31.12%]; δ_H (299.95 MHz, CD_2Cl_2) 8.68 (1H, d, $J=8.0$ Hz), 7.93 (1H, d, $J=8.4$ Hz), 7.77 (1H, d, $J=7.6$ Hz), 7.60–7.42 (4H, m, Ar*H*), 0.01 (9H, s, $Si(CH_3)_3$); δ_F (282.20 MHz, CD_2Cl_2) −71.2; δ_C (50.32 MHz, CD_2Cl_2): 135.1, 133.3, 132.1, 129.6, 127.7, 127.2, 126.8, 126.2, 124.6 (*Ar*), 123.8 (q, $^1J_{CF}=291.7$ Hz, *C*F_3), 83.6 (sept, $^2J_{CF}=29.8$ Hz, *C*$(CF_3)_2$), 0.77 (s, *C*H_3); MS: *m/z* (%) = 366 (100, [M^+]), 351 (10, [M−CH_3]), 331 (6, [M−CH_3-HF]), 302 (28, [M−3CH_3-F]), 297 (42, [M−CF_3]), 293 (28, [M−$SiMe_3$]), 277 (6, [M−$OSiMe_3$]), 257 (35), 255 (18, [M−Me_3SiF-F]), 235 (30), 225 (18, [M−2CF_3H-H]), 207 (15), 177 (14), 155 (86, [M−Me_3SiCF_3-CF_3]), 128 (8, [M−$C(CF_3)_2OSiMe_2$–CH_2]), 77 (4), 73 (8, [Me_3Si]), 18 (38, H_2O).

4.3.3. Trimethyl[2,2,2-trifluoro-1-methyl-1-(trifluoromethyl)ethoxy]silane (2c). Yield: 0.79 g (62%); colourless liquid; bp 98–99 °C. (lit.[28] bp 99 °C); δ_H (299.95 MHz, $CDCl_3$) 1.57 (3H, m, C*H*$_3$), 0.20 (s, 9H, $Si(CH_3)_3$); δ_F (282.20 MHz, $CDCl_3$): −79.8.

4.3.4. Trimethyl[2,2,2-trifluoro-1-(2-furyl)-1-(trifluoromethyl)ethoxy]silane (2d). Yield: 1.15 g (75%); colourless liquid; bp 50 °C/12 Torr; [Found: C, 39.4; H, 4.1; F, 37.3. $C_{10}H_{12}F_6O_2Si$ requires C, 39.21; H, 3.95; F, 37.22%]; δ_H (299.95 MHz, $CDCl_3$) 7.52 (1H, dd, $J=1.8$, 0.6 Hz) 6.63 (1H, dd, $J=3.3$, 0.6 Hz), 6.46 (1H, dd, $J=3.3$, 1.8 Hz), 0.05 (9H, s, $Si(CH_3)_3$); δ_F (282.20 MHz, $CDCl_3$) −76.1; δ_C (50.32 MHz, C_6D_6) 143.6 (Ar), 122.6 (q, $^1J_{CF}=291.0$ Hz, *C*F_3), 112.9 (sept, $^3J_{CF}=2.1$ Hz, *C*$C(CF_3)_2$), 111.2 (*Ar*), 76.5 (sept, $^2J_{CF}=31.2$ Hz, *C*$(CF_3)_2$), 0.21 [$Si(CH_3)_3$]; MS: *m/z* (%) = 306 (4, [M^+]), 291 (42, [M−CH_3]), 237 (17, [M−CF_3]), 217 (4, [M−$OSiMe_3$]), 195 (100, [M−Me_3SiF-F]), 167 (26, [M−CF_3H–CF_3]), 145 (6), 117 (10), 95 (28, [M−Me_3SiCF_3–CF_3]), 77 (8), 73 (7, [Me_3Si]), 18 (100, [H_2O]).

4.3.5. Trimethyl[1-*tert*-butoxy-2,2,2-trifluoro-1-(trifluoromethyl)ethoxy]silane (2e). Yield: 0.78 g (50%); colourless liquid; bp 63 °C/15 Torr; [Found: C, 38.6; H, 6.0; F, 36.3. $C_{10}H_{18}F_6O_2Si$ requires C, 38.45; H, 5.81; F, 36.50%]; δ_H (299.95 MHz, C_6D_6) 1.29 (9H, s, $C(CH_3)_3$), 0.16 (9H, s, $Si(CH_3)_3$); δ_F (282.0 MHz, C_6D_6) −79.8; δ_C (50.32 MHz, C_6D_6) 121.3 (q, $^1J_{CF}=291.7$ Hz, *C*F_3), 94.5 (sept, $^2J_{CF}=33$ Hz, *C*$(CF_3)_2$), 80.7 (*C*$(CH_3)_3$), 30.0 (3C, $C(CH_3)_3$), 0.8 [$Si(CH_3)_3$]; MS: *m/z* (%) = 297 (4, [M−CH_3]), 291 (16, [M−HF-H]), 243 (4, [M−CF_3]), 237 (8, [M−$HSiMe_3$-H]), 195 (52, [$(CF_3)_2COSiH$]), 131 (18, [$(CF_3)C=CF_2$]), 73 (18, [Me_3Si]), 57 (100, [$C(CH_3)_3$]), 18 (100, [H_2O]).

4.3.6. Trimethyl[2,2,2-trifluoro-1-(2-pyridyl)-1-(trifluoromethyl)ethoxy]silane (2g). Yield: 0.82 g (52%); colourless liquid; bp 34 °C/0.07 Torr; [Found: C, 41.7; H, 4.2; F, 36.1; N, 4.5. $C_{11}H_{13}F_6NOSi$ requires C, 41.64; H, 4.13; F, 35.93; N, 4.41%]; δ_H (299.95 MHz, $CDCl_3$) 8.65 (1H, d, $J=5.0$ Hz), 7.80 (1H, td, $J=8.0$, 1.9 Hz), 7.69 (1H, d, $J=8.0$ Hz), 7.40 (1H, ddd, $J=8.0$, 4.9, 1.0 Hz), 0.24 (9H, s, $Si(CH_3)_3$); δ_F (282.20 MHz, $CDCl_3$) −75.1; δ_C (50.32 MHz, CD_2Cl_2) 150.3, 148.2, 137.5, 126.4, 123.6 (*Ar*), 122.8 (q, $^1J_{CF}=288.6$ Hz, *C*F_3) 81.0 (sept, $^2J_{CF}=29.1$ Hz, *C*$(CF_3)_2$), 2.3 [$Si(CH_3)_3$]; MS: *m/z* (%) = 317 (5, [M^+]), 302 (100, [M−CH_3]), 206 (10, [M−Me_3SiF-F]), 178 (15, [M−CF_3H-F]), 128 (10), 106 (4, [M−Me_3SiCF_3-CF_3]), 77 (4, [M−$HC(CF_3)_2OSiMe_3$]), 18 (10, H_2O).

4.3.7. Trimethyl[2,2,2-trifluoro-1-(3-pyridyl)-1-(trifluoromethyl)ethoxy]silane (2h). Yield: 1.14 g (72%); colourless liquid; bp 80 °C/10 Torr; [Found: C, 41.8; H, 4.2; F, 36.1; N, 4.5. $C_{11}H_{13}F_6NOSi$ requires C, 41.64; H, 4.13; F, 35.93; N, 4.41%]; δ_H (299.95 MHz, $CDCl_3$) 8.89 (1H, br s), 8.69 (1H, dd, $J=4.9$, 1.5 Hz), 7.93 (1H dd, $J=8.3$, 0.7 Hz), 7.37 (1H, ddd, $J=8.3$, 4.9, 0.7 Hz), 0.26 (9H, s, $Si(CH_3)_3$); δ_F (282.20 MHz, $CDCl_3$) −75.9.

4.3.8. Trimethyl[2,2,2-trifluoro-1-(4-pyridyl)-1-(trifluoromethyl)ethoxy]silane (2i). Yield: 0.95 g (60%); colourless liquid; bp 94–95 °C/20 Torr; [Found: C, 41.6; H, 4.1; F, 35.8; N, 4.3. $C_{11}H_{13}F_6NOSi$ requires C, 41.64; H, 4.13; F, 35.93; N, 4.41%]; δ_H (299.95 MHz, $CDCl_3$) 8.71 (1H, dd, $J=4.7$, 1.6 Hz), 7.53 (d, 1H, $J=4.9$ Hz), 0.26 (9H, s, $Si(CH_3)_3$); δ_F (282.20 MHz, $CDCl_3$) −74.1; δ_C (50.32 MHz, CD_2Cl_2): 150.1, 141.5 (*Ar*), 122.6 (q, $^1J_{CF}=288.4$ Hz, *C*F_3), 122.2 (*Ar*), 79.6 (sept, $^2J_{CF}=30.5$ Hz, *C*$(CF_3)_2$), 1.2 [$Si(CH_3)_3$]; MS: *m/z* (%) = 317 (10, [M^+]), 302 (60, [M−CH_3]), 256 (9), 206 (100, [M−Me_3SiF-F]), 178 (15, [M−CF_3H-F]), 147 (18), 128 (16), 106 (3, [M−Me_3SiCF_3-CF_3]), 77 (13, [M−$HC(CF_3)_2OSiMe_3$]), 73 (5, [Me_3Si]), 18 (10, H_2O).

4.3.9. Trimethyl{[(2*E*)-3-phenyl-1,1-bis(trifluoromethyl)prop-2-enyl]oxy}silane (2j).[13] Yield: 1.39 g (81%); colourless liquid; bp 49–50 °C/0.02 Torr; δ_H (299.95 MHz, $CDCl_3$) 7.53–7.29 (m, 5H), 7.00 (d, 1H, $J=16.2$ Hz), 6.21 (d, 1H, $J=16.2$ Hz), 0.27 (s, 9H, $Si(CH_3)_3$); δ_F (282.20 MHz, $CDCl_3$) −76.3.

4.3.10. 1,1,1,3,3,3-Hexafluoro-2-phenylpropan-2-ol (3a). *Method A*. To a solution of appropriate substrate (**1a**, **4a**, **5**, **6**) (5 mmol) in DME (8 mL) at −50 °C Me_3SiCF_3 (1.50 g, 10.5 mmol) and $[Me_4N]F$ (0.94 g, 10 mmol) were added. The mixture was stirred for 1 h at −30 °C and overnight at room temperature. The precipitate formed was filtered off, a 2 M aqueous solution of HCl (20 mL) was added and the product was extracted with Et_2O (2×10 mL). The extract was washed with H_2O (5 mL), dried ($MgSO_4$) and purified by vacuum distillation.

Method B. To a solution of trimethyl[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)ethoxy]silane **2a** (0.95 g, 3 mmol) in THF (5 mL), 6 M HCl (5 mL) was added. The mixture was stirred overnight at room temperature. H_2O (25 mL) was added and the product was extracted with Et_2O (2×10 mL). The combined organic phases were washed with H_2O (5 mL), dried ($MgSO_4$) and purified by vacuum distillation.

Yield: [Method A] 0.84 g (81%) (from **1a**); 0.84 g (81%) (from **4a**); 0.91 g (87%) (from **5**); 0.8 g (77%) (from **6**); [Method B] 0.81 g (81%) (from **2a**); colourless liquid; bp 53 °C/12 Torr. (lit.[29] bp 50 °C/10 Torr); δ_H (299.95 MHz, $CDCl_3$) 7.79 (2H, m) 7.29–7.00 (3H, m, overlapping), 4.58 (s, O*H*); δ_F (282.20 MHz, $CDCl_3$) −75.3.

4.3.11. 1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-ol (3f). To a solution of trifluoroacetic acid anhydride (3.50 g, 16.7 mmol) in DME (15 mL) at −50 °C Me_3SiCF_3 (5.00 g, 35.0 mmol) and $[Me_4N]F$ (3.10 g, 33.4 mmol) were added. The mixture was stirred for 1 h at −30 °C and overnight at rt. The solvent and other volatile materials were condened under high vacuum over a period of 1 h leaving a white powder. Concentrated H_2SO_4 (5 mL) was injected into the reaction vessel cooled with an ice bath, and after 0.5 h the resulting volatile products were collected in a trap (−196 °C) by pumping from the reactor at 20 °C for 2 h. Fractional distillation using a 10 cm Vigreux distilling column afforded 3.35 g (87%) of **3f**. Bp 45 °C (lit.[30] bp 48 °C); δ_F (282.20 MHz, Et_2O) −74.7.

4.3.12. 1,1,1,3,3,3-Hexafluoro-2-[4-(2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl)-phenyl]-propan-2-ol (8). To a solution of terephthaloyl chloride (1.00 g, 5.0 mmol) in DME (12 mL) at −50 °C Me_3SiCF_3 (3 g, 21 mmol) and $[Me_4N]F$ (1.88 g, 20 mmol) were added. The mixture was stirred for 1 h at −30 °C and overnight at rt. A 2 M aq solution of HCl (25 mL) was added and the product was extracted with Et_2O (2×15 mL). The extract was washed with H_2O (10 mL), dried ($MgSO_4$), the solvent evaporated and the residue purified by crystallisation from Et_2O. Yield: 1.68 g (82%); colourless solid; mp 85–86 °C (lit.[31] mp 86 °C; lit.[8a] mp 85 °C); δ_H (299.95 MHz, $CDCl_3$) 7.80 (4H, s), 3.99 (2H, s, O*H*); δ_F (282.20 MHz, $CDCl_3$) −76.1.

Acknowledgements

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Oxidation of aromatic aldehydes and ketones by H_2O_2/CH_3ReO_3 in ionic liquids: a catalytic efficient reaction to achieve dihydric phenols

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Abstract—A convenient and efficient application of hydrogen peroxide/methyltrioxorhenium in ionic liquids [bmim]BF_4 and [bmim]PF_6 for the oxidation of hydroxylated and methoxylated benzaldehydes and acetophenones to the corresponding phenols is described. Good yields of products were obtained in short reaction times.

1. Introduction

The dihydric phenols such as catechol, hydroquinone and their methyl ethers, are high value chemicals. They are widely used as agrochemicals, antioxidants, pharmaceuticals, flavoring agents, polymerization inhibitors. For example, catechol is the basic chemical for the synthesis of the 4-*tert*-butylcatechol, an industrial antioxidant for foods and cosmetics[1] and for the synthesis of the pharmaceutical adrenalone;[2] guaiacol is used as good starting material for the industrial synthesis of vanillin, a prime flavor molecule;[3] hydroquinone is largely employed in photographic processes.[4]

Classical synthesis of this kind of phenols can be performed by catalytic oxidation of aromatic hydrocarbons,[5] hydroxylation of phenols,[6] oxidative decarboxylation of aryl carboxylic acids,[7] hydrolysis of halobenzenes.[8] Alternatively, the oxidation of benzaldeydes and acetophenones with alkaline hydrogen peroxide was an easy synthetic pathway (Dakin reaction).[9] However, under these conditions, reactions were too slow to be commercially attractive. Hydrogen peroxide/boric acid,[10] hydrogen peroxide/selenium compounds,[11] sodium perborate and sodium percarbonate,[12] *m*-chloroperbenzoic acid[13] were other useful reagents to convert aromatic aldehydes to the corresponding phenols, but these procedures required long reactions time, in some cases up to 30 h. Recently, Sn-Beta zeolites were used to activate hydrogen peroxide[14] providing an interesting example of good reactivity of aromatic aldehydes in short reaction times.

In recent years, methyltrioxorhenium (CH_3ReO_3, MTO)[15] has been shown to possess interesting catalytic properties in oxidation reactions with hydrogen peroxide as oxygen atom donor.[16] The reactive intermediate is a bis-peroxo metal [$CH_3ReO(O_2)_2$] complexes **dpRe** (Fig. 1) whose structure was established by X-ray analysis.[17] Recently, an efficient oxidation of hydroxylated and methoxylated benzaldeydes with hydrogen peroxide/methyltrioxorhenium in conventional solvents was described: under these conditions between 16 and 24 h were necessary to achieve complete oxidation.[18]

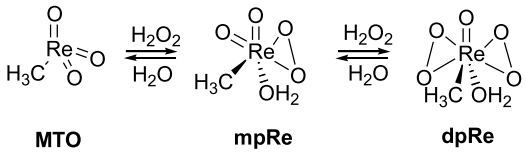

Figure 1. Catalytic system H_2O_2/CH_3ReO_3.

Keywords: Oxidation; Hydrogen peroxide/methyltrioxorhenium; Ionic liquids; Benzaldehydes; Acetophenones; Dihydric phenols.
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During recent years, the ionic liquids [bmim]BF_4 and [bmim]PF_6, where [bmim]$^+$ is the 1-butyl-3-methylimidazolium cation, were used as substitutes for molecular solvents in catalytic reactions (Fig. 2).[19] These kind of liquids have several interesting and benign properties: they show low volatility, chemical, physical and thermal stability and can furthermore be recycled and reused.[20] Moreover, catalytic oxidations proceed faster than in conventional solvents.[21] For example, hydrogen peroxide/boric acid in [bmim]PF_6 converted aromatic aldehydes into phenols very quickly (1–2 h)[22] and the *m*-chloroperbenzoic acid promoted Baeyer–Villiger oxidation of simple ketones and benzaldehydes was achieved in 2–4 h.[23]

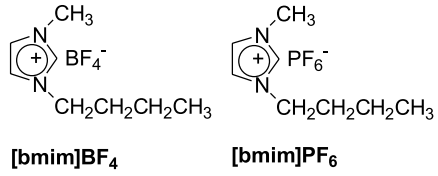
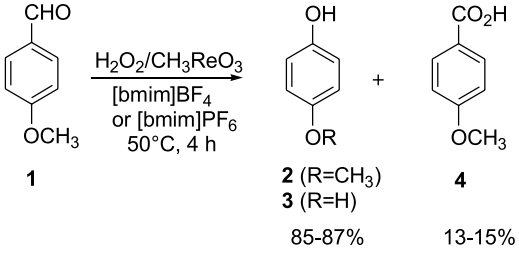


Figure 2. Ionic liquids [bmim]BF_4 and [bmim]PF_6.

By continuing our studies into oxidations using the catalytic system hydrogen peroxide/methyltrioxorhenium in ionic liquids,[24] we report now the results on the oxidative conversion of substituted aromatic aldehydes and ketones in [bmim]BF_4 and [bmim]PF_6 to the corresponding phenols. Good yields of products in short reaction times and under controlled conditions were obtained.



Scheme 1. Oxidative conversion of 4-methoxybenzaldehyde **1**.

2. Results and discussion

As a model substrate, for the initial investigations, we chose 4-methoxybenzaldeyde **1** (Scheme 1). Our results are summarized in Table 1. Both in [bmim]BF_4 and [bmim]PF_6, the oxidation to 4-methoxyphenol **2** are faster at 50 °C and better in terms of yield and selectivity (entries 3, 4), than at 25 °C (entries 1, 2); small amount of hydroquinone **3** and 4-methoxybenzoic acid **4** were also isolated. Our results also showed that the nature of the anion of the ionic liquid was not important for the reactivity of the substrate and the reaction times. When the experiments were carried out under identical conditions but omitting the catalyst, we found that 4-methoxyphenol **2** was formed only in traces ($<5\%$). Experimentally, all the reactions were carried out at 50 °C for 4 h, the products were then selectively and quantitatively extracted from the ionic liquid solution by several extractions with small portions of diethyl ether. The second run was performed by adding fresh substrate and hydrogen peroxide to the ionic liquid solution: the catalytic system was still stable and efficient for five successive recycling experiments as reported in Table 2. However as general trend, we found a small increase in the yield of the 4-methoxybenzoic acid **4**, most probably as a consequence of added water.

Good results were obtained with activated benzaldehydes such as **5**, **7**, **11** and **13**. The corresponding phenols **3**, **8**, **9**, **14** were obtained in good yields (Scheme 2, Table 3, entries 1–8). Nevertheless, benzaldehydes with *meta*-substituted electron-donating groups **16**, **19** and unsubstitued benzaldehyde **22**, failed to oxidize to the Dakin products: in these

Table 1. Oxidation of 4-methoxybenzaldeyde **1** with hydrogen peroxide/methyltrioxorhenium in [bmim]BF_4 and [bmim]PF_6[a]

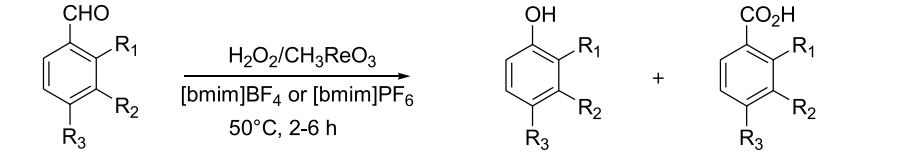
Entry	Ionic liquid	Conv. (%)	Yield (%) of **2**	Yield (%) of **3**	Yield (%) of **4**
1[b]	[bmim]BF_4	20	95	—	—
2[b]	[bmim]PF_6	18	98	—	—
3[c]	[bmim]BF_4	>98	77	10	13
4[c]	[bmim]PF_6	>98	75	10	15

[a] Conversions and yields were determined after chromatographic purification of reaction mixtures.
[b] H_2O_2 (35% water solution): 8 equiv; CH_3ReO_3 (2%), 25 °C, 24 h.
[c] H_2O_2 (35% water solution): 4 equiv; CH_3ReO_3 (2%), 50 °C, 4 h.

Table 2. Oxidation of 4-methoxybenzaldeyde **1** with H_2O_2/CH_3ReO_3 in [bmim]BF_4 and in [bmim]PF_6 as a recyclable system[a]

Run no.[b]	Conv. (%)[c]	Yield (%) of **2**[c]	Yield (%) of **3**[c]	Yield (%) of **4**[c]	Conv. (%)[d]	Yield (%) of **2**[d]	Yield (%) of **3**[d]	Yield (%) of **4**[d]
1	>98	77	10	13	>98	75	10	15
2	95	76	13	11	95	75	10	15
3	90	77	11	12	88	73	8	19
4	88	60	16	24	85	64	11	25
5	84	64	14	22	80	60	12	28
6	66	68	11	22	68	56	14	30

[a] Yields and conversions were calculated after chromatographic purification of the reaction mixture.
[b] After each run, the successive one was performed adding only fresh substrate and oxidant to the ionic liquid solution under the same experimental conditions.
[c] Data in [bmim]BF_4.
[d] Data in [bmim]PF_6.



5, 7, 11, 13, 16, 19, 22 → **3, 8, 9, 14, 17, 20, 23** + **6, 10, 12, 15, 18, 21, 24**

5, 3, 6: R_1=R_2=H, R_3=OH; **7, 8, 10**: R_1=OCH_3, R_2=R_3=H; **11, 9, 12**: R_1=OH, R_2=R_3=H;
13, 14, 15: R_1=H, R_2=R_3=OCH_3; **16, 17, 18**: R_1=R_3=H, R_2=OCH_3; **19, 20, 21**: R_1=R_3=H, R_2=OH; **22, 23, 24**: R_1=R_2=R_3=H

Scheme 2. Oxidation of benzaldehydes with hydrogen peroxide/methyltrioxorhenium in [bmim]BF_4 and [bmim]PF_6.

Table 3. Experimental data of oxidations depicted in Scheme 3[a]

Entry	Substrate	Phenols	Benzoic acid	Conditions[b]	Conv. (%)	Yield (%) of phenols	Yield (%) of benzoic acid
1	**5**	**3**	**6**	[bmim]BF_4, H_2O_2 (2 equiv), 50 °C, 2 h	>98	95	5
2	**5**	**3**	**6**	[bmim]PF_6, H_2O_2 (2 equiv), 50 °C, 2 h	95	95	5
3	**7**	**8** (**9**)	**10**	[bmim]BF_4, H_2O_2 (4 equiv), 50 °C, 4 h	>98	75 (10)[c]	15
4	**7**	**8** (**9**)	**10**	[bmim]PF_6, H_2O_2 (4 equiv), 50 °C, 4 h	>98	75 (10)[c]	15
5	**11**	**9**	**12**	[bmim]BF_4, H_2O_2 (4 equiv), 50 °C, 6 h	96	84	16
6	**11**	**9**	**12**	[bmim]PF_6, H_2O_2 (4 equiv), 50 °C, 6 h	90	87	13
7	**13**	**14**	**15**	[bmim]BF_4, H_2O_2 (4 equiv), 50 °C, 4 h	90	80	20
8	**13**	**14**	**15**	[bmim]PF_6, H_2O_2 (4 equiv), 50 °C, 4 h	90	78	22
9	**16**	**17**	**18**	[bmim]BF_4, H_2O_2 (4 equiv), 50 °C, 4 h	>98	—	>98
10	**16**	**17**	**18**	[bmim]PF_6, H_2O_2 (4 equiv), 50 °C, 2 h	>98	—	>98
11	**19**	**20**	**21**	[bmim]BF_4, H_2O_2 (10 equiv), 50 °C, 24 h	95	—	95
12	**19**	**20**	**21**	[bmim]PF_6, H_2O_2 (10 equiv), 50 °C, 24 h	95	—	98
13	**22**	**23**	**24**	[bmim]BF_4, H_2O_2 (10 equiv), 50 °C, 24 h	95	—	98
14	**22**	**23**	**24**	[bmim]PF_6, H_2O_2 (10 equiv), 50 °C, 24 h	95	—	98

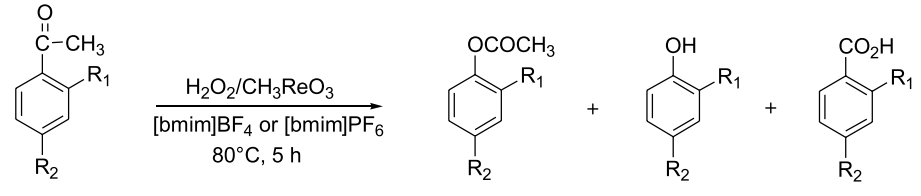
[a] Yields and conversions were calculated after chromatographic purification of the reaction mixtures.
[b] CH_3ReO_3 (2%).
[c] In parentheses were reported the yields of phenol **9**.

cases the main products were the corresponding benzoic acids **18**, **21**, **24** (Scheme 2, Table 3, entries 9–14).

Besides aromatic aldehydes, we tested the efficiency of the hydrogen peroxide/methyltrioxorhenium catalytic system in the conversion of the aromatic ketones **25**, **27**, **29** and **31** to the corresponding phenols (Scheme 3). Our results showed lower reactivity at 50 °C for the acetophenones used: we found that by raising the temperature up to 80 °C, phenols **2**, **3**, **8** and **9** can be obtained after 3–5 h (Table 4) in good to high yields. The esters **26**, **28**, **30**, **32**, obtained as secondary products, can be easily converted into phenols by simple alkaline work-up. Benzoic acids **4**, **6**, **10** and **12** were isolated in low yields.

3. Conclusions

C-2 and C-4 hydroxylated or methoxylated benzaldehydes and acetophenones were converted to the corresponding phenols in good yields and short reaction times, with the hydrogen peroxide/methyltrioxorhenium catalytic system, used in ionic liquids. After extraction of the products, the ionic liquid solution still showed catalytic activity. Work is



25, 27, 29, 31 → **26, 28, 30, 32** + **2, 3, 8, 9** + **4, 6, 10, 12**

25, **26**, **2**, **4**: R_1=H, R_2=OCH_3
27, **28**, **3**, **6**: R_1=H, R_2=OH
29, **30**, **8. 10**: R_1=OCH_3, R_2=H
31, **32**, **9**, **12** : R_1=OH, R_2=H

Scheme 3. Oxidative conversion of substituted acetophenones with hydrogen peroxide/methyltrioxorhenium in [bmim]BF_4 and [bmim]PF_6.

Table 4. Oxidation of substituted acetophenones with hydrogen peroxide/methyltrioxorhenium in [bmim]BF_4 and [bmim]PF_6[a]

Entry	Substrate	Ester	Phenols	Conditions[b]	Conv. (%)	Yield (%) of phenols	Yield (%) of the ester	Yield (%) of the benzoic acid
1	**25**	**26**	**2** (**3**)	[bmim]BF_4, H_2O_2 (8 equiv), 80 °C, 5 h	90	76 (10)[c]	11	3
2	**25**	**26**	**2** (**3**)	[bmim]PF_6, H_2O_2 (3 equiv), 80 °C, 3 h	96	56 (22)[c]	3	19
3	**27**	**28**	**3**	[bmim]BF_4, H_2O_2 (8 equiv), 80 °C, 5 h	98	90	10	—
4	**27**	**28**	**3**	[bmim]PF_6, H_2O_2 (3 equiv), 80 °C, 3 h	91	>98	—	—
5	**29**	**30**	**8**	[bmim]BF_4, H_2O_2 (8 equiv), 80 °C, 5 h	87	55	30	15
6	**29**	**30**	**8**	[bmim]PF_6, H_2O_2 (3 equiv), 80 °C, 3 h	95	71	—	29
7	**31**	**32**	**9**	[bmim]BF_4, H_2O_2 (8 equiv), 80 °C, 5 h	95	47	53	—
8	**31**	**32**	**9**	[bmim]PF_6, H_2O_2 (6 equiv), 80 °C, 5 h	90	45	55	—

[a] Yields and conversions were calculated after chromatographic purification of the reaction mixtures.
[b] H_2O_2 (35% water solution); CH_3ReO_3 (2%).
[c] In parentheses were reported the yield of phenol **3**.

in progress to test the chemoselectivity of these conditions in more complex molecules, that possess other oxidizable groups.

4. Experimental

All commercial products were of the highest grade available and were used without further purifications. Hydrogen peroxide was 35% aqueous solution (Aldrich). Synthesis of [bmim]BF_4 and of [bmim]PF_6 were carried out according to Ref. 25. Thin layer chromatography was carried out using Merck silica gel 60F-254 plates with UV indicator. Reaction products were purified by flash chromatography on columns packed with silica gel, 230–400 mesh. NMR spectra were recorded on a Bruker AC 200 spectrometer and are reported in δ values. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. Gas chromatography-mass spectroscopy of the reaction products were performed using a SPB column (25 m×0.30 mm and 0.25 mm film thickness) and an isothermal temperature profile of 60 °C for the first 2 min, followed by a 10 °C/min temperature gradient to 280 °C for 15 min. The injector temperature was 280 °C. Chromatography grade helium was used as the carrier gas. Melting points were determined with a Büchi apparatus and are uncorrected.

4.1. General procedure for the oxidation of benzaldeydes and acetophenones with H_2O_2/CH_3ReO_3 in ionic liquids

The substrate (1.0 mmol) was dissolved in [bmim]BF_4 or [bmim]PF_6 (1 ml). Then, hydrogen peroxide (35% aqueous solution, 2–8 equiv) and CH_3ReO_3 (0.02 mmol) were added. Reactions were monitored by thin layer chromatography and by chromatography-mass spectroscopy. After extraction with diethyl ether and evaporation of the organic solvent, the products were purified by flash chromatography using dichloromethane as eluent. Their identity was confirmed by ^1H, ^{13}C NMR and GC-MS analyses, comparing the experimental data with those of authentic compounds.

4.2. Hydrolysis of esters 27, 29, 31 and 30

Alkaline hydrolysis were carried out according to Ref. 11.

4.2.1. 4-Methoxyphenol (2). White solid, mp 55–57 °C, (lit.,[10] 56–57 °C). δ_H ($CDCl_3$, 200 MHz): 3.75 (3H, s, OCH_3), 6.76 (4H, d, J=1.6 Hz, Ar-H); δ_C ($CDCl_3$, 200 MHz): 55.9, 115.0, 116.2, 149.6, 153.4; *m/z* (EI) 124 (M^+, 80.1%).

4.2.2. Hydroquinone (3). White solid, mp 169–171 °C, (lit.,[10] 170–171 °C). δ_H (DMSO-d_6, 200 MHz): 5.69 (2H, s, Ar-H), 7.73 (2H, s, Ar-H); δ_C (DMSO-d_6, 200 MHz): 115.8, 149.8; *m/z* (EI) 110 (M^+, 100%).

4.2.3. 4-Methoxybenzoic acid (4). White solid, mp 178–180 °C, (lit.,[26] 179–181 °C). δ_H ($CDCl_3$/CD_3OD, 200 MHz): 3.79 (3H, s, OCH_3), 6.85 (2H, d, J=14.5 Hz, Ar-H), 7.94 (2H, d, J=14.5 Hz, Ar-H); δ_C ($CDCl_3$/CD_3OD, 200 MHz): 55.2, 114.6, 131.8, 163.3, 168.7; *m/z* (EI) 152 (M^+, 85.3%).

4.2.4. 2-Methoxyphenol (8). Liquid δ_H ($CDCl_3$, 200 MHz): 3.86 (3H, s, OCH_3), 6.85–7.02 (4H, m, Ar-H); δ_C ($CDCl_3$, 200 MHz): 55.8, 110.8, 114.6, 120.2, 121.4, 145.7, 146.6; *m/z* (EI) 124 (M^+, 68.8%).

4.2.5. Catechol (9). White solid, mp 102–104 °C, (lit.,[10] 103–104 °C). δ_H ($CDCl_3$/CD_3OD, 200 MHz): 6.45–6.51 (2H, m, Ar-H), 6.55–6.64 (2H, m, Ar-H); δ_C ($CDCl_3$/CD_3OD 200 MHz): 114.9, 119.7, 144.2; *m/z* (EI) 110 (M^+, 100%).

4.2.6. 2-Methoxybenzoic acid (10). White solid, mp 183–184 °C, (lit.,[27] 184–185 °C). δ_H ($CDCl_3$, 200 MHz): 3.98 (3H, s, OCH_3), 6.73–7.11 (2H, m, Ar-H), 7.49 (1H, t, J=8.5 Hz, Ar-H), 8.02 (1H, d, J=7.8 Hz, Ar-H); δ_C ($CDCl_3$, 200 MHz): 56.6, 111.8, 117.5, 121.8, 133.4, 135.1, 158.3, 166.3; *m/z* (EI) 152 (M^+, 35.3%).

4.2.7. 2-Hydroxybenzoic acid (12). White solid, mp 159–161 °C, (lit.,[27] 158–160 °C). δ_H ($CDCl_3$/DMSO-d_6, 200 MHz): 6.80–6.95 (2H, m, Ar-H), 7.45–7.55 (1H, m, Ar-H), 7.82 (1H, d, J=9.0 Hz, Ar-H); δ_C ($CDCl_3$/DMSO-d_6, 200 MHz): 112.7, 116.9, 118.7, 130.2, 135.2, 161.5, 172.1; *m/z* (EI) 138 (M^+, 40.5%).

4.2.8. 3,4-Dimethoxyphenol (14). White solid, mp 78–80 °C (lit.,[10] 79 °C). δ_H ($CDCl_3$, 200 MHz) 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3); 6.32 (1H, dd, J=2.7, 8.5 Hz, Ar-H), 6.44 (1H, d, J=2.7 Hz, Ar-H), 6.68 (1H, d, J=8.5 Hz, Ar-H); δ_C ($CDCl_3$, 200 MHz): 55.7, 56.5, 100.6, 105.8, 112.5, 142.9, 149.8, 150.2; *m/z* (EI) 154 (M^+, 63.2%).

4.2.9. 3,4-Dimethoxybenzoic acid (15). White solid, mp 179–182 °C, (lit.,[27] 180–182 °C). δ_H ($CDCl_3$, 200 MHz): 3.91 (3H, s, OCH_3); 3.92 (3H, s, OCH_3); 6.88 (1H, d, J= 8.4 Hz, Ar-H), 7.56 (1H, s, Ar-H), 7.74 (1H, dd, J=1.6, 8.4 Hz, Ar-H); δ_C ($CDCl_3$, 200 MHz): 55.9, 56.0, 110.2, 112.3, 124.5, 148.6, 153.6, 165.4, 171.5; *m/z* (EI) 182 (M^+, 100%).

4.2.10. 3-Methoxybenzoic acid (18). White solid, mp 104–105 °C (lit.,[10] 105–107 °C). δ_H ($CDCl_3$, 200 MHz): 3.83 (3H, s, OCH_3); 7.14–7.17 (1H, dd, J=8.3, 0.9 Hz, Ar-H), 7.37 (1H, t, J=8.0 Hz, Ar-H), 7.71 (1H, dd, J=7.8, 1.2 Hz, Ar-H); δ_C ($CDCl_3$, 200 MHz): 55.3, 114.3, 120.3, 122.6, 129.4, 130.5, 159.5, 172.1; *m/z* (EI) 152 (M^+, 100%).

4.2.11. 3-Hydroxybenzoic acid (21). White solid, mp 202–204 °C (lit.,[27] 202–203 °C). δ_H ($CDCl_3$/CD_3OD, 200 MHz): 6.93 (1H, dd, J=8.1, 2.5 Hz, Ar-H), 7.37–7.46 (1H, t, J= 7.8 Hz, Ar-H), 7.37–7.46 (2H, m, Ar-H); δ_C ($CDCl_3$, 200 MHz): 116.1, 120.2, 121.4, 129.2, 131.2, 156.6, 169.2; *m/z* (EI) 138 (M^+, 100%).

4.2.12. Benzoic acid (24). White solid, mp 121–123 °C (lit.,[10] 123–124 °C). δ_H ($CDCl_3$, 200 MHz): 7.45–7.50 (2H, m, Ar-H), 7.59–7.64 (1H, m, Ar-H), 8.13 (2H, d, J=7.5 Hz, Ar-H); δ_C ($CDCl_3$, 200 MHz): 128.4, 130.2, 133.8, 172.5; *m/z* (EI) 122 (M^+, 64.7%).

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Total synthesis of TT-1 (rasfonin), an α-pyrone-containing natural product from a fungus *Trichurus terrophilus*

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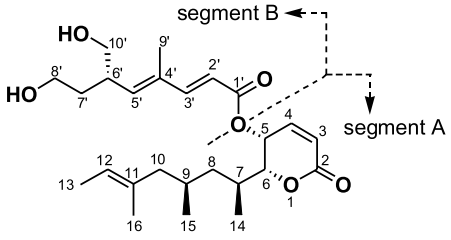
Abstract—Total synthesis of TT-1 (**1**=rasfonin), an α-pyrone-containing natural product from a Fungi Imperfecti *Trichurus terrophilus* culture was achieved by a stereoselective method in optically active form, which further provided evidence for the whole structure of TT-1 (**1**) including the absolute stereochemistry.

1. Introduction

In 2000, an α-pyrone-containing natural product, TT-1, was isolated from the ethyl acetate extract of a Fungi Imperfecti *Trichurus terrophilus* culture by Fujimoto and co-workers in our laboratory.[1] Almost at the same time, Hayakawa and co-workers reported isolation of rasfonin, which had the same planar structure as TT-1, from the fermented mycelia of an Ascomycete *Talaromyces* sp. 3656-A1.[2] Rasfonin was reported as a new apoptosis inducer in *ras*-dependent cells, while TT-1 significantly suppressed proliferation (blastogenesis) of mouse splenic lymphocytes stimulated with mitogens, concanavalin A (Con A) and lipopolysaccharide (LPS), with IC_{50} values of 0.7 and 0.5 μg/mL, respectively.[1] We investigated the absolute stereochemistry of five chiral centers of **1** on the basis of synthesis of partial structural units (segments **A** and **B**) of **1** in optically active forms and comparison of their spectral and optical data with those of natural specimens, and reported in 2003 that **1** had 5*R*, 6*R*, 7*S*, 9*R*, and 6′*S*-configurations.[3] In the synthesis of segment A of **1**, we previously obtained 5-membered lactone (**2**) instead of 6-membered lactone (**3**),[3] and we here describe the stereoselective synthesis of the 6-membered lactone (**3**) by a modified procedure and the total synthesis of TT-1 (**1**) to provide further unequivocal evidence for the whole structure of TT-1 (**1**) including the absolute stereochemistry.



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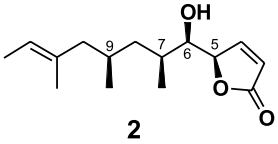

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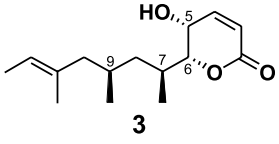

3

2. Results and discussion

2.1. Synthesis of segment A

Our modified synthesis of segment A (**3**) (Scheme 1) began with the known monoacetate (**4**),[4–7] which was converted into *E*-unsaturated ester (**5**, $J_{4,5}$=15.6 Hz)[8] by a four-step reaction [(i) protection with *t*-butyldimethylsilyl (TBS) ether; (ii) alkaline hydrolysis of the acetate; (iii) Swern oxidation; (iv) Horner–Emmons reaction]. The asymmetric dihydroxylation of ester (**5**) with AD-mix β[9] led to the α,β-dihydroxy ester (**6**), which was protected with a benzyl acetal, and the $LiAlH_4$ reduction of the ester moiety afforded the alcohol (**7**). Treatment of **7** with borane-methyl sulfide in the presence of boron trifluoride diethyl etherate[10] led to reductive deprotection of the benzyl acetal to give a 1,2-diol

Keywords: TT-1 (rasfonin); *Trichurus terrophilus*; α-Pyrone; Total synthesis.
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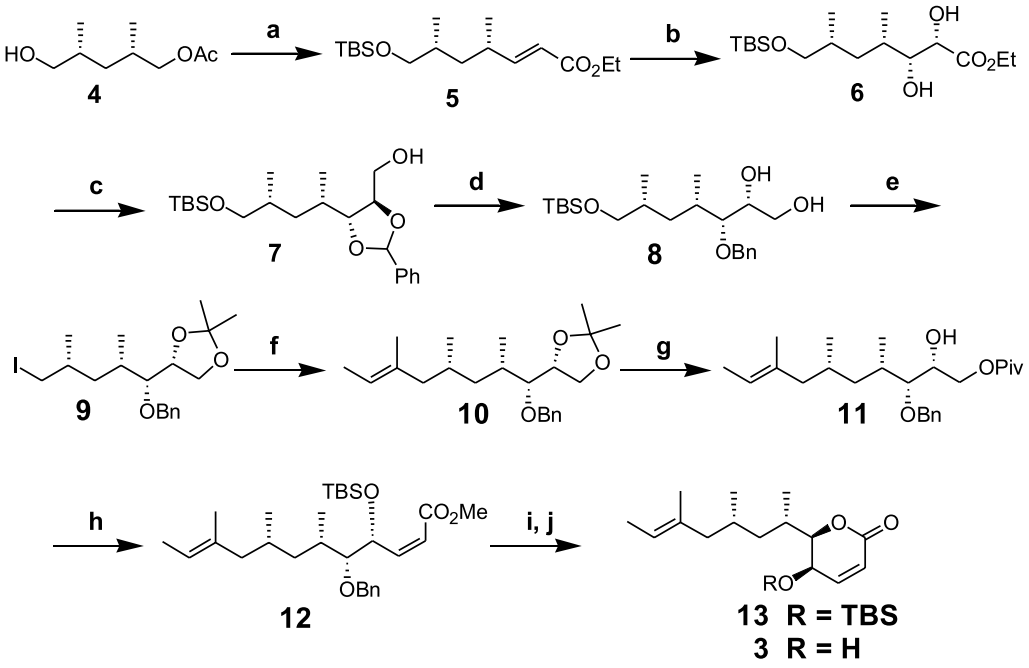
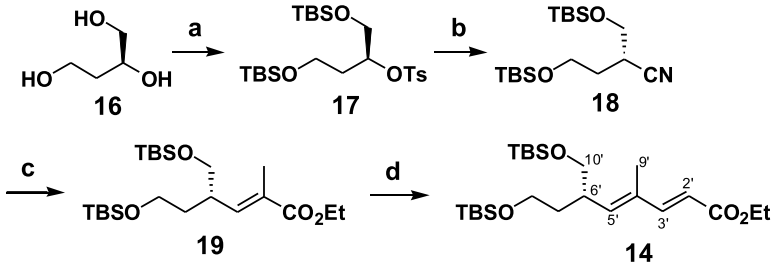


Scheme 1. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, rt, 1 h (82%); (ii) NaOH aq, MeOH, rt, 2 h (97%); (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 0 °C 2 h (84% for 2 steps); (b) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C-rt, 45 h (80%); (c) (i) $PhCH(OCH_3)_2$, TsOH, CH_2Cl_2, rt, 1 h (90%); (ii) $LiAlH_4$, THF, 0 °C, 0.5 h (81%); (d) BH_3 SMe_2, BF_3 OEt_2, CH_2Cl_2, 0 °C, 1 h (70%); (e) (i) $(CH_3)_2C(OCH_3)_2$, TsOH, acetone, rt, 1 h (91%); (ii) TBAF, THF, rt, 1 h (91%); (iii) I_2, Ph_3P, imidazole, benzene, rt, 2 h (95%); (f) 2-bromo-*cis*-2-butene, Li, THF, 0 °C-rt, 2 h (62%); (g) (i) TsOH, MeOH, rt, 2 h (84%); (ii) PivCl, pyridine, 0 °C-rt, 14 h (93%); (h) (i) TBSCl, imidazole, DMF, rt, 14 h (95%); (ii) DIBAL, CH_2Cl_2, −78 °C, 1 h (86%); (iii) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; (iv) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −78 °C, 2 h (80% for 2 steps); (i) (i) DDQ, H_2O, CH_2Cl_2, rt, 2 h (78%); (ii) DIBAL, CH_2Cl_2, −78 °C, 1 h; (iii) MnO_2, CH_2Cl_2, rt (68% for 2 steps); (j) TBAF, THF, rt, 2 h (89%).

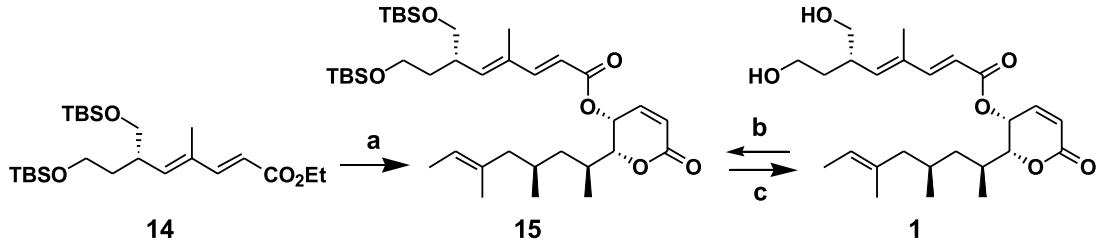
(**8**) selectively (formation of 1,3-diol was not detectable). The 1,2-diol (**8**) was protected with an acetonide, and deprotection of the TBS ether and treatment with iodine and triphenylphosphine gave the iodide (**9**). The iodide (**9**) was treated with the alkenyllithium reagent[11] derived from 2-bromo-*cis*-2-butene to give the alkene (**10**). Deprotection of the acetonide group of **10** and selective protection of the primary hydroxy group with pivaloyl ester afforded **11**. The remaining secondary hydroxy group of **11** was protected by the TBS ether, which was converted into *Z*-unsaturated ester (**12**, $J_{3,4}=11.7$ Hz) through three steps [(i) removal of the pivaloyl group with DIBAL; (ii) Swern oxidation; (iii) Still's variant of the Horner–Emmons reaction[12]]. Deprotection of the benzyl ether with DDQ, and reduction with DIBAL followed by allylic oxidation with MnO_2[13] afforded the 6-membered lactone (**13**), whose TBS ether was removed by treatment with tetrabutylammonium fluoride to afford segment A (**3**).

2.2. Coupling of segments A and B

Preparation of the ethyl ester of the di-TBS ether of segment B (**14**) was described previously,[3] and summarized in Scheme 2 and Section 3. Coupling of segment A (**3**) with the acid obtained by alkaline hydrolysis of the ethyl ester (**14**) was carried out, as shown in Scheme 3, by treatment with 1,3-dicyclohyxylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) to give the TT-1 di-TBS ether (**15**). The TT-1 di-TBS ether (**15**) was also prepared from natural product the TT-1 (**1**) by treatment with TBSOTf in the presence of 2,6-lutidine in dichloromethane. The ^1H and ^{13}C NMR and FABMS spectra of synthetic **15** and natural-product-derived **15** proved to be completely identical and the sign of their optical rotation data were both levorotatory. The di-TBS ether of **15** was removed by treatment with *p*-toluenesulfonic acid to give TT-1 (**1**) to complete the total synthesis of TT-1 (**1**).



Scheme 2. (a) (i)TBSCl, imidazole, DMF, 0 °C, 2 h (85%); (ii) TsCl, pyridine, rt, 72 h (80%). (b) NaCN, DMSO, 90 °C, 3.5 h (54%). (c) (i) DIBAL, CH_2Cl_2, −78 °C, 1 h; (ii) $Ph_3P=C(CH_3)CO_2Et$, CH_2Cl_2, rt, 73 h (47% for 2 steps). (d) (i) DIBAL, CH_2Cl_2, −78 °C, 1 h; (ii) MnO_2, CH_2Cl_2, rt, 14 h; (iii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 0 °C, 1 h (81% for 3 steps).



Scheme 3. (a) (i) 2 N NaOH aq, MeOH, rt, 19 h (80%); (ii) segment A (**3**), DCC, DMAP, CH_2Cl_2, rt, 17 h (86%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 4 h (43%); (c) *p*-TsOH, MeOH, rt, 1 h (21%).

From these results, the total synthesis of TT-1 (**1**) was accomplished and the whole structure of **1** has been unambiguously established by the present study.

3. Experimental

3.1. General procedures

Optical rotations were recorded on a JASCO J-20. IR spectra were measured on NaCl disks in a Hitachi 260-10 infrared spectrophotometer. NMR spectra were recorded on JEOL JNM GSX-A400, A500 and ecp600 spectrometers. High-resolution fast atom bombardment (HRFAB) mass spectra were acquired on a JMS HX-110 and JMS AX-500 mass spectrometer.

3.1.1. (2*E*,4*S*,6*R*)-Ethyl 7-(*t*-Butyldimethysilyloxy)-4,6-dimethyl-2-heptenoate (5). The known monoacetate[4–7] (**4**, 12.94 g) was dissolved in DMF (100 mL) and treated with TBSCl (13.66 g) in the presence of imidazole (11.85 g) at room temperature for 1 h. After addition of water, the reaction mixture was extracted with ether (100 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to afford a TBS ether (17.42 g, 82%), which was subjected to hydrolysis by treatment with 2 M NaOH aqueous solution (100 mL) and MeOH (150 mL) at room temperature for 2 h. The reaction mixture was extracted with chloroform (150 mL×6), and dried over $MgSO_4$, and evaporation of the organic phase under reduced pressure afforded an alcohol (14.49 g, 97%). This alcohol (6.98 g) was added to the solution of DMSO (8.1 mL) and oxalyl chloride (7.5 mL) in CH_2Cl_2 (150 mL) at −78 °C, and stirred at room temperature for 1 h under argon atmosphere. After addition of triethylamine (24.4 mL), the reaction mixture was gradually warmed to room temperature and stirred for 1 h. After addition of water, the mixture was extracted with $CHCl_3$ (100 mL×5), washed with water, dried over $MgSO_4$ to give an aldehyde, which was without purification subjected to the following Horner–Emmons reaction. To a solution of sodium hydride (60% in oil, 1.27 g) in DME (50 mL), triethyl phosphonoacetate (6.3 mL) was added at 0 °C under argon atmosphere and the mixture was stirred for 1 h. The aldehyde obtained above was added to this solution and the mixture was stirred for 1 h additionally. After addition of ammonium chloride aqueous solution, extraction with ethyl acetate (100 mL×5) and purification of the organic phase with silica gel column chromatography (EtOAc/hexane, 1:19) afforded the unsaturated ester (**5**, 7.53 g, 84% for 2 steps): $[\alpha]_D^{26}$ −0.7 (*c* 2.00, $CHCl_3$); IR ν (neat) 2957, 1703, 1652, 1462, 1369, 1259, 1181, 1094, and 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, $SiCH_3$), 0.85 (3H, d, J=6.6 Hz, H-9), 0.88 (9H, s, $SiC(CH_3)_3$), 1.05 (3H, d, J=6.6 Hz, H-8), 1.09 (1H, m, H-5), 1.28 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.50 (1H, ddd, J=4.6, 9.1, 13.9 Hz, H-5), 1.60 (1H, m, H-6), 2.43 (1H, m, H-4), 3.38 (2H, dd, J=4.6, 6.1 Hz, H-7), 4.18 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.78 (1H, dd, J=1.0, 15.6 Hz, H-2), and 6.80 (1H, dd, J=8.3, 15.6 Hz, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.4(2C), 14.3, 16.6, 18.3, 20.5, 25.9(3C), 33.4, 34.2, 39.9, 60.1, 68.4, 119.8, 154.4, and 116.9; FABMS *m/z* 315 $[M+H]^+$; HRFABMS found *m/z* 315.2382 (calcd for 315.2355, $C_{17}H_{35}O_3Si$).

3.1.2. (2*R*,3*R*,4*S*,6*R*)-Ethyl 7-(*t*-Butyldimethysilyloxy)-2,3-dihydroxy-4,6-dimethylheptanoate (6). AD-mix-β (40.43 g) was dissolved in 60 mL of *t*-BuOH/H_2O (1:1), and the solution was stirred at room temperature for 1 h. To this solution, methanesulfonamide (2.79 g) was added and the mixture was cooled to 0 °C. The ester (**5**, 8.97 g) was added to this solution and stirred for 45 h at room temperature. After addition of sodium sulfite (40 g), extraction with ethyl acetate (100 mL×6) followed by purification with silica gel column chromatography (EtOAc/hexane, 1:1) afforded the diol (**6**, 7.79 g, 80%): $[\alpha]_D^{26}$ −7.1 (*c* 2.08, $CHCl_3$); IR ν (neat) 3377, 2957, 2929, 2857, 1723, 1465, 1387, 1255, 1222, 1136, and 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.90 (1H, m, H-5), 0.91 (3H, d, J=6.6 Hz, H-9), 1.02 (3H, d, J=6.6 Hz, H-8), 1.31 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.53 (1H, ddd, J=5.2, 7.3, 13.8 Hz, H-5), 1.71 (1H, m, H-6), 1.78 (1H, m, H-4), 3.03 (1H, brd, J=4.4 Hz, H-3), 3.37 (1H, dd, J=6.1, 9.7 Hz, H-7), 3.45 (1H, dd, J=5.4, 9.7 Hz, H-7), 3.56 (1H, brd, J=5.9 Hz, H-2), and 4.26 (2H, q, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.4(2C), 14.2, 16.1, 18.1, 25.9(3C), 33.3, 34.0, 37.2, 43.4, 62.1, 67.6, 71.4, 76.2, and 174.1; FABMS *m/z* 349 $[M+H]^+$; HRFABMS found *m/z* 349.2402 (calcd for 349.2411, $C_{17}H_{37}O_5Si$).

3.1.3. (2*R*,3*R*,4*S*,6*R*)-7-(*t*-Butyldimethysilyloxy)-2,3-benzylidendioxy-4,6-dimethylheptanol (7). A solution of the diol (6, 7.79 g) in dichloromethane (40 mL) was treated with benzaldehyde dimethylacetal (6.8 mL) in the presence of *p*-toluenesulfonic acid monohydrate (230 mg) at room temperature for 1 h. After addition of sodium hydrogen carbonate aqueous solution, the mixture was extracted with ethyl acetate (50 mL×6), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) afforded an ester (8.12 g, 83%). A part of this ester (7.07 g) in THF solution (10 mL) was added to the solution of $LiAlH_4$ (952 mg) in THF (40 mL), and the mixture was

stirred at 0 °C for 30 min. After addition of water and neutralization with 2 M HCl, the mixture was extracted with ethyl acetate (30 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:9) to afford the alcohol (**7**, 5.17 g, 83%): $[\alpha]_D^{26}+2.5$ (*c* 2.00, $CHCl_3$); IR (neat) ν 3414, 2954, 2928, 2884, 2856, 1459, 1406, 1387, 1219, 1093, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, SiCH_3), 0.89 (9H, s, SiCCH_3), 0.92 (3H, d, J=6.6 Hz, H-9), 1.06 (3H, d, J=6.8 Hz, H-8), 1.07 (1H, m, H-5), 1.51 (1H, m, H-5), 1.76 (1H, m, H-6), 1.87 (1H, m, H-4), 3.37 (1H, dd, J=6.1, 9.8 Hz, H-7), 3.48 (1H, dd, J=4.9, 9.8 Hz, H-7), 3.76 (2H, t, J=4.8 Hz, H-1), 3.81 (1H, dd, J=5.1, 6.8 Hz, H-3), 4.09 (1H, dt, J=6.8, 4.8 Hz, H-2), 5.97 (1H, s, OC*H*Ph), 7.38–7.49 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.4(2C), 15.4, 18.2, 25.9(3C), 32.8, 33.1, 37.2, 63.4, 65.4, 67.4, 79.8, 82.2, 103.1, 127.0, 128.4(2C), 129.5(2C), 137.3; FABMS *m/z* 395 $[M+H]^+$; HRFABMS found *m/z* 395.2618 (calcd for 395.2618, $C_{22}H_{39}O_4Si$).

3.1.4. (2*R*,3*R*,4*S*,6*R*)-3-Benzyloxy-7-(*t*-butyldimethysilyloxy)-4,6-dimethyl-1,2-heptanediol (8). To a solution of the alcohol (**7**, 6.68 g) in dichloromethane (80 mL), dimethylsulfide borane (1.8 mL) was slowly added at 0 °C under argon atmosphere, and the mixture was stirred and gradually warmed to room temperature over 1 h. This reaction mixture was cooled again to 0 °C and boron trifluoride ethyl ether complex (2.15 mL) was added. The mixture was further stirred for 10 min. After addition of water, extraction with EtOAc (50 mL×5) followed by purification with silica gel column chromatography (EtOAc/hexane, 1:1) afforded a 1,2-diol (**8**, 4.68 g, 70%): $[\alpha]_D^{27}-22.9$ (*c* 2.00, $CHCl_3$); IR ν (neat) 3448, 2956, 2928, 2857, 1462, 1421, 1388, 1265, 1091, and 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (6H, s, SiCH_3), 0.89 (9H, s, SiCCH_3), 0.90 (3H, d, J=6.6 Hz, H-9), 0.98 (3H, d, J=6.9 Hz, H-8), 1.04 (1H, m, H-5), 1.65 (1H, m, H-5), 1.75 (1H, m, H-6), 1.86 (1H, m, H-4), 3.35 (1H, dd, J=4.8, 5.7 Hz, H-3), 3.41 (2H, dd, J=5.3, 7.8 Hz, H-7), 3.54 (1H, m, H-1), 3.63 (1H, m, H-1), 3.74 (1H, m, H-2), 4.55 (1H, d, J=11.2 Hz, OCH_2Ph), 4.74 (1H, s, OCH_2Ph), and 7.30–7.37 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.4(2C), 15.5, 17.8, 18.3, 25.9(3C), 32.7, 33.2, 37.7, 64.5, 68.0, 72.0, 74.6, 82.2, 127.8(2C), 127.9, 128.5(2C), and 138.2; FABMS *m/z* 397 $[M+H]^+$; HRFABMS found *m/z* 397.2747 (calcd for 397.2774, $C_{22}H_{41}O_4Si$).

3.1.5. (2*R*,3*R*,4*S*,6*R*)-3-Benzyloxy-7-iodo-1,2-isopropylidendioxy-4,6-dimethylheptane (9). A solution of the diol (**8**, 5.35 g) in dichloromethane (40 mL) was treated with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid monohydrate (120 mg) at room temperature for 1 h. After addition of sodium hydrogen carbonate aqueous solution, the mixture was extracted with ethyl acetate (50 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford an acetonide (5.38 g, 91%), which was dissolved in THF (30 mL) and treated with tetrabutylammonium fluoride, 1.0 M solution in THF (16 mL) at room temperature for 1 h. After addition of water, the mixture was extracted with ethyl acetate (50 mL×4), washed with brine, dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:4) to give an alcohol (3.63 g, 91%). A part of this alcohol (1.50 g) was dissolved in benzene (40 mL), and treated with imidazole (809 mg), triphenylphosphine (3.13 g), and iodine (2.38 g) at room temperature for 2 h. After addition of sodium sulfite aqueous solution, extraction with EtOAc (3 mL×4) followed by purification with silica gel column chromatography (EtOAc/hexane, 1:9) afforded an iodide (**9**, 1.92 g, 95%): $[\alpha]_D^{27}+32.8$ (*c* 2.00, $CHCl_3$); IR ν (neat) 2956, 2928, 2857, 1462, 1421, 1388, 1265, 1091, and 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.91 (3H, d, J=6.6 Hz, H-9), 0.93 (3H, d, J=6.9 Hz, H-8), 1.09 (1H, m, H-5), 1.30 (1H, m, H-5), 1.42 (3H, s, OCCH_3), 1.43 (2H, m, H-4,6), 1.46 (3H, s, OCCH_3), 3.00 (1H, dd, J=5.9, 9.6 Hz, H-7), 3.08 (1H, dd, J=4.1, 9.6 Hz, H-7), 3.29 (1H, dd, J=1.0, 7.8 Hz, H-3), 3.52 (1H, dt, J=1.0, 7.8 Hz, H-1), 4.00 (1H, dt, J=1.0, 7.8, H-1), 4.33 (1H, q, J=7.8 Hz, H-2), 4.64 (1H, d, J=11.2 Hz, OCH_2Ph), 4.86 (1H, s, OCH_2Ph), and 7.33–7.39 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.4, 17.9, 20.8, 25.8, 26.8, 31.3, 32.6, 40.9, 66.5, 73.7, 79.1, 81.8, 109.3, 127.5(2C), 128.0, 128.2(2C), and 139.1; FABMS *m/z* 433 $[M+H]^+$; HRFABMS found *m/z* 433.1224 (calcd for 433.1240, $C_{19}H_{30}IO_3$).

3.1.6. (2*R*,3*R*,4*S*,6*R*,8*E*)-3-Benzyloxy-1,2-isopropylidendioxy-4,6,8-trimethyl-8-heptene (10). To the mixture of lithium metal (87.1 mg) and anhydrous ether (4 mL) under argon atmosphere, 2-bromo-*cis*-2-butene (851 mg) was added over 30 min, and the mixture was stirred for 2 h at room temperature. Then, the mixture was cooled to 0 °C and a solution of the iodide (**9**, 901 mg) in THF (6 mL) was added to this mixture, which was gradually warmed to room temperature and stirred for 2 h. After addition of ammonium chloride aqueous solution, the mixture was extracted with ethyl acetate (30 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to give the alkene (**10**, 461 mg, 62%): $[\alpha]_D^{27}+20.8$ (*c* 2.00, $CHCl_3$); IR ν (neat) 2958, 2930, 1654, 1455, 1378, 1250, 1214, 1159, and 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.77 (3H, d, J=6.3 Hz, H-12), 0.93 (3H, d, J=6.6 Hz, H-11), 0.95 (1H, m, H-5), 1.38 (3H, s, OCCH_3), 1.39 (1H, m, H-5), 1.45 (2H, m, H-4,6), 1.54 (3H, d, J=6.4 Hz, H-10), 1.55 (3H, s, H-13), 1.57 (1H, m, H-7), 1.61 (1H, m, H-6), 1.70 (1H, m, H-4), 1.90 (1H, brdd, J=5.5, 13.0 Hz, H-7), 3.32 (1H, dd, J=1.8, 8.1 Hz, H-3), 3.50 (1H, t, J=8.1 Hz, H-1), 4.00 (1H, dd, J=6.2, 8.1 Hz, H-1), 4.29 (1H, m, H-2), 4.55 (1H, d, J=11.7 Hz, OCH_2Ph), 5.15 (1H, d, J=11.7 Hz, OCH_2Ph), 5.14 (1H, q, J=6.4 Hz, H-9), and 7.30–7.38 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.3, 14.9, 15.7, 25.8, 26.9, 27.9, 32.7, 41.8, 47.9, 66.5, 73.9, 77.2, 79.4, 120.1, 127.2, 127.6(2C), 128.1(2C), 134.4, and 139.4; FABMS *m/z* 361 $[M+H]^+$; HRFABMS found *m/z* 361.2736 (calcd for 361.2743, $C_{23}H_{37}O_3$).

3.1.7. (2*R*,3*R*,4*S*,6*R*,8*E*)-3-Benzyloxy-2-hydroxy-4,6,8-trimethyl-8-decenyl pivaloate (11). A solution of the alkene (**10**, 891 mg) in methanol (20 mL) was treated with *p*-toluenesulfonic acid monohydrate (86 mg) at room temperature for 2 h. After addition of water, the mixture was extracted with ethyl acetate (30 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:4) to give a diol (662 mg, 84%), a part of which (507 mg) was dissolved in pyridine (1 mL) at 0 °C and treated with pivaloyl chloride (0.32 mL) at room

temperature for 14 h. After addition of water and neutralization with 2 M HCl, the mixture was extracted with ethyl acetate (20 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to give the pivaloyl ester (**11**, 668 mg, 93%): $[\alpha]_D^{27}-16.0$ (*c* 2.00, $CHCl_3$); IR ν (neat) 3448, 2962, 2929, 1730, 1654, 1480, 1457, 1397, 1375, 1283, 1160, 1095, and 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.83 (3H, d, $J=6.3$ Hz, H-12), 0.98 (3H, d, $J=6.8$ Hz, H-11), 1.06 (1H, m, H-5), 1.24 (9H, s, OCCH_3), 1.49 (1H, m, H-5), 1.54 (3H, d, $J=6.6$ Hz, H-10), 1.55 (3H, s, H-13), 1.66 (1H, m, H-7), 1.73 (1H, m, H-6), 1.84 (1H, m, H-4), 2.04 (1H, m, H-7), 3.32 (1H, t, $J=4.4$ Hz, H-3), 3.88 (1H, dt, $J=5.8$, 4.4 Hz, H-2), 4.09 (2H, d, $J=5.8$ Hz, H-1), 4.59 (1H, d, $J=11.0$ Hz, CH_2Ph), 4.67 (1H, d, $J=11.0$ Hz, CH_2Ph), 5.17 (1H, q, $J=6.6$ Hz, H-9), and 7.30–7.36 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.3, 15.6, 20.4, 27.2(3C), 28.4, 32.6, 38.8, 42.3, 47.3, 65.6, 70.3, 74.7, 81.8, 120.1, 127.3(2C), 127.8, 128.5(2C), 134.3, 138.1, and 178.3; FABMS *m/z* 405 $[M+H]^+$; HRFABMS found *m/z* 405.2979 (calcd for 405.3005, $C_{25}H_{41}O_4$).

3.1.8. (2*Z*,4*R*,5*R*,6*S*,8*R*,10*E*)-Methyl 5-benzyloxy-4-(*t*-butyldimethylsilyloxy)-6,8,10-trimethyl-dodecadienate (12). The pivaloyl ester (**11**, 668 mg) was dissolved in DMF (6 mL) and treated with TBSCl (752 mg) in the presence of imidazole (1.16 g) at room temperature for 14 h. After addition of water, the reaction mixture was extracted with ether (30 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford a TBS ether (806 mg, 95%), a part of which (771 mg) was dissolved in dichloromethane (14 mL). To this solution, 0.93 M diisobutylaluminium hydride in hexane solution (3.6 mL) was added, and the mixture was stirred at −78 °C under argon atmosphere. After addition of potassium sodium (+)-tartarate aqueous solution, the mixture was extracted with ethyl acetate (20 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford an alcohol (553 mg, 86%). A part of this alcohol (259 mg) was dissolved in dichloromethane (4 mL) and treated with Dess-Martin periodinane (389 mg) at room temperature for 1 h. After addition of water, the mixture was extracted with ether (10 mL×3), washed with aqueous solution of sodium hydrogen carbonate and sodium thiosulfate (1:1), dried over $MgSO_4$, and evaporated under reduced pressure to afford an aldehyde, which was used without purification in the following reaction. A solution of 18-crown-6 (802 mg) in THF (6 mL) at −78 °C under argon atmosphere, 0.5 M toluene solution of potassium bis(trimethylsilyl)-amide (1.4 mL) and bis-(2,2,2-trifluoroethyl)-(methoxycarbonyl methyl)phosphonate (0.14 mL) were added and the mixture was stirred at −78 °C for 1 h. To this solution, the aldehyde obtained above dissolved in THF (3 mL) was added, and the mixture was further stirred for 2 h. After addition of ammonium chloride aqueous solution, the mixture was extracted with ethyl acetate (10 mL×4), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:9) to afford the unsaturated ester (**12**, 233 mg, 80% for 2 steps): $[\alpha]_D^{26}+19.4$ (*c* 2.20, $CHCl_3$); IR ν (neat) 2954, 2928, 2857, 1726, 1653, 1459, 1437, 1254, 1197, 1179, and 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 0.75 (3H, d, $J=6.1$ Hz, H-14), 0.88 (9H, s, SiCCH_3), 0.95 (3H, d, $J=6.6$ Hz, H-13), 0.96 (1H, m, H-7), 1.40 (1H, m, H-7), 1.51 (3H, s, H-15), 1.52 (3H, d, $J=6.6$ Hz, H-12), 1.57 (1H, m, H-9), 1.62 (1H, m, H-8), 1.77 (1H, m, H-6), 1.89 (1H, m, H-9), 3.27 (1H, dd, $J=3.0$, 6.3 Hz, H-5), 3.69 (3H, s, OCH_3), 4.52 (1H, d, $J=11.7$, CH_2Ph), 4.58 (1H, d, $J=11.7$, CH_2Ph), 5.14 (1H, q, $J=6.6$ Hz, H-11), 5.58 (1H, dd, $J=6.3$, 9.5 Hz, H-4), 5.80 (1H, d, $J=11.8$ Hz, H-2), 6.15 (1H, dd, $J=9.5$, 11.8 Hz, H-3), and 7.29–7.35 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −4.5(2C), 13.3, 15.5, 15.6, 19.9, 25.9(3C), 28.1, 31.4, 42.2, 47.6, 51.3, 69.9, 74.4, 84.9, 119.4, 119.8, 127.3(2C), 128.0(2C), 134.5, 139.4, 149.6, and 166.2; FABMS *m/z* 489 $[M+H]^+$; HRFABMS found *m/z* 489.3423 (calcd for 489.3400, $C_{29}H_{49}O_4Si$).

3.1.9. (5*R*,6*R*,1′*S*,3′*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-6-(1′,3′,5′-trimethyl-hept-5-enyl)-5,6-dihydro-pyran-2-one (13). The unsaturated ester (**12**, 5.0 mg) was dissolved in dichloromethane (0.2 mL), and this solution was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (23.1 mg) and water (0.013 mL) at room temperature for 2 h. After addition of water, extraction with chloroform (50 mL×4) and purification with silica gel column chromatography (EtOAc/hexane, 1:9) afforded an alcohol (3.0 mg, 78%), which was dissolved in dichloromethane (0.2 mL) at −78 °C under argon atmosphere. To this solution, 0.93 M dichloromethane solution of DIBAL (0.2 mL) was added, and this mixture was stirred for 1 h. After warming to room temperature, potassium sodium (+)-tartarate aqueous solution was added, and the mixture was extracted with ethyl acetate (10 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was dissolved in dichloromethane (0.3 mL). To this solution, manganese dioxide (4.2 mg) was added, and this mixture was stirred at room temperature for 23 h. Filtration through celite to remove MnO_2 followed by purification with silica gel preparative TLC gave the 6-membered lactone (**13**, 2.0 mg, 68% for 2 steps): $[\alpha]_D^{21}-160$ (*c* 1.50, $CHCl_3$); IR ν (neat) 3053, 2986, 2958, 2929, 2857, 1723, 1654, 1458, 1421, 1380.8, 1159, 1126, and 1053 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.03 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 0.76 (3H, d, $J=6.6$ Hz, H-15), 0.88 (9H, s, SiCCH_3), 0.98 (1H, m, H-8), 1.11 (3H, d, $J=6.6$ Hz, H-14), 1.37 (1H, m, H-8), 1.53 (1H, m, H-10), 1.55 (3H, s, H-16), 1.56 (3H, d, $J=6.6$ Hz, H-13), 1.75 (1H, m, H-9), 2.10 (1H, m, H-10), 2.14 (1H, m, H-7), 3.87 (1H, ddd, $J=2.4$, 8.5, 16.1 Hz, H-6), 4.26 (1H, dt, $J=5.6$, 2.4 Hz, H-5), 5.17 (1H, q, $J=6.6$ Hz, H-12), 6.08 (1H, dd, $J=1.0$, 9.7 Hz, H-3), and 6.87 (1H, dd, $J=5.6$, 9.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −4.3 (2C), 13.3, 14.8, 15.2, 15.4, 20.6, 25.7 (3C), 27.6, 30.8, 40.2, 46.1, 61.7, 85.3, 120.0, 122.8, 134.3, 144.6, and 163.9; FABMS *m/z* 367 $[M+H]^+$; HRFABMS found *m/z* 367.2644 (calcd for 367.2668, $C_{21}H_{39}O_3Si$).

3.1.10. (5*R*,6*R*,1′*S*,3′*R*)-5-Hydroxy-6-(1′,3′,5′-trimethyl-hept-5-enyl)-5,6-dihydro-pyran-2-one (3). The 6-membered lactone (**13**, 8.1 mg) was dissolved in THF (0.15 mL) and treated with 1.0 M solution of tetrabutylammonium fluoride in THF (0.03 mL) at room temperature for 2 h. After addition of water, the mixture was extracted with ethyl acetate (10 mL×3), dried over $MgSO_4$, and purified with silica gel prepatative TLC (EtOAc/hexane, 1:1) to give an

alcohol (segment A, **3**, 5.0 mg, 89%): $[\alpha]_D^{24}-72.5$ (*c* 2.00, $CHCl_3$); IR ν (neat) 3385, 2927, 1712, 1381, 1265, and 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.84 (3H, d, $J=6.8$ Hz, H-15), 1.15 (3H, d, $J=6.4$ Hz, H-14), 1.65 (6H, br.s; H-13 and H-16), 3.92 (1H, dd, $J=9.1$, 1.9 Hz, H-6), 4.23 (1H, br.s, H-5), 5.20 (1H, q, $J=6.4$ Hz, H-12), 6.13 (1H, dd, $J=9.4$ Hz, H-3), and 7.01 (1H, dd, $J=9.4$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 13.4, 15.6, 15.7, 21.0, 27.9, 31.3, 39.8, 46.4, 60.7, 85.2, 120.1, 123.2, 134.5, 144.2, and 163.9; FABMS *m/z* 253 $[M+H]^+$; HRFABMS found *m/z* 253.1807 (calcd for 253.1804, $C_{15}H_{25}O_3$).

3.1.11. Preparation of segment B di-TBS ether (14) (Scheme 2). The known triol[14] (**16**, 2.968 g) was dissolved in DMF (30 mL) and treated with TBSCl (9.697 g) in the presence of imidazole (9.532 g) at room temperature for 2 h under argon atmosphere. After addition of water, the reaction mixture was extracted with $CHCl_3$ (100 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:1) to afford a TBS ether (7.954 g, 85%), part of which (2.011 g) was treated with TsCl (1.711 g) in pyridine (12 mL) at room temperature for 72 h. After addition of water, the reaction mixture was neutralized with potassium hydrogensulfate, and extracted with $CHCl_3$ (100 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:19) to afford a tosylate (**17**, 2.337 g, 80%): $[\alpha]_D^{22}-16.8$ (*c* 0.20, $CHCl_3$); IR ν (neat) 2955, 2929, 2885, 2857, 1598, 1471, 1462, 1362, 1256, 1177, and 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H −0.01(3H, s, SiCH_3), 0.00 (3H, s, SiCH_3), 0.01 (6H, s, SiCH_3), 0.85 (18H, s, SiC(CH_3)$_3$), 1.80 (1H, m, H-3), 1.90 (1H, m, H-3), 2.44 (3H, s, ArCH_3), 3.48 (1H, ddd, $J=6.0$, 7.1, 10.5 Hz, H-4), 3.56 (1H, dt, $J=10.5$, 6.0 Hz, H-4), 3.72 (2H, d, $J=8.0$ Hz, H-1), 7.31 (2H, d, $J=8.0$ Hz, Ar), and 7.80 (2H, d, $J=8.0$ Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$)δ_C −5.5, −5.4, 21.6, 25.7(2C), 25.9(2C), 25.9, 34.3, 58.7, 64.3, 81.0, 127.8(2C), 129.7(2C), and 144.8; FABMS *m/z* 489 $[M+H]^+$; HRFABMS found *m/z* 489.2490 (calcd for 489.2526, $C_{23}H_{45}O_5SSi_2$).

To a solution of sodium cyanide (517.8 mg) in DMSO (52 mL), the tosylate (**17**, 2.337 g) was added, and the mixture was stirred at 90 °C for 3.5 h. After cooling to room temperature and addition of water, the mixture was extracted with extracted with $CHCl_3$ (50 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:4) to afford a nitrile (**18**, 887 mg, 54%): $[\alpha]_D^{22}+15.6$ (*c* 0.50, $CHCl_3$); IR ν (neat) 2955, 2930, 2885, 2858, 1472, 1256, and 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H −0.08 (6H, s, SiCH_3), 0.10 (6H, s, SiCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.91 (9H, s, SiC(CH_3)$_3$), 1.83 (2H, m, H-3), 2.95 (1H, dq, $J=8.5$, 5.8 Hz, H-2), and 3.78 (4H, m, H-1, 4); ^{13}C NMR (100 MHz, $CDCl_3$) δ_H −5.4(4C), 18.3, 26.0(6C), 31.8, 59.9, 63.1, and 120.9; FABMS *m/z* 344 $[M+H]^+$; HRFABMS found *m/z* 344.2416 (calcd for 344.2441, $C_{17}H_{38}O_2Si_2N$).

To the solution of the nitrile (**18**, 171.8 mg) in CH_2Cl_2 under argon atmosphere at −78 °C, 0.93 M dichloromethane solution of DIBAL was added, and this mixture was stirred for 1 h. After warming to room temperature, potassium sodium (+)-tartarate aqueous solution was added, and the mixture was extracted with $CHCl_3$ (30 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was dissolved in dichloromethane (0.5 mL). This solution was treated with (1-carbethoxyethylidene)-triphenylphosphorane (364.5 mg) under argon atmosphere at room temperature for 73 h. After evaporation under reduced pressure, the residue was purified with silica gel column chromatography (EtOAc/hexane, 3:97) to afford an ester (**19**, 100.6 mg, 47% for 2 steps): $[\alpha]_D^{22}+21.0$ (*c* 0.11, $CHCl_3$); IR ν (neat) 2954, 2929, 2895, 2858, 1713, 1653, 1472, 1388, 1362, and 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.08 (6H, s, SiCH_3), 0.10 (6H, s, SiCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.91 (9H, s, SiC(CH_3)$_3$), 1.28 (1H, t, $J=$ 7.2 Hz, –OCH$_2$CH_3), 1.45 (1H, m, H-5), 1.81 (1H, m, H-4), 1.86 (3H, d, $J=1.4$ Hz, H-7), 2.78 (1H, m, H-4), 3.52 (1H, m, H-8), 3.54 (2H, dd, $J=4.1$, 6.1 Hz, H-6), 3.60 (1H, m, H-8), 4.18 (2H, q, $J=7.2$ Hz, –OCH_2CH$_3$), and 6.57 (1H, dd, $J=1.4$, 10.5 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.4(4C), 12.9, 14.3, 18.3, 25.8(6C), 34.3, 38.4, 60.4, 60.9, 65.9, 129.0, 143.5, and 168.2; FABMS *m/z* 431 $[M+H]^+$; HRFABMS found *m/z* 431.2990 (calcd for 431.3013, $C_{22}H_{47}O_4Si_2$).

To the solution of the ester (**19**, 85.7 mg) in CH_2Cl_2 under argon atmosphere at −78 °C, 0.93 M dichloromethane solution of DIBAL (0.44 mL) was added, and this mixture was stirred for 1 h. After warming to room temperature, potassium sodium (+)-tartarate aqueous solution was added, and the mixture was extracted with $CHCl_3$ (30 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give a residue, which was dissolved in dichloromethane (10 mL). This solution was treated with MnO_2 (161.2 mg) at room temperature for 13 h. After evaporation under reduced pressure, the residue (aldehyde) was used to the next reaction. A mixture of triethyl phosphonoacetate and sodium hydride (50% in oil, 21 mg) in dimethoxyethane (2.5 mL) was stirred at 0 °C under argon atmosphere for 1 h. To this mixture, the aldehyde obtained as above was added and stirred for 1 h. After addition of water, the mixture was extracted with ether (20 mL×5), dried over $MgSO_4$, and purified with silica gel column chromatography (EtOAc/hexane, 1:49) to afford the segment B di-TBS ether (**14**, 74.3 mg, 81% for 3 steps): $[\alpha]_D^{22}+20.2$ (*c* 0.60, $CHCl_3$); IR ν (neat) 2954, 2928, 2857, 1718, 1624, 1471, 1388, 1364, 1300, 1256, and 1169 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.01 (12H, s, SiCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 1.30 (1H, t, $J=$ 7.2 Hz, –OCH$_2$CH_3), 1.41 (1H, ddt, $J=8.5$, 13.5, 5.3 Hz, H-7), 1.80 (3H, d, s, H-9), 1.86 (ddt, $J=8.5$, 13.5, 5.3 Hz, H-7), 2.82 (1H, ddt, $J=4.2$, 10.4, 6.2 Hz, H-6), 3.50 (1H, ddt, $J=5.1$, 6.4, 10.1 Hz, H-8), 3.52 (2H, t, $J=6.2$ Hz, H-10), 3.60 (1H, ddt, $J=5.1$, 6.4, 10.1 Hz, H-8), 4.52 (2H, q, $J=7.2$ Hz, –OCH_2CH$_3$), 5.74 (1H, d, $J=10.1$ Hz, H-5), 5.80 (1H, d, $J=15.6$ Hz, H-2), and 7.31 (1H, d, $J=15.6$ Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.3(4C), 12.7, 14.3, 18.2, 25.8(6C), 34.3, 38.3, 60.2, 60.8, 66.1, 115.9, 134.0, 143.5, 149.6, and 167.6; FABMS *m/z* 457 $[M+H]^+$; HRFABMS found *m/z* 457.3132 (calcd for 457.3169, $C_{24}H_{49}O_4Si_2$).

3.1.12. Coupling of segments A and B. Segment B di-TBS ether (**14**, 8.0 mg) in methanol (0.5 mL) was treated with

2 M sodium hydroxide aqueous solution (0.5 mL) at room temperature for 19 h. After addition of water, the mixture was extracted with ethyl acetate (10 mL×4), dried over $MgSO_4$, and evaporated under reduced pressure to give an acid (segment B, 6.0 mg, 80%). The alcohol (segment A, **3**, 2.0 mg) and the acid (segment B, 4.0 mg) were dissolved in dichloromethane (0.2 mL), and this mixture was treated with 1,3-dicyclohyxylcarbodiimide (DCC, 2.0 mg) in the presence of 4-dimethylaminopyridine (DMAP, 1.2 mg) at room temperature for 17 h. After addition of water, the mixture was extracted with ether (10 mL×4), dried over $MgSO_4$, and silica gel prepatative TLC (EtOAc/hexane, 1:4) to give TT-1 di-TBS ether (**15**, 4.5 mg, 86%): $[\alpha]_D^{23}-125$ (*c* 2.0, $CHCl_3$); IR ν (neat) 1718, 1617, 1256, 1157, and 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 0.00 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 0.78 (3H, d, J=7.0 Hz, H-15), 0.87 (9H, s, SiCCH_3), 0.88 (9H, s, SiCCH_3), 1.15 (3H, d, J=6.5 Hz, H-14), 1.52 (3H, br.s, H-16), 1.53 (3H, d, J=6.2 Hz, H-13), 1.79 (3H, s, H-9′), 2.83 (1H, br.s, H-6′), 3.48–3.62 (4H, m, H-8′ and H-10′), 4.13 (1H, dd, J=8.8, 1.8 Hz, H-6), 5.12 (1H, q, J=6.2 Hz, H-12), 5.36 (1H, dd, J=6.0, 1.8 Hz, H-5), 5.73–5.85 (2H, m, H-2′ and H-5′), 6.21 (d, J=9.5 Hz, H-3), 7.05 (1H, dd, J=9.5, 6 Hz, H-4), and 7.34 (1H, d, J=15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C −5.43, −5.40, −5.38, −5.30, 12.7, 13.3, 15.5, 15.9, 18.2, 18.2, 20.6, 25.84, 25.88, 27.9, 31.4, 34.6, 38.4, 40.0, 46.3, 60.7, 61.6, 66.0, 83.3, 114.1, 120.0, 124.9, 134.0, 134.1, 140.7, 145.3, 151.6, 163.3, and 166.4; FABMS *m/z* 663 $[M+H]^+$; HRFABMS found *m/z* 663.4480 (calcd for 663.4476, $C_{37}H_{67}O_6Si_2$).

3.2. Preparation of TT-1 di-TBS ether (15) from TT-1 (1)

To the solution of TT-1 (**1**, 5.0 mg) in dichloromethane (0.1 mL), 2,6-lutidine (5.4 mL) was added at 0 °C under argon atmosphere. To this solution, TBSOTf (7.9 μL) was added dropwise over 5 min and the mixture was stirred for 4 h at 0 °C. After addition of water (0.5 mL), the reaction mixture was extracted with $CHCl_3$ (10 mL×4), dried over $MgSO_4$, and purified with preparative TLC (silica gel, EtOAc/hexane, 1:4) to afford a TT-1 TBS ether (**15**, 3.3 mg, 43%), which was completely identical with synthetic **15** on the basis of comparison of ^1H and ^{13}C NMR and FABMS spectral data, and the sign of the optical rotation was also the same ($[\alpha]_D^{24}-70$ (*c* 2.0, $CHCl_3$)).

3.3. Conversion of TT-1 di-TBS ether (15) into TT-1 (1)

TT-1 TBS ether (**15**, 2.2 mg) was dissolved in MeOH (0.55 mL) and treated with *p*-toluenesulfonic acid mono hydrate (28 mg) at room temperature for 1 h. After addition of water, the mixture was extracted with $CHCl_3$ (10 mL×4), dried over $MgSO_4$, and purified with HPLC (Develosil ODS-HG; 10×250 mm; flow rate: 2.0 mL; UV detection at 251 nm; eluent: CH_3CN/H_2O, 1:1) to afford TT-1 (**1**, 0.3 mg, 21%).

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Kinetic and computational studies on aminolysis of bicyclic carbonates bearing alicyclic structure giving alicyclic hydroxyurethanes

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Abstract—Aminolysis of bicyclic carbonates, which consist of five-membered cyclic carbonate and five- or six-membered alicyclic groups, was examined. Kinetic studies revealed that the aminolysis of the bicyclic carbonate with cyclohexane ring proceeded more smoothly than that of the bicyclic carbonate with cyclopentane ring. Computational calculation suggested that the different reaction rates originate from the distinct ring-strain of the cyclic carbonate groups affected by the conformation of the alicyclic groups.

1. Introduction

Reactions of cyclic carbonates have been extensively explored to develop efficient preparative method for various carbonyl compounds and polymers.[1–16] The importance of the reactions is also emphasized by the improvement that cyclic carbonates can be prepared from carbon dioxide with safe and cost-effective procedures,[4–16] whereas carbonate synthesis had depended on highly toxic phosgene or its derivatives.[1–3] For instance, oxiranes and carbon dioxide react in the presence of catalysts (e.g., quaternary ammonium halides, alkali-metal halides, and transition metal compounds) to produce five-membered cyclic carbonates even under atmospheric pressure.[4–6]

Aminolysis of a cyclic carbonate is one of the most studied reactions; and provides a urethane derivative having one hydroxyl group (i.e. hydroxyurethane),[1–10] which cannot be obtained by traditional urethane synthesis based on reaction of alcohols and isocyanates. This aminolysis is as highly chemo-selective as that the nucleophilic addition is not affected by the presence of water and alcohols.[4] This feature enables the aminolysis to be applied for varieties of reaction conditions and substrates, hence has been allowing synthesis of diverse poly(hydroxyurethane)s.[1–7] For example, we have demonstrated that polyadditions of bifunctional carbonates with diamines provides poly(hydroxyurethane)s, yields and molecular weights of which are not affected by the presence of water, alcohol, or esters.[4] Even L-lysine inherently possessing a carboxyl group can be employed as a diamine.[5]

In spite of the usefulness of aminolysis of cyclic carbonates, this reaction has been less applied for synthesis of alicyclic hydroxyurethanes, which are intermediates of biologically active compounds,[15–18] except for synthesis of forskolin derivatives.[15,16] Clarifying the aminolysis behavior of cyclic carbonates with alicyclic structure will be very informative in synthesis of alicyclic alcohols bearing urethane moieties as the protected alcohol groups. In addition, introduction of alicyclic structure to polymer backbone leads to higher thermal and optical properties,[19–23] therefore will afford poly(hydroxyurethane)s with improved properties. We accordingly describe the aminolysis behavior of cyclic carbonates bound to five- and six-membered alicyclic structures.

2. Experimental

2.1. Materials

N,*N*-Dimethyl acetamide (DMAC, Kanto Chemical Co., Tokyo, Japan) was dried over CaH_2 and distilled under reduced pressure. 2,4-Dioxabicyclo[3.3.0]octane-3-one (**1a**)

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was prepared by the previously reported method for synthesis of 7,9-dioxabicyclo[4.3.0]-1-nonane-8-one (**1b**),[24] spectroscopic data of which were comparable to those reported in a literature.[25] The bicyclic carbonate with cyclohexane ring (**1b**) was prepared according to the literature.[24] Other materials were used as received.

2.1.1. Synthesis of 1a. Lithium bromide (2.18 g, 25.1 mmol), cyclopentene oxide (42.1 g, 500 mmol), and 1-methyl-2-pyrrolidinone (500 mL) were added to a 1 L three-neck flask containing a magnetic stir bar equipped with a three-way cock under CO_2 atmosphere. Then the mixture was stirred at 100 °C for 120 h. The resulting solution was cooled to room temperature and washed with brine. The water layer was washed with diethyl ether to extract the objective product. The combined organic layer was dried over anhydrous $MgSO_4$ and volatile substances were evaporated off under reduced pressure. The residual solid was purified by column chromatography (SiO_2, eluent: ethyl acetate/hexane 1/1 [v/v]) followed by sublimation to give **1a** in 66% yield (42.0 g). Mp = 36.3–36.9 °C. ^{1}H NMR ($CDCl_3$, δ in ppm) 5.12–5.15 (dd, J = 3.78, 3.51 Hz, 2H, –C*H*–), 2.10–2.19 (m, 4H, –CHCH_2–), 1.62–1.86 (m, 2H, –CHCH$_2$CH_2–). ^{13}C NMR ($CDCl_3$, δ in ppm) 155.55 (>*C*=O), 81.80 (–*C*H–), 32.97 (–*C*HCH$_2$–), 21.36 (–CHCH$_2$*C*H$_2$–). IR (KBr) 1805 cm^{-1} (υ, C=O). EA calcd. For $C_6H_8O_3$: C 56.24; H 6.29. Found: C 56.17; H 6.27.

2.1.2. Synthesis of 1b. The procedure for **1a** was employed using cyclohexene oxide instead of cyclopentene oxide and the reaction time was prolonged to 144 h. Purification was carried out by column chromatography (SiO_2, eluent: ethyl acetate) followed by flash distillation under reduced pressure to give **1** in 31% yield (22.1 g). Mp = 40.0–41.0 °C. ^{1}H NMR ($CDCl_3$, δ in ppm) 4.67–4.74 (t, J = 3.78 Hz, 2H, –C*H*–), 1.87–1.91 (m, 4H, –CHCH_2–), 1.36–1.70 (m, 4H, –CHCH$_2$CH_2–). ^{13}C NMR ($CDCl_3$, δ in ppm) 155.42 (>*C*=O), 75.66 (–*C*H–), 26.51 (–*C*HCH$_2$–), 18.90 (–CHCH$_2$*C*H$_2$–). IR (KBr) 1805 cm^{-1} (υ, C=O). EA calcd. For $C_7H_{10}O_3$: C 59.14; H 7.09. Found: C 59.10; H 7.25.

2.1.3. Aminolysis of 1a with *n*-hexylamine. *n*-Hexylamine (0.797 g, 7.81 mmol) and **1a** (1.00 g, 7.81 mmol) were added to a test tube equipped with a three-way cock under nitrogen atmosphere. The mixture was stirred at 70 °C and the reaction was conducted until the complete consumption of **1a** had been confirmed by thin layer chromatography. The reaction mixture was subjected to column chromatography (SiO_2, eluent: ethyl acetate/hexane [v/v = 1/1]) to afford **2a** (0.97 g, 54%) as colorless oil. ^{1}H NMR ($CDCl_3$, δ in ppm) 5.21 (m, 1H, –COOC*H*–), 4.86–4.91 (q, J = 10.4 Hz, 1H, –N*H*), 4.16 (m, 1H, –C*H*OH–), 3.12–3.20 (m, 2H, –NHCH_2–), 2.93 (s, 1H, –O*H*), 1.41–2.08 (10H, –CHCH_2CHCH_2–, CH$_3$(CH$_2$)$_2$(CH_2)$_2$–) 1.20–1.41 (4H, CH$_3$(CH_2)$_2$–), 0.89 (t, J = 6.75 Hz, 3H, CH_3–). ^{13}C NMR ($CDCl_3$, δ in ppm) 156.66 (>*C*=O), 77.08 (–COO*C*H–), 73.39 (–*C*H(OH)–), 41.02 (–NH*C*H–), 31.34 (CH$_3$CH$_2$-*C*H$_2$–), 30.57 (–NHCH*C*H$_2$–), 29.75 (–C(OH)H*C*H$_2$–), 28.18 (CH$_3$(CH$_2$)$_2$*C*H$_2$–), 26.30 (–COOCH*C*H$_2$CH$_2$–), 22.40 (–COOCHCH$_2$*C*H$_2$–), 19.27 (CH$_3$*C*H$_2$–), 13.85 (*C*H$_3$–). IR (KBr) 3332 (υ, –O*H*), 1533, 1697 cm^{-1} (υ C=O). EA calcd. For $C_{12}H_{23}NO_3$: C 62.85; H 10.11; N 6.11. Found: C 62.60; H 10.18; N: 6.25.

2.1.4. Aminolysis of 1b with *n*-hexylamine. The procedure for **1a** was employed using **1b** instead of **1a**. Purification was performed by column chromatography (SiO_2, eluent: ethyl acetate/hexane [v/v = 1/1]) to afford **2b** (1.40 g, 82%) as white solid. Mp = 53.8–54.6 °C. ^{1}H NMR ($CDCl_3$, δ in ppm) 4.91 (s, 1H, –COOC*H*–), 4.80–4.83 (d, J = 7.56 Hz, 1H, –N*H*), 3.87 (d, J = 2.97 Hz, 1H, –C*H*OH–), 3.13–3.20 (q, J = 13.23 Hz, 2H, –CH_2–), 2.50 (s, 1H, –O*H*), 1.43–2.00 (12H, –CHCH_2CH_2–, CH$_3$(CH$_2$)$_2$(CH_2)$_2$–), 1.20–1.43 (4H, CH$_3$(CH_2)$_2$–), 0.89 (t, J = 7.02 Hz, 3H, CH_3–). ^{13}C NMR ($CDCl_3$, δ in ppm) 156.59 (>*C*=O), 74.26 (–COO*C*H–), 69.48 (–*C*H(OH)–), 40.96 (–NH*C*H–), 31.31 (CH$_3$CH$_2$-*C*H$_2$–), 30.05 (–NHCH*C*H$_2$–), 29.70 (–C(OH)H*C*H$_2$–), 27.25 (–COOCH*C*H$_2$–), 26.28 (CH$_3$(CH$_2$)$_2$*C*H$_2$–), 22.38 (CH$_3$*C*H$_2$–), 21.81 (–COOCHCH$_2$*C*H$_2$–), 21.01 (–C(OH)HCH$_2$*C*H$_2$–), 13.81 (*C*H$_3$–). IR (KBr) 3335 (υ –O*H*), 1543, 1697 cm^{-1} (υ, C=O). EA calcd. For $C_{13}H_{25}NO_3$: C 64.16; H 10.36; N 5.76. Found: C 64.37; H 10.51; N: 5.89.

2.2. Measurements

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-LA-270 instrument using tetramethylsilane as an internal standard (270 and 67.5 MHz for ^{1}H and ^{13}C NMR, respectively). Fourier transform infrared (FT-IR) spectra were measured on a Horiba FT-210 instrument.

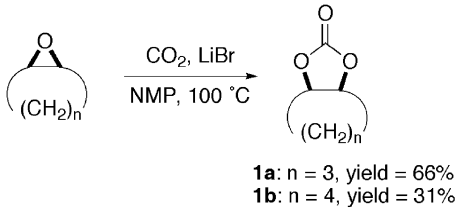
2.3. Computational calculations

Computational calculations were performed with Spartan '04 Windows (Wavefunction, Irvine, CA) using the 3-21G basis set on the restricted Hartree-Fock method (HF-3-21G) to optimize molecular structures. The initial conformations and geometries were obtained by molecular mechanics calculation.

3. Results and discussion

3.1. Preparation of bicyclic carbonates

Bicyclic carbonates with alicyclic structures were prepared by a LiBr catalyzed reaction of alicyclic oxiranes with carbon dioxide (Scheme 1). Although reactions of oxiranes with carbon dioxide generally proceed smoothly within 24 h to provide five-membered cyclic carbonates in high to quantitative yields, the reactions affording **1a** and **1b** took longer time (5 days) and the yields were relatively lower. The lower reactivity of **1a** and **1b** may originate from the

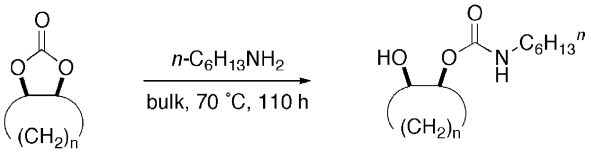


Scheme 1.

steric hindrance of the cyclic structure. The better yield of **1a** than that of **1b** can be ascribable to the different ring-strain of the resulting carbonate ring. That is, ab initio computational calculation with the HF-3-21G basis set showed that the dihedral angles of O–C–C–O bonds in the carbonate rings are 0.27 and 35.39° for **1a** and **1b**, respectively (the optimized geometries are shown later). This result suggests that the carbonate ring in **1b** is more strained than that of **1a**, resulting in the lower yield of **1b**. The *syn*-geometries on the methine protons were confirmed by ^{1}H NMR spectroscopy for both **1a** and **1b**.

3.2. Aminolysis of bicyclic carbonates

Aminolysis of the carbonates **1a** and **1b** by *n*-hexylamine were carried out in bulk at 70 °C for 110 h to afford the corresponding hydroxyurethanes **2a** and **2b** in 54 and 82%, respectively (Scheme 2). Although the steric hindrance and the ring strain can be nominated as the possible factors to rule the reactivity, we assumed that the ring strain is considered as the major factor (discussed later). Namely, if the steric hindrance was the major factor, **1a** having the smaller ring structure must be more reactive than **1b**. The conversions of **1a** and **1b** during the aminolysis were traced by ^{1}H NMR spectroscopy. In the aminolysis of **1a**, **1b**, and ethylene carbonate (**3**) by *n*-hexylamine in bulk at 50 °C, the rates of the reaction were in the order of **3**>**1b**>**1a**, indicating the less reactivities of **1a** and **1b** toward **3** (Fig. 1).



1a: n = 3
1b: n = 4

2a: n = 3, yield = 54%
2b: n = 4, yield = 82%

Scheme 2.

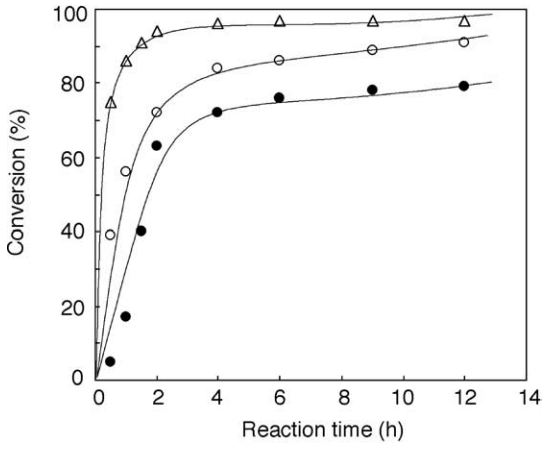


Figure 1. Time-conversion curves in the aminolysis of **1a** (●) and **1b** (○), and **3** (△) with *n*-hexylamine at 50 °C.

Since the reactivity of **1a** was lower than that of **1b**, we calculated the reaction rate constants k and the activation energies E_a in order to evaluate the reactivity quantitatively. The experiments for the kinetic analysis were carried out using **1** (4.0 mmol) and *n*-hexylamine (4.0 mmol) in DMAC (2.0 mL) at various temperatures under nitrogen atmosphere. If the concentrations of unreacted **1** and *n*-hexylamine can be premised to be equal under the reaction conditions, the reaction rates are expressed by Eq. (1).

$$-\mathrm{d}[C]/\mathrm{d}t = k[C]^2 ([C] : \text{concentration of } \mathbf{1}) \quad (1)$$

Eq. (1) can be transformed to Eq. (2).

$$1/[C] - 1/[C]_0 = kt([C]_0 : \text{initial concentration of } \mathbf{1}) \quad (2)$$

Figure 2 illustrates the correlation between reaction time and $1/[C]-1/[C]_0$, where linear relationships through the origin can be observed, demonstrating the validity of the premise above. The slopes of the lines revealed the reaction rate constants as $k_{\mathbf{1a}}=5.9\times10^{-3}$ and $k_{\mathbf{1b}}=13.2\times10^{-3}$ (L mol^{-1} h), respectively. We further evaluated the kinetics of the reactions at 100, 110, and 120 °C in order to estimate the activation energies E_a based on the Arrhenius equation $k=Ae^{-E_a/RT}$ that can be transformed as Eq. (3).

$$\ln k = -E_a/RT + \ln A \quad (3)$$

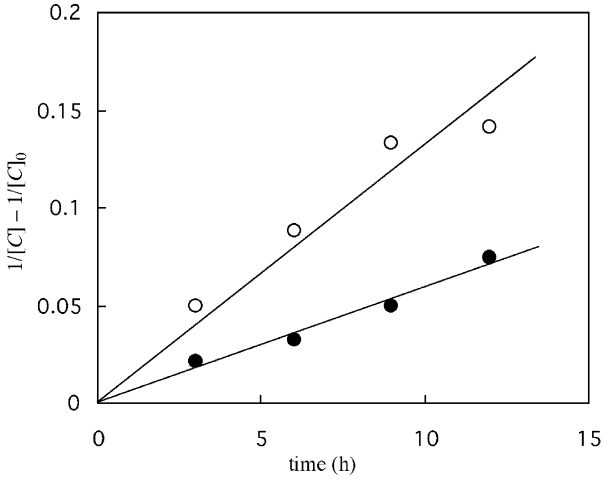


Figure 2. Time–$(1/[C]-1/[C]_0)$ relationships in the aminolysis of **1a** (●) and **1b** (○) with *n*-hexylamine in DMAC at 90 °C.

Figure 3 illustrates the relationship between the logarithms of ks and the inverses of the reaction temperature. The linear relationship of the lines enabled us to estimate the activation energies as $E_{a\mathbf{1a}}=29.9$ and $E_{a\mathbf{1b}}=22.4$ (kcal mol^{-1}), respectively.

We also investigated the aminolysis behavior by computational calculation to confirm the aforementioned assumption that ring strain ruled the reactivities of the alicyclic cyclic carbonates. Figure 4 illustrates the optimized geometries of **1a**, **1b**, and their hydroxyurethane derivatives from methylamine. The cyclic carbonate with cyclohexane ring (**1b**) has a strained carbonate ring with the O–C–C–O dihedral angle of 35.39° (Table 1, Fig. 4), while the carbonate ring in **1a** is not strained. This difference has probably originated from the fact that the stable conformation of cyclohexane rings is the chair conformation with higher torsion angles of H–C–C–H bonds, while that of cyclopentane rings is the relatively planer conformation

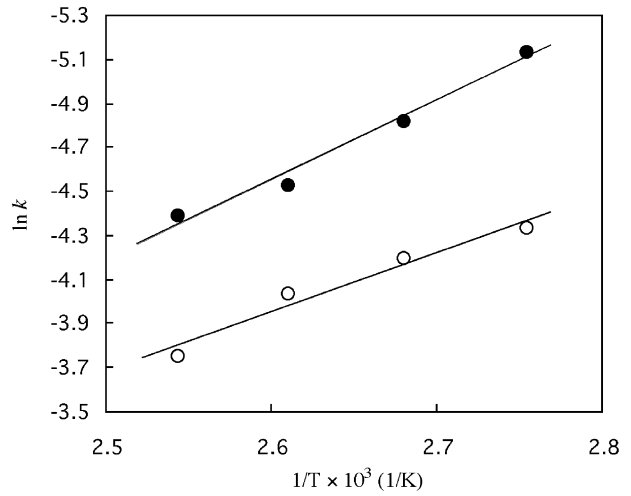


Figure 3. Relationship between ln k and $1/T$ in the aminolysis of **1a** (●) and **1b** (○) with *n*-hexylamine in DMAC.

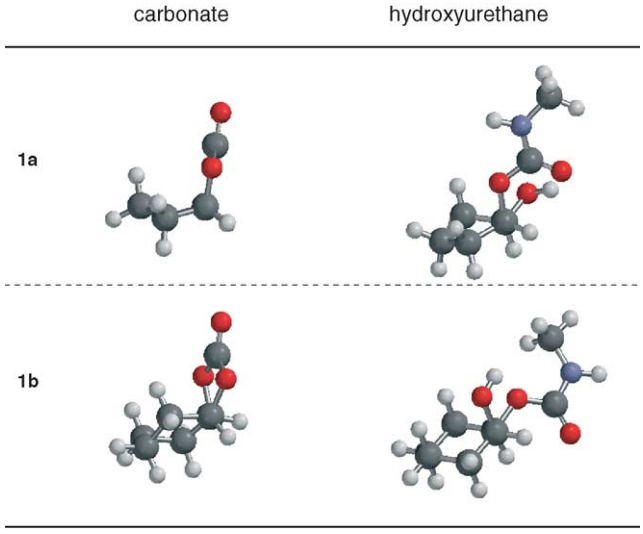


Figure 4. Optimized geometry of **1a**, **1b**, and the analogous urethane derivatives.

Table 1. Torsion angles of O–C–C–O bonds and heat of reaction of the cyclic carbonates (**1a** and **1b**) and the corresponding hydroxyurethanes[a]

Compounds	Torsion angle (degree)	Δ Torsion angle (degree)[b]	Heat of reaction (kcal/mol)
1a	−0.27	45.42	−19.17
1a-urethane	45.15		
1b	−35.39	92.55	−22.27
1b-urethane	57.16		

[a] Calculated from the structures minimized by the HF-3-21G basis set.
[b] Torsion angle differences between hydroxyurethanes and carbonates.

with lower torsion angles of H–C–C–H bonds. The changes in the dihedral angles of O–C–C–O bonds in the cyclic carbonates and hydroxyurethanes (45.42° for **1a** and 92.55° for **1b**) agreed well with the reactivity. The heat of reaction on the aminolysis of **1a** and **1b** was calculated as −19.17 and −22.27 kcal/mol, respectively, which also agreed well with the kinetic results. These data further supported the different reactivity of cyclic carbonates consisting of bicyclic systems.

4. Summary

We have investigated the aminolysis of bicyclic carbonates, prepared from alicyclic oxiranes and carbon dioxide, that provides hydroxyurethanes with alicyclic structure. Kinetic studies revealed that the activation energies depend upon the alicyclic structure (i.e. **1b** with cyclohexane ring is more reactive than **1a** with cyclopentane ring). This difference is supposed to originate from the different ring-strain of the carbonate groups owing to the constraint from the alicyclic rings. This quantitative analysis would have disclosed helpful information on the reactions of carbonates directly attached to cyclic systems, which will be applied to preparations of polymers and functional alicyclic compounds.

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5′-Noraristeromycin derivatives isomeric to aristeromycin and 2′-deoxyaristeromycin

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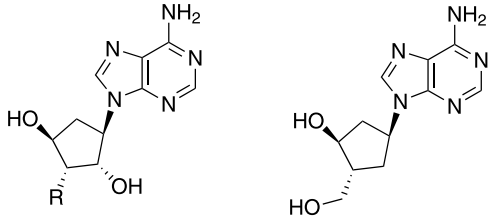
Abstract—A straightforward synthesis of (1*S*,2*R*,3*R*,4*R*)-4-(6-aminopurin-9-yl)-2-hydroxymethylcyclopentane-1,3-diol (**2**), an isomer of aristeromycin, and its 2′-deoxy derivative **3** from readily available disubstituted cyclopentenes is presented. An antiviral analysis of **2** showed it to have significant activity versus Epstein–Barr virus (IC_{50} 0.62 μg/mL in the Elisa assay) and to be free of cytotoxicity effects against the host cells. In a much less comprehensive antiviral analysis, **3** also was active towards Epstein–Barr (IC_{50} 7.58 μg/mL in the Elisa assay) but this was accompanied by cellular toxicity.

1. Introduction

Oligonucleotides possessing carbanucleoside monomeric units have received little attention.[1,2] Such derivatives would be expected to render, among other properties, nuclease stability[3] to the oligos in which they are incorporated and may have a role to play in nanotechnology.[4] As an outgrowth of our antiviral studies with 5′-nor carbanucleosides (for example, 5′-noraristeromycin, **1**)[5] (Fig. 1) we became interested in their inclusion in oligomers.[6] However, as a consequence of lacking the C-5′ methylene in the nucleoside monomer, such oligos would have shortened internucleotide phosphate bonds. As a consequence, oligomeric structural perturbations would arise that would be difficult to correlate with the customary furanose-based oligomers. To develop 5′-nor carbanucleosides that would not offer an oligomeric product with shortened phosphorus to phosphorus distances, 3′-homo-5′-noraristeromycin (**2**) and its 2′-deoxy derivative **3** were sought. The preparation of **2** and **3** is reported. For comparative purposes to **1**, the antiviral properties of **2** are given.



1, R=OH
2, R=CH_2OH

3

Figure 1.

2. Chemistry

The synthesis of **2** was envisioned as starting with the readily available chiral hydroxyacetate **4**[7] because of its facile conversion to **5**,[8] which possesses functionality appropriately placed for the cyclopentyl component of **2**. Epoxidation of **5** gave predominantly the α-epoxide **6** (α:β, 10:1), which was based on Henbest's rule,[9] literature precedence,[10a,b] and correlation with the confirmed (vide infra) structure of **8**. Epoxide **6** was protected as its benzyl ether **7**. This was followed by reaction with adenine to provide a mixture of two regioisomers in a 3:1 ratio. Identification of the two isomers by NMR could not be achieved due to overlapping signals. However, X-ray analysis (Fig. 2) revealed **8**[10] as the major component, possibly arising as a result of the benzyl ether assisting epoxide ring opening.

Hydrogenolytic deprotection of the benzyl ether **8** under various circumstances was unsuccessful. However, treatment of **8** with boron trichloride, followed by addition of methanol to the reaction mixture and heating gave the

Keywords: 3′-Homo carbocylic nucleosides; Epoxide ring opening; Mitsunobu reaction.
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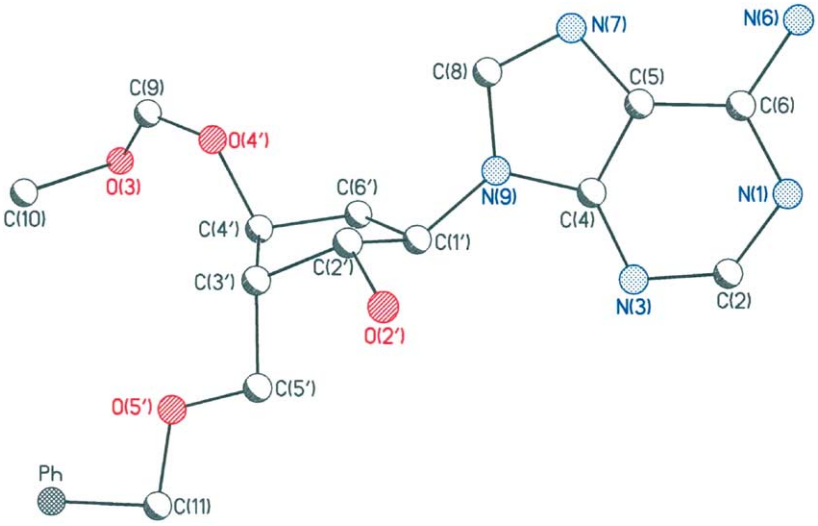


Figure 2. X-ray structure for compound **8**.

desired **2** in a very low yield as a consequence of purification difficulties.

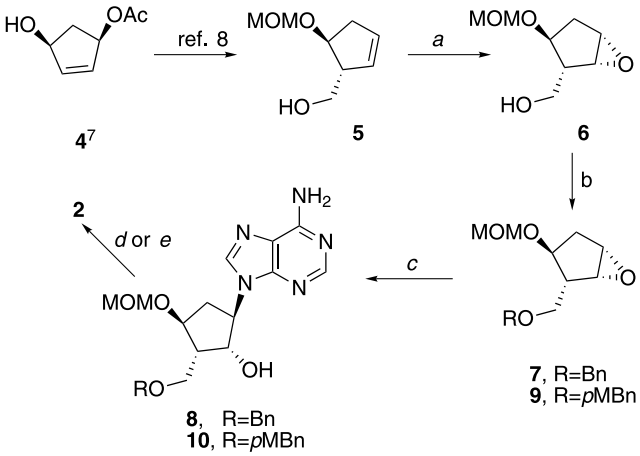
To improve the yield of **2** an alternative protection of **6** was sought. In this regard, **6** was converted to the *p*-methoxybenzyl derivative **9**. Opening of epoxide **9** with adenine provided two isomers (1.5:1). The major isomer **10** was deprotected with 10% trifluoroacetic acid followed by refluxing in 5 N hydrochloric acid to give **2** in 78% yield (compared to 10% from **8**). The NMR spectra of **2** from both methods were superimposable.

The synthesis of **3** began with the known[11] enone **11**. Using a copper promoted 1,4-addition[12] of *t*-butoxymethyl lithium, **11** was converted into **12**. L-Selectride reduction of **12** yielded alcohol **13**. Mitsunobu coupling of **13** with 6-chlorpurine produced **14**, which, upon ammonolysis and deprotection, provided the desired **3**.

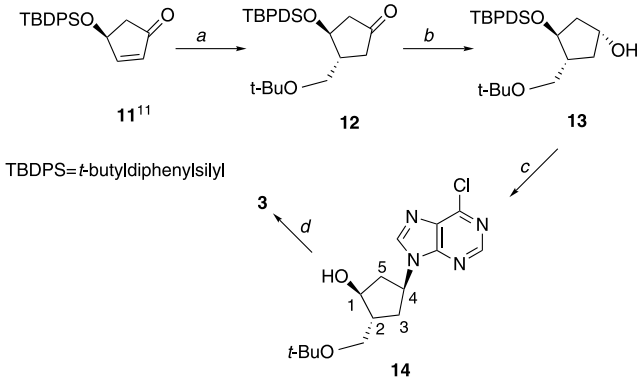
Confirmation of the structure of **14** was achieved via NMR analysis by, first, carrying-out a proton–proton COSY determination to assign the cyclopentyl ring protons. In that direction, the C-1 hydroxyl proton (3.93 ppm and identified by solvent exchange) correlated only with the H-1 (4.23 ppm). In turn, H-1 correlates with H-5 (H-5_α at 2.73 ppm and H-5_β at 2.22–2.15 ppm,) and, to a lesser degree, with H-2 (2.46 ppm). Proton-2 correlated with the two exocyclic methylene protons and the two H-3 (2.15–2.08 ppm) while H-4 (5.12 ppm) correlated with all four H-3 and H-5.

With this information available a NOESY analysis of **14** was performed: major correlations were observed between (i) H-1, H-5_α and H-4; (ii) H-4, H-3_α and the exocyclic methylene protons; and, (iii) H-2 and H-3_β.

For the previously stated purposes of this project, the synthetic methods described to **2** and **3** conveniently lend themselves to variation of the heterocyclic base unit (step d of Scheme 1 and step c of Scheme 2).



Scheme 1. Reagents: *a*, *m*CPBA, CH_2Cl_2, 84.5%; *b*, BnCl or *p*MBnCl, NaH, DMF, 82% for both; *c*, adenine, NaH, 15-C-5, 56.5% and 34%; *d*, for R=Bn, BCl_3 then MeOH, CH_2Cl_2, 10%; *e*, for R=*p*MBn, 10% TFA then 5 N HCl, CH_2Cl_2 then MeOH, 78%.



Scheme 2. Reagents: *a*, $(t\text{-}BuOCH_2)_2CuLi$, *t*-BuOMe, THF, 87%; *b*, L-selectride, THF, 79%; *c*, (i) 6-chloropurine, PPh_3, DIAD, THF; (ii) TBAF, THF, 30.5% overall for 2 steps; *d*, (i) NH_3, MeOH; (ii) TFA, H_2O, 75% overall for two steps.

3. Antiviral results

Compound **2** was subjected to antiviral analysis.[13] No activity was found except against Epstein–Barr virus (in Daudi cells: Elisa assay, IC_{50} 0.62 μg/mL; DNA hybridization assay, IC_{50} 20 μg/mL; acyclovir IC_{50} 1.7 μg/mL in both assays).[14a] Compound **2** was non-toxic to the following host cells: human foreskin fibroblast, Daudi, MA-104, MDCK, human embryonic lung, Vero, and human hepatoblastoma 2.2.15. The promising effects of **2** towards Epstein–Barr virus prompted a similar assay for **3**[13b] (in Daudi cells: Elisa assay, IC_{50} 7.58 μg/mL; DNA hybridization assay, IC_{50} 0.1 μg/mL; acyclovir IC_{50} 1.3 μg/mL in the Elisa assay and 0.4 in the DNA assay).[14a] However, **3** demonstrated significant toxicity to the Daudi cells (CC_{50} 47.1 μg/mL in both assays). Analog **3** showed no effects against the other herpes viruses.

4. Experimental

4.1. General

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. The NMR spectra were recorded on Bruker AC 250 and AV 400 spectrometers. All ^{1}H chemical shifts are reported in δ relative to internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (J) are expressed in Hz. The X-ray analysis was conducted using a Bruker SMART APEX CCD diffractometer. The optical rotation determinations were carried out on a Jasco P1010 polarimeter and the ultraviolet spectra recorded using a Hitachi U2000 spectrophotometer. Atlantic Microlabs, Atlanta, Georgia, performed the elemental analyses. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm Whatman Partisil R Diamond K6F plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

4.1.1. (1*R*,2*R*,3*S*,5*S*)-3-Methoxymethoxy-2-phenethyl-6-oxabicyclo[3.1.0]hexane (7). To an ice-cold stirring solution of **5**[8] (600 mg, 3.82 mmol) in 50 mL of CH_2Cl_2 was added a solution of *m*CPBA (4.93 g, 77% max.) in CH_2Cl_2 (30 mL). The ice bath was removed and the reaction mixture was kept at rt overnight. The reaction mixture was washed sequentially with saturated Na_2CO_3 (3×50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The resultant crude material (NMR analysis indicating two products in a 10:1 ratio) was purified by silica gel column chromatography (hexanes–EtOAc, 2:1) to give **6** (the major product) as a colorless, sticky liquid (620 mg, 84.5%): ^{1}H NMR ($CDCl_3$) δ 4.59 (s, 2H), 4.00–3.88 (m, 2H), 3.67–3.50 (m, 3H), 3.38 (s, 3H), 2.65 (dd, J=7.5 Hz, 1H), 2.21 (m, 1H), 2.10 (brs, 1H), 1.69–1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 96.8, 76.9, 62.5, 56.9, 55.73, 54.9, 49.0, 35.1.

To a solution of the above oil (530 mg, 3.06 mmol) in DMF (10 mL) in an ice-cooled bath were added NaH (88.23 mg, 3.70 mmol) and benzyl bromide (0.409 mL, 3.37 mmol). This mixture was stirred for 2 h at room temperature and then evaporated at reduced pressure. The residue was then diluted with EtOAc (20 mL), washed with H_2O (10 mL) and brine (10 mL) and the organic phase dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate evaporated under reduced pressure to give a residue that was purified by silica gel column chromatography (hexanes–EtOAc, 10:1 to 3:1) to provide **7** (620 mg, 82%) as white solid, mp 43 °C: ^{1}H NMR ($CDCl_3$) δ 7.36–7.25 (m, 5H), 4.61 (m, 3H), 4.56 (s, 3H), 3.76–3.44 (m, 5H), 3.29 (s, 1H), 2.53 (dd, J=7.25 Hz, 1H), 2.33 (m, 1H), 1.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 138.5, 128.5, 127.8, 127.7, 96.5, 76.7, 73.5, 69.5, 56.9, 55.5, 55.4, 47.3, 34.9. Anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; Found: C, 68.19; H, 7.66.

4.1.2. (1*R*,2*S*,3*S*,5*R*)-5-(6-Aminopurin-9-yl)-2-benzyloxymethyl-3-methoxymethoxycyclopentanol (8). A suspension of adenine (686 mg, 5 mmol) and NaH (120 mg, 5 mmol) in DMF (10 mL) was stirred at 135 °C for 15 min. To this mixture **7** (440 mg, 1.77 mmol) in DMF (10 mL) and 15-crown-5 (0.1 mL) were added at room temperature. The mixture was then heated at 135 °C for 3.5 h. The mixture was evaporated in vacuo and the residue then diluted with CH_2Cl_2 (50 mL). The new solution was washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a foam (two regioisomers, 3:1 by the NMR). The resulting foam was purified very carefully by silica gel column chromatography (MeOH–CH_2Cl_2, 1:20) to give 310 mg (56.5%) of **8** as a white solid, mp 137–138 °C: ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.89 (s, 1H), 7.26 (m, 5H), 5.70 (brs, 2H), 4.75–4.50 (m, 7H), 4.25 (q, J=6.6 Hz, 1H), 3.81 (s, 1H), 3.79 (s, 1H), 3.35 (s, 3H), 2.89 (m, 1H), 2.55 (m, 1H), 2.23 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 155.68, 152.7, 150.5, 139.7, 138.0, 128.7, 128.1, 128.0, 120.2, 95.3, 76.5, 73.7, 67.9, 62.1, 55.8, 47.9, 35.8, 18.4. Anal. calcd for $C_{20}H_{25}N_5O_4\cdot 0.25H_2O$: C, 59.41; H, 6.25; N, 17.12. Found: C, 59.38; H, 6.34; N, 17.07.

4.1.3. (1*R*,2*S*,3*S*,5*R*)-5-(6-Aminopurin-9-yl)-2-(4-methoxybenzyloxymethyl)-3-(methoxymethoxy)cyclopentanol (10). To a solution of **6** (880 mg, 5.08 mmol) in DMF (10 mL) cooled in an ice bath was added NaH (134.1 mg, 5.59 mmol). After 10 min, *p*-methoxybenzyl chloride (0.68 mL, 5.59 mmol) was added. The mixture was stirred for 2 h at room temperature and then evaporated under reduced pressure. The resultant residue was diluted with EtOAc (20 mL) and this solution washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 10:1 to 3:1) to yield **9** (620 mg, 82%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J=10 Hz, 2H), 6.86 (d, J=10 Hz, 2H), 4.54 (s, 2H), 4.51 (s, 2H), 3.80 (s, 3H), 3.70–3.40 (m, 5H), 3.29 (s, 3H), 2.70 (dd, J=7.5 Hz, 1H), 2.40 (m, 1H), 1.85 (m, 1H).

A suspension of adenine (1.85 g, 13.5 mmol) and NaH (240 mg, 10 mmol) in DMF (10 mL) was stirred at 130 °C for 15 min. To this, **9** (440 mg, 1.77 mmol) in DMF (10 mL) and 15-crown-5 (0.4 mL) were added at room temperature. This mixture was then heated at 130 °C for 6 h. The mixture was evaporated in vacuo and the residue diluted with EtOAc (50 mL). The new mixture was washed with brine (20 mL), dried ($MgSO_4$), and the filtrate evaporated to give a yellow foam (two regioisomers, 1.5:1 by the NMR). The major isomer was purified from the residue by silica gel column chromatography (5% MeOH in CH_2Cl_2) to give 610 mg (34%) of **10**[15] as a white solid, mp 136.3 °C: ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.89 (s, 1H), 7.28 (d, J=10.0 Hz, 2H), 6.86 (d, J=10 Hz, 2H), 5.76 (brs, 2H), 4.67–4.60 (m, 4H), 4.55 (d, J=7.5 Hz, 2H), 4.23 (q, J=7.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 1H), 3.75 (s, 1H), 3.54 (s, 3H), 2.90 (m, 1H), 2.59 (m, 1H), 2.22 (m, 1H), 1.98 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 154.10, 150.5, 150.24, 147.3, 145.0, 134.26, 124.6, 124.1, 114.7, 108.6, 90.8, 72.0, 71.7, 71.1, 67.9, 62.2, 56.6, 50.3, 50.0, 47.5, 30.40. Anal. calcd for $C_{21}H_{27}N_5O_5$: C, 58.73; H, 6.34; N, 16.31. Found: C, 58.78; H, 6.31; N, 16.39.

4.1.4. (1*S*,2*R*,3*R*,4*R*)-4-(6-Aminopurin-9-yl)-2-(hydroxymethyl)cyclopentane-1,3-diol (2). (a) From **8**. To a solution of **8** (766 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added BCl_3 (7.2 mL, 1.0 M in CH_2Cl_2). This mixture was stirred at the same temperature for 2 h and MeOH (10 mL) was added dropwise. Water (10 mL) was then added and the mixture refluxed for overnight. Neutralization of the mixture with NH_4OH followed by evaporation led to a residue that was subjected to silica gel column chromatography (CH_2Cl_2–MeOH, 7:1 to 3:1) to give a white solid. Recrystallization of this material using MeOH–CH_2Cl_2 resulted in **2** (50 mg, 10%) as a white solid, mp 175.5–177 °C; $[\alpha]_D^{23.5}=-20.42$ (*c* 0.10, MeOH); uv (MeOH) λ_{max} 239 nm (ε 453.3); ^{1}H NMR (DMSO) δ 8.19 (s, 1H), 8.12 (s, 1H), 7.24 (brs, 2H), 5.22 (d, J=5 Hz, 1H), 5.13 (d, J=4.9 Hz, 1H), 4.60–4.51 (m, 2H), 4.31 (t, J=5.3 Hz, 1H), 4.04 (m, 1H), 3.69 (m, 1H), 3.53 (m, 1H), 2.60 (m, 1H), 2.10–1.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 155.9, 155.8, 151.9, 140.0, 119.1, 74.9, 70.4, 60.6, 58.4, 42.4, 37.9. Anal. calcd for $C_{11}H_{15}N_5O_3\cdot 0.7H_2O$: C, 47.50; H, 5.90; N, 25.19. Found: C, 47.83; H, 5.59; N, 24.96.

(b) From **10**. Compound **10** (100 mg, 2.42 mmol) was stirred in a solution of 10% trifluoroacetic acid (10 mL in CH_2Cl_2) for 20 min, during which time it became a clear pink solution. The mixture was then evaporated and the residue co-evaporated with anhydrous EtOH (3×20 mL). The material left from this process was stirred in a solution of 5 N HCl in MeOH (10 mL) at 50 °C overnight. Evaporation and then co-evaporation with MeOH (3× 20 mL) gave a yellow solid that was then dissolved in MeOH and neutralized with IRA-67 resin. Filtration, concentration of the filtrate and purification of the residue by silica gel column chromatography (5% MeOH in CH_2Cl_2) gave **2** (50 mg, 78%), whose spectral properties were identical to **2** obtained from **8**.

4.1.5. (1*R*,3*S*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-(*tert*-butoxymethyl)cyclopentanol (13). Under N_2 *sec*-butyllithium solution (1.4 M in hexanes, 30 mL, 42 mmol) was added dropwise to a suspension of potassium *tert*-butoxide (4.71 g, 42.0 mmol) in anhydrous *tert*-butylmethyl ether (200 mL) at −70 °C over 5 min under N_2. After stirring 3.5 h at this temperature, a solution of LiBr (7.27 g, 82.0 mmol) in dry THF (100 mL) was added dropwise at −70 °C over 10 min. This mixture was then allowed to warm to −15 °C at which point it was stirred for 30 min. Upon re-cooling to −70 °C, a solution of $CuBr\cdot SMe_2$ (4.31 g, 20.7 mmol) in di*iso*propyl sulfide (30 mL) was added dropwise over 10 min. To this a solution of **11**[11] (4.32 g, 13.8 mmol) in dry THF (25 mL) was added dropwise over 5 min. The new reaction mixture was allowed to cool to −30 °C over 15 min and then stirred at this temperature for an additional 30 min. The reaction was then quenched with MeOH/AcOH (1:1, v/v, 25 mL), which was followed by pouring into NH_4Cl/NH_4OH solution (25 mL). After removal of the aqueous layer, the organic phase was washed with a mixture of saturated NH_4Cl and 3% NH_4OH (1:1) and then with brine. The organic layer was dried (Na_2SO_4) and then filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to give **12** as a colorless oil (4.81 g, 87%): ^{1}H NMR ($CDCl_3$) δ 7.74–7.40 (m, 10H), 4.38 (m, 1H), 3.13 (m, 2H), 2.50–2.06 (m, 5H), 1.09 (s, 9H), 1.03 (s, 9H).

To a solution of **12** (1.41 g, 3.5 mmol) in anhydrous THF (20 mL), was added L-selectride (3.7 mL, 1 M in THF) at −78 °C. The resulting mixture was stirred at the same temperature for 40 min and then quenched with sat. aqueous NH_4Cl solution (10 mL). Water (20 mL) was added to this and the mixture extracted with EtOAc (2×100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated and the resultant epimeric mixture (3:1 by NMR) purified by silica gel column chromatography (20% EtOAc in hexanes) to give, as the major product, **13**[16] (1.1 g, 79%) as a colorless oil. Anal. calcd for $C_{26}H_{38}O_3Si$: C, 73.19; H, 8.98; Found: C, 73.36; H, 9.07.

4.1.6. (1*S*,2*R*,4*S*)-4-(6-Aminopurin-9-yl)-2-(*tert*-butoxymethyl)cyclopentanol (14). To a stirring suspension of 6-chloropurine (0.51 g, 3.20 mmol) and triphenylphosphine (0.72 g, 3.20 mmol) in THF (20 mL) at −78 °C was added, dropwise, di*iso*propyl azodicarboxlate (0.70 g, 3.20 mmol). To this mixture was added a solution of **13** (1.17 g, 2.91 mmol) in dry THF (10 mL). The new mixture was warmed to room temperature over 2 h and stirred at this temperature overnight. Following concentration in vacuo, column chromatography (silica gel) (hexanes–EtOAc, 7:1) provided a yellow oil (750 mg). This oil (750 mg) was placed in THF (20 mL) and to this *tetra*butylammonium fluoride (2 mL of 1 M solution in THF) was added. This mixture was stirred for 2 h at room temperature. This mixture was then evaporated and the residue carefully purified by silica gel column chromatography (15% EtOAc in hexanes) to give **14** (0.2 g, 30.5%, two steps) as a white solid, mp 134–136 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (s, 1H), 8.34 (s, 1H), 5.12 (m, 1H), 4.23 (m, 1H), 3.93 (d, J=4.75 Hz, 1H), 3.51 (dd, J=3.75, 4.25 Hz, 1H), 3.31 (t, J=4.75 Hz, 1H), 2.73 (ddd, J=14.4, 6.68, 5.44 Hz, 1H), 2.46 (m, 1H), 2.30 (m, 1H), 2.22–2.15 (m, 1H), 2.15–2.08 (m, 1H) 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 151.5, 151.2, 146.9, 145.1, 132.6, 76.8, 73.4, 64.2, 55.0, 48.1, 36.7, 27.7.

Anal. calcd for $C_{15}H_{21}N_4O_2Cl$: C, 54.47; H, 6.53; N, 10.92; Cl, 17.25. Found: C, 54.84; H, 6.52; N, 10.55; Cl, 16.92.

4.1.7. (1*S*,2*R*,4*S*)-4-(6-Aminopurin-9-yl)-2-(hydroxymethyl)cyclopentanol (3). A solution of **14** (1.3 g, 4.3 mmol) in dry MeOH (30 mL) saturated with ammonia was kept at 120 °C for 48 h in a Parr stainless steel, sealed reaction vessel. The reaction mixture was evaporated and the resulting white foam stirred overnight in trifluoroacetic acid (20 mL, 50 v/v% in H_2O) at 50 °C. This mixture was then evaporated and the residue co-evaporated with anhydrous EtOH (3×20 mL). The new residue was purified by silica gel column chromatography (50% EtOAc in MeOH) to give **3** as a white solid (750 mg, 75%, two steps), mp 184–186 °C: $[\alpha]_D^{23.7} = +34.0$ (*c* 0.053, MeOH); uv (MeOH) λ_{max} 239 nm (ε 906.6); ^{1}H NMR (DMSO) δ 8.25 (s, 1H), 8.17 (s, 1H), 7.38 (brs, 2H), 4.93 (m, 1H), 4.71 (brs, 1H), 3.99 (q, J=4.5 Hz, 1H), 3.53–3.34 (m, 2H), 2.41 (m, 1H), 2.22–1.99 (m, 4H), 1.01 (t, J=7.0 Hz, 1H). ^{13}C NMR (DMSO) δ 155.2, 151.5, 149.1, 140.0, 118.9, 72.0, 62.1, 56.0, 52.3, 49.9, 33.8. Anal. calcd for $C_{11}H_{15}N_5O_2 \cdot 0.4H_2O$: C, 51.47; H, 6.16; N, 27.29; Found: C, 51.71; H, 6.08; N, 27.14.

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13. (a) Viruses subjected to **2** were herpes simplex 1 and 2, human cytomegalo, varicella zoster, Epstein–Barr, hepatitis B, vaccinia, cowpox, influenza A (H3N2), respiratory syncytial, and yellow fever. The antiviral and cytotoxicity assays were performed following procedures previously reported.[14] (b) Derivative **3** was only assayed against the herpes viruses.
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15. Confirmation of **10** as the regioisomeric form shown in Scheme 1 was achieved by its conversion to **2** whose structure was related to the X-ray analysis of **8**.
16. Compound **13** was identified as the major product based on its reaction with 6-chloropurine under Mitsunobu reaction conditions[17] to produce **14**, a structure assigned by NMR analysis (see text).
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Tetrahedron

The application of vinylogous iminium salt derivatives to an efficient relay synthesis of the pyrrole containing alkaloids polycitone A and B

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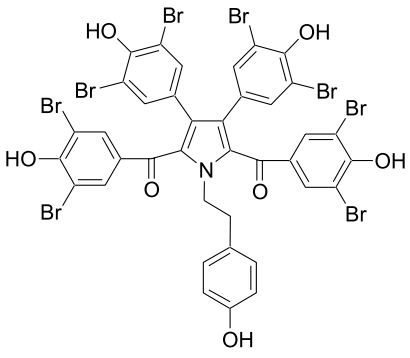
Abstract—A new and efficient relay synthesis of the marine natural products polycitone A and B is described. The new strategy relies on the formation of 2,4-disubstituted pyrroles from a vinamidinium salt followed by electrophilic substitution at the 5-position of the pyrrole and Suzuki coupling at the 4-position to produce the tetrasubstituted heterocycle efficiently and with complete control of regiochemistry.

1. Introduction

Polycitone A (**1a**) and B (**1b**) (Fig. 1) represent novel members of a growing class of pyrrole-containing marine natural products, which exhibit significant bioactivity[1] as inhibitors of retroviral reverse transcriptases and cellular DNA polymerases. These substances were first isolated and reported by Kashman[2] and co-workers and the first total synthesis was recently accomplished by Steglich[3] and co-workers. The Steglich synthesis (Scheme 1) employs a very elegant biomimetic approach involving the ammonia promoted cyclodehydration of an appropriate 1,4-diketone **2**



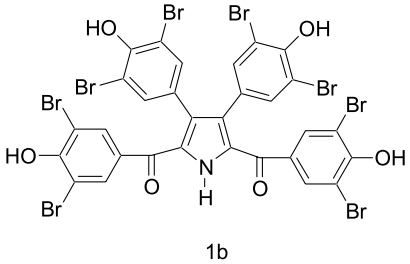


Figure 1.

Keywords: Vinamidinium salt; Pyrrole; Marine natural product.
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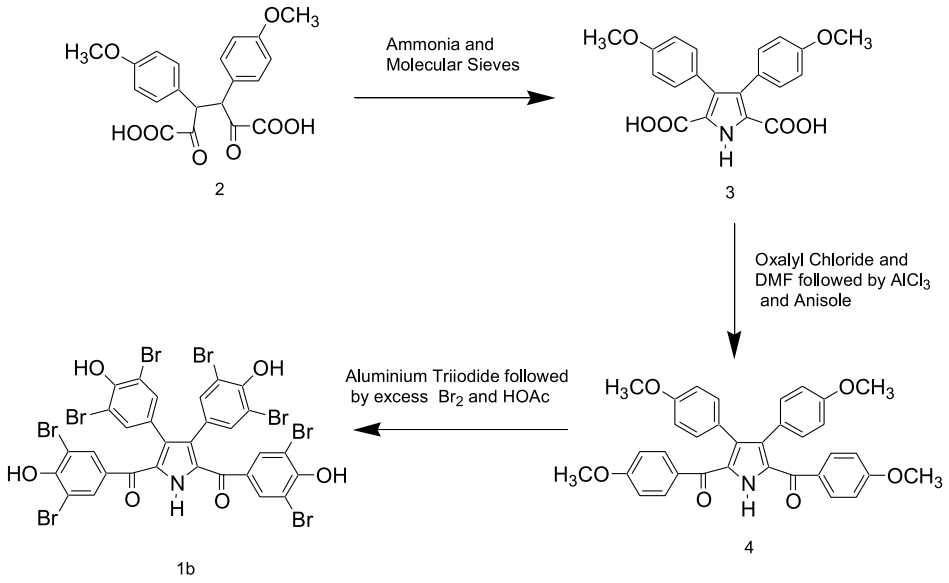


Scheme 1.

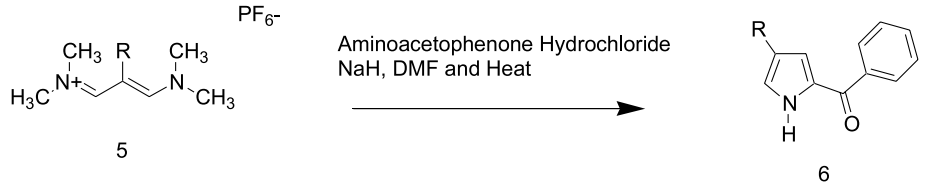
to form a 3,4-diarylpyrrole-2,5-dicarboxylic acid **3**. This 3,4-diarylpyrrole-2,5-dicarboxylic acid is then reacted with anisole under Friedel–Crafts conditions to produce the corresponding 2,5-dibenzoyl derivative **4**, which is O-dealkylated and brominated to produce polycitone B (**1b**) in 55% overall yield. By subsequent O-protection, N-alkylation and O-deprotection, polycitone B (**1b**) was converted to polycitone A (**1a**) in three steps and 39% yield.

It is clear from the work of Steglich and co-workers that symmetrical diketone **4** is a key synthetic intermediate for the polycitone natural products and also for analogs. Since SAR studies have yet to be accomplished for this class of alkaloids, new synthetic approaches, which provide substantial structural and functional group diversity, are required. We have previously reported the preparation of diaryl substituted chloropropeniminium salts and their corresponding β-chloroenals. Reacting either of these materials with glycinate esters efficiently produced 2,3,4-trisubstituted pyrroles[4] and these substances served as key synthons for the preparation of the pyrrole containing alkaloids lukianol A, lamellarin O[5] and ningalin B.[6] For the synthesis of polycitone A and B we have opted for a somewhat different approach, which allows for the incorporation of much greater structural diversity. This new strategy begins with the initial reaction of a 2-arylvinamidinium hexafluorophosphate with an α-aminoacetophenone in order to construct a 2-aroyl-4-arylpyrrole. Our initial studies of such a reaction are reported in Table 1.

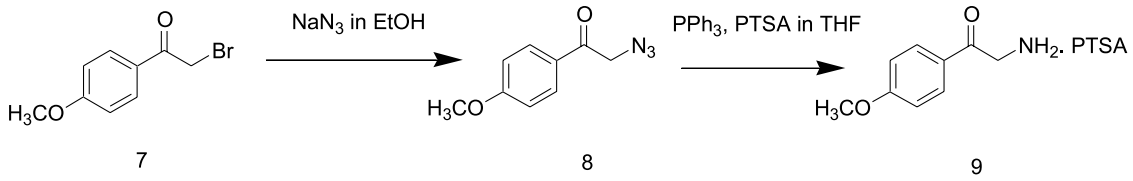
2. Results and discussion

α-Aminoketones are considerably less well behaved for pyrrole formation as compared to α-aminoesters due to self-condensation reactions. However, treatment of a series of 2-arylvinamidinium hexafluorophosphates **5**, which are readily available from the corresponding aryl acetic acids, with α-aminoacetophenone hydrochloride in refluxing DMF in the presence of sodium hydride (Table 1) results in quite reasonable yields of the desired 4-aryl-2-benzoylpyrroles **6**. The α-aminoketones can be easily and efficiently prepared according to Scheme 2 by conversion of an α-bromoketone **7** to the α-azidoketone **8** followed by reduction to the amine by triphenylphosphine and crystallization as the PTSA salt **9**. Consequently, reaction of

Table 1. Reaction of aminoacetohenone with 2-arylvinamidinium salts



Compound	R	% Yield
a	4-MeOPh	81
b	3,4-$(MeO)_2$Ph	55
c	4-MePh	77
d	Ph	85
e	4-BrPh	79
f	4-ClPh	73
g	4-FPh	63



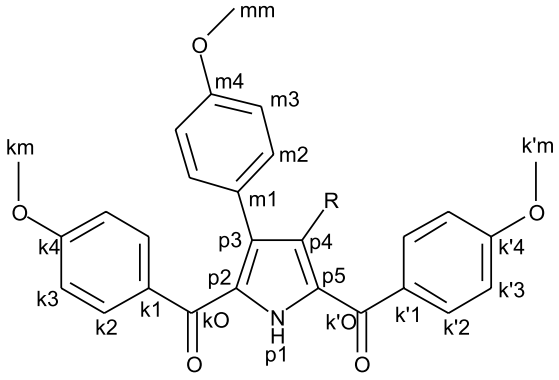
Scheme 2.

aminoketone **9** (Scheme 3) with the 4-methoxyphenyl vinamidinium salt **11** (obtained from aryl acetic acid **10**) under base mediated conditions produced the desired polycitone precursor **12** in 77% yield. This substance was then acylated with 4-methoxybenzoic acid in the presence of trifluoroacetic anhydride/trifluoroacetic acid (TFAA/TFA) according to the conditions of Edstrom[7] and co-workers in which case the 5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2-carbethoxypyrrole (**13**) was obtained in 97% yield.

The regiochemistry of this trisubstituted pyrrole **13** was determined by NOESY, DQF-COSY and HMBC experiments, which allowed for the assignment of all signals in the proton and carbon NMR spectra (Table 2). Iodination of this pyrrole **13** with NaOH/I_2 in DMF yielded the 3-iodo derivative **14a** in 91% yield and this compound was also subjected to a NOESY NMR experiment, which confirmed the indicated regiochemical assignments (Table 2). The 3-iodopyrrole **14a** was then subjected to standard Suzuki cross-coupling conditions[8] with conventional heating (Method A) in which case a 21% yield of the 'Steglich synthon' **4** was obtained. A substantial amount of starting material was observed in this experiment thereby suggesting this transformation to be rather sluggish, which may be due to the steric congestion surrounding the iodine bearing carbon.

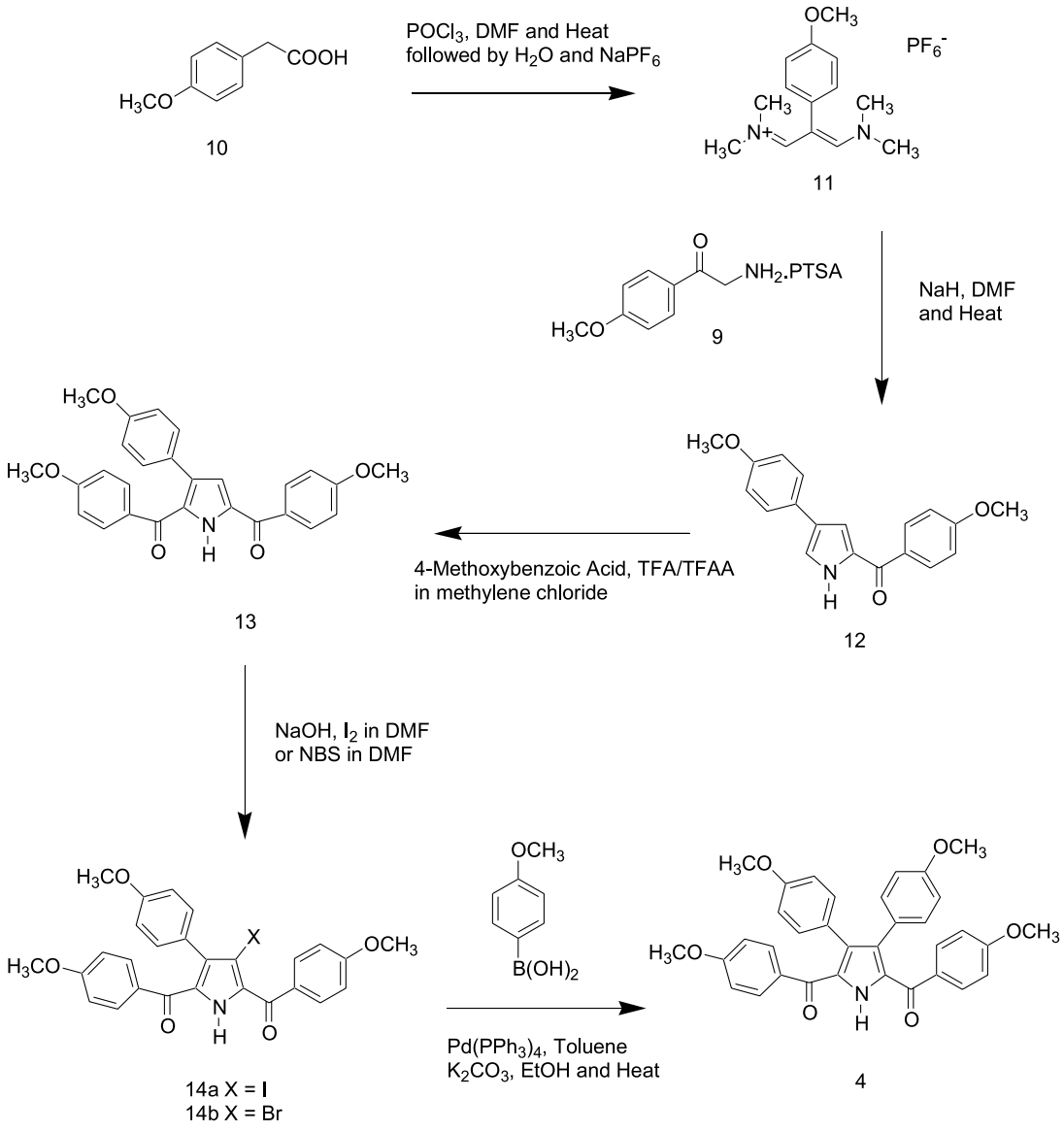
Microwave accelerated heating has become an important tool[9] to facilitate many types of organic reactions and we

Table 2. NMR Chemical shift assignments for compounds **13** and **14a** via NOESY, HMBC and DQF-COSY studies[a]



Label	R=H **13**		R=I **14a**	
	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR
p1		10.103		10.150
p2	132.65		132.21	
p3	131.61		135.30	
p4	118.24	6.958	130.76	
p5	130.51		133.70	
kO	186.31		185.56	
k1	129.67		128.95	
k2	132.04	7.640	131.73	7.478
k3	113.31	6.701	113.04	6.602
k4	163.11		162.87	
km	55.40	3.801	55.37	3.769
k′O	183.80		185.70	
k′1	130.27		129.43	
k′2	131.45	8.031	132.41	7.923
k′3	113.89	7.033	114.00	7.032
k′4	163.88		163.79	
k′m	55.53	3.927	55.57	3.928
m1	127.02		126.50	
m2	130.53	7.139	132.33	7.083
m3	113.65	6.720	113.36	6.721
m4	158.77		159.12	
mm	55.29	3.771	55.22	3.767

[a] Carbon NMR shifts are reported to 2 decimal places and proton NMR shifts are reported to 3 decimal places so as to differentiate signals, which were extremely close to one another. NMR spectra were obtained in $CDCl_3$ solutions at room temperature.

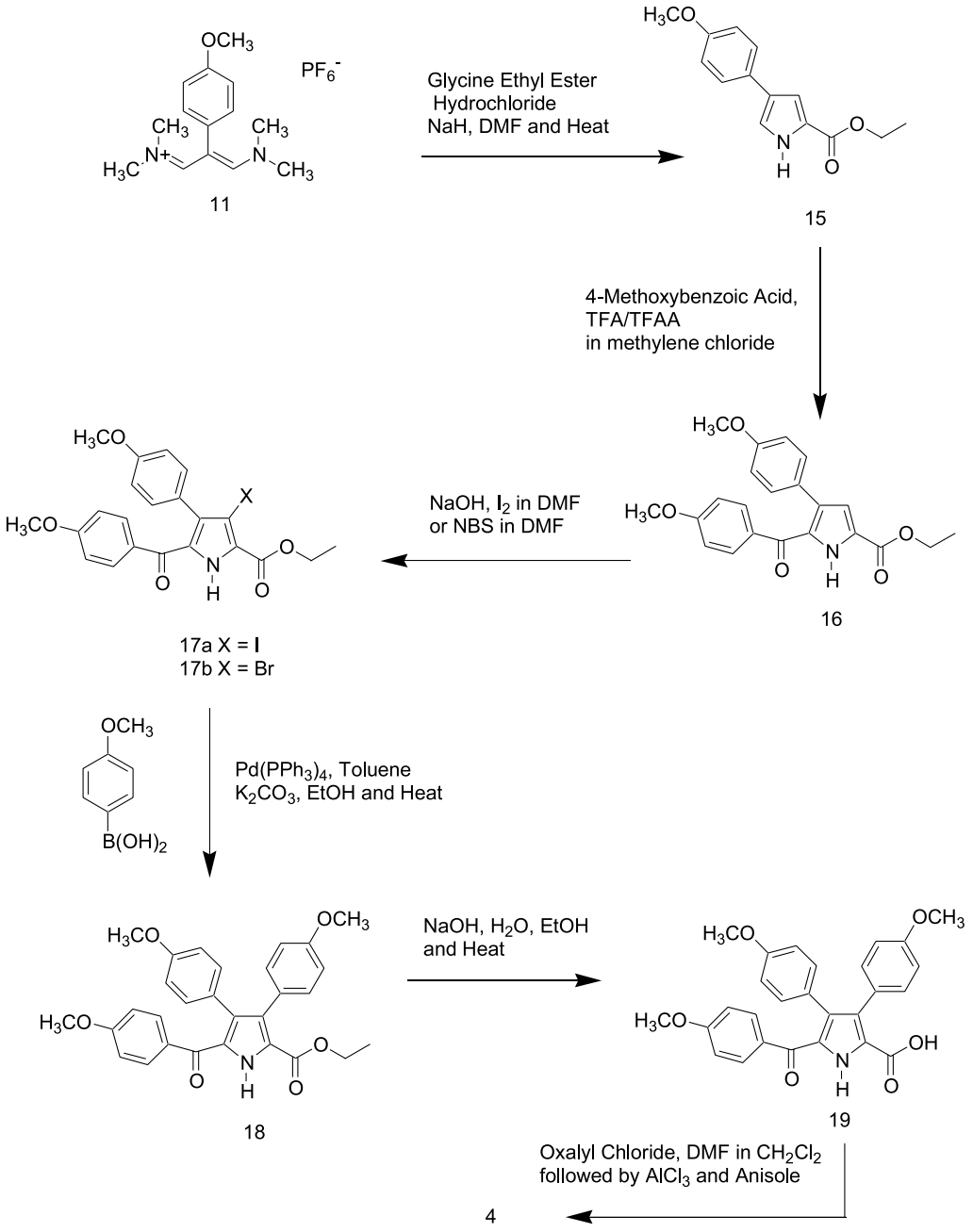


Scheme 3.

opted to repeat the cross-coupling process with the aid of a Personal Chemistry Emrys Liberator US microwave reaction system (Method B) for 2 h at 110 °C and 50 W in which case a 64% yield of the Steglich synthon was obtained. The product **4** of both reaction sequences (Methods A and B) exhibited mass spectra, proton and carbon NMR chemical shifts and NMR coupling constants identical to the values reported by Steglich[3,10] and co-workers (Scheme 1).

In addition, the symmetrical nature of **4** greatly facilitates the unambiguous assignment of its structure. It is of interest to note that the material **4** prepared in our laboratory had a melting point of 163–164 °C while the compound prepared by the Steglich group[10] had a melting point of 131–132 °C. In addition to studying the Suzuki cross-coupling reaction of the 3-iodopyrrole **14a**, the 3-bromo analog **14b** was prepared in 68% yield by reaction of **13** with NBS in DMF. When the 3-bromo analog (**14b**) was subjected to Suzuki cross-coupling conditions (both conventional and microwave accelerated), none of the desired Steglich synthon **4** could be observed. Although the bromo analog **14b** failed to cross-couple, the five step synthesis of the Steglich synthon **4** via the 3-iodopyrrole **14a** proved to be highly efficient (43% overall yield from the vinamidinium salt), convenient and very amenable to creating a variety of analogs late in the synthetic sequence.

We have previously reported[11] the preparation of 2-carbethoxy-4-(4-methoxyphenyl)pyrrole (**15**) (87% yield) by the base mediated condensation of glycine ethyl ester with the 4-methoxyphenyl vinamidinium salt (**11**). We anticipated applying a series of reactions (Scheme 4) analogous to those represented in Scheme 3 to this compound **15** and this would allow for the formation of tetrasubstituted pyrrole **18**, which could also be an appropriate precursor to the Steglich synthon **4** albeit via a few additional steps. Consequently, reaction of 2-carbethoxy-4-(4-methoxyphenyl)pyrrole (**15**) with 4-methoxybenzoic acid and TFA/TFAA produced a 94% yield of 2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (**16**), which was subjected



Scheme 4.

to NOEDIF NMR analysis thereby confirming the 2,3,5-trisubstitution pattern. This pyrrole **16** was subjected to both iodination and bromination conditions as previously described in which case the 3-iodo analog **17a** and 3-bromo analog **17b** were obtained in 89 and 99% yields, respectively. Exposure of the 3-bromopyrrole or the 3-iodopyrrole to Suzuki cross-coupling conditions with 4-methoxyphenyl boronic acid yielded the corresponding pyrrole ester **18** in 89 and 79% yields, respectively. It is of interest to note that both reactions were accomplished using conventional heating methods as opposed to microwave acceleration thereby suggesting a greater reactivity of the pyrrole ester **17a** and **17b** over the pyrrolo ketone **14a** and **14b** under Suzuki cross-coupling conditions. The resulting pyrrole ester **18** was then converted to the corresponding carboxylic acid **19** in 77% yield by base mediated hydrolysis. Conversion of the carboxylic acid to the acid chloride and subsequent acylation with anisole to yield the Steglich synthon **4** was accomplished in 75% yield. The overall yield for the preparation of **4** by this method from the 2,4-disubstituted pyrrole **15** was 42%.

3. Conclusions

In summary, we have demonstrated a new synthetic approach to an important family of bioactive, pyrrole containing marine natural products. This is accomplished by constructing 2,4-disubstituted pyrroles from vinamidinium salts, electrophilically substituting the 5-position of the pyrrole followed by halogenation and a microwave accelerated Suzuki coupling at the 3-position and ultimately

yielding the tetrasubstituted heterocycle. It is important to note that each pyrrole substitutent (e.g. compound **18**) is introduced independently and can be easily varied so as to accommodate in depth SAR studies for polycitone A and B analogs. We are currently in the process of applying this same strategy to other important pyrrole containing marine natural products.

4. Experimental

4.1. General

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific) and all reactions were carried out under a nitrogen or argon atmosphere. All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were obtained on either a GE Omega 300 MHz spectrometer, a Bruker 500 MHz spectrometer or a Varian Gemini 200 MHz spectrometer in either $CDCl_3$ or d_6-DMSO solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment or a Perkin–Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska at Lincoln. Low resolution GC–MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Radial chromatographic separations were carried out on a Harrison Chromatotron using silica gel plates of 2 mm thickness with a fluorescent backing using ethyl acetate/hexane as the eluant. Flash chromatographic separations were carried out on a Biotage Horizon HFC instrument, which had been equipped with a #1542-2 silica cartridge, and ethyl acetate/hexane was used as the eluant. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. Vinamidinium salts utilized for pyrrole formation were prepared according to standard procedures.[12] All purified reaction products gave TLC results, GC–MS spectra, flash chromatograms and ^{13}C NMR spectra consistent with a sample purity of $>95\%$.

4.1.1. 2-Benzoyl-4-(4-methoxyphenyl)pyrrole (6a). Into a 250 mL, round bottom flask was placed 1.0 g (2.64 mmol) of vinamidinium salt (**5a**) and 0.454 g (2.64 mmol) of α-aminoacetophenone hydrochloride. After a magnetic stir bar and dry DMF (60 mL) were added to the flask, the mixture was stirred at room temperature for 3 h. Another 250 mL, round-bottom flask was equipped with a magnetic stir bar, a reflux condenser, and placed under a nitrogen atmosphere. To this flask was added 0.158 g (0.66 mmol) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride was washed twice with dry hexane and the washings were removed via cannula. Dry DMF (20 mL) was slowly added to the flask and the resulting mixture was allowed to stir for several minutes. The vinamidinium salt solution was added dropwise to the sodium hydride solution and the resultant mixture was stirred for 1 h at room temperature followed by refluxing for 2 h. The reaction was quenched with methanol and the solvent was removed in vacuo and the residue was partitioned between water (50 mL) and chloroform (50 mL) and the aqueous phase was extracted with additional portions of chloroform (2×50 mL). The combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was dissolved in ethyl acetate (50 mL) and passed through a 4 g plug of 200 mesh silica gel. The silica gel was washed with a mixture of 80:20 hexane/ethyl acetate and the solvent was removed in vacuo from the filtrate. The product was purified by radial chromatography using a mixture of 80:20 hexane/ethyl acetate as eluent. After removal of solvent from the chromatography fractions, 0.594 g (81% yield) of a light yellow solid was obtained, which exhibited the following properties: mp 200–201 °C; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.92 (d, $J=8.7$ Hz, 2H), 7.09 (m, 1H), 7.38 (m, 1H), 7.40–7.65 (m, 5H), 7.95 (d, $J=8.3$ Hz, 2H) and 9.78 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 57.4, 116.3, 118.1, 123.5, 128.5, 129.0, 129.2, 130.4, 131.0, 133.6, 134.0, 140.3, 160.4 and 186.9 ppm; IR (CCl_4) 3260, 1613 and 1247 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{18}H_{15}NO_2$ calcd 277.1103, found 277.1106.

4.1.2. 2-Benzoyl-4-(3,4-dimethoxyphenyl)pyrrole (6b). This compound was prepared from **5b** by the same procedure as previously described affording a 55% purified yield of a light yellow solid, which exhibited the following properties: mp 163–164 °C; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.94 (s, 3H), 6.89 (d, $J=8.2$ Hz, 1H), 6.98–7.12 (m, 3H), 7.37 (m, 1H), 7.46–7.66 (m, 3H), 7.95 (d, $J=8.2$ Hz, 2H) and 9.58 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 58.0, 111.0, 113.6, 118.1, 119.8, 123.6, 129.4, 129.5, 130.5, 131.0, 133.6, 134.0, 140.2, 150.0, 151.2 and 186.8 ppm; IR (CCl_4) 3212 and 1612 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{19}H_{17}NO_3$ calcd 307.1208, found 307.1208.

4.1.3. 2-Benzoyl-4-(4-methylphenyl)pyrrole (6c). This compound was prepared from **5c** by the above procedure affording a 77% purified yield of a light yellow solid, which exhibited the following properties: mp 190–191 °C; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 7.12 (m, 1H), 7.18 (d, $J=8.0$ Hz, 2H), 7.40–7.65 (m, 6H), 7.95 (d, $J=8.2$ Hz, 2H) and 9.80 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 23.1, 118.3, 123.8, 127.3, 129.5, 130.4, 131.0, 131.5, 133.4, 133.6, 134.0, 138.2, 140.3 and 186.9 ppm; IR (CCl_4) 3256 and 1610 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{18}H_{15}NO$ calcd 261.1154, found 261.1163.

4.1.4. 2-Benzoyl-4-phenylpyrrole (6d). This compound was prepared from **5d** by the above procedure affording a 85% purified yield of a light yellow solid, which exhibited the following properties: mp 191–192 °C; ^1H NMR ($CDCl_3$) δ 7.15 (m, 1H), 7.20–7.61 (m, 9H), 7.95 (d, $J=8.3$ Hz, 2H) and 9.80 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 118.4, 124.1, 127.4, 128.5, 129.4, 130.5, 130.8, 131.0, 133.7, 134.0, 136.3, 140.2 and 187.0 ppm; IR (CCl_4) 3256 and 1614 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{13}NO$ calcd 247.0997, found 247.1001.

4.1.5. 2-Benzoyl-4-(4-bromophenyl)pyrrole (6e). This compound was prepared from **5e** by the above procedure affording a 79% purified yield of a light yellow solid, which exhibited the following properties: mp 226–227 °C; ^1H NMR ($CDCl_3$) δ 7.10 (m, 1H), 7.37–7.7 (m, 8H), 7.94 (d, $J=8.2$ Hz, 2H) and 9.88 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 122.9, 125.8, 131.1, 131.7, 134.2, 135.7, 135.9, 138.6, 138.7, 139.1, 140.9, 145.4 and 191.0 ppm; IR (CCl_4)

3250 and 1616 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{12}BrNO$ calcd 325.0102, found 325.0118.

4.1.6. 2-Benzoyl-4-(4-chlorophenyl)pyrrole (6f). This compound was prepared from **5f** by the above procedure affording a 73% purified yield of a light yellow solid, which exhibited the following properties: mp 208–209 °C; ^1H NMR ($CDCl_3$) δ 7.11 (m, 1H), 7.28–7.65 (m, 8H), 7.95 (d, $J=8.1$ Hz, 2H) and 9.88 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 118.2, 124.1, 128.2, 128.6, 130.5, 130.9, 133.9, 134.1, 134.2, 134.8, 140.1 and 187.0 ppm; IR (CCl_4) 3259 and 1617 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{12}ClNO$ calcd 281.0607, found 281.0606.

4.1.7. 2-Benzoyl-4-(4-flurophenyl)pyrrole (6g). This compound was prepared from **5g** by the above procedure followed by recrystallization with a mixture of 70:30 hexane/ethyl acetate and affording a 63% purified yield of a light yellow solid, which exhibited the following properties: mp 177–178 °C; ^1H NMR ($CDCl_3$) δ 6.98–7.15 (m, 3H), 7.37 (m, 1H), 7.40–7.65 (m, 5H), 7.94 (d, $J=8.3$ Hz, 2H) and 9.65 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 122.6 (d, $J=20.6$ Hz), 123.0, 130.7, 132.0, 134.0 (d, $J=7.8$ Hz), 135.7, 136.0, 138.1 (d, $J=3.0$ Hz), 138.5, 139.0, 145.5, 167.9 (d, $J=245.6$ Hz) and 190.9 ppm; IR (CCl_4) 3266 and 1613 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{17}H_{12}FNO$ calcd 265.0903, found 265.0904.

4.1.8. 2′-Amino-4-methoxyacetophenone *p*-toluenesulfonic acid salt (9). Into a 3000 mL flask was placed 20.0 g (87.3 mmol) of 2′-bromo-4-methoxyacetophenone along with dry ethanol (500 mL). Once the solution became homogeneous, 5.70 g (87.3 mmol) of sodium azide was added in one portion. The reaction mixture was allowed to stir at room temperature for 24 h and the ethanol was removed in vacuo to give a yellow, oily solid. The solid was dissolved in chloroform (150 mL) and the organic layer was washed with water (3×100 mL), brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give an amber oil. This oil was dissolved in THF (400 mL) and to the solution was added 22.9 g (87.3 mmol) of triphenylphosphine. Once the solution was homogeneous, 49.6 g (261 mmol) of PTSA was added in small portions and the reaction mixture was allowed to stir for 24 h. The resulting product was filtered and allowed to dry under vacuum to give 24.7 g (80%) of a white solid, which was suitable for further reactions and exhibited the following properties: mp 188–189 °C; ^1H NMR (d_6-DMSO) δ 2.27 (s, 3H), 3.85 (s, 3H), 4.52 (s, 2H), 7.10 (d, $J=8.0$ Hz, 4H), 7.46 (d, $J=8.0$ Hz, 2H), 7.98 (d, $J=8.0$ Hz, 2H) and 8.08 (broad s, 3H) ppm; ^{13}C NMR (d_6-DMSO) δ 20.7, 44.9, 55.7, 114.3, 125.6, 126.7, 128.1, 130.7, 137.7, 145.9, 164.3 and 191.4 ppm; IR (KBr) 3100 (broad absorption) and 1690 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_9H_{12}NO_2$ 166.0868, found 166.0875.

4.1.9. 2-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (12). Into a 250 mL erylenmyer flask was placed 2.00 g (5.29 mmol) of 4-methoxyphenyl vinamidiniun hexafluorophosphate (**11**), 2.07 g (5.82 mmol) of 2′-amino-4-methoxyacetophenone *p*-toluenesulfonic acid salt (**9**), 0.593 g (5.29 mmol) of DABCO and DMF (50 mL). The mixture was allowed to stir for 1 h at room temperature and subsequently added over a 1 h period to a 250 mL 3-neck round bottom flask containing 0.381 g (15.8 mmol) of sodium hydride (60% by wt. mineral oil dispersion) in 75 mL of DMF. The reaction mixture was heated at reflux for 18 h, cooled to room temperature, quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3×50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 1.24 g (77% yield) of a dark solid which was suitable for further transformations. An analytical sample was prepared by purification of a 0.500 g sample by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give 0.213 g of a yellow solid, which exhibited the following properties: mp 153–154 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.92 (s, 3H), 6.94 (d, $J=9.0$ Hz, 2H), 7.03 (d, $J=9.0$ Hz, 2H), 7.10 (m, 1H), 7.36 (m, 1H), 7.48 (d, $J=9.0$ Hz, 2H), 8.00 (d, $J=9.0$ Hz, 2H) and 9.88 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.3, 55.5, 113.7, 114.3, 115.4, 121.0, 126.5, 127.0, 127.2, 130.9, 131.2, 131.7, 158.4, 162.9 and 183.7 ppm; FTIR (neat) 3250 and 1588 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{19}H_{17}NO_3$ 307.1208, found 307.1207.

4.1.10. 2,5-Bis(4-methoxybenzoyl)-3-(4-methoxyphenyl)-pyrrole (13). Into a 250 mL 3-neck flask was placed 5.22 g (34.4 mmol) of 4-methoxybenzoic acid and methylene chloride (35 mL). To the stirring suspension was added 7.22 g (34.4 mmol) of trifluroacetic anhydride. After 5 min the solution became homogeneous and 9.16 g (80.4 mmol) of trifluroacetic acid was added in one portion. To the stirring solution was added 2.35 g (7.65 mmol) of 2-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole and the reaction mixture was allowed to stir overnight. After 17 h the reaction mixture was carefully quenched with saturated, aqueous sodium bicarbonate, diluted with ethyl acetate (200 mL), washed with 10% aqueous sodium hydroxide (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 3.26 g (97% yield) of a black solid. An analytical sample was prepared by automated flash chromatography of a 0.500 g sample of crude material on silica gel using a gradient elution of hexane/ethyl acetate to give 0.325 g of a yellow solid which exhibited the following properties: mp 148–150 °C; for detailed ^1H and ^{13}C NMR analysis of compound **13** see Table 2; FTIR (neat) 3242 and 1592 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{23}NO_5$ 441.1576, found 441.1578.

4.1.11. 2,5-Bis(4-methoxybenzoyl)-3-iodo-4-(4-methoxyphenyl)pyrrole (14a). Into a 100 mL flask was placed 0.750 g (1.70 mmol) of 2,5-bis(4-methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole along with DMF (40 mL). To the stirring solution was added 0.285 g (5.07 mmol) of potassium hydroxide and after 5 min 0.560 g (2.21 mmol) of iodine was added. The reaction mixture was allowed to stir overnight (18 h) and was then quenched with 20% aqueous sodium thiosulfate (50 mL) with stirring. The reaction mixture was extracted with ethyl acetate (3×50 mL). The organic layers were combined and washed once with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 0.880 g (91% yield) of a dark oil. An analytical sample (0.500 g

sample of crude material) was prepared by automated flash chromatography of a on silica using a gradient elution of hexane/ethyl acetate to give 0.350 mg of yellow solid, which exhibited the following properties: mp 77–79 °C; For detailed ^{1}H and ^{13}C NMR analysis of compound **14a** see Table 2; FTIR (neat) 3215 and 1596 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{22}NO_5I$ 567.0543, found 567.0564.

4.1.12. 2,5-Bis(4-methoxybenzoyl)-3-bromo-4-(4-methoxyphenyl)pyrrole (14b). Into a 50 mL flask was placed 0.430 g (1.21 mmol) of 2,5-bis(4-methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole along with DMF (30 mL). To the stirring solution was added 0.324 g (1.82 mmol) of NBS in one portion and the resulting reaction mixture was allowed to stir at room temperature overnight. Subsequently, the DMF was removed in vacuo and the resulting residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with water (3×50 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.430 g (68% yield) of a brown solid. An analytical sample was prepared by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give a yellow solid, which exhibited the following properties: mp 147–149 °C (recrystallized from MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 3.78 (s, 3H), 3.93 (s, 3H), 6.62 (d, J=9.0 Hz, 2H), 6.72 (d, J=9.0 Hz, 2H), 7.03 (d, J=9.0 Hz, 2H), 7.11 (d, J=9.0 Hz, 2H), 7.51 (d, J=9.0 2H), 7.94 (d, J=9.0 Hz, 2H) and 9.97 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.2, 55.4, 55.5, 113.1, 113.4, 113.8, 124.8, 128.9, 129.5, 130.1, 131.0, 131.3, 131.6, 131.8, 132.2, 132.3, 159.1, 162.9, 163.7, 185.1 and 185.5 ppm; FTIR (neat) 3231 and 1584 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{22}NO_5Br$ calcd for 519.0681, found 519.0674.

4.1.13. 2,5-Bis(4-methoxybenzoyl)-3,4-bis(4-methoxyphenyl)pyrrole (4) (Method A). Into a 250 mL, 3-neck flask was placed 0.225 g (0.396 mmol) of 2,5-bis(4-methoxybenzoyl)-3-iodo-4-(4-methoxy-phenyl)pyrrole and 50 mL of a 3:1 mixture, respectively, of toluene/ethanol. The solution was allowed to become homogeneous and then 0.072 g (0.475 mmol) of 4-methoxyphenylboronic acid and 0.076 g (0.554 mmol) of potassium carbonate were added. The system was purged with Ar and to the stirring suspension was added 0.004 g (0.0039 mmol) of $Pd(PPh_3)_4$. The reaction mixture was heated at 80 °C overnight. After 18 h the reaction mixture was allowed to cool and was filtered through a plug of sand/silica/celite. The cake was washed with ethyl acetate (50 mL) and the resulting organic layer was washed with 10% aqueous sodium hydroxide (3×50 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 0.280 g of a brown solid. The crude material was subjected to automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give 0.048 g (21% yield) of a yellow solid,[12] which exhibited the following properties: mp 163–164 °C (lit.[3] 131–132 °C); ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 6H), 3.76 (s, 6H), 6.53 (d, J=8.8 Hz, 4H), 6.60 (d, J=9.0 Hz, 4H), 6.78 (d, J=8.8 Hz, 4H), 7.53 (d, J=9.0 Hz, 4H) and 10.03 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.1, 55.3, 113.0, 113.2, 125.8, 129.7, 129.9, 130.5, 131.8, 132.2, 158.3, 162.7 and 186.7 ppm; FTIR (neat) 3289 and 1596 cm^{-1}; MS (EI, M+) *m/z* 547.

4.1.14. 2,5-Bis(4-methoxybenzoyl)-3,4-bis(4-methoxyphenyl)pyrrole (4) (Method B). Into a 7 mL test tube (microwave reaction vessel) was placed 0.100 g (0.176 mmol) of 2,5-bis(4-methoxybenzoyl)-3-iodo-4-(4-methoxyphenyl)pyrrole along with 5 mL of 3:1 toluene/ethanol and a stir bar. To the solution was added 0.079 g (0.529 mmol) of 4-methoxyphenylboronic acid 0.082 g (0.598 mmol) of potassium carbonate and 0.002 g (0.00176 mmol) of $Pd(PPh_3)_4$. The reaction mixture was subjected to the following microwave conditions: 5 min initial stir time; 100 W power setting; 110 °C; 2 h run time. After 2 h the reaction mixture was filtered through a plug of sand/silica/celite and the cake was washed with ethyl acetate (50 mL). The organic filtrate was washed with 10% aqueous sodium hydroxide (3×25 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.250 g of a brown-yellow semi-solid. The crude mixture was purified by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give 0.061 g (64% yield) of a yellow solid, which exhibited ^{1}H NMR and ^{13}C NMR spectra and TLC behavior identical to the compound prepared by Method A.

4.1.15. 2-Carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (16). To a solution of 3.13 g (20.57 mmol) of 4-methoxybenzoic acid in dry methylene chloride (25 mL) was added 4.32 g (20.5 mmol) of trifluoroacetic anhydride and the resulting solution was stirred for 15–20 min at room temperature. This was followed by the addition of 5.48 g (48.0 mmol) of trifluoroacetic acid and the resulting mixture was stirred for an additional 5 min. Subsequently, 1.68 g (6.86 mmol) of 2-carbethoxy-4-(4-methoxyphenyl)pyrrole[11] was added to the reaction mixture in which case the solution darkened immediately. The resulting solution was then stirred at room temperature for 3 days and the reaction was carefully quenched with saturated, aqueous sodium bicarbonate. The reaction mixture was then diluted with ethyl acetate (100 mL), washed with 10% aqueous sodium hydroxide (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was subjected to radial chromatography using hexane/ethyl acetate as the eluant in which case 2.45 g (94% yield) of brown solid was obtained, which exhibited the following properties: mp 145–147 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J=7.1 Hz, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 4.39 (q, J=7.1 Hz, 2H), 6.63 (d, J=8.9 Hz, 2H), 6.66 (d, J=8.9 Hz, 2H), 6.99 (d, J=2.9 Hz, 1H), 7.06 (d, J=8.9 Hz, 2H), 7.54 (d, J=8.9 Hz, 2H) and 9.86 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 16.4, 31.7, 57.2, 57.3, 63.1, 115.1, 115.5, 118.1, 127.5, 129.1, 131.5, 131.6, 132.5, 133.7, 134.1, 160.6, 162.4, 164.9 and 188.1 ppm; IR (KBr) 3309, 1711 and 1597 cm^{-1}; HRMS (EI, M+) *m/z* for $C_{22}H_{21}NO_5$ calcd 379.1420, found 379.1421.

4.1.16. 2-Carbethoxy-3-iodo-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (17a). To a stirred solution of 2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-pyrrole (1.00 g, 2.64 mmol) in DMF (60 mL) was added potassium hydroxide (0.44 g, 7.90 mmol). After 10 min, iodine (0.87 g, 3.43 mmol) was added in one portion and the reaction mixture was stirred for 18 h while protecting it

from light. The reaction mixture was quenched with 20% aqueous sodium thiosulfate (70 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 1.18 g (89% yield) of a brown oil. An analytical sample was prepared by automated flash chromatography on silica gel using a gradient elution of hexane/ethyl acetate to give a dark yellow solid, which exhibited the following properties: mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (t, J=6.9 Hz, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 4.46 (q, J=6.9 Hz, 2H), 6.59 (d, J=9.0 Hz, 2H), 6.71 (d, J=9.0 Hz, 2H), 7.04 (d, J=9.0 Hz, 2H), 7.45 (d, J=9.0 Hz, 2H) and 10.15 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.4, 55.2, 55.4, 61.5, 75.1, 113.0, 113.3, 125.8, 126.4, 128.4, 130.8, 131.7, 132.3, 135.1, 159.1, 159.5, 162.9 and 185.5 ppm; FTIR (neat) 3310, 1714 and 1594 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{22}H_{20}NO_5I$ 505.0386, found 505.0395.

4.1.17. 3-Bromo-2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (17b). Into a 100 mL round bottom flask was placed 0.250 g (0.660 mmol) of 2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole along with DMF (50 mL). To the reaction mixture was added 0.176 g (0.990 mmol) of NBS and the resulting solution was stirred for 23 h at room temperature. The solvent was removed in vacuo and the remaining residue was dissolved in ethyl acetate (100 mL), washed with water (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.300 g (99% yield) of a brown solid. An analytical sample was prepared by automated flash chromatography on silica using a gradient elution of hexane/ethyl acetate to give a solid, which exhibited the following properties: mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J=7.2 Hz, 3H), 3.78 (s, 6H), 4.44 (q, J=7.2 Hz, 2H), 6.58 (d, J=9.0 Hz, 2H), 6.70 (d, J=9.0 Hz, 2H), 7.06 (d, J=9.0 Hz, 2H), 7.46 (d, J=9.0 Hz, 2H) and 10.10 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.3, 55.2, 55.3, 61.4, 104.9, 113.0, 113.4, 123.0, 124.7, 128.9, 129.9, 131.1, 131.8, 132.1, 159.0, 159.5, 162.9 and 185.5 ppm; FTIR (neat) 3256, 1678 and 1592 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{22}H_{20}NO_5Br$ 457.0525, found 457.0529.

4.1.18. 3,4-Bis-(4-methoxyphenyl)-2-carbethoxy-5-(4-methoxybenzoyl)pyrrole (18) (Method C). In an Ar purged 100 mL flask was placed 0.427 g (0.280 mmol) of 4-methoxyphenylboronic acid, 0.452 g (0.327 mmol) of potassium carbonate, and 50 mL of a 3:1 toluene/ethanol mixture. To the stirring suspension was added 1.07 g (2.34 mmol) of 3-bromo-2-carbethoxy-5-(4-methoxybenzoyl)-4-(4-methoxy-phenyl)pyrrole. Once the pyrrole dissolved, 0.0270 g (0.0234 mmol) of $Pd(PPh_3)_4$ was added and the reaction mixture was heated at reflux for 22 h. The reaction mixture was allowed to cool to room temperature, filtered through a plug of sand/silica/celite and the cake was washed with ethyl acetate (100 mL). The filtrate was washed with 10% aqueous sodium hydroxide (3×50 mL), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 0.990 g (87% yield) of a brown semi-solid. An analytical sample was prepared by automated flash chromatography on silica using a gradient elution of hexane/ethyl acetate to give a soild, which exhibited the following properties: mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J=7.2 Hz, 3H), 3.68 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 4.28 (q, J=7.2 Hz, 2H), 6.50 (d, J=9.0 Hz, 2H), 6.59 (d, J=9.0 Hz, 2H), 6.73 (d, J=9.0 Hz, 2H), 6.80 (d, J=9.0 Hz, 2H), 7.10 (d, J=9.0 Hz, 2H), 7.50 (d, J=9.0 Hz, 2H) and 9.93 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.2, 55.0, 55.1, 55.3, 60.8, 112.9, 113.0, 113.1, 122.1, 125.4, 125.7, 129.6, 129.7, 130.7, 131.7, 131.8, 132.0, 132.2, 158.3, 158.6, 160.4, 162.7 and 186.5 ppm; FTIR (neat) 2963, 1693 and 1600 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{29}H_{27}NO_6$ 485.1838, found 485.1833.

4.1.19. 3,4-Bis-(4-methoxyphenyl)-2-carbethoxy-5-(4-methoxybenzoyl)pyrrole (18) (Method D). Into a nitrogen purged round bottom flask was placed 4-methoxyphenyl boronic acid (0.896 g, 5.9 mmol), potassium carbonate (0.816 g, 5.9 mmol), 200 mL of a toluene/ethanol solution (3:1) and a stir bar. To the stirred suspension was added 2-carbethoxy-3-iodo-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)pyrrole (1.93 g, 3.8 mmol). Once the pyrrole became dissolved in solution, $Pd(PPh_3)_4$ (0.066 g, 0.057 mmol) was added and the reaction mixture was heated to reflux. Upon reflux, 8 drops of water were added to the reaction mixture. Reflux was continued and after 24 h additional boronic acid (0.40 g, 2.6 mmol) and Pd catalyst (0.04 g, 0.034 mmol) were added and reflux was continued for another 24 h. The reaction mixture was cooled to room temperature, filtered through a plug of sand/silica gel/celite and the plug was washed with ethyl acetate (100 mL). The filtrate was extracted with 10% aqueous sodium hydroxide (3×50 mL), with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo, to yield 1.45 g of a dark yellow solid (79% yield), which exhibited physical properties identical to the product described in the above reaction. This material was sufficiently pure by spectroscopic characterization and TLC for direct use in subsequent reactions.

4.1.20. 3,4-Bis-(4-methoxyphenyl)-5-(4-methoxybenzoyl)-2-pyrrolecarboxylic acid (19). Into a 100 mL flask was placed 0.300 g of 3,4-bis-(4-methoxyphenyl)-2-carbethoxy-5-(4-methoxybenzoyl)pyrrole and 50 mL of a 50/50 mixture of ethanol/water. To the stirring suspension was added 0.100 g (2.47 mmol) of aqueous sodium hydroxide and the reaction mixture was heated at reflux for 22 h. Subsequently, the reaction mixture was allowed to cool to room temperature and was acidified with 6 M hydrochloric acid. An appropriate amount of water was added to induce crystallization and the resulting solid was collected by vacuum filtration and dried in vacuo to give 0.217 g (77% yield) of a brown solid, which exhibited the following properties: mp 212–215 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 6.51 (d, J=9.0 Hz, 2H), 6.60 (d, J=9.0 Hz, 2H), 6.74 (d, J=9.0 Hz, 2H), 6.81 (d, J=9.0 Hz, 2H), 7.12 (d, J=9.0 Hz, 2H), 7.52 (d, J=9.0 Hz, 2H) and 10.13 (broad s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 55.1, 55.3, 113.1, 113.2, 120.9, 124.9, 125.5, 129.4, 130.7, 130.8, 131.6, 131.9, 132.0, 132.2, 158.3, 158.7, 162.9, 164.1 and 186.5 ppm; FTIR (neat) 3231, 1681 and 1588 cm^{-1}; HRMS (EI, M+) *m/z* calcd for $C_{27}H_{23}NO_6$ 457.1525, found 457.1521.

4.1.21. 2,5-Bis(4-methoxybenzoyl)-3,4-bis(4-methoxyphenyl)pyrrole (4) (Method E). To a stirred suspension of 3,4-bis-(4-methoxyphenyl)-5-(4-methoxybenzoyl)pyrrole-2-carboxylic acid (0.370 g, 0.800 mmol) in dichloromethane (20 mL) at 0 °C were added oxalyl chloride (0.80 mL, 1.60 mmol) and a catalytic amount (3.0 μL) of DMF. The reaction mixture was warmed to room temperature, stirred for 2 h and the volatile materials were removed in vacuo. The residue was taken up in methylene chloride (20 mL) and cooled to 0 °C. With stirring under a nitrogen atmosphere, aluminum trichloride [2.80 mL (2.80 mmol) of a 1 M solution in nitrobenzene] and anisole (4.0 mmol) were added to the methylene chloride solution and the resulting reaction mixture was stirred overnight at room temperature. The reaction was quenched by pouring it into ice water (100 mL) and this was followed by extraction with aqueous sodium bicarbonate (3×50 mL), drying the organic phase over anhydrous magnesium sulfate, filtering and concentrating in vacuo to yield 0.597 g of a brown semi-solid. This material was purified by automated flash chromatography on silica using a gradient elution of hexane/ethyl acetate to give 0.330 g (75% yield) of yellow solid (**4**), which exhibited ^{1}H NMR and ^{13}C NMR spectra and TLC behavior identical to the material prepared by methods A and B.

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10. We are very appreciative of the helpful communications from Professor Wolfgang Steglich during the completion of this work and the preparation of this manuscript. We also greatly appreciate the receipt of proton and carbon NMR spectra, which enabled direct comparisons to be made between our synthetic 2,5-bis(4-methoxybenzoyl)-3,4-bis(4-methoxyphenyl)pyrrole (**4**) and Professor Steglich's material. The reason for a difference in melting points between our sample and that reported by Steglich and co-workers is not clear. Polymorphic behavior of **4** is certainly one possibility but, since there is no remaining material from the Steglich synthesis, a direct comparison of the two samples is not possible.
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Synthesis of α-galactosyl ceramide and the related glycolipids for evaluation of their activities on mouse splenocytes

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Abstract—Phytosphingosine and its short-chain analog were efficiently synthesized with 19% overall yield in 10 steps, respectively, starting from an inexpensive D-lyxose. Galactosyl donors of sulfide and phosphite types bearing benzoyl protecting groups of 4- and 6-OH underwent glycosylation in excellent α-anomeric selectivity. A variety of α-galactosyl, fucosyl and glucosyl ceramides and serine-type lipids were prepared, and their activities involved in the proliferation of mouse splenocytes and the expression of cytokines were elucidated. Besides α-galactosyl ceramides, a galactosyl serine-type lipid also exhibited substantial effect on the expression of cytokines IFN-γ and IL-4.

1. Introduction

CD1 molecules are β2-microglobulin-associated proteins that are related to MHC I and II molecules.[1] Four CD1 isoforms, CD1a, CD1b, CD1c, and CD1d, have been found in humans.[2] Only human CD1d is homologous to mouse and rat CD1 molecules.[3] This protein is normally expressed by thymocytes and various cells with antigen-presenting functions, such as B cells and dendritic cells. The primary function of CD1 proteins is to present glycolipid antigens through lipid–protein interactions with receptors on T-cells, and thus activating the immune system.[4] The analysis of amino acid sequences reveals that CD1 molecules have highly hydrophobic antigen-binding grooves,[1] The X-ray diffraction analysis further indicates that the crystal structure of mouse CD1d has a hydrophobic antigen-presenting groove with two large pockets, which can probably accommodate the lipid tails of antigens.[5]

In 1993, six species of bioactive glycolipids having α-galactosylceramide structures were isolated from the marine sponge *Agelas mauritianus*.[6] Years later, KRN7000 (also called α-GalCer for common use) was chosen from the derivatives of these structures as a candidate for clinical applications.[7] The α-GalCer can be recognized by an entire population of mouse and human CD1d-restricted lymphocytes.[8] An unusual feature of α-GalCer is the α anomeric linkage of galactose to the lipid, unlike the ubiquitous β-glycosidic bond in nearly all known natural glycosphingolipids of normal mammalian cells. α-GalCer stimulates the fast release of large amounts of cytokines from most mouse NKT cells,[8] which are characterized by expression of an invariant Vα14 TCR.[9] Interaction of α-GalCer with CD1 receptors causes T cells to secrete primarily interferon γ (IFN-γ) and interleukin-4 (IL-4) resulting in TH1 and TH2 immune responses, respectively.[10] This activation raises the prospect of novel, lipid-based vaccines and adjuvants.[11] An analogue of α-GalCer, with a truncated sphingosine chain, was recently shown to induce the production predominantly of IL-4 by NKT cells.[12] Modification of the lipid chain in the α-GalCer structure likely causes immunoactivity switching to demonstrate a profound relationship between structure and activity.[13]

In continuation of our efforts on the development of glycolipids as vaccine adjuvants, we are particularly interested in the study of α-GalCer and its analogs. Although a few syntheses of α-GalCer have been described,[7,14] most of previous methods require extensive synthetic steps and the use of expensive starting material for

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synthesizing phytosphingosine,[15] the lipid moiety of α-GalCer. In this article, we report an efficient route for constructing phytosphingosine from commercially available D-lyxose, and several methods for synthesizing α-GalCer and its analogs in stereoselective manners.

2. Result and discussion

Figure 1 shows a retrosynthetic pathway of α-GalCer **1**. The azido group in synthon **3** would be reduced to amine, and the obtained galactosyl phytosphingosine can be coupled with appropriate fatty acids to give **1** and its analogues, e.g. the short-chain derivative **2**. Phytosphingosine **8** in the protected form is a key intermediate that can be obtained by Wittig olefination with the D-lyxose derivative **11**, followed by replacement of the C4 hydroxyl group by an azido group. Execution of this synthetic plan is shown in Scheme 1. The 2,3-dihydroxy groups of D-lyxose were selectively protected as an acetal using 2,2-dimethoxypropane,[16] and the primary hydroxyl group was subsequently protected as a trityl ether,[17] giving **11** in 71% yield. Wittig olefination of **11** using $Ph_3PC_{13}H_{27}Br$ or $Ph_3PC_4H_9Br$ in the presence of lithium hexamethyldisilazide (LHMDS)[18] yielded alkenes **12** (93% yield) and **13** (85% yield). The *E*/*Z* ratio of **12** was estimated to be 2:1 and 3:1 for **13** according to the ^1H NMR spectral analysis. Saturation of double bonds in **12** and **13** by catalytic hydrogenation afforded **14** and **15**, respectively, in 91 and 88% yields. The hydroxy group in **14** (or **15**) was activated as a triflate, which underwent an S_N2 reaction with tetramethylguanidinium azide (TMGA) to give azido compound **16** (or **17**) with inverted configuration.[19] As attempts of selective removal of the trityl group in **16** (or **17**) failed, simultaneous deprotection[15b] of the acetal and trityl groups were carried out by treating with acetic acid in MeOH at 60 °C to yield triol **18** (or **19**). The sphingosine derivatives **20** and **21** suitable to glycosylation were thus prepared from **18** and **19** by a sequence of tritylation, benzylation and de-tritylation. The whole synthetic process took 10 steps to convert D-lyxose into phytosphingosines (**20** and **21**) in 19% overall yield.

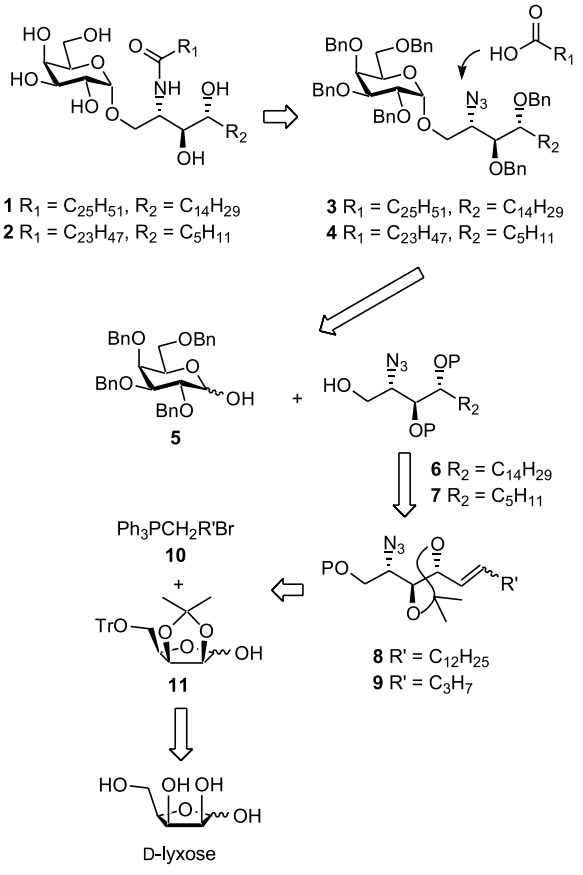
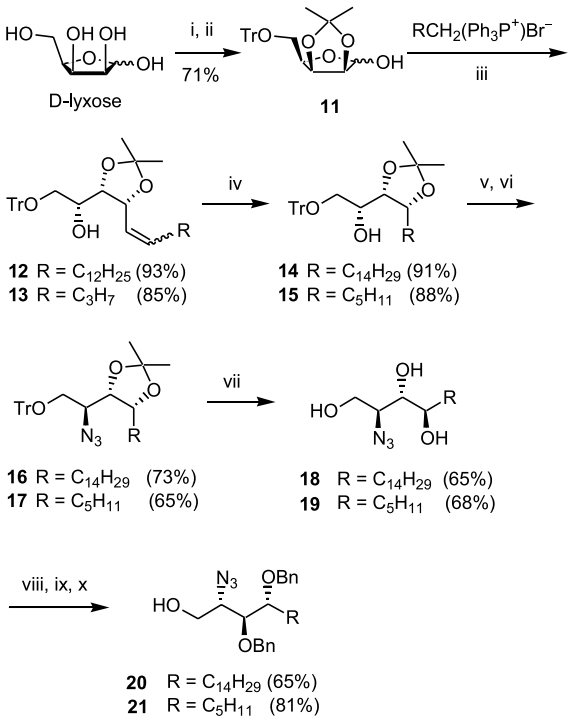
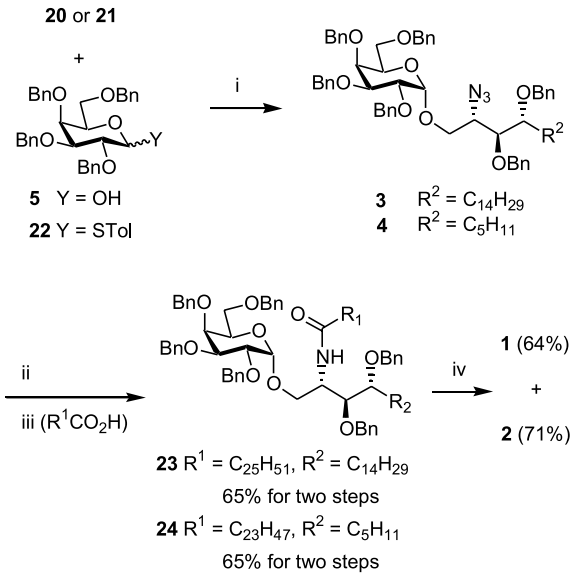


Figure 1. *Retro*-synthesis of α-GalCer (**1**) and a short-chain analogue **2**.



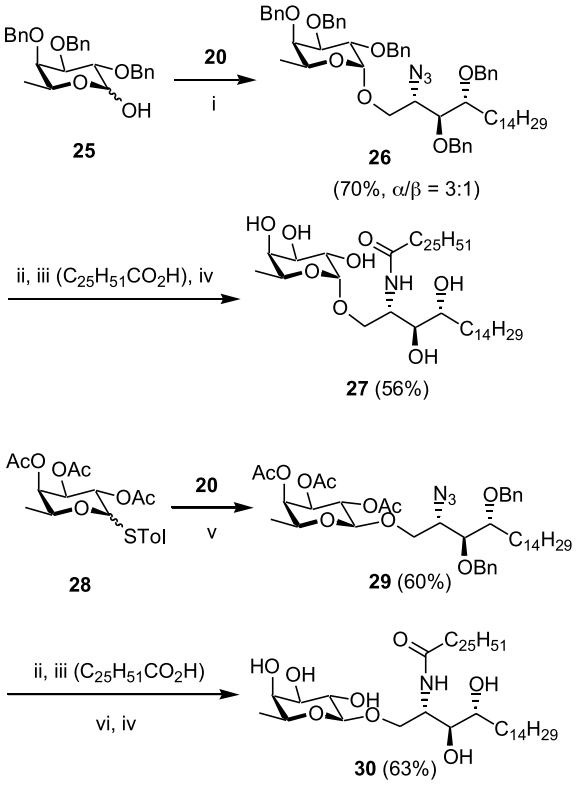
Scheme 1. Synthesis of phytosphingosind derivatives **20** and **21**. Reagents and conditions: (i) 2-methoxypropene, CSA. (ii) TrCl, pyridine, 80 °C, 6 h. (iii) LHMDS, THF. (iv) H_2, $Pd(OH)_2$, EtOAc. (v) Tf_2O, 2,6-lutidine, CH_2Cl_2. (vi) Tetramethylguanidinium azide. (vii) AcOH, MeOH, 60 °C. (viii) TrCl, pyridine. (ix) BnBr, NaH, DMF. (x) AcOH, H_2O.

The benzyl groups were adopted as the protecting groups in both glycosyl acceptors (e.g. **20** and **21**) and donors (e.g. **5** and **22**) because catalytic hydrogenation can be applied for complete deprotection in the final step to obtain α-GalCer **1** and its truncated phytosphingosine analogue **2** (Scheme 2). Coupling of phtytosphingosine **20** with galactosyl donor **22** (*S*-glycoside, R=STol) by using *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) as promoters[20] afforded **3** in 93% yield, albeit in no anomeric selectivity (α/β=1:1). When tetrabenzyl galactose **5** (R=OH) was used in dehydrative glycosylation[21] with **20**, 83% yield of **3** was obtained in a better α-selectivity (α/β=3:1). Compound **4** was similarly obtained in α/β=3:1 by coupling compound **21** with **5**. In principle, the azido and benzyloxyl group can be reduced concurrently. However, reductions by using Raney Ni, Birch reduction and hydrogenation using different catalysts [e.g. Pd/C and $Pd(OH)_2$] and various solvents (e.g. EtOAc, MeOH, EtOH and HOAc etc.) under a hydrogen pressure of 1 atm or 50 kg/cm^2 resulted in complicated mixture. Thus, azide **3**



Scheme 2. Synthesis of α-GalCer (**1**) and a short-chain analogue **2**. Reagents and conditions: (i) using **5**: Me_2S, 2-Cl-pyridine, Tf_2O, CH_2Cl_2, 4 Å MS; using **22**: NIS, TfOH, CH_2Cl_2, 4 Å MS. (ii) Ph_3P, pyr., H_2O, 60 °C, 6 h. (iii) R^1CO_2H, EDC, HOBt, 20 h. (iv) H_2, Pd/C, 40 kg/cm^2.

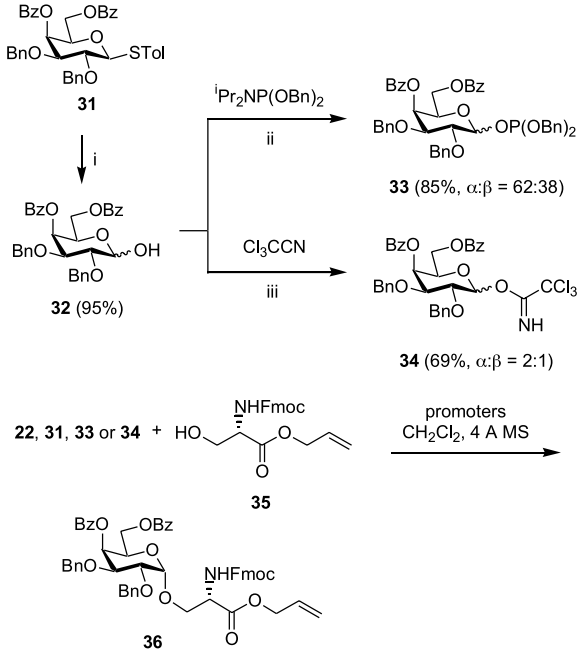
was reduced using Staudinger reaction[22] to give the amine intermediate, which coupled with hexacosanoic acid by using EDC and HOBT as the promoters to give compound **23** in 65% yield. The similar reduction of **4** and the subsequent coupling reaction with tetracosanoic acid yielded **24**. Finally, removal of the benzyl groups culminated in α-GalCer **1** and the short-chain analogue **2**.



Scheme 3. Synthesis of α- and β-fucosyl ceramides **27** and **30**. Reagents and conditions: (i) Me_2S, 2-Cl-pyridine, Tf_2O, CH_2Cl_2, 4 Å MS. (ii) Ph_3P, pyr., H_2O. (iii) PyBop, CH_2Cl_2. (iv) H_2, Pd/C, 40 kg/cm^2. (v) NIS, TfOH, 4 Å MS, CH_2Cl_2, −15 °C. (vi) NaOMe, MeOH.

Fucosyl ceramide does not occur in nature, so the synthesis and examination of the bioactivities of L-fucosyl ceramides (FucCers) **27** and **30** are of interest. Dehydrative glycosylation of phytosphingosine **20** with tribenzylfucose **25**[23] was performed to give an anomeric mixture of **26** (α/β=3:1), whereas the coupling reaction with *S*-tolyl triacetylfucoside **28** afforded only β-anomer **29** (Scheme 3). By the procedure similar to that for the synthesis of α-GalCer **1**, the α-FucCer **27** was synthesized from **26** in 56% overall yield by a sequence of azide reduction, amide formation and debenzylation. β-FucCer **30** was similarly prepared except for removal of the acetyl groups by sodium methoxide in methanol.

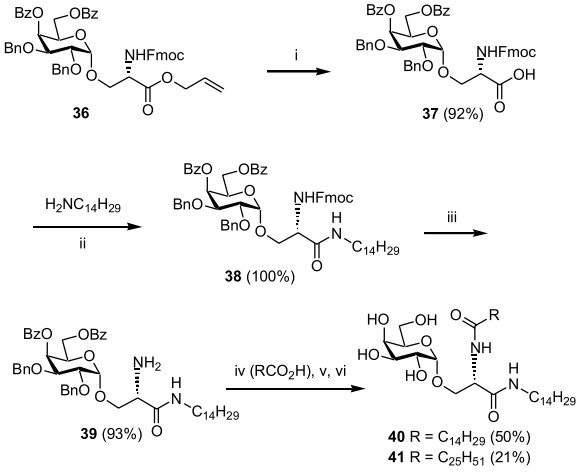
Serine-based lipid has been reported to exhibit the similar bioactivity as a ceramide mimic.[24] It would be interesting to know if serine-based lipid or its amide analogue could mimic the functions of phytosphingosine. In order to pursue the α-selective glycosylation with the L-serine derivative **35**, different types of galactosyl donors including sulfide **22**, sulfide **31**, phosphite **33** and imidate **34** were investigated (Scheme 4). Hydrolysis of sulfide **31** with NBS in the presence of water,[25] followed by treatments with *i*-Pr_2-$NP(OBn)_2$ or trichloroacetonitrile according to standard carbohydrate chemistry, gave dibenzyl phosphite **31**[26] and trichloroimidate **34**,[27] respectively. Glycosylation reactions of **35** generally afforded high yields (89–95%) of **36**, however, in varied anomeric selectivities depending on the use of different galactosyl donors.[26,28]



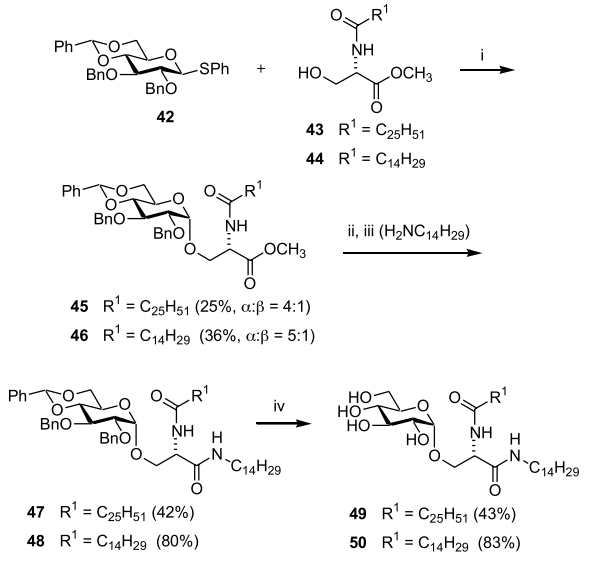
Scheme 4. Synthesis of galactosyl donors and coupling with serine derivative **35**. Reagents and conditions: (i) NBS, Me_2CO/H_2O=9:1, rt, 2 h. (ii) 1*H*-tetrazole, THF, rt, 2 h. (iii) DBU, THF, rt, 30 min.

Using tetrabenzyl *S*-galactoside **22**, the glycosylation was realized by the promotion of NIS and TfOH to give α and β-anomers (2:1) of **36**. The α/β selectivity was increased to 9:1 when *S*-galactoside **31** with benzoate protecting groups at 4- and 6-positions, differing from the benzyl groups in **22**, was applied in the glycosylation. Incorporation of benzoate

group at 4- or 6-position of galactoside or glucoside, in comparison to benzyl group, is known to enhance the α-selectivity of thiotolyl donor.[28] We were surprised and fortunate to find that coupling of an α/β mixture (6:1) of the phosphite donor **31** with the serine derivative **35** in the presence of TfOH gave only the α-glycosylation product **36** in 95% yield. On the other hand, glycosylation of imidate **34** (α anomer) in the presence of TMSOTf gave predominantly the β-anomor of **36** (α/β=1:10). It was presumed that glycosylation of phosphite donor proceeded with an S_N1-like mechanism, whereas that of imidate donor followed an S_N2-like pathway. During the glycosylation of phosphite **33**, the benzoyl groups at 4- and 6-positions might participate in stabilization of the oxonium intermediate. As the β-face was blocked, the serine derivative **35** could only have access to the oxonium intermediate from the α-face.



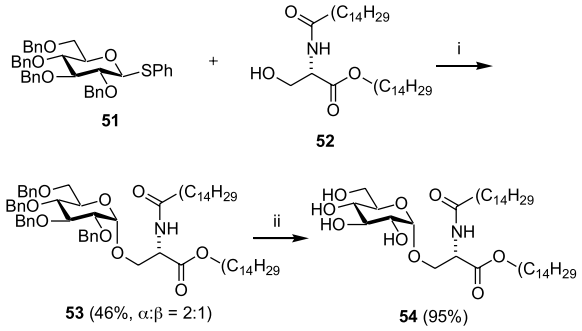
Scheme 5. Synthesis of galactosyl serine-type ceramide analogues **40** and **41**. Reagents and conditions: (i) $Pd(PPh_3)_4$, THF. (ii) HBTU, HOBt, CH_2Cl_2. (iii) 40% H_2NEt/THF. (iv) EDC, HOBt, DMF. (v) MeONa, MeOH. (vi) H_2, $Pd(OH)_2$, EtOH, $CHCl_3$, 50 kg/cm^2.



Scheme 6. Synthesis of α-glucosyl serine-type ceramides **49** and **50**. Reagents and conditions: (i) NIS, cat. TfOH, 4 Å MS, CH_2Cl_2, −15 to −10 °C. (ii) aq. NaOH (1 N), THF. (iii) EDC, HOBT, CH_2Cl_2. (iv) H_2, $Pd(OH)_2$/C, cat. AcOH, EtOAc/MeOH (1:1).

As shown in Scheme 5, the allyl group of **36** was removed by using $Pd(PPh_3)_4$ catalyst,[29] and the resulting acid was coupled with 1-tetradecylamine to yield amide **38**. Deprotection of the Fmoc group gave amine **39**. Amidation of **39** with carboxylic acids, followed by removal of benzoyl and benzyl groups, thus gave **40** and **41** with serine-type long-chain amide moieties as the structurally simpler mimics of α-GalCer.

In order to evaluate the role of 4-OH group of α-GalCer in immunoactivity, the α-glucosyl serine-type ceramides (e.g. **49** and **50**) were prepared. Glycosylation of *S*-glucoside **42** with the *N*-acyl derivatives of methyl L-serine (**43** and **44**) was carried out by the promotion of NIS and TfOH to give **45** and **46** predominating in the α-anomers (Scheme 6). Saponification and amidation of **45** and **46** with tetradecylamine, followed by romoval of the benzyl and benzylidene protecting groups, led to the α-glucosyl serine-type ceramides **49** and **50**. By a similar procedure, the α-glucosyl serine-type lipid **54** was also prepared (Scheme 7).



Scheme 7. Synthesis of α-glucosyl serine-type ester **54**. Reagents and conditions: (i) NIS, cat. TfOH, 4 Å MS, CH_2Cl_2, −15 to −10 °C. (ii) H_2, $Pd(OH)_2$/C, cat. AcOH, EtOAc/MeOH (1:1).

The glycolipids **1**, **2**, **27**, **30**, **40**, **41**, **50** and **54** were submitted to evaluate their activities. First, colorimetric assay using 3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide (MTT)[30] was conducted to evaluate the proliferation of glycolipid-stimulated mouse spleen cells in the presence of various concentrations of the glycolipids. α-GalCer **1** and the truncated analog **2** at a concentration of 100 ng/mL significantly promoted the cell proliferation activity comparing to the control samples (Fig. 2). The galactosyl serine-type lipid **40** at the same concentration also slightly enhanced the cell proliferation activity.

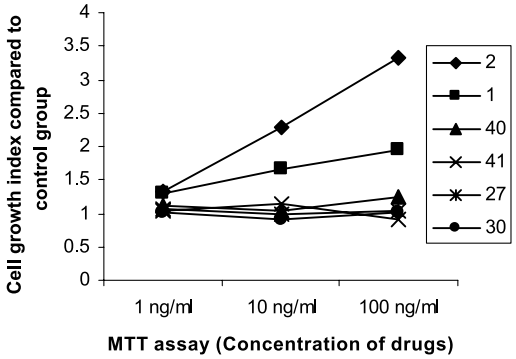


Figure 2. MTT assay for glycolipids **1**, **2**, **27**, **30**, **40** and **41**.

The expression levels of the cytokines, IFN-γ and IL-4, in mouse spleen cells were determined by an ELISA assay (enzyme-linked immunosorbent assay)[31] using 100 ng/mL glycolipids. Only compounds **1**, **2** and **40** were observed to stimulate IFN-γ and IL-4 expression after 24 h (Fig. 3). The related long-term cytokine stimulation by **1** and **2** is shown in Figure 4. Both compounds had similar effect on INF-γ production while compound **2** had a stronger effect on IL-4 production. Notably, these results are not the same as that obtained for compounds **1** and **2** on NKT cells.[12] The

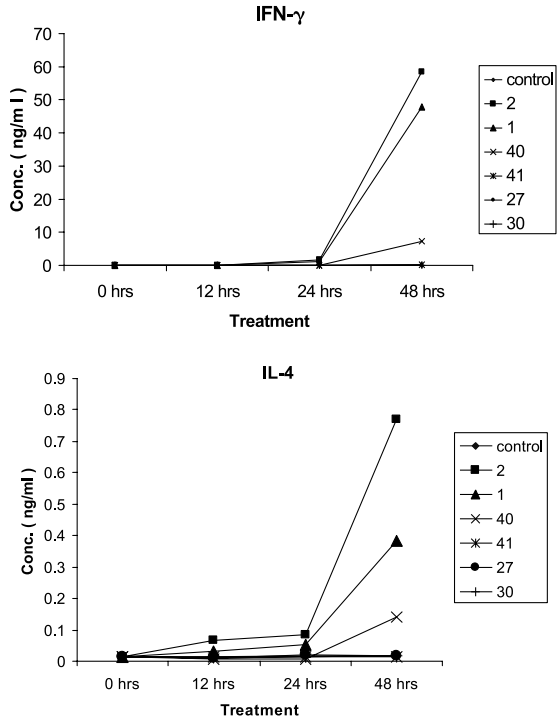


Figure 3. Cytokine assays for α-GalCer (**1**) and other glycolipids. For clarity, the lines of inactive compounds **50** and **54** are omitted. Untreated cells are taken as the control.

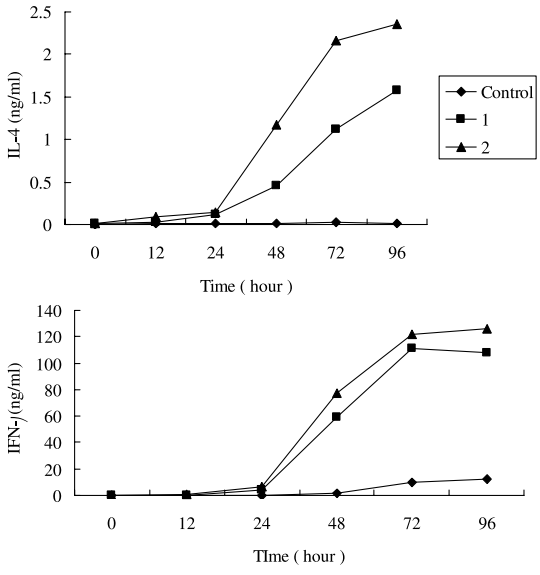


Figure 4. Long-term cytokine assays for α-GalCer (**1**) and a short-chain analogue **2** using untreated cells as the control.

simplified α-GalCer analog **40**, having a serine-type lipid to replace phytosphingosine, still retained some immunoactivity. Although compounds **1** and **2** are better antigens to stimulate the production of cytokines, compound **40** has the advantage of simple synthesis. The fucosyl ceramides (**27** and **30**) and glucosyl serine-type lipids (**50** and **54**) did not show any immuno-activity.

In conclusion, we have devised an expedient method for the synthesis of glycosphingolipids, starting from an inexpensive sugar, D-lyxose. We have also carried out the syntheses of galactosyl, fucosyl and glucosyl ceramides in α-anomeric selectivity. The bioassays indicated that α-galactosyl ceramides **1** and **2** exhibited substantial effects on the proliferation of mouse splenocytes as well as the expression of cytokines IFN-γ and IL-4. The galactosyl serine-type ceramide **40** also showed similar bioactivities, though to less degrees. Works on the synthesis of a glycolipid library and extensive evaluation of the immuno-modulating activities of these immuno-stimulators are in progress.

3. Experimental

Compounds **1**,[32] **3**,[33] **5**,[34] **11**,[35] **18**,[15a] **19**,[15a] **20**,[36] **22**,[20] **23**,[35] **25**,[37] **28**,[38] **35**,[39] **42**[40] and **51**[41] have previously been reported, and our prepared samples showed consistent ^{1}H and ^{13}C NMR spectral data to the structural assignments.

3.1. Representative procedure for glycosylation. Using aldose (method A)

To a solution of galactosyl donor **5** (300 mg, 0.57 mmol), dimethylsulfide (54 μL, 0.74 mmol), 4 Å molecular sieve (100 mg) and 2-chloropyridine (150 μL, 1.58 mmol) in anhydrous CH_2Cl_2 (2 mL) under Ar at −45 °C was added trifluoromethanesulfonic anhydride (94 μL, 0.56 mmol). The reaction mixture was stirred for 20 min at 0 °C and 20 min at room temperature. Phytosphingosin derivative **21** (150 mg, 0.37 mmol) in CH_2CL_2 (2 mL) was slowly added via cannula under positive nitrogen pressure. The reaction mixture was stirred at room temperature for 20 h, and then filtered. The crude filtrate was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (EA/Hex from 9:1 to 4:1) to give the product **4** as yellow oil (285 mg, 82%).

3.2. Using glycosyl sulfide (method B)

To a mixture of glycosyl sulfide **28** (200 mg, 0.5 mmol), phytosphingosin derivative **20** (220.2 mg, 0.42 mmol) and 4 Å molecular sieves (400 mg) in CH_2Cl_2 (2.5 mL) was added NIS (453.6 mg, 2.0 mmol) at 0 °C under Ar. The reaction mixture was stirred for 30 min, and TfOH (1.9 μL, 0.02 mmol) was added. After 30 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc, and washed with aqueous $Na_2S_2O_3$, saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. The

residue was chromatographed on a silica gel column (EtOAc/hexane, 1:2) to give product **29** (200.0 mg, 60%).

3.3. Using glycosyl phosphite (method C)

A mixture of serine derivative **35** (0.55 g, 1.5 mmol), galactosyl phosphite **33** ($\alpha/\beta=6/1$, 1.33 g, 1.6 mmol) and 4 Å molecular sieves in dried CH_2H_2 (20 mL) was stirred for 10 min at room temperature under Ar. Trifluoromethanesulfonic acid (26 μL, 0.3 mmol) was added, and the mixture was stirred at room temperature for another 1 h. In this period of reaction, compound **35** was completely consumed as shown by TLC analysis. The reaction mixture was filtered through a short pad of Celite. The filtrate was diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (EtOAc/Hex: from 8:1 to 3:1) to obtain the product **36** (α-anomer) as yellow oil (1.30 g, 95%).

3.4. Representative procedure for Wittig reaction

To a mixture of triphenyl-tridecyl-phosphonium bromide (4.86 g, 9.2 mmol) in anhydrous THF (20 mL) was added lithium hexamethyldisilazide (LHMDS, 9.2 mL of 1 M solution in THF) at 0 °C under Ar, and stirred at 0 °C for 60 min. A solution of **11**[34] (2.0 g, 4.6 mmol) in anhydrous THF (10 mL) was treated with LHMDS (4.6 mL, 4.6 mmol) at 0 °C for 60 min under Ar to give the **11**-anion solution. The mixture of the above prepared phosphonium solution and **11**-anion solution was stirred at 0 °C to room temperature for 9 h, and then quenched with MeOH. After removal of volatiles under reduced pressure, the residue was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (EtOAc/hexane, 9:1 to 3:1) to give the product **12** as colorless oil (2.58 g, 93%). The *E*/*Z* ratio is about 2:1 as determined by the ^1H NMR analysis.

3.5. Representative procedure for catalytic hydrogenation

To a solution of compound **24** (40 mg, 0.032 mmol) in a cosolvent system of $CHCl_3$ and EtOH (1:4, 1 mL) was added Pd/C (10 mg). The reaction was shaken under high pressure of hydrogen (50 kg/cm^2) for 6 h. The reaction mixture was filtered over a short pad of Celite, and the filtercake was washed with CH_2Cl_2/MeOH cosolvent (1:1). The filtrate was concentrated under reduced pressure, and the resulting residue was purified by LH20 (MeOH/$CHCl_3=1:1$) and then silica gel chromatography (MeOH/$CHCl_3=1:15$) to give the product **2** as white solid (16 mg, 71%).

3.6. Representative procedure for substitution of hydroxyl group by azide

To a mixture of **14** (91 mg, 0.15 mmol), 2,6-lutidine (21 μL, 0.18 mmol) and 4 Å molecular sieves (30 mg) in anhydrous CH_2Cl_2 (0.5 mL) under Ar at −40 °C was added trifluoromethanesulfonic anhydride (30 μL, 0.18 mmol). After stirring at −40 °C for 30 min, tetramethylguanidinium azide (71 mg, 0.45 mmol) was added in one portion, and the reaction mixture was slowly warmed to room temperature and stirred for 18 h. The mixture was filtered over a short pad of Celite, and the filtrate was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column to give product **16** as colorless oil (76 mg, 73%).

3.7. Representative procedure for azide reduction and amide formation

To a solution of compound **4** (100 mg, 0.11 mmol) in pyridine (4 mL) and water (0.4 mL) cosolvent system was added triphenylphosphine (57 mg, 0.22 mmol). The reaction mixture was heated to 40 °C for 12 h, concentrated, and the residue was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude amine product was used for the next step without further purification.

To a solution of the crude amine product and tetracosanoic acid (53 mg, 0.14 mmol) in dried DMF (1 mL) was added triethylamine (30 μL, 0.22 mmol), EDC (33 mg, 0.17 mmol) and HOBt (23 mg, 0.17 mmol) at 0 °C under Ar. The reaction mixture was stirred at 0 °C to room temperature for 12 h, and then concentrated. The residue was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (EA/Hex = 1:19 to 1:9) to give the desired product **24** as white foam (88 mg, 65% in two steps).

3.8. Preparation of spleen cells

Male BALB/c mice about 8-weeks-old were sacrificed and the spleen cells were isolated. Briefly, spleen cells were aseptically prepared by mechanical disruption and red blood cells were removed by ACK lysis buffer (NH_4Cl 150 mM, $KHCO_3$ 1 mM, EDTA 0.1 mM) treatment. Viable cells were washed with PBS saline, then counted and resuspended in RPMI-1640 supplemented with 50 μM 2-mercaptoethanol, 10 mM HEPES, 2 mM L-glutamine and 10% FCS.

MTT assay. Spleen cell solution (100 μL of 2.5×10^6 cell/mL containing 1, 10 and 100 ng/mL of test compound or vehicle DMSO only) were dispensed into 96-well plate and cultured at 37 °C incubator containing 5% CO_2 for two days. After cultured, 20 μL of MTT stock solution (5 mg/mL dissolved in PBS and filtered) was added to the cultured cells and then incubated the cells for a further 4 h. For dissolving the dark blue formazan product (converted from MTT in active mitochondria), 120 μL of 0.04 N HCl in isopropyl alcohol was added to each wells. The colorimetric values were measured by microtiter plate reader with filter settings of 570 and 630 nm as reference. The cell growth index was calculated by the following formula: cell growth

index = (value$_{(test\ compounds)}$ − value$_{(blank)}$)/(value$_{(control)}$ − value$_{(blank)}$))×100. The value$_{(control)}$ was the detected value of the cells cultured with medium containing vehicle, while the value$_{(blank)}$ was that of medium only.

3.9. Cytokine assay

Spleen cells were suspended in RPMI-1640 medium containing 10% FCS in cell density of 5×10^6 cells/mL. The cell solution was added test compound to a final concentration of 100 ng/mL or none as control and was dispensed 200 μL/well into 96-well plate. The culture plates were incubated at 37 °C incubator containing 5% CO_2 for 0, 12, 24 and 48 h. At each time point, the culture supernatant was drawn for IFN-γ and IL-4 detection using standard sandwich ELISA. All procedures were conducted according to the standard protocol of the assay kits from Quantikine® M. (catalog number was MIF00 for INF-γ and M4000 for IL-4).

3.9.1. (2*S*,3*S*,4*R*)-1-*O*-(α-D-Galactopyranosyl)-2-(*N*-tetracosanoylamino)-1,3,4-nonanetriol (2). ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.82 (t, J=7.2 Hz, 3H), 0.89 (t, J=6.8 Hz, 3H), 1.10–1.50 (br, 46H), 1.58–1.70 (m, 1H), 1.78–1.94 (m, 3H), 2.46 (t, J=7.4 Hz, 2H), 4.28–4.34 (m, 2H), 4.36–4.47 (m, 3H), 4.52 (t, J=5.6 Hz, 1H), 4.56 (d, J=3.2 Hz, 1H), 4.63–4.72 (m, 2H), 5.27 (m, 1H), 5.58 (d, J=3.6 Hz, 1H), 8.47 (d, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ 14.7, 23.4, 23.5, 26.6, 26.9, 30.1, 30.2, 30.3, 30.5, 32.6, 32.9, 34.8, 37.3, 51.9, 63.1, 69.1, 70.2, 71.5, 72.1, 72.9, 73.5, 77.2, 102.0, 173.7. HRMS (MALDI-TOF, M+H$^+$) calcd for $C_{39}H_{78}NO_9$: 704.5677. Found: 704.5663.

3.9.2. (2*S*,3*S*,4*R*)-1-*O*-(α-L-Fucopyranosyl)-2-(*N*-hexacosanoylamino)-1,3,4-octadecanetriol (27). ^{1}H NMR ($CDCl_3$/MeOH=1/1, 400 MHz): δ 0.86 (t, 6H, J=6.8 Hz), 1.21 (d, 3H, J=6.4 Hz), 1.25 (m, 72H), 2.19 (t, 2H, J=7.6 Hz), 3.41 (dd, 1H, J=3.6, 10.0 Hz), 3.46–3.53 (m, 1H), 3.59–3.62 (m, 1H), 3.65–3.76 (m, 2H), 3.72 (dd, 1H, J=3.6, 6.8 Hz), 3.95–3.97 (m, 2H), 4.17–4.19 (m, 1H), 4.74 (d, 1H, J=3.6 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 13.0, 15.1, 21.9, 25.3, 28.7, 28.7, 28.9, 28.9, 29.0, 31.2, 63.5, 65.7, 66.7, 68.2, 69.6, 69.9, 71.5, 71.6, 98.6, 173.8. HRMS (MALDI-TOF, M+Na$^+$) calcd for $C_{50}H_{99}NO_8Na$: 864.7268, found 864.7252.

3.9.3. (2*S*,3*S*,4*R*)-1-*O*-(β-L-Fucopyranosyl)-2-(*N*-hexacosanoylamino)-1,3,4-octadecanetriol (30). ^{1}H NMR ($CDCl_3$/MeOH=1/1, 400 MHz) δ 0.87 (t, 6H, J=6.8 Hz), 1.25–1.28 (m, 75H), 2.19 (t, 2H, J=7.6 Hz), 3.45–3.49 (m, 3H), 3.56–3.63 (m, 2H), 3.67 (dd, 1H, J=5.2, 7.2 Hz), 3.87–3.88 (m, 2H), 4.07–4.11 (m, 1H), 4.23 (d, 1H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 12.9, 15.1, 21.8, 25.1, 25.2, 28.5, 28.6, 28.6, 28.7, 28.8, 28.9, 28.9, 29.0, 31.1, 35.7, 49.8, 68.4, 70.2, 70.4, 71.0, 71.6, 73.1, 73.3, 102.9, 174.1. HRMS (MALDI-TOF, M+H$^+$) calcd for $C_{50}H_{100}NO_8$: 842.7449, found 842.7440.

3.9.4. Pentadecanoic acid [1-tetradecylcarbamoyl-2-(α-D-galactopyranosyl)-ethylamide (40). ^{1}H NMR (400 MHz, pyridine-d_5) δ 0.87 (t, J=6.6 Hz, 6H), 1.14–1.48 (br, 44H), 1.56–1.68 (m, 2H), 1.72–1.85 (m, 2H), 2.47 (t, J=7.4 Hz, 2H), 3.47 (dd, J=6.8, 12.8 Hz, 2H), 4.26 (dd, J=7.4, 10.6 Hz, 1H), 4.35–4.52 (m, 4H), 4.55 (t, J=5.8 Hz, 1H), 4.60 (d, J=3.2 Hz, 1H), 4.68 (dd, J=3.8, 9.8 Hz, 1H), 5.35 (dt, J=5.2, 7.4 Hz, 1H), 5.56 (d, J=3.6 Hz, 1H), 8.85 (t, J=5.4 Hz, 1H). ^{13}C NMR (100 MHz, pyridine-d_5) δ 14.7, 23.4, 26.6, 27.80, 30.1, 30.1, 30.1, 30.3, 30.4, 32.6, 37.0, 40.4, 53.8, 63.2, 70.1, 70.7, 71.5, 72.01, 73.7, 102.0, 171.3, 173.8. HRMS (MALDI-TOF, M+H$^+$) calcd for $C_{38}H_{75}N_2O_8$: 687.5523. Found: 687.5527.

3.9.5. *O*-(α-D-Glucopyranosyl)-*N*-pentadecanoyl-L-serine tetradecyl amide (50). TLC (MeOH/$CHCl_3$=1:10) R_f 0.15; ^{1}H NMR (CD_3OD, 400 MHz) δ 4.86 (1H, H-1, mixed with water peak), 4.56 (1H, dd, J=6.2, 5.9 Hz, H-2), 3.88 (1H, dd, J=10.5, 6.2 Hz, H-1′), 3.85 (1H, dd, J=11.8, 2.4 Hz, H-6), 3.78 (1H, dd, J=10.5, 5.9 Hz, H-1′), 3.70 (1H, dd, J=11.8, 5.6 Hz, H-6), 3.63 (1H, dd, J=9.7, 9.2 Hz, H-3), 3.58 (1H, ddd, J=9.9, 5.6, 2.4 Hz, H-5), 3.45 (1H, dd, J=9.7, 3.8 Hz, H-2), 3.32 (1H, dd, J=9.9, 9.2 Hz, H-4), 3.26–3.21 (2H, m, H-3′), 2.30 (2H, t, J=7.5 Hz, H-4′), 1.67–1.64 (2H, m), 1.57–1.54 (2H, m), 1.50–1.10 (44H, br), 0.94 (6H, t, $CH_3\times2$); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.4, 172.2, 101.0, 75.2, 74.2, 73.6, 71.8, 69.1, 62.8, 54.9, 40.8, 37.0, 33.2, 31.0, 30.9, 30.9, 30.8, 30.7, 30.6, 30.6, 30.5, 28.2, 27.0, 23.9, 14.6; FAB-MS *m*/*z* 687.5 (M$^+$+1); HRMS calcd. for $C_{38}H_{75}N_2O_8$ (M$^+$+H) 687.5523, Found: 687.5531.

3.9.6. *O*-(α-D-Glucopyranosyl)-*N*-pentadecanoyl-L-serine tetradecyl ester (54). TLC (MeOH/$CHCl_3$=1/7) R_f 0.33; ^{1}H NMR (CD_3OD, 400 MHz) δ 4.83 (1H, d, J=3.8 Hz, H-1), 4.69 (1H, dd, J=5.6, 4.4 Hz, H-2′), 4.18 (2H, t, J=6.6 Hz, H-3′), 3.99 (1H, dd, J=10.8, 4.4 Hz, H-1′), 3.95 (1H, dd, J=10.8, 5.6 Hz, H-1′), 3.84 (1H, dd, J=11.8, 2.3 Hz, H-6), 3.71 (1H, dd, J=11.8, 5.5 Hz, H-6), 3.64 (1H, t, J=9.3 Hz, H-3), 3.59 (1 H, ddd, J=9.8, 5.3, 2.3 Hz, H-5), 3.43 (1H, dd, J=9.7, 3.8 Hz, H-2), 3.33 (1H, t, J=9.4 Hz, H-4), 2.31 (2H, t, J=7.2 Hz, H-5′), 1.73–1.66 (4H, m, H-4′, 6′), 1.50–1.20 (44H, br), 0.94 (6H, t, $CH_3\times2$); ^{13}C NMR (C_5D_5N, 100 MHz) δ 174.0, 171.7, 102.3, 75.6, 75.1, 74.2, 72.5, 70.2, 65.9, 63.2, 54.4, 36.7, 32.5, 30.4, 30.3, 30.3, 30.2, 30.2, 30.1, 30.0, 29.9, 29.3, 26.6, 26.5, 23.4, 14.7; FAB-MS *m*/*z* 688.1 (M$^+$ +1); HRMS calcd. for $C_{38}H_{74}NO_9$ (M$^+$ +1) 688.5364, Found: 688.5389; HRMS calcd. for $C_{38}H_{73}NNaO_9$ (M$^+$+Na) 710.5183, Found: 710.5168.

Supporting information available. Synthetic procedure, characterization and NMR spectra of new compounds **4**, **12–17**, **19**, **21**, **24**, **26**, **29**, **36–39**, **41**, **45–48**, and **53**.

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Synthesis and biological evaluation of (±)-cryptotanshinone and its simplified analogues as potent CDC25 inhibitors

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Abstract—(±)-Cryptotanshinone and its simplified analogues were synthesized via SmI_2 promoted radical cyclization to construct the furan ring. Analogues **18** and **26** were identified as effective inhibitors of dual specificity protein phosphatase CDC25B which is a key enzyme for cell cycle progression, and they also inhibited growth in A-549 human lung cancer cell line.

1. Introduction

Quinones are biologically important compounds, especially because of their cytotoxic activity and pharmacological action. Many efficient antineoplastic drugs are quinones (anthracyline derivatives, mitoxantrone, actinomycin), quinonoid derivatives (quinolones, genistein, bactracyclin) or drugs that can easily be converted to quinones by in vivo oxidation (etoposide).[1] The antitumor activities of the quinones, including naphthoquinone, were revealed more than three decades ago when the National Cancer Institute published a report in which 1500 synthetic and natural quinones were screened for their anticancer activities.[2] Many 1,2-naphthoquinones were reported to be cytotoxic against a number of tumor cell lines.[3] Because of their effectiveness in drug-resistant cells, these agents appear to hold promise as effective chemotherapeutic agents.[3]

The dual specificity phosphatases (CDC25), play a pivotal role in the regulation of the cell cycle by activating cyclin-dependent kinases (CDK)[4] and participating in Raf-1-mediated cell signaling.[5] Three CDC25 homologues exist in human, CDC25A, CDC25B and CDC25C.[4,6–8] Over-expression of CDC25A and B was observed in a variety of cancers with a striking association with tumor aggressiveness and poor prognosis,[9–12] which making CDC25 an attractive drug target for cancer therapy. Over the last few years, some small molecule CDC25 inhibitors have been described in the literature.[13–28] Some quinones, including *ortho*-quinones, displayed inhibitory activity against CDC25.

The rhizome of *Salvia miltiorrhiza* Bunge, also known as 'Tanshen' or 'Danshen', is an ancient drug in Chinese traditional medicine,[29] which has been used widely to treat coronary heart disease, menstrual disorders, miscarriage, hypertension, and viral hepatitis.[30] There have been more than 50 *ortho*-quinone diterpenes, called tanshinones, isolated from Danshen. In our program of high-throughput screening for CDC25 protein phosphatases inhibitors, the tanshinones were chosen for evaluation. We found that (−)-cryptotanshinone (Fig. 1) was a moderate inhibitor of CDC25B phosphatase (IC_{50} 10.98 μM). Cryptotanshinone is a typical compound having *ortho*-quinone skeleton among these tanshinones. Cryptotanshinone has been reported to be an effective inhibitor of topoisomerase I[31] and exhibit significant cytotoxicity against a number of cultured human tumor cell lines.[32]

Although there have been many synthetic studies of the tanshinones,[33–39] these synthetic routes are not convenient for us to further modify these compounds because of the unavailable materials and harsh reactions. In order to further study the biological activities of the tanshinonnes, we have developed a facile strategy to prepare (±)-cryptotanshinone **11** via a SmI_2 promoted radical cyclization reaction.[40] Using this strategy, we synthesized new simplified analogues of

Keywords: CDC25 Inhibitor; Cryptotanshinone; Analogues; Antitumor.
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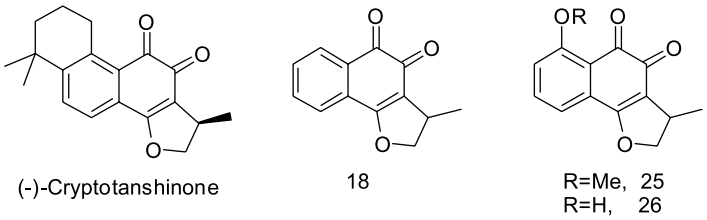


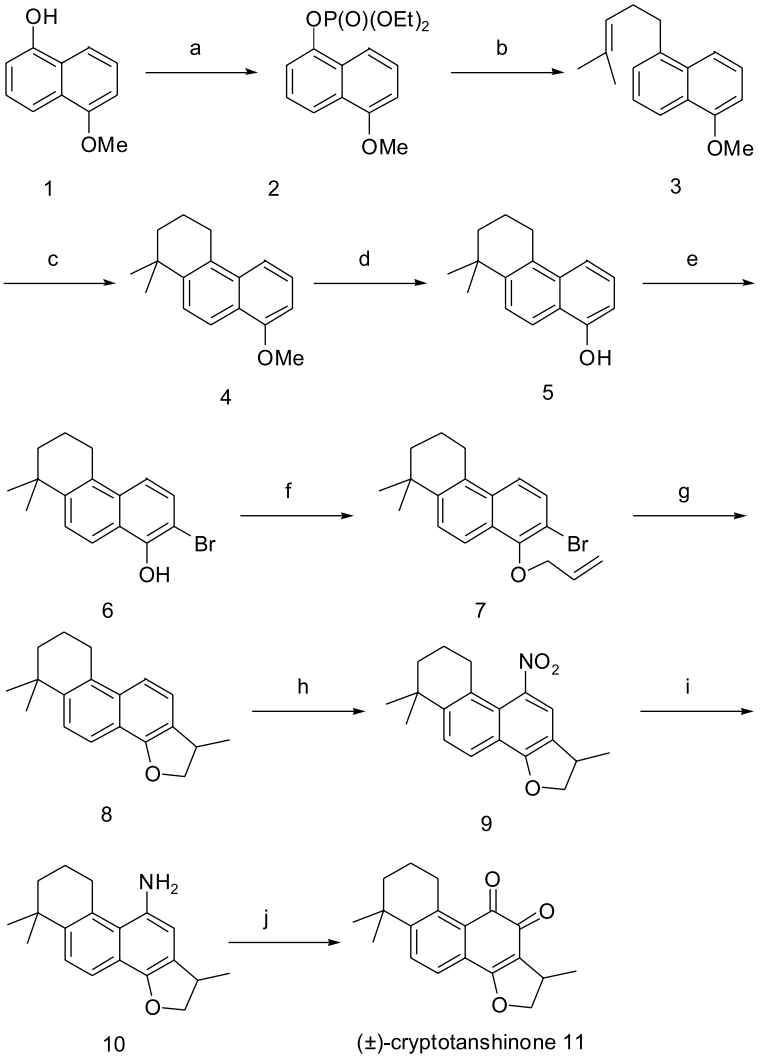
Figure 1.

(±)-cryptotanshinone **11** to investigate the structure–activity relationship as CDC25 inhibitors. The simplified analogues **18** and **26** demonstrated powerful inhibitory activity against protein phosphatase CDC25B and cytotoxic activity against A-549 tumor cell lines.

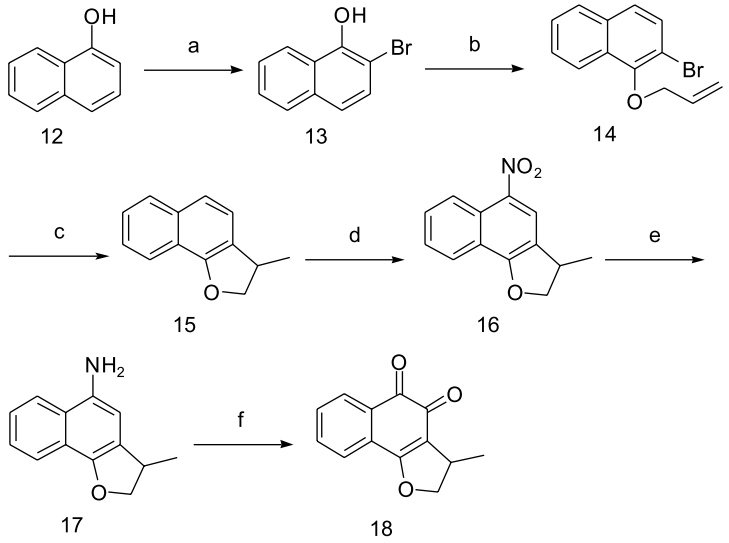
2. Results and discussion

Cryptotanshinone is tetracyclic compound, and its B and C rings are basic naphthalene structure. We use the accessible 5-methoxy-naphthalen-1-ol **1**[41] as starting material. Firstly, we constructed the A ring of cryptotanshinone. Compound **1** was treated with NaH and diethyl phosphorochloridate in dry THF to give aryl diethyl phosphates **2**. In the presence of $NiCl_2$(dppp), compound **3** was obtained via cross-coupling of **2** with Grignard reagent derived from 1-bromo-4-methylpent-3-ene.[42] Then, cyclization of **3** to **4** proceeded in excellent yield upon exposure $AlCl_3$ in CH_2Cl_2 at 0 °C for 30 min[39] to finish the building of A ring (Scheme 1).

Then, we built the naphthofuran (D ring) through the SmI_2-initiated radical cyclization reaction.[43] The treatment of **4** with BBr_3 at 0 °C provided the naphthol **5** in 95%.[44] Bromine diluted with carbon tetrachloride was added dropwise to **5** in carbon tetrachloride at the condition of



Scheme 1. Reagents and conditions: (a) $ClP(O)(OEt)_2$, NaH, THF; (b) $C_6H_{11}MgBr$, cat. $NiCl_2$ (dppp), Et_2O; (c) $AlCl_3$, CH_2Cl_2, 0 °C; (d) BBr_3, CH_2Cl_2, 0 °C; (e) Br_2, CCl_4; (f) allyl bromide, K_2CO_3, acetone; (g) SmI_2, HMPA, THF; (h) HNO_3, AcOH, 0 °C; (i) H_2, Pd/C, EtOH; (j) Fremy's salt, 0.06 M NaH_2PO_4.



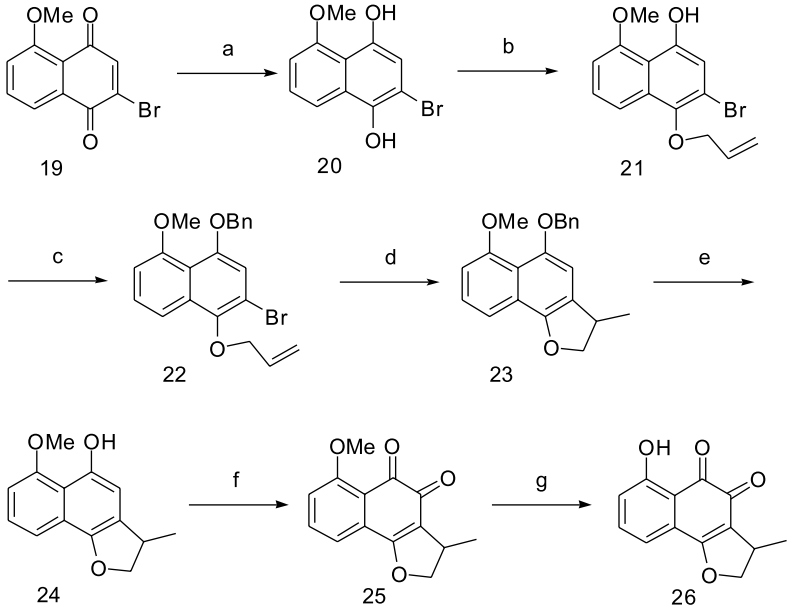
Scheme 2. Reagents and conditions: (a) Br_2, CCl_4, 24 h; (b) allyl bromide, K_2CO_3, acetone; (c) SmI_2, HMPA, THF; (d) HNO_3, AcOH; (e) H_2, Pd/C, EtOH; (f) Fremy's salt, 0.06 M NaH_2PO_4.

ice-water bath to afford **6**.[41] The desired product **6** was treated with allyl bromide and K_2CO_3 to yield allyl ether **7** as colorless oil.[45] Conversion of **7** into naphthofuran compound **8** via SmI_2-promoted intramolecular cyclization was executed in good yield.[43]

After constructing of A and D rings, we need to build *ortho*-quinone group to finish our synthesis of (±)-cryptotanshinone. By using mild aromatic nitration condition, **8** was smoothly converted into the nitrated derivative **9**, which was catalytically reduced to amine **10**.[46] Without further purification, compound **10** was oxidized directly with Fremy's salt to give (±)-cryptotanshinone **11** as an orange needles.[47]

Compound **18**, a simplified analogue of (±)-cryptotanshinone without the A ring, was prepared in six steps with a similar procedure, using 1-naphthol as the starting material (Scheme 2).

The analogue **26**, which possesses a hydroxy group instead of A ring was synthesized, as shown in Scheme 3. The intermediate **19** was prepared in four steps in high yield according to the literature method.[48] The reduction of **19** with $Na_2S_2O_4$ afforded the unstable naphthol **20**. Compound **20** was dissolved in acetone immediately, and treated with allyl bromide and potassium carbonate to give **21**. The protection of another hydroxy group of **21** with a benzyl group afforded **22** in 51% yield (from **19**). The dihydronaphthofuran was constructed using a similar procedure as described above. The catalytic hydrogenation of **23** and the following oxidation of **24** with $AgNO_3$ in absolute ethanol



Scheme 3. Reagents and conditions: (a) $Na_2S_2O_4$, Et_2O/H_2O; (b) allyl bromide, K_2CO_3, acetone; (c) BnBr, K_2CO_3, acetone; (d) SmI_2, HMPA, THF; (e) H_2, Pd/C, EtOAc; (f) $AgNO_3$, absolute EtOH; (g) $AlCl_3$, CH_2Cl_2.

Table 1. CDC25B inhibitory activities of cryptotanshinones and analogues

Compound	(−)-Cryptotanshinone	(±)-Cryptotanshinone **11**	**18**	**25**	**26**
IC_{50} (μM)	10.98±1.16	20.63±1.29	4.96±0.22	>81.89	3.21±0.76

Table 2. Cytotoxic activity against A-549 tumor cell line of cryptotanshinones and analogues

Compound	(−)-Cryptotanshinone	(±)-Cryptotanshinone **11**	**18**	**25**	**26**
IC_{50} (μM)	6.39	8.23	3.65	9.46	2.07

yielded the desired product **25** as orange solid. Compound **26** was prepared by the treatment of **25** with $AlCl_3$ in CH_2Cl_2.

Cryptotanshinones and its analogues were evaluated for their CDC25B inhibitory activity (Table 1). Natural (−)-cryptotanshinone, our synthetic (±)-cryptotanshinone (**11**) and its analogues **18** and **26** inhibited CDC25B in vitro with IC_{50} values from 3.21 to 20.63 μM. Interestingly, (−)-cryptotanshinone showed a CDC25B inhibitory activity 2-fold higher than its racemate (**11**), which proved that the stereochemistry of the C-3 in furan ring played an important role in the activity against CDC25B phosphatase. The absence of the A ring of cryptotanshinone could increase the activity. The simplified analogues **18** (IC_{50} 4.96 μM), which lack of the A ring, showed a higher CDC25B inhibitory activity than (±)-cryptotanshinone in four folds. So the naphthofuran *ortho*-quinone skeleton seems necessary for CDC25B inhibitory activity. The analogue **26**, which possesses a hydroxy group instead of A ring, was the most potent (IC_{50} 3.21 μM). However, protecting the hydroxy group with a methyl group (compound **25**), led to a complete loss of activity. In cytotoxic assay, (−)-cryptotanshinone, **11**, **18**, **25** and **26** were cytotoxic against A-549 tumor cells with IC_{50} values of 6.39, 8.23, 3.65, 9.46 and 2.07 μM (Table 2), respectively. The simplified analogues **18** and **26** also demonstrated more potent cytotoxic activity against tumor cells than cryptotanshinones.

3. Conclusion

In summary, we reported a novel synthetic method for (±)-cryptotanshinone and its new simplified analogs. The simplified analogues **18** and **26** were identified as micromolar inhibitors of CDC25B, and demonstrated powerful cytotoxic activity against A-549 tumor cell line. The A ring of cryptotanshinone was not necessary for its CDC25B inhibitory activity and cytotoxic activity. The stereochemistry of the C-3 in furan ring played an important role in the activity against CDC25B phosphatase. Thus these naphthofuran *ortho*-quinones would serve as attractive lead molecules of drug development efforts against the CDC25 phosphatase. The further investigation of the effect of the stereochemistry of the C-3 in the analogues on the biological activity is in process in our laboratory.

4. Experimental

4.1. General

Melting points were taken on Buchi510 apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on either Gemini-300 or Bruker AM-400. Chemical shifts (δ ppm) were reported for signal center, and coupling constant J are reported in units of Hz. High-resolution mass spectra were recorded on Varian MAT-711, MAT-95 or HT-5989 mass spectrometer. Column chromatography was performed on 200–300 mesh silica gel. All reagents were used directly as obtained commercially, unless otherwise noted.

4.1.1. Phosphoric acid diethyl ester 5-methoxy-naphthalen-1-yl ester (2). To a solution of **1** (1.74 g, 10 mmol) in 30 mL of THF at 0 °C was added NaH (80% dispersion in mineral oil) (0.36 g, 12 mmol). After 30 min, diethyl phosphorochloridate (1.60 mL, 11 mmol) was added and stirred for additional 20 min. Water was added and the mixture was extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (petroleum/CH_2Cl_2/acetone=15:4:1) to afford **2** as a red-brown oil (2.48 g, 80%); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, J=7.1 Hz, 6H), 3.96 (s, 3H), 4.22 (q, J=7.1 Hz, 4H), 6.82 (d, J=7.7 Hz, 1H), 7.33 (m, 2H), 7.49 (d, J=7.7 Hz, 1H), 7.72 (d, J=8.5 Hz, 1H), 8.07 (d, J=8.2 Hz, 1H).

4.1.2. 1-Methoxy-5-(4-methyl-pent-3-enyl)-naphthalene (3). To a mixture of $C_6H_{11}MgBr$ (4.8 mmol in 3.6 mL THF) and $NiCl_2$ (dppp) was added a solution of **2** (1.6 mmol, 0.5 g) in THF (3 mL), and the mixture was stirred under an atmosphere of nitrogen overnight. The mixture was poured into ice water and extracted with ethyl acetate. The organic extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (petroleum/ethyl acetate=20:1) to afford **3** as colorless oil (0.174 g, 45%); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 3H), 1.71 (s, 3H), 2.47 (m, 2H), 3.11 (t, J=7.9 Hz, 2H), 4.02 (s, 3H), 5.33 (m, 1H), 6.84 (d, J=7.5 Hz, 1H), 7.34–7.42 (m, 3H), 7.66 (d, J=8.6 Hz, 1H), 8.18 (d, J=8.2 Hz, 1H); EIMS (*m*/*z*): 240 (M^+), 171, 158, 143, 128, 115.

4.1.3. 8-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydro-phenanthrene (4). A solution of 3 (2.0 g, 8.33 mmol) in 60 mL of CH_2Cl_2 was cooled to 0 °C. $AlCl_3$ (1.2 g, 9 mmol)

was added in one portion. The solution was stirred at 0 °C for 30 min and then poured into ice water. The aqueous phase was separated and extracted with diethyl ether, and the combined organic phase was washed with water, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (petroleum/ethyl acetate=20:1) furnished **4** as a yellow oil (1.9 g, 95%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 6H), 1.73 (m, 2H), 1.94 (m, 2H), 3.10 (t, J=6.5 Hz, 3H), 3.98 (s, 3H), 6.78 (d, J=7.6 Hz, 1H), 7.38 (m, 1H), 7.48 (d, J=8.2 Hz, 1H), 7.57 (d, J=8.2 Hz, 1H), 8.10 (d, J=9.0 Hz, 1H); EIMS (*m*/*z*): 240 (M^+), 225, 158, 143, 115; HRMS calcd for $C_{17}H_{20}O$ 240.1514, found 240.1519.

4.1.4. 8,8-Dimethyl-5,6,7,8-tetrahydro-phenanthren-1-ol (5). A solution of **4** (2.0 g, 8.33 mmol) in 40 mL of dry CH_2Cl_2 was cooled to 0 °C. BBr_3 (3 mL) was added dropwise. The solution was stirred at 0 °C for 2 h, then saturated $NaHCO_3$ solution was added slowly. The mixture was extracted with diethyl ether, and the combined organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (petroleum/ethyl acetate=8:1) furnished **5** (1.79 g, 95%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 6H), 1.72 (m, 2H), 1.94 (m, 2H), 3.08 (t, J=6.3 Hz, 2H), 6.76 (d, J=7.5 Hz, 1H), 7.29 (dd, J=8.5, 7.5 Hz, 1H), 7.49 (d, J=7.3 Hz, 1H), 7.55 (d, J=8.7 Hz, 1H), 7.98 (d, J=8.8 Hz, 1H); EIMS (*m*/*z*): 226 (M^+), 211, 115; HRMS calcd for $C_{16}H_{18}O$ 226.1358, found 226.1354.

4.1.5. 2-Bromo-8,8-dimethyl-5,6,7,8-tetrahydro-phenanthren-1-ol (6). Compound **5** (1.0 g, 4.42 mmol) was dissolved in CCl_4 and bromine (0.71 g, 4.43 mmol) was added dropwise at 0 °C. The mixture was stirred for 1 h, and then 3% $Na_2S_2O_3$ was added. After being stirred for additional 10 min, the mixture was extracted with CH_2Cl_2. The organic phase was washed sequentially with sodium thiosulfate, water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography (petroleum/ethyl acetate=15:1) to afford **6** (1.21 g, 90%) as colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 6H), 1.72 (m, 2H), 1.93 (m, 2H), 3.05 (t, J=6.32 Hz, 2H), 5.87 (s, 1H), 7.41 (d, J=8.79 Hz, 1H), 7.45 (d, J=9.06 Hz, 1H), 7.50 (d, J=9.06 Hz, 1H), 8.04 (d, J=8.78 Hz, 1H); EIMS (*m*/*z*): 306, 304, 291, 289, 210; HRMS calcd for $C_{16}H_{17}OBr$ 304.0463, found 304.0467.

4.1.6. 8-Allyloxy-7-bromo-1,1-dimethyl-1,2,3,4-tetrahydro-phenanthrene (7). K_2CO_3 (1.98 g, 15.7 mmol) was added to a solution of **6** (1.2 g, 3.93 mmol) dissolved in 40 mL of acetone. Allyl bromide was added in one portion and the mixture was stirred at room temperature for 4 h. The mixture was filtered and concentrated in vacuo. The crude residue was purified by column chromatography (petroleum/ethyl acetate=20:1) to afford **7** as colorless oil (1.29 g, 95%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 6H), 1.72–1.75 (m, 2H), 1.92–1.97 (m, 2H), 3.09 (t, J=6.42 Hz, 2H), 4.61 (m, 2H), 5.36 (m, 1H), 5.55 (m, 1H), 6.25 (m, 1H), 7.54 (d, J=8.99 Hz, 1H), 7.57 (d, J=9.16 Hz, 1H), 7.64 (d, J=9.17 Hz, 1H), 7.97 (d, J=8.98 Hz, 1H); EIMS (*m*/*z*): 346, 344, 305, 303, 196; HRMS calcd. for $C_{19}H_{21}OBr$ 344.0776, found 344.0779).

4.1.7. 1,6,6-Trimethyl-1,2,6,7,8,9-hexahydro-phenanthro[1,2-*b*]furan (8). To a 0.1 M THF solution of SmI_2 (40 mL, 2 mmol) and HMPA (2.4 mL, 14 mmol) was added a solution of **7** (0.317 g, 0.92 mmol) in dry THF at 25 °C. The solution was stirred under an atmosphere of nitrogen for 3 h. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic extracts were washed with H_2O, 3% $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum/ethyl acetate=20:1) to afford **8** as a colorless oil (0.215 g, 88%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38–1.42 (m, 9H), 1.74–1.78 (m, 2H), 1.93–1.99 (m, 2H), 3.11 (t, J=6.30 Hz, 2H), 3.73 (m, 1H), 4.30 (dd, J=7.00, 8.70 Hz, 1H), 4.89 (t, J=8.70, 9.00 Hz, 1H), 7.34 (d, J=8.70 Hz, 1H), 7.45 (d, J=8.65 Hz, 1H), 7.51 (d, J=8.62 Hz, 1H), 7.82 (d, J=8.70 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 142.4, 132.9, 130.8, 127.8, 125.6, 124.6, 121.5, 119.2, 115.8, 79.1, 38.8, 37.3, 37.2, 34.2, 31.5, 31.4, 27.2, 19.9, 19.8, 19.6; EIMS (*m*/*z*): 266, 251, 169; HRMS calcd for $C_{19}H_{22}O$ 266.1671, found 266.1662.

4.1.8. 1,6,6-Trimethyl-10-nitro-1,2,6,7,8,9-hexahydro-phenanthro[1,2-*b*]furan (9). Compound **8** (0.212 g, 0.8 mmol) and AcOH (0.35 mL) were cooled to 0 °C and concentrated HNO_3 (0.04 mL) was added dropwise. After this addition, the mixture was placed in the refrigerator at 10 °C for 20 min and then diluted with H_2O. The resulting precipitate was extracted with ethyl acetate. The organic extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum/ethyl acetate=20:1) to afford **9** as yellow oil (0.216 g, 87%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 6H), 1.38 (d, J=6.87 Hz, 3H), 1.68–1.77 (m, 4H), 2.76 (t, J=6.05 Hz, 2H), 3.75 (m, 1H), 4.37 (dd, J=7.14, 8.93 Hz, 1H), 4.96 (dd, J=9.07, 9.20 Hz, 1H), 7.59 (d, J=8.93 Hz, 1H), 7.68 (s, 1H), 7.87 (d, J=8.93 Hz, 1H); EIMS (*m*/*z*): 311, 294, 251; HRMS calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1524.

4.1.9. (±)-Cryptotanshinone 11. Compound **9** (0.2 g, 0.643 mmol) in EtOH was hydrogenated over 10% Pd/C (40 mg) for 4.5 h. The catalyst was filtered off and the solvent was removed in vacuo to give the amine **10**. The crude amine was dissolved in acetone (10 mL) and treated with Fremy's salt (550 mg, 2.06 mmol) in 55 mL of 0.06 M NaH_2PO_4. The mixture was stirred at room temperature for 30 min and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (petroleum/ethyl acetate=6:1) to afford **11** as an orange solid (95 mg, 50%), mp 172–173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 6H), 1.33 (d, J=6.87 Hz, 3H), 1.64–1.67 (m, 2H), 1.76–1.81 (m, 2H), 3.22 (t, J=6.42 Hz, 2H), 3.60 (m, J=6.79 Hz, 1H), 4.36 (dd, J=6.04, 9.33 Hz, 1H), 4.89 (dd, J=9.48, 9.48 Hz, 1H), 7.50 (d, J=8.10 Hz, 1H), 7.62 (d, J=8.10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.2, 175.6, 170.7, 152.3, 143.6, 132.5, 128.3, 126.2, 122.4, 118.2, 81.4, 37.7, 34.8, 34.5, 31.8 (2C), 29.6, 19.0, 18.8; EIMS (*m*/*z*): 296, 253, 171; HRMS calcd for $C_{19}H_{20}O_3$ 296.1412, found 296.1404.

4.1.10. 2-Bromo-1-naphthalenol (13). According to the

procedure described above for **6**, compound **12** (4.14 g, 28.7 mmol) was converted to **13** (5.314 g, 83%) as white needles: mp: 46–47 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.00 (s, 1H), 7.32 (d, J=8.8 Hz, 1H), 7.47 (d, J=8.9 Hz, 1H), 7.49–7.54 (m, 2H), 7.78 (m, 1H), 8.24 (m, 1H); EIMS(*m*/*z*): 224 (M^+), 222 (M^+), 143, 144, 114, 115.

4.1.11. 1-Allyloxy-2-bromonaphthalene (14). According to the procedure described above for **7**, compound **13** (4.00 g, 17.9 mmol) was converted to **14** (4.615 g, 98%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (d, J= 5.5 Hz, 2H), 5.35 (dd, J=10.2, 1.2 Hz, 1H), 5.54 (dd, J= 17.1, 1.4 Hz, 1H), 6.25 (m, 1H), 7.48–7.62 (m, 4H), 7.84 (dd, J=6.8, 2.3 Hz, 1H), 8.15 (dd, J=8.2, 1.8 Hz, 1H); EIMS (*m*/*z*): 264 (M^+), 262 (M^+), 223, 221, 195, 193, 183, 181, 114.

4.1.12. 2,3-Dihydro-3-methylnaphtho[1,2-*b*]furan (15). According to the procedure described above for **8**, compound **14** (0.526 g, 2.00 mmol) was converted to **15** (0.360 g, 98%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, J=6.8 Hz, 3H), 3.75 (m, 1H), 4.32 (dd, J=7.4, 8.6 Hz, 1H), 4.92 (dd, J=9.1, 8.8 Hz, 1H), 7.36 (d, J=8.1 Hz, 1H), 7.41–7.52 (m, 3H),7.84 (dd, J=6.8, 2.7 Hz, 1H), 8.01 (dd, J=7.8, 2.4 Hz, 1H); EIMS (*m*/*z*): 184 (M+), 169, 141, 115.

4.1.13. 2,3-Dihydro-3-methy-5-nitronaphtho[1,2-*b*]furan (16). According to the procedure described above for **9**, compound **15** (0.360 g, 1.957 mmol) was converted to **16** (0.251 g, 56%) as an orange solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (d, J=6.9 Hz, 3H), 3.80 (m, 1H), 4.45 (dd, J=7.0, 9.1 Hz, 1H), 5.04 (dd, J=9.1, 9.1 Hz), 7.56 (dd, J= 8.0, 8.2 Hz, 1H), 7.70 (dd, J=8.3, 8.8 Hz, 1H), 8.06 (d, J= 8.4 Hz, 1H), 8.36 (s, 1H), 8.83 (d, J=9.0 Hz, 1H); EIMS (*m*/*z*): 229 (M^+), 214, 199, 168, 139.

4.1.14. 2,3-Dihydro-3-methylnaphtho[1,2-*b*]furan-4,5-dione (18). According to the procedure described above for (±)-cryptotanshinone **11**, compound **16** (0.20 g, 0.87 mmol) was converted to **18** (102 mg, 55%) as a red solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, J=6.7 Hz, 3H), 3.64 (m, 1H), 4.42 (dd, J=9.31, 9.47 Hz, 1H), 4.93 (dd, J=9.62, 9.63 Hz, 1H), 7.55–7.66 (m, 3H), 8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.3, 175.4, 169.8, 134.6, 131.9, 130.8, 129.4, 127.6, 124.3, 120, 81.5, 34.4, 18.9; EIMS (*m*/*z*): 214 (M^+), 186, 171; HRMS calcd for $C_{13}H_{10}O_3$ 214.06, found 214.0617.

4.1.15. 1-Allyloxy-4-benzoxy-5-methoxynaohthalene (22). A suspension of **19** (1.03 g, 3.86 mmol) in 50 mL diethyl ether was stirred with a freshly prepared solution of $Na_2S_2O_4$ (5.00 g, 28.7 mmol) in 50 mL water. After the mixture was stirred for 30 min, the organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give **20** as a tan solid. Without purification, **20** was dissolved in 20 mL of acetone and K_2CO_3 (2.92 g, 38.6 mmol) was added. After the suspension was stirred for several minutes, allyl bromide (0.934 g, 7.72 mmol) was added dropwise. The endpoint of the reaction was detected by TLC. Then the mixture was concentrated in vacuo to remove the solvent and remaining allyl bromide. The residue was dissolved in 20 mL of acetone, and benzyl bromide (1.915 g, 7.72 mmol) was added. The mixture was stirred at room temperature for 12 h, filtered with celite, and concentrated in vacuo. Purification by column chromatography (petroleum/ethyl acetate=30:1) afforded **22** (0.785 g, 51% from **19**) as colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.94 (s, 3H), 4.56 (m, 2H), 5.16 (s, 2H), 5.34 (m, 1H), 5.50 (m, 1H), 6.24 (m, 1H), 6.90–7.70 (m, 9H); EIMS (*m*/*z*): 400, 398, 307, 227; HRMS calcd for $C_{21}H_{19}BrO_3$ 398.0518, found 398.0538.

4.1.16. 5-Benzoxy-6-methoxy-3-methylnaphtho[1,2-*b*]furan (23). According to the procedure described above for **8**, compound **22** (0.64 g, 1.60 mmol) was converted to **23** (0.44 g, 85%) as a colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (d, J=6.87 Hz, 3H), 3.71 (m, 1H), 3.82 (s, 3H), 4.25 (dd, J=7.83, 8.53 Hz, 1H), 4.85 (dd, J=8.53, 8.72 Hz, 1H), 5.22 (s, 2H), 6.83–7.57 (m, 9H); EIMS (*m*/*z*): 320, 229, 149; HRMS calcd for $C_{21}H_{20}O_3$ 320.1412, found 320.1419.

4.1.17. 2,3-Dihydro-6-methoxy-3-methylnaphtho[1,2-*b*]furan-4,5-dione (25). Compound **23** (0.312 g, 1.357 mmol) was dissolved in 20 mL of ethyl acetate, and hydrogenated over 10% Pd/C (50 mg) overnight. The catalyst was filtered off, and the solvent was removed in vacuo to give **24**. The crude product **24** was dissolved in 40 mL of absolute ethanol, and powdered $AgNO_3$ (1.454 g, 8.507 mmol) was added. After the mixture had been gently refluxed for 15 min, water was added to quench the reaction, followed by an extraction with dichloromethane. The extracts were washed with water and brine, dried over $MgSO_4$ concentrated in vacuo. The crude product was purified by chromatography (petroleum/ethyl acetate=3:1) to afford **25** (0.116 g, 50%) as an orange red solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (d, J=6.89 Hz, 3H), 3.61 (m, 1H), 3.98 (s, 3H), 4.36 (dd, J=6.21, 9.23 Hz, 1H), 4.89 (dd, J=9.57, 9.57 Hz, 1H), 7.17 (d, J=8.56 Hz, 1H), 7.27 (d, J=7.39 Hz, 1H), 7.59 (dd, J=7.39, 8.56 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.5, 34.5, 56.1, 81.1, 116.5, 117.0, 117.5, 119.0, 129.1, 135.8, 161.5, 169.3, 175.2, 180.1; EIMS (*m*/*z*): 246, 244, 216, 201, 115; HRMS calcd. for $C_{14}H_{12}O_4$ 244.0736, found 244.0733.

4.1.18. 2,3-Dihydro-6-hydroxy-3-methylnaphtho[1,2-*b*]furan-4,5-dione (26). To the solution of **25** (80 mg, 0.328 mmol) in 10 mL of dry CH_2Cl_2, was added powdered $AlCl_3$ (0.660 g, 4.96 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, then at room temperature for 6 h, poured into ice water, and concentrated hydrochloric acid was added. The resulting mixture was extracted with ethyl acetate. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by chromatography (petroleum/ethyl acetate=1:1) afforded **26** (74.5 mg, 98%) as a red solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, J=6.8 Hz, 3H), 3.60 (m, 1H), 4.38 (dd, J=6.04, 9.34 Hz, 1H), 4.90 (dd, J=9.62, 9.61 Hz, 1H), 7.12 (d, J=8.65 Hz, 1H), 7.18 (d, J= 7.32 Hz, 1H), 7.54 (dd, J=8.65, 7.28 Hz, 1H), 11.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 34.8, 81.7, 113.4, 117.6, 120.1, 123.3, 127.4, 137.8, 164.5, 169.4, 175.0, 185.5; EIMS (*m*/*z*): 230, 187, 159; HRMS calcd for $C_{13}H_{10}O_4$ 230.0579, found 230.0570.

4.2. CDC25B inhibition assay

CDC25B phosphatase catalytic domain was expressed with the Glutathionine *S*-transferase (GST) and purified by the GSTrap affinity chromatograph. GST-CDC25B active enzyme was stored in 50 mM Tris–HCl Ph 8.0, 50 mM NaCl, 10 mM Glutathionine, 2 mM DTT and 2 mM EDTA at −80 °C. The typical inhibition assay was carried out in 100 μL system containing 50 mM Tris–HCl PH8.0, 50 mM NaCl, 2 mM DTT, 2 mM EDTA, 1% glycerol, 10 μM OMEP, 2% DMSO and 70∼100 nM GST-CDC25B. The reaction was monitored by Victor (Perkin–Elmer; excitation filter 485 nm and emission filter 530 nm) at the room temperature.

4.3. Cytotoxicity assay

Cytotoxicity assay was performed on human lung cancer (A-549) cell line. Cells (6000–10,000) in 100 μL culture medium per well were seeded into 96-well microtest plates (Falcon, CA). Cells were treated in triplicate with gradient concentration of test drugs and incubated at 37 °C for 72 h. The growth inhibitory effect on A-549 cell line was measured by the Sulforhodamine B (SRB; Sigma, St. Louis, MO) assay. The drug concentration required for 50% growth inhibition (IC_{50}) of tumor cells was determined from the dose-response curve.

Acknowledgements

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Synthesis and conformational analysis of 18-membered Aib-containing cyclohexapeptides

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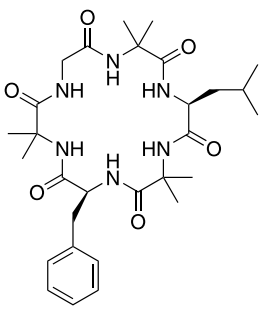
Abstract—The synthesis and conformational analysis of two Aib-containing cyclic hexapeptides, *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) **1** and *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) **2**, is described. The linear precursors of **1** and **2** were prepared using solution phase techniques, and the cyclization efficiency of three different coupling reagents (HATU, PyAOP, DEPC) was examined. The success of the cyclization was found to be reagent dependent. Solid-state conformational analysis of **1** and **2** was performed by X-ray crystallography and has revealed some unusual features as all three Aib residues of **1** assume nonhelical conformations. Furthermore, the residue Aib^4 adopts an extended conformation ($\phi = -175.9(3)°$, $\psi = +178.6(2)°$), which is, to the best of our knowledge, the first observation of an Aib residue adopting an extended conformation in a cyclopeptide. The structure of **1** is also a rare example in which an Aib residue occupies the $(i+1)$ position of a type II′ β-turn, stabilized by a bifurcated hydrogen bond. The cyclic peptide **2** adopts a more regular conformation in the solid state, consisting of two fused β-turns of type I/I′, stabilized by a pair of intramolecular hydrogen bonds. In addition, the conformational study of the cyclic peptide **1** in DMSO-d_6 by NMR spectroscopy and molecular dynamics simulations revealed a structure, which is very similar to its structure in the crystalline state.

1. Introduction

Cyclic peptides continue to be challenging targets for chemical synthesis.[1] As the synthesis of linear peptides generally proceeds well, the key step for the chemical synthesis of cyclic peptides is usually the cyclization reaction. In particular, the cyclization of small peptides of less than seven amino acid residues is often difficult.[2] Incorporation of turn-inducing elements such as Gly, Pro, D-amino acids and *N*-alkylated amino acids into the peptide backbone is known to improve cyclization yields.[3] Although conformational constraints are usually introduced into peptides through cyclization, cyclic peptides can still possess a remarkable flexibility.[4,5] Thus, the incorporation of sterically hindered C(2)-tetrasubstituted α-amino acids into the peptide backbone leads to more rigid compounds. In addition, cyclic penta- and hexapeptides are often chosen for the synthesis of model cyclopeptides, since larger cyclic peptides already exhibit greater flexibility.[6] Conformation-constrained cyclic peptides may have enhanced metabolic stability, receptor selectivity, and bioavailability, all of which may lead to useful medicinal properties.

Our previous successful synthesis of cyclic hexapeptides containing several Aib (α-aminoisobutyric acid) residues and two Gly residues in positions 1 and 4 of the peptide backbone[7,8] prompted us to investigate the cyclization of hexapeptides containing only one Gly residue as the turn-inducing element. Here, we describe the synthesis of two cyclic hexapeptides *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**) and *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) (**2**), composed of three protein amino acids, i.e. Gly, Leu, Phe and three α-aminoisobutyric acids. The crystal structures of both cyclic peptides were examined by X-ray diffraction in order to study the influence of the Aib residues on the conformation of the backbone of the cyclic hexapeptides. A NMR-based structure determination of **1** in solution was also performed in the present study.



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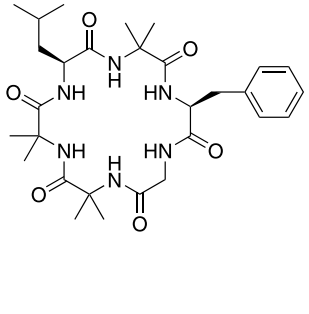

2

Keywords: Cyclic peptides; Peptide synthesis; α-Aminoisobutyric acid; Peptide conformation.
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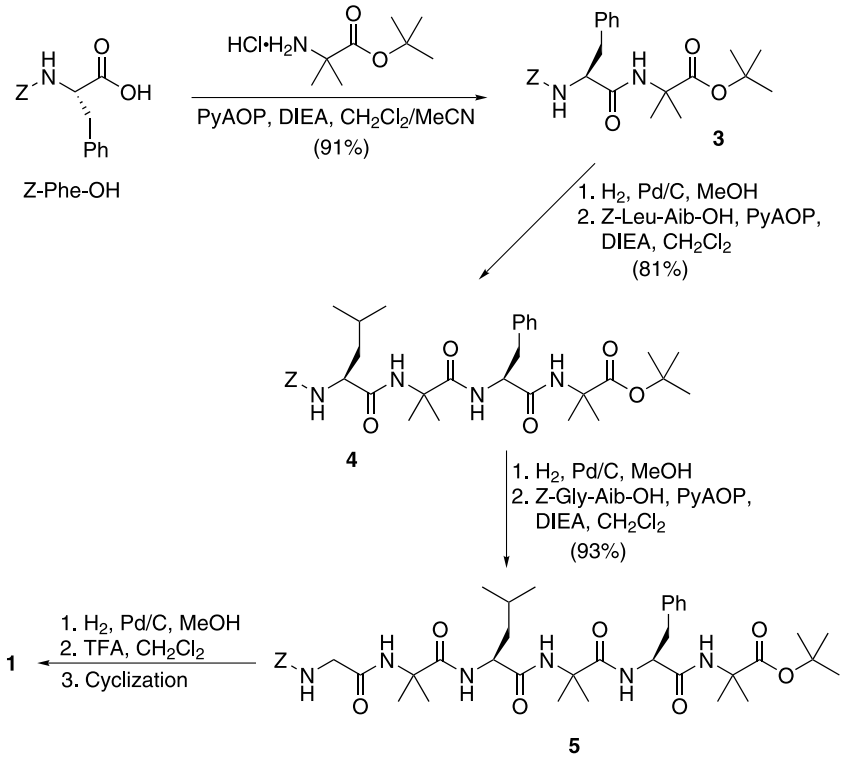
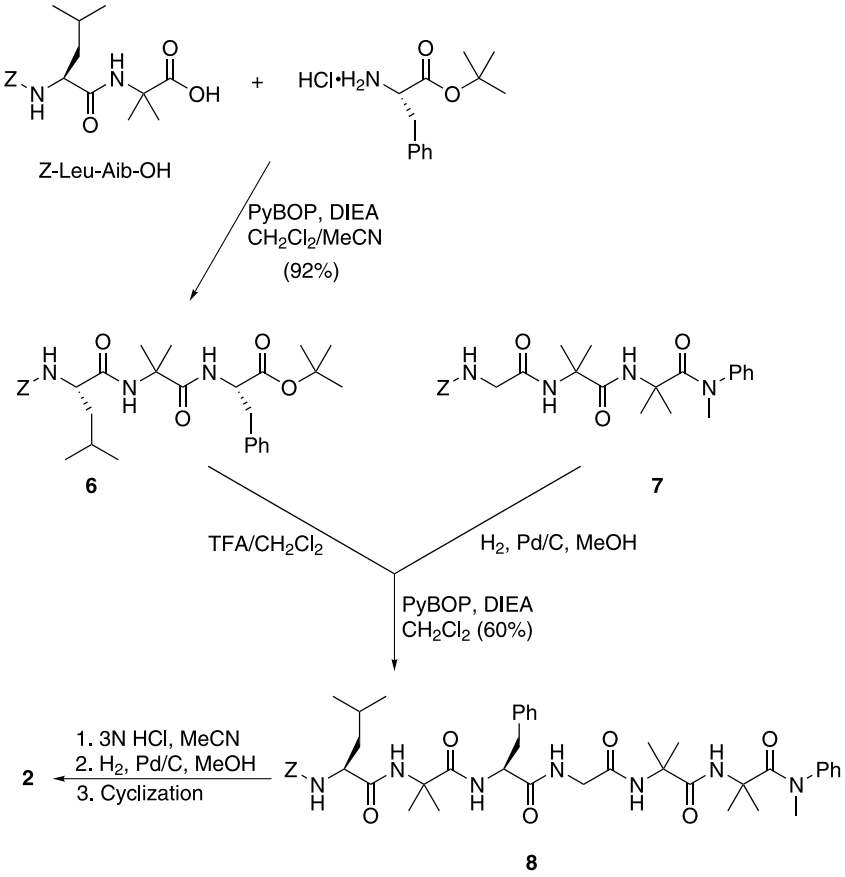


Scheme 1.



Scheme 2.

Table 1. Conditions used for the cyclization of Aib-containing hexapeptides **5** and **8**

Cyclic peptide	Cyclization method	Reaction time	Yield (%)
Cyclo(Gly-Aib-Leu-Aib-Phe-Aib) **1**	HATU/HOAt (3 equiv)	1 day	24
	PyAOP/HOAt (5 equiv)	3 days	31
	DEPC (10 equiv)	6 days	53
Cyclo(Leu-Aib-Phe-Gly-Aib-Aib) **2**	HATU/HOAt (3 equiv)	3 days	16
	DEPC (10 equiv)	6 days	33
	PyAOP/HOAt (3 equiv)	3 days	48

2. Results and discussion

2.1. Preparation and cyclization of linear hexapeptides

The linear hexapeptides Z-Gly-Aib-Leu-Aib-Phe-Aib-O*t*Bu (**5**) and Z-Leu-Aib-Phe-Gly-Aib-Aib-N(Me)Ph (**8**) were synthesized by solution-phase methods as shown in Schemes 1 and 2. A [2+2+2]-fragment condensation was chosen in the case of **5**. At first, the dipeptide Z-Phe-Aib-O*t*Bu (**3**) was prepared by coupling Z-Phe-OH with HCl·H-Aib-O*t*Bu using PyAOP as the coupling reagent. Then, **3** was *N*-deprotected to give H-Phe-Aib-O*t*Bu by means of catalytic hydrogenation. The PyAOP-mediated coupling of the latter with Z-Leu-Aib-OH[9] afforded tetrapeptide Z-Leu-Aib-Phe-Aib-O*t*Bu (**4**) in high yield. Removal of the Z protecting group of **4**, and coupling of the resulting H-Leu-Aib-Phe-Aib-O*t*Bu with Z-Gly-Aib-OH in the presence of PyAOP afforded the linear hexapeptide **5**.

For the synthesis of the linear hexapeptide **8**, a convergent [3+3] strategy was employed. Thus, the tripeptide Z-Leu-Aib-Phe-O*t*Bu (**6**) was prepared by coupling Z-Leu-Aib-OH with the hydrochloride of H-Phe-O*t*Bu using PyBOP as the coupling reagent. Treatment of **6** with TFA in CH_2Cl_2, followed by the reaction with H-Gly-Aib-Aib-N(Me)Ph, which was obtained by deprotection of Z-Gly-Aib-Aib-N(Me)Ph (**7**),[7] led, in the presence of PyAOP, to the hexapeptide **8** in moderate yield.

The linear hexapeptides Z-Gly-Aib-Leu-Aib-Phe-Aib-O*t*Bu (**5**) and Z-Leu-Aib-Phe-Gly-Aib-Aib-N(Me)Ph (**8**) were then deprotected at the N- and C-terminus and treated with the coupling reagents HATU, PyAOP and DEPC to investigate the cyclization tendency of each peptide. All of the cyclization reactions were performed in diluted DMF solutions (10^{-4}–10^{-3} M) using a large excess of coupling reagent and base (DIEA). The yields of the cyclization reactions are shown in Table 1. In the first attempts we used HATU as the activating agent, since it has proven to be versatile and highly efficient.[2] However, the cyclohexapeptides **1** and **2** were obtained only in relatively low yields. One explanation for the less efficient macrolactamization than expected could be that HATU participated in a side reaction at the amino terminus to give a guanidino derivative. This side reaction is known to occur when an excess of the aminium salt based coupling reagents is used.[10] To avoid this problem, phosphonium reagents such as PyBOP and PyAOP are recommended.[11] Thus, PyAOP together with HOAt was employed in the cyclization step, leading to **1** in moderate yield while **2** was obtained in good yield. Next, the macrolactamization ability of the organophosphorus reagent DEPC was tested. Because of the slower reaction rate under the DEPC/DIEA conditions, reaction times of up to six days were used. This time, the cyclic hexapeptide **1** was obtained in good yield, while cyclopeptide **2** was isolated in moderate yield. As is evident from these results, the success of the cyclization is dependent upon the choice of the cyclization reagent. However, **1** and **2** were obtained in remarkably similar overall moderate (30%) to good yields (50%). Comparing the best cyclization protocols for **1** and **2** it was surprising that the lactamization between the less hindered pair H_2N-Gly and Aib-CO proceeded only slightly better than that between NH_2 of the sterically demanding Leu residue and Aib-CO. It appears that the conformation or (and) sequence of the linear precursor played a more important role than the size of the residue at the N-terminus.

The cyclic structures of **1** and **2** were established by standard two-dimensional NMR techniques. The assignment of all H- and C-signals was possible by using 2D HSQC and HMBC spectra. A combination of these two types of spectra allowed the complete assignment of the amide NH, CO and C(α) signals of all residues, as well as enabling the signals of different Aib residues to be distinguished. In addition, selected ROESY correlations observed in DMSO-d_6 solution are shown in Figure 1.

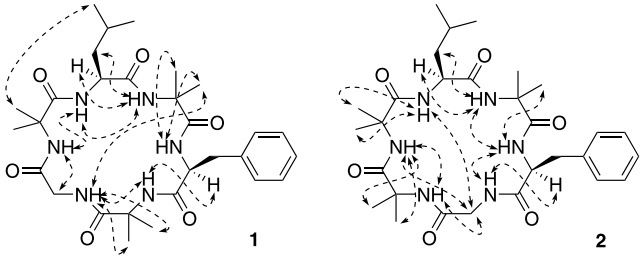


Figure 1. Selected ROESY correlations for compounds **1** and **2** in DMSO-d_6.

2.2. Solid state conformation

Cyclic peptides are frequently found among natural products and exhibit a wide range of biological activities.[12] Therefore, their conformations have been studied extensively both in the solid state and in solution, since the chemical properties and biological activities of such structures are known to be closely related to their molecular conformation.[13–15] The crucial determinants of the conformation of cyclic peptides are the turns (β, γ) and intramolecular hydrogen bonds. Cyclic hexapeptides have been used as model peptides for β-turns since these peptides, due to geometric factors, generally adopt a conformation with two β-turns, stabilized by a pair of two intramolecular hydrogen bonds between residues i and $i+3$.[16] Turns do not necessarily contain hydrogen bonds,

but the lack of hydrogen bonds generally results in distorted or unstable structures.

By extensive crystallographic studies, α-amino isobutyric acid (Aib) has been shown to favor left- or right-handed 3_{10}/α-helical conformations in a wide variety of acyclic peptides of differing lengths and sequences.[17–20] Indeed, Aib residues with very few exceptions almost invariably adopt conformations with ϕ and ψ values near $\pm(60\pm20)^\circ$ and $\pm(30\pm20)^\circ$, respectively. In addition, theoretical calculations show the presence of minima in a semiextended region of the ϕ, ψ space ($\phi=\pm(60\pm20)^\circ$, $\psi=\pm(120\pm20)^\circ$).[17]

There are relatively few reports concerning crystallographic studies of Aib residues incorporated into cyclic peptides,[21–25] so the structural information about the conformational preferences of Aib residues in cyclic molecules is rather scarce. The cyclic tetrapeptide dehydrochlamydocin[21] and the cyclic pentapeptide *cyclo*(Phe-Phe-Aib-Leu-Pro)[22] both have the Aib residue at the center of a γ-turn with unexpected values of the torsion angles ϕ, ψ that lie in the nonhelical conformational space. The torsion angles (ϕ, ψ) of the Aib residues in the crystal structures of *cyclo*(Gly-Aib-Gly)$_2$,[23] [Aib^{5,6}-D-Ala^8]cyclolinopeptide A,[24] and *cyclo*(Pro-Phe-Phe-Aib-Leu)$_2$[25] all lie well inside the 3_{10}/α-helical region of the conformational space, as is observed in linear peptides.

In our research group, we have synthesized several Aib-containing cyclopentapeptides,[19,20] and the crystal-structures of three of them have been established by X-ray crystallography. The structures of *cyclo*[Gly-(*RS*)-Phe(2Me)-Aib-Aib-Gly][19] and *cyclo*[Gly-Aib-(*RS*)-Phe(2Me)-Aib-Gly][20] are very similar and have a β-turn, which is stabilized by a hydrogen bond between NH of Gly^1 and CO of Phe(2Me)^3 and CO of Aib^3, respectively. Whereas in the structure of *cyclo*[Gly-Aib-(*RS*)-Phe(2Me)-Aib-Gly] the torsion angles of both Aib residues show values typical for the helical region (*cyclo*[Gly-Aib-(*R*)-Phe(2Me)-Aib-Gly]: $\phi(\text{Aib}^2)=+50.4(7)^\circ$, $\psi(\text{Aib}^2)=+42.9(6)^\circ$, $\phi(\text{Aib}^4)=-47.2(7)^\circ$, $\psi(\text{Aib}^4)=-46.4(6)^\circ$; *cyclo*[Gly-Aib-(*S*)-Phe(2Me)-Aib-Gly]: $\phi(\text{Aib}^2)=-52.9(7)^\circ$, $\psi(\text{Aib}^2)=-31.2(7)^\circ$, $\phi(\text{Aib}^4)=+50.0(7)^\circ$, $\psi(\text{Aib}^4)=+44.9(7)^\circ$), those of Aib^3 of *cyclo*[Gly-(*RS*)-Phe(2Me)-Aib-Aib-Gly] do not correspond with the helical conformational space ($\phi=-159.7(2)^\circ$, $\psi=+166.3(2)^\circ$). In the asymmetric unit of the crystal structure of the third cyclopentapeptide, i.e. *cyclo*[Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe],[20] there are two independent molecules with quite different conformations. One of the molecules forms a β-turn with a Aib$^4\rightarrow$Gly^1 hydrogen bond, whereas the other molecule is characterized by a γ-turn (NH(Aib^4)$\rightarrow$CO(Pro^3) hydrogen bond) and an α-turn (NH(Phe^5)–CO(Gly^1) hydrogen bond). In the molecule containing a β-turn, Aib^4 shows ϕ, ψ values that belong to the nonhelical conformational space ($\phi=+154.8(4)^\circ$, $\psi=-51.0(4)^\circ$).

As a part of our investigation of the synthesis of cyclic hexapeptides containing Aib residues,[7,26] we have been interested in the conformations of these cyclic molecules in order to estimate if the incorporation of several Aib residues into cyclic hexapeptide structures stabilizes certain types of turns. Previously, we have investigated the cyclization and conformation of hexapeptides containing two or three Aib residues, and two Gly residues in positions 1 and 4 of the peptide backbone.[7] The crystal structures of two cyclic peptides, *cyclo*(Gly-Aib-Aib-Gly-Aib-Phe) and *cyclo*(Gly-(*S*)-Phe(2Me)-Aib-Gly-Aib-Phe), showed that these molecules have two fused β-turns. The observed β-turns were stabilized by intramolecular hydrogen bonds between the NH of Gly^1 and the C=O of Gly^4 and between the NH of Gly^4 and C=O of Gly^1. Different types of β-turn conformations, i.e. I, I′ and III′, have been observed depending on the sequence, with Aib residues occupying positions ($i+1$) and/or ($i+2$) of the turns.

The solid-state conformations of the new cyclohexapeptides *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**) and *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) (**2**) were examined by X-ray crystallography. Crystals of **1** suitable for the X-ray analysis were obtained from a mixture of MeOH/*i*-PrOH/$CHCl_3$ and acetone, and those of **2** were grown from MeOH/EtOH/*i*-PrOH and water. The ORTEP plots[27] of the molecules with the atom numbering schemes are presented

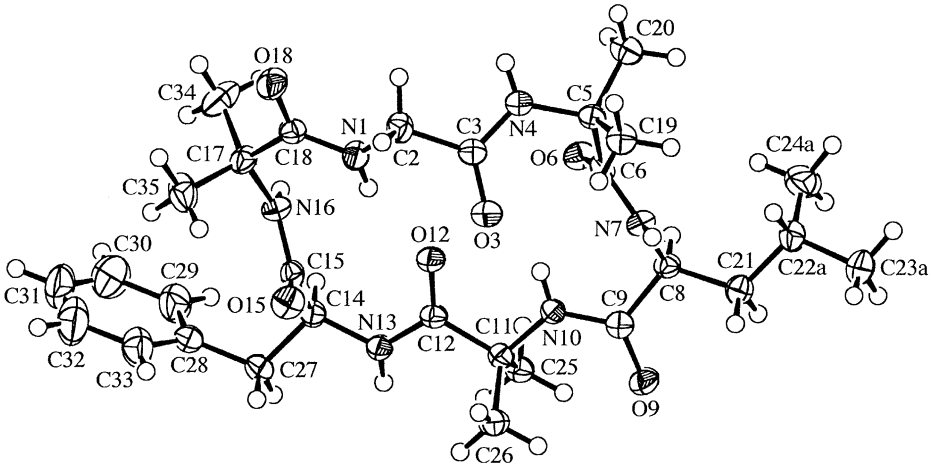


Figure 2. *ORTEP plot*[27] of the molecular structure of **1** (50% Probability ellipsoids, arbitrary numbering of atoms, only one of the disordered arrangements of the Leu side chain is shown).

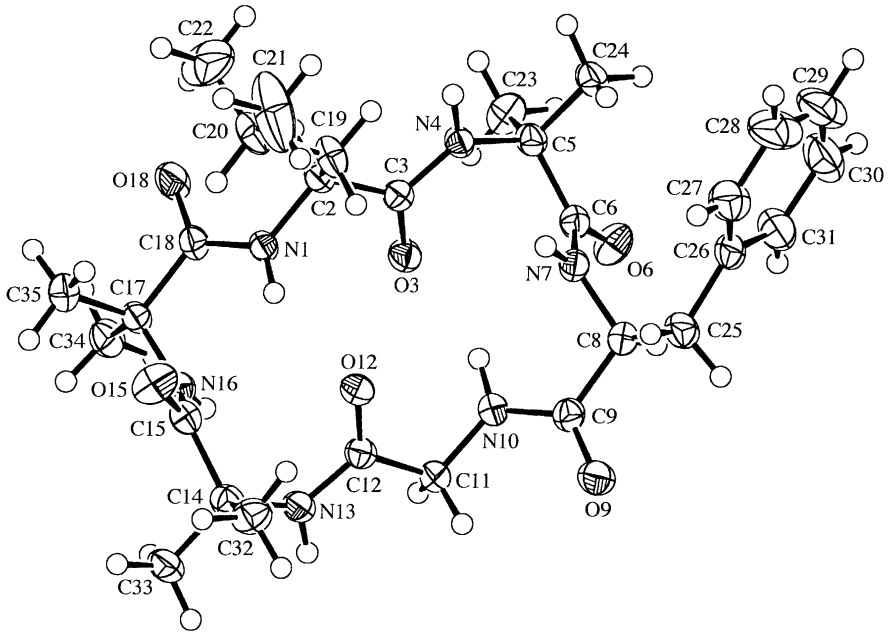


Figure 3. *ORTEP plot*[27] of the molecular structure of **2** (50% Probability ellipsoids, arbitrary numbering of atoms, solvent molecules omitted for clarity).

Table 2. Backbone torsion angles [°] for the crystal structures of **1** and **2**

1		Gly[1]	Aib[2]	Leu[3]	Aib[4]	Phe[5]	Aib[6]
	ϕ	−170.0(3)	+55.2(3)	−90.7(3)	−175.9(3)	−45.4(4)	+76.9(4)
	ψ	+119.6(3)	−130.4(3)	+42.6(3)	+178.6(2)	+127.2(3)	−7.7(4)
	ω	+178.2(2)	−164.7(2)	+166.1(2)	−171.8(2)	+169.1(2)	−178.1(3)
2		Leu[1]	Aib[2]	Phe[3]	Gly[4]	Aib[5]	Aib[6]
	ϕ	−113.0(3)	−57.1(3)	−113.3(3)	+117.8(3)	+56.4(3)	+93.8(3)
	ψ	−171.7(2)	−34.4(3)	+22.8(3)	+169.4(2)	+41.2(3)	−15.3(3)
	ω	−165.6(2)	−171.4(2)	−178.3(2)	+170.3(2)	+172.5(2)	−173.8(2)

in Figures 2 and 3. The isopropyl part of the Leu side chain of **1** is disordered over two almost equally occupied conformations, while the asymmetric unit of **2** contains one molecule of the cyclic peptide plus two water molecules, one disordered EtOH molecule and one disordered *i*-PrOH molecule. Two approximately equally occupied positions were modelled for each of the disordered solvent molecules. The backbone torsion angles of the cyclopeptides are summarized in Table 2 and the hydrogen bonding parameters in Tables 3 and 4.

Surprisingly, all three Aib residues of *cyclo*(Gly[1]-Aib[2]-Leu[3]-Aib[4]-Phe[5]-Aib[6]) (**1**) assume conformations in the nonhelical region of the *Ramachandran* diagram (Table 2). The deviation of the backbone conformation from the helical region is less pronounced at Aib[6]. The residue Aib[2] adopts a rare semiextended conformation with torsion angles ϕ, ψ almost identical to those previously reported for a cyclic hexapeptide having a disulfide linkage.[28] Interestingly, very similar ϕ, ψ values were also observed for one Aib residue in the linear tetrapeptide Boc-Leu-Aib-Phe-Aib-OMe, which was reported to form a continuous hydrogen-bonded supramolecular helix.[29] The residue Aib[4] adopts a fully extended conformation, so far known to be characteristic of the higher homologs of Aib, like α,α-diethylglycine (Deg),[30–32] and α,α-dipropylglycine (Dpg).[33,34] The torsion angles ϕ and ψ of the Phe and Aib[6] residues in the Aib[4]-Phe[5]-Aib[6]-Gly[1] sequence show values close to those for a type II β-turn with an intramolecular 1←4 hydrogen bond (N(1)–H…O(12))

Table 3. Hydrogen bonding parameters for *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**)

Donor D-H	Acceptor A	Distance [Å] D-H	Distance [Å] H…A	Distance [Å] D…A	Angle [°] D-H…A
N(1)–H(1)	O(12)	0.81(3)	2.34(3)	3.126(4)	163(3)
N(4)–H(4)	O(3[i])	0.84(3)	2.30(3)	3.131(4)	172(3)
N(7)–H(7)	O(18[ii])	0.94(3)	2.00(3)	2.877(3)	154(3)
N(10)–H(10)	O(12)	0.83(3)	2.17(3)	2.604(3)	113(3)
N(10)–H(10)	O(6)	0.83(3)	2.38(3)	3.083(3)	143(3)
N(13)–H(13)	O(6[iii])	0.87(3)	2.11(3)	2.972(3)	171(3)
N(16)–H(16)	O(9[iv])	0.94(3)	1.95(4)	2.867(3)	163(3)

Primed atoms refer to the molecule in the following symmetry-related positions: [i] $2-x, -1/2+y, 1/2-z$; [ii] $2-x, 1/2+y, 1/2-z$; [iii] $1-x, 1/2+y, 1/2-z$; [iv] $1-x, -1/2+y, 1/2-z$.

Table 4. Hydrogen bonding parameters for *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) (**2**)

Donor D-H	Acceptor A	Distance [Å] D-H	Distance [Å] H…A	Distance [Å] D…A	Angle [°] D-H…A
N(1)–H(1)	O(12)	0.87(4)	2.24(4)	3.042(3)	154(3)
N(4)–H(4)	O(44^{i})	0.89(4)	1.90(4)	2.782(3)	171(3)
N(7)–H(7)	O(38a)	0.89(4)	2.21(4)	2.92(1)	136(3)
N(7)–H(7)	O(38b)	0.89(4)	2.18(4)	2.87(1)	135(3)
N(10)–H(10)	O(3)	0.93(4)	2.18(4)	3.078(3)	161(3)
N(13)–H(13)	O(43)	0.88(4)	1.91(4)	2.787(3)	176(3)
N(16)–H(16)	O(42a)	0.73(3)	2.48(3)	3.10(1)	145(3)
N(16)–H(16)	O(42b)	0.73(3)	2.38(3)	2.99(1)	141(3)
O(38a)–H(381)	O(12)	0.84	1.91	2.75(2)	173
O(38b)–H(382)	O(12)	0.84	2.26	2.87(2)	129
O(42a)–H(421)	O(3)	0.84	2.15	2.79(2)	132
O(42b)–H(422)	O(3)	0.84	1.96	2.74(2)	154
O(43)–H(431)	O(15^{ii})	0.98(6)	1.83(6)	2.805(3)	174(4)
O(43)–H(432)	O(18^{iii})	0.79(5)	1.96(5)	2.750(3)	177(4)
O(44)–H(441)	O(6^{iv})	0.87(6)	1.89(6)	2.754(3)	171(5)
O(44)–H(442)	O(9)	0.95(5)	1.80(5)	2.734(3)	168(4)

Primed atoms refer to the molecule in the following symmetry-related positions: $^{i}-1+x, y, z$; $^{ii}1-x, -1/2+y, 2-z$; $^{iii}1+x, y, z$; $^{iv}1-x, 1/2+y, 1-z$.

involving the NH of Gly^1 and the C=O of Aib^4 (Tables 2 and 3). In contrast, the backbone conformation of the sequence Gly^1-Aib^2-Leu^3-Aib^4 cannot be strictly categorized. It could best be described as a distorted type II′ β-turn, with values for ϕ_{i+1} (+55.2(3)°), ψ_{i+1} (−130.4(3)°) and ϕ_{i+2} (−90.7(3)°) being close to the ideal values ($\phi_{i+1}=+(60\pm30)°$; $\psi_{i+1}=-(120\pm30)°$, $\phi_{i+2}=-(80\pm30)°$) for this type of turn, and ψ_{i+2} (+42.6(3)°) deviating largely from the ideal value ($\psi_{i+2}=0\pm50°$) (Table 2). The residue Aib^2 is obviously forced to assume the conformation of a D-amino acid as it prefers the $(i+1)$ position of a β-turn of type II′.[16] As a consequence of the large deviation of ψ_{i+2} from ideality, no 1←4 intramolecular hydrogen bond is observed between the NH of Aib^4 and C=O of Gly^1. However, the extended conformation of Aib^4 gives rise to an intramolecular hydrogen bond between the NH and C=O groups within this residue (N(10)–H…O(12), Table 3), which is unusual and has only infrequently been inferred from crystal structure data of some dipeptides.[17] Furthermore, the NH group of Aib^4 acts not only as a donor for C=O of Aib^4, but also as a donor for the carbonyl group of Aib^2, and is thus involved in inverse bifurcation.[35]

The cyclic peptide *cyclo*(Leu^1-Aib^2-Phe^3-Gly^4-Aib^5-Aib^6) (**2**) was found to possess a more regular structure with two fused β-turns stabilized by two intramolecular hydrogen bonds, one between C=O of Leu^1 and NH of Gly^4 (N(10)–H…O(3), Table 4) and the other between C=O of Gly^4 and NH of Leu^1 (N(1)–H…O(12)). Furthermore, the conformation of only one of the Aib residues, Aib^6, shows slight deviation from the helical region of the conformational space. The values of torsion angles ϕ and ψ reveal the presence of a type I β-turn across Leu^1-Aib^2-Phe^3-Gly^4 and a type I′ β-turn spanning the residues Gly^4-Aib^5-Aib^6-Leu^1 (Table 2).

2.3. Solution conformational analysis

The conformation of the cyclic hexapeptide *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**) in DMSO-d_6 solution has been determined by ^{1}H NMR spectroscopy. The structure calculation was performed by restrained molecular dynamics in torsion angle space by applying the simulated annealing protocol implemented in the program DYANA.[36] The NOE intensities were calibrated with the tools of the program, and yielded an input of 45 upper-distance limits (11 intra-residual, 29 sequential and 5 medium/long-range) (Tables 5–7). The final calculation was started with 100 randomized conformers, and a bundle of 20 DYANA conformers with the lowest target function was selected for structure analysis and visualization with the program MOLMOL.[37] The results of DYANA calculations for **1** are shown in Figure 4, and the observed average backbone torsion angles (ϕ, ψ) are listed in Table 8.

As is evident from Figure 4 and Table 8, **1** is well structured in solution and with a mean RMSD value of the backbone atoms of 0.3 Å very similar to the backbone conformation found in the crystal structure, although some torsion angles

Table 5. Intraresidual upper distance restraints derived from integration of ROESY cross-peak volumes for the cyclic peptide *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**)

Residue	Atom	Residue	Atom	Distance [Å]
Gly^1	HN	Gly^1	HA1	2.87
Leu^3	HN	Leu^3	HB2	2.77
Leu^3	HA	Leu^3	HB2	2.68
Leu^3	HA	Leu^3	HB3	2.62
Leu^3	HA	Leu^3	QD1	3.64
Leu^3	HA	Leu^3	QD2	5.69
Phe^5	HN	Phe^5	HA	2.83
Phe^5	HN	Phe^5	HB2	2.99
Phe^5	HN	Phe^5	HB3	3.27
Phe^5	HA	Phe^5	HB2	2.65
Phe^5	HA	Phe^5	HB3	2.71

Table 6. Sequential upper distance restraints derived from integration of ROESY cross-peak volumes for the cyclic peptide *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**)

Residue	Atom	Residue	Atom	Distance [Å]
Gly^1	HN	Aib^2	HN	4.69
Gly^1	HN	Aib^6	HN	3.24
Gly^1	HN	Aib^6	QB1	4.74
Gly^1	HN	Aib^6	QB2	5.34
Gly^1	HA1	Aib^2	HN	2.83
Gly^1	HA2	Aib^2	HN	2.71
Aib^2	HN	Leu^3	HN	3.42
Aib^2	QB1	Leu^3	HN	4.55
Aib^2	QB1	Leu^3	HA	6.38
Aib^2	QB1	Leu^3	QD1	7.56
Aib^2	QB1	Leu^3	QD2	7.56
Aib^2	QB2	Leu^3	QD1	7.57
Aib^2	QB2	Leu^3	QD2	7.57
Leu^3	HN	Aib^4	HN	3.11
Leu^3	HA	Aib^4	HN	2.62
Leu^3	HA	Aib^4	QB1	5.88
Leu^3	HB2	Aib^4	HN	3.79
Leu^3	HB3	Aib^4	HN	3.83
Aib^4	QB1	Phe^5	HA	6.04
Aib^4	QB1	Phe^5	QD	8.66
Aib^4	QB2	Phe^5	HN	4.10
Aib^4	QB2	Phe^5	QD	8.67
Phe^5	HN	Aib^6	HN	4.07
Phe^5	HA	Aib^6	HN	2.40
Phe^5	HA	Aib^6	QB2	6.54
Phe^5	HB2	Aib^6	HN	4.82
Phe^5	HB3	Aib^6	HN	4.29
Phe^5	QD	Aib^6	QB2	8.29
Phe^5	QE	Aib^6	QB2	8.67

Table 7. Medium and long range upper distance restraints derived from integration of ROESY cross-peak volumes for the cyclic peptide **1**

Residue	Atom	Residue	Atom	Distance [Å]
Gly^1	HN	Aib^4	HN	4.20
Gly^1	HN	Aib^4	HB1	5.73
Gly^1	HN	Phe^5	HN	4.14
Gly^1	HN	Phe^5	HA	3.61
Aib^4	QB1	Aib^6	HN	6.54

deviate significantly. In particular, the residue Aib^4 assumes almost identical, for an Aib residue unexpected, extended conformations in both the solid state and in the solution. The average conformer exhibits two β-turns, one type I-like β-turn centered at Aib^2-Leu^3 and one type II-like β-turn across Aib^4-Phe^5-Aib^6-Gly^1. The large ^3J(HN, HC(α)) coupling constant of 9 Hz at Leu^3 which correlates to a torsion angle ϕ around $-100°$ provide further support for the occurrence of the type I β-turn in solution. An analysis of the hydrogen-bonding patterns using the final NMR coordinates shows a significant population of intramolecular hydrogen bonding between the carbonyl group of Gly^1 and the NH of the Aib^4 residue, which is contrary to the observation found in the crystal structure where a hydrogen bond is formed between the CO group of Aib^4 and the NH group of Gly^1.

3. Conclusion

In conclusion, we have shown that it is possible to cyclize hexapeptides containing three constrained Aib residues, two rather large proteinogenic amino acid residues (Leu, Phe) and only one Gly residue as a turn-inducing element, in good yields. Since *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**) and *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) (**2**) have been obtained in similar overall cyclization yields, being 24–53% for **1** and 16–48% for **2**, the choice of coupling reagent apparently played a more important role in the cyclization than the sequence of the linear precursor. In addition, the coupling reagents PyAOP and DEPC proved to be superior to HATU. The structures of **1** and **2** were examined in the solid state by X-ray crystallography in order to gain information about the conformational preferences of Aib residues incorporated into cyclic peptides. A detailed comparison of the crystal structures of **1** and **2** with those obtained previously[7] for *cyclo*(Gly-Aib-Aib-Gly-Aib-Phe) and *cyclo*(Gly-(*S*)-Phe(2Me)-Aib-Gly-Aib-Phe), reveals severe conformational restraints imposed on the peptide backbone of cyclic hexapeptide **1** consisting of alternating Aib and proteinogenic amino acid residues. Thus, all three Aib residues of **1** assume torsion angles well outside the helical region of the conformational space, which is highly uncommon. It appears that the conformational constraint is less pronounced in the other three cyclopeptides having two adjoining Aib residues or one Aib residue adjacent to another α,α-disubstituted amino acid residue such as Phe(2Me) (Phe(2Me)=α-methylphenylalanine). Each of

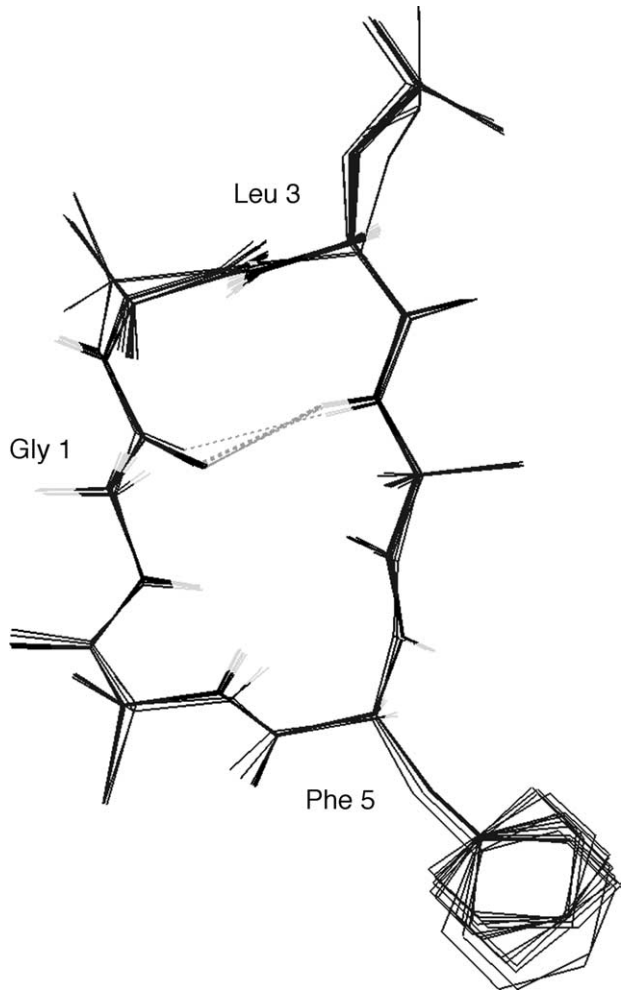


Figure 4. Superimposition of the final 14 NMR structures for **1**.

Table 8. Observed average backbone torsion angles for the cyclic peptide **1** as obtained from the final 14 NMR structures

Residue	ϕ	ψ
Gly[1]	−105.2	+170.0
Aib[2]	−63.8	−26.5
Leu[3]	−123.6	+31.2
Aib[4]	−162.9	−165.3
Phe[5]	−84.6	+88.1
Aib[6]	+80.9	+21.1

these cyclic hexapeptides possesses only one Aib residue that shows slight deviation of torsion angles from the helical region of the conformational space.

4. Experimental

4.1. General

Solvents were purified by standard procedures. Thin-layer chromatography (TLC): Merck TLC aluminium sheets, silica gel 60 F_{254}. Column chromatography (CC): Uetikon-Chemie 'Chromatographiegel' C-560. Mp: Büchi 510 apparatus; uncorrected. IR Spectra: Perkin–Elmer-1600 FT-IR spectrophotometer; in KBr; absorptions in cm^{-1}. ^1H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra: Bruker ARX-300 instrument; ^1H (600 MHz) and ^{13}C NMR (150.9 MHz) spectra of cyclic peptides: Bruker DRX-600 instrument; in (D_6)DMSO at 300 K unless otherwise stated; δ in ppm, coupling constants J in Hz. ROESY spectra were measured with a mixing time of 300 ms. Acquisition parameters of the ROESY experiment of **1**: F_1: ND0 1, TD 512, SFO1 600.1325 MHz, FIDRES 11.252340 Hz, SW 9.600 ppm, FnMODE undefined; F_2: TD 2048, NS 16, SWH 5787.037 Hz, AQ 0.1770836 s, RG 32, d0 0.000003 s, D1 3.000000 s, d11 0.030000 s, d12 0.000020 s. Acquisition parameters of the ROESY experiment of **2**: F_1: ND0 1, TD 512, SFO1 600.1325 MHz, FIDRES 10.783298 Hz, SW 9.200 ppm, FnMODE undefined; F_2: TD 2048, NS 32, SWH 5530.974 Hz, AQ 0.1852796 s, RG 128, d0 0.000003 s, D1 3.000000 s, d11 0.030000 s, d12 0.000020 s. MS: Finnigan SSQ-700 or MAT-90 instrument for CI; Finnigan TSQ-700 triple quadrupole spectrometer for ESI; *m/z* (rel.%). Abbreviations: DEPC: diethylphosphorocyanidate, DIEA: *N*-ethyl-*N*,*N*-diisopropylamine, HATU: *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HOAt: 1-hydroxy-7-azabenzotriazole, PyAOP: (7-azabenzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate, PyBOP: (1*H*-benzotriazol-1-yloxy)-tris(pyrrolidino) phosphonium hexafluorophosphate.

General Procedure A (GP A). To a solution of a Z-protected peptide in MeOH was added Pd/C (10% on activated charcoal) and the mixture was hydrogenated overnight under atmospheric pressure using an H_2-filled balloon. The catalyst was removed by filtration through a pad of celite and the solvent evaporated under reduced pressure. The crude product was further purified by filtration through a short column of SiO_2, dried under vacuum and used directly in the next reaction step.

General Procedure B (GP B). To a solution of an *N*-protected peptide acid (or *N*-protected amino acid) in abs. CH_2Cl_2 (or CH_2Cl_2/MeCN mixture) were added the amino component (1.0 or 1.1 equiv), PyAOP (or PyBOP, 1.1 equiv), and DIEA (2 equiv without and 3 equiv with hydrochloride salts present). The mixture was stirred at rt under N_2 until the starting material was consumed (TLC). The solvent was then evaporated, the residue was dissolved in EtOAc and washed with 5% aq $KHSO_4$ solution, 5% aq $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), concentrated, purified by CC and dried under high vacuum.

General Procedure C (HATU-mediated Cyclization) (GP C). The free linear hexapeptide was dissolved in abs. DMF (0.7 or 1.5 mM) and cooled to 0 °C in an ice bath. To the solution was added HATU (3 equiv), HOAt (3 equiv, 0.5 M solution in DMF) and DIEA (1% v/v) under stirring. The solution was kept at 0 °C for 2 h and at rt for 3 days. The solvent was removed under reduced pressure, the residue dissolved in EtOAc and washed with 1 M HCl solution, water, and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude cyclopeptide was further purified by CC.

General Procedure D (DEPC-mediated Cyclization) (GP D). The free linear hexapeptide was dissolved in abs. DMF

(1.5 mM) and the solution was cooled to 0 °C in an ice bath. Then, a solution of 5 equiv of DEPC in abs. DMF (1 ml) was added under stirring, and DIEA (1% v/v) was added slowly over a period of 15 min. The solution was warmed to rt and stirred. The addition of DEPC (2.5 equiv) was repeated after 2 and 4 days, and the reaction mixture was stirred for an additional 2 days. The solvent was then evaporated under reduced pressure, the residue was taken up in EtOAc and washed with 5% aq $KHSO_4$ solution, 5% aq $NaHCO_3$ solution, and brine. The organic phase was then dried ($MgSO_4$) and concentrated to give the crude cyclohexapeptide, which was purified by CC.

General Procedure E (PyAOP-mediated Cyclization) (GP E). The free linear hexapeptide was dissolved in abs. DMF (0.6–1.0 mM) under stirring. Then, PyAOP (3 or 5 equiv), HOAt (3 or 5 equiv, 0.5 M solution in DMF) and DIEA were added at rt and the solution was stirred at rt for an additional 3 days. The solvent was then removed under reduced pressure, the residue dissolved in EtOAc and washed with 10% citric acid solution, 5% $NaHCO_3$ solution, and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil which was purified by CC.

4.2. Preparation of *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (1)

4.2.1. *tert*-Butyl *N*-[(benzyloxy)carbonyl]-(*S*)-phenylalanyl-dimethylglycinate (Z-Phe-Aib-O*t*Bu) (3). Z-Phe-OH (0.6 g, 2.0 mmol) was coupled with HCl·H-Aib-O*t*Bu (0.431 g, 2.2 mmol), using PyAOP (1.147 g, 2.2 mmol) and DIEA (0.775 g, 6.0 mmol) in CH_2Cl_2/MeCN (6/4 ml) according to GP B. Reaction time: 20 h at rt. Purification of the crude product by CC (SiO_2, EtOAc/hexane 15:10) afforded 0.798 g (91%) of dipeptide **3**. White powder. Mp 119.5–121.0 °C. IR: 3325s, 3236m, 3065m, 2979m, 2948m, 1727s, 1708s, 1660s, 1544s, 1498m, 1470m, 1455m, 1384m, 1370m, 1291s, 1260s, 1235s, 1215m, 1147s, 1085w, 1065m, 1044m, 1028m, 912w, 853w, 757m, 740m, 700s. ^{1}H NMR: 8.23 (s, NH of Aib); 7.42 (d, J= 8.95 Hz, NH of Phe); 7.34–7.19 (m, 10 arom. H); 4.94 (br s, PhCH_2O); 4.35–4.20 (m, CH(2) of Phe); 2.93–2.92, 2.77–2.73 (2m, CH_2(3) of Phe); 1.35 (s, Me_3C); 1.33, 1.30 (2s, 2Me of Aib). ^{13}C NMR: 172.7, 170.6 (2s, 2 CO); 155.6 (s, CO (urethane)); 138.0, 136.9 (2s, 2 arom. C); 129.1, 128.1, 127.8, 127.5, 127.2, 126.1 (6d, 10 arom. CH); 79.3 (s, Me_3C); 64.9 (t, PhCH_2O); 55.6 (d, C(2) of Phe); 55.3 (s, C(2) of Aib); 37.6 (t, C(3) of Phe); 27.3 (q, Me_3C); 24.6 (q, 2Me of Aib). ESI-MS (NaI+MeOH): 463 (100, [M+Na]$^+$). Anal. calcd for $C_{25}H_{32}N_2O_5$ (440.54): C 68.16, H 7.32, N 6.36; found: C 68.06, H 7.20, N 6.25.

4.2.2. *tert*-Butyl *N*-[(benzyloxy)carbonyl]-(*S*)-leucyl-dimethylglycyl-(*S*)-phenylalanyl-dimethylglycinate (Z-Leu-Aib-Phe-Aib-O*t*Bu) (4). Z-Phe-Aib-O*t*Bu (**3**) (0.475 g, 1.08 mmol) was *N*-deprotected by following GP A (H_2, 55 mg Pd/C, 15 ml MeOH, overnight). The crude product was filtered through a short SiO_2-column with EtOAc/MeOH (15:1) and dried under vacuum to give 0.328 g (99%) H-Phe-Aib-O*t*Bu as a white foam, which was used directly in the next step.

Z-Leu-Aib-OH[9] (0.375 g, 1.07 mmol) was coupled with H-Phe-Aib-O*t*Bu (0.328 g, 1.07 mmol), using PyAOP (0.56 g, 1.1 mmol) and DIEA (0.276 g, 2.14 mmol) in abs. CH_2Cl_2 (10 ml) according to GP B. Reaction time: 20 h at rt. Purification by CC (SiO_2, EtOAc/hexane 20:1) yielded 0.556 g (81%) of tetrapeptide **4** as a white foam. IR: 3325s, 3064w, 3032m, 2979m, 2960m, 2936m, 2872w, 1735s, 1665s, 1535s, 1469m, 1455m, 1385m, 1367m, 1258s, 1222s, 1148s, 1081w, 1029m, 940w, 850w, 788w, 752m, 698m. ^{1}H NMR (CD_3OD): 7.34–7.16 (m, 10 arom. H); 5.12 (s, PhCH_2O); 4.48–4.46, 4.05–3.95 (2m, CH(2) of Leu and CH(2) of Phe); 3.32–3.29 (m, 1H of CH_2(3) of Phe); 2.94 (dd, J=14.2, 10.6 Hz, 1H of CH_2(3) of Phe); 1.80–1.51 (m, CH_2(3) and CH(4) of Leu); 1.44, 1.43, 1.32, 1.16 (4s, 4Me of 2Aib and Me_3C); 0.96, 0.92 (2d, J=6.6 Hz, 2Me(5) of Leu). ^{13}C NMR (CD_3OD): 176.4, 175.3, 174.9, 172.5 (4s, 4 CO); 158.9 (s, CO (urethane)); 139.1, 137.9 (2s, 2 arom. C); 130.1, 129.4, 129.3, 129.0, 128.6, 127.5 (6d, 10 arom. CH); 81.9 (s, Me_3C); 67.7 (t, PhCH_2O); 57.7, 57.6 (2s, 2 C(2) of 2Aib); 55.9 (d, C(2) of Phe); 41.3, 37.8 (2t, C(3) of Phe and C(3) of Leu); 28.1 (q, Me_3C); 25.7 (d, C(4) of Leu); 25.4, 24.9, 24.7, 23.1, 22.1 (5q, 4Me of 2Aib and 2Me(5) of Leu); C(2) of Leu not detectable. ESI-MS (NaI+MeOH): 661 (100, [M+Na]$^+$). Anal. calcd for $C_{35}H_{50}N_4O_7$ (638.80): C 65.81, H 7.89, N 8.77; found: C 65.66, H 8.04, N 8.70.

4.2.3. *tert*-Butyl *N*-[(benzyloxy)carbonyl]-glycyl-dimethylglycyl-(*S*)-leucyl-dimethylglycyl-(*S*)-phenylalanyl-dimethylglycinate (Z-Gly-Aib-Leu-Aib-Phe-Aib-O*t*Bu) (5). Z-Leu-Aib-Phe-Aib-O*t*Bu (**4**) (0.527 g, 0.82 mmol) was *N*-deprotected according to GP A (H_2, 55 mg Pd/C, 10 ml MeOH, overnight). The crude product was filtered through a short SiO_2-column with EtOAc/MeOH (17:1) and dried under vacuum to afford 0.4 g (96%) of H-Leu-Aib-Phe-Aib-O*t*Bu as a white foam. This material (0.4 g, 0.79 mmol) was coupled with Z-Gly-Aib-OH[7] (0.234 g, 0.79 mmol) by following GP B, using PyAOP (0.521 g, 1.0 mmol) and DIEA (0.255 g, 1.6 mmol) in abs. CH_2Cl_2 (10 ml). Reaction time: 20 h at rt. CC (SiO_2, EtOAc/hexane/MeOH 10:7:1) gave 0.576 g (93%) of hexapeptide **5** as a white foam. IR: 3322s, 3065w, 3033w, 2982m, 2959m, 2873w, 1664s, 1534s, 1456m, 1387m, 1368m, 1261m, 1151s, 1082w, 1051w, 979w, 852s, 740w, 699m. ^{1}H NMR (CD_3OD): 7.35–7.15 (m, 6 arom. H); 5.17–5.05 (m, PhCH_2O); 4.42–4.39, 4.15–3.70 (2m, CH(2) of Phe, CH(2) of Leu and CH_2(2) of Gly); 3.35–2.80 (m, CH_2(3) of Phe); 1.90–1.47 (m, CH_2(3) and CH(4) of Leu); 1.45, 1.44, 1.38, 1.18 (4s, 6Me of 3Aib and Me_3C); 0.94, 0.89 (2d, J=6.3 Hz, 2Me(5) of Leu). ^{13}C NMR (CD_3OD): 177.1, 177.0, 174.9, 174.5, 172.8, 172.1 (6s, 6 CO); 159.5 (s, CO (urethane)); 139.3, 137.9 (2s, 2 arom. C); 130.1, 129.5, 129.3, 129.1, 128.6, 127.5 (6d, 10 arom. CH); 81.8 (s, Me_3C); 67.8 (t, PhCH_2O); 57.9, 57.8, 57.7 (3s, 3 C(2) of 3Aib); 56.5, 54.1 (2d, C(2) of Phe and C(2) of Leu); 45.4, 39.9, 37.5 (3t, C(2) of Gly, C(3) of Phe and C(3) of Leu); 28.1 (q, Me_3C); 26.1 (d, C(4) of Leu); 26.5, 26.0, 25.9, 25.5, 24.9, 24.3, 23.7, 21.5 (8q, 6Me of 3Aib and 2Me(5) of Leu). ESI-MS (NaI+MeOH): 804 (100, [M+Na]$^+$).

4.2.4. *Cyclo*(Gly^1-Aib^2-Leu^3-Aib^4-Phe^5-Aib^6) (1). Z-Gly-Aib-Leu-Aib-Phe-Aib-O*t*Bu (**5**) (0.555 g, 0.71 mmol) was *N*-deprotected according to GP A (H_2, 60 mg Pd/C, 10 ml MeOH, 20 h). Thus, 0.417 g (91%) of H-Gly-Aib-Leu-Aib-Phe-Aib-O*t*Bu were obtained as a white foam, which was

dissolved in abs. CH_2Cl_2 (20 ml), and TFA (20 ml) was added at rt. The mixture was stirred for 6 h. Excess TFA was removed under reduced pressure, followed by addition and evaporation of two portions of CH_2Cl_2 (10 ml). Upon drying under high vacuum, 0.461 g of the free linear hexapeptide were obtained as its TFA salt in quantitative yield.

HATU-mediated cyclization: 0.121 g (0.17 mmol) of H-Gly-Aib-Leu-Aib-Phe-Aib-OH·TFA were dissolved in abs. DMF (112 ml) and subjected to cyclization according to GP C, with HATU (0.194 g, 0.51 mmol), HOAt (69 mg, 0.51 mmol), and DIEA (1.2 ml). Reaction time: 1 day. Purification by CC (SiO_2, CH_2Cl_2/MeOH 10:1, EtOAc/MeOH 15:1) afforded 23 mg (24%) of pure cyclohexapeptide **1**.

DEPC-mediated cyclization: 0.121 g (0.17 mmol) of the free linear peptide TFA salt were dissolved in abs. DMF (112 ml) and the cyclization was performed according to GP D using DEPC (0.139 g, 0.85 mmol) and DIEA (1.2 ml). After 2 and 4 days of stirring, additional DEPC (69 mg, 0.425 mmol) was added. Reaction time: 6 days. The obtained yellow oil was purified by CC (SiO_2, EtOAc/MeOH 15:1, performed twice) to provide 51 mg (53%) of pure **1**.

PyAOP-mediated cyclization: 0.121 g (0.17 mmol) of the free linear peptide TFA salt were dissolved in abs. DMF (170 ml) and treated with PyAOP (0.441 g, 0.85 mmol), HOAt (0.116 g, 0.85 mmol), and DIEA (1.7 ml) following GP E. Purification by CC (SiO_2, CH_2Cl_2/MeOH 17:1, performed twice) afforded 30 mg (31%) of pure **1**. White powder. Mp (dec.) 284–286 °C. IR: 3317s, 3061w, 2968m, 2871w, 1704m, 1650s, 1536s, 1457m, 1390m, 1367m, 1264m, 1219m, 1188m, 1080w, 1029w, 744w, 698m. ^{1}H NMR: 8.22 (s, NH of Aib^2); 8.05 (s, NH of Aib^6); 7.80 (d, J=8.9 Hz, NH of Leu^3); 7.62 (d, J=7.6 Hz, NH of Phe^5); 7.55 (s, NH of Aib^4); 7.27–7.16 (m, 5 arom. H of Phe^5, NH of Gly^1); 4.33–4.27 (m, CH(2) of Leu^3 and CH(2) of Phe^5); 3.77 (dd, J=17.0, 5.8 Hz, 1H of CH_2(2) of Gly^1); 3.70 (dd, J=17.0, 3.2 Hz, 1H of CH_2(2) of Gly^1); 2.94 (dd, J=13.5, 7.7 Hz, 1H of CH_2(3) of Phe^5); 2.85 (dd, J=13.5, 7.2 Hz, 1H of CH_2(3) of Phe^5); 1.62–1.47 (m, CH_2(3) and CH(4) of Leu^3); 1.46, 1.38 (2s, 2Me of Aib^4); 1.37, 1.29 (2s, 2Me of Aib^2); 1.26, 1.19 (2s, 2Me of Aib^6); 0.88, 0.82 (2d, J=6.4 Hz, 2Me(5) of Leu^3). ^{13}C NMR: 174.2 (s, CO of Aib^4); 174.0 (s, CO of Aib^2); 173.7 (s, CO of Aib^6); 171.3 (s, CO of Leu^3); 170.0 (s, CO of Phe^5); 168.2 (s, CO of Gly^1); 137.7 (s, 1 arom. C of Phe^5); 129.3, 128.0, 126.2 (3d, 5 arom. CH of Phe^5); 56.4 (s, C(2) of Aib^4); 56.2 (s, C(2) of Aib^2); 56.0 (s, C(2) of Aib^6); 55.1 (d, C(2) of Phe^5); 50.9 (d, C(2) of Leu^3); 42.8 (t, C(2) of Gly^1); 40.2 (t, C(3) of Leu^3); 36.6 (t, C(3) of Phe^5); 27.0 (q, 1Me of Aib^6); 26.9 (q, 1Me of Aib^2); 25.9 (q, 1Me of Aib^4); 24.3 (d, C(4) of Leu^3); 23.47 (q, 1Me of Aib^2); 23.38 (q, Me(5) of Leu^3); 23.14 (q, 1Me of Aib^4); 23.09 (q, 1Me of Aib^6); 21.1 (q, Me(5) of Leu^3). ESI-MS (NaI+MeOH): 595 (100, $[M+Na]^+$). Anal. calcd for $C_{29}H_{44}N_6O_6$ (572.71): C 60.82, H 7.74, N 14.67; found: C 60.60, H 7.73, N 14.56.

4.3. Preparation of *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) (2)

4.3.1. *tert*-Butyl *N*-[(benzyloxy)carbonyl]-(*S*)-leucyl-dimethylglycyl-(*S*)-phenylalaninate (Z-Leu-Aib-Phe-O*t*Bu) (6). Z-Leu-Aib-OH[9] (0.25 g, 0.71 mmol) was coupled with HCl·H-Phe-O*t*Bu (0.202 g, 0.78 mmol) in abs. CH_2Cl_2/MeCN (6/2 ml) according to GP B, using PyBOP (0.371 g, 0.71 mmol) and DIEA (0.276 g, 2.14 mmol, overnight). Purification of the crude product by CC (SiO_2, CH_2Cl_2/MeOH 17:1, performed twice) afforded 0.362 g (92%) of tripeptide **6** as a white foam. IR: 3401m, 3368m, 3237m, 3033w, 2973m, 2951m, 1870w, 1720s, 1663s, 1651s, 1515s, 1457m, 1439m, 1389w, 1367m, 1246s, 1220m, 1166m, 1118w, 1040m, 861w, 846w, 780w, 755w, 743w, 700m. ^{1}H NMR: 8.05 (br s, NH of Aib); 7.52–7.48 (m, NH of Leu and NH of Phe); 7.33–7.17 (m, 10 arom. H); 5.06–4.95 (m, PhCH_2O), 4.34–4.31, 4.00–3.97 (2m, CH(2) of Phe and CH(2) of Leu); 2.96–2.93 (m, CH_2(3) of Phe); 1.70–1.31 (m, CH_2(3) and CH(4) of Leu, 2Me of Aib and Me_3C); 0.88–0.84 (m, 2Me(5) of Leu). ^{13}C NMR: 173.6, 171.7, 170.1 (3s, 3CO); 156.0 (s, CO (urethane)); 137.2, 136.8 (2s, 2 arom. C); 129.0, 128.1, 127.9, 127.6, 127.4, 126.3 (6d, 10 arom. CH); 80.5 (s, Me_3C); 65.2 (t, PhCH_2O); 55.8 (s, C(2) of Aib); 54.2, 53.3 (2d, C(2) of Leu and C(2) of Phe); 40.0, 36.8 (2t, C(3) of Leu and C(3) of Phe); 27.4 (q, Me_3C); 24.0 (d, C(4) of Leu); 25.5, 23.8, 22.8, 21.4 (4q, 2Me of Aib and 2Me(5) of Leu). ESI-MS (NaI+MeOH): 576 (100, $[M+Na]^+$). Anal. calcd for $C_{31}H_{43}N_3O_6$ (553.69): C 67.24, H 7.83, N 7.59; found: C 67.23, H 7.82, N 7.54.

4.3.2. Benzyl *N*-((*S*)-1-{[(1,1-dimethyl-2-{[1-(*S*)-benzyl-2-({2-[(1,1-dimethyl-2-{[1,1-dimethyl-2-(methylphenylamino)-2-oxoethyl]amino}-2-oxoethyl)amino]-2-oxoethyl}amino)-2-oxoethyl]amino}-2-oxoethyl)amino]oxomethyl}-3-methylbutyl) carbamate (Z-Leu-Aib-Phe-Gly-Aib-Aib-N(Me)Ph) (8). Z-Leu-Aib-Phe-O*t*Bu (**6**) (0.7 g, 1.26 mmol) was dissolved in CH_2Cl_2 (15 ml), TFA was added (15 ml), and the mixture was stirred for 6 h at rt. The solvent was then evaporated and the crude product filtered through a short SiO_2-column using CH_2Cl_2/MeOH (12:1) to give 0.586 g (93%) of Z-Leu-Aib-Phe-OH as a white foam, which was used directly in the next reaction.

Z-Gly-Aib-Aib-N(Me)Ph (**7**)[7] (0.234 g, 0.5 mmol) was *N*-deprotected following GP A (H_2, 25 mg Pd/C, 6 ml MeOH, overnight). The crude product was dried under vacuum to give 0.159 g (95%) of H-Gly-Aib-Aib-N(Me)Ph, which was used in the next reaction step without further purification.

The coupling of Z-Leu-Aib-Phe-OH (0.215 g, 0.43 mmol) with H-Gly-Aib-Aib-N(Me)Ph (0.159 g, 0.48 mmol) in abs. CH_2Cl_2 (6 ml) was achieved according to GP B, using PyAOP (0.26 g, 0.5 mmol) and DIEA (0.129 g, 1.0 mmol, overnight). Purification by CC (SiO_2, CH_2Cl_2/MeOH 20:1) afforded 0.21 g (60%) of hexapeptide **8** as a white foam. IR: 3309s, 3062w, 3032m, 2957m, 2872w, 1662s, 1594m, 1533s, 1455s, 1389m, 1364m, 1332m, 1266m, 1221m, 1173m, 1118m, 1091m, 1045w, 1028w, 922w, 741w, 704m. ^{1}H NMR (CD_3OD): 7.40–7.16 (m, 15 arom. H); 5.14–4.99 (m, PhCH_2O); 4.05–3.59 (m, CH(2) of Leu, CH(2) of Phe and CH_2(2) of Gly); 3.35–2.90 (m, MeN and CH_2(3) of Phe); 1.75–1.46 (m, CH_2(3) and CH(4) of Leu, 4Me of 2Aib); 1.30, 1.27 (2s, 2Me of Aib); 0.96–0.91 (m, 2Me(5) of Leu). ^{13}C NMR (CD_3OD): 177.0, 176.2, 176.1, 175.4,

174.4, 171.3 (6s, 6CO (amide)); 158.5 (s, CO (urethane)); 139.3, 138.1 (2s, 3 arom. C); 130.2, 130.1, 129.9, 129.4, 129.0, 128.5, 128.4, 128.2, 127.6 (9d, 15 arom. CH); 67.6 (t, Ph*C*H_2O); 58.6, 58.3, 57.7 (3s, 3 C(2) of 3Aib); 57.1, 55.3 (2d, C(2) of Leu and C(2) of Phe); 44.8, 41.3 (2t, C(3) of Leu and C(2) of Gly); 41.27 (q, MeN); 36.4 (t, C(3) of Phe); 25.7 (d, C(4) of Leu); 26.3, 25.3, 24.7, 23.2, 22.1 (5q, 6Me of 3Aib and 2Me(5) of Leu). ESI-MS (NaI+MeOH): 837 (100, $[M+Na]^+$). Anal. calcd for $C_{44}H_{59}N_7O_8 \cdot 1/3H_2O$ (819.99): C 64.45, H 7.33, N 11.96; found: C 64.35, H 7.36, N 11.96.

4.3.3. *cyclo*(Leu[1]-Aib[2]-Phe[3]-Gly[4]-Aib[5]-Aib[6]) (2). Peptide **8** (0.42 g, 0.52 mmol) was dissolved in MeCN (3 ml) and then 3 ml of 6 N HCl were added dropwise. The mixture was stirred at rt overnight. The MeCN was evaporated under reduced pressure and 2 N HCl (3 ml) was added. The product was extracted with CH_2Cl_2, the organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. After drying under vacuum, 0.369 g (98%) of Z-Leu-Aib-Phe-Gly-Aib-Aib-OH were obtained as a white foam. Then, 0.318 g (0.44 mmol) of this compound were *N*-deprotected according to GP A (H_2, 35 mg Pd/C, 6 ml MeOH, 20 h). After drying under vacuum, 0.241 g (93%) of the free linear hexapeptide were obtained as a pale yellow foam, which was used in the cyclization step without further purification.

HATU-mediated cyclization: 84 mg (0.14 mmol) of the free linear hexapeptide were dissolved in abs. DMF (200 ml) and subjected to macrolactamization according to GP C, with HATU (0.162 g, 0.43 mmol), HOAt (58 mg, 0.43 mmol), and DIEA (2 ml). Reaction time: 3 days. Purification by CC (SiO_2, CH_2Cl_2/MeOH 12:1, performed twice) afforded 13 mg (16%) of pure cyclohexapeptide **2** as a white foam.

DEPC-mediated cyclization: 88 mg (0.15 mmol) of the free linear precursor were dissolved in abs. DMF (100 ml) and the cyclization was performed according to GP D, using DEPC (0.141 g, 0.75 mmol) and DIEA (1 ml). After 2 and 4 days, additional DEPC (60.5 mg, 0.375 mmol) was added to the stirred mixture. Reaction time: 6 days. The obtained yellow oil was purified by CC (SiO_2, CH_2Cl_2/MeOH 14:1, performed trice) to afford 28 mg (33%) of pure **2** as a white foam.

PyAOP-mediated cyclization: 64 mg (0.11 mmol) of the free linear precursor were dissolved in abs. DMF (180 ml) and treated with PyAOP (0.169 g, 0.32 mmol), HOAt (44 mg, 0.32 mmol) and DIEA (1.8 ml) by following GP E. Purification by CC (SiO_2, CH_2Cl_2/MeOH 12:1, performed thrice) yielded 30 mg (48%) of pure **2** as a white foam. IR: 3327s, 3030w, 2957m, 2871w, 1657s, 1534s, 1469m, 1455m, 1385m, 1365m, 1277m, 1225m, 1179m, 1030w, 945w, 820w, 748w, 702m. ^{1}H NMR: 8.28 (s, NH of Aib[5]); 8.14 (s, NH of Aib[2]); 7.43 (br s, NH of Gly[4]); 7.41 (d, J=9.7 Hz, NH of Leu[1]); 7.39 (s, NH of Aib[6]); 7.32 (d, J=9.0 Hz, NH of Phe[3]); 7.24–7.14 (m, 5 arom. H of Phe[3]); 4.59–4.55 (m, CH(2) of Phe[3]); 4.28–4.20 (m, CH(2) of Leu[1] and 1H of CH_2(2) of Gly[4]); 3.62–3.59 (m, 1H of CH_2(2) of Gly[4]); 3.31–3.28 (m, 1H of CH_2(3) of Phe[3]); 2.93–2.89 (m, 1H of CH_2(3) of Phe[3]); 1.88–1.83 (m, 1H of CH_2(3) of Leu[1]); 1.72–1.68 (m, CH(4) of Leu[1]); 1.60–1.55 (m, 1H of CH_2(3) of Leu[1]); 1.43 (s, Me of Aib[6]); 1.31, 1.30 (2s, 2Me of Aib[5]); 1.23 (s, Me of Aib[6]); 1.12, 1.03 (2s, 2Me of Aib[2]); 0.899, 0.897 (2d, J=6.4, 6.8 Hz, 2Me(5) of Leu[1]). ^{13}C NMR: 173.5 (s, CO of Aib[2]); 173.2 (s, CO of Aib[5]); 173.0 (s, CO of Aib[6]); 172.9 (s, CO of Leu[1]); 170.7 (s, CO of Phe[3]); 169.1 (s, CO of Gly[4]); 138.6 (s, 1 arom. C of Phe[3]); 128.9, 127.9, 126.0 (3d, 5 arom. CH of Phe[3]); 56.9 (s, C(2) of Aib[6]); 56.3 (s, C(2) of Aib[5]); 55.9 (s, C(2) of Aib[2]); 53.2 (d, C(2) of Phe[3]); 50.1 (d, C(2) of Leu[1]); 41.2 (t, C(2) of Gly[4]); 40.4 (t, C(3) of Leu[1]); 35.5 (t, C(3) of Phe[3]); 28.0 (q, Me of Aib[6]); 26.1 (q, Me of Aib[5]); 25.7 (q, Me of Aib[2]); 24.0 (d, C(4) of Leu[1]); 23.8 (q, Me(5) of Leu[1]); 23.7 (q, Me of Aib[2]); 23.22 (q, Me of Aib[6]); 23.19 (q, Me of Aib[5]); 20.9 (q, Me(5) of Leu[1]). ESI-MS (NaI+MeOH): 595 (100, $[M+Na]^+$). Anal. calcd for $C_{29}H_{44}N_6O_6 \cdot 1/2H_2O$ (581.71): C 59.88, H 7.80, N 14.45; found: C 60.02, H 7.98, N 14.36.

4.4. X-Ray crystal-structure determination of 1 and 2

All measurements were made on a Nonius KappaCCD area-detector diffractometer[38] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below[39] and views of the molecules are shown in Figures 2 and 3. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Standard reflection intensities were not monitored. Equivalent reflections, other than Friedel pairs, were merged. The structures were solved by direct methods using SIR92,[40] which revealed the positions of all non-hydrogen atoms.

The *iso*-propyl part of the Leu side chain in **1** is disordered. Two positions were defined for the disordered atoms and refinement of the site occupation factors yielded a value of 0.53(2) for the major conformation. Bond length and similarity restraints were applied to all chemically equivalent bond lengths and angles involving the disordered atoms. Neighboring atoms within and between each conformation of the disordered isopropyl group were also restrained to have similar atomic displacement parameters.

The asymmetric unit of **2** contains one molecule of the peptide plus two water molecules, one disordered EtOH molecule and one disordered *i*-PrOH molecule. Two positions were defined for each of the atoms of the two disordered solvent molecules and the site occupation factors of the major conformations refined to 0.51(2) and 0.50(2) for the EtOH and *i*-PrOH molecules, respectively. Similarity restraints were applied to the chemically equivalent bond lengths within the disordered molecules and neighboring atoms within and between each conformation of the disordered molecule were also restrained to have similar atomic displacement parameters.

The non-hydrogen atoms were refined anisotropically. The amide H-atoms in both structures, and the water H-atoms in **2**, were placed in positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic

displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). The orientations of the hydroxy O–H vectors in the solvent molecules of **2** were chosen so as to be directed towards the nearest hydrogen bond acceptor atom. The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2-F_c^2)^2$. Corrections for secondary extinction were applied. For **1** and **2**, 11 and two reflections, respectively, were omitted from the final refinement. In each case, the enantiomer used in the refinement was chosen to correspond with the known *S*-configuration of the chiral centers derived from precursor molecules.

Neutral atom scattering factors for non-hydrogen atoms were taken from Ref. 41 and the scattering factors for H-atoms were taken from Ref. 42. Anomalous dispersion effects were included in F_c;[43] the values for f' and f'' were those of Ref. 44. The values of the mass attenuation coefficients are those of Ref. 45. All calculations were performed using the *SHELXL97* program.[46]

In **1**, each N–H group of the peptide molecule acts as a donor for hydrogen bonds. Two of the interactions, N(1)–H and N(10)–H, are intramolecular hydrogen bonds. N(1)–H interacts with the amide O(12)-atom that is diagonally opposed in the peptide ring to give a loop with a graph set motif[47] of S(10). N(10)–H does not interact with a diametrically opposed amide O-atom, but forms bifurcated intramolecular hydrogen bonds with the amide O-atoms (O(6) and O(12), respectively) of the two adjacent peptide units. These two interactions have graph set motifs of S(7) and S(5). N(4)–H forms an intermolecular hydrogen bond with the amide O-atom of the same peptide unit of a neighboring molecule and thereby links the molecules into extended chains which run parallel to the [010] direction and have a graph set motif of C(4). N(7)–H, N(13)–H and N(16)–H form intermolecular hydrogen bonds with amide O-atoms of almost diagonally opposed peptide units from three different neighboring molecules. Each of these interactions links the molecules into extended chains which run parallel to the [010] direction and have a graph set motif of C(10). Together, the intermolecular hydrogen bonds link the molecules into extended two-dimensional networks which lie parallel to the (001) plane.

In **2**, all available N–H and O–H donors in the structure are involved in hydrogen bonds. The peptide molecule has two intramolecular hydrogen N–H…O bonds which diagonally cross the molecule to link the amide N–H donors with amide O-atoms that are seven atoms further along the peptide backbone. Each of these interactions has a graph set motif of S(10), which, despite the cyclic nature of the peptide, is the same as usually observed in open chain peptides. The remaining four amide N–H donors form intermolecular hydrogen bonds with the O-atoms from each of the four symmetry-independent solvent molecules, so that the two water molecules, the EtOH molecule and the *i*-PrOH molecule each accept one hydrogen bond. Each of the solvent O–H donors, in turn, forms an intermolecular hydrogen bond with an amide O-atom of a peptide molecule. The EtOH and *i*-PrOH molecules both act as acceptors and donors of hydrogen bonds involving the same peptide molecule to give a closed trimeric system. In each case, this builds a loop with a graph set motif of $R_2^2(10)$. In contrast, the water molecules form hydrogen bonds between different peptide molecules and thereby link all of the peptide and solvent molecules in the structure into an infinite three-dimensional framework. Although there are two symmetry-independent water molecules in the structure, each generates the same hydrogen-bonding pattern. The path via one H-atom from each water molecule creates a chain with a binary graph set motif of $C_2^2(7)$, while the path via the other H-atom from each water molecule creates a chain with a binary graph set motif of $C_2^2(10)$.

Crystal data for **1**: $C_{29}H_{44}N_6O_6$, $M=572.70$, colorless, prism, crystal dimensions $0.10\times0.12\times0.25$ mm, orthorhombic, space group $P2_12_12_1$, $Z=4$, reflections for cell determination 3164, 2θ range for cell determination 4–50°, $a=9.7189(2)$ Å, $b=10.0614(2)$ Å, $c=31.9151(7)$ Å, $V=3120.8(1)$ Å^3, $T=160$ K, $D_X=1.219$ g cm^{-3}, $\mu(\mathrm{Mo}K_\alpha)=0.0863$ mm^{-1}, $2\theta_{(max)}=50°$, total reflections measured 27,778, symmetry independent reflections 3146, reflections with $I>2\sigma(I)$ 2265, reflections used in refinement 3135, parameters refined 433; restraints 68, $R(F)$ [$I>2\sigma(I)$ reflections] = 0.0407, $wR(F^2)$ [all data] = 0.0870 ($w=[\sigma^2(F_o^2)+(0.0332P)^2]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.000, secondary extinction coefficient 0.005(1), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.18; −0.18e Å^{-3}.

Crystal data for **2**: $C_{29}H_{44}N_6O_6\cdot$EtOH$\cdot$*i*-PrOH$\cdot2H_2O$, $M=714.89$, colorless, prism, crystal dimensions $0.30\times0.30\times0.35$ mm, monoclinic, space group $P2_1$, $Z=2$, reflections for cell determination 4747, 2θ range for cell determination 4–55°, $a=10.0827(1)$ Å, $b=12.5382(1)$ Å, $c=15.7976(2)$ Å, $\beta=96.4866(4)°$, $V=1984.33(4)$ Å^3, $T=160$ K, $D_X=1.196$ g cm^{-3}, $\mu(\mathrm{Mo}K_\alpha)=0.0878$ mm^{-1}, $2\theta_{(max)}=55°$, total reflections measured 44,105, symmetry independent reflections 4757, reflections with $I>2\sigma(I)$ 4044, reflections used in refinement 4755, parameters refined 573; restraints 164, $R(F)$ [$I>2\sigma(I)$ reflections] = 0.0459, $wR(F^2)$ [all data] = 0.1280 ($w=[\sigma^2(F_o^2)+(0.0817P)^2+0.2355P]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.040, secondary extinction coefficient 0.025(4), final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.42; −0.29e Å^{-3}.

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DDQ induced oxidative cyclisations of 1,2-dihydronaptho[2,1-*b*]furans

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Abstract—The DDQ mediated oxidative cyclisation reactions of a series of dihydronaptho[2,1-*b*]furans were examined. In the presence of an acid catalyst, the reaction yielded polycyclic ethers and lactones in good to excellent yields.

1. Introduction

2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) is a common oxidant used in dehydrogenation reactions leading to aromatised products[1–3] and in the oxidation of aromatic and allylic alcohols to aldehydes and ketones.[4–6] DDQ can be used to generate benzylic and napthylic cations on suitably activated systems via hydride abstraction. The cations thus generated can undergo nucleophilic addition and intramolecular cyclisation reactions leading to oxygen containing heterocycles when the substrates are substituted with suitable latent nucleophiles.[7–9]

We have recently developed a route to 1,2-dihydronaptho[2,1-*b*]furans **3** utilising 1,2-dioxines **1** and stabilised phosphorus ylides.[10] We considered these products to be ideal substrates for DDQ induced oxidation due to the stabilising effect of the furan ring on the intermediate napthylic cation. The products generated in this previous study also contained an ester group that could act as the nucleophile for the intramolecular trapping of the napthylic cation. It was hypothesised that this ester or derivative thereof could participate in the reaction and give rise to novel cyclisation products. Some aryl-fused furofurans are found in nature such as psorofebrin[11,12] and platypodantherone[13] and we believed that by investigating DDQ induced oxidative cyclisations on dihydronapthofurans, we could develop a route to these types of compounds. We now report on the oxidative cyclisation reactions of a series of substituted 1,2-dihydronapthofurans facilitated by DDQ.

Keywords: DDQ; Dihydronapthofuran; Cyclisation.
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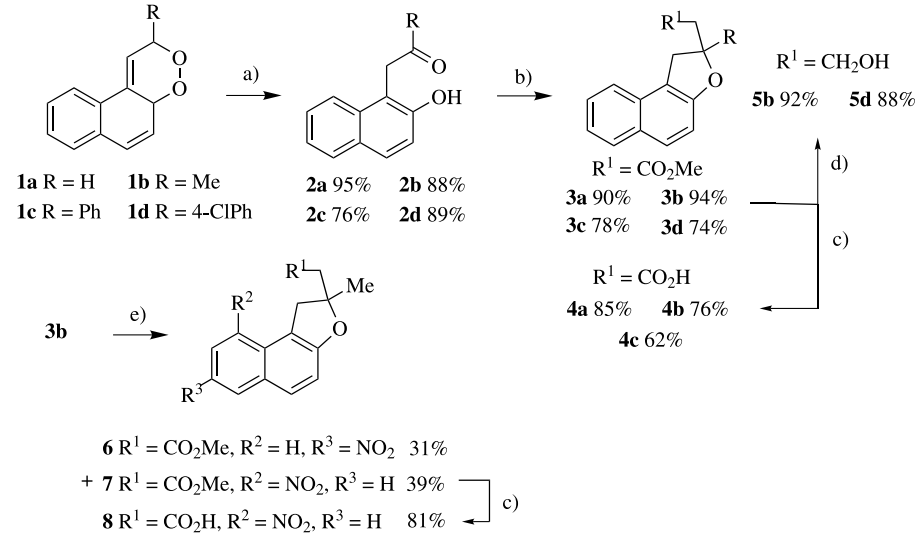
2. Results and discussion

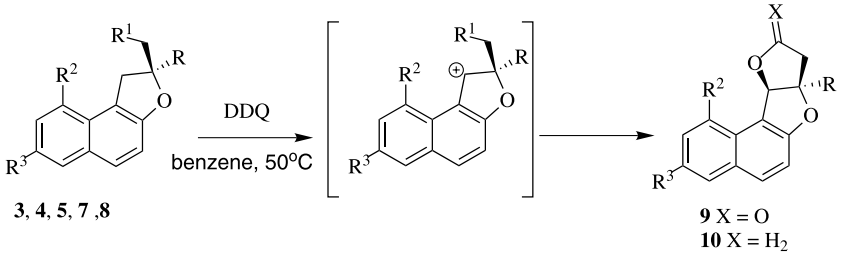
The synthesis of the starting dihydronapthofurans **3a–d** was achieved using our previously published procedure, Scheme 1.[10] Thus, Rose Bengal bis(triethylammonium) salt sensitised photooxidation of 1-vinylnapthalenes gave the 1,2-dioxines **1a–d**. These 1,2-dioxines underwent rearrangement when allowed to react with DABCO to afford the 1-(β-keto)-2-napthols **2a–d** in excellent yield. Reaction of the napthols **2a–d** with methyl(triphenylphosphoranylidene)acetate afforded the requisite dihydronapthofurans **3a–d** via a Wittig/oxy-Michael sequence.

Further functional group modifications were made on the dihydronapthofurans **3a–d** such that the scope of the oxidative cyclisation could be examined. Saponification of the esters **3a–c** afforded the acids **4a–c** and $LiAlH_4$ reduction of **3b** and **3d** gave the alcohols **5b** and **5d**, respectively. To the best of our knowledge, electrophilic aromatic substitution has not been examined on 1,2-dihydronaptho[2,1-*b*]furans, although the dehydrogenated naptho[2,1-*b*]furans are known to react primarily at the C6 position.[14] When **3b** was exposed to standard nitration conditions, electrophilic substitution occurred at both the C7 and C9 positions on the naphthalene skeleton to afford **6** and **7** in good overall yield. The identity of these isomers was determined using both COSY and ROESY 2D NMR techniques.

With a range of substrates in hand, the DDQ facilitated oxidative cyclisation reactions of napthofurans **3**, **4**, **5**, **7** and **8** were examined, Scheme 2 and Table 1. Initially, when the ester **3a** was heated to 50 °C in dry benzene in the presence of 1.1 equivalents of DDQ, no reaction was observed. To



Scheme 1. Key: (a) DABCO; (b) $Ph_3P{=}CHCO_2Me$; (c) KOH, $MeOH/H_2O$, 16 h; (d) $LiAlH_4$, THF, 16 h; (e) HNO_3, AcOH, 1 h.



Scheme 2.

enhance the reactivity of the DDQ, addition of an acid catalyst to the reaction medium was examined. In the presence of *p*-toluenesulfonic acid, the esters **3a–d** and **7** reacted with DDQ affording the furofuranones **9a–e** in good yield, entries 1–5. The dihydronapthofuran acids **4a–c** and **8** underwent smooth reaction to give the furofuranones **9a–c**,**e** without the need for an acid catalyst, entries 6–9. The yields obtained from the acids **4a–c** and **8** were virtually identical to the yields seen in the corresponding ester series **3a–c** and **7**.

Cyclisation of the alcohols **5b** and **5d** also proceeded smoothly to afford the furofurans **10b** and **10d** in the absence of an acid catalyst in excellent yield. The requirement for the acid catalyst in the ester series may be due to the reduced ability of the ester group, relative to the acid and alcohol groups, to stabilise the cation in the rate-determining cation-forming step. Oxidations involving DDQ are often performed in acidic solvents to activate DDQ towards hydride abstraction.[15]

The ^{1}H NMR data for the furolactones were consistent with the proposed structures. Each lactone exhibited a singlet at ca. δ 6.20 ppm due to the napthylic proton and an AB quartet at ca. δ 3.00 ppm. The lactone products exhibited characteristic IR absorptions at 1785 cm^{-1} and the stereochemistry of the products were confirmed when the X-ray structures of **9b** and **9e** were obtained, Figure 1.[16] The

Table 1. Oxidative cyclisations of 1,2-dihydronaptho[2,1-*b*]furans

Entry[a]	Starting material	R	R^1	R^2	R^3	Product	Yield (%)
1[b]	**3a**	H	CO_2Me	H	H	**9a**	40
2[b]	**3b**	Me	CO_2Me	H	H	**9b**	64
3[b]	**3c**	Ph	CO_2Me	H	H	**9c**	80
4[b]	**3d**	4-ClPh	CO_2Me	H	H	**9d**	85
5[b,c]	**7**	Me	CO_2Me	H	NO_2	**9e**	88
6	**4a**	H	CO_2H	H	H	**9a**	38
7	**4b**	Me	CO_2H	H	H	**9b**	81
8	**4c**	Ph	CO_2H	H	H	**9c**	71
9[c]	**8**	Me	CO_2H	H	NO_2	**9e**	91
10	**5b**	Me	CH_2OH	H	H	**10b**	81
11	**5d**	4-ClPh	CH_2OH	H	H	**10d**	87

[a] Reactions were performed in dry benzene at 50 °C for 1 h.
[b] Performed in the presence of a catalytic amount (2 mg) of *p*-toluenesulfonic acid.
[c] Reaction heated to reflux for 16 h.

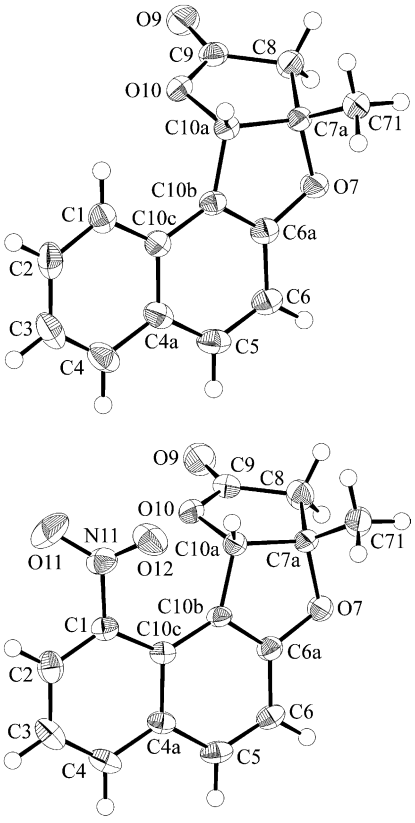


Figure 1. X-ray structures of **9b** and **9e**.

structure of **9e** also confirmed the substitution pattern obtained from the electrophilic aromatic substitution reaction of **3b**.

Mechanistically, the reaction proceeds via a two-step sequence with initial hydride abstraction by DDQ to give the napthyl cation and the $DDQH^-$ anion. The napthylic cation is trapped by the oxygen of the alcohol, acid or ester and then the $DDQH^-$ anion abstracts either a proton or methyl to yield the reduced $DDQH_2$ or DDQH(Me), respectively and the cyclisation product.

The oxidative cyclisation of a dihydrofuran with a nitrogen bearing arm was also examined, Scheme 3. The reaction of amide **11** afforded nitrile **12** and required two equivalents of DDQ for the reaction to achieve completion. This result suggests an oxygen transfer mechanism as depicted with a faster second hydride abstraction due to the stabilising effect of the α-oxygen atom. Nitrile **12** exhibited a resonance in the ^{1}H NMR attributed to the C1 carbonyl carbon at δ 197.3 ppm and an IR absorption at 2258 cm^{-1} corresponding to the nitrile moiety confirming the assigned structure.

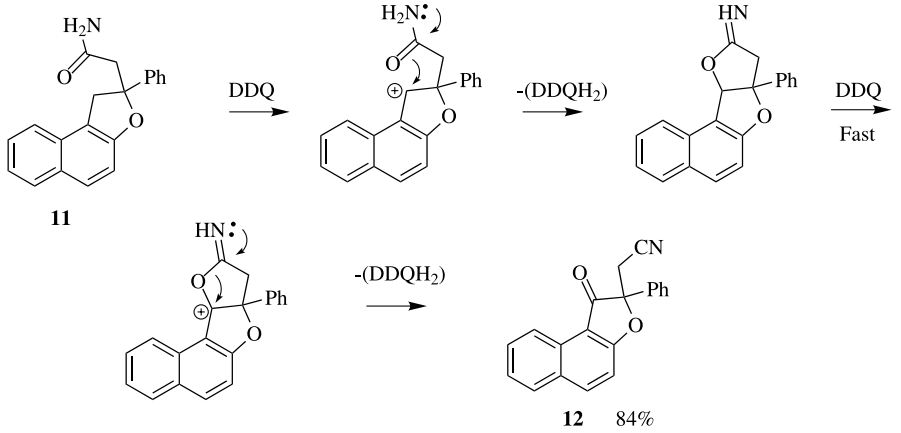
The oxidative cyclisation of dihydronapthofurans is a useful method for the construction of aryl furofuran ring systems, a ring structure found in natural products such as platypodantherone and psorofebrin. The naphthalene ring serves as a rigid template for the ether or lactone construction while stabilising the carbocation formation. Ring closures of this type could be used in the construction of arylfurofuranone natural products.

3. Experimental

3.1. General experimental

Solvents were dried by appropriate methods wherever needed. Benzene was dried by distillation over calcium hydride prior to use. Thin-layer chromatography (TLC) was performed using aluminium sheets silica gel 60 F_{254} (40× 80 mm) from Merck. Melting points were taken on a Reichert Thermovar Kofler apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR spectrophotometer as nujol mulls unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian INOVA (600 MHz) or on a Varian Gemini 2000 instrument, TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards unless otherwise specified. Dihydrofurans **3a–d** and compounds **1d** and **2d** were prepared according to our previously reported procedure.[10]

3.1.1. (±) (2*R*,4a*R*)-2-(4-Chlorophenyl)-2,4a-dihydronaphtho[2,1-*c*][1,2]dioxine 1d. Light yellow solid; mp 78–82 °C; R_f 0.32 (30:70 CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.52 (dd, J=3.0, 3.0 Hz, 1H) 5.78 (dd, J=10.2, 2.4 Hz, 1H), 6.02 (dddd, J=3.0, 3.0, 3.0, 2.4 Hz, 1H), 6.15 (ddd, J=3.0, 3.0, 1.2 Hz, 1H), 6.45 (dd, J=10.2, 3.0 Hz, 1H), 7.08 (dd, J=7.8, 1.2 Hz, 1H),



Scheme 3.

7.22–7.28 (m, 2H), 7.32–7.34 (m, 2H), 7.38–7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 80.9, 82.0, 119.3, 123.6, 124.1, 127.4, 128.6, 128.6, 129.2, 129.3, 129.9, 130.9, 132.2, 134.4, 136.3, 138.0; MS *m/z* (%) 296 (M^+, 20), 278 (57), 265 (32), 139 (100), 111 (31); HRMS calcd for $C_{18}H_{13}O_2^{35}Cl$: 296.0604; found: 296.0610.

3.1.2. 1-(4-Chlorophenyl)-2-(2-hydroxy-1-naphthalenyl)-1-ethanone 2d. White solid; mp 212–220 °C (decomposes); IR (Nujol) 3421, 1674, 1630, 1587, 1570, 1518 cm^{-1}; ^{1}H NMR ($CDCl_3$/d_6-DMSO, 300 MHz) δ 4.70 (s, 2H), 7.20–7.27 (m, 2H), 7.37–7.44 (m, 3H), 7.64–7.75 (m, 3H), 8.09–8.11 (m, 1H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$/d_6-DMSO, 75 MHz) δ 35.9, 112.7, 117.9, 122.2, 122.4, 126.1, 128.1, 128.3, 128.4, 129.6, 133.6, 135.0, 138.8, 152.3, 197.3, (1 masked aromatic); MS *m/z* (%) 296 (M^+, 32), 157 (100), 139 (67), 128 (45); Anal. Calcd for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.42; Cl, 11.95; Found C, 72.64; H, 4.34; Cl, 12.18.

3.1.3. Methyl 2-[2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]acetate 3c. Colorless oil; R_f 0.46 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1738, 1633, 1601, 1579, 1522, 1494 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.13 (d, J=14.6 Hz, 1H), 3.16 (d, J=14.6 Hz, 1H), 3.48 (s, 3H), 3.77 (d, J=15.7 Hz, 1H), 4.14 (d, J=15.7 Hz, 1H), 7.26–7.50 (m, 6H), 7.58–7.62 (m, 3H), 7.72–7.75 (m, 1H), 7.81–7.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.2, 46.4, 51.6, 89.1, 112.0, 117.7, 122.7, 123.0, 124.8, 126.6, 127.5, 128.4, 128.7, 129.2, 129.4, 130.7, 144.8, 155.9, 169.9; EIMS *m/z* 318 (M^+, 32), 286 (22), 257 (2), 244 (100), 181 (11); HRMS calcd for $C_{21}H_{18}O_3$: 318.1256; found 318.1255.

3.1.4. Methyl 2-[2-(4-chlorophenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]acetate 3d. Pale yellow viscous oil; R_f 0.49 (80:20 hexane/ethyl acetate); IR (neat) 1738, 1633, 1601, 1579, 1521 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.11 (d, J=14.9 Hz, 1H), 3.14 (d, J=14.9 Hz, 1H), 3.51 (s, 3H), 3.73 (d, J=15.6 Hz, 1H), 4.11 (d, J=15.6 Hz, 1H), 7.21–7.24 (m, 1H), 7.29–7.36 (m, 3H), 7.44–7.52 (m, 3H), 7.56–7.59 (m, 1H), 7.71–7.74 (m, 1H), 7.79–7.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 41.4, 46.2, 51.6, 89.2, 112.0, 117.4, 122.6, 123.1, 126.4, 126.8, 128.5, 128.7, 129.4, 129.5, 130.6, 133.4, 143.2, 155.7, 169.7; EIMS *m/z* 352 (M^+, 19), 291 (22), 278 (100), 181 (20); HRMS calcd for $C_{21}H_{17}O_3^{35}Cl$: 352.0866; found 352.0860.

3.2. General procedure for the hydrolysis of esters 3a–c and 7

3.2.1. 2-(1,2-Dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 4a. A solution of dihydrofuran **3a** (138 mg, 0.57 mmol) and potassium hydroxide (400 mg, excess) in methanol (10 ml) was stirred for 16 h. The solution was acidified with 1 *N* HCl and then extracted with CH_2Cl_2 (2×20 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude acid was recrystallised from chloroform to give a white solid (110 mg, 85%); mp 138.5–139.5 °C; IR (CH_2Cl_2) 2760, 1693, 1631, 1599, 1577, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (dd, J=6.0, 16.2 Hz, 1H), 3.01 (dd, J=16.2, 7.2 Hz, 1H), 3.23 (dd, J=15.4, 6.9 Hz, 1H), 3.74 (dd, J=15.4, 9.6 Hz, 1H), 5.40 (dddd, J=6.0, 7.2, 6.9, 9.6 Hz, 1H), 7.11–7.14 (m, 1H), 7.30–7.35 (m, 1H), 7.45–7.51 (m, 1H), 7.57–7.60 (m, 1H), 7.68–7.71 (m, 1H), 7.80–7.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 34.3, 40.6, 79.1, 112.1, 117.6, 122.7, 123.1, 126.8, 128.8, 129.3, 129.4, 130.7, 156.4, 175.1; EIMS *m/z* 228 (M^+, 9), 168 (39), 69 (54), 55 (56), 41 (100); Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30; Found C, 73.40; H, 5.03.

3.2.2. 2-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 4b. Recrystallised from *n*-heptane/dichloromethane; mp 124–126 °C; IR (Nujol) 1711, 1633, 1574, 1603, 2670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3H), 2.91 (s, 2H), 3.33 (d, J=15.9 Hz, 1H), 3.61 (d, J=15.9 Hz, 1H), 7.07–7.10 (m, 1H), 7.27–7.33 (m, 1H), 7.45–7.49 (m, 1H), 7.56–7.59 (m, 1H), 7.67–7.70 (m, 1H), 7.79–7.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 26.6, 40.4, 45.0, 86.7, 112.3, 117.8, 122.7, 122.9, 126.7, 128.7, 129.2, 129.3, 130.9, 155.5, 175.4; EIMS *m/z* 242 (M^+, 39), 144 (100), 105 (98), 77 (53); Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82; Found C, 74.15; H, 5.74.

3.2.3. 2-(2-Phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 4c. Recrystallised from hot dichloromethane/hexane (1:1); mp 154.5–155.5 °C; IR (Nujol) 1722, 1657, 1603, 1577, 1521, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.17 (d, J=15.5 Hz, 1H), 3.18 (d, J=15.5 Hz, 1H), 3.74 (d, J=15.9 Hz, 1H), 4.03 (d, J=15.9 Hz, 1H), 7.24–7.37 (m, 5H), 7.44–7.47 (m, 1H), 7.53–7.56 (m, 3H), 7.70–7.73 (m, 1H), 7.78–7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.7, 45.9, 89.4, 112.1, 117.6, 122.7, 123.2, 124.8, 126.8, 127.7, 128.5, 128.7, 129.4, 129.6, 130.7, 144.2, 155.7, 173.6; EIMS *m/z* 304 (M^+, 64), 257 (28), 244 (100), 181 (15); Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30; Found C, 78.77; H, 5.44.

3.3. General procedure for the reduction of esters 3b,d

3.3.1. 2-(2-Methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)-1-ethanol 5b. To a stirred solution of dihydrofuran **3b** (206 mg, 0.805 mmol) in anhydrous THF (5 ml) was added $LiAlH_4$ (30 mg, 0.790 mmol) at ambient temperature. After 16 h the reaction was quenched with ethyl acetate (1 ml) and 1 *N* HCl (10 ml) added. The mixture was extracted with CH_2Cl_2 (2×20 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography afforded a colorless oil (169 mg, 92%); R_f 0.24 (90:10 CH_2Cl_2/ethyl acetate); IR (CH_2Cl_2) 3614, 3566, 1632, 1599, 1586, 1522 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.56 (s, 3H), 1.71 (br s, 1H), 2.09 (ddd, J=5.4, 6.2, 14.5 Hz, 1H), 2.19 (ddd, J=5.6, 7.4, 14.5 Hz, 1H), 3.28 (d, J=15.3 Hz, 1H), 3.43 (d, J=15.3 Hz, 1H), 3.86 (ddd, J=5.6, 6.2, 11.5 Hz, 1H), 3.95 (ddd, J=5.4, 7.4, 11.5 Hz, 1H) 7.06–7.07 (m, 1H), 7.29–7.32 (m, 1H), 7.45–7.48 (m, 1H), 7.55–7.57 (m, 1H), 7.68–7.69 (m, 1H), 7.80–7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.9, 41.2, 43.4, 59.5, 89.8, 112.4, 118.1, 122.8, 123.0, 126.9, 128.9, 129.3, 129.4, 131.2, 155.9; EIMS *m/z* 228 (100), 209 (12), 195 (54), 183 (45); HRMS calcd for $C_{15}H_{16}O_2$: 228.1150; found 228.1158.

3.3.2. 2-[2-(4-Chlorophenyl)-1,2-dihydronaphtho[2,1-*b*]furan-2-yl]-1-ethanol 5d. Gummy colorless oil; R_f 0.25 (95:5 CH_2Cl_2/ethyl acetate); IR (CH_2Cl_2) 3683, 3608, 1633,

1603, 1579, 1522, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.94 (br s, 1H), 2.37 (ddd, $J=5.6$, 5.6, 14.7 Hz, 1H), 2.50 (ddd, $J=6.0$, 7.6, 14.7 Hz, 1H), 3.63–3.67 (m, 2H), 3.73 (ddd, $J=5.6$, 7.4, 11.4 Hz, 1H), 3.79 (d, $J=15.2$ Hz, 1H), 7.20–7.22 (m, 1H), 7.30–7.34 (m, 3H), 7.43–7.46 (m, 3H), 7.51–7.53 (m, 1H), 7.72–7.74 (m, 1H), 7.80–7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.3, 44.2, 59.0, 91.7, 111.8, 117.2, 122.5, 123.1, 126.1, 126.7, 128.5, 128.6, 129.3, 129.4, 130.5, 133.0, 143.6, 155.5; EIMS *m/z* 324 (M^+, 100), 291 (81), 279 (49), 215 (27); Anal. Calcd for $C_{20}H_{17}O_2Cl$: C, 73.96; H, 5.28; Found C, 73.88; H, 5.33.

3.4. Reaction of methyl 2-(2-methyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetate 3b with nitric acid

To a stirred solution of dihydronapthofuran **3b** (325 mg, 1.27 mmol) in glacial acetic acid (20 ml) cooled in an ice water bath was added nitric acid (4 ml, 50% in glacial acetic acid). The vessel was warmed to 30 °C and left to stir for 1 h at ambient temperature. The solution was poured onto ice water and the mixture extracted with dichloromethane (2× 20 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude residue was purified by flash chromatography (80:20 hexane/ethyl acetate) to give **6** (120 mg, 31%) and **7** (150 mg, 39%).

3.4.1. Methyl 2-(2-methyl-7-nitro-1,2-dihydronaphtho-[2,1-*b*]furan-2-yl)acetate 6. Yellow oil; R_f 0.33 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1738, 1626, 1603, 1537, 1506, 1338 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.67 (s, 3H), 2.86 (d, $J=15.3$ Hz, 1H), 2.89 (d, $J=15.3$ Hz, 1H), 3.33 (d, $J=16.2$ Hz, 1H), 3.66 (d, $J=16.2$ Hz, 1H), 3.66 (s, 3H), 7.19 (d, $J=8.7$ Hz, 1H), 7.60 (d, $J=9.1$ Hz, 1H), 7.85 (d, $J=8.7$ Hz, 1H), 8.21 (dd, $J=9.1$, 2.4 Hz, 1H), 8.74 (d, $J=2.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.9, 39.6, 44.8, 51.6, 88.1, 114.3, 119.0, 120.1, 123.7, 125.6, 127.2, 131.7, 133.6, 143.0, 159.1, 170.1; EIMS *m/z* 301 (M^+, 17), 227 (100), 181 (38), 152 (22); HRMS calcd for $C_{16}H_{15}NO_5$: 301.0950; found 301.0941.

3.4.2. Methyl 2-(2-methyl-9-nitro-1,2-dihydronaphtho-[2,1-*b*]furan-2-yl)acetate 7. Yellow orange oil; R_f 0.41 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1738, 1636, 1599, 1579, 1525, 1352 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 1.27 (s, 3H), 2.37 (d, $J=15.0$ Hz, 1H), 2.39 (d, $J=15.0$ Hz, 1H), 3.09 (d, $J=16.2$ Hz, 1H), 3.18 (s, 3H), 3.48 (d, $J=16.2$ Hz, 1H), 6.60 (dd, $J=8.2$, 7.6 Hz, 1H), 6.93 (d, $J=8.8$ Hz, 1H), 7.17 (d, $J=8.8$ Hz, 1H), 7.25 (dd, $J=7.6$, 1.2 Hz, 1H), 7.31 (dd, $J=8.2$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6, 40.8, 44.8, 51.6, 87.3, 114.2, 114.7, 120.8, 122.6, 122.9, 130.4, 130.6, 133.4, 146.0, 159.0, 170.0; EIMS *m/z* 301 (M^+, 25), 284 (22), 267 (28), 227 (100), 181 (79), 152 (47). HRMS calcd for $C_{16}H_{15}NO_5$: 301.0950; found 301.0941.

3.4.3. 2-(2-Methyl-9-nitro-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetic acid 8. Yellow solid recrystallised from hot aqueous ethanol; mp 160–162 °C; IR (Nujol) 1709, 1624, 1595, 1576, 1522, 1500, 1331 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 3H), 2.82 (d, $J=15.3$ Hz, 1H), 2.84 (d, $J=15.3$ Hz, 1H), 3.17 (d, $J=16.2$ Hz, 1H), 3.41 (d, $J=16.2$ Hz, 1H), 7.23 (d, $J=8.8$ Hz, 1H), 7.32 (dd, $J=8.0$, 8.0 Hz, 1H), 7.80 (dd, $J=8.0$, 1.1 Hz, 1H), 7.81 (d, $J=$ 8.8 Hz, 1H), 7.99 (dd, $J=8.0$, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 26.4, 41.1, 44.6, 87.1, 114.4, 114.7, 121.0, 122.7, 123.1, 130.6, 130.8, 133.5, 146.1, 159.0, 174.0; EIMS *m/z* 287 (M^+, 53), 270 (57), 253 (53), 227 (85), 181 (100), 152 (72), 45 (90); Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88; Found C, 63.26; H, 4.69; N, 4.98.

3.5. General procedure for the reaction of esters 3a–d and 7 with DDQ

To a stirred solution of dihydronapthofuran (0.11 mmol) and DDQ (29 mg, 0.12 mmol) in dry benzene (8 ml) was added *p*-toluenesulphonic acid (2 mg, 0.01 mmol) dissolved in benzene (0.5 ml). The solution was heated to 50 °C for 1 h and then cooled and concentrated in vacuo to ca. 1 ml. The solution was filtered through a plug of cotton wool and the residue purified by flash chromatography.

3.6. General procedure for the reaction of acids 4a–c, 8 and alcohols 5b,d with DDQ

A stirred solution of dihydronapthofuran (0.11 mmol) and DDQ (29 mg, 0.12 mmol) in dry benzene (8 ml) was heated to 50 °C for 1 h and then cooled and concentrated in vacuo to ca. 1 ml. The solution was filtered through a plug of cotton wool and the residue purified by flash chromatography.

3.6.1. (±) (7a*R*,10a*R*)-7a,8,9,10a-Tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9a. White solid; mp 205–207 °C (lit. 207–208 °C)[17]; R_f 0.58 (40:60 ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.05 (dd, $J=19.0$, 2.0 Hz, 1H), 3.17 (dd, $J=19.0$, 6.6 Hz, 1H), 5.56 (ddd, $J=2.0$, 6.6, 6.6 Hz, 1H), 6.46 (d, $J=6.6$ Hz, 1H), 7.12–7.15 (m, 1H), 7.38–7.43 (m, 1H), 7.55–7.60 (m, 1H), 7.83–7.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.5, 81.5, 83.4, 112.1, 115.1, 122.1, 124.1, 128.1, 128.7, 129.6, 130.6, 133.4, 159.2, 174.7.

3.6.2. (±) (7a*R*,10a*R*)-7a-Methyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9b. White crystalline solid; mp 147–149 °C (CH_2Cl_2/hexane); R_f 0.39 (70:30 hexane/ethyl acetate); IR (CH_2Cl_2) 1780, 1635, 1601, 1585, 1525 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.73 (s, 3H), 2.93 (d, $J=18.9$ Hz, 1H), 3.22 (d, $J=18.9$ Hz, 1H), 6.06 (s, 1H), 7.09–7.12 (m, 1H), 7.37–7.42 (m, 1H); 7.54–7.59 (m, 1H), 7.83–7.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5, 41.2, 88.0, 90.1, 112.4, 114.6, 122.2, 123.9, 128.0, 128.7, 129.5, 131.0, 133.4, 158.5, 174.4; EIMS *m/z* 240 (M^+, 12), 195 (17), 181 (39), 115 (23), 44 (100); Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found C, 75.08; H, 5.07.

3.6.3. (±) (7a*S*,10a*R*)-7a-Phenyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9c. White solid; mp 171–172 °C; R_f 0.65 (70:30 hexane/ethyl acetate); IR (CH_2Cl_2) 1784, 1635, 1603, 1583, 1525, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.38 (d, $J=18.9$ Hz, 1H), 3.53 (d, $J=18.9$ Hz, 1H), 6.35 (s, 1H), 7.26–7.29 (m, 1H), 7.36–7.45 (m, 4H), 7.52–7.57 (m, 3H), 7.80–7.85 (m, 2H), 7.90–7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.4, 89.7, 93.2, 112.1, 114.6, 122.2, 124.1, 124.5, 128.1, 128.7, 128.8, 129.0, 129.8, 130.8, 133.6, 139.6, 158.9, 174.0; EIMS *m/z*

302 (M^+, 14), 257 (100), 181 (49), 115 (42), 77 (60); Anal. Calcd for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67; Found C, 79.14; H, 4.83.

3.6.4. (±) (7a*S*,10a*R*)-7a-(4-Chlorophenyl)-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan-9-one 9d. White solid; mp 200–208 °C (decomposes); R_f 0.42 (80:20 hexane/ethyl acetate); IR (Nujol) 1785, 1636, 1582, 1526, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.33 (d, J= 19.2 Hz, 1H), 3.53 (d, J=19.2 Hz, 1H), 6.31 (s, 1H), 7.25–7.28 (m, 1H), 7.37–7.43 (m, 3H), 7.47–7.58 (m, 3H), 7.80–7.86 (m, 2H), 7.91–7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.2, 89.5, 92.7, 112.0, 114.4, 122.2, 124.3, 125.9, 128.2, 128.8, 129.2, 129.9, 130.7, 133.7, 134.7, 138.1, 158.7, 173.6; EIMS *m/z* 336 (M^+, 46), 307 (59), 291 (100), 278 (38), 226 (26); Anal. Calcd for $C_{20}H_{13}O_3Cl$: C, 71.33; H, 3.89, Cl, 10.53. Found C, 71.05; H, 3.85; Cl, 10.27.

3.6.5. (±) (7a*R*,10a*R*)-7a-Methyl-1-nitro-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[2,1-*d*]furan-9-one 9e. The general procedure was employed, however, the reaction mixture was refluxed overnight to give a yellow solid; mp 190–195 °C (sealed tube, decomposes); R_f 0.58 (40:60 ethyl acetate/hexane); IR (CH_2Cl_2) 1784, 1628, 1599, 1579, 1529 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.78 (s, 3H) 2.89 (d, J=19.2 Hz, 1H), 3.11 (d, J=19.2 Hz, 1H), 6.12 (s, 1H), 7.25 (d, J=8.7 Hz, 1H), 7.44 (dd, J=7.8, 7.8 Hz, 1H), 7.98 (d, J=8.7 Hz, 1H), 7.99 (dd, J=7.8, 1.2 Hz, 1H), 8.07 (dd, J=8.7, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5, 41.0, 88.6, 90.1, 112.2, 114.7, 122.3, 122.9, 125.3, 131.1, 134.2, 134.6, 145.8, 161.6, 173.5; MS *m/z* (%): 285 (M^+, 100), 240 (8), 226 (64), 201 (48), 145 (65). HRMS, $C_{15}H_{11}NO_5Na$: calcd, 308.0535; found 308.0531.

3.6.6. (±) (7a*R*,10a*R*)-7a-Methyl-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan 10b. White solid; mp 63–65 °C; R_f 0.56 (80:20 hexane/ethyl acetate); IR (CH_2Cl_2) 1633, 1601, 1585, 1523 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.67 (s, 3H), 2.11 (ddd, J=13.2, 11.1, 7.5 Hz, 1H), 2.37 (ddd, J=1.9, 4.9, 13.2 Hz, 1H), 3.59 (ddd, J=4.9, 7.5, 11.1 Hz, 1H), 3.98 (ddd, J=1.9, 7.5, 7.5 Hz, 1H), 5.64 (s, 1H), 7.05–7.06 (m, 1H), 7.31–7.34 (m, 1H), 7.49–7.52 (m, 1H), 7.76–7.81 (m, 2H), 7.88–7.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 23.4, 40.8, 66.5, 87.4, 96.0, 112.1, 116.2, 122.3, 123.2, 127.3, 128.6, 129.4, 131.4, 131.7, 158.4; EIMS *m/z* 226 (M^+, 100), 195 (57), 181 (60), 171 (20); Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24; Found C, 79.52; H, 6.46.

3.6.7. (±) (7a*S*,10a*R*)-7a-(4-Chlorophenyl)-7a,8,9,10a-tetrahydrofuro[3,2-*b*]naphtho[1,2-*d*]furan 10d. Gummy colorless oil; R_f 0.48 (15:85 ethyl acetate/hexane); IR (CH_2Cl_2) 3055, 1635, 1603, 1581, 1522, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.54 (ddd, J=7.3, 11.5, 13.5 Hz, 1H) 2.66 (ddd, J=1.3, 4.8, 13.5 Hz, 1H), 3.74 (ddd, J=4.8, 7.5, 8.0 Hz, 1H), 4.21 (ddd, J=1.3, 7.5, 8.0 Hz, 1H), 5.96 (s, 1H), 7.19–7.21 (m, 1H), 7.32–7.35 (m, 3H), 7.49–7.52 (m, 3H), 7.80–7.83 (m, 2H), 7.86–7.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.3, 67.2, 90.1, 98.4, 111.6, 115.7, 122.3, 123.5, 126.2, 127.5, 128.7, 128.7, 129.8, 131.2, 132.1, 133.6, 140.2, 158.6; EIMS *m/z* 323 (M^+, 100), 292 (97), 171 (40); Anal. Calcd for $C_{20}H_{15}O_2Cl$: C, 74.42; H, 4.68. Found C, 74.53; H, 4.68.

3.6.8. 2-(2-Phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)acetamide 11. To a stirred solution of acid **4c** (492 mg, 1.62 mmol) in dry CH_2Cl_2 (10 ml) was added thionyl chloride (1 ml). After 4 h the volatiles were removed under a stream of nitrogen. The residue was taken up in dry ether (25 ml), the vessel cooled to −78 °C and dry ammonia was condensed into the vessel for 5 min before the contents of the reaction were allowed to reach room temperature. Saturated NaCl (10 ml) was added to the mixture and the aqueous phase extracted with CH_2Cl_2 (2×20 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent removed in vacuo. Purification by flash chromatography (florisil®, 70:30 CH_2Cl_2/ethyl acetate) gave a cream colored solid (352 mg, 76%); mp 155–158 °C; R_f 0.30 (70:30 CH_2Cl_2/ethyl acetate); IR (CH_2Cl_2) 3510, 3398, 1685, 1633, 1589, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 (s, 2H), 3.70 (d, J=15.6 Hz, 1H), 3.90 (d, J=15.6 Hz, 1H), 5.28 (br s, 1H), 6.27 (br s, 1H), 7.24–7.57 (m, 9H), 7.75–7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 42.9, 48.2, 89.9, 111.7, 117.7, 122.8, 123.4, 124.6, 126.9, 127.7, 128.7, 129.5, 129.7, 130.7, 144.1, 155.2, 171.2, (one masked aromatic); EIMS *m/z* 303 (M^+, 21), 278 (13), 244 (100), 215 (14); Anal. Calcd for $C_{20}H_{17}O_2N$: C, 79.19; H, 5.65; N, 4.62; Found C, 78.88; H, 5.75; N, 4.84.

3.6.9. (1-Oxo-2-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-yl)methyl cyanide 12. Colorless oil; R_f 0.25 (25:75 ethyl acetate/hexane); IR (Nujol) 2258, 1704, 1632, 1586, 1529, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.20 (d, J= 16.8 Hz, 1H), 3.35 (d, J=16.8 Hz, 1H) 7.39–7.54 (m, 5H), 7.68–7.73 (m, 3H), 7.85–7.89 (m, 1H), 8.17–8.22 (m, 1H), 8.64–8.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.6, 87.1, 111.3, 113.5, 114.7, 123.2, 124.6, 125.9, 128.7, 129.0, 129.2, 129.3, 129.8, 130.3, 134.4, 141.2, 174.0, 197.3; EIMS *m/z* 299 (57), 259 (100), 231 (14), 126 (33); HRMS calcd for $C_{20}H_{13}O_2N$: 299.0946; found: 299.0954.

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Lewis acid mediated reactions of cyclopropyl aryl ketones with arylaldehydes, facile preparation of 2-(2-hydroxyethyl)-1,3-diarylpropenones

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Abstract—In the presence of Lewis acid TMSOTf, ring-opening reaction of aryl cyclopropyl ketone with arylaldehyde took place under mild conditions to give 2-(2-hydroxyethyl)-1,3-diarylpropenone in good yield. By protection of hydroxy group with triethylsilyl group (TES), the corresponding ring-opened product **7** was obtained in high yield with good geometrical selectivity.

1. Introduction

Cyclopropane derivatives, as versatile building blocks have been more than laboratory curiosities for quite some time.[1] In order to activate strained three-membered ring, electron-donating or accepting substituents are generally involved in their reactions to make polar processes more favorable. However, cyclopropane involved synthetically useful reactions frequently contains two activating groups.[2] The ring-opening reactions of monoactivated cyclopropane derivatives are in general sluggish due to their low reactivities. So far several examples have been reported under severe conditions either assisted by stronger nucleophiles such as I^- and stronger Lewis acids such as $TiCl_4$, or assisted by the β-effect of silicon atom of trimethylsilyl group (Scheme 1).[3] Therefore, it is necessary to develop a method for the ring-opening reaction of simple monoactivated cyclopropane derivatives under mild conditions.

α,β-Enones represent a common feature in many useful reactions,[3d] for example, Diels–Alder reactions,[4a] Stetter reaction,[4b] Michael additions,[4c] Baylis–Hillman reactions,[4d] Juliá-Colonna epoxidatons,[4e] and Robinson annulations.[4f] Furthermore, in addition to possessing cytotoxic activities and anticancer properties (Chalcones),[5] α,β-enones are frequently used as branching points for the creation of drug-like heterocyclic libraries (isoxazolines,[6a,b] tetrahydropyrimidines,[6a,b] dihydropyrimidiones,[6c] pyrimidines,[6c] pyridine,[6c,d] benzothiazepines,[6e] pyrazoles,[6c] pyrazolones,[6f] dihydropyran-2-ones,[6g] and pyrazolines[6h]). Olsson also achieved central cyclic or α,β-enone core products from α-substituted α,β-enone compounds through combinatorial scaffold approaches.[3h] Herein we present a Lewis acid mediated ring-opening reaction of arylcarbonyl activated cyclopropanes (monoactivated cyclopropane) with arylaldehydes under mild conditions which gives α-substituted α,β-enone compounds in good yields.

2. Results and discussion

As a first try, we searched for a protocol of the reaction of phenyl cyclopropyl ketone **1a** with 4-chlorobenzaldehyde **2a** mediated by a variety of Lewis acids in dichloromethane (DCM). We found that TfOH (1.0 equiv) or TMSOTf (1.0 equiv) can effectively promoted this reaction to give α,β-enone **3a** as mixtures of *Z*- and *E*-isomers in moderate yield along with a trace amount of [3+2] cycloaddition products **4a** and **5a** in which product **5a** was determined as a dimer of **3a** (Table 1, entries 2 and 5) by spectroscopic data and NOESY spectrum (see Supporting information). Other Lewis acids such as $BF_3 \cdot OEt_2$, $Cu(OTf)_2$, AgOTf, $Zn(OTf)_2$, $Zr(OTf)_4$ and other metal triflates did not promote this reaction. Using 1,2-dichloroethane (DCE) as solvent at higher temperature (60 °C to reflux), the yield of **3a** was raised to 66% at 60 °C and 81% under reflux in the presence of TMSOTf (1.0 equiv) (Table 1, entries 7–8). In

Keywords: Cyclopropyl aryl ketones; Monoactivated cyclopropane; Lewis acid; TMSOTf; TESOTf; Ring-opening reaction; 2-(2-Hydroxyethyl)-1,3-diarylpropenone.
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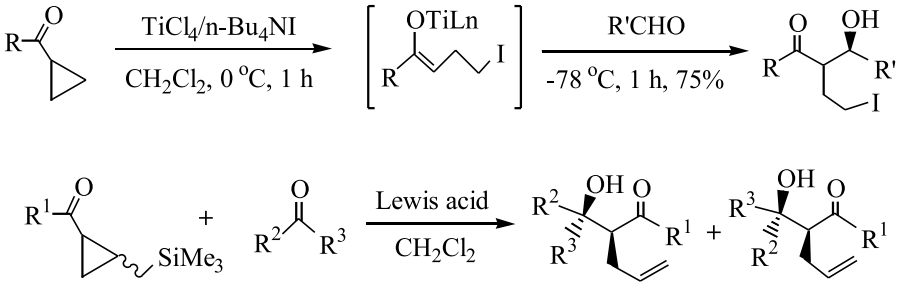
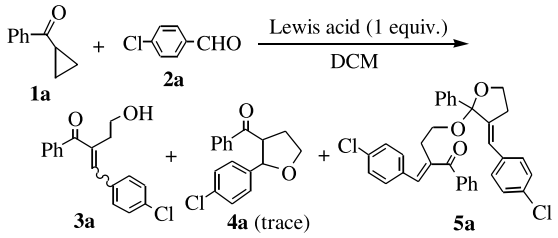


Scheme 1. Ring-opening reaction of monoactivitated cyclopropane assisted by I^- and $TiCl_4$, or assisted by the β-effect of silicon atom.

Table 1. Reaction of phenyl ketone **1a** and 4-chlorobenzaldehyde **2a** mediated by various Lewis acids



Entry	Lewis acid	Solvent	Temp.	Yield/[%][a]	Yield/[%][a]
				3a (*Z*/*E*)	**5a**
1	BF_3 OEt_2	DCM	r.t.	9 (0/100)	0
2	TfOH	DCM	r.t.	57 (15/85)	Trace
3	TfOH	DCE	60 °C	61 (16/84)	Trace
4	TfOH	DCE	Reflux	79 (45/55)	Trace
5	TMSOTf	DCM	r.t.	59 (25/75)	Trace
6[b]	TMSOTf	DCM	r.t.	10 (0/100)	0
7	TMSOTf	DCE	60 °C	66 (18/82)	Trace
8	TMSOTf	DCE	Reflux	81 (31/69)	Trace
9	TESOTf	DCE	Reflux	54 (19/81)	13

[a] Isolated yields, sterochemistry is determined by NOESY spectrum.
[b] TMSOTf (0.2 equiv).

addition, **3a** was also isolated in 61% at 60 °C and 79% under reflux in the presence of TfOH (1.0 equiv), respectively (Table 1, entries 3–4). Catalytic amounts of TMSOTf did not effectively promote this reaction (Table 1, entry 6). TESOTf was proven not as effective as TMSOTf (Table 1, entry 9).

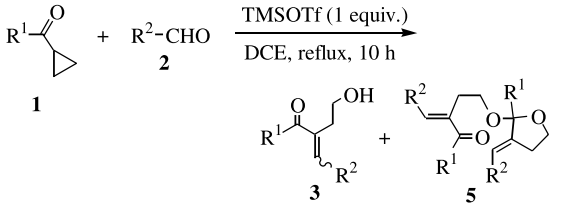
We next carried out the reactions of a variety of aryl cyclopropyl ketones with various arylaldehydes under the optimized reaction conditions. In all of the cases we examined, α,β-enones **3** were dominantly formed along with dimers **5**.[7] The results are summarized in Table 2 which indicates that α,β-enones **3**, in some cases, were obtained in low yields because of the formation of dimers **5**, and the cleanly isolated products **3** will also immediately become mixtures of **3** and **5** due to the equilibrium shown in Scheme 2.

In order to avoid the dimerization of **3**, we decide to protect the hydroxy group. As shown in Scheme 3, after the Lewis acid mediated reaction was finished, we utilized isocyanatobenzene and TESOTf to protect the hydroxy group, respectively. The corresponding carbamate **6** was obtained in 50% yield as mixtures of *Z*- and *E*-isomers. We were delighted to find that the subsequent use of TESOTf twice could efficiently promote this reaction and trap the formed hydroxy group in the presence of lutidine to give the corresponding product **7d** in 60% yield. Interestingly, **7d** was predominantly obtained as *E*-configuration under this conditions (Scheme 3).

The reaction of a variety of aryl cyclopropyl ketones with various arylaldehydes was carried out in the presence of TESOTf. The corresponding α,β-enones **7** were obtained exclusively in good to high yields in all cases as *E*-dominated configuration. The results are summarized in Table 3. In this reaction, R^1 and R^2 could be various substituted aromatic and heterocyclic groups (Table 3, entries 1–10).

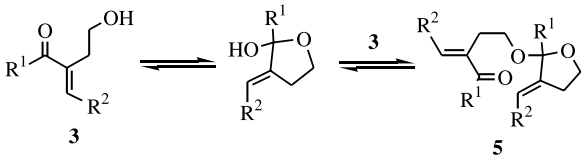
Concerning the formation of **7**-*E*, we have observed that **3**-*E* is isolated as a major product in reaction mixtures (Table 2) and compounds **3** and **5** are formed in equilibrium under ambient atmosphere as shown in Scheme 2. Interestingly, using compound **4a** as starting material, γ-hydroxy ketone **3a** was obtained in the presence of TMSOTf under reflux in DCE to give 68% isolated yield as mixtures of *Z*- and *E*-isomers (Scheme 4). This result suggests that trace amount of product **4a** is the active intermediate in this reaction. Therefore, we believe that the transformation of **3**-*Z* and **3**-*E* proceeds through intermediate **4** (Scheme 5). In any sense, **3**-*Z* suffers from severe steric interaction between

Table 2. Reaction of arylaldehydes with various arylcarbonyl activated cyclopropanes

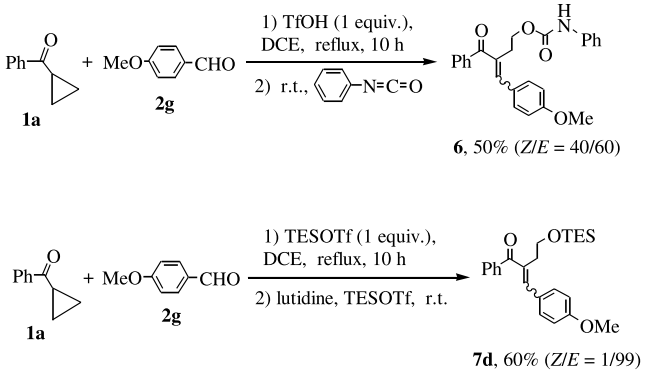


Entry	R^1	R^2	Yield/[%][a] 3 (*Z*/*E*)
1	**1a**, C_6H_5	**2b**, *p*-FC_6H_4	**3b**, 53 (17/83)
2	**1a**, C_6H_5	**2c**, *m*-ClC_6H_4	**3c**, 49 (26/74)
3	**1a**, C_6H_5	**2d**, *p*-BrC_6H_4	**3d**, 35 (0/100)
4	**1a**, C_6H_5	**2e**, C_6H_5	**3e**, 55 (30/70)
5	**1a**, C_6H_5	**2f**, *p*-MeC_6H_4	**3f**, 62 (0/100)[b]
6	**1a**, C_6H_5	**2g**, *p*-$MeOC_6H_4$	**3g**, 23 (20/80)[b]
7	**1a**, C_6H_5	**2h**, 2-furanyl	**3h**, 31 (0/100)[b]
8	**1b**, *p*-FC_6H_4	**2a**, *p*-ClC_6H_4	**3i**, 42 (0/100)
9	**1c**, *p*-MeC_6H_4	**2a**, *p*-ClC_6H_4	**3j**, 88 (24/76)
10	**1d**, *m*,*m*-$(Me)_2C_6H_3$	**2a**, *p*-ClC_6H_4	**3k**, 53 (0/100)
11	**1e**, *p*-$MeOC_6H_4$	**2a**, *p*-ClC_6H_4	**3l**, 84 (43/56)
12	**1e**, *p*-$MeOC_6H_4$	**2d**, *p*-BrC_6H_4	**3m**, 77 (23/77)
13	**1f**, 2-thiophenyl	**2a**, *p*-ClC_6H_4	**3n**, 55 (18/82)

[a] Isolated yields, sterochemistry of **3a** and **3m** is determined by NOESY, the remaining compounds were tentatively assigned according to the general trend.
[b] Determined by ^{1}H NMR spectroscopic data.



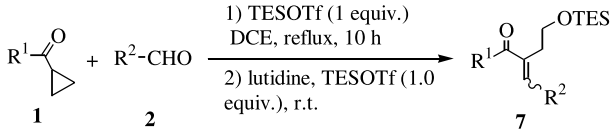
Scheme 2. Dimerization of **3**.



Scheme 3. Selection of the protection of hydroxy group.

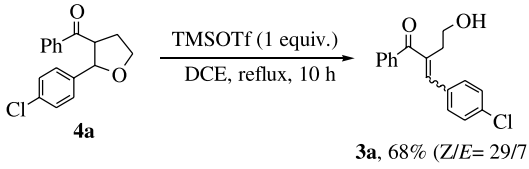
R^1 and R^2, and thus, **3**-*E* was formed in a thermodynamically favored way (Scheme 5). At any rate, the reversibility of the conjugate addition of an alcohol affected the geometrical selectivity in this reaction and give the thermodynamically stable **3**-*E* exclusively. Therefore, the enhanced stereochemistry could be explained by the equilibrium shown in Scheme 5 in which the thermodynamically favored major isomer **3**-*E* reacts with TESOTf to give **7**-*E* in the presence of lutidine. Namely, the equilibrium leans to the formation of **7**-*E* in the presence of

Table 3. Reaction of aryl cyclopropyl ketone **1** with various arylaldehydes **2** in the presence of TESOTf

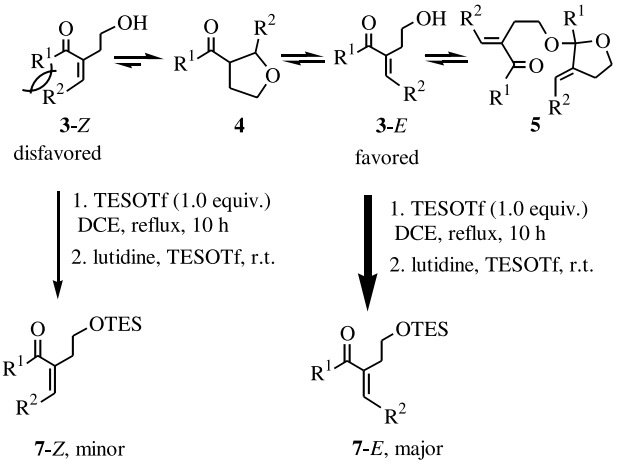


Entry	R^1	R^2	Yield/[%][a] 7 (*Z*/*E*)
1	**1a**, C_6H_5	**2a**, *p*-ClC_6H_4	**7a**, 75 (0/100)
2	**1a**, C_6H_5	**2e**, C_6H_5	**7b**, 62 (0/100)
3	**1a**, C_6H_5	**2f**, *p*-MeC_6H_4	**7c**, 81 (0/100)
4	**1a**, C_6H_5	**2g**, *p*-$MeOC_6H_4$	**7d**, 60 (1/99)[b]
5	**1a**, C_6H_5	**2h**, 2-furanyl	**7e**, 69 (1/100)[b]
6	**1b**, *p*-FC_6H_4	**2f**, *p*-MeC_6H_4	**7f**, 73 (0/100)
7	**1c**, *p*-MeC_6H_4	**2f**, *p*-MeC_6H_4	**7g**, 93 (0/100)
8	**1d**, *m*,*m*-$(Me)_2C_6H_3$	**2f**, *p*-MeC_6H_4	**7h**, 87 (0/100)
9	**1e**, *p*-$MeOC_6H_4$	**2f**, *p*-MeC_6H_4	**7i**, 74 (0/100)
10	**1f**, 2-thiophenyl	**2f**, *p*-MeC_6H_4	**7j**, 79 (0/100)

[a] Isolated yields.
[b] Determined by ^{1}H NMR spectroscopic data.



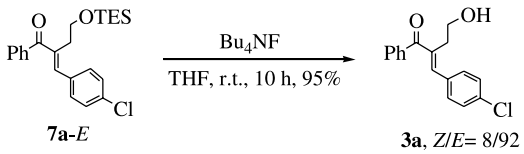
Scheme 4. Preparation of γ-hydroxyl ketone **3a** from compound **4a** in the presence of TMSOTf.



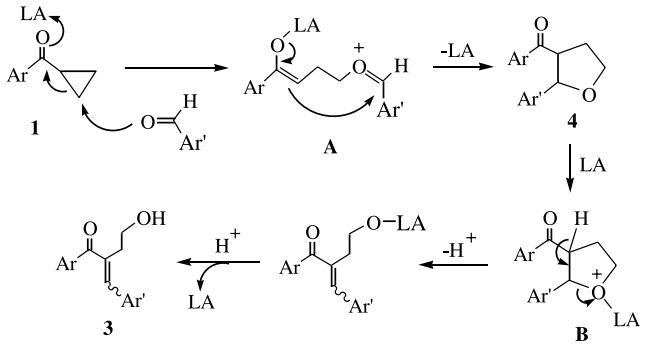
Scheme 5. Formation route of **7**-*E* in the reaction mixtures.

TESOTf and lutidine (Scheme 5). The dimerization of **3**-*E* partially take places to afford the sterically demanding dimer **5** as shown in Scheme 3 (compound **5a** has been isolated in enough purity).

At room temperature, Bu_4NF can easily cleave triethylsilyl group from **7a**-*E* to give 2-(2-hydroxyethyl)-1,3-diaryl-propenone **3a** in high yield. Since equilibrium shown in Scheme 5 exists, mixtures of *Z*- and *E*-isomers were obtained with ratio of 8/92 at the beginning (Scheme 6).



Scheme 6. Deprotection of **7a**-*E*.



Scheme 7. The plausible reaction mechanism in the reaction of aryladehydes with arylcarbonyl activated cyclopropane mediated by Lewis acid.

Further store under ambient atmosphere will be accompanied by the formation of dimer **5**. Therefore, the products **3** should be used for the next reaction immediately because of their labilities.

Based on the above results, a plausible reaction mechanism is proposed in Scheme 7. In the presence of Lewis acid, the attack of carbonyl oxygen atom of arylaldehyde to three-membered ring of cyclopropyl aryl ketone **1** gives enolate oxonium ion **A**, which produces the key intermediate **4** through intramolecular aldol reaction, as a [3+2] cycloaddition product. 2-(2-Hydroxyethyl)-1,3-diarylpropenone **3** is formed through proton transfer of the intermediate **B** derived from **4** in the presence of Lewis acid. Overall, this reaction is facile process for the preparation of 2-(2-hydroxyethyl)-1,3-diarylpropenones.

3. Conclusion

In conclusion, we have found that Lewis acid TMSOTf can effectively mediate the ring-opening reaction of cyclopropyl aryl ketones with arylaldehydes to give the products 2-(2-hydroxyethyl)-1,3-diarylpropenones **3** along with dimers **5**. The products **3** are labile compounds because of the subsequent rapid dimerization. The subsequent twice use of Lewis acid TESOTf gives hydroxyl group protected products **7** with high geometrical selectivities (predominantly *E* configuration) in good yields.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively. Mass spectra were recorded by EI, SCI and ESI methods, and HRMS was measured on Kratos Analytical Concept mass spectrometer (EI), Bruker FT mass spectrometer (ESI), and IonSpec 4.7 Tesla FFMS (MALDI). Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Yinlong GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

4.2. General procedure for the reactions of cyclopropyl aryl ketones with arylaldehyde

Under argon atmosphere, the mixture of cyclopropyl aryl ketone (**1**, 0.5 mmol), arylaldehyde (**2**, 0.5 mmol) and TMSOTf (1.0 equiv) was dissolved in 1,2-dichloroethane (DCE, 1.5 mL) and the reaction mixture was refluxed for 10 h. The reaction solution was cooled to room temperature and then quenched by the addition of aqueous $NaHCO_3$ solution. The reaction mixture was washed with H_2O (50 mL) and extracted by dichloromethane (3×15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography using petroleum ether/ethyl acetate (10/1) as an eluent to give ring-opened product 2-(2-hydroxyethyl)-1,3-diarylpropenone **3** as an oily product.

Under argon atmosphere, the mixture of cyclopropyl aryl ketone (**1**, 0.5 mmol), arylaldehyde (**2**, 0.5 mmol) and TESOTf (1.0 equiv) was dissolved in 1,2-dichloroethane (DCE, 1.5 mL) and the reaction mixture was refluxed for 10 h. The reaction solution was cooled to room temperature, then lutidine (480 μL, 4.0 mmol) and TESOTf (216 μL, 1.0 mmol) were added subsequently and the reaction solution was stirred for another 2 h. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography using petroleum ether as an eluent to give the product 1,3-diaryl-2-(2-triethylsilanyloxyethyl)propenone **7** as an oily product.

4.3. The reaction of cyclopropyl phenyl ketone with 4-methoxyphenylaldehyde 2g or Furanylaldehyde 2h

Aldehyde **2g** or **2h** (0.5 equiv) was added dropwise to a refluxing mixture of phenyl cyclopropyl ketone and TESOTf (1.0 equiv) for 1 h. Then the reaction solution was stirred under reflux for another 2 h. The reaction was cooled to room temperature and then was quenched by the addition of aqueous $NaHCO_3$ solution. The reaction mixture was washed with H_2O (50 mL) and extracted by dichloromethane (3×15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography using petroleum as an eluent to give product **3g** (23%) or **3h** (31%) as a red oily product.

4.4. The procedure of desilylation of compound 7a

$Bu_4NF\cdot 3H_2O$ (236 mg, 0.74 mmol) was added to a solution of 3-(4-chlorophenyl)-1-phenyl-2-(2-triethylsilanyloxyethyl)propenone **7a** (150 mg, 0.37 mmol) in THF (10 mL) and the reaction mixture was stirred at room temperature for 10 h. Then the solvent was removed under

reduced pressure and the residue was purified by a silica gel column chromatography using petroleum ether/ethyl acetate (10/1) as an eluent to give product **3a**-*E* (94 mg) and **3a**-*E* (8 mg) as red oil.

4.4.1. *E*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-phenylpropenone (3a-*E*). This compound was obtained as a red oil, yield: 80 mg, 56%. IR (CH_2Cl_2): ν 1014, 1045, 1093, 1179, 1246, 1316, 1374, 1447, 1490, 1578, 1595, 1646, 1736, 2931, 3060, 3462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.82 (s, 1H, OH), 2.96 (t, J=6.3 Hz, 2H, CH_2), 3.85 (t, J=6.3 Hz, 2H, CH_2), 7.15 (s, 1H, CH), 7.35 (d, J=8.7 Hz, 2H, Ar), 7.36 (dt, J=6.6 Hz, J=7.2 Hz, 2H, Ar), 7.45 (dt, J=1.5 Hz, J=6.6 Hz, 2H, Ar), 7.56 (tt, J=7.2 Hz, J=1.5 Hz, 1H, Ar), 7.78 (d, J=8.7 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 31.0, 61.4, 128.3, 128.8, 129.73, 130.5, 132.3, 133.5, 134.7, 137.9, 139.2, 142.1, 199.9; MS (EI) *m/z*: 288 (3), 286 (M^+, 9), 256 (38), 255 (27), 221 (22), 115 (55), 105 (87), 77 (100), 51 (33); HRMS (EI) Calcd. for $C_{17}H_{15}O_2Cl$: 286.0761, Found: 286.0764.

4.4.2. *Z*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-phenyl-propenone (3a-*Z*). This compound was obtained as a red oil, yield: 36 mg, 25%. IR (CH_2Cl_2): ν 1013, 1048, 1092, 1176, 1234, 1265, 1312, 1378, 1404, 1449, 1491, 1579, 1594, 1653, 1720, 2927, 3059, 3429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.72 (dt, J=0.9 Hz, J=6.0 Hz, 2H, CH_2), 3.82 (t, J=6.0 Hz, 2H, CH_2), 6.81 (s, 1H, CH), 7.03 (d, J=7.5 Hz, 2H, Ar), 7.06 (dt, J=5.7 Hz, J=7.5 Hz, 2H, Ar), 7.34 (tt, J=5.7 Hz, J=1.5 Hz, 2H, Ar), 7.48 (tt, J=1.5 Hz, J=7.5 Hz, 1H, Ar), 7.88 (d, J=7.5 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 39.8, 61.3, 128.4, 128.5, 128.7, 129.5, 129.8, 131.5, 133.6, 133.8, 135.2, 138.9, 200.9; MS (EI) *m/z*: 288 (1), 286 (M^+, 4), 257 (21), 255 (22), 221 (21), 115 (28), 105 (100), 77 (67), 51 (16); HRMS (EI) Calcd. for $C_{17}H_{15}O_2Cl$: 286.0761, Found: 286.0767.

4.4.3. *E*-3-(4-Fluorophenyl)-2-(2-hydroxyethyl)-1-phenylpropenone (3b-*E*). Only the mixture of **3b**-*E* and the dimer were obtained as a red oil, yield: 59 mg, 44%. IR (CH_2Cl_2): ν 1054, 1098, 1159, 1177, 1229, 1265, 1292, 1307, 1379, 1447, 1508, 1578, 1600, 1646, 1720, 2887, 2927, 3058, 3472 cm^{-1}; ^1H NMR of **3b**-*E* (300 MHz, $CDCl_3$, TMS): δ 2.98 (t, J=6.0 Hz, 2H, CH_2), 3.88 (t, J=6.0 Hz, 2H, CH_2), 7.05 (dd, J=8.1 Hz, $J_{H\text{-}F}$=8.9 Hz, 2H, Ar), 7.12 (dt, J=5.7 Hz, J=7.5 Hz, 2H, Ar), 7.19 (s, 1H, CH), 7.46 (dt, J=5.7 Hz, J=0.9 Hz, 2H, Ar), 7.56 (tt, J=7.2 Hz, J=0.9 Hz, 1H, Ar), 7.78 (dd, J=8.1 Hz, $J_{H\text{-}F}$=3.3 Hz, 2H, Ar); MS (EI) *m/z*: 270 (M^+, 7), 239 (22), 133 (66), 105 (74), 77 (100), 57 (45), 51 (62), 49 (84), 43 (83); HRMS (EI) Calcd. for $C_{17}H_{15}O_2F$: 270.1056, Found: 270.1079.

4.4.4. *Z*-3-(4-Fluorophenyl)-2-(2-hydroxyethyl)-1-phenylpropenone (3b-*Z*). This compound was obtained as a red oil, yield: 12 mg, 9%. IR (CH_2Cl_2): ν 1047, 1160, 1177, 1229, 1290, 1312, 1449, 1508, 1579, 1600, 1653, 2852, 2924, 3062, 3433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.31 (s, 1H, OH), 2.72 (dt, J=0.9 Hz, J=6.0 Hz, 2H, CH_2), 3.82 (t, J=6.0 Hz, 2H, CH_2), 6.79 (dd, J=6.6 Hz, $J_{H\text{-}F}$=8.4 Hz, 2H, Ar), 6.84 (s, 1H, CH), 7.09 (dt, J=7.2 Hz, J=7.5 Hz, 2H, Ar), 7.32 (dt, J=1.2, 7.2 Hz, 2H, Ar), 7.47 (tt, J=7.5 Hz, J=1.2 Hz, 1H, Ar), 7.78 (dd, J=6.6 Hz, $J_{H\text{-}F}$=1.5 Hz, 2H, Ar); MS (EI) *m/z*: 270 (M^+, 9), 241 (23), 240 (66), 239 (46), 133 (64), 109 (17), 105 (100), 77 (99), 51 (32); HRMS (EI) Calcd. for $C_{17}H_{15}O_2F$: 270.1056, Found: 270.1077.

4.4.5. *E*-3-(3-Chlorophenyl)-2-(2-hydroxyethyl)-1-phenylpropenone (3c-*E*). Only the mixture of **3c**-*E* and the dimer were obtained as a red oil, yield: 51 mg, 36%. IR (CH_2Cl_2): ν 1028, 1055, 1080, 1158, 1227, 1265, 1283, 1428, 1447, 1475, 1563, 1594, 1649, 1721, 2853, 2924, 3061, 3493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.97 (t, J=6.6 Hz, 2H, CH_2), 3.88 (t, J=6.6 Hz, 2H, CH_2), 7.13 (s, 1H, CH), 7.30 (t, J=8.1 Hz, 1H, Ar), 7.32 (dt, J=1.2 Hz, J=7.5 Hz, 2H, Ar), 7.41 (s, 1H, Ar), 7.47 (dt, J=6.3 Hz, J=7.5 Hz, 2H, Ar), 7.58 (tt, J=6.3 Hz, J=1.2 Hz, 1H, Ar), 7.81 (d, J=8.1 Hz, 2H, Ar); MS (EI) *m/z*: 288 (4), 286 (M^+, 12), 257 (21), 256 (19), 221 (14), 115 (53), 105 (76), 86 (26), 77 (100), 51 (38), 49 (20); HRMS (EI) Calcd. for $C_{17}H_{15}O_2Cl$: 286.0761, Found: 286.0786.

4.4.6. *Z*-3-(3-Chlorophenyl)-2-(2-hydroxyethyl)-1-phenylpropenone (3c-*Z*). This compound was obtained as a red oil, yield: 18 mg, 13%. IR (CH_2Cl_2): ν 1046, 1080, 1177, 1235, 1377, 1449, 1466, 1564, 1579, 1594, 1655, 1720, 2851, 2924, 2956, 3412 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.73 (dt, J=0.9 Hz, J=6.0 Hz, 2H, CH_2), 3.83 (t, J=6.0 Hz, 2H, CH_2), 6.81 (s, 1H, CH), 6.99 (t, J=8.1 Hz, 1H, Ar), 7.02 (dt, J=1.2 Hz, J=7.5 Hz, 2H, Ar), 7.11 (s, 1H, Ar), 7.33 (dt, J=6.3 Hz, J=7.5 Hz, 2H, Ar), 7.47 (tt, J=6.3 Hz, J=1.2 Hz, 1H, Ar), 7.87 (d, J=8.1 Hz, 2H, Ar); MS (EI) *m/z*: 288 (2), 286 (M^+, 5), 257 (29), 256 (64), 221 (27), 115 (39), 105 (100), 77 (82), 43 (23); HRMS (EI) Calcd. for $C_{17}H_{15}O_2Cl$: 286.0761, Found: 286.0783.

4.4.7. *E*-3-(4-Bromophenyl)-2-(2-hydroxyethyl)-1-phenylpropenone (3d-*E*). This compound was obtained as a red oil, yield: 57 mg, 35%. IR (CH_2Cl_2): ν 1010, 1040, 1073, 1159, 1178, 1261, 1282, 1317, 1380, 1447, 1487, 1585, 1597, 1645, 2252, 2884, 2927, 3061, 3443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.91 (s, 1H, OH), 2.96 (t, J=6.3 Hz, 2H, CH_2), 3.86 (t, J=6.3 Hz, 2H, CH_2), 7.14 (s, 1H, CH), 7.31 (d, J=8.4 Hz, 2H, Ar), 7.44–7.59 (m, 5H, Ar), 7.78 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 31.0, 61.4, 123.0, 128.3, 129.7, 130.7, 131.7, 132.3, 133.9, 137.8, 139.2, 142.3, 200.0; MS (EI) *m/z*: 315 (27), 313 [(M-17)$^+$, 27], 128 (13), 115 (17), 105 (100), 77 (44); HRMS (MALDI) Calcd. for $C_{17}H_{15}O_2Br$+H: 331.0334, Found: 331.0337.

4.4.8. *E*-2-(2-Hydroxyethyl)-1,3-diphenylpropenone (3e-*E*). This compound was obtained as a red oil, yield: 48 mg, 38%. IR (CH_2Cl_2): ν 1002, 1027, 1054, 1159, 1177, 1265, 1319, 1379, 1447, 1492, 1577, 1597, 1464, 2885, 2926, 3026, 3057, 3443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 3.00 (t, J=6.3 Hz, 2H, CH_2), 3.88 (t, J=6.3 Hz, 2H, CH_2), 7.24 (s, 1H, CH), 7.37–7.56 (m, 8H, Ar), 7.80 (d, J=7.2 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 31.1, 61.8, 128.3, 128.6, 128.8, 129.2, 129.8, 132.2, 135.1, 138.1, 138.7, 143.9, 200.4; MS (EI) *m/z*: 252 (M^+, 2), 234 (4), 222 (13), 115 (12), 105 (49), 86 (67), 84 (100), 77 (31); HRMS (EI) Calcd. for $C_{17}H_{16}O_2$: 252.1150, Found: 252.1160.

4.4.9. *Z*-2-(2-Hydroxyethyl)-1,3-diphenylpropenone (3e-*Z*). This compound was obtained as a red oil, yield: 21 mg, 17%. IR (CH_2Cl_2): ν 1047, 1176, 1235, 1379, 1449, 1597, 1655, 2855, 2927, 3435 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.74 (t, $J=5.7$ Hz, 2H, CH_2), 3.84 (t, $J=5.7$ Hz, 2H, CH_2), 6.89 (s, 1H, CH), 7.09–7.14 (m, 5H, Ar), 7.33 (dt, $J=7.2$ Hz, $J=8.4$ Hz, 2H, Ar), 7.46 (tt, $J=1.5$ Hz, $J=7.2$ Hz, 1H, Ar), 7.90 (dt, $J=1.5$ Hz, $J=8.4$ Hz, 2H, Ar).

4.4.10. *E*-2-(2-Hydroxyethyl)-1-phenyl-3-p-tolylpropenone (3f). Only the mixture of **3f**-*Z*, **3f**-*E* and the dimer were obtained as a red oil, yield: 82 mg, 62%. IR (CH_2Cl_2): ν 1043, 1113, 1159, 1177, 1265, 1319, 1380, 1447, 1511, 1578, 1643, 1716, 2886, 2924, 3026, 3057, 3459 cm^{-1}; ^1H NMR of **3f**-*E* (300 MHz, $CDCl_3$, TMS): δ 2.38 (s, 3H, CH_3), 3.03 (t, $J=6.3$ Hz, 2H, CH_2), 3.91 (t, $J=6.3$ Hz, 2H, CH_2), 7.08 (s, 1H, CH), 7.15 (dt, $J=6.6$ Hz, $J=7.2$ Hz, 2H, Ar), 7.30 (d, $J=7.2$ Hz, 1H, Ar), 7.41 (dt, $J=1.5$ Hz, $J=7.2$ Hz, 2H, Ar), 7.56 (tt, $J=1.5$ Hz, $J=6.6$ Hz, 1H, Ar), 7.78 (d, $J=7.2$ Hz, 2H, Ar); MS (EI) *m/z*: 266 (M^+, 3), 248 (2), 236 (18), 233 (12), 221 (22), 122 (27), 105 (100), 77 (57), 51 (12); HRMS (MALDI) Calcd. for $C_{18}H_{18}O_2+H$: 267.1386, Found: 267.1378.

4.4.11. *E*-2-(2-Hydroxyethyl)-3-(4-methoxyphenyl)-1-phenylpropenone (3g). Only the mixture of **3g**-*Z*, **3g**-*E* and the dimer were obtained as a red oil, yield: 40 mg, 28%, *Z*/*E*=20/80 (determined by ^1H NMR spectroscopic data). IR (CH_2Cl_2): ν 1032, 1070, 1115, 1159, 1177, 1252, 1385, 1421, 1450, 1464, 1511, 1604, 1643, 1716, 2837, 2933, 3058, 3507 cm^{-1}; ^1H NMR of **3g**-*E* (300 MHz, $CDCl_3$, TMS): δ 3.05 (t, $J=6.3$ Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.92 (t, $J=6.3$ Hz, 2H, CH_2), 6.93 (d, $J=8.4$ Hz, 1H, Ar), 7.22 (s, 1H, CH), 7.41–7.48 (m, 5H, Ar), 7.77 (d, $J=8.4$ Hz, 2H, Ar); MS (EI) *m/z*: 282 (M^+, 6), 265 (1), 252 (10), 233 (7), 221 (13), 121 (13), 115 (12), 105 (100), 103 (15), 78 (9), 77 (63); HRMS (EI) Calcd. for $C_{18}H_{18}O_3$: 282.1256, Found: 282.1262.

4.4.12. 3-Furan-2-yl-2-(2-hydroxyethyl)-1-phenylpropenone (3h). Only the mixture of **3h**-*Z*, **3h**-*E* and the dimmer were obtained as a red oil, yield: 28 mg, 23%, E/Z=7/93 (determined by ^1H NMR spectroscopic data). IR (CH_2Cl_2): ν 1022, 1155, 1178, 1220, 1266, 1317, 1369, 1421, 1448, 1616, 1643, 1717, 2929, 3055, 3420 cm^{-1}; ^1H NMR of **3h**-*E* (300 MHz, $CDCl_3$, TMS): δ 3.17 (t, $J=6.3$ Hz, 2H, CH_2), 3.94 (t, $J=6.3$ Hz, 2H, CH_2), 6.63 (d, $J=3.6$ Hz, 1H, Ar), 6.48 (dd, $J=3.6$ Hz, $J=7.8$ Hz, 1H, CH), 6.96 (s, 1H, CH), 7.28–7.74 (m, 5H, Ar), 8.11 (d, $J=7.8$ Hz, 1H, Ar); MS (EI) *m/z*: 242 (M^+, 5), 212 (12), 122 (49), 105 (100), 86 (16), 84 (25), 77 (68), 51 (34), 50 (15); HRMS (MALDI) Calcd. for $C_{15}H_{15}O_3+H$: 243.1022, Found: 243.1023.

4.4.13. *E*-3-(4-Chlorophenyl)-1-(4-fluorophenyl)-2-(2-hydroxyethyl)propenone (3i-*E*). This compound was obtained as a red oil, yield: 64 mg, 42%. IR (CH_2Cl_2): ν 1013, 1056, 1093, 1156, 1232, 1281, 1308, 1375, 1407, 1491, 1506, 1597, 1648, 2887, 2928, 3481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.96 (t, $J=6.3$ Hz, 2H, CH_2), 3.87 (t, $J=6.3$ Hz, 2H, CH_2), 7.11 (s, 1H, CH), 7.14 (dd, $J=8.7$ Hz, $J_{H\text{-}F}=8.7$ Hz, 2H, Ar), 7.38 (s, 4H, Ar), 7.78 (dd, $J=8.7$ Hz, $J_{H\text{-}F}=5.7$ Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 31.1, 61.4, 115.5 (d, $J_{C\text{-}F}=21.8$ Hz), 128.8, 130.5, 132.4 (d, $J_{C\text{-}F}=9.1$ Hz), 133.3, 134.0 (d, $J_{C\text{-}F}=3.0$ Hz), 134.8, 139.1, 141.6, 165.3 (d, $J_{C\text{-}F}=253.1$ Hz), 198.5; MS (EI) *m/z*: 306 (1), 304 (M^+, 3), 287 (2), 274 (15), 239 (22), 149 (10), 123 (100), 115 (17), 95 (43), 86 (19), 84 (30), 75 (12); HRMS (MALDI) Calcd. for $C_{17}H_{15}O_2ClF+H$: 305.0745, Found: 305.0740.

4.4.14. *E*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-p-tolylpropenone (3j-*E*). Only the mixture of **3j**-*E* and dimer were obtained as a red oil, yield: 115 mg, 77%. IR (CH_2Cl_2): ν 1013, 1055, 1092, 1157, 1180, 1261, 1282, 1312, 1377, 1406, 1490, 1606, 1645, 2886, 2924, 3029, 3468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.42 (s, 1H, CH_3), 2.95 (t, $J=6.0$ Hz, 2H, CH_2), 3.84 (t, $J=6.0$ Hz, 2H, CH_2), 7.12 (s, 1H, CH), 7. 25 (d, $J=7.8$ Hz, 2H, Ar), 7.36 (s, 4H, Ar), 7.71 (d, $J=7.8$ Hz, 2H, Ar); MS (EI) *m/z*: 302 (2), 300 (M^+, 6), 285 (4), 271 (14), 255 (46), 119 (88), 115 (19), 91 (50), 84 (100), 49 (18), 47 (20); HRMS (MALDI) Calcd. for $C_{18}H_{17}ClO_2+H$: 301.0995, Found: 301.0999.

4.4.15. *Z*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-p-tolylpropenone (3j-*Z*). This compound was obtained as a red oil, yield: 16 mg, 11%. IR (CH_2Cl_2): ν 1014, 1043, 1092, 1177, 1237, 1377, 1407, 1491, 1604, 1655, 1712, 2840, 2924, 3030, 3425 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.42 (s, 3H, CH_3), 2.70 (t, $J=5.7$ Hz, 2H, CH_2), 3.81 (t, $J=5.7$ Hz, 2H, CH_2), 6.75 (s, 1H, CH), 7.04–7.10 (m, 4H, Ar), 7.14 (d, $J=8.1$ Hz, 2H, Ar), 7.61 (d, $J=8.1$ Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 21.7, 39.8, 61.3, 128.4, 128.8, 129.5, 129.6, 129.7, 130.9, 133.4, 133.9, 138.9, 145.0, 200.6; MS (EI) *m/z*: 302 (1), 300 (M^+, 3), 285 (2), 270 (23), 257 (19), 255 (53), 119 (100), 115 (26), 65 (26); HRMS (MALDI) Calcd. for $C_{18}H_{17}ClO_2+Na$: 323.0815, Found: 323.0820.

4.4.16. *E*-3-(4-Chlorophenyl)-1-(3,5-dimethylphenyl)-2-(2-hydroxyethyl)propenone (3k-*E*). This compound was obtained as a red oil, yield: 83 mg, 53%. IR (CH_2Cl_2): ν 1013, 1048, 1093, 1207, 1299, 1315, 1381, 1439, 1490, 1602, 1643, 2921, 3445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.36 (s, 6H, CH_3), 2.96 (t, $J=6.0$ Hz, 2H, CH_2), 3.85 (t, $J=6.0$ Hz, 2H, CH_2), 7.16 (s, 1H, CH), 7.19 (s, 1H, Ar), 7.33–7.40 (m, 6H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 21.1, 31.0, 61.4, 127.4, 128.7, 130.5, 133.6, 133.9, 134.6, 137.9, 138.0, 139.3, 142.0, 200.3; MS (EI) *m/z*: 316 (4), 314 (M^+, 11), 285 (22), 269 (31), 261 (13), 255 (4), 159 (14), 133 (100), 115 (29), 105 (63), 91 (50), 84 (48), 79 (29), 77 (29); HRMS (MALDI) Calcd. for $C_{19}H_{19}ClO_2+Na$: 337.0971, Found: 337.0973.

4.4.17. *E*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-(4-methoxyphenyl)propenone (3l-*E*). Only the mixture of **3l**-*E* and the dimer were obtained as a red oil, yield: 76 mg, 48%. IR (CH_2Cl_2): ν 1013, 1030, 1092, 1170, 1254, 1310, 1375, 1420, 1441, 1463, 1490, 1509, 1573, 1598, 1641, 1713, 2840, 2934, 3053, 3446 cm^{-1}; ^1H NMR of **3l**-*E* (300 MHz, $CDCl_3$, TMS): δ 2.96 (t, $J=6.0$ Hz, 2H, CH_2), 3.86 (t, $J=6.0$ Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 6.97 (d, $J=9.0$ Hz, 2H, Ar), 7. 10 (s, 1H, CH), 7.39 (s, 4H, Ar), 7.87 (d, $J=9.0$ Hz, 2H, Ar); MS (EI) *m/z*: 318 (4), 316 (M^+, 11), 287 (35), 286 (17), 285 (18), 257 (13), 255 (34), 251 (7), 135

(100), 115 (10), 77 (11); HRMS (EI) Calcd. for $C_{18}H_{17}ClO_3$: 316.0866, Found: 316.0855.

4.4.18. *Z*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-(4-methoxyphenyl)propenone (3l-*Z*). This compound was obtained as a red oil, yield: 57 mg, 36%. IR (CH_2Cl_2): ν 1014, 1030, 1092, 1169, 1252, 1313, 1376, 1421, 1442, 1462, 1491, 1509, 1572, 1598, 1648, 1712, 2841, 2933, 3054, 3449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.68 (t, J=6.0 Hz, 2H, CH_2), 3.80 (t, J=6.0 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 6.72 (s, 1H, CH), 6.81 (d, J=8.7 Hz, 2H, Ar), 7.07(s, 4H, Ar), 7.87 (d, J=8.7 Hz, 2H, Ar); MS (EI) *m/z*: 318 (2), 316 (M^+, 4), 287 (18), 286 (25), 285 (12), 257 (11), 255 (27), 251 (6), 135 (100), 115 (23), 92 (24), 84 (54), 77 (37); HRMS (EI) Calcd. for $C_{18}H_{17}ClO_3$: 316.0866, Found: 316.0870.

4.4.19. *E*-3-(4-Bromophenyl)-2-(2-hydroxyethyl)-1-(4-methoxyphenyl)propenone (3m-*E*). Only the mixture of **3m**-*E* and the dimer were obtained as a red oil, yield: 107 mg, 59%. IR (CH_2Cl_2): ν 1009, 1030, 1073, 1170, 1253, 1282, 1308, 1487, 1509, 1598, 1640, 2839, 2933, 3052, 3444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.93 (t, J=6.0 Hz, 2H, CH_2), 3.82 (t, J=6.0 Hz, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.94 (d, J=9.0 Hz, 2H, Ar), 7. 05 (s, 1H, CH), 7.30 (d, J=8.7 Hz, 4H, Ar), 7.51 (d, J=8.7 Hz, 2H, Ar), 7.51 (d, J=9.0 Hz, 2H, Ar); MS (EI) *m/z*: 362 (7), 360 (M^+, 7), 344 (2), 331 (27), 301 (20), 263 (11), 251 (7), 161 (8), 135 (100), 115 (16), 77 (17); HRMS (MALDI) Calcd. for $C_{18}H_{18}BrO_3$+H: 361.0440, Found: 361.0426.

4.4.20. *Z*-3-(4-Bromophenyl)-2-(2-hydroxyethyl)-1-(4-methoxyphenyl)propenone (3m-*Z*):. This compound was obtained as a pale-yellow oil, yield: 32 mg, 18%. IR (CH_2Cl_2): ν 1009, 1029, 1073, 1167, 1247, 1314, 1376, 1421, 1487, 1509, 1572, 1597, 1649, 2840, 2932, 2961, 3412 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.69 (t, J=5.7 Hz, 2H, CH_2), 3.80 (t, J=5.7 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 6.71 (s, 1H, CH), 6.83 (d, J=8.7 Hz, 2H, Ar), 7.01(d, J=8.7 Hz, 2H, Ar), 7.24 (d, J=8.4 Hz, 2H, Ar), 7.88 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 39.7, 61.2, 66.4, 114.0, 121.6, 128.0, 130.0, 130.5, 131.3, 131.9, 134.3, 139.1, 161.2, 199.5; MS (EI) *m/z*: 362 (5), 360 (M^+, 5), 332 (31), 299 (29), 263 (5), 251 (9), 161 (9), 135 (100), 115 (20), 77 (20); HRMS (MALDI) Calcd. for $C_{18}H_{18}BrO_3$+H: 361.0440, Found: 361.0425.

4.4.21. *E*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-thiophen-2-yl-propenone (3n-*E*). This compound was obtained as a red oil, yield: 66 mg, 45%, IR (CH_2Cl_2): ν 1013, 1051, 1092, 1231, 1262, 1258, 1309, 1353, 1413, 1490, 1513, 1621, 1712, 1884, 2926, 3053, 3448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.94 (t, J=6.3 Hz, 2H, CH_2), 3.84 (t, J=6.3 Hz, 2H, CH_2), 7.16 (t, J=4.8 Hz, 1H, Ar), 7.37–7.44 (m, 5H, Ar), 7.71–7.46 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 31.6, 61.3, 127.9, 128.8, 130.5, 133.5, 134.4, 134.5, 134.6, 139.2, 139.4, 143.3, 191.0; MS (EI) *m/z*: 294 (2), 292 (M^+, 6), 262 (30), 247 (3), 239 (9), 227 (31), 211 (5), 149 (12), 115 (24), 111 (100), 84 (46); HRMS (MALDI) Calcd. for $C_{15}H_{14}O_2SCl$+H: 293.0403, Found: 293.0393.

4.4.22. *Z*-3-(4-Chlorophenyl)-2-(2-hydroxyethyl)-1-thiophen-2-yl-propenone (3n-*Z*). This compound was obtained as a red oil, yield: 15 mg, 10%, IR (CH_2Cl_2): ν 1013, 1050, 1092, 1248, 1279, 1352, 1378, 1410, 1490, 1513, 1593, 1625, 2924, 3088, 3308 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.73 (t, J=6.3 Hz, 2H, CH_2), 3.84 (t, J=6.3 Hz, 2H, CH_2), 6.77 (s, 1H, CH), 6.94 (dd, J=4.8 Hz, J=3.6 Hz, 1H, Ar), 7.13 (s, 4H, Ar), 7.51 (dd, J=3.6 Hz, J=0.9 Hz, 2H, Ar), 7.60 (dd, J=4.8 Hz, J=0.9 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 39.7, 61.4, 128.4, 128.5, 129.8, 131.5, 133.7, 133.9, 135.1, 135.6, 139.0, 142.8, 192.8; MS (EI) *m/z*: 294 (1), 292 (M^+, 2), 262 (21), 247 (2), 239 (3), 227 (20), 211 (2), 149 (8), 139 (78), 115 (14), 111 (100), 75 (29); HRMS (MALDI) Calcd. for $C_{15}H_{13}O_2SCl$+Na: 315.0222, Found: 315.0227.

4.4.23. [2-(4-Chlorophenyl)-tetrahydrofuran-3-yl]phenylmethanone (4a). This compound was obtained as a red oil. IR (CH_2Cl_2): ν 1014, 1067, 1089, 1180, 1216, 1280, 1363, 1410, 1448, 1491, 1580, 1597, 1680, 2871, 2926, 3058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.24–2.35 (m, 1H, CH_2), 2.42–2.55 (m, 1H, CH_2), 3.82–3.90 (m, 1H, CH), 4.04–4.11 (m, 1H, CH_2), 4.22–4.30 (m, 1H, CH_2), 5.26 (d, J=7.2 Hz, 1H, CH), 7.28 (s, 4H, Ar), 7.43 (t, J=7.5 Hz, 2H, Ar), 7.56 (t, J=7.5 Hz, 1H, Ar), 7.84 (d, J=7.5 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 32.2, 54.8, 68.4, 82.3, 127.2, 128.4, 128.5, 128.7, 133.3, 133.4, 136.3, 140.1, 199.5; MS (EI) *m/z*: 288 (5), 286 (M^+, 14), 258 (61), 257 (74), 223 (2), 181 (11), 146 (27), 139 (17), 105 (100), 77 (54); HRMS (EI) Calcd. for $C_{17}H_{15}O_2Cl$: 286.0755, Found: 286.0727.

4.4.24. 3-(4-Chlorophenyl)-1-phenyl-2-(2-triethylsilanyloxyethyl)propenone (7a). This compound was obtained as a red oil, yield: 150 mg, 75%. IR (CH_2Cl_2): ν 1015, 1046, 1092, 1229, 1260, 1282, 1315, 1386, 1413, 1447, 1458, 1490, 1596, 1650, 1705, 2875, 2910, 2955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.58 (q, J=8.4 Hz, 6H, CH_2,), 0.93 (t, J=8.4 Hz, 9H, CH_2), 2.96 (t, J=6.3 Hz, 2H, CH_2), 3.86 (t, J=6.3 Hz, 2H, CH_2), 7.13 (s, 1H, CH), 7.34 (d, J=6.9 Hz, 2H, Ar), 7.42–7.54 (m, 5H, Ar), 7.79 (d, J=6.9 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.7, 31.1,, 61.0, 128.1, 128.5, 129.7, 130.7, 131.9, 133.9, 134.41, 138.5, 139.6, 141.7, 198.9; MS (EI) *m/z*: 400 (M^+, 1), 371 (99), 307 (6), 269 (10), 233 (21), 139 (61), 125 (29), 117 (79), 105 (90), 77 (100); Anal. Calcd. for $C_{23}H_{29}ClO_2Si$: C, 68.89, H, 7.29%; Found: C, 69.20, H, 7.37%.

4.4.25. 1,3-Diphenyl-2-(2-triethylsilanyloxyethyl)propenone (7b). This compound was obtained as a red oil, yield: 114 mg, 62%. IR (CH_2Cl_2): ν 1016, 1047, 1094, 1178, 1231, 1263, 1320, 1379, 1414, 1448, 1494, 1577, 1597, 1650, 2875, 2955, 3026, 3060, 3516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.58 (q, J=8.4 Hz, 6H, CH_2), 0.93 (t, J=8.4 Hz, 9H, CH_2), 3.10 (t, J=6.6 Hz, 2H, CH_2), 3.87 (t, J=6.6 Hz, 2H, CH_2), 7.20 (s, 1H, CH), 7.32–7.41 (m, 5H, Ar), 7.51–7.55 (m, 3H, Ar), 7.80 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.7, 31.1, 61.1, 128.1, 128.3, 128.5, 129.3, 129.7, 131.8, 135.4, 138.5, 138.9, 143.1, 199.2; MS (EI) *m/z*: 366 (M^+, 1), 337 (100), 319 (2), 259 (6), 234 (26), 217 (12), 203 (7), 129 (10), 115 (34), 105 (38), 77 (33); HRMS (ESI) Calcd. for $C_{23}H_{30}O_2Si$+H: 367.2093, Found: 367.2091.

4.4.26. 1-Phenyl-3-p-tolyl-2-(2-triethylsilanyloxyethyl)-propenone (7c). This compound was obtained as a red

oil, yield: 154 mg, 81%. IR (CH_2Cl_2): ν 1018, 1047, 1094, 1178, 1232, 1264, 1290, 1320, 1379, 1414, 1448, 1458, 1511, 1578, 1598, 1647, 1719, 2876, 2912, 2954, 3025, 3509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.60 (q, J=7.8 Hz, 6H, CH_2), 0.95 (t, J=7.8 Hz, 9H, CH_2), 2.39 (s, 3H, CH_3), 3.03 (t, J=6.3 Hz, 2H, CH_2), 3.89 (t, J=6.3 Hz, 2H, CH_2), 7.20 (s, 1H, CH), 7.22 (d, J=7.2 Hz, 2H, Ar), 7.43–7.55 (m, 5H, Ar), 7.79 (d, J=7.2 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.8, 21.3, 31.1, 61.1, 128.1, 19.1, 129.4, 129.7, 131.7, 132.5, 138.0, 138.8, 138.8, 143.8, 199.3; MS (EI) *m/z*: 380 (M^+, 1), 351 (100), 335 (5), 259 (11), 248 (28), 233 (28), 216 (7), 143 (7), 115 (31), 105 (39), 77 (27); HRMS (ESI) Calcd. for $C_{24}H_{32}O_2Si+H$: 381.2250, Found: 381.2236.

4.4.27. 3-(4-Methoxyphenyl)-1-phenyl-2-(2-triethylsilanyloxyethyl)propenone (7d). This compound was obtained as a red oil, yield: 119 mg, 60%. IR (CH_2Cl_2): ν 1034, 1177, 1255, 1034, 1319, 1379, 1417, 1447, 1459, 1511, 1577, 1604, 1642, 1720, 2876, 2911, 2955, 3448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.50 (q, J=8.4 Hz, 6H, CH_2), 0.88 (t, J=8.4 Hz, 9H, CH_2), 2.96 (t, J=6.3 Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.82 (t, J=6.3 Hz, 2H, CH_2), 6.85 (d, J=7.2 Hz, 2H, Ar), 7.19 (s, 1H, CH), 7.34–7.48 (m, 5H, Ar), 7.67 (d, J=7.2 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.7, 31.1, 55.2, 61.2, 113.8, 127.9, 128.0, 129.5, 131.2, 131.5, 136.8, 139.0, 143.9, 160.0, 199.3; MS (EI) *m/z*: 396 (M^+, 4), 367 (86), 335 (3), 264 (33), 259 (12), 233 (38), 221 (8), 159 (14), 115 (36), 105 (100), 87 (37), 77 (64); Anal. Calcd. for $C_{24}H_{32}O_3Si$: C, 72.68, H, 8.13%; Found: C, 72.83, H, 8.15%.

4.4.28. 3-Furan-2-yl-1-phenyl-2-(2-triethylsilanyloxyethyl)propenone (7e). This compound was obtained as a red oil, yield: 123 mg, 69%. IR (CH_2Cl_2): ν 1005, 1072, 1271, 1317, 1447, 1615, 1645, 1721, 2877, 2912, 2955, 3415 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.53 (q, J=8.1 Hz, 6H, CH_2), 0.88 (t, J=8.1 Hz, 9H, CH_2), 3.12 (t, J=6.6 Hz, 2H, CH_2), 3.79 (t, J=6.6 Hz, 2H, CH_2), 6.44 (dd, J=1.8 Hz, J=3.0 Hz, 1H, Ar), 6.62 (d, J=3.0 Hz, 1H, Ar), 6.87 (s, 1H, CH), 7.38 (dt, J=7.5 Hz, J=7.2 Hz, 2H, CH), 7.47 (t, J=7.5 Hz, 1H, Ar), 7.49 (s, 1H, Ar), 7.63 (d, J=7.2 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.7, 31.8, 61.6, 112.2, 115.6, 128.1, 129.3, 130.0, 131.4, 134.6, 138.6, 144.5, 151.1, 198.6; MS (EI) *m/z*: 356 (M^+, 9), 327 (100), 259 (5), 224 (39), 195 (7), 165 (11), 117 (54), 105 (60), 87 (53), 77 (68); Anal. Calcd. for $C_{21}H_{28}O_3Si$: C, 70.74, H, 7.92%; Found: C, 70.74, H, 8.13%.

4.4.29. 1-(4-Fluorophenyl)-3-p-tolyl-2-(2-triethylsilanyloxyethyl)propenone (7f). This compound was obtained as a red oil, yield: 145 mg, 73%, *Z*/*E*=0/100. IR (CH_2Cl_2): ν 1015, 1045, 1094, 1155, 1186, 1231, 1262, 1292, 1319, 1378, 1409, 1458, 1505, 1598, 1648, 2876, 2912, 2955, 3026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.57 (q, J=7.5 Hz, 6H, CH_2), 0.92 (t, J=7.5 Hz, 9H, CH_2), 2.38 (s, 3H, CH_3), 3.00 (t, J=6.6 Hz, 2H, CH_2), 3.85 (t, J=6.6 Hz, 2H, CH_2), 7.12 (s, 1H, CH), 7.12 (dd, J=8.4 Hz, $J_{H\text{-}F}$=8.4 Hz, 2H, Ar), 7.20 (d, J=7.8 Hz, 2H, Ar), 7.44 (d, J=7.8 Hz, 2H, Ar), 7.82 (dd, J=8.4 Hz, $J_{H\text{-}F}$=5.4 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.7, 21.3, 31.3, 61.1, 115.1 (d, $J_{C\text{-}F}$=21.9 Hz), 129.1, 129.4, 132.3 (d, $J_{C\text{-}F}$=8.6 Hz), 132.5, 134.9 (d, $J_{C\text{-}F}$=3.0 Hz), 138.2, 138.7, 142.8, 165.0 (d, $J_{C\text{-}F}$=251.9 Hz), 197.8; MS (EI) *m/z*: 398 (M^+, 1), 369 (100), 353 (2), 303 (11), 266 (24), 251 (26), 234 (5), 143 (11), 95 (32), 87 (37), 75 (31); Anal. Calcd. for $C_{24}H_{31}FO_2Si$: C, 72.32, H, 7.84%; Found: C, 72.27, H, 7.75%.

4.4.30. 1,3-Di-p-tolyl-2-(2-triethylsilanyloxyethyl)propenone (7 g). This compound was obtained as a red oil, yield: 186 mg, 94%, *Z*/*E*=0/100. IR (CH_2Cl_2): ν 1018, 1046, 1093, 1180, 1232, 1263, 1291, 1319, 1378, 1413, 1458, 1510, 1608, 1645, 2875, 2911, 2954, 3026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.60 (q, J=7.8 Hz, 6H, CH_2), 0.96 (t, J=7.8 Hz, 9H, CH_2), 2.39 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.02 (t, J=6.6 Hz, 2H, CH_2), 3.88 (t, J=6.6 Hz, 2H, CH_2), 7.18 (s, 1H, CH), 7.20 (d, J=8.1 Hz, 2H, Ar), 7.26 (d, J=8.1 Hz, 5H, Ar), 7.46 (d, J=8.1 Hz, 2H, Ar), 7.72 (d, J=8.1 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.7, 21.3, 21.5, 31.3, 61.2, 128.7, 129.1, 129.4, 129.9, 132.7, 136.0, 138.2, 138.6, 142.4, 142.8, 199.0; MS (EI) *m/z*: 394 (M^+, 1), 365 (100), 349 (18), 273 (15), 262 (38), 247 (62), 215, (10), 143 (15), 129 (19), 119 (76), 91 (64), 75 (44); Anal. Calcd. for $C_{25}H_{34}O_2Si$: C, 76.09, H, 8.68%; Found: C, 76.23, H, 8.43%.

4.4.31. 1-(3,5-Dimethylphenyl)-3-p-tolyl-2-(2-triethylsilanyloxyethyl)propenone (7 h). This compound was obtained as a red oil, yield: 178 mg, 87%. IR (CH_2Cl_2): ν 1016, 1067, 1094, 1206, 1241, 1265, 1303, 1320, 1381, 1415, 1458, 1511, 1603, 1646, 2876, 2913, 2955, 3032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.51 (q, J=8.1 Hz, 6H, CH_2), 0.86 (t, J=8.1 Hz, 9H, CH_2), 2.26 (s, 6H, CH_3), 2.28 (s, 3H, CH_3), 2.92 (t, J=6.6 Hz, 2H, CH_2), 3.77 (t, J=6.6 Hz, 2H, CH_2), 7.08 (d, J=7.8 Hz, 2H, Ar), 7.10 (s, 1H, CH), 7.12 (s, 2H, Ar), 7.37 (d, J=7.8 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.8, 21.2, 21.3, 31.1, 61.2, 127.4, 129.1, 129.4, 132.7, 133.3, 137.7, 138.3, 138.6, 139.0, 143.3, 199.8; MS (EI) *m/z*: 408 (M^+, 1), 379 (100), 363 (14), 287 (16), 276 (33), 261 (52), 244 (8), 229 (10), 143 (11), 133 (46), 115 (56), 105 (71), 87 (13); Anal. Calcd. for $C_{26}H_{36}O_2Si$: C, 76.42, H, 8.88%; Found: C, 76.50, H, 8.75%.

4.4.32. 1-(4-Methoxyphenyl)-3-p-tolyl-2-(2-triethylsilanyloxyethyl)propenone (7i). This compound was obtained as a pale-yellow oil, yield: 151 mg, 74%, *Z*/*E*=0/100. IR (CH_2Cl_2): ν 1031, 1047, 1093, 1140, 1171, 1254, 1290, 1319, 1378, 1416, 1459, 1509, 1574, 1600, 1642, 2875, 2954, 3032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.53 (q, J=7.5 Hz, 6H, CH_2), 0.89 (t, J=7.5 Hz, 9H, CH_2), 2.32 (s, 3H, CH_3), 2.97 (t, J=6.6 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.80 (t, J=6.6 Hz, 2H, CH_2), 6.88 (d, J=8.1 Hz, 2H, Ar), 7.08 (s, 1H, CH), 7.14 (d, J=7.5 Hz, 2H, Ar), 7.40 (d, J=8.1 Hz, 2H, Ar), 7.79(d, J=7.5 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.2, 6.7, 21.2, 31.5, 55.3, 61.1, 113.2, 129.0, 129.3, 131.1, 132.0, 132.7, 138.2, 138.3, 141.4, 162.7, 198.0; MS (EI) *m/z*: 410 (M^+, 1), 381 (100), 365 (6), 349 (8), 289 (14), 278 (34), 263 (58), 135 (71), 115 (53), 103 (29), 87 (59), 75 (58); Anal. Calcd. for $C_{25}H_{34}O_3Si$: C, 73.13, H, 8.35%; Found: C, 73.13, H, 8.48%.

4.4.33. 1-Thiophen-2-yl-3-p-tolyl-2-(2-triethylsilanyloxyethyl)propenone (7j). This compound was obtained as a pale-yellow oil, yield: 152 mg, 79%, *Z*/*E*=0/100. IR (CH_2Cl_2): ν 1018, 1054, 1094, 1186, 1232, 1264, 1291,

1317, 1353, 1378, 1414, 1457, 1512, 1627, 2875, 2914, 2954, 3024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 0.55 (q, $J=8.4$ Hz, 6H, CH_2), 0.90 (t, $J=8.4$ Hz, 9H, CH_2), 2.39 (s, 3H, CH_3), 2.98 (t, $J=6.6$ Hz, 2H, CH_2), 3.83 (t, $J=6.6$ Hz, 2H, CH_2), 7.12 (dd, $J=4.8$ Hz, $J=3.9$ Hz, 1H, Ar), 7.21 (d, $J=8.1$ Hz, 2H, Ar), 7.40 (s, 1H, CH), 7.47 (d, $J=8.1$ Hz, 2H, Ar), 7.65–7.68 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 4.3, 6.7, 21.3, 31.7, 61.2, 127.6, 129.1, 129.4, 132.6, 133.4, 133.8, 138.4, 138.6, 140.7, 144.1, 196.6; MS (EI) *m/z*: 386 (M^+, 1), 357 (100), 341 (7), 254 (16), 239 (21), 205 (43), 187 (8), 177 (18), 111 (89), 105 (23), 87 (43), 75 (28); HRMS (ESI) Calcd. for $C_{22}H_{30}O0_2$-SSi+H: 387.1814, Found: 387.1818.

4.4.34. 2-{2-[3-(4-Chlorobenzylidene)-2-phenyltetrahydrofuran-2-yloxy]ethyl}-3-(3-chlorophenyl)-1-phenylpropenone (5a). This compound was obtained as a red oil. IR (CH_2Cl_2): ν 1013, 1056, 1091, 1158, 1210, 1264, 1313, 1372, 1405, 1432, 1447, 1490, 1578, 1594, 1651, 1734, 1903, 1963, 2886, 2928, 3058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 2.85–2.90 (m, 2H, CH_2), 3.00–3.11 (m, 2H, CH_2), 3.52–3.59 (m, 1H, CH_2), 3.69–3.77 (m, 1H, CH_2), 4.03–4.11 (m, 1H, CH_2), 4.23–4.30 (m, 1H, CH_2), 6.14 (s, 1H, CH), 7.04 (s, 1H, CH), 7.08 (d, $J=8.7$ Hz, 2H, Ar), 7.23 (d, $J=8.7$ Hz, 2H, Ar), 7.31–7.50 (m, 11H, Ar, CH), 7.55 (d, $J=6.9$ Hz, 2H, Ar), 7.78 (d, $J=6.9$ Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 28.6, 30.1, 60.6, 66.1, 108.8, 124.1, 126.4, 128.1, 128.3, 128.3, 128.6, 128.8, 129.7, 129.7, 130.7, 132.0, 132.6, 133.8, 134.4, 136.3, 136.1, 139.3, 139.9, 140.9, 143.6, 198.5; MS (EI) *m/z*: 287 (2), 285 [(M-269)$^+$, 6], 271 (21), 269 (60), 256 (4), 115 (10), 105 (100), 77 (47); Anal. Calcd. for $C_{34}H_{28}Cl_2O_3$: C, 73.51, H, 5.08%; Found: C, 73.52, H, 5.15%.

4.4.35. Phenyl-carbamic acid 3-benzoyl-4-(4-methoxyphenyl)-but-3-enyl ester (6). Only the mixture of **6**-*Z* and **6**-*E* was obtained as a red oil, yield: 100 mg, 50%.; ^1H NMR of **6**-*E* (300 MHz, $CDCl_3$, TMS): δ 3.20 (t, $J=6.9$ Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.30 (t, $J=6.0$ Hz, 2H, CH_2), 6.57 (s, 1H, NH), 6.92 (d, $J=9.0$ Hz, 2H, Ar), 7.04 (t, $J=7.2$ Hz, 2H, Ar), 7.23 (s, 1H, CH), 7.25–7.33 (m, 4H, Ar), 7.41–7.46 (m, 4H, Ar), 7.51–7.53 (m, 1H, Ar), 7.73 (d, $J=9.0$ Hz, 2H, Ar); MS (EI) *m/z*: 296 [(M-105)$^+$, 1], 264 (89), 249 (5), 233 (20), 221 (6), 205 (9), 159 (27), 105 (100), 77 (62); HRMS (EI) Calcd. for $C_{25}H_{23}NO_4$: 401.1627, Found: 401.1650.

5. Supporting information

The Noesy spectrum of **3a**-*Z* and the ^1H and ^{13}C NMR spectra of **5a** are included in Supporting information. This material is available free of charge via the Internet website.

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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.2004.12.028

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7. In all of the cases shown in Table 2, none of the cyclized product **4** was detected.

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Amine- and phosphine-free palladium(II)-catalyzed homocoupling reaction of terminal alkynes

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Abstract—An efficient, amine- and phosphine-free palladium(II)-catalyzed homocoupling of terminal alkynes has been developed. In the presence of $PdCl_2$, CuI, Me_3NO, and NaOAc, homocoupling of various terminal alkynes underwent smoothly to afford the corresponding diynes in moderate to high yields without any phosphine ligands. In contrast, the presence of a phosphine ligand (PPh_3) disfavored this palladium-catalyzed homocoupling procedure. Bases, solvents, and CuI have fundamental influence on the palladium-catalyzed homocoupling of terminal alkynes.

1. Introduction

Diynes are useful building blocks in organic synthesis and a recurring functional group in many natural products and bioactive compounds.[1–3] As a result, considerable effort has been directed to the development of new and efficient methods for the synthesis of diynes since 1869.[3–6] Palladium-catalyzed homocoupling reaction of terminal alkynes transformation represents one of the most attractive routes to synthesize symmetrical diynes due to their mildness and efficiency.[3g,f,6] This homocoupling method is generally carried out in the presence of phosphine ligands (Ph_3P) and amines (for example, *i*-Pr_2NH, *i*-Pr_2NEt, Dabco, and Et_3N). For example, Zhang and co-workers[6f] have reported an efficient protocol for homocoupling of alkynes using $PdCl_2(PPh_3)_2$, CuI, ethyl bromoacetate and amine (triethylamine or Dabco) as the catalytic system. Fairlamb and co-workers[6g] have also described an efficient $PdCl_2(MeCN)_2$ and CuI catalyzed homocoupling of alkynes procedure in Et_3N/MeCN, and more loadings of PPh_3 were required to improve the reaction. Generally, phosphine ligands are generally sensitive to air and expensive which puts significant limits on their synthetic applications.[7] Amines also have characteristic foul smell and pungent flavor. For these reasons, the development of an effective procedure for homocoupling of alkynes under amine- and phosphine-free conditions would be significant. Here, we report our findings that $PdCl_2$, in combination with CuI, Me_3NO (as the reoxidant), and NaOAc (instead of amines as the base), was proven to be an extremely effective catalytic system for the homocoupling of various terminal alkynes.

2. Results and discussion

2.1. Palladium-catalyzed homocoupling of phenylacetylene (1a)

To evaluate the efficiency of $PdCl_2$/CuI/Me_3NO, homocoupling of phenylacetylene (**1a**) was tested in the absence of any phosphine ligands, and the results were summarized in Table 1. The results showed that the combination of $PdCl_2$, CuI, and Me_3NO was an effective catalytic system for the reaction. Initially, several bases including NaOAc, Na_2CO_3, Et_3N, and pyridine were examined, and the results indicated that NaOAc was the most effective (entries 1–7). Treatment of phenylacetylene (**1a**) with $PdCl_2$ (5.6 mol%), CuI (2.5 mol%), and Me_3NO (2 equiv) in MeCN at room temperature, gave the corresponding diyne **2a** in only 41% isolated yield after 14 h when 3 equiv of Et_3N was used (entry 6), whereas the isolated yield of **2** sharply rised to 96% after 10 h when NaOAc (3 equiv) was used (entry 3). The results also demonstrated that the loadings of NaOAc affected the reaction, and 3 equiv of NaOAc provided the highest yields (entries 1–4).

Oxidative reagents were then investigated (entries 3 and 8–10). The results indicated that oxidative reagents have

Keywords: Phosphine-free; Palladium; Homecoupling reaction; Terminal alkynes.
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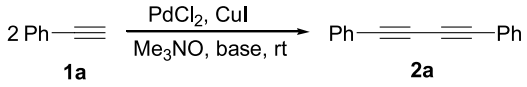
Table 1. Palladium-catalyzed homocoupling of phenylacetylene (**1a**)[a]



Entry	Base (equiv)	Solvent	Time (h)	Conversion (%)[b]	Yield (%)[c]
1	NaOAc (1)	CH_3CN	10	100	68
2	NaOAc (2)	CH_3CN	10	100	75
3	NaOAc (3)	CH_3CN	10	100	96
4	NaOAc (4)	CH_3CN	10	100	90
5	Na_2CO_3 (3)	CH_3CN	14	9	7
6	NEt_3 (3)	CH_3CN	14	47	41
7	Pyridine (3)	CH_3CN	14	57	51
8[d]	NaOAc (3)	CH_3CN	24	100	<5
9[e]	NaOAc (3)	CH_3CN	10	100	84
10[f]	NaOAc (3)	CH_3CN	10	20	18
11	NaOAc (3)	EtOH	12	31	28
12	NaOAc (3)	MeOH	12	38	34
13	NaOAc (3)	C_6H_6	12	20	16
14	NaOAc (3)	THF	12	55	49
15	NaOAc (3)	Dioxane	12	47	45
16[g]	NaOAc (3)	CH_3CN/H_2O	12	36	34
17[h]	NaOAc (3)	CH_3CN	12	39	33
18[i]	NaOAc (3)	CH_3CN	12	32	28
19[j]	NaOAc (3)	CH_3CN	16	<5	Trace
20[k]	NaOAc (3)	CH_3CN	12	100	95
21[l]	NaOAc (3)	CH_3CN	23	100	70
22[m]	NaOAc (3)	CH_3CN	17	100	60

[a] Reaction conditions: **1a** (1 mmol), $PdCl_2$ (5.6 mol%), CuI (2.5 mol%), $Me_3NO\cdot 2H_2O$ (2 equiv), and solvent (5 mL) at room temperature under nitrogen.
[b] Conversion of **1a** was determined by GC analysis.
[c] Isolated yield.
[d] $CuCl_2$ (2 equiv) instead of $Me_3NO\cdot 2H_2O$. Red oil was obtained as the major product.
[e] $Me_3NO\cdot 2H_2O$ (1 equiv).
[f] Without $Me_3NO\cdot 2H_2O$.
[g] $CH_3CN/H_2O=4:1$.
[h] Without CuI.
[i] Without both CuI and $Me_3NO\cdot 2H_2O$.
[j] Without $PdCl_2$.
[k] $Pd(OAc)_2$ (5.6 mol%) instead of $PdCl_2$.
[l] $PdCl_2(PPh_3)_2$ (5.6 mol%) instead of $PdCl_2$.
[m] PPh_3 (11.2 mol%) was added.

fundamental influence on the reaction. Without any oxidative reagent, a low yield was isolated after 10 h in the presence of $PdCl_2$ (5.6 mol%), CuI (2.5 mol%), and NaOAc (3 equiv), whereas the present of 2 equiv of Me_3NO resulted in 96% yield of **2**. But the yield was decreased to 84% with decreasing the loadings of Me_3NO to 1 equiv. $CuCl_2$ also served as an oxidant for the conversion of **1a** to **2a** catalyzed by $PdCl_2$, but was inferior to Me_3NO (entry 8).[8] A series of solvents including MeCN, EtOH, MeOH, C_6H_6, THF, dioxane, and $MeCN/H_2O$ were also examined, and MeCN was found to be the most effective solvent for the homocoupling reaction (entries 3 and 11–16).

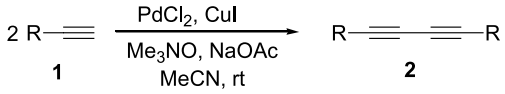
It is noteworthy that both $PdCl_2$ and CuI played crucial roles in the reaction (entries 3 and 17–19). Without the aid of CuI, only 33% yield of **2** was isolated after 12 h in the presence of $PdCl_2$ (5.6 mol%), Me_3NO (2 equiv), and NaOAc (3 equiv). Similarly, trace amount of **2** was observed in the absence of $PdCl_2$.

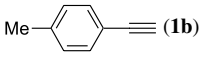
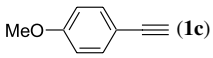
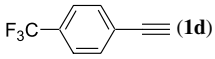
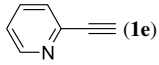
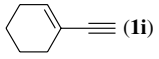
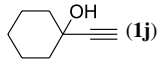
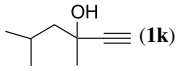
Finally, various palladium catalytic systems were evaluated (entries 3 and 19–22). In addition to $PdCl_2$, $Pd(OAc)_2$ served as an effective catalyst for the homocoupling reaction of alkyne **1a** to form diyne **2a** (entries 3 and 20). In contrast, neither $PdCl_2(PPh_3)_2$ nor $PdCl_2/PPh_3$ as the catalytic system was effective as $PdCl_2$ for the conversion of **1a** to **2a** (entries 3, 21 and 22). This observation suggested that the presence of PPh_3, a phosphine ligand, disfavored the reaction.

2.2. Palladium-catalyzed homocoupling of terminal alkynes 1b–l

As summarized in Table 2, homocoupling of various terminal alkynes were carried out smoothly to afford the corresponding diynes in moderate to good yields under the optimum reaction conditions. The results showed that the palladium-catalyzed homocoupling reaction tolerated a variety of functional groups, and the yields and rates depended upon the substrates. For homocoupling of aromatic alkynes **1b–e**, the aromatic alkynes **1b** and **1c** bearing electron-donating groups proved to be more effective. In the presence of $PdCl_2$ (5.6 mol%), $Me_3NO\cdot 2H_2O$ (2 equiv), CuI (2.5 mol%), and NaOAc (3 equiv), aromatic alkynes **1b–e** were coupled to afford the corresponding diynes **2b–e** in 98, 90, 65 and 78% yields, respectively (entries 1–4 in Table 2). Interestingly, for homocoupling of aliphatic alkynes **1f–h**, the corresponding products **2f–h** were also obtained in moderate to good yields (70, 81 and 100% yields, respectively, entries 5–7). A number of other alkynes with different functional groups such as 1-ethynyl cyclohexene (**1i**), 1-ethynyl cyclohexanol

Table 2. Palladium-catalyzed homocoupling of alkynes[a]



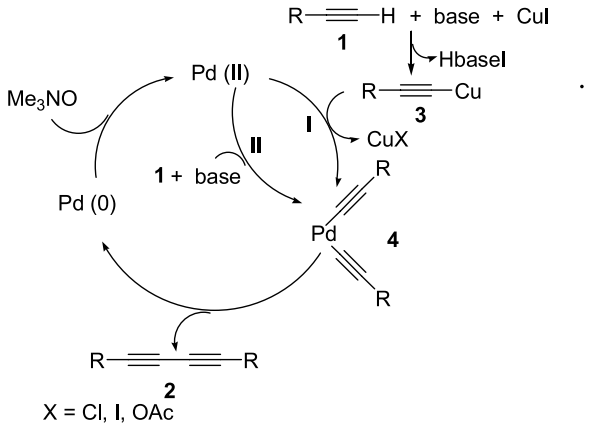
Entry	Alkyne	Time (h)	Yield (%)[b]
1	 (**1b**)	12	98
2	 (**1c**)	20	90
3	 (**1d**)	12	65
4	 (**1e**)	48	78
5	*n*-C_5H_{11}— (**1f**)	24	70
6	n-C_8H_{17}— (**1g**)	24	81
7	*t*-Bu— (**1h**)	9	100
8	 (**1i**)	16	82
9	 (**1j**)	13	88
10	 (**1k**)	15	68
11	—CH_2OAc (**1l**)	12	67

[a] Reaction conditions: **1** (1 mmol), $PdCl_2$ (5.6 mol%), CuI (2.5 mol%), $Me_3NO\cdot 2H_2O$ (2 equiv), NaOAc (3 equiv), and MeCN (5 mL) at room temperature.
[b] Isolated yield.

(**1j**), 3,3,5-trimethyl hex-1-yn-3-ol (**1k**), and propargyl acetate (**1l**) underwent the homocoupling reaction smoothly to afford the corresponding diynes **2i–l** in 82, 88, 68 and 67% yields, respectively (entries 8–11).

2.3. Mechanism

As outlined in Scheme 1, we have formulated a working mechanism for the palladium-catalyzed homocoupling of terminal alkynes based on the proposed mechanism of the previous reports and our results.[6] With the aid of a base, the reaction of **1** with CuI afforded intermediate **3** readily. Then the replacement reaction of Pd(II) with intermediate **3** would occur to form a dialkynylpalladium(II) intermediate **4** and regenerate the active Cu(I) species. Reductive elimination of the dialkynylpalladium(II) intermediate **4** could undergo to form the desired diyne **2** and Pd(0). Finally, Pd(0) was oxidated by Me_3NO to regenerate the active Pd(II) species leading to a new catalytic cycle.



Scheme 1.

It should be noted that: (1) the presence of both amines and phosphine ligands were disfavored to the present palladium-catalyzed homocoupling reaction. The reason might be that reduction of Pd(II) to Pd(0) by amines or phosphine ligands occurs to slow the reaction;[9] (2) without the aid of CuI, there are 33% isolated yield of **2** after 12 h in the presence of $PdCl_2$ (5.6 mol%), Me_3NO (2 equiv), and NaOAc (3 equiv), whereas without $PdCl_2$, trace amount of **2** was observed in the presence of CuI (2.5 mol%), Me_3NO (2 equiv), and NaOAc (3 equiv). This observation suggested that with the aid of base, the dialkynylpalladium(II) intermediate **4** could be formed from either direct attack of Pd(II) to **1** (Pathway II) or replacement of Pd(II) with Cu(I) of intermediate **3** (Pathway I), and the latter (Pathway I) is faster. This result also demonstrated that Me_3NO was not an effective oxidant for the Cu(I)-catalyzed Glaser coupling reaction.[11]

3. Conclusion

In summary, we have developed a mild and efficient protocol for homocoupling of various terminal alkynes in the presence of $PdCl_2$, CuI, Me_3NO and NaOAc. This Pd(II)-catalyzed procedure not only tolerates a range of functional groups, but also does not require any phosphine

ligands. Currently, further efforts to study the mechanism and apply the new approach in organic synthesis are underway in our laboratory.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded on an INOVA-400 (Varian) spectrometer with $CDCl_3$ as the solvent. All reagents were directly used as obtained commercially.

4.2. Typical experimental procedure for the palladium-catalyzed homocoupling of alkynes

A mixture of alkyne **1** (1 mmol), $PdCl_2$ (5.6 mol%), CuI (2.5 mol%), $Me_3NO\cdot 2H_2O$ (2 equiv), NaOAc (3 equiv), and MeCN (5 mL) was stirred under N_2 at room temperature until complete consumption of starting material as judged by TLC and GC analysis. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography to afford **2** (hexane or hexane/ethyl acetate). All products **2** are known and all the melting points are uncorrected.[6,10]

4.2.1. 1,4-Diphenyl buta-1,3-diyne (2a).[6,10] White solid, mp 86–88 °C (lit.[10a] 88 °C); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.54–7.52 (m, 4H), 7.38–7.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.5, 129.2, 128.5, 121.8, 81.5, 73.9. MS *m/z* (%): 202 (M^+, 100).

4.2.2. 1,4-Bis(*p*-methylphenyl) buta-1,3-diyne (2b).[6,10a,e] White solid, mp 138–140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, J=8.0 Hz, 4H), 7.14 (d, J=8.0 Hz, 4H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.5, 132.4, 129.2, 118.8, 81.5, 73.4, 21.6. MS *m/z* (%): 230 (M^+, 100).

4.2.3. 1,4-Bis(*p*-methoxyphenyl) buta-1,3-diyne (2c).[6,10] White solid, mp 140–142 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, J=8.8 Hz, 4H), 6.85 (d, J=8.8 Hz, 4H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2, 134.0, 114.1, 113.9, 81.2, 72.9, 55.3. MS *m/z* (%): 262 (M^+, 100)

4.2.4. 1,4-Bis(trifloromethylphenyl) buta-1,3-diyne (2d).[10e] White solid, mp 166–168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, J=8.4 Hz, 4H), 7.62 (d, J=8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.8, 131.2, 130.9, 125.5, 125.4, 125.2, 125.0, 122.3, 81.0, 75.6. MS *m/z* (%): 338 (M^+, 100).

4.2.5. 1,4-Bis(2-pyridine) buta-1,3-diyne (2e).[10e] White solid, mp 116–118 °C (lit.[10f] 118–119 °C); ^1H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, J=4.4 Hz, 2H), 7.71 (t, J=7.6 Hz, 2H), 7.56 (d, J=8.4 Hz, 2H), 7.31 (t, J=4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.3, 141.8, 134.3, 128.4, 123.8, 80.8, 73.2. MS *m/z* (%): 204 (M^+, 100).

4.2.6. Tetradeca-6,8-diyne (2f).[10e] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.25 (t, J=7.2 Hz, 4H), 1.54–1.46 (m, 4H), 1.39–1.28 (m, 8H), 0.89 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.5, 65.2, 31.0, 28.0, 22.2, 19.2, 13.9. MS *m/z* (%): 190 (M^+, 1), 161 (15), 105 (57), 91 (100).

4.2.7. Eicosa-9,11-diyne (2g).[6] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.27 (t, J=7.2 Hz, 4H), 1.57–1.50 (m, 4H), 1.43–1.38 (m, 4H), 1.34–1.20 (m, 16H), 0.90 (t, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.5, 65.2, 31.8, 29.1, 29.0, 28.8, 28.3, 22.6, 19.2, 14.1. MS *m/z* (%): 245 ($M^+ - C_2H_5$, 2), 161 (23), 147 (25), 133 (30), 119 (42), 105 (56), 91 (100).

4.2.8. 2,2,7,7-Tetramethyl octa-3,5-diyne (2h).[6,10g] White solid, mp 128–130 °C (lit.[10g] 130–130.5 °C); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.23 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 86.3, 63.6, 30.6, 28.0. MS *m/z* (%): 162 (M^+, 8), 161 (25), 133 (37), 119 (55), 91 (100).

4.2.9. 1,4-Bis(cyclohex-1-enyl) buta-1,3-diyne (2i).[6f] White solid, mp 63–65 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.25 (t, J=4.0 Hz, 2H), 2.12–2.10 (m, 8H), 1.66–1.57 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.0, 119.9, 82.7, 71.5, 28.6, 25.8, 22.1, 21.3. MS *m/z* (%): 210 (M^+, 3), 111 (20), 85 (71), 71 (95), 57 (100).

4.2.10. 1,4-Bis(1-hydroxycyclohexyl) buta-1,3-diyne (2j).[6f] White solid, mp 173–175 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.95–1.91 (m, 4H), 1.82 (s, 2H), 1.71 (t, J=8.0 Hz, 4H), 1.63–1.53 (m, 8H), 1.26–1.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 83.0, 69.2, 68.3, 39.7, 25.0, 23.1. MS *m/z* (%): 246 (M^+, 1), 210 (100).

4.2.11. 2,4,9,11-Tetramethyl dodeca-5,7-diyne-4,9-diol (2k).[10h] White solid, mp 78–80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.82 (s, 2H), 1.95–1.56 (m, 2H), 1.61 (d, J=6.4 Hz, 4H), 1.51 (s, 6H), 1.02 (d, J=5.2 Hz, 6H), 1.00 (d, J=5.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 83.4, 68.6, 67.7, 51.5, 34.6, 25.1, 24.2, 24.0. MS *m/z* (%): 250 (M^+, 1), 232 (1), 85 (51), 71 (100).

4.2.12. Acetic acid 6-acetoxy hexa-2,4-diynyl ester (2l).[6g] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.74 (s, 4H), 2.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 73.6, 70.3, 52.8, 20.6. MS *m/z* (%): 194 (M^+, 5), 135 (3), 76 (100).

Acknowledgements

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Multi-functionalization of gallic acid towards improved synthesis of α- and β-DDB

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Abstract—The synthesis of mono-, di- and trisubstituted gallic acids and their ester with similar or different groups including different acetal and ketals is described. Regioselective bromination on two *ortho*-positions of methyl gallate, which is very crucial for many organic syntheses, was achieved in high yield and purity. The α- and β-DDB were synthesized in high overall yield and purity from the regioselective bromoderivatives.

1. Introduction

The preparation of alkylated polyphenol derivatives from gallic acid has attracted the attention of synthetic chemists for many years.[1] This is mainly due to the fact that these compounds have a variety of medicinal and industrial applications, including their use as antioxidants[2] and mediators in modulation of the genotoxicity of food carcinogens.[3] Recently, these compounds have been used as starting materials in the mesomorphic materials engineering.[4,5]

The synthesis of different chiral biphenyl derivatives such as 4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy-2,2′-dimethoxycarbonylbiphenyl (α-DDB), 6,6′-dimethoxy-4,5,4′,5′-dimethylenedioxy-2,2′-dimethoxycarbonylbiphenyl (β-DDB) (Fig. 1) involves the proper functionalization of the gallic acid unit.[6,7] These DDBs are used in traditional Chinese medicine as antihapetotoxic (liver injury), anticonvulsive (cerebral protection) and also exhibit antitumor, antiHIV and antifungal activities among other properties.[7] Besides these, different functionalized gallic acid units can be used for the synthesis of a variety of alkyl and glycoside derivatives of ellagic acid,[8] which have many biological activities such as antitumor, antiHIV, anticancer, antihepatatic, etc.[9] and are also the major component of many cosmetics and skin care creams. The synthesis of different biologically active natural polyhydroxystilbens[10] and some alkaloids[11] also involved the utilization of a properly functionalized gallic acid unit.

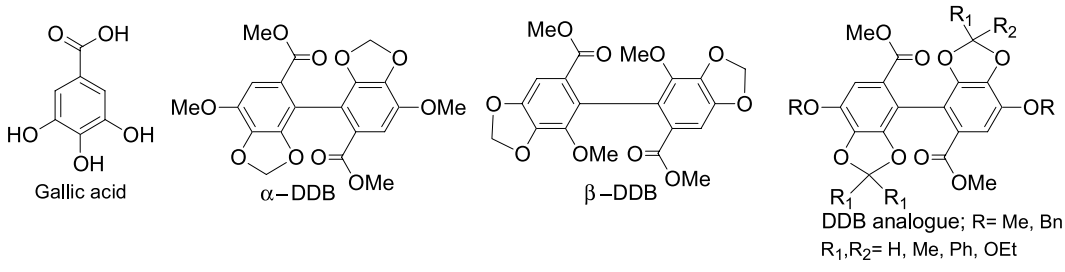

Figure 1. Gallic acid and α- and β-DDB.

Keywords: Gallic acid; Multi-functionalization; Regioselective bromination; α-DDB; β-DDB.
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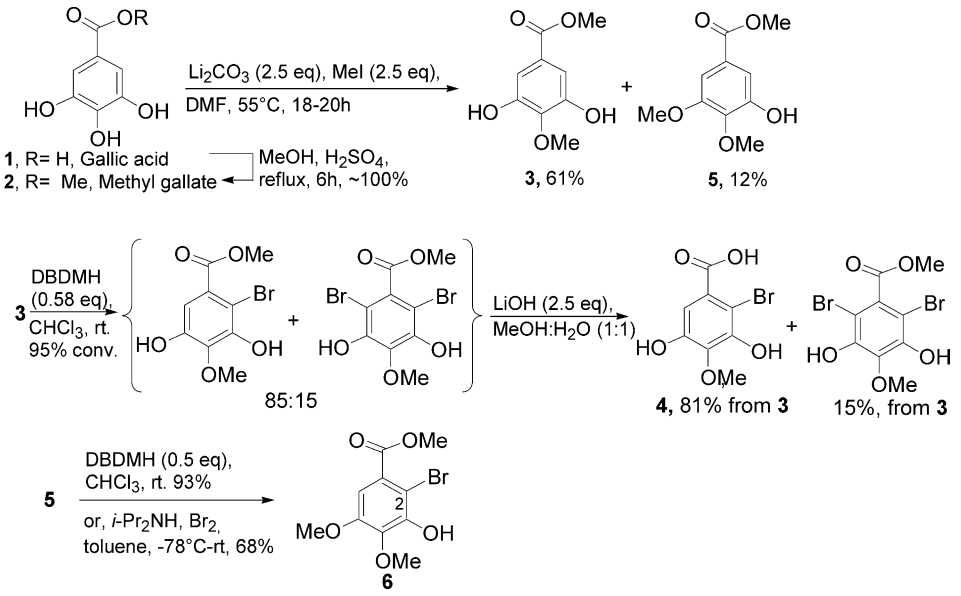


Scheme 1. Methoxylation and monobromination of methyl gallate.

So from the above discussion, it is known that the functionalization of gallic acid or methyl gallate plays an important role in the synthesis of a wide variety of biologically active natural products.

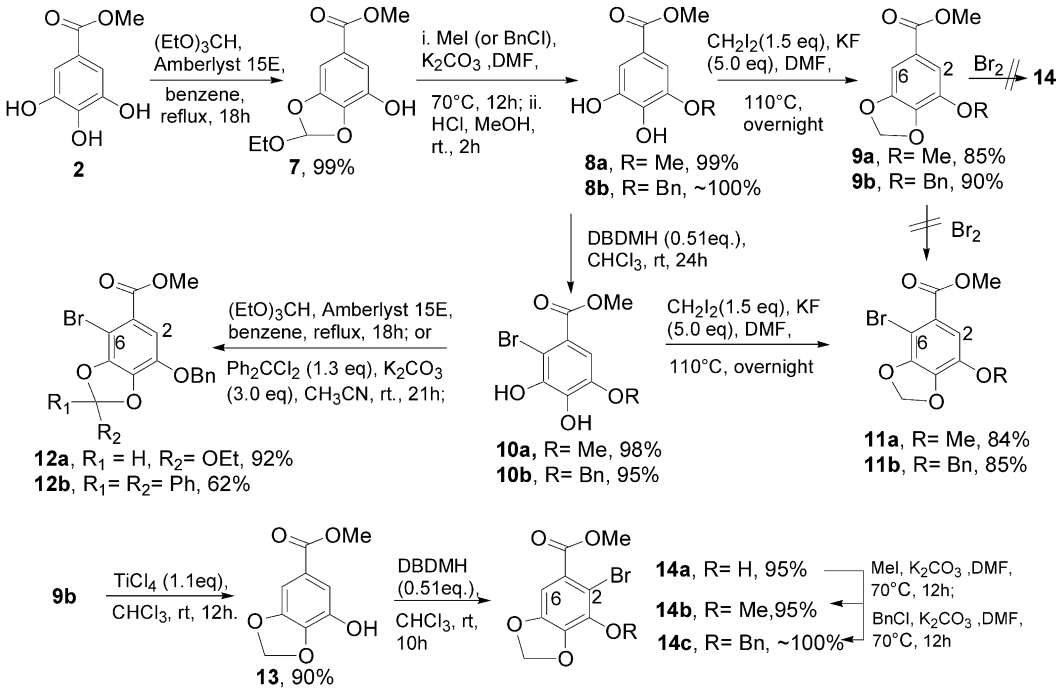
So far, very few reports have appeared regarding the functionalization of gallic acid or methyl gallate. Most of them were concerned mainly with similar groups such as long-chain alkyls, alkyl halides, alcohols[12] and conjugated enes.[13] In this work, we wish to report a flexible route not only for functionalization of the hydroxy groups, but also for the regioselective bromination of two *ortho*-positions of methyl gallate. This regioselective bromination plays an important role in synthesis of different biologically active biphenyl derivatives.[6,7] This highly diversified functionalizations of methyl gallate will provide an easy access to the synthesis of a variety of organic compounds, as well as a useful data library. Similarly, these protection strategies can also be used for other catechols or polyhydroxy aromatic compounds, such as pyrogallol.

2. Results and discussion

The starting material, methyl gallate **2**, is commercially available or can be prepared very easily by treating the gallic acid with MeOH and H_2SO_4 followed by recrystallization from hot water in almost quantitative yield. The 4-MeO derivative **3** was prepared using the known method[14] by treating with Li_2CO_3 and MeI in DMF at 55 °C, and at the same time dimethoxy derivative **5** was formed as a byproduct. Compound **5** can also be prepared by further methoxylation of **3**. But the monobromination of **3** was quite difficult. Bromination with Br_2 in various solvent systems ($CHCl_3$, $CHCl_3/H_2O$, CCl_4, CCl_4/H_2O, acetic acid, dioxane, diisopropyl amine/toluene,[15] etc.) under different reaction conditions was failed to give the desired monobromo compound as a unique product rather than as an inseparable mixture of the starting material, monobromo and dibromo derivatives in varying ratios from 1:2:1 to 1:8:8. Then, finally, the reaction succeeded mostly by using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the brominating agent. Treatment of **3** with 0.50–0.58 mol equiv of DBDMH in $CHCl_3$ at room temperature yielded the bromide in 95% conversion, but it was found to contain the undesired dibromo ester (GC-MS, ^{1}H NMR). The desired monobromo component was then separated from the undesired dibromo ester by selective hydrolysis. The mixture of bromides obtained from **3** was treated with 2.0–2.5 equiv of LiOH in $MeOH/H_2O$ (1:1) at room temperature for 6 h to result in selective hydrolysis of the monobromo ester to the corresponding monobromo acid **4** (Scheme 1, 81% from **3**). The undesired dibromo ester remained unhydrolyzed and was separated easily by simple column chromatography (15% from **3**). Compound **5** gave the corresponding bromo derivative **6** as a single product in 93% yield upon treatment with 0.5 equiv of DBDMH in $CHCl_3$.

As mentioned before, regioselectively brominated derivatives **11** and **14** (Scheme 2) are very potent for the synthesis of many biologically active biphenyls. The regioselective bromination at the 2- or 6-position are the key steps in all reported syntheses. A mixture of 2-bromo, 6-bromo and 2,6-dibromo components were reported in low yield over multi-steps procedure, using regioselective nitration–reduction followed by the Sandmeyer reaction.[6,7] Matsuoka has reported a single debromination of 2,6-dibromo derivatives with Zn and aqueous sodium hydroxide in 84% yield.[16]

For the regioselective synthesis of bromo derivatives **11** and **14**, 3-*O*-alkyl gallate **8** was prepared from **2** via the acetal **7**. Methylenedioxy protection of 4,5-dihydroxy of **8** provided the fully protected methyl gallate **9** (Scheme 2). But the regioselective bromination of **9** at C-6 (or C-2) by a variety of ways ($Br_2/CH_2Cl_2/H_2O$, NBS/CH_3SO_3H, DBDMH/CF_3COOH, DBDMH/*p*-TsOH, etc.) failed. Treatment of **9** with Br_2 in various reaction media resulted in very trace conversion to the bromide. Though the conversion of the



[a]For easy explanation of the position of bromide, the two *ortho*-positions have been arbitrarily assigned as C-2 and C-6.

Scheme 2. Routes for the preparation of regioselective bromo derivatives for the synthesis of DDB.[a]

reaction was increased to 100% by using organic acid[17] as additive, but an inseparable mixture of 6-Br and 2-Br isomers was formed in 12:5 ratio (mixture of **11** and **14**). Finally, interestingly, we prepared both monobromo regioisomers **11** and **14** in very good yield and purity[18] using the same brominating agent, DBDMH by changing the starting material. We did the bromination of **8** followed by dioxy protection to **11** rather than bromination of **9** to **11**. Simple treatment of **8** with DBDMH in $CHCl_3$ gave the corresponding 6-bromo derivatives **10** (the position of bromide was not confirmed at this stage but was confirmed in the next step for compound **11b**). Compounds **10** were converted to the desired methylenedioxy protected compound **11** and differently protected compound **12**. The benzyl deprotection of **9b** provided methyl 3-hydroxy-4,5-methylenedioxybenzoate **13**, which upon regioselective bromination at the 2-position yielded another desired bromo isomer **14a** that was converted to the corresponding methyl and benzyl derivatives **14b**, **14c**, respectively. Thus, compounds **11** and **14** were prepared from commercially available methyl gallate **2** in excellent overall yield (**11a**, 82%; **11b**, 79.5%; **14b**, 71% from **2**), much higher yield than the reported one (lit.[7] 53 and 25% of **11a** and **14b**, respectively). The position of the bromide in compounds **11** and **14** was confirmed by measuring the NOE effect of **11b** and **14c** (Fig. 2).

The preparation of 6-Br derivatives **14** was carried out in fewer steps via compounds **7** and **15** as shown in Scheme 3. Unfortunately, neither **7** nor **15** gave the desired bromide upon treatment with DBDMH and the starting material **2** was recovered. Upon treatment with Br_2/*iso*-Pr_2NH/toluene **7** also did not give the desired bromide, whereas **15** gave a mixture of the bromide **16** and the starting material in low yield (55%). This problem could not be solved even after protecting the remaining –OH of **15**. Finally, it was found that selective bromination at C-2 goes well, if the 3,4-dioxy-protection of **15** is changed to other acetals (**17**, **19**). For the acetalization of 3,4-dihydroxy group of **2**, some ketones were used in the presence of montmorrilonite clay, K10 or KSF, but the yield of acetal **17** was poor, whereas that with Ph_2CCl_2 gave acetal **19** in a moderate yield. Then, upon treatment with DBDMH, **17** and **19** gave the corresponding bromides **18** and **20** in very high yield and purity (**18**, 88%; **20**, 100%, respectively). Now, the only remaining hydroxy group of **20** (R=H) can be protected by desired groups and similarly the existing dioxy-protection also can be changed to other suitable group. For example, **14b** can be prepared

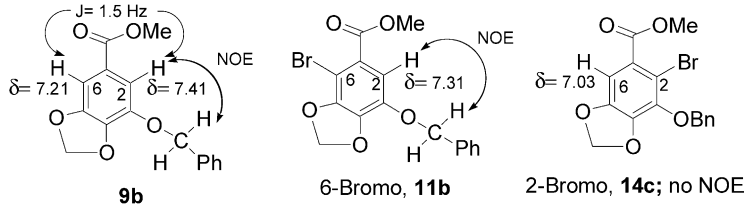
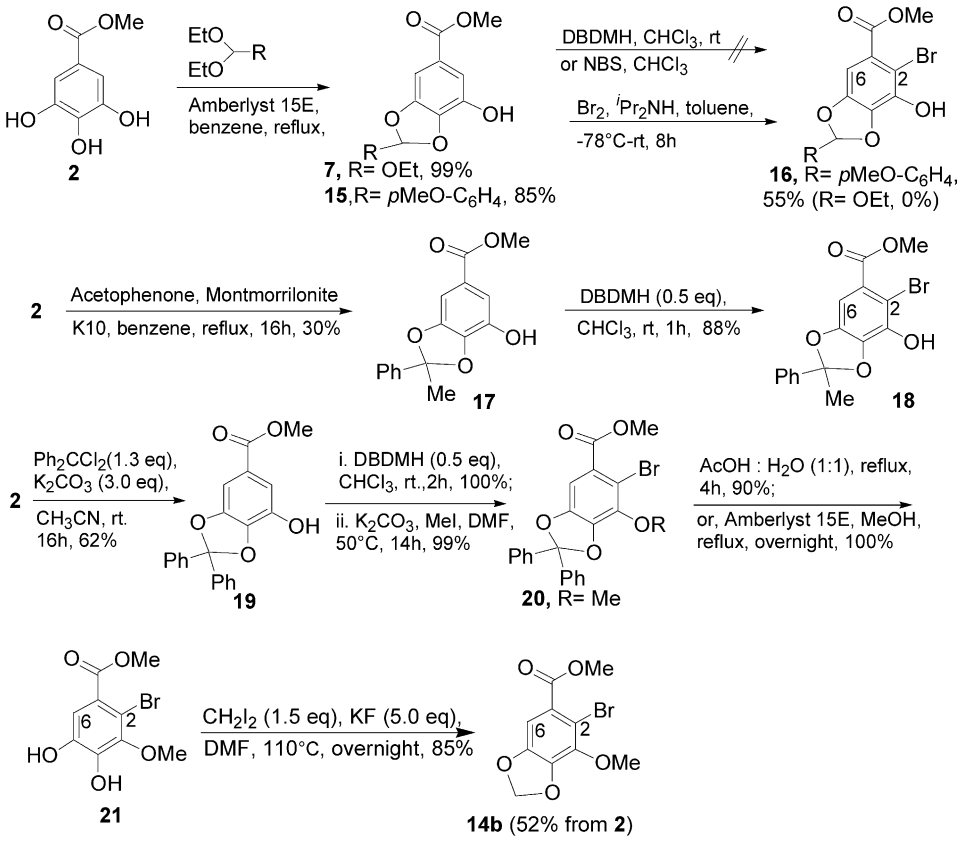


Figure 2. The NOE study for the compounds **9b**, **11b** and **14c**.



Scheme 3. Alternative route for the regioselective synthesis of 2-Br derivatives.

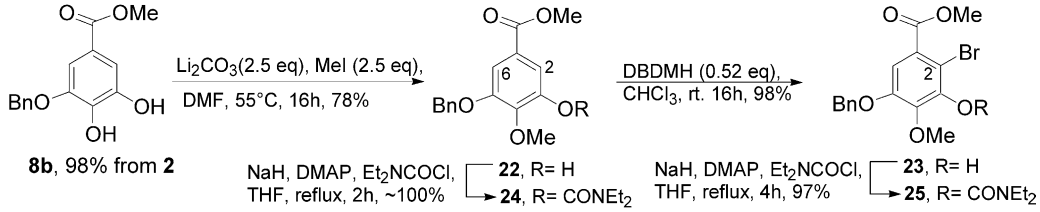
via **21**. Thus, the 2-Br derivative can be obtained with a variety of protecting groups, rather than only the reported 3,4-methylene acetal group (**14**).

We wished to functionalize the three –OH groups of methyl gallate with three different protecting groups. For example, the selective protection of only one –OH of **3** with methoxymethyl– was unsuccessful. Using even less than 0.5 equiv of chloromethyl methyl ether (MOMCl) yielded a mixture of mono-, di-MOM and the starting material **3**. Then for example, compound **22** was prepared from **8b** in good yield as shown in Scheme 4. The corresponding bromide **23** was then prepared by simple treatment with DBDMH in $CHCl_3$ in almost quantitative yield. Now the only remaining –OH of **22** or **23** can be protected with any suitable protecting group as required. For example, treatment of **22** or **23** with diethylcarbamoyl chloride gave the corresponding carbamide **24** and **25** in 100 and 97% yield, respectively (Scheme 4). These carbamides can be used for the anionic Fries rearrangement, remote anionic Fries rearrangement,[19] and for further functionalization at the 2-position of **24**.

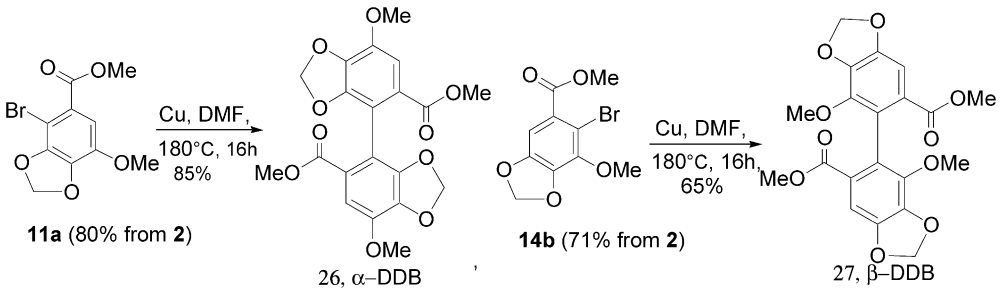
Bromination of compound **5** (Scheme 1) and **22** (Scheme 4) is particularly noteworthy. At first, the bromination at the 2-position (*ortho*-position of –OH) was tried using Br_2/*iso*-Pr_2NH/toluene as the reported method.[15] Though the yield of **6** was satisfactory (68%, lit.[15] 74%), it was only 61% yield of **23**, and was found to be a mixture of mono- and dibromo components in 1.5:1 ratio. In addition to the lower yield, the Br_2/*iso*-Pr_2NH/toluene method is somewhat tedious. Finally, treatment of **5** and **22** with DBDMH gave the corresponding bromide **6** and **23** in excellent yield and purity[18] (93 and 98%, respectively).

2.1. Preparation of α- and β-DDB

The regioselective bromo derivatives **11a**, **14b** so far obtained in excellent overall yield in Scheme 2 and/or Scheme 3 underwent the Ullmann coupling smoothly and resulted in α-DDB and β-DDB respectively (Scheme 5). Treatment of **11a** and **14b** with activated[20] Cu in DMF at 175–185 °C yielded the corresponding coupling product α- and β-DDB in 85 and 65% yield, respectively. Thus, the synthesis of α- and β-DDB was completed in 70 and 46%



Scheme 4. Multi-functionalization of methyl gallate.



Scheme 5. Preparation of α- and β-DDB.

overall yield from the commercially available **2**, much higher overall yield than that recently reported[7] (21 and 13%, respectively[21] from the same compound **2**).

In summary, a wide variety of functionalized/protected methyl gallates was prepared in very good yield and purity. Regioselective bromo derivatives with different protecting groups have also been prepared in very good to excellent yield and purity. These brominations were achieved by the simple addition of solid DBDMH in $CHCl_3$ at room temperature, which is particularly suitable for a small-scale reaction compared to the other methods utilizing liquid molecular bromine. Besides the synthesis of α- and β-DDB in very high overall yield, these functionalized methyl gallate or bromo derivatives can be served as an important precursor for the synthesis of many other biologically active organic molecules as well as other biphenyl derivatives (DDB analogues, Fig. 1) which may have some biological importance.

3. Experimental

3.1. General

All moisture-sensitive reactions were carried out under nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agents. Reactions were monitored on TLC on silica gel 60 F_{254} and visualized under UV light and/or 5% ethanolic solution of phosphomolybdic acid. Flash chromatography was performed on silica gel (Merck, 60N, spherical, neutral, 40–50 mash). Melting points were determined with a Mel-TEMP apparatus. IR was recorded on a Thermo Nicolet Avatar 360T2 instrument using either KBr or ATR. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded by JEOL AL 300 instrument. GC-MS was studied in a SHIMADZU GCMS-QP5000 instrument (column length 30 m, Idm 0.25 mm, column temperature 50–250 °C). Elemental analysis of all the new compounds was carried out by Perkin Elmer 2400 series II CHNS/O analyzer, whereas the spectral data of the known compounds were matched with the references cited.

3.2. General procedure for the Amberlyst 15E catalyzed reaction of acetals with polyphenols

A mixture of compound **2** or **10**, Amberlyst 15E (5 mg/mmol), and appropriate protecting reagent (diethyl acetal derivative, 3.0 equiv) in benzene (10 ml/mmol) was refluxed for 16–20 h with azeotropic removal of the EtOH/benzene mixture by using the Dean Stark trap. After completion, the reaction mixture was filtered over celite and the solvent was removed and directly put on a silica gel column eluted with 10–15% EtOAc in hexane.

3.2.1. Methyl 3-hydroxy-4,5-(ethoxymethylenedioxy)-benzoate (7). Compound **2** (2.50 g, 13.58 mmol), $(EtO)_3CH$, (6.03 g, 40.74 mmol) and Amberlyst 15E (62.0 mg) was treated as mentioned in Section 3.2 and yielded 3.21 g (98.5% lit.[22] 52%) of **7** as a white solid; mp 91–92 °C; IR (ATR): 3351, 1709, 1618, 1438, 1316, 1254, 1081, 1038, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J=7.1 Hz), 3.75 (q, 2H, J=7.1 Hz), 3.88 (s, 3H), 5.56 (bs, 1H), 6.96(s, 1H), 7.19 (d, 1H, J=1.5 Hz), 7.39 (d, 1H, J=1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.68, 52.38, 59.71, 102.71, 113.96, 120.04, 124.03, 137.08, 138.68, 147.14, 166.95; GC-MS *m/z* (%): 240 (M, 15), 209 (5), 195 (23), 184 (39), 153 (100). Spectral data were identical with the reported data.[22]

3.2.2. Methyl 2-bromo-3,4-(ethoxymethylenedioxy)-5-benzyloxybenzoate (12a). Using the similar procedure as of **7**, **12a** was obtained in 92% yield from **10a** as white solid; mp 80–81 °C; IR (ATR): 1722, 1432, 1318, 1171, 1081, 1035, 938, 752, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$,) δ 1.28 (t, 3H, J=7.1 Hz), 3.73 (q, 2H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 14.68, 52.28, 59.85, 71.79, 94.16, 114.41, 119.91, 124.17, 127.65, 128.32, 128.59, 135.90, 137.24, 140.43, 146.57, 165.41. Anal. Calcd for $C_{18}H_{17}BrO_6$: C, 52.83; H, 4.19; Found: C, 52.62; H, 4.35.

3.2.3. Methyl-3-hydroxy-4,5-(*p*-methoxybenzylmethyl-enedioxy)benzoate (15). Compound **2** (2.00 g, 10.9 mmol) was treated with *p*-anisaldehyde dimethylacetal (6.83 g, 3.0 equiv) and Amberlyst 15E (50 mg) in benzene (80 ml) as mentioned in Section 3.2 to give the compound **15** (2.78 g, 85%) as a slight yellow solid; mp 128–131 °C; IR (ATR): 3321, 1684, 1634, 1617, 1519, 1450, 1341, 1257, 1170, 1077, 1026, 1004, 832, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 3.87 (s, 3H), 5.20 (bs, 1H), 6.95 (d, 2H, J=9.0 Hz), 7.00 (s, 1H), 7.17 (d, 1H, J=1.5 Hz), 7.34 (d, 1H, J=1.5 Hz) 7.50 (d, 2H, J=8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 52.26, 55.36, 102.98, 111.93, 114.11, 124.11, 127.34, 128.04, 138.67, 138.84, 148.91, 161.35, 166.84. Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67; Found: C, 63.18; H, 4.33.

3.3. General procedure of bromination by 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)

Solid DBDMH (0.50–0.58 mol equiv) was added in part into the solution of starting material (Ar-OH) in $CHCl_3$ (5–7 ml/mmol) at room temperature. Upon addition of the DBDMH, the solution became red or deep brown colored, the next portion of DBDMH was added after the disappearance of color and so on. The progress of the reaction was monitored by GC-MS, and sometimes can easily be understood by observing the persistence of the color of the reaction mixture (in case of slight excess DBDMH used). After completion of the reaction, removal of the solvent followed by the separation of the solid byproduct (derived from DBDMH) by simple filtration provided the almost pure bromo product. For the compounds with low solubility, 10% aq solution of sodium hydrosulfite ($Na_2S_2O_4$) was added into the reaction mixture and the organic layer ($CHCl_3$) was separated that yielded the almost pure product. The crude obtained in both cases were almost pure and was used in the next step without further purification, or a simple column wash gave pure product.

3.3.1. 2-Bromo-3,5-dihydroxy-4-methoxybenzoic acid (4). The compound **3** gave corresponding bromide upon treatment with 0.58 mol equiv of DBDMH as described in Section 3.3. The bromide was found to contain 15% of dibromo derivative (GC-MS, ^{1}H NMR). The bromide mixture was then treated with 2.5 equiv of LiOH in MeOH/H_2O (1:1) at rt for 6 h which resulted in selective hydrolysis of the desired mono bromo ester to corresponding acid **4**, whereas the dibromo ester derivative remained unhydrolyzed and thus was separated by silica gel column chromatography (20–25% EtOAc in hexane). (81% of **4** from **3**). Light brown solid; mp 127–135 °C (decomp.); IR (ATR): 3452, 2946, 1692, 1575, 1422, 1334, 1235, 1063, 980, 804 cm^{-1}; ^{1}H NMR ($CDCl_3$–CD_3OD) δ 3.95 (s, 3H), 7.12 (S, 1H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 60.34, 99.61, 110.71, 127.30, 138.18, 147.69, 148.55, 168.17. Anal. Calcd for $C_8H_7BrO_5$: C, 36.53; H, 2.68; Found: C, 36.42; H, 2.37.

3.3.2. Methyl 2-bromo-3-hydroxy-4,5-dimethoxybenzoate (6). According to Ref. 15, **6** was obtained in 68% from **5**; but treatment of **5** with 0.5 equiv of DBDMH as described in Section 3.3 gave 93% of **6** as a slight brown crystal; mp 116–118 °C (lit.[15] 113 °C); IR (ATR): 3370, 1712, 1572, 1442, 1222, 1000, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 6.22 (s, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.44, 56.14, 61.13, 101.34, 107.03, 126.84, 138.69, 147.35, 150.96, 166.27; GC-MS *m/z* (%): 292 (M, 96), 290 (M, 85), 277 (27), 275 (29), 261 (50), 259 (53), 93 (49), 66 (89), 53 (100). The ^{1}H NMR data was identical with the reported data.[15]

3.3.3. Methyl 2-bromo-3,4-dihydroxy-5-methoxybenzoate (10a). Using the general procedure in Section 3.3, **8a** (850 mg, 4.20 mmol) was treated with 0.51 equiv of DBDMH in $CHCl_3$ (15 ml) for 24 h yielded **10a** (1.16 g, 98%) as a slight yellow crystal; mp 140–142 °C; IR (ATR): 3461, 3341, 1717, 1601, 1429, 1292, 1210, 1101, 1018, 923, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.94 (s, 3H), 5.84 (s, 1H), 5.92 (s, 1H), 7.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.30, 56.42, 103.26, 107.06, 121.81, 136.68, 141.36, 145.67, 165.94; GC-MS *m/z* (%): 278 (M, 50), 276 (M, 51), 263 (5), 261 (5), 247 (62), 245 (61), 53 (100).

3.3.4. Methyl 2-bromo-3,4-dihydroxy-5-benzyloxybenzoate (10b). Following the similar procedure as preparation of **10a**, **10b** was prepared in 95% yield from **8b** as a light yellow crystal; mp 116–118 °C; IR (ATR): 3370, 1712, 1342, 1222, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 5.14 (s, 2H), 5.91 (s, 1H), 5.92 (s, 1H), 7.27 (s, 1H), 7.38–7.52 (m, 5H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 52.14, 71.34, 103.24, 108.31, 121.44, 127.96, 128.45, 128.62, 133.74, 137.64, 142.61, 144.93, 167.37. Anal. Calcd for $C_{15}H_{13}BrO_5$: C, 51.01; H, 3.71. Found: C, 49.90; H, 3.77.

3.3.5. Methyl 2-bromo-3-hydroxy-4,5-methylenedioxybenzoate (14a). Using the general procedure in Section 3.3 (time = 10 h), **14a** was obtained from **13** in 95% yield as crystal; mp 110–113 °C; IR (ATR): 3426, 1707, 1505, 1423, 1360, 1302, 1218, 1074, 1030, 935 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 5.89 (s, 1H), 6.10 (s, 2H), 7.11 (s, 1H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 52.43, 102.93, 104.62, 105.57, 124.00, 137.29, 137.62, 147.97, 165.49; GC-MS *m/z* (%): 276 (M, 49), 274 (M, 51), 245 (91), 243 (90), 77 (83), 53 (100). Anal. Calcd for $C_9H_7BrO_5$: C, 39.30; H, 2.57. Found: C, 39.50; H, 2.45.

3.3.6. Methyl 2-bromo-3-hydroxy-4,5-(methylphenylmethylenedioxy)benzoate (18). Using the general procedure in Section 3.3 (time = 1 h), **18** was obtained from **17** in 88% as thick oil. IR (ATR): 3469, 1709, 1609, 1493, 1436, 1368, 1212, 1137, 923, 766, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 3.88 (s, 3H), 5.84 (s, 1H), 7.11 (s, 1H), 7.37–7.40 (m, 3H), 7.57–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.04, 39.41, 104.82, 120.17, 123.58, 124.82, 129.31, 137.12, 139.97, 147.65, 165.57; GC-MS *m/z* (%): 366 (M, 2), 364 (M, 2), 351 (0.7), 349 (0.7), 335 (2), 333 (2), 264 (5), 262 (5), 233 (2), 231 (2), 103 (100). Anal. Calcd for $C_{16}H_{13}BrO_5$: C, 52.62; H, 3.59. Found: C, 52.68; H, 3.43.

3.3.7. Methyl 2-bromo-3-hydroxy-4-methoxy-5-benzyloxybenzoate (23). Compound **22** (505 mg, 1.75 mmol) in $CHCl_3$ (10 ml) was added 250 mg (0.87 mmol) DBDMH at once and stirred at room temperature for 16 h. Then the solvent was evaporated in vacuo. and purified as mentioned in Section 3.3 gave 622 mg (98%) of **23** as a colorless crystal; mp 123–125 °C; IR (KBr): 3324, 1721, 1573, 1489, 1441, 1351, 1228, 1142, 1098, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.98 (s, 3H), 5.12 (s, 2H), 6.27 (s, 1H), 7.14 (s, 1H), 7.37–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 52.44, 61.21, 71.13, 101.51, 108.62, 126.72, 127.49, 128.28, 128.64, 135.93, 139.11, 147.51, 159.92, 166.20; GC-MS *m/z* (%): 368 (M, 0.4), 366 (M, 0.4), 337 (0.2), 335 (0.2), 287 (0.9), 91 (100). Anal. Calcd for $C_{16}H_{15}BrO_5$: C, 52.34; H, 4.12. Found: C, 52.34; H, 4.01.

3.4. General procedure for the methoxylation

The hydroxy starting materials were treated with MeI (2.0–2.5 equiv), K_2CO_3 (2.0–2.5 equiv) in DMF (5–7 ml/mmol) at 55–60 °C for 4–14 h. The crude was extracted with diethyl ether, washed with brine, dried over $MgSO_4$ and

concentrated. The crude was almost pure and a simple column wash gave the pure product.

3.4.1. Methyl 3,5-dihydroxy-4-methoxybenzoate (3). Compound **3** was prepared as mentioned in Ref. 14 (2.5 equiv MeI, 2.5 equiv Li_2CO_3, in DMF at 50–55 °C for 18 h) in 61% yield along with 12% compound **5**. Light yellow colored solid; mp 143–146 °C (lit.[10] 148 °C); IR (ATR): 3409, 1707, 1598, 1505, 1432, 1363, 1272, 1164, 1004, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.96 (s, 3H), 5.61 (s, 2H), 7.23 (s, 2H); ^{13}C NMR ($CDCl_3$–CD_3OD): 51.88, 60.13, 108.99, 125.02, 139.32, 149.66, 167.37; GC-MS *m/z* (%): 198 (M, 79), 183 (48), 167 (100), 155 (22). Spectral data were identical with the reported data.[10]

3.4.2. Methyl 3-hydroxy-4,5-dimethoxybenzoate (5). Compound **5** was obtained as a side product during the preparation of compound **3** from **2** (12%). This was also prepared by treating **3** with 1.0 equiv of K_2CO_3 and 1.0 equiv of MeI in DMF at 50–55 °C. The resulted mixture of starting material, desired dimethoxy and undesired trimethoxy derivatives was separated by silica gel column to give **5** as colorless crystal; mp 73–75 °C (lit.[22] 73 °C); IR (KBr): 3404, 3219, 1696, 1457, 1346, 1218, 1092, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 5.85 (s, H), 7.20 (d, 1H, J=2.1 Hz), 7.31 (d, 1H, J=2.1 Hz); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 52.15, 55.96, 60.93, 105.57, 109.88, 125.53, 139.44, 148.95, 151.91, 166.67; GC-MS *m/z* (%): 212 (M, 100), 197 (64), 181 (66), 151 (20), 141 (40). Spectral data were identical with the reported data.[23]

3.4.3. Methyl 3-methoxy-4,5-dihydroxybenzoate (8a). Using the general procedure in Section 3.4, compound **7** gave the corresponding methoxy derivative, which upon treatment with 2 N aq HCl at room temperature for 2 h in MeOH gave **8a** (99% yield over two steps) as a colorless crystal; mp 115–119 °C; IR (ATR): 3382, 1708, 1593, 1506, 1436, 1243, 1161, 1058, 1000, 964, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.92 (s, 3H), 5.49 (s, 1H), 5.86 (s, 1H), 7.21 (d, 1H, J=1.8 Hz), 7.34 (d, 1H, J=1.8 Hz); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 51.85, 55.96, 104.94, 110.78, 120.38, 138.51, 144.21, 147.18, 167.56; GC-MS *m/z* (%): 198 (M, 44), 168 (100), 167 (52), 140 (25), 53 (33). Spectral data were identical with the reported data.[24]

3.4.4. Methyl 2-bromo-3-methoxy-4,5-methylenedioxybenzoate (14b). Using the general method in Section 3.4, 2.32 g (95%) of **14b** was obtained from 2.33 g of **14a**. Compound **14b** was also prepared from **21** in 85% yield using the general procedure in Section 3.6. White solid; mp 87–88 °C (lit.[7a] 82–83 °C); IR (ATR): 1721, 1431, 1282, 1090, 1043, 942 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 4.02 (s, 3H), 6.04 (s, 2H), 7.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.41, 60.28, 102.38, 105.50, 109.12, 126.39, 140.50, 148.32, 166.24; GC-MS *m/z* (%): 290 (M, 62), 288 (M, 73), 259 (91), 257 (95), 217 (6), 215 (6), 201 (7), 199 (7), 143 (30), 77 (100), 53 (79). Anal. Calcd for $C_{10}H_9BrO_5$: C, 41.55; H, 3.14. Found: C, 41.53; H, 3.00.

3.4.5. Methyl 2-bromo-3-methoxy-4,5-(diphenylmethylenedioxy)benzoate (20). Compound **19** (750 mg, 2.15 mmol) was treated with 307 mg (0.5 equiv) of DBDMH as mentioned in Section 3.3 for 2 h, yielded the corresponding bromo derivative (100%), which upon methoxylation as the general procedure in Section 3.4 gave the compound **20** (938 mg, 99%) as a slight brown solid; mp 68–72 °C; IR (ATR): 1731, 1596, 1478, 1434, 1366, 1284, 1206, 1095, 1042, 1028, 918, 780, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 4.09 (s, 3H), 7.08 (s, 1H), 7.53–7.40 (m, 6H), 7.53–7.56 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 52.36, 60.37, 105.63, 109.00, 119.06, 126.25, 126.29, 128.33, 128.37, 128.43, 129.54, 139.05, 140.07, 140.85, 147.89, 166.29. Anal. Calcd for $C_{22}H_{17}BrO_5$: C, 59.88; H, 3.88. Found: C, 60.17; H, 3.90.

3.4.6. Methyl 3-hydroxy-4-methoxy-5-benzyloxybenzoate (22). Among several runs, the best result was obtained by treating **8b** (2.50 g, 9.12 mmol), Li_2CO_3 (1.01 g, 1.5 equiv), MeI (2.0 equiv), in DMF (50 ml) at 55–60 °C for 16 h under nitrogen atmosphere. After completion, the reaction mixture was extracted with Et_2O, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Chromatographic separation (20% EtOAc in hexane) yielded 2.07 g (78%) of **22** along with 554 mg (20%) of undesired dimethoxy derivative as a colorless solid; mp 108–111 °C; IR (ATR): 3359, 1703, 1589, 1504, 1438, 1355, 1228, 1089, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.92 (s, 3H), 5.14 (s, 2H), 5.86 (s, 1H), 7.29 (d, 1H, J=1.8 Hz), 7.32 (d, 1H, J=1.8 Hz), 7.34–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 52.17, 61.03, 70.92, 107.03, 110.04, 125.46, 127.52, 128.14, 128.59, 136.31, 139.81, 149.06, 150.93, 166.61; GC-MS *m/z* (%): 288, (M, 1.7), 257 (0.7), 141 (0.8), 91 (100). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.55; H, 5.52.

3.5. General procedure for benzyloxylation

The hydroxy starting materials were treated with 2.0 equiv of BnCl, 2.0 equiv of K_2CO_3 in DMF (10 ml/mmol) at 70 °C for 12–14 h. The crude was extracted with diethyl ether, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude was almost pure and a simple column wash gave the pure product.

3.5.1. Methyl 3-benzyloxy-4,5-dihydroxybenzoate (8b). Using the general method in Section 3.5, compound **7** gave the corresponding benzyloxy derivative, which upon treatment with 2 N aq HCl at room temperature for 2 h in MeOH gave **8b** in 100% yield over two steps as colorless solid; mp 142–145 °C (lit.[23] 145–147 °C); IR (ATR): 3412, 3342, 1686, 1434, 1326, 1239, 1055, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H), 5.14 (s, 2H), 5.36 (s, 1H), 5.84 (s, 1H), 7.31 (d, 1H, J=1.8 Hz), 7.35 (d, 1H, J=1.8 Hz), 7.39–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 51.76, 71.03, 106.36, 110.92, 120.36, 127.71, 128.06, 128.38, 136.08, 138.62, 144.33, 167.33; GC-MS *m/z* (%): 274 (M, 0.5), 243 (0.4), 127 (0.6), 91 (100). Spectral data were identical with the reported one.[23]

3.5.2. Methyl 2-bromo-3-benzyloxy-4,5-methylenedioxybenzoate (14c). Using the general procedure in Section 3.5, 1.20 g (~100%) of **14c** was obtained from 904 mg (3.28 mmol) of **14a** as a white solid; mp 70–72 °C; IR (ATR): 1713, 1431, 1364, 1282, 1242, 1176, 1096, 1040, 944 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 5.25 (s, 2H),

6.03 (s, 2H), 7.25 (s, 1H), 7.32–7.41 (m, 3H), 7.47–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.36, 74.23, 102.36, 105.76, 109.84, 126.17, 126.62, 128.02, 128.25, 128.37, 136.27, 139.62, 140.92, 148.11, 166.14; GC-MS *m/z* (%): 366 (M, 0.4), 364 (M, 0.4), 335 (0.2), 333 (0.2), 285 (1.3), 91 (100). Anal. Calcd for $C_{16}H_{13}BrO_5$: C, 52.62; H, 3.59. Found: C, 52.80; H, 3.50.

3.6. General procedure for the methylenedioxy-protection

A mixture of starting material (dihydroxy compound) (1 equiv), KF (5 equiv) and CH_2I_2 (1.5 equiv) in DMF (8–9 ml/mmol) was heated at 110 °C for overnight. After completion, the reaction mixture was extracted with diethyl ether, washed with brine, dried over $MgSO_4$, and condensed in vacuo. Silica gel column chromatography eluted with 20–25% EtOAc in hexane gave the pure desired product.

3.6.1. Methyl 3-methoxy-4,5-methylenedioxybenzoate (9a). Using the general procedure in Section 3.6, 625 mg (85%) of **9a** was obtained from 693 mg (3.50 mmol) of **8a** as a transparent crystal; mp 85–87 °C (lit.[7a] 88–89 °C); IR (ATR): 1704, 1632, 1431, 1366, 1328, 1239, 1175, 1106, 1037, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.94 (s, 3H), 6.05 (s, 2H), 7.20 (d, 1H, J=1.5 Hz), 7.33 (d, 1H, J=1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 52.08, 56.45, 102.22, 103.77, 109.85, 124.30, 139.37, 143.19, 148.58, 166.29; GC-MS *m/z* (%): 210 (M, 59), 179 (100), 151 (32), 95 (21). ^{1}H NMR data was identical with the reported data.[7a]

3.6.2. Methyl 3-benzyloxy-4,5-methylenedioxybenzoate (9b). Using the general procedure in Section 3.6, 394 mg (90%) of **9b** was obtained from 420 mg (1.53 mmol) of **8b** as a transparent solid; mp 70–73 °C; IR (ATR): 1713, 1430, 1364, 1326, 1247, 1101, 751, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 5.20 (s, 2H), 6.06 (s, 2H), 7.21 (d, 1H, J=1.5 Hz), 7.41 (d, 1H, J=1.8 Hz), 7.35–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 52.10, 71.46, 102.18, 104.00, 112.11, 124.33, 127.65, 128.19, 128.57, 136.21, 139.87, 142.21, 148.85, 166.26; GC-MS *m/z* (%): 286 (M, 6), 255 (2), 91(100). Spectral data were identical with the reported data.[26]

3.6.3. Methyl 2-bromo-3,4-methylenedioxy-5-methoxy-benzoate (11a). Using the general procedure in Section 3.6, 100 mg of isolated **11a** (84%) was obtained from 89 mg (0.32 mmol) of **10a**, as a colorless solid; mp 101–102 °C (lit.[7a] 104–105 °C); IR (ATR): 1724, 1433, 1324, 1248, 1175, 1107, 1041, 935 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.92 (s, 3H), 6.12 (s, 2H), 7.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.25, 56.75, 94.40, 102.37, 112.39, 124.24, 138.29, 142.16, 147.97, 165.42; GC-MS *m/z* (%): 290 (M, 42), 288 (M, 50), 259 (69), 257 (68), 231 (5), 229 (5), 217 (5), 215 (5), 201 (16), 199 (16), 77(100). Anal. Calcd for $C_{10}H_9BrO_5$: C, 41.55; H, 3.14. Found: C, 41.40; H, 2.98.

3.6.4. Methyl 2-bromo-3,4-methylenedioxy-5-benzyloxy-benzoate (11b). Using the general procedure in Section 3.6, 1.06 g (85%) of **11b** was obtained from 1.20 g (3.40 mmol) of **10b** as a colorless solid; mp 77–80 °C; IR (ATR): 1721, 1430, 1343, 1322, 1174, 1094, 1040, 939, 747, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 5.17 (s, 2H), 6.12 (s, 2H), 7.32 (s, 1H), 7.35–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 52.26, 71.81, 94.69, 102.32, 114.73, 124.26, 127.69, 128.36, 128.63, 135.92, 138.79, 141.09, 148.22, 165.36; GC-MS *m/z* (%): 366 (M, 0.6), 364 (M, 0.6), 335 (0.2), 333 (0.2), 149 (0.5), 147 (0.5), 91 (100). Anal. Calcd for $C_{16}H_{13}BrO_5$: C, 52.62; H, 3.59. Found: C, 52.85; H, 3.50.

3.6.5. Methyl 2-bromo-4,5-(biphenylmethylenedioxy)-benzoate (12b). Compound **10b** (680 mg, 1.32 mmol) was treated with K_2CO_3 (3.0 equiv) and Ph_2CCl_2 (1.3 equiv) in CH_3CN (10 ml) at room temperature for 21 h under nitrogen atmosphere. After completion, the reaction mixture was extracted with EtOAc followed by usual workup and silica gel column chromatography gave 668 mg (62%) isolated desired product **12b**. Light yellow needles; mp 155–156 °C; IR (ATR): 1722, 1432, 1318, 1171, 1081, 1035, 938, 752, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 5.21 (s, 2H), 7.28 (s, 1H), 7.32–7.40 (m, 11H), 7.55–7.59 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 52.22, 71.95, 94.78, 115.17, 118.90, 124.07, 126.16, 126.41, 127.63, 128.24, 128.33, 128.57, 129.52, 136.16, 138.46, 138.94, 140.92, 165.48. Anal. Calcd for $C_{28}H_{21}BrO_5$: C, 65.00; H, 4.09. Found: C, 65.20; H, 4.10.

3.6.6. Methyl 3-hydroxy-4,5-methylenedioxybenzoate (13). $TiCl_4$ (0.08 ml, 1.2 equiv) was added in 202 mg (0.71 mmol) of **9b** in $CHCl_3$ (5 ml), at room temperature and the reaction mixture was stirred for 12 h. After completion, it was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and purified by column chromatography eluted with 25–30% EtOAc in hexane yielded 116 mg (90%) isolated **13** as colorless solid; mp 168–172 °C (lit.[24] 164 °C); IR (ATR): 3313, 1684, 1637, 1448, 1353, 1192, 1170, 1063, 1033, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 5.07 (bs, 1H), 6.05 (s, 2H), 7.15 (d, 1H, J=1.2 Hz), 7.31 (d, 1H, J=1.5 Hz); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 51.89, 101.79, 102.03, 113.78, 123.71, 128.00, 140.17, 148.62, 166.98; GC-MS *m/z* (%): 196 (M, 39), 165 (100), 137 (26), 53 (31). Spectral data were identical with the reported data.[25]

3.6.7. Methyl 2-bromo-3-hydroxy-4,5-(*p*-methoxybenzyl-methylenedioxy)benzoate (16). Compound **16** was prepared in 55% yield from **15** according to Ref. 15. Light brown colored solid; mp 121–123 °C; IR (ATR): 3345, 1670, 1599, 1577, 1511, 1427, 1332, 1258, 1214, 1162, 1045, 1019, 925, 829, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 1H), 3.90 (s, 3H), 5.89 (bs, 1H), 6.95 (s, 1H), 6.97 (s, 1H), 7.06 (s, 1H), 7.12 (s, 1H), 7.48 (s, 1H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 52.07, 55.03, 96.41, 103.24, 105.18, 111.96, 113.32, 113.73, 113.80, 124.85, 127.85, 127.77, 147.41, 161.16. Anal. Calcd for $C_{16}H_{13}BrO_6$: C, 50.42; H, 3.44; Found: C, 50.29; H, 3.12.

3.6.8. Methyl 3-hydroxy-4,5-(methyl, phenyl methylene-dioxy)benzoate (17). Compound **2** (200 mg, 1.08 mmol), montmorillonite clay K10 (117 mg) and acetophenone (2.0 equiv) in 15 ml of benzene was refluxed for 16 h with removal of generated water by passing through a trap of 3A molecular sieves. After completion, the reaction mixture was filtered over celite, dried over $MgSO_4$, and removed the solvent in vacuo. Separation by silica gel column chromatography (eluted with 20% EtOAc in hexane) provided

30 mg of desired **17** (30%). ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 3.85 (s, 3H), 5.08 (bs, 1H), 7.15 (d, 1H, J=1.5 Hz), 7.28 (d, 1H, J=1.8 Hz), 7.37–7.40 (m, 3H), 7.56–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.07, 52.41, 107.73, 120.15, 123.42, 124.80, 129.25, 137.20, 140.01, 147.71, 165.70; GC-MS *m/z* (%): 286 (M, 6), 271 (4), 255 (2), 184 (16), 153 (14), 103 (100).

3.6.9. Methyl 3-hydroxy-4,5-(diphenylmethylenedioxy)-benzoate (19). Using the same procedure as of **12b**, compound **19** was obtained in 62% from commercially available **2**. IR (ATR): 3384, 1697, 1517, 1440, 1385, 1328, 1259, 1212, 1074, 1015, 781, 765, 707, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 5.61 (bs, 1H), 7.22 (d, 1H, J=1.5 Hz), 7.32 (q, 1H, J=1.5 Hz), 7.35–7.40 (m, 6H), 7.53–7.58 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 52.25, 103.27, 114.12, 118.72, 124.16, 126.27, 128.29, 129.37, 138.19, 139.06, 139.44, 148.33, 166.87; GC-MS *m/z* (%): 348 (M, 13), 317 (1), 271 (46), 211 (9), 165 (30), 105 (100), 77 (45).

3.6.10. Methyl 2-bromo-3-methoxy-4,5-di-hydroxy-benzoate (21). Refluxing of 67 mg (0.13 mmol) of **20**, in AcOH/H_2O (1:1, 1.5 ml) for 4 h yielded 38 mg (90%) of **21**. Similarly, refluxing of 46 mg (0.09 mmol) of **20** with 15 mg of Amberlyst 15E in MeOH (1 ml) for overnight yielded 29 mg (100%) of **21** as a crystalline solid; mp 63–65 °C; IR (ATR): 3530, 3230, 1694, 1589, 1514, 1431, 1364, 1313, 1253, 1209, 1062, 1022, 913, 774 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.93 (s, 3H), 5.48 (s, 1H), 6.04 (s, 1H), 7.32 (s, 1H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 52.15, 60.44, 107.86, 114.28, 122.24, 142.34, 144.39, 145.46, 166.76; GC-MS *m/z* (%): 278 (M, 45), 276 (M, 46), 263 (33), 261 (25), 257 (29), 105 (100). Anal. Calcd for $C_9H_9BrO_5$: C, 39.01; H, 3.27. Found: C, 39.11; H, 3.10.

3.6.11. Methyl 3-diethylcarbamoyloxy-4-methoxy-5-benzyloxybenzoate (24). A mixture of **22** (3.49 g, 12.1 mmol), NaH (1.5 equiv), diethylcarbamoyl chloride (1.5 equiv) and DMAP (cat.) in THF (65 ml) was refluxed for 2 h under the nitrogen atmosphere. Removal of the solvent followed by usual workup provided 4.52 g (100%) of crude **24**, which was almost pure and was used in the next step without further purification. A portion of 200 mg was purified for the analytical purpose. White crystalline solid; mp 95–97 °C; IR (ATR): 1714, 1412, 1333, 1260, 1155, 1081, 992, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, J=7.1 Hz), 1.28 (t, 3H, J=7.1 Hz), 3.38 (q, 2H, J=7.1 Hz), 3.52 (q, 2H, J=7.1 Hz), 3.87 (s, 3H), 3.92 (s, 3H), 5.15 (s, 2H), 7.33–7.45 (m, 5H), 7.47 (d, 1H, J=1.8 Hz), 7.56 (d, 1H, J=2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.18, 14.03, 42.23, 42.53, 52.13, 60.76, 71.10, 112.35, 117.95, 124.80, 127.44, 128.06, 128.55, 136.32, 144.61, 146.17, 152.21, 153.77, 166.12; GC-MS *m/z* (%): 387 (M, 0.5), 357 (0.2), 100 (100), 91 (25), 72 (37). Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.09; H, 6.61; N, 3.61.

3.6.12. Methyl 2-bromo-3-diethylcarbamoyloxy-4-methoxy-5-benzyloxybenzoate (25). Using the same procedure as for **24**, 97% of **25** was obtained from **23** as a white crystal; mp 110–113 °C; IR (ATR): 1731, 1720, 1333, 1259, 1216, 1149, 1083, 1004, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, J=7.2 Hz), 1.28 (t, 3H, J=7.2 Hz), 3.38 (q, 2H, J=7.2 Hz), 3.52 (q, 2H, J=7.2 Hz), 3.90 (s, 3H), 3.92 (s, 3H), 5.12 (s, 2H), 7.34–7.45 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 13.32, 14.16, 42.24, 42.53, 52.40, 61.00, 71.25, 110.31, 113.93, 126.38, 127.45, 128.21, 128.51, 128.61, 135.96, 143.75, 146.29, 150.94, 152.57, 165.82. Anal. Calcd for $C_{21}H_{24}BrNO_6$: C, 54.09; H, 5.19; N, 3.00. Found: C, 54.20; H, 5.18; N, 3.08.

3.7. General procedure for the Ullmann coupling

To the mixture of bromo derivatives **11a** or **14b** and equal amount (by weight) of activated Cu in dry DMF (0.5 ml/mmol) was added and the resulted thick slurry was heated for 3 h at 110 °C with stirring. Then, another 3 ml/mmol of DMF was added and the mixture was heated at 180–185 °C for 16–18 h. After cooling at around 100 °C, the reaction mixture was poured into ice crushed and extracted with $CHCl_3$, dried over $MgSO_4$. The highly florescent desired coupling product was purified by silica gel column chromatography eluted with 30–40% $CHCl_3$ in hexane.

3.7.1. 4,4′-Dimethoxy-5,6,5′,6′-dimethylenedioxy-2,2′-dimethoxycarbonylbiphenyl (α-DDB) (26). Using the general procedure in Section 3.7, compound **26** was obtained in 85% yield from **11a** as a slight yellow solid; mp 145–147 °C; IR(ATR): 1719, 1633, 1430, 1320, 1194, 1173, 1100, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 6H), 3.96 (s, 6H), 5.99 (s, 4H), 7.38 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 51.85, 56.48, 102.28, 110.90, 112.21, 123.40, 138.10, 142.36, 147.07, 166.32. Anal. Calcd for $C_{20}H_{18}O_{10}$. C, 57.42; H, 4.34. Found: C, 57.34; H, 4.43.

3.7.2. 6,6′-Dimethoxy-4,5,4′,5′-dimethylenedioxy-2,2′-dimethoxycarbonylbiphenyl (β-DDB) (27). Using the general procedure in Section 3.7, compound **27** was obtained in 65% yield from **14b** as a slight yellow solid; mp 199–201 °C (lit.[7a] 207 °C); IR (ATR): 1720, 1618, 1477, 1433, 1364, 1282, 1220, 1084, 1040 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 6H), 3.78 (s, 6H), 6.06 (s, 4H), 7.24 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 51.76, 59.71, 101.85, 104.81, 123.55, 127.20, 140.27, 140.95, 148.24, 166.28. Anal. Calcd for $C_{20}H_{18}O_{10}$. C, 57.42; H, 4.34. Found: C, 57.21; H, 4.12.

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Highly stereoselective and stereospecific syntheses of a variety of quercitols from D-(−)-quinic acid

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Abstract—The highly stereoselective synthesis of (−)-*epi*-, (−)-*allo*- and *neo*-quercitols as well as stereospecific synthesis of (−)-*talo*- and (+)-*gala*-quercitols have been achieved. The general strategy is employing dihydroxylation of the isolated double bond of various kinds of protected chiral (1,4,5)-cyclohex-2-ene-triols, which are derived from D-(−)-quinic acid. The choosing of protecting groups from either BBA (butane 2,3-bisacetal) or acetyl groups will result in the various degrees of stereoselectivity of dihydroxylation. On the other hand, the cyclohexylidene acetal moiety is attributed to the stereospecificity during dihydroxylation to afford the request molecules.

1. Introduction

Quercitol, which is a generic term for cyclohexanepentol or deoxyinositol, has 16 stereoisomers in its family.[1] Among these isomers, there were only (+)-*proto*-, (−)-*proto*- and (−)-*vibo*-quercitols to be found in nature.[2] Due to their biological activities against glycosidases, their syntheses have been attracting a great deal of interest to the synthetic community.[3] At present, ten possible diasteroisomers, *proto*-,[4,5,6] *allo*-,[7,8] *talo*-,[1,2,8,9,10] *epi*-,[1,11] *vibo*-,[12,13,14] *gala*-,[4c,15,16,17] *scyllo*-,[12,18] *neo*-,[1] *cis*-[19] and *muco*-quercitols,[20] have been synthesized from different approaches to provide their either racemic or chiral forms. Recently, we have reported a facile synthesis of (+)-*proto*-quercitol through an important intermediate, (1*R*,4*R*,5*R*)-triacetoxy-cyclohex-2-ene, which was derived from D-(−)-quinic acid.[21] During this course, one key step was employing this intermediate to be dihydroxylated stereospecifically with $KMnO_4/MgSO_4$ condition resulting in moderate yield. This success prompted us that a variety of quercitols might be efficiently synthesized from dihydroxylation of different kinds of protecting chiral (1,4,5)-cyclohex-2-ene-triol analogues. Throughout dihydroxylation, we have found that the protecting groups could affect the outcomes in either stereoselective or stereospecific manners by analysis the resulting quercitols.

2. Results and discussion

Our synthesis is depicted in Scheme 1 and the results are summarized in Table 1. Compounds **1a**,[21] **3a**[21] and **5a**[22] were acetylated to afford **2a**, **4a** and **6a**, respectively. While **1a** and **2a** were individually dihydroxylated under $KMnO_4/MgSO_4$ condition,[2,4b,4d] the oxidation step gave one product in each case with moderate yield. The resulting stereochemistry of **1b** and **2b** was not determined at this stage. However, the same quercitol **1c** was obtained from either **1b** or **2b** until the removal of their protecting group(s). The spectroscopic data of the resulting quercitol **1c**, (−)-*talo*-quercitol, are in accordance with that of (+)-*talo*-quercitol[10] except the sign of optical rotation. Based on this result, it was obvious that the oxidation proceeded stereospecifically at the same side with the hydroxyl and acetoxy groups but *anti* relationship to the cyclohexylidene acetal group in both cases. Consequently, the same procedure was also employed on compounds **3a** and **4a**. Not surprisingly, the (+)-*gala*-quercitol[23] (**3c**) was received as the sole product. The oxidation happened preferably to the face that was opposite to the stereochemistry of C1 as well as the cyclohexylidene acetal protection of C4 and C5. The stereospecific reactions that occurred in **1a**–**4a** might be explained by the steric effect. The different quercitols will be received if permanganate ion is approaching to the same face with the pseudoaxial oxygen at C4, but that causes the destabilization (Fig. 1). Thus, this factor mainly controlled the stereochemical outcome of dihydroxylation no matter the stereochemistry of C1 with or without protection by acetyl group. Therefore, dihydroxylation occurred at the *anti* relationship to the

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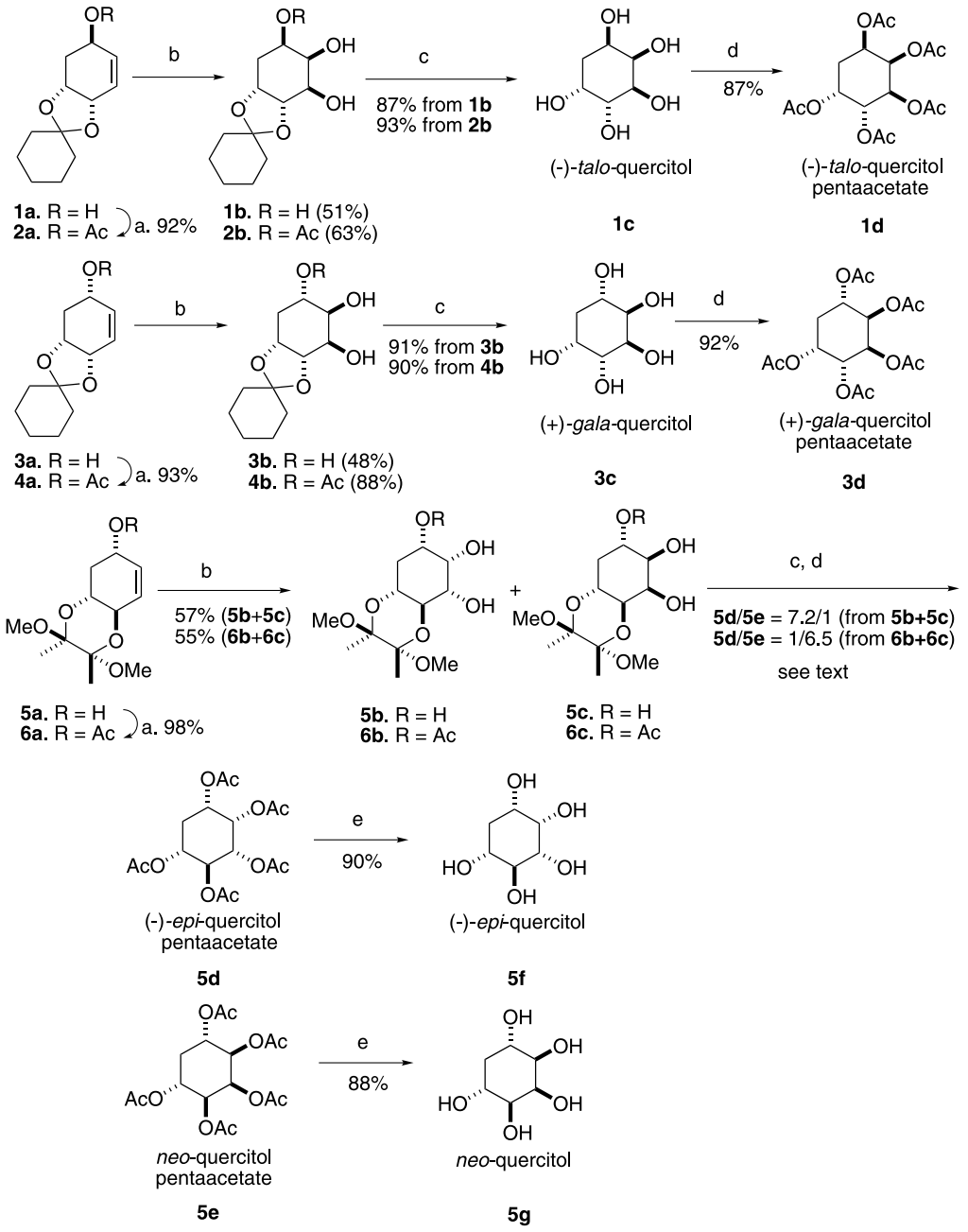


Scheme 1. Reagents and conditions: (a) 1.2 equiv Ac_2O, pyridine; (b) 1.5 equiv $KMnO_4$, 1.5 equiv $MgSO_4$, EtOH, H_2O, rt; (c) (i) 80% TFA (for **1b**, **3b**, **5b**, **5c**, **6b** and **6c**), (ii) 80% TFA then 7 N NH_3/MeOH (for **2b** and **4b**); (d) excess Ac_2O, pyridine; (e) 7 N NH_3/MeOH.

Table 1. Dihydroxylation of **1a**, **2a**, **3a**, **4a**, **5a** and **6a**

Compound	Yield[a]	Quercitol	$[\alpha]_D$, mp °C (literature)	Quercitol pentaacetate	$[\alpha]_D$, mp °C (literature)
1a/2a	51/63	**1c**	−64.4, 238–248 (+61, 248)[b]	**1d**	−25.4, 184–187 (+28, 183)[b]
3a/4a	48/88	**3c**	+50, 220–230 (−48, 258)[c]	**3d**	+22, an oil (−24, 117)[c]
5a/6a	57/55	**5f**	−3.3, 180–182 (−5, 194)[d]	**5d**	−14.5, an oil (not avilable)
		5g	191–192 (182)[e]	**5e**	237–242 (239)[e]

[a] Yield of dihydroxylation: $KMnO_4$, $MgSO_4$, EtOH, H_2O, rt.
[b] Ref. 1 for (+)-*talo*-quercitol and its pentaacetate.
[c] Ref. 1 for (−)-*gala*-quercitol and its pentaacetate.
[d] Ref. 1 for (−)-*epi*-quercitol and its pentaacetate.
[e] Ref. 1 for *neo*-quercitol and its pentaacetate.

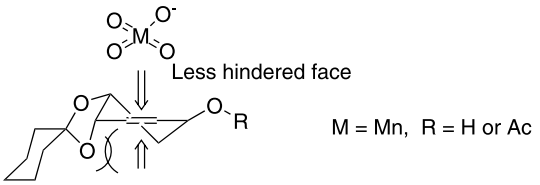


Figure 1. Rationalization of stereospecific dihydroxylation of compounds **1a** and **2a**.

cyclohexylidene acetal moiety and gave the stereospecific oxidation in **1a**, **2a**, **3a** and **4a**. However, we could not eliminate the possibility with respect to the hydroxyl group orienting the dihydroxylation with the assistance of hydrogen bonding in **3a**, but the steric effect deriving from the cyclohexylidene group was somewhat a more determining factor. The above examples were the same as those of Bacli's reports in the syntheses of (±)-*talo*-[2] and (±)-*gala*-quercitols[4c] even though a different protecting group was chosen in our case.

Consequently, compound **5a**[22] was dihydroxylated to give an inseparable mixture of **5b** and **5c**. Thereafter, they were subjected to acetylation and gave the separable compounds **5d** and **5e** with a ratio of 7.2:1 in 87% total yield. Conversely, compound **5e** was isolated as the dominant product when **6a** was dihydroxylated to afford 76% total yield of **5d** and **5e** with a ratio of 1:6.5. Our explanation to these opposite results is indicated in Figure 2. In compounds **5a** and **6a**, the stereo arrangements of BBA group were located at pseudoequatorial positions to accommodate a stable chair form. Therefore, it allowed a less sterically crowded environment than those of previous cases thus contributing equal stereoselectivity to both faces during dihydroxylation. Based on AM1 calculation, the effective distance of ideal intermolecular hydrogen bonding between C1 hydroxyl group with one of closest permanganate's oxygen is 2.17213 Å (Fig. 2a) which is shorter than 2.54892 Å in case of permanganate ion approaching from the opposite site (Fig. 2b). From this point of view, the influence of hydroxyl directing the dihydroxylation through intermolecular hydrogen bonding became the more important factor in **5a**. Consequently, the (−)-*epi*-quercitol (**5f**) was isolated as a major product. On the other hand, the hydroxyl directing effect diminished in **6a** and the permanganate ion was allowed to approach the less sterically hindered face to give the *neo*-quercitol (**5g**) as the main product.

In order to understand where the different kinds of protecting groups affected the outcomes during dihydroxylation, we decided to prepare the triacetates of **7a**, **8a** and **9a** (Scheme 2). It was noteworthy that racemate **8a** has been used in the synthesis of (±)-*gala*-quercitol,[4c] but no study has been shown whereas **7a** and **9a** were conducted under dihydroxylation. We have experienced that moderate yields were obtained from dihydroxylation in $KMnO_4/MgSO_4$ condition in Scheme 1. In order to compare their results, the alternative oxidation using $RuCl_3 \cdot 3H_2O/NaIO_4/H_2SO_4$ condition[24] allowed us to receive the better yields as summarized in Table 2. However, we have found that either stereoselectivity or stereospecificity of **7a** and **9a** decreased dramatically in dihydroxylation except **8a** which gave the (+)-*gala*-quercitol (**3c**) only. The distinction between Scheme 1 and 2 were attributed to both the cyclohexylidene acetal and BBA protecting groups that restricted the more rigid conformations than those of acetyl group upon different chiral (1,4,5)-cyclohex-2-ene-triols. Thus, it is not surprising that the more flexible conformations of **7a** and **9a** gave all less stereoselectivity in dihydroxylation. When compound **7a** was dihydroxylated, an inseparable mixture **7b** and **7c** was obtained. Their separation could be easier after they were acetylated to afford **1d** and **7d** in 39 and 35% yields, respectively. Compound **7d** was subsequently deacetylated to give the (−)-*allo*-quercitol (**7e**).[25] Therefore, the (−)-*talo*- (**1d**) and (−)-*allo*-quercitol pentaacetates (**7d**) were received in almost 1:1 ratio with a 74% combined yield. This observation was distinct from the results of **1a** and **2a** in which the (−)-*talo*-quercitol (**1c**) was the only isolated product (Scheme 1). These opposite results were due to the pseudoequatorial acetyl groups at C1 and C4 of **7a** to contribute equally in stereoselectivity upon dihydroxylation. The (+)-*gala*-quercitol **3c** obtained from **8a** was the same result that appeared in **3a**, **4a** and in Balci's report.[4c] While compound **9a** was dihydroxylated and followed by acetylation, the resulting (−)-*epi*- (**5d**) and *neo*-quercitol pentaacetates (**5e**) were with a 1:1.4 ratio based on ^1H NMR integration. Although the *neo*-quercitol **5g** was slightly dominant in this reaction, however, its stereoselectivity was still far less to that of case of **6a**. The low stereoselectivity was defined the same reason as mentioned in **7a**.

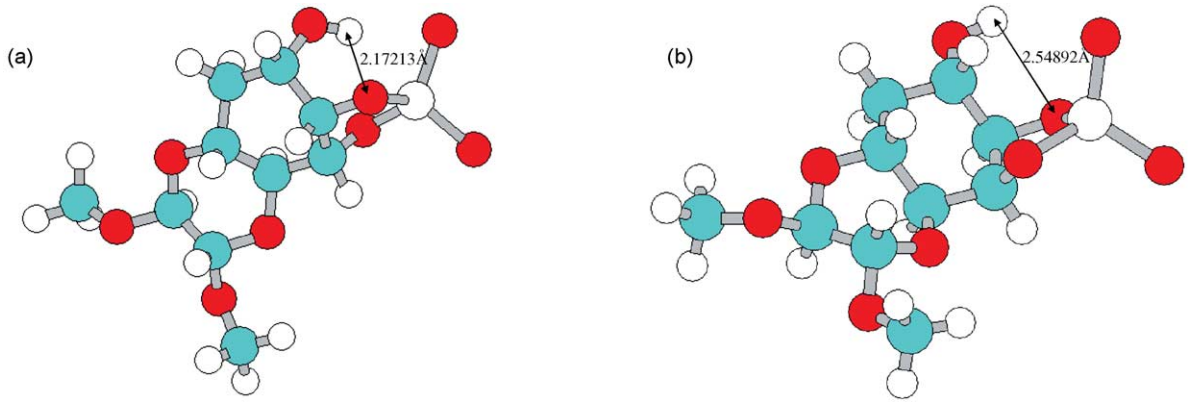
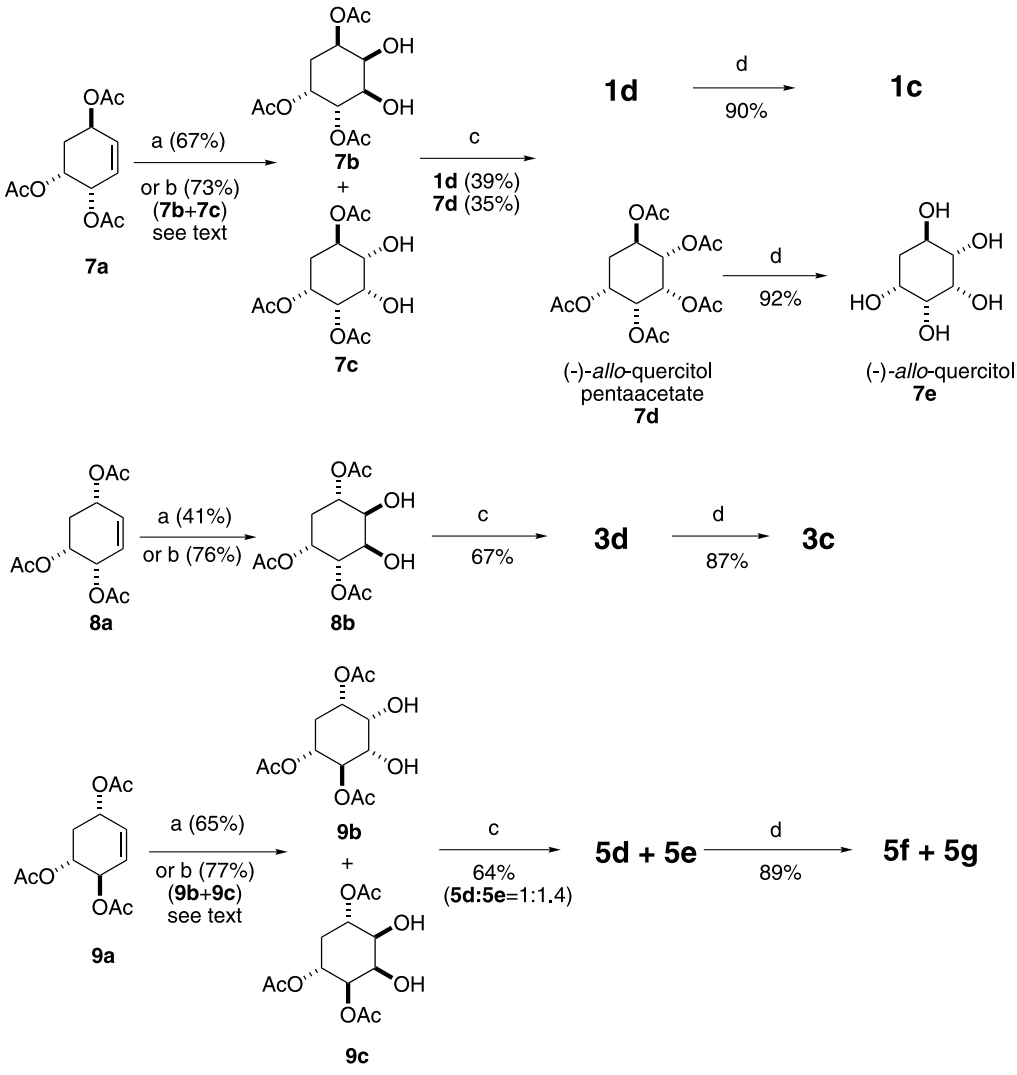


Figure 2. The AM1 calculation of the ideal distance of intermolecular hydrogen bonding in stereoselective dihydroxylation of compound **5a**.



Scheme 2. Reagents and conditions: (a) Method A: 1.5 equiv $KMnO_4$, 1.5 equiv $MgSO_4$, EtOH, H_2O, rt; (b) Method B: $RuCl_3 \cdot 3H_2O$, $NaIO_4$, H_2SO_4, EtOAc, CH_3CN, 0 °C; (c) 5 equiv Ac_2O, pyridine; (d) 7 N NH_3/MeOH.

3. Conclusion

We have successfully synthesized the (−)-*talo*-, (−)-*epi*-, (+)-*gala*-, (−)-*allo*- and *neo*-quercitols from D-(−)-quinic acid with an expedient method. We have learned that the stereoselectivity and stereospecificity of dihydroxylation can be manipulated by choosing the appropriate protecting groups to the analogues of chiral (1,4,5)-cyclohex-2-ene-triols. The stereospecific reaction occurred while cyclohexylidene acetal moiety was used as a protecting group in **1a** and **2a** in which the (−)-*talo*-quercitol was the only isolated product. To the contrary, (−)-*talo*- and (−)-*allo*-quercitols were received with almost equal amounts in **7a** while acetyl groups served as a protecting group. In compounds **5a** and **6a**, the BBA group presented no influence in stereospecificity but their stereoselectivity was controlled by the directing effect of hydroxyl group. Although their degrees of stereoselectivity were moderate,

Table 2. Dihydroxylation of (1,4,5)-triacetoxy-cyclohex-2-enes **7a**, **8a** and **9a**

Compound	Yield[a]/yield[b]	Quercitol pentaacetate (yield)[c]	$[\alpha]_D$, mp °C (literature)	Quercitol (yield)	$[\alpha]_D$, mp °C (literature)
7a	67/73	**1d** (39%)		**1c** (90%)	
		7d (35%)	−15, 103–110 (+11.6, 114)[d]	**7e** (92%)	−23, 237–258 (+23.3, >200)[d]
8a	41/76	**3d** (67%)		**3c** (87%)	
9a	65/77	**5d/5e** (64%) (1:1.4)[e]		**5f/5g**[f] (89%)	

[a] Yield of dihydroxylation; Method A: $KMnO_4$, $MgSO_4$, EtOH, H_2O, rt.
[b] Yield of dihydroxylation; Method B: $RuCl_3 \cdot 3H_2O$, $NaIO_4$, H_2SO_4, EtOAc/CH_3CN (v/v = 1/1).
[c] From Method A.
[d] Ref. 8 for (+)-*allo*-quercitol and its pentaacetate.
[e] The ratio of **5d** versus **5e** was based on the ^1H NMR integration.
[f] The combined yield of **5f** and **5g** were derived from the deacetylation of a mixture of **5d** and **5e**.

however, they were still superior to the results observed in **9a** in which the stereoselectivity dropped tremendously while the acetyl group was used as a protecting group.

4. Experimental

Melting points were recorded on a polarized optical microscopy and equipped with Mettler Toledo FP82HT hot stage and Mettler Toledo FP90 central processor. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-300 MHz. For ^{1}H and ^{13}C NMR spectra, the internal standards were referenced to δ 7.26 and 77.0 ppm, respectively, for $CDCl_3$. While deuterium oxide was used, the internal standard was referenced to 4.69 ppm for ^{1}H NMR and CD_3OD at 49.0 ppm for ^{13}C NMR. The optical rotations were measured on a Horiba Sepa-300 spectrometer. Purification was employed by flash column chromatography using silica gel (230–400 mesh). The purified solid was dissolved in methanol and hexane was added to force the recrystallization occurred.

4.1. General procedures of dihydroxylation

4.1.1. $KMnO_4/MgSO_4$/EtOH condition. All of the reactions were conducted in 0.1–0.2 M. To **1a**, for example, in ethyl alcohol solution at 0 °C was added slowly a mixture of $KMnO_4$ (1.5 equiv) and $MgSO_4$ (1.5 equiv) in distilled water. The reaction was completed within 3–4 h. The resulting mixture was filtrated through celite and the solid was washed with EtOAc and hot water several times. The organic layer was separated, dried with $MgSO_4$ and concentrated. The resulting mixture was purified by flash column chromatography.

4.1.2. $RuCl_3\cdot 3H_2O/NaIO_4/H_2SO_4$ condition. All of the reactions were conducted in 0.1–0.2 M. To an aqueous solution of $NaIO_4$ at 0 °C was added a catalytic amount of concentrated H_2SO_4 and $RuCl_3\cdot 3H_2O$ (5 mol%). To this mixture was slowly added **7a**, for example, in EtOAc/CH_3CN (v/v=1/1). The reaction was completed within 10 min and quenched with $Na_2S_2O_3$ (saturated). The aqueous layer was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$) and concentrated. The resulting mixture was purified by flash column chromatography.

4.1.3. (−)-*talo*-Quercitol [(−)-1-deoxy-*neo*-inositol] (1c).[2] Recrystallization from MeOH and hexane afforded a white solid, 87% yield. $[\alpha]_D^{24}=-64.6$ (*c* 0.5, H_2O); lit.[1] +61, H_2O for (+)-*talo*-quercitol. Mp 238–248 °C; lit.[1] 248 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.82–4.05 (m, 3H), 3.52–3.57 (br s, 2H), 1.78 (dd, J=10.0, 3.2 Hz, 2H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 73.7, 71.4, 70.8, 68.8, 66.8, 33.2. HRMS (FAB) calcd for $C_6H_{13}O_5$ (M^++H) 165.0763. Found 165.0754.

4.1.4. (−)-*talo*-Quercitol pentaacetate [(−)-*penta*-*O*-acetyl-1-deoxy-*neo*-inositol] (1d).[2] Purification by flash column chromatography (hexane/EtOAc=5/1) afforded a white solid, 87% yield. $[\alpha]_D^{24}=-25.4$ (*c* 0.3, $CHCl_3$); lit.[1] +28, $CHCl_3$ for (+)-*talo*-quercitol pentaacetate. Mp 184–187 °C; lit.[1] 183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.62 (br s, 1H), 5.52 (dd, J=6.3, 3.3 Hz, 1H), 5.31 (dd, J=10.6, 2.8 Hz, 1H), 5.23 (ddd, J=11.3, 5.1, 2.8 Hz, 1H), 5.20 (dd, J=10.6, 3.3 Hz, 1H), 1.90–2.2 (m+5×CH_3CO, 17H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.1, 170.0, 169.9, 169.6, 69.6, 69.0, 67.7, 66.8, 66.1, 28.9, 20.9, 20.7, 20.6, 20.5. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^++H) 375.1291. Found 375.1289.

4.1.5. (+)-*gala*-Quercitol [(+)-2-deoxy-*allo*-inositol] (3c).[17b] Recrystallization from MeOH and hexane provided a white solid, 91% yield. $[\alpha]_D^{25}=+50$ (*c* 0.6, H_2O); lit.[16] +50, H_2O. Mp 220–230 °C; lit.[16] 254–255 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.87–3.97 (m, 2H), 3.82 (t, J=3.3 Hz, 1H), 3.70 (ddd, J=11.2, 9.0, 4.5 Hz, 1H), 3.58 (dd, J=9.0, 3.3 Hz, 1H), 1.90 (dt, J=11.6, 4.5 Hz, 1H), 1.62 (dt, J=11.6, 11.2 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 73.1, 72.9, 72.6, 68.8, 67.3, 34.4. HRMS (FAB) calcd for $C_6H_{13}O_5$ (M^++H) 165.0763. Found 165.0758.

4.1.6. (+)-*gala*-Quercitol pentaacetate [(+)-*penta*-*O*-acetyl-2-deoxy-*allo*-inositol] (3d).[4c] Purification by flash column chromatography in gradient (CH_2Cl_2/hexane=1/2–2/1) afforded a pale yellow oil, 92% yield. $[\alpha]_D^{24}=+22$ (*c* 0.5, $CHCl_3$); lit.[1] −24, $CHCl_3$ for (−)-*gala*-quercitol pentaacetate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (dd, J=5.3, 3.4 Hz, 1H), 5.20–5.30 (m, 3H), 5.11 (ddd, J=13.4, 8.8, 4.6 Hz, 1H), 2.15–2.25 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.97–2.06 (m+3×CH_3, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 169.8, 169.4 (×2), 69.8, 68.2, 67.7, 66.7, 29.1, 20.9, 20.8, 20.7. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^++H) 375.1291. Found 375.1296.

4.1.7. (−)-*epi*-Quercitol [(−)-2-deoxy-*epi*-inositol] (5f).[10a] Recrystallization from MeOH and hexane gave a white solid, 91% yield. $[\alpha]_D^{25}=-3.3$ (*c* 0.3, H_2O); lit.[1] −5, H_2O. Mp 180–182 °C; lit.[1] 194 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.88 (dd, J=2.9, 1.4 Hz, 1H), 3.60–3.75 (m, 1H), 3.35–3.40 (m, 2H), 3.31 (dd, J=10.2, 2.9 Hz, 1H), 1.82–1.92 (m, 1H), 1.64 (dt, J=11.8, 5.9 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 75.2, 73.8, 72.7, 70.2, 67.4, 34.8.

4.1.8. (−)-*epi*-Quercitol pentaacetate [(−)-*penta*-*O*-acetyl-2-deoxy-*epi*-inositol] (5d). Purification by flash column chromatography (hexane/EtOAc=5/1) afforded a pale yellow oil, 90% yield. $[\alpha]_D^{26}=-14.5$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50–5.60 (m, 1H), 5.40 (t, J=10.2 Hz, 1H), 4.85–5.10 (m, 3H), 2.20–2.30 (m, 1H), 2.18 (s, 3H), 2.14 (dd, J=7.7, 6.7 Hz, 1H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 170.1, 169.9, 169.8, 169.6, 169.5, 70.7, 69.3, 69.2, 68.7, 66.0, 29.4, 20.8, 20.7, 20.6, 20.5. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^++H) 375.1291. Found 375.1291.

4.1.9. *neo*-Quercitol pentaacetate [*penta*-*O*-acetyl-2-deoxy-*neo*-inositol] (5e). Purification by flash column chromatography (hexane/EtOAc=4/1) gave a white solid, 93% yield. Mp 191–192 °C; lit.[1] 182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.59 (t, J=2.9 Hz, 1H), 5.24 (ddd, J=11.5, 10.2, 5.1 Hz, 2H), 5.03 (dd, J=10.2, 2.9 Hz, 2H), 2.52 (dt, J=12.5, 5.1 Hz, 1H), 2.15 (s, 3H), 2.02 (s, 6H), 1.99 (s, 6H), 1.53 (dd, J=12.5, 11.5 Hz, 1H). ^{13}C NMR

(75.4 MHz, $CDCl_3$): δ 169.8, 169.7, 70.8, 68.9, 67.2, 31.6, 20.8, 20.7, 20.5. HRMS (FAB) calcd for $C_{16}H_{23}O_{10}$ (M^+ + H) 375.1291. Found 375.1295.

4.1.10. *neo*-Quercitol [2-deoxy-*neo*-inositol] (5g). Recrystallization from MeOH and hexane gave a white solid, 89% yield. Mp 237–242 °C; lit.[1] 239 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.94 (t, J=2.8 Hz, 1H), 3.69 (ddd, J=14.4, 11.5, 4.8 Hz, 2H), 3.35 (dd, J=9.7, 2.8 Hz, 2H), 2.08 (dt, J=12.3, 4.8 Hz, 1H), 1.22 (dd, J=12.3, 11.9 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 75.2 (×2), 73.6, 68.4 (×2), 37.7. HRMS (FAB) calcd for $C_6H_{13}O_5$ (M^+ + H) 165.0763. Found 165.0768.

4.1.11. (−)-*allo*-Quercitol pentaacetate [(−)-*penta*-*O*-acetyl-5-deoxy-*allo*-inositol] (7d).[8] Purification by flash column chromatography in gradient (EtOAc/hexane= 1/10–1/4) gave a white solid, 35% yield. $[\alpha]_D^{24}=-15$ (c 0.5, $CHCl_3$); lit.[8] +11.6, $CHCl_3$ for (+)-*allo*-quercitol pentaacetate. Mp 103–110 °C; lit.[8] 114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (t, J=3.4 Hz, 1H), 5.22–5.32 (m, 3H), 5.10 (dd, J=7.0, 3.5 Hz, 1H), 2.27 (ddd, J=14.4, 7.6, 4.0 Hz, 1H), 1.97–2.15 (m, 15H), 1.75–1.89 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 169.8, 169.6, 169.5, 69.0, 68.3, 67.9, 67.2, 66.7, 28.6, 20.9, 20.8, 20.6.

4.1.12. (−)-*allo*-Quercitol [(−)-5-deoxy-*allo*-inositol] (7e).[8] Recrystalization from MeOH and hexane gave a white solid, 96% yield. $[\alpha]_D^{24}=-23$ (c 0.4, H_2O); lit.[8] +23.3, H_2O for (+)-*allo*-quercitol. Mp 237–258 °C; lit.[8] 262 °C. ^{1}H NMR (300 MHz, D_2O): δ 3.93 (ddd, J=13.5, 4.2, 2.5 Hz, 3H), 3.69 (t, J=4.2 Hz, 1H), 3.45 (dd, J=8.1, 3.1 Hz, 1H), 2.02 (ddd, J=14.1, 6.0, 4.6 Hz, 1H), 1.49 (ddd, J=14.1, 9.4, 3.2 Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O+CD_3OD): δ 74.7, 73.3, 71.5, 70.4, 67.3, 34.5.

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