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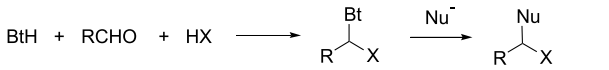
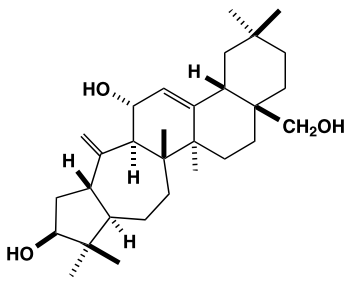
Contents

REPORT

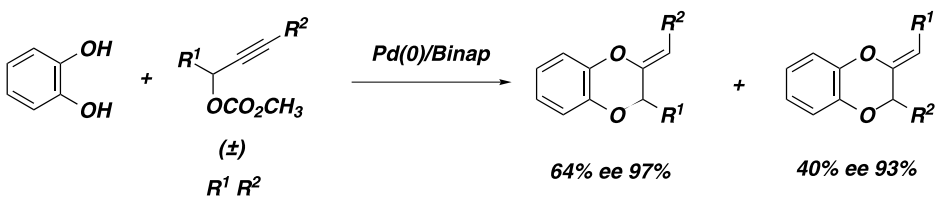


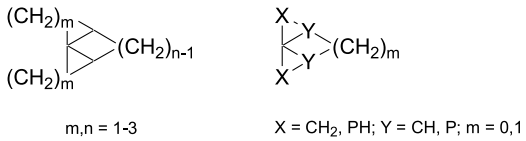
Bt = benzotriazol-1-yl, X = NR_2, NHCOR, NHCSR, $NHSO_2R$, OR, SR, SiR_3

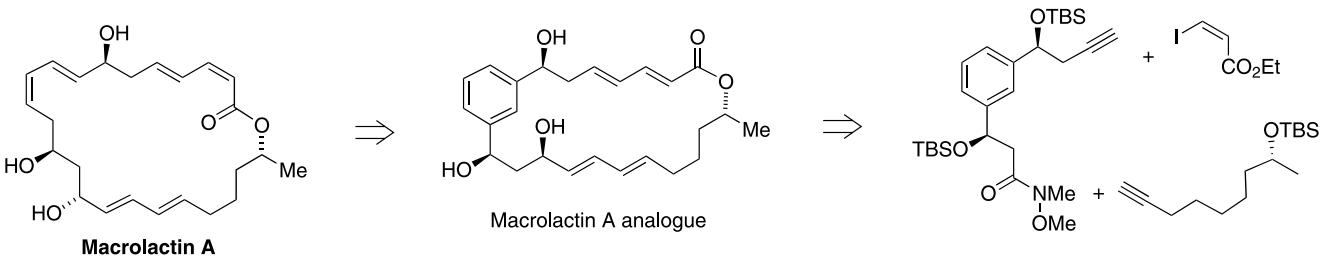
ARTICLES

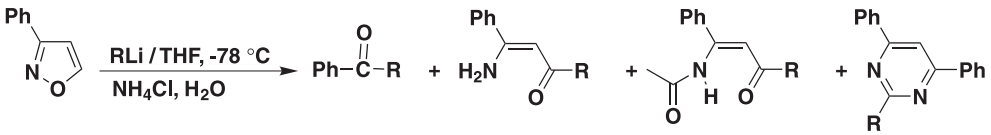


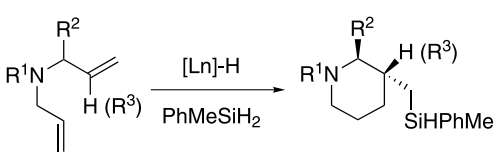
Three triterpenoidal glycosides, justiciosides E–G, were isolated from the aerial portion of *Justicia betonica*.

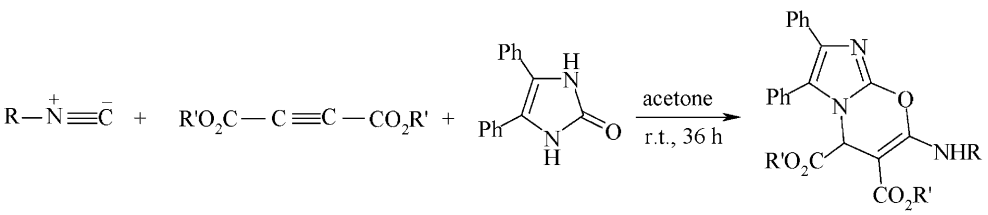


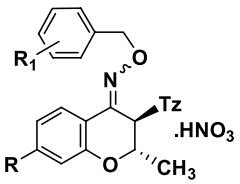




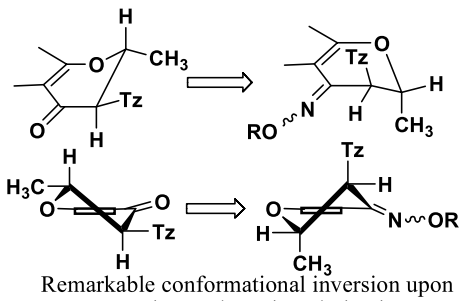




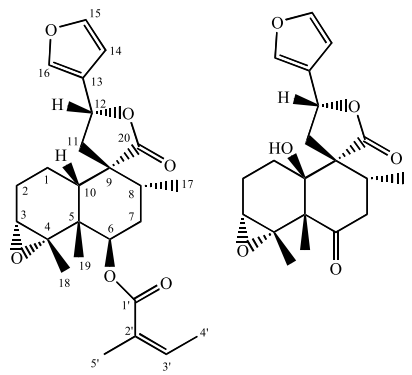




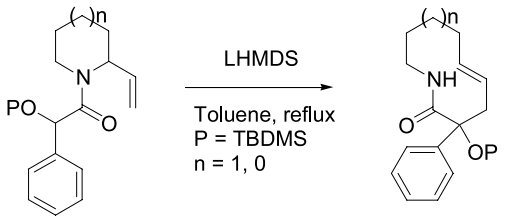
(±)-*trans*- (*E*)- or (*Z*)-oxime ethers
Tz = 1*H*-1,2,4-triazol-1-yl; 4*H*-1,2,4-triazol-4-yl
R = H; Cl R_1 = 4-Cl; 2,4-Cl_2

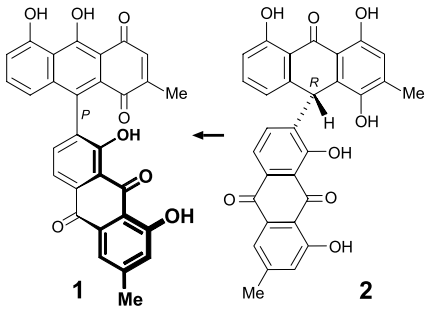


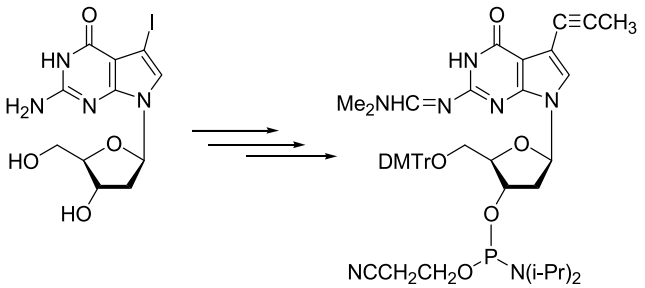
Remarkable conformational inversion upon conversion to the oxime derivatives

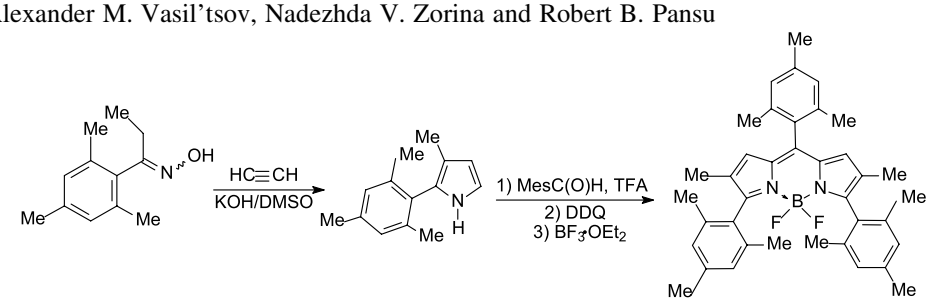


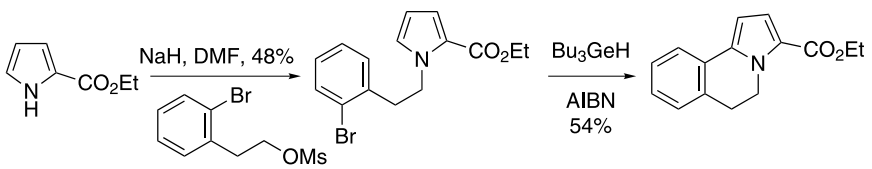
1 **2**



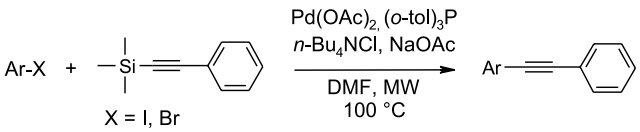




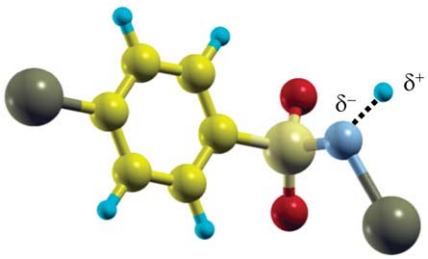


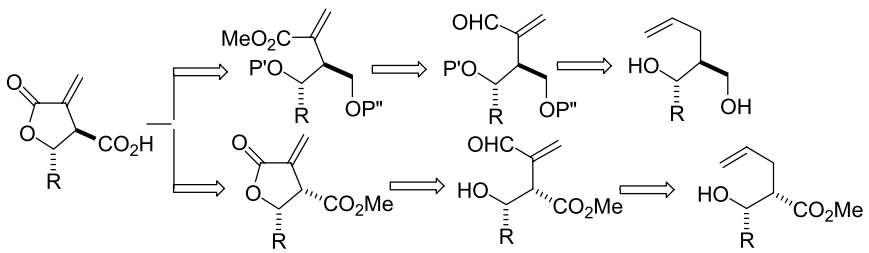


2-(2-Bromophenyl)ethyl groups have been used as building blocks in radical cyclisation reactions to synthesis tri- and tetra-cyclic heterocycles.



A computational study at the Density Functional Theory level was performed on bioactive and model sulfonamides with the aim of determining the factors affecting the acidity of the sulfonamido group. The effects of introducing different substituents at either the *para*-aryl or the N^1-sulfonamide positions were independently analyzed. The implications for the design of suitable sulfonamide prodrugs are discussed.





OTHER CONTENTS

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Benzotriazole mediated amino-, amido-, alkoxy- and alkylthio-alkylation

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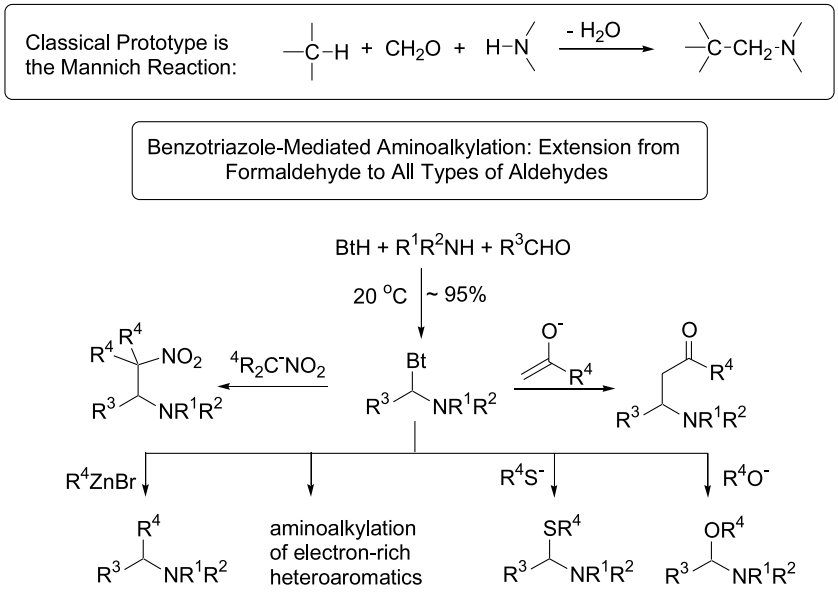
1. Introduction

The growing applications of benzotriazole methodology as a versatile synthetic tool have been periodically reviewed.[1–6] Readily available benzotriazole intermediates of type **A** react with a variety of nucleophiles for easy access to products of amino-alkylation (X=NR_2), amido-alkylation (X=NHCOR), thioamido-alkylation (X=NHCSR), sulfonamido-alkylation (X=NHSO2R), alkoxy-alkylation (X=OR), alkylthio-alkylation (X=SR) or silyl-alkylation (X=SiR_3).

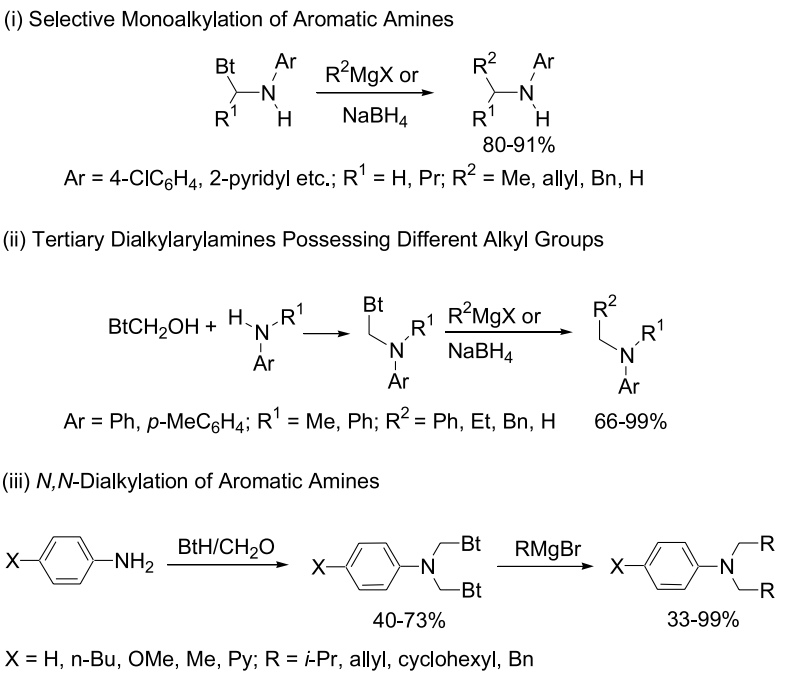
A

Bt = benzotriazol-1-yl, X = NR_2, NHCOR, NHCSR, $NHSO_2R$, OR, SR, SiR_3

Benzotriazole-mediated amino-alkylations have greatly broadened the utility of Mannich-type condensations; reaction of aldehydes with benzotriazole in the presence of amines or amides gives intermediates of



Scheme 1.

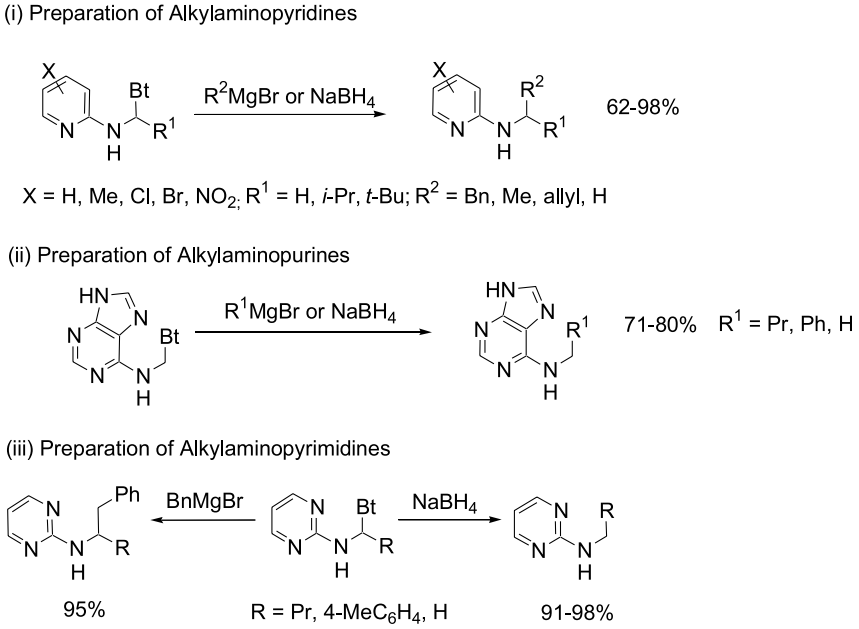


Scheme 2.

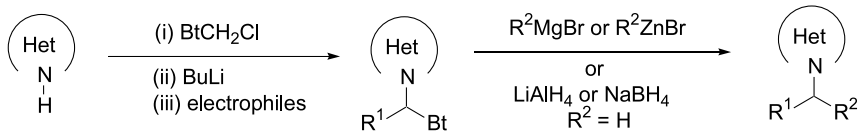
type **A**. Similar reactions of benzotriazole with aldehydes, ketals, vinyl ethers, enamines or thiols give the corresponding intermediates useful for the synthesis of ethers, esters, enol ethers, enamines and thioethers. In addition to acting as a versatile leaving group, a benzotriazolyl group activates α-deprotonation, which results in new applications. The present review highlights novel advances that have been made in benzotriazolyl-mediated α-hetero-alkylations since the last two reviews in 1994.[2,3]

2. Benzotriazole mediated amino-alkylation

Classically, the Mannich reaction was restricted to formaldehyde. Modern variants of the Mannich reaction have been recently reviewed.[7] Scheme 1 indicates that benzotriazole methodology can extend the Mannich reaction to all types of aldehydes.[4] The amino-alkylations of other systems demonstrated in Scheme 1 for thiols, alcohols and phenols, electron rich aromatics and several other types of functionalities are discussed below.



Scheme 3.



Heterocyclic group: pyrrol-1-yl: 6 examples, 42-96%
indol-1-yl: 7 examples, 37-94%
carbazol-9-yl: 10 examples, 45-96%
benzimidazol-1-yl: 2 examples, 56-86%

R^1 = H, $PhCH_2$, n-Bu, $(CH_2)_5CH(OH)$, 4-$MeC_6H_4CH(OH)$, Me_3Si, $(^iPr)_3Si$, $Me_2(^tBu)Si$, Ph_3Si. R^2 = H, n-Bu, Ph

Scheme 4.

2.1. N-Alkylation of aromatic amines

The preparation of *N*-alkylarylamines by direct alkylation of primary aromatic amines requires a large excess of the starting amine, separation of the product from the reaction mixture is difficult and tertiary *N*,*N*-(dialkyl)arylamines are usually formed. Considerable progress in the monoalkylation of primary amines came with the discovery that adducts derived from Schiff bases can be used for the preparation of secondary amines. 1-(1′-Arylaminoalkyl)-benzotriazole adducts derived from an aromatic amine, an aliphatic aldehyde, and benzotriazole, are smoothly reduced to amines by sodium borohydride. Alternatively, the benzotriazole moiety can be readily replaced by an alkyl group using Grignard reagents. Thus, aromatic amines can be selectively monoalkylated using benzotriazole methodology and diverse N-substituents can be introduced using different aldehydes and organometallic reagents as shown in Scheme 2(i).[8]

Tertiary dialkylarylamines are products of interest in many areas of applied chemistry. Such amines can be conveniently prepared using the procedure shown in Scheme 2(ii) in which *N*,*N*′-(benzotriazolylmethyl)-arylamines react readily with Grignard reagents to produce *N*,*N*′-dialkyl-arylamines.[9] The alkyl groups in the product contain an extra methylene group and this method is therefore especially valuable when effective alkylating agents for direct alkylation of the amine are not easily available (e.g. neopentyl), or for alkylating agents that easily undergo elimination in basic solution. Scheme 2(iii) shows the extension of this procedure to the synthesis of *N*,*N*-dialkyl aromatic amines.[10]

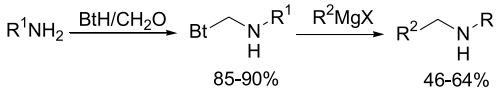
2.2. N-Alkylation of heteroaromatic amines

The methods mentioned above are particularly advantageous with respect to the N-alkylation of heteroaromatic amines.[8] It is well known that compounds such as *C*-amino pyridines react preferentially with alkyl halides and similar reagents at the heterocyclic N-atom. In contrast, benzotriazole methodology enables the introduction of alkyl groups selectively into the exocyclic amino group as shown in Scheme 3 for alkylaminopyridines, alkylaminopyrimidines and alkylaminopurines.

2.3. Preparation of N-substituted heterocycles

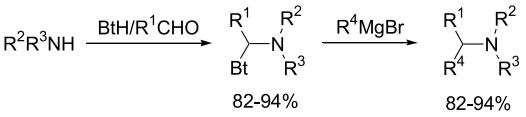
N-Alkylation of indole and pyrrole is usually accomplished

(i) Unsymmetrical Secondary Aliphatic Amines



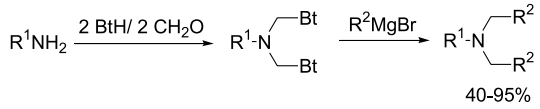
R^1 = c-C_6H_{11}, c-C_5H_9, Ph(CH)Me, n-C_8H_{17}, t-Bu, s-Bu; R^2 = Ph, Bn, Et

(ii) Unsymmetrical Tertiary Amines from Secondary Amines



R^1 = Ph, naphthyl, 4-pyridyl, p-tolyl etc; NR^2R^3 = morpholinyl, piperidinyl, NBnBn; R^4 = allyl, crotyl, 1-methyl-1-propenyl, ≡—R^5

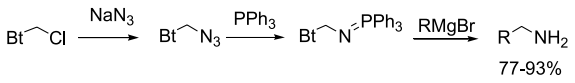
(iii) Partially Symmetrical Tertiary Amines from Primary Aliphatic Amines



R^1 = H, OH, Me, n-C_8H_{17}, CH_2Bt; R^2 = i-Pr, Ph, n-C_8H_{17}

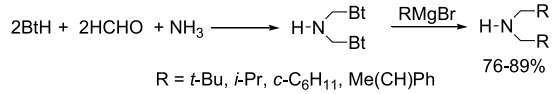
Scheme 5.

(i) Preparation of Primary Amines



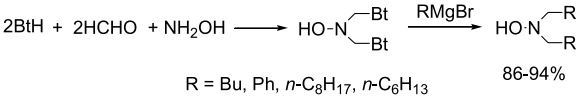
R = c-C_6H_{11}, Ph, 2-thienyl, 2-naphthyl, ≡—Ph

(ii) Preparation of Symmetrical Secondary Amines



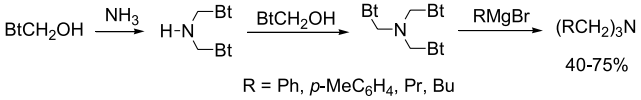
R = t-Bu, i-Pr, c-C_6H_{11}, Me(CH)Ph

(iii) Preparation of Symmetrical Hydroxylamines



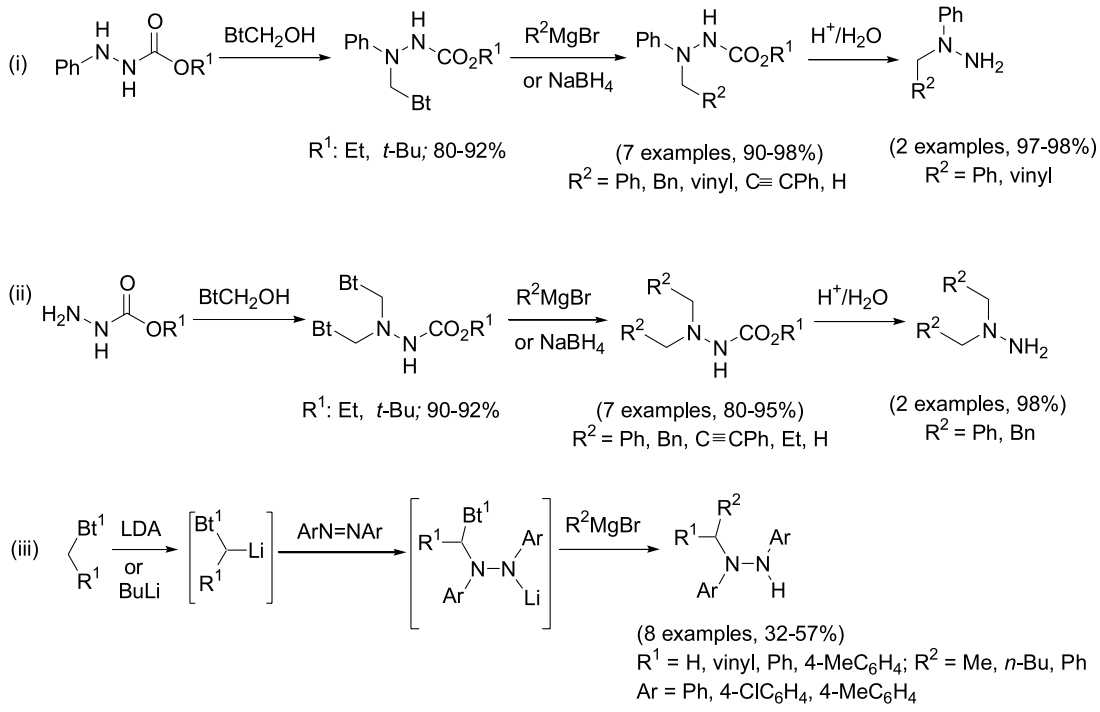
R = Bu, Ph, n-C_8H_{17}, n-C_6H_{13}

(iv) Preparation of Symmetrical Tertiary Amines



R = Ph, p-MeC_6H_4, Pr, Bu

Scheme 6.



Scheme 7.

via their anions generated by alkali salts.[11] In some cases, exclusive N-alkylation is observed, while in others C-alkylation products are also formed. The regioselectivity depends on the metal counter ion, the solvent and the alkylating reagent used.[12] Direct alkylation of carbazole with alkyl halides, with a base and a phase-transfer catalyst[13] or with TlOEt[14] has also been reported. N-Alkylation of imidazole can be effected in the presence of alkaline reagents[15] and also with a phase-transfer catalyst.[16]

However, in most of the alkylations described above, only primary alkyl groups could be introduced efficiently. Low yields were obtained with sterically hindered alkyl halides in the alkylation of pyrrole and benzimidazole and no reaction was observed with branched-chain alkyl halides in the case of carbazole. Benzotriazole has been shown to be a useful synthetic auxiliary for the preparation of various N-substituted heterocycles. Reactions of indole, pyrrole, carbazole and benzimidazoles with 1-chloromethylbenzotriazole give the corresponding *N*-(benzotriazol-1-ylmethyl)-heterocycles,[17] which on lithiation and subsequent reaction with electrophiles give intermediates as shown in Scheme 4. Displacement of benzotriazolyl group in the N-heterocycle derivatives by Grignard reagents, organozinc reagents, lithium aluminum hydride or sodium borohydride provide N-substituted heterocycles.[18] A wide range of *N*-α-silylalkylated carbazoles and indoles has also been prepared by this method.[19]

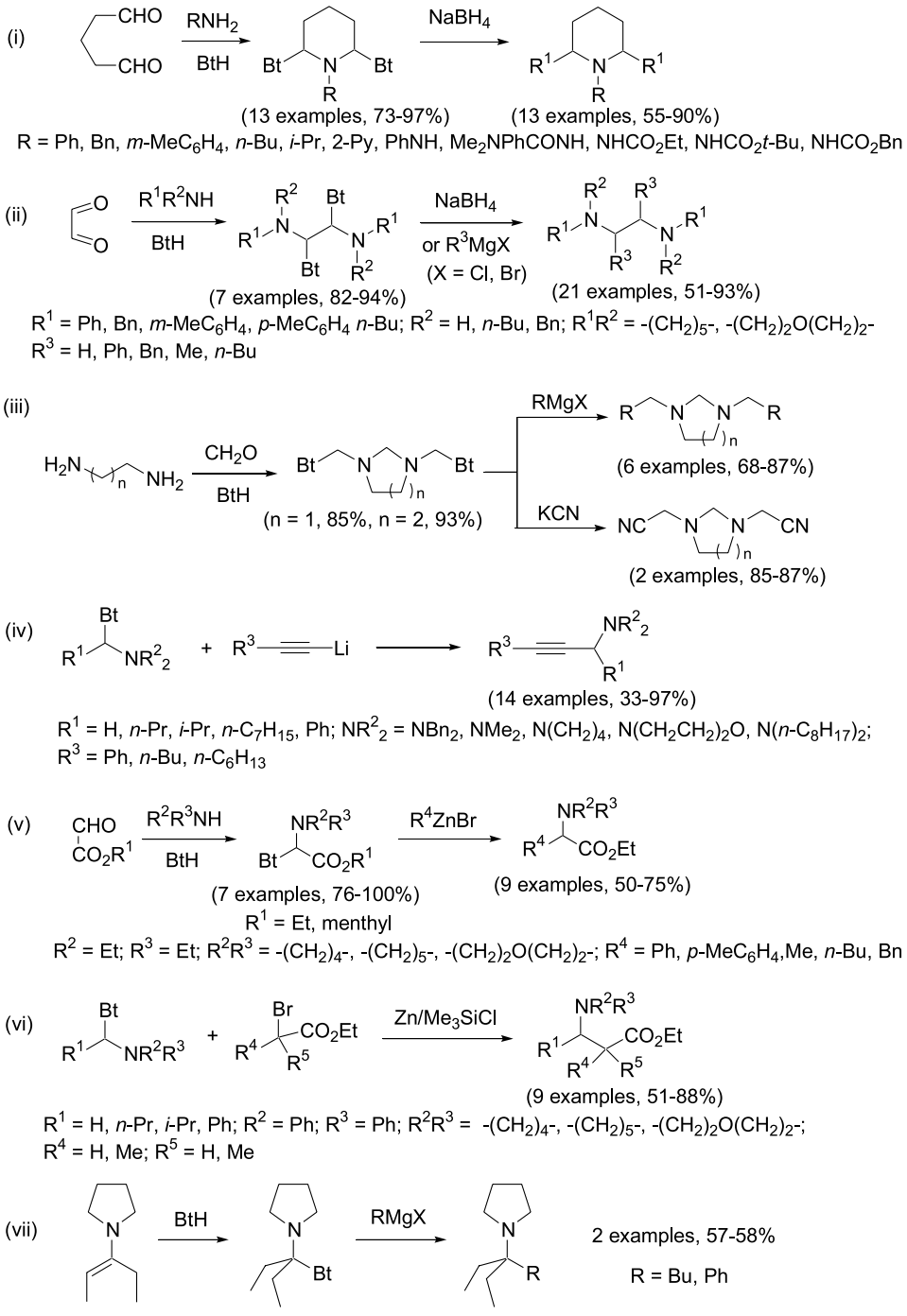
2.4. N-Alkylation of aliphatic amines

The most frequently employed process for the monoalkylation of primary amines involves the preparation and subsequent reduction of the corresponding Schiff base. However, such imines sometimes decompose or polymerize unless at least one aryl group is present at the carbon or nitrogen atom.[20a–c] Use of temporary protection of one of the nitrogen positions using arylsulfonyl,[20d] triflate,[20e] diethyl phosphate,[20f] or cyano[20g] groups allows a greater degree of control but removal of these protecting groups may require vigorous conditions and adds extra steps. The selective conversion of primary aliphatic amines into unsymmetrical secondary amines can be achieved by Grignard reactions of 1-[(alkylamino)methyl]-benzotriazoles. This method employs simple procedures and mild conditions, and is specific in that only monoalkylation of the primary amines results as shown in Scheme 5(i).[21a] An example of the preparation of unsymmetrical tertiary amines from secondary amines is shown in Scheme 5(ii) in which *N*-(α-benzotriazolylalkyl)amines serve as precursors for allylamines and propargylamines in a two-step procedure starting from benzotriazole, an amine, an aldehyde, followed by reaction with the corresponding vinyl or propargyl Grignard reagent.[21b] Scheme 5(iii) shows an extension of this method for the preparation of partially symmetrical tertiary amines from primary aliphatic amines.[21c]

2.5. N-Alkylation of ammonia and hydroxylamines

The preparation of primary amines by the connection of a $H_2N–CH_2$ fragment to a functionalized carbon atom proceeds via nucleophilic[20a,22a] or electrophilic[20a,22b–d] aminomethylation reactions. Use of *N*,*N*-bis(trimethylsilyl)-methoxymethylamine, a synthetic equivalent to $^{+}CH_2NH_2$ involves tedious preparation from hexamethyldisilazane through Li- or Na-bistrimethyl silylamide and gives only moderate yields in some cases.[23a–c]

Scheme 6(i) shows the preparation of *N*-triphenylphosphorylidene-1-(benzotriazol-1-yl) methylamine, a synthetic equivalent to $^{+}CH_2NH_2$. It can be conveniently

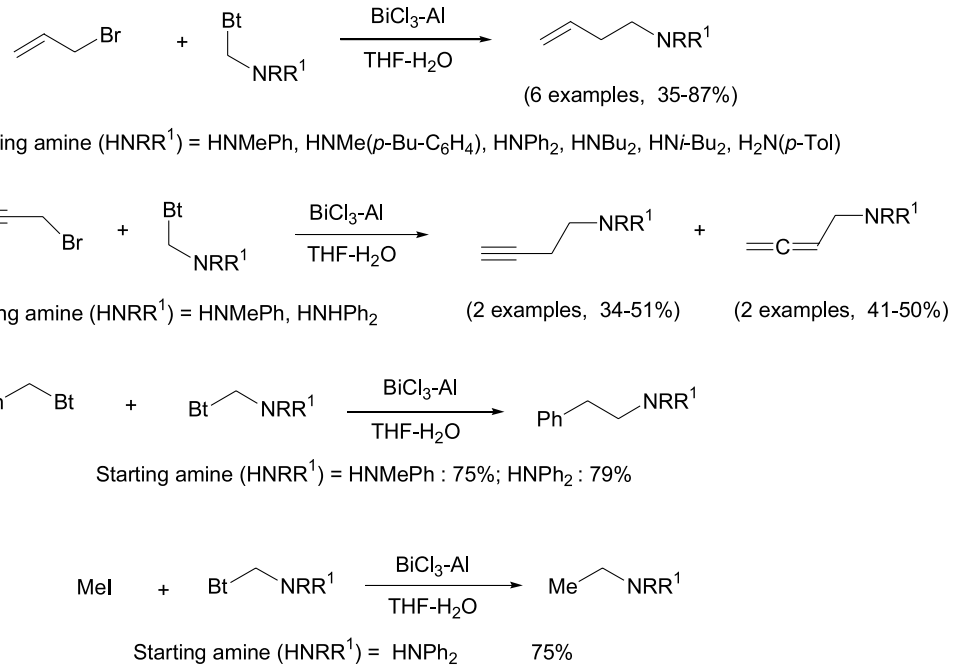


Scheme 8.

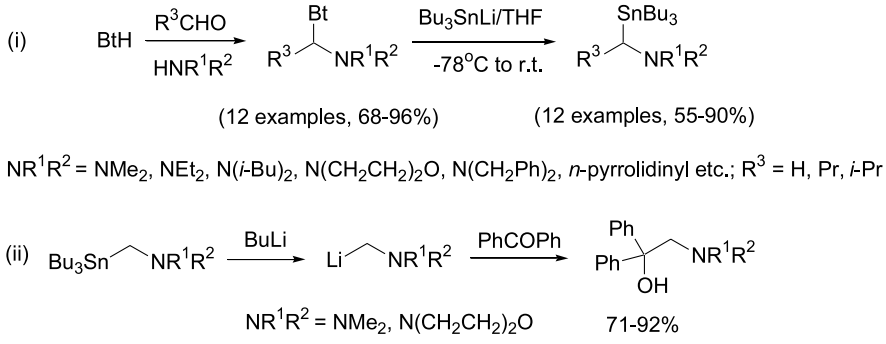
prepared by Staudinger phosphorylation of the easily available 1-azidomethylbenzotriazole in nearly quantitative yield and is a white solid, stable to prolonged periods at room temperature. The reaction of this reagent with Grignard reagents effects a one-pot preparation of primary amines of type R-CH_2NH_2.[24]

The use of benzotriazole methodology for the synthesis of secondary or tertiary amines offers several advantages over existing strategies. The overall conversion is achieved in two reaction steps, with the isolated yield of the amine being high. Secondary amines are formed as the sole products, avoiding the difficult separation procedures necessary in many amine or ammonia alkylation procedures. For unhindered aliphatic primary amines, it is difficult to stop the reaction at the monoalkylation stage and tertiary amines or even quarternary salts are formed. The use of benzotriazole methodology avoids this problem. The intermediate 1-(benzotriazol-1-yl)alkyl adducts need not be isolated in many cases and this improves the overall yield. Finally, the option of reaction with a variety of organometallic reagents allows the synthesis of diversely substituted amines.

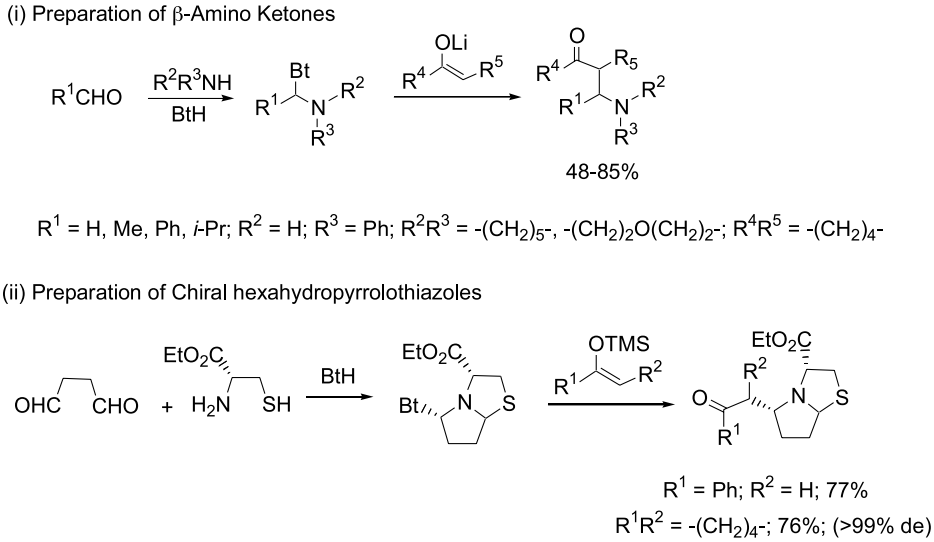
Scheme 6(ii) shows the preparation of symmetrical secondary amines from ammonia in two steps. Reaction of benzotriazole, formaldehyde and ammonia gives the



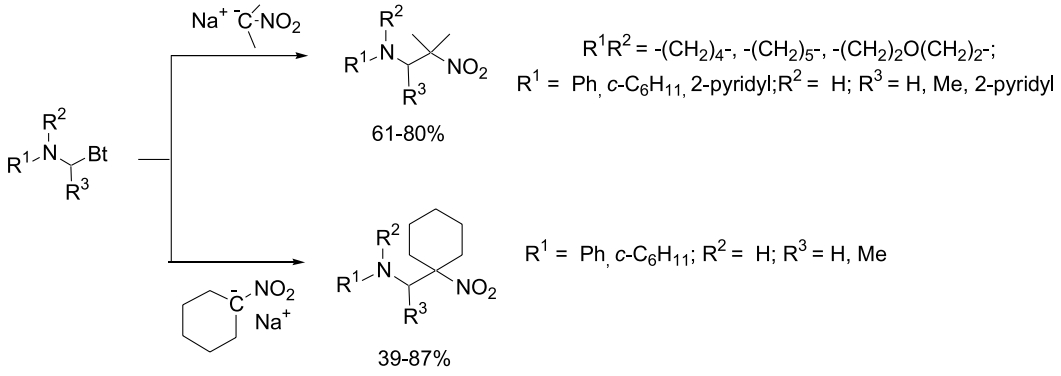
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

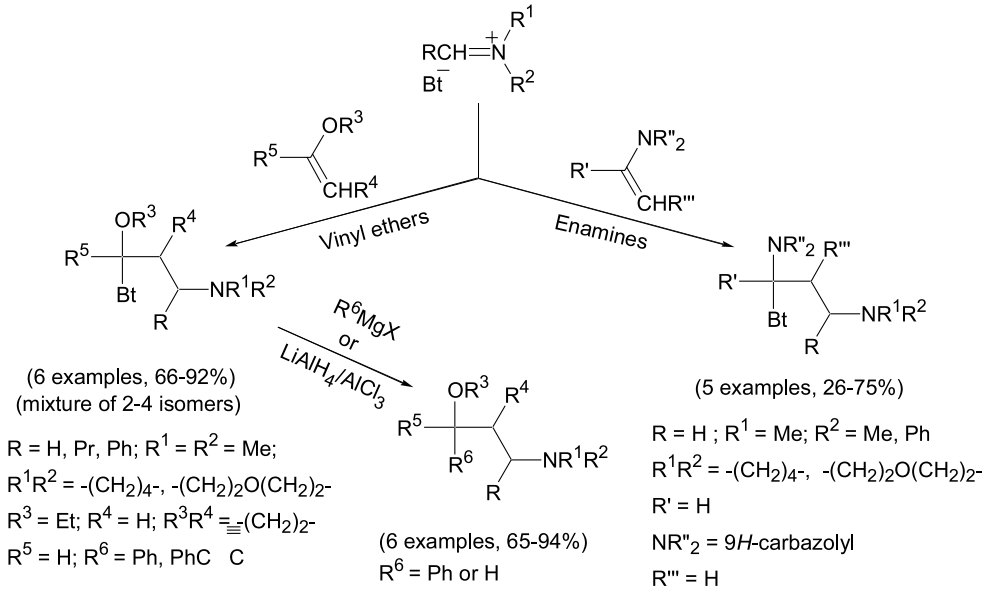
corresponding bis[1-(benzotriazol-1-yl)alkyl]amine, subsequent reactions of this adduct with Grignard reagents give *N*,*N*-dialkyl amines.[25] An analogous preparation of symmetrical *N*,*N*-dialkylhydroxylamines is illustrated by the reaction of *N*,*N*-bis(benzotriazol-1-ylmethyl)hydroxylamine with various Grignard reagents in Scheme 6(iii).[21c] Finally, symmetrical tertiary amines can be prepared very easily using the tris-benzotriazole derivative shown in Scheme 6(iv).[21c]

2.6. N-Alkylation of hydrazines

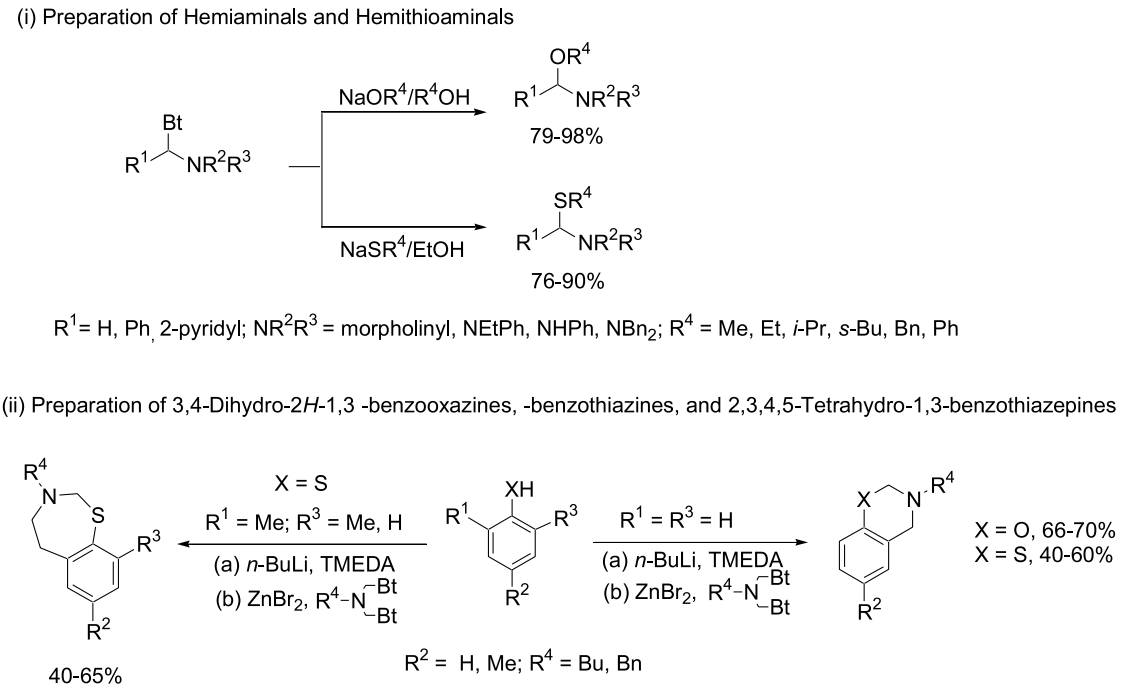
1,1-Dialkylhydrazines are important for the preparation of substituted indoles,[26,27] hydrazones,[27] tetrazines[28] and dibenzazepines.[29] Some disubstituted hydrazines show neuroprotective properties.[30] 1,1-Dialkylhydrazines are generally prepared from: (i) 1-substituted hydrazines by direct alkylation;[30,31] (ii) secondary amines via nitrosation,[32a,b] or amination[32c] (iii) hydrazones[33] (iv) 1,1-disubstituted ureas[34] or (v) diarylcarbamoyl azides.[35] The above methods suffer from certain limitations such as carcinogenicity of the intermediate, availability of the starting compounds and moderate yields.

Benzotriazole methodology based preparation of 1,1-disubstituted hydrazines offers a convenient alternate route. 1-(1-Hydroxymethyl)benzotriazole converts 1-phenyl-2-(*t*-butoxycarbonyl)hydrazine and *t*-butyl carbazate into their 2-mono-*N*- or 2,2-bis-*N*-[(benzotriazol-1-yl)methyl] derivatives in high yields [Scheme 7(i) and (ii)]. These adducts react readily with Grignard reagents to give the corresponding 2-substituted or 2,2-disubstituted hydrazines, which are hydrolyzed to produce 1-alkyl-1-aryl- or 1,1-dialkyl-hydrazines.[36]

Addition of alkyl- and aryllithium to the –N=N– bond of azo compounds gives trisubstituted hydrazines.[37,38] Unfortunately, a limitation in this method is that lithium derivatives cannot be replaced by other carbanion sources such as Grignard reagents, as these alternatives usually result in one-electron reduction of the azo compounds.[39] Benzotriazole has the ability to undergo facile replacement by Grignard reagents. A variety of substituents can be made available for addition to the –N=N– bond of azobenzenes using α-lithio-1-alkylbenzotriazoles as shown above in Scheme 7(iii), substitution of the benzotriazole moiety with Grignard reagents readily affords the desired trisubstituted hydrazines.[40]



Scheme 13.

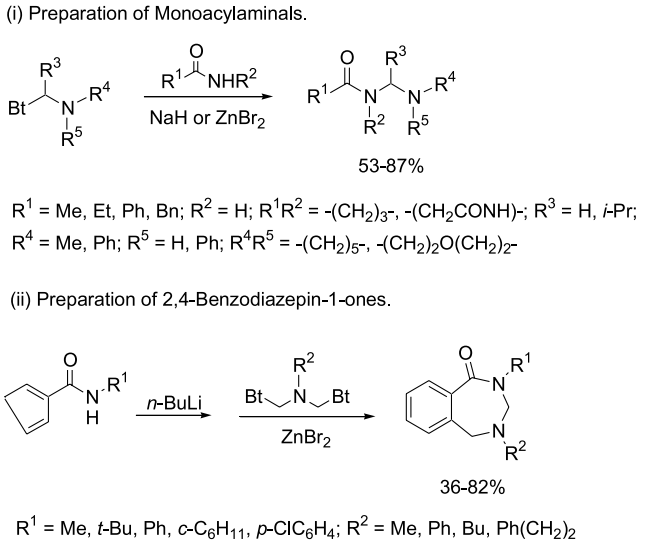


Scheme 14.

2.7. Preparation of polyfunctional amines

Benzotriazole reacts with aldehydes and amines in one pot to give different types of cyclic or acyclic amino derivatives, depending on the type of aldehyde used and the reaction conditions. Condensation of benzotriazole and glutaraldehyde with various primary amines or 1-mono- or 1,1-disubstituted hydrazines form 2,6-bis(benzotriazolyl) N-substituted piperidines, which on reduction with sodium borohydride give the corresponding N-substituted piperidines as shown in Scheme 8(i).[41] When glyoxal is used in the condensation with benzotriazole and an aromatic amine or an aliphatic secondary amine, an acyclic bis(benzotriazole) product is obtained, which on reaction with Grignard reagents or sodium borohydride gives symmetrical vicinal tertiary and secondary diamines [Scheme 8(ii)].[42] Primary aliphatic 1,2- or 1,3-diamines yield imidazolidine derivatives, further reaction with Grignard reagents or with cyanide anion substitutes the benzotriazole moiety [Scheme 8(iii)].[43]

Propargyl amines have been prepared by the reaction of 1-(dialkylaminoalkyl)benzotriazoles with 1-alkyne lithium salt.[44] Dialkylamino(1-benzotriazolyl)acetic esters, obtained from the condensation of secondary amines with ethyl glyoxylate and benzotriazole, react with organozinc to give tertiary α-amino esters [Scheme 8(v)].[45] 1-Dialkylamino-1-(1-benzotriazolyl)alkanes, prepared by condensation of benzotriazole, an aldehyde and a secondary amine; react with substituted ethyl 2-bromoalkanoates under Reformatsky type conditions to give β-aminoesters [Scheme 8(vi)].[46a] Benzotriazole adds rapidly to the pyrrolidine enamine of diethyl ketone, and behaves similarly to the cyano derivative, overcoming serious limitations of the Bruylants reaction such as toxicity of the reagent and possibility of an alternative attack of the nucleophile on the nitrile carbon atom. The benzotriazole adduct, on reaction with organometallic reagents could be transformed to various derivatives [Scheme 8(vii)].[46b]

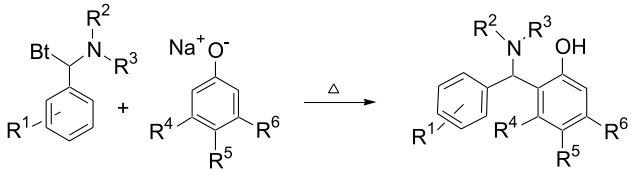


Scheme 15.

2.8. Alkylation in aqueous media with $BiCl_3$-Al

N-Alkylation of different types of amines has been discussed in Sections 2.1–2.4. The precursor in the second step is *N*-(aminoalkyl)benzotriazole, which can be regarded as masked iminium cation and is reactive towards organometallics such as Grignard reagents, yielding the corresponding N-alkylated amines. Alkylations in aqueous media offer several advantages over standard Grignard procedure: simplicity of the experimental conditions, possibility of alkylating those compounds, which contain substituents with active hydrogens or those with solubility only in aqueous media. Thus, the reaction of

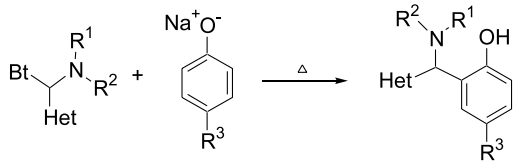
(i) *o*-Aminobenzylation of Phenols



51-87%

R^1 = H, *p*-CO_2Me, *p*-NO_2, *p*-OMe, *p*-Me; NR^2R^3 = morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl; R^4 = H, Me; R^5 = H, Cl, Br, OMe, Me, Ph, *i*-Pr; R^6 = H, Me; R^5R^6 = CH=CH-CH=CH

(ii) *o*-Aminoheteroarylmethylation of Phenols



74-82%

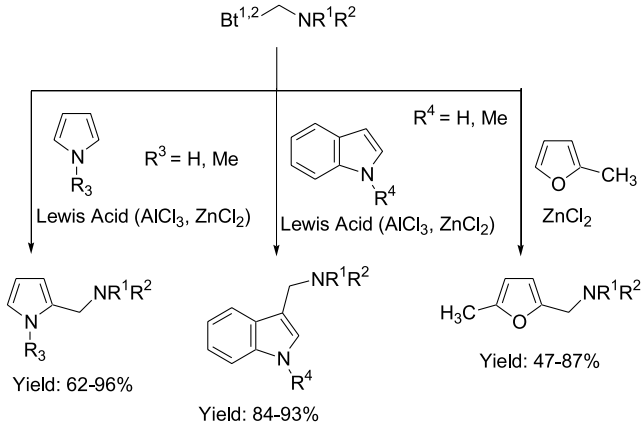
Het = 4-pyridinyl, 3-pyridinyl, 2-thiophenyl; NR^1R^2 = morpholinyl, piperidinyl; R^3 = Br, Ph, OMe

Scheme 16.

N-(aminoalkyl)benzotriazoles with alkyl bromides, promoted by bismuth (III) chloride–aluminum in THF–water provides the corresponding homoalkylated amines in high yields, which has been generalized as shown in Scheme 9.[47]

2.9. Amino-alkylation of organostannanes

1-(*N*,*N*-Dialkylamino)alkyltributylstannanes are precursors for 1-(*N*,*N*-dialkylamino)alkylorganolithium reagents which are important synthons in organic synthesis. The reported methods for the preparation of 1-(*N*,*N*-dialkylamino)alkyltributylstannanes are limited to the synthesis of 1-(*N*,*N*-dialkylamino)methyltributylstannanes,[48] and require thiophenol or liquid aminoacetal.[49] Reaction of tributylstannylmagnesium chloride with immonium salts is a more convenient method for this preparation.[50] Benzotriazole methodology further simplifies the preparation of 1-(*N*,*N*-dialkylamino)alkyltributylstannanes. Thus, 1-(*N*,*N*-dialkylamino)alkylbenzotriazole, prepared easily from benzotriazole, an aldehyde and the corresponding amine, reacts with tributyltinlithium to give the desired derivatives in high yields [Scheme 10(i)]. Transmetallation of these derivatives with butyllithium is well known to give very useful aminomethyllithiums, which react with a variety of electrophiles to afford the corresponding β-amino tertiary alcohols [Scheme 10(ii)].[51]



Scheme 17.

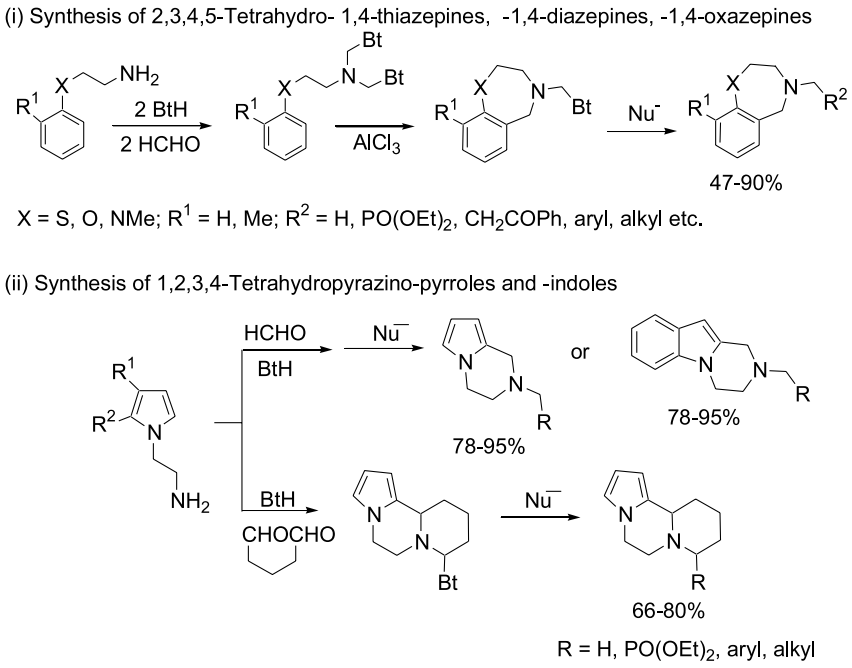
2.10. Amino-alkylation of ketones

The preparation of ketone Mannich bases utilizing aldehydes other than formaldehyde remains a rarely attempted transformation particularly for aliphatic and heterocyclic aldehydes.

Scheme 11(i) shows some of the extended Mannich reactions in which aldehydes have been used in the place of formaldehyde in the aminoalkylation of ketones. A wide variety of β-amino ketones have been prepared in moderate to good yields by the reaction of enolates of ketones with the readily available adducts from an aldehyde, an amine and benzotriazole.[52a] Scheme 11(ii) shows the extension of this procedure for the preparation of chiral hexahydropyrrolothiazoles in which the adduct has been prepared by the reaction of L-cysteine ethyl ester with succindialdehyde and benzotriazole.[52b]

2.11. Amino-alkylation of nitro compounds

A similar aminoalkylation of nitro compounds is shown in Scheme 12.[53] The cases where R^3 is a hydrogen atom could be prepared just as easily using the classical Mannich reaction but when R^3 is anything other than hydrogen, such compounds were previously unknown. The reaction of benzotriazolyl adducts with alkylnitronate anions leads to



Scheme 18.

the corresponding *N*-(β-nitroalkyl)amines and this method is especially suitable for the synthesis of derivatives with secondary amino groups.

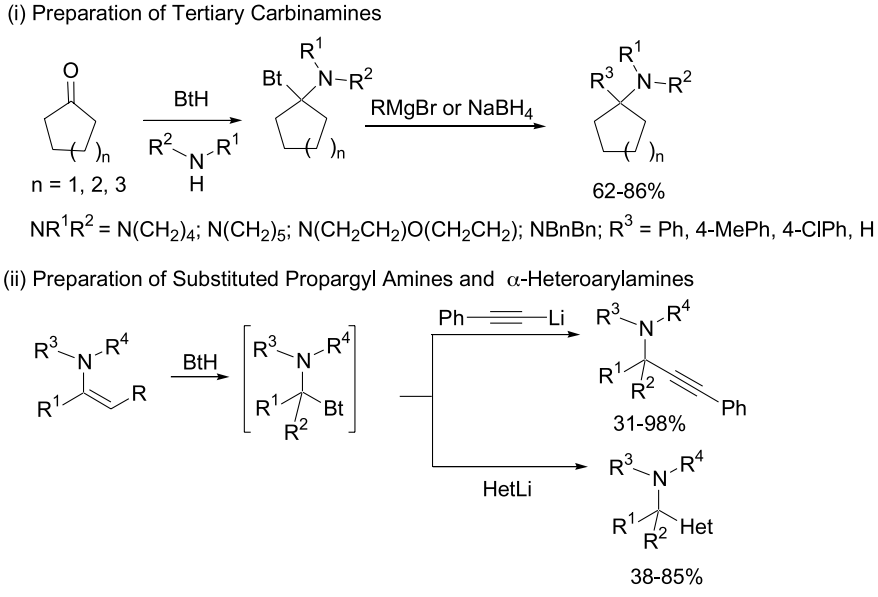
2.12. Amino-alkylation of enamines and vinyl ethers

1-(α-Aminoalkyl)benzotriazoles in solution undergo partial ionization giving benzotriazolyl anion and the corresponding iminium cation which can be trapped by enamines[54] and vinyl ethers[54a,55] to give *N*-(1-dialkylamino-3-aminoalkyl)benzotriazoles and *N*-(1-alkoxy-3-aminoalkyl)benzotriazoles. These intermediates react with Grignard reagents or lithium aluminum hydride to give 1,3-diamines and 1,3-aminoethers, respectively (Scheme 13).

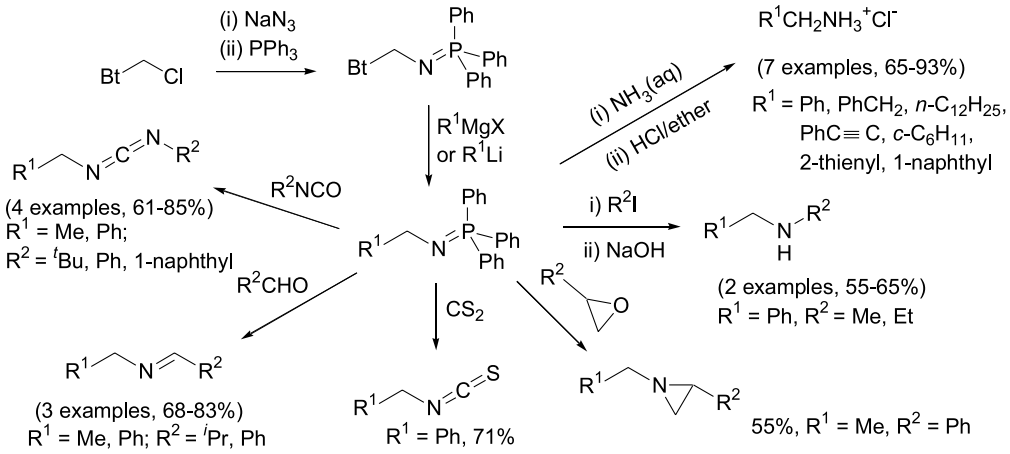
2.13. Amino-alkylation of alcohols and thiols

Previous methods are generally limited to formaldehyde as the carbonyl component and thus to the preparation of *N*-(alkoxymethyl)amines,[56a] further, yields are usually moderate because the products suffer rapid hydrolysis.[56b] No satisfactory method is available for aliphatic aldehydes.

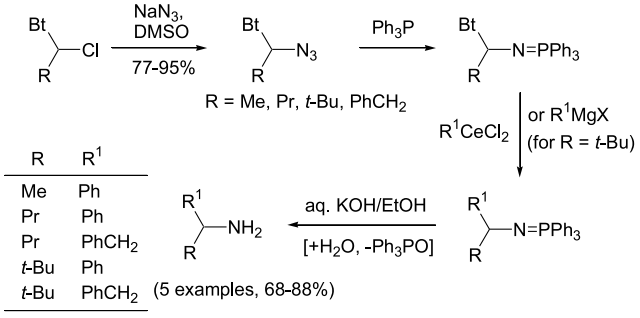
The aminoalkylation of alcohols and thiols is easily carried



Scheme 19.



Scheme 20.



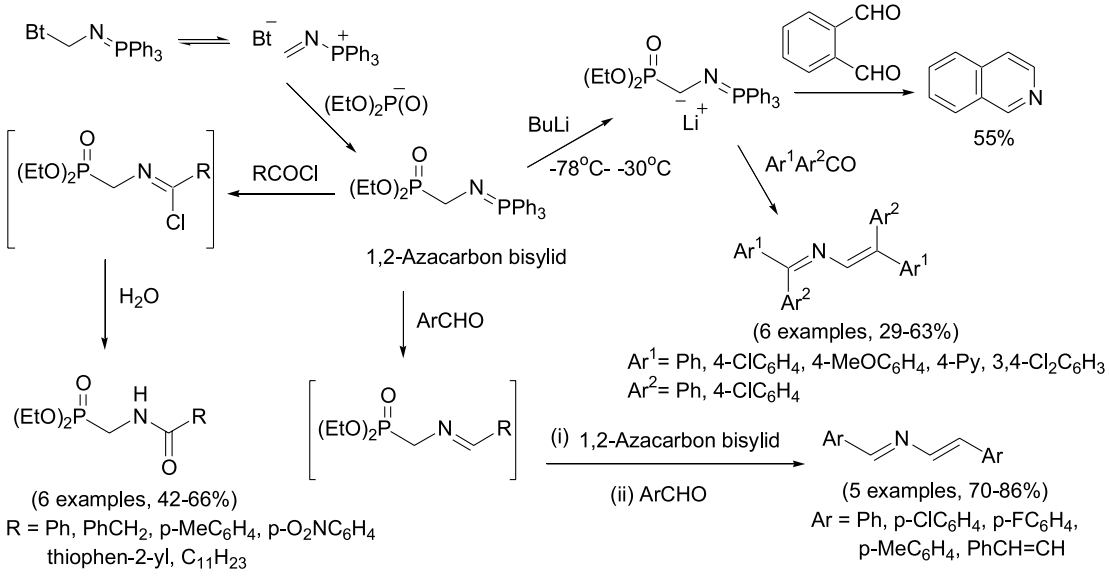
Scheme 21.

out by benzotriazole methodology to give the corresponding hemiaminals and hemithioaminals as exemplified in Scheme 14(i). The *N*-(α-benzotriazolylalkyl)amines used as intermediates are easily prepared from aldehydes and amines. The aminoalkylation conditions for alcohols and thiols are mild and non-acidic, and no water is produced during the reaction which is important because these *N*,*O*-acetals and *N*,*S*-acetals are easily hydrolyzed.[57a]

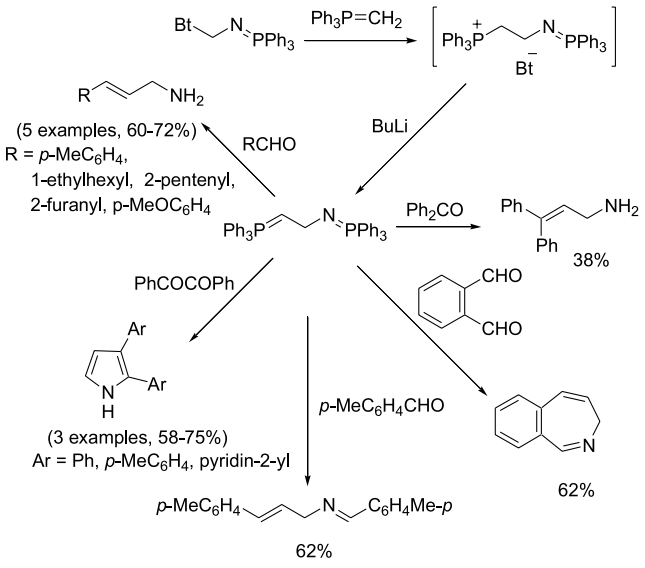
Benzoxazines and benzothiazines have also been synthesized by direct *ortho*-lithiation of phenols and thiophenols in one-pot by use of *N*,*N*-bis[(benzotriazol-1-yl)methyl]amines as 1,3-biselectrophile synthons as shown in Scheme 14(ii).[57b]

2.14. Amino-alkylation of amides

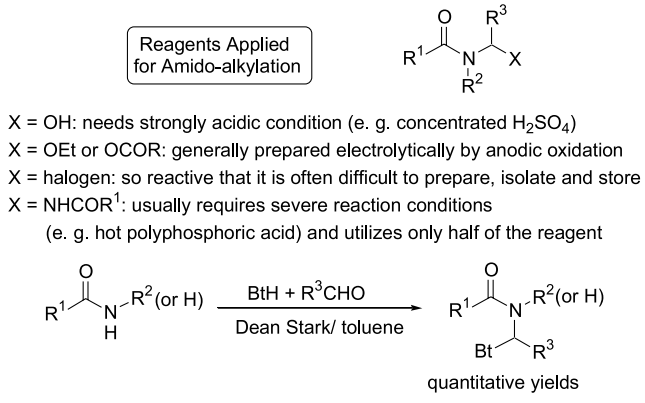
Mono-acyl-aminals are used in reverse peptide methodology and have been utilized for the protection of amides and amines. Their preparation has been simplified using benzotriazole as shown in a general synthesis of a range of mono-acyl-aminals by the reaction of *N*-(α-aminoalkyl)-benzotriazoles with amides in the presence of a base. In less reactive cases zinc bromide was used to facilitate this reaction. Different types of amides, including cyclic or acyclic, primary or secondary, and aromatic- or aliphatic-substituted have been converted into *N*-(α-aminoalkyl)-amides shown in Scheme 15(i).[58a] This scheme also shows an application to a cyclic case in which 2,4-benzodiazepin-1-ones were prepared in moderate to good yields by the



Scheme 22.



Scheme 23.



Scheme 24.

reaction of bis(benzotriazolylmethyl)amines with *ortho*-metalated *N*-substituted benzamides.[58b]

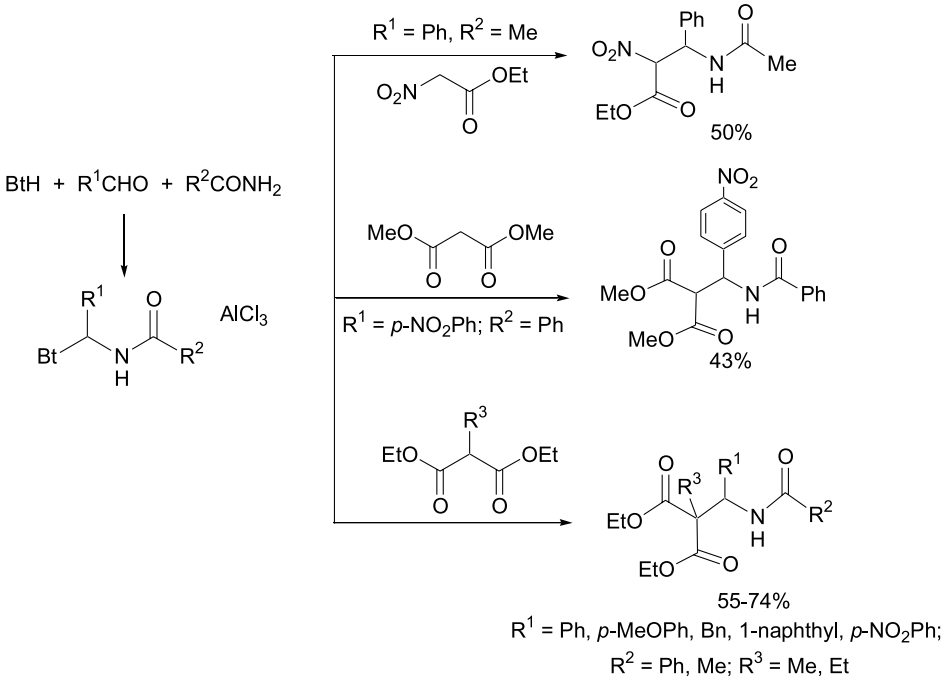
2.15. Amino-alkylation of phenols

The well-known Mannich aminoalkylation of phenols has been extended to analogous α-amino alkylations using the benzotriazole methodology. Such an extension is of interest because of the potential utility of phenolic Mannich-type bases as industrial materials.

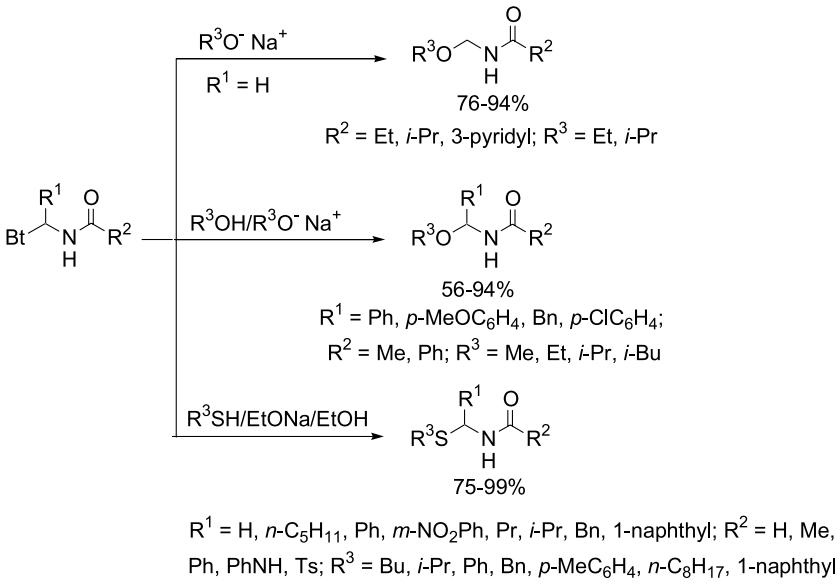
Scheme 16 shows that phenols are selectively amino-alkylated in the *ortho* position by the displacement of the benzotriazole moiety from *N*-[α-(dialkylamino)alkyl]-benzotriazoles with phenolate anions.[59] This provides a convenient synthesis of phenolic Mannich bases derived from a variety of aromatic [Scheme 16(i)] and hetero-aromatic aldehydes [Scheme 16(ii)].

2.16. Amino-alkylation of heteroaromatics

C-Aminoalkylations of electron rich heterocycles generally involve Mannich reaction of an amine hydrochloride (or of the amine in acetic acid) and formaldehyde with the heterocycle.[60] These reactions have also been carried out with bis(dialkylamino)methanes (aminals) or alkoxy-dialkylaminomethanes (aminol ethers) activated by acetyl chloride,[61] sulfur dioxide,[62] or by chlorosilane derivatives.[63] Iminium salts add directly,[64a] or via trimethylsilyl enol ethers[64b] to heteroaromatic substrates to form tertiary or secondary amines. The benzotriazole methodology is a convenient route for the aminoalkylation of heteroaromatic substrates. Reaction of various secondary and tertiary aminoalkylbenzotriazoles with heteroaromatic substrates under mild conditions in the presence of Lewis acids give the corresponding secondary or tertiary amines in yields that are mostly higher than those of the other methods (Scheme 17).[65]



Scheme 25.

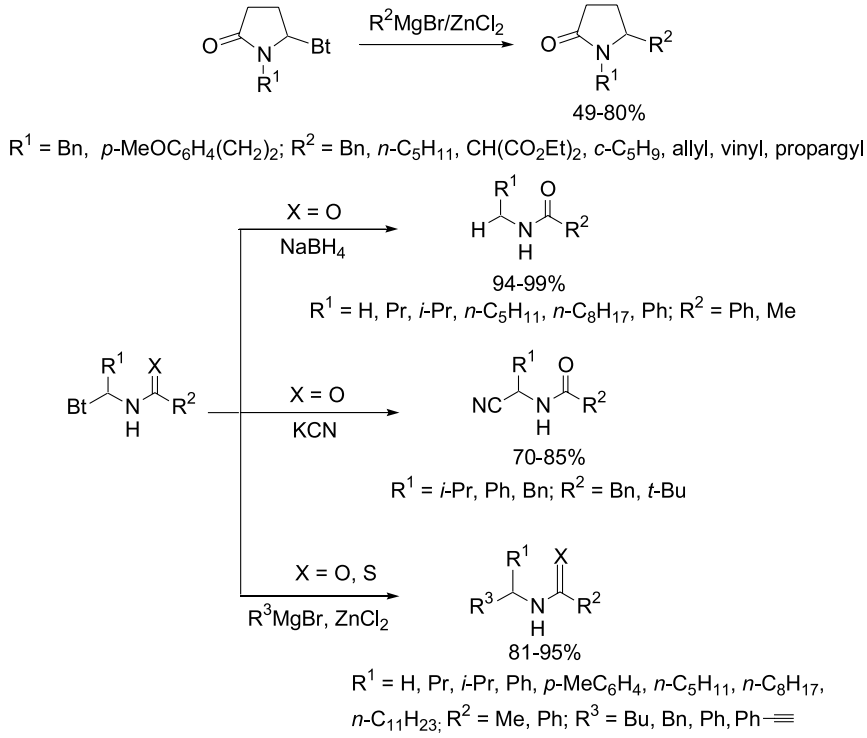


Scheme 26.

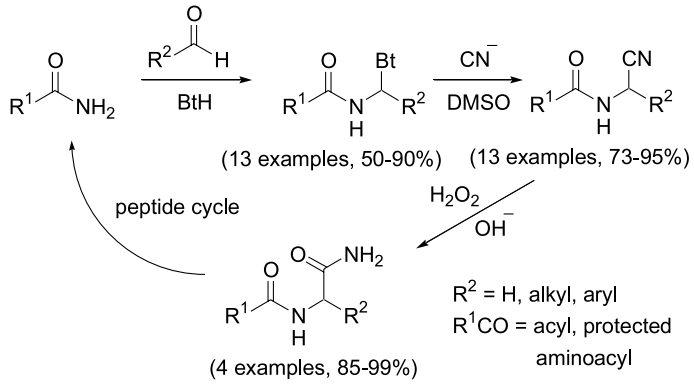
2.17. Intramolecular amino-alkylation

Relatively few publications report the preparation of 2,3,4,5-tetrahydro-1,4-benzothiazepines containing no carbonyl groups, and most of these involve reduction of a carbonyl group containing precursor. Similarly, most syntheses of 2,3,4,5-tetrahydro-1,4-benzothiazepines, 1,4-benzoxazepines and 1,4-benzodiazepines not involving reduction of a corresponding carbonyl or unsaturated derivative is available using benzotriazole methodology.

Scheme 18(i) shows some selected examples of intramolecular aminoalkylation. Diverse 4-substituted 2,3,4,5-tetrahydro-1,4-benzothiazepines, 1,4-benzoxazepines and 1,4-benzodiazepines have been synthesized by intramolecular cyclizations to form the benzotriazolylmethyl substituted azepines followed by nucleophilic substitutions of the benzotriazolyl groups with Grignard reagents, triethyl phosphate, sodium borohydride and a silyl enol ether.[66a] Synthesis of 1,2,3,4-tetrahydropyrazino-pyrroles and -indoles is shown in Scheme 18(ii) by the condensation reactions of benzotriazole and 2-(pyrrol-1-yl)-1-ethylamine



Scheme 27.



R^1 = $PhCH_2O$ (Z), *t*-BuO (*t*-Boc), $BzNHCH_2$, ZNHCH(Bzl), ZNHCH(*s*-Bu), ZNHCHPH, ZNHCH(*i*-Pr)-L, ZNHCH(*i*-Pr), ZPhNHCH(*i*-Pr);
R^2 = H, Pr, *i*-Pr, *i*-Bu, Ph

Scheme 28.

with formaldehyde and glutaric dialdehyde, respectively, followed by the nucleophilic substitution of the benzotriazolyl group.[66b,c]

2.18. Amino-alkylating reagents derived from ketones

All the foregoing examples of aminoalkylation have been illustrated by aminoalkylating agents derived from an amine, benzotriazole and an aldehyde. We have also explored the possible development of such methods to aminoalkylating reagents derived from ketones. Scheme 19(i) shows the preparation of pharmaceutically-active, highly branched, tertiary amines by the reaction of Grignard reagents with adducts of cyclic ketones, benzotriazole and secondary amines.[67a] Some of the examples from our ongoing new work on the preparation of propargylamines and α-heteroarylamines are also shown.[67b]

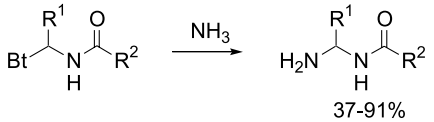
2.19. Amino-methylation to give primary amine derivatives

The preparation of primary amines has been accomplished by connecting H_2N–CH_2 fragment to a functionalized carbon atom, both by using nucleophilic and by electrophilic aminoethylation reactions. Primary amines can be prepared via reaction of organometallic reagents to C=N double or C≡N triple bonds.[68] *N*,*N*-Bis(trimethylsilyl)-methoxymethylamine has been reported as a synthetic equivalent to $^+CH_2NH_2$, and used for the synthesis of primary amines.[69] However, these reagents involve tedious preparation, are expensive and carcinogenic. Primary amines can be conveniently prepared by benzotriazole methodology using 1-(triphenylphosphorylideneamino-methyl)benzotriazole, a $^+CH_2NH_2$ synthon, which is conveniently prepared by Staudinger phosphorylation of 1-azidomethylbenzotriazole. This intermediate on reaction with Grignard or lithium reagents gives phosphazenes, which on basic workup give primary amines (Scheme 20).[24]

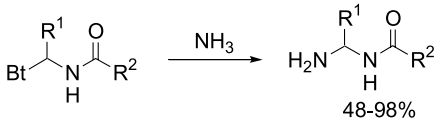
The benzotriazole methodology has been extended to various amine derivatives. One-pot reaction of 1-(triphenylphosphorylideneaminomethyl)benzotriazole with Grignard reagents followed by addition of an electrophilic substrate such as isocyanate, aldehyde, carbondisulphide, oxirane or alkyl halide gives carbodiimide, Schiff base, isothiocyanate, aziridine or secondary amine, respectively (Scheme 20).[70] This methodology has many advantages such as: (i) the starting iminophosphorane is a crystalline solid, which is stable and can be conveniently prepared in high overall yields, (ii) the intermediate N-substituted iminophosphoranes need not be isolated.

2.20. Amino-methylation to give *sec*-alkyl primary amines

The most general methods for the synthesis of *sec*-alkyl primary amines are from imines.[71] Some other recent methods for this synthesis are from aldehydes,[72] ketones[73]

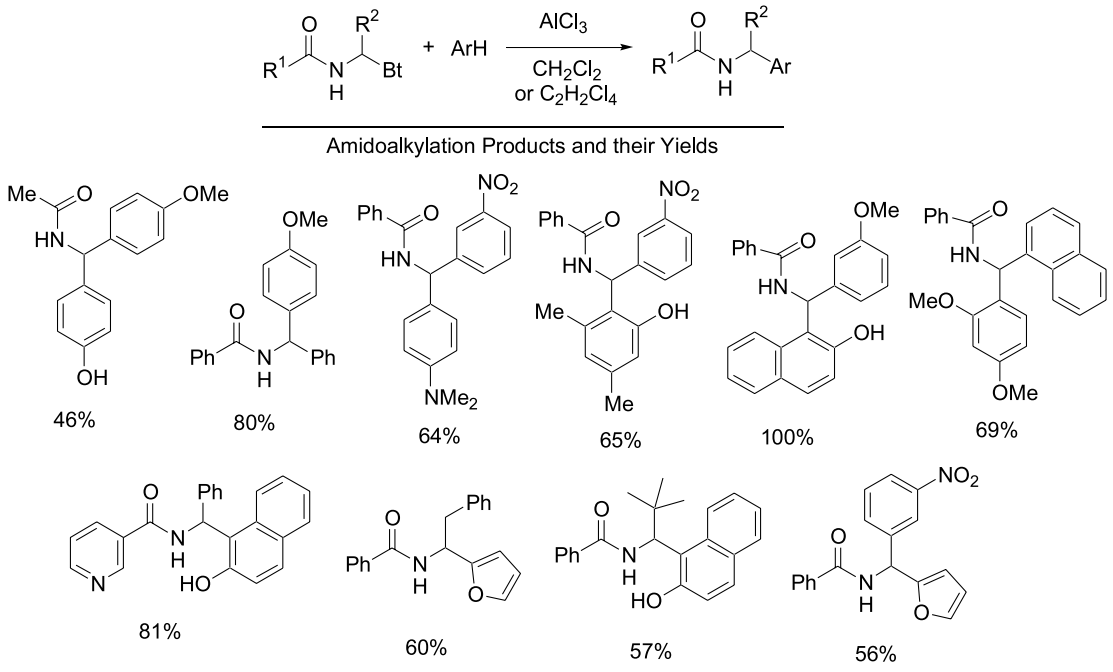


R^1 = H, Pr, *i*-Pr, *i*-Bu, Bn, $CONH_2$, CO_2H; R^2 = OBn, Me, Ph



R^1 = *i*-Pr, *i*-Bu, $CONH_2$, COOH; R^2CO = Bz-Gly, Z-L-Val, Z-1-Leu, Z-Phg, Z-Phe, Bz-Gly, Z-Gly

Scheme 29.



Scheme 30.

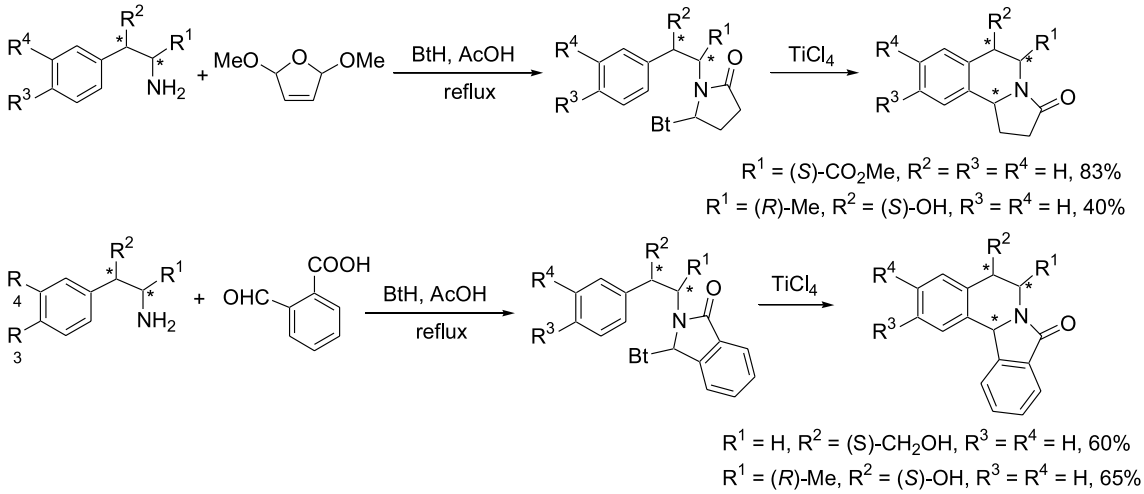
and alkyl halides.[74] An alternative two-pot method for the synthesis of non-chiral *sec*-alkyl primary amines from aldehydes using benzotriazole methodology involves the displacement of benzotriazole from α-(benzotriazol-1-yl)alkyliminophosphoranes as the key step. The one pot reaction of benzotriazole, aldehydes and thionyl chloride followed by treatment with sodium azide give 1-(α-azidoalkyl)benzotriazoles. These products were converted to iminophosphoranes by Staudinger phosphorylation with triphenylphosphine. Reactions of organocerium (III) dichlorides or Grignards with iminophosphoranes, followed by base hydrolysis produce desired amines (Scheme 21).[75]

2.21. 1,2-Aza-carbon bisylide

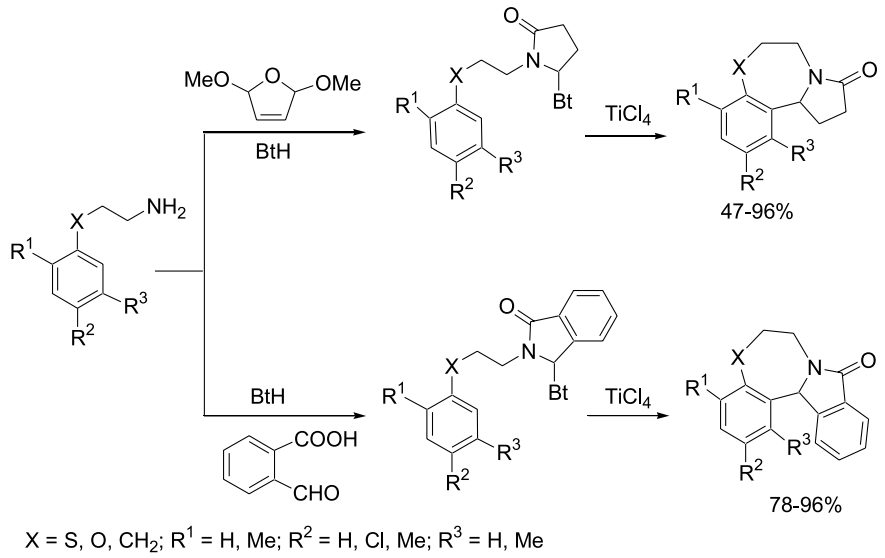
Bis-ylides and bis-aza-bis-ylides are important in the preparation of cyclic olefins and heterocycles by bis-Wittig reactions.[76] 1,2-Mono-aza-bis-ylides have been recently used in synthesis of various acyclic[77] and heterocyclic compounds.[78] Diethyl [(triphenylphosphorylideneamino)-methyl] phosphonate (1,2-monoazabisylide), prepared in situ by treatment of 1-(triphenylphosphorylideneamino-methyl) benzotriazole (betmip) with diethyl phosphite anion undergo direct reactions with various electrophiles. Thus, it provides convenient preparations of 1,4-diaryl-2-azabutadienes, 1,1,4,4-tetraaryl-2-azabutadines, diethyl [(acylamino)methyl]phosphonates, and isoquinolines (Scheme 22).[79]

2.22. 1,3-Aza-carbon bisylide

1-Aza-1,3-bis(triphenylphosphorylidene)propane, prepared in situ by the reaction of 1-(triphenylphosphorylidene-aminomethyl)benzotriazole (betmip) with methylidene-triphenylphospho-rane, followed by treatment with butyllithium, undergoes direct reactions with different



Scheme 31.



Scheme 32.

types of aldehydes and ketones in one pot. It reacts with a single molar equivalent of an aldehyde to give the primary allylamine. Thus, the use of this compound provides convenient preparations of 3*H*-2-benzazepine, 2,3-diarylpyrroles and primary allylamines (Scheme 23).[80]

3. Benzotriazole-mediated amido-alkylation, thioamido-alkylation and sulfonamido-alkylation

Amido-alkylation is a well-established technique for introducing the NCHRNRCOR group into a compound and many amidoalkylating agents have been suggested as shown in Scheme 24. By far the most convenient and general amidoalkylating agent is that derived from the condensation of a primary (or secondary) amide with benzotriazole and an aldehyde as shown at the bottom of Scheme 24. Such reagents have been used in a wide range of inter- and intramolecular amidoalkylation reactions.

3.1. Amido-alkylation of CH-active compounds

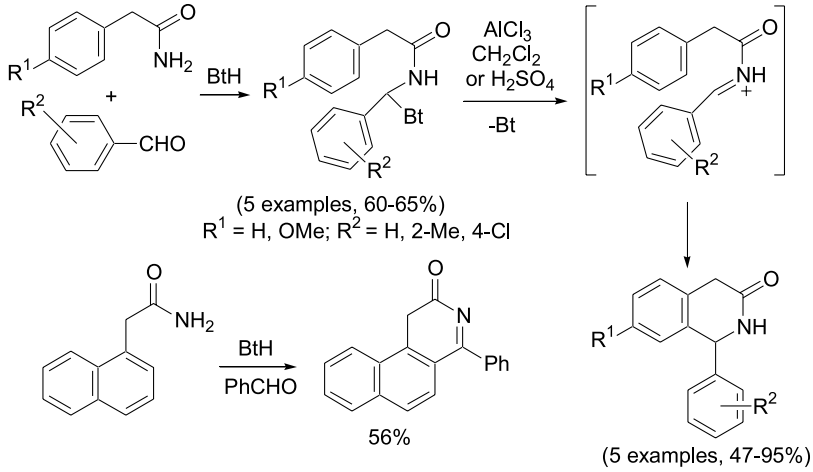
The optimum approach for the amidoalkylation of active methylene compounds involves the use of *N*-(benzotriazolylalkyl)amides. In comparison, *N*-(α-hydroxyalkyl)-amides[81a] and *N*-(α-chloroalkyl)amides[81b] give similar yields but involve reaction conditions that are not suitable for compounds that are sensitive to acidic or basic media.

Scheme 25 shows that *N*-(1-benzotriazol-1-ylalkyl)amides, easily prepared from an amide, can amidoalkylate active CH compounds such as malonic and nitroacetic esters.[81c]

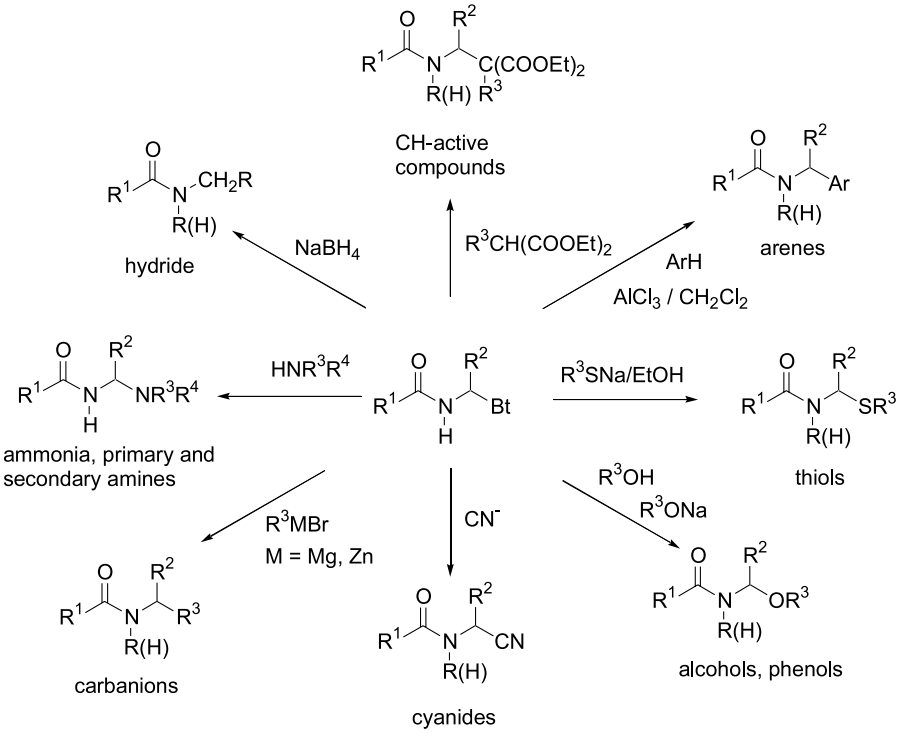
3.2. Amido-alkylation of alcohols and thiols

Efficient access to *N*-(α-isopropoxyalkyl)amides has been reported by ionization-rearrangement reactions of *N*-trifluoxy amides.[82a] This method allows the presence of sensitive functional groups but fails when a secondary or benzylic carbon is placed adjacent to the nitrogen. No such limitations are expected in the benzotriazole methodology shown below.

The amidoalkylation of alcohols and thiols to give the corresponding hemiaminals and hemithioaminals is illustrated in Scheme 26. Thus, the *N*-(benzotriazol-1-ylmethyl)



Scheme 33.

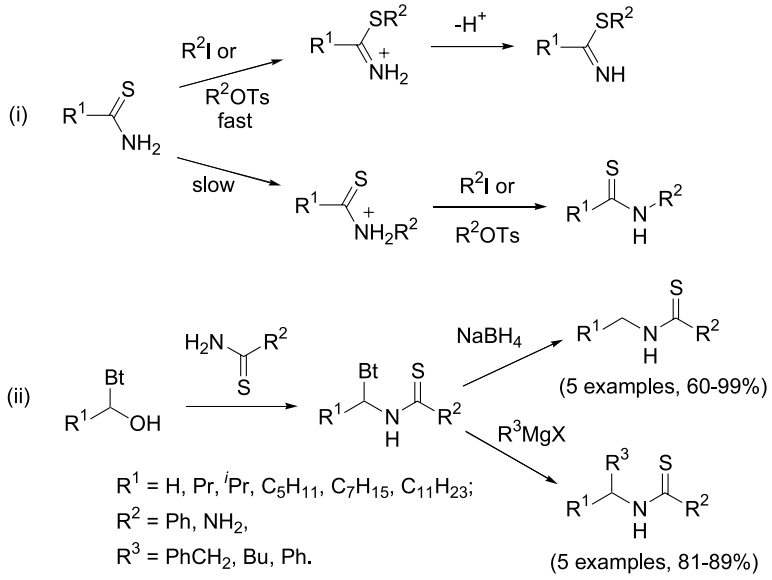


Scheme 34.

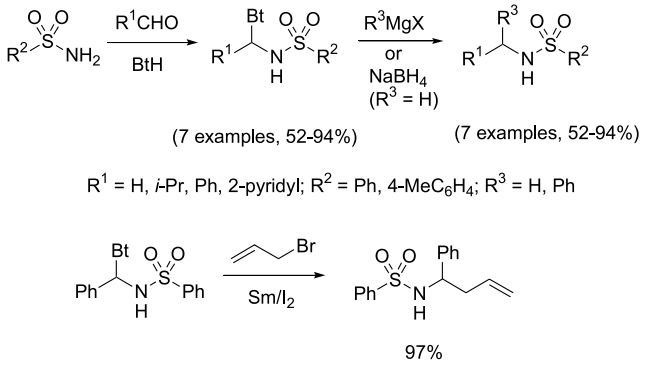
amides prepared from alkyl amides react readily with sodium alkoxides to give the 'classical' amidoalkylation reagents (alkoxy as the leaving group).[82b,c] *N*-(Benzotriazol-1-ylmethyl) amides also react readily with a variety of thiols (both aliphatic and aromatic) and sodium ethoxide under mild conditions to give *N*-acylhemithioaminals in good yields.[82d] This methods avoids the use of an acid and is applicable to open-chain systems.

3.3. Amido-alkylation of RMgBr and BH_4^-

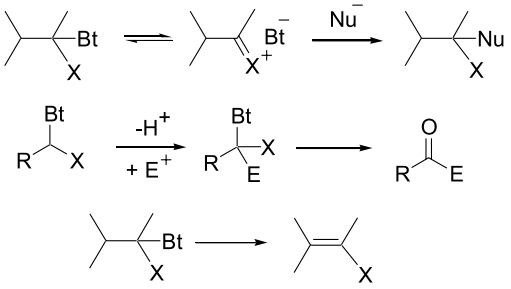
In Scheme 27 it is shown that amidoalkylating reagents react readily with organozinc reagents (prepared in situ from Grignard reagents and $ZnCl_2$) to afford replacement of the benzotriazole group by an alkyl or aryl residue.[83a] Also with sodium borohydride the benzotriazole group is simply replaced by hydrogen[83b] Another example is the preparation of an α-cyanoalkyl amide using KCN.[83c] Amides and thioamides of type $RC(=X)NHCHR^1R^2$ have been prepared in high yield with the formation of a new C–R^2 bond (exclusive monoalkylation α to the amide or thioamide nitrogen) by the reaction of Grignard reagents with readily available adducts from an amide or thioamide, aldehyde and benzotriazole.[83d]



Scheme 35.



Scheme 36.



Scheme 37.

3.4. Amido-alkylation of CN^-: the peptide cycle

There are few reports on α-acylamino nitriles in the literature; benzotriazole methodology simplifies their synthesis. Adducts resulting from Mannich-type condensation of benzotriazole with an aldehyde and an amide react with cyanide to give α-acylamino nitriles in high yields. On hydrolysis the nitrile group forms primary amide, which again becomes a reactive site to undergo condensation with an aldehyde and an amine. Thus, a cyclic sequence is generated, which enables the stepwise synthesis of peptides (Scheme 28).[84]

3.5. Amido-alkylation of amines

As an alternative to the aminoalkylation of amides described above (Section 2.14), the corresponding amido-alkylation with amines is also feasible as shown in Scheme 29. Adducts derived from an amide, an aldehyde and benzotriazole, react with ammonia to give various monoacylated aminals. Using protected amino acid amides as the amide component leads to gem-dipeptide derivatives in a convenient route for peptide analogue synthesis.[85]

3.6. Amido-alkylation of aromatic compounds

Amidoalkylation of aromatic compounds is a useful route to di- and polysubstituted aromatics, containing hydroxy, alkoxy and alkylamino substituents, and to some α-ami-aminoalkyl substituted heterocycles.[86] *N*-[1-(Benzotriazol-1-yl)alkyl amides react with a variety of active aromatic and heteroaromatic compounds in the presence of aluminum chloride to give the desired aminoalkylated products in good yields (Scheme 30).[87] *N*-[1-(Benzotriazol-1-yl)alkyl amides are easily prepared from a wide ranges of aldehydes and are stable amidoalkylating reagents; milder reaction conditions, high yields and simple work-up procedure make this method very advantageous.

3.7. Intramolecular amido-alkylation

Examples of intramolecular amidoalkylation for the preparation of pyrroloisoquinolines and 1,4-benzothiazenes and their O- and N-analogs are shown in Schemes 31 and 32, respectively.[88,89] Most reported methods require at least three steps to synthesize such fused ring systems,[90] intramolecular amidoalkylation using benzotriazole methodology allows a two step synthesis in good yields.

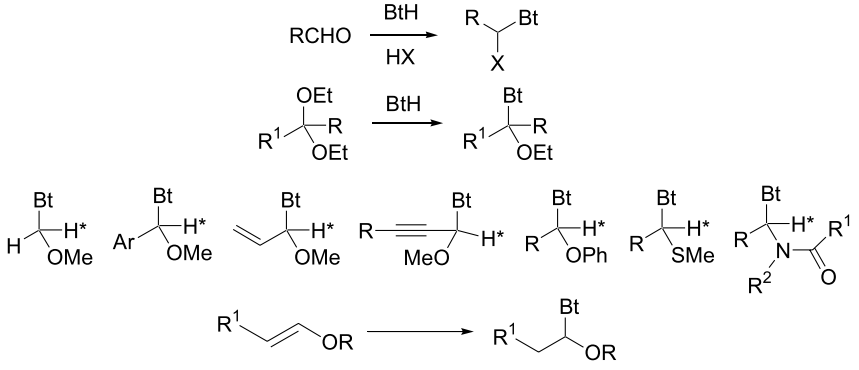
Intramolecular amido-alkylation using benzotriazole methodology for the synthesis of 1-aryl-1,4-dihydro-3(2*H*)-isoquinolinones is shown in Scheme 33. Similarly the synthesis of 2-substituted and 2,3-disubstituted benzofurans has also been reported.[91]

3.8. Benzotriazole mediated amido-alkylation: summary

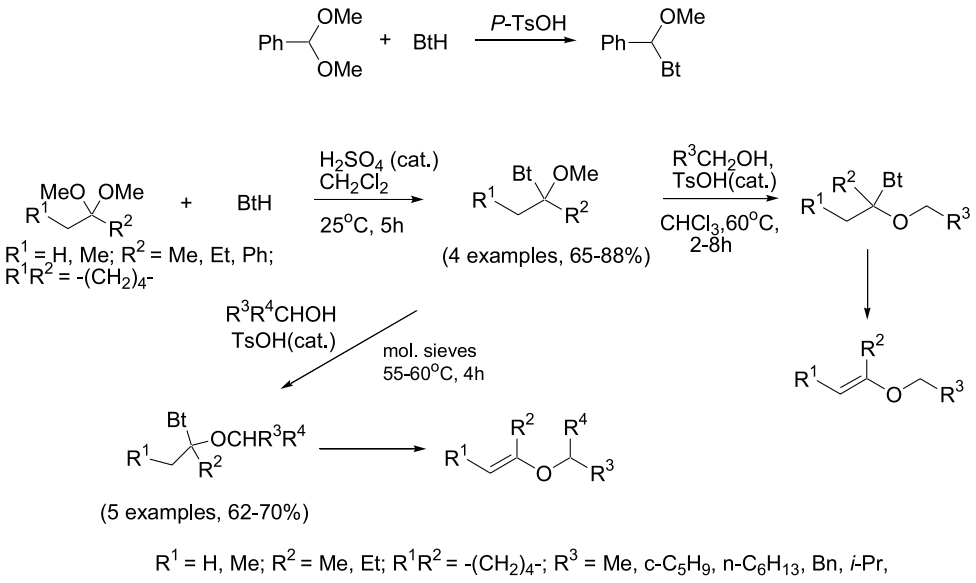
Scheme 34 shows a summary of the types of reactions described above.

3.9. Thioamido-alkylation

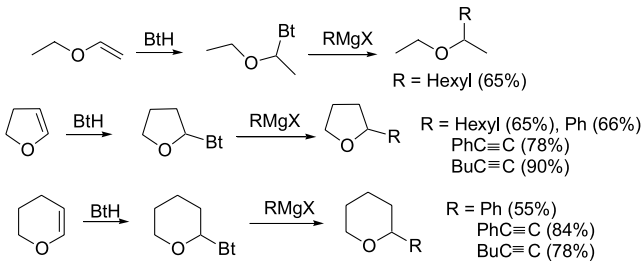
The classical method of alkylation of thioamides by alkyl halides or alkyl tosylates is shown in Scheme 35(i). It has been found that thioamides give N-substitution products on aminoalkylation,[92] hydroxylation,[93] and alkoxylation,[94] which are thermodynamically controlled reactions.



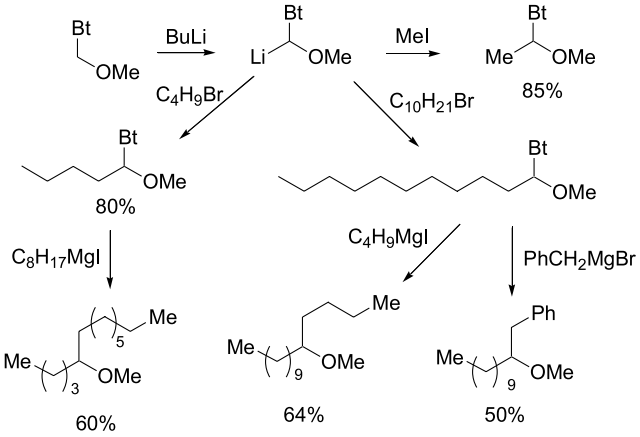
Scheme 38.



Scheme 39.



Scheme 40.



Scheme 41.

Benzotriazole methodology based thioamido alkylation is shown in Scheme 35(ii).[95]

3.10. Sulfonamido-alkylation

N-Alkylation of sulfonamides using benzotriazole methodology is shown in Scheme 36. The adduct obtained from aldehyde, sulfonamide and benzotriazole reacts with Grignard reagents or sodium borohydride to give the sulfonamidoalkylation products in good yields.[96a] Similar reactions have also been reported with allyl samarium bromide.[96b]

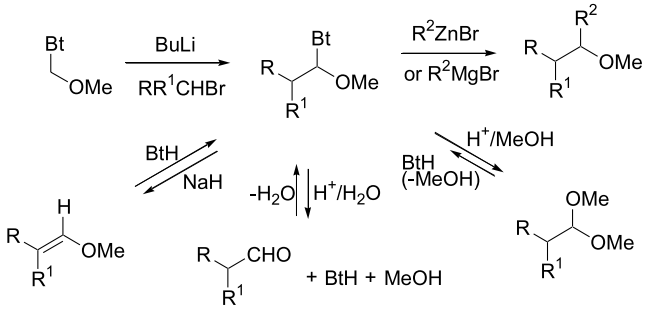
4. Alkoxy-alkylation

4.1. Utility of Bt–C–X compounds

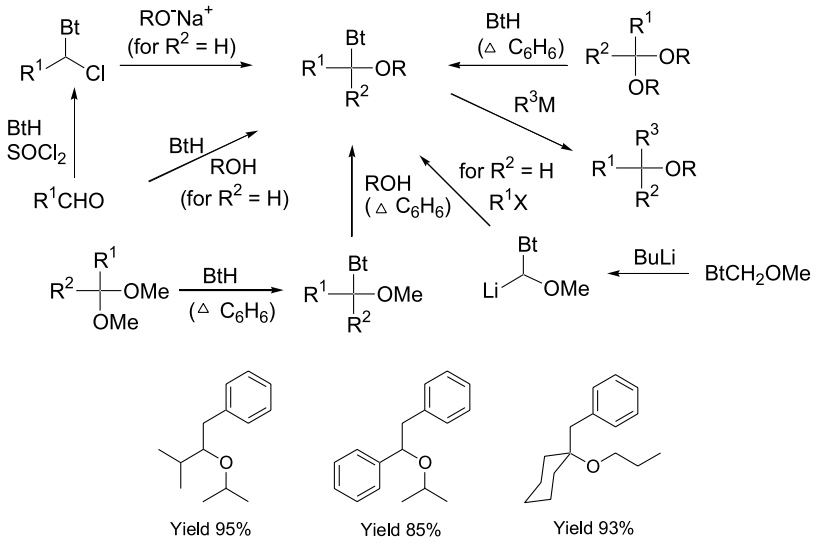
When *N*-benzotriazolyl group and a heteroatom (X=N, O, S or halogen) are attached to a carbon atom, the adduct may exist in equilibrium as shown in Scheme 37. This can undergo reactions with different types of nucleophiles to substitute the benzotriazole group. Similar class of compounds also reacts with electrophiles, where both benzotriazole and the heteroatom are eliminated to form a carbonyl compound (Scheme 37). When the α-carbon contains a proton, elimination takes place to form an unsaturated compound.[8]

4.2. Preparation of Bt–C–X compounds (X=N, O, S, or halogen)

Bt–C–X Compounds are useful for various transformations as discussed in Section 4.1, these can be prepared by the reaction of benzotriazole with aldehydes, ketals, vinyl ethers or enamines (Scheme 38).[8]



Scheme 42.



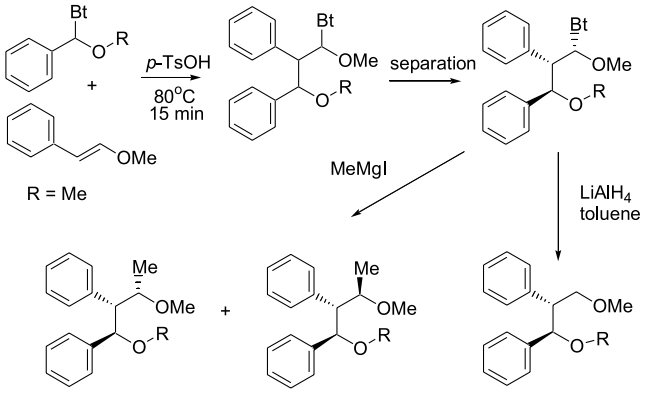
Scheme 43.

4.3. Preparation of RR′C(OR″)Bt from acetals and ketals

1-(1-Alkoxyalkyl)benzotriazoles [RR′C(OR″)Bt] prepared from acetals and ketals are useful intermediates for the synthesis of aliphatic ethers and enol ethers.[97] Since acetals derived from aldehydes and higher alcohols can be relatively easily prepared and directly transformed into the corresponding enol ethers, the importance of benzotriazole methodology has been studied on derivatives of ketones. Dimethyl ketals of various ketones form the corresponding 1-(1-methoxyalkyl)benzotriazoles by reaction with benzotriazole and catalytic amount of sulfuric acid. The methoxy group in the resulting product can be replaced by several other primary alkoxy groups. (Scheme 39). Ketone enol ethers having secondary alkoxy group (OR″) can be easily prepared from this intermediate, which by the conventional methods give low yields.[97b]

4.4. Preparation of α-alkylated saturated ethers from vinyl ethers

Benzotriazole adds readily to various vinyl ethers to form the respective 1-(α-alkoxyalkyl)benzotriazole, which on reaction with phenyl or alkynyl magnesium reagents give the corresponding α-phenyl or α-alkynyl ethers (Scheme 40).[98]



Scheme 44.

4.5. Preparation of ethers by lithiation of 1-methoxymethylbenzotriazole

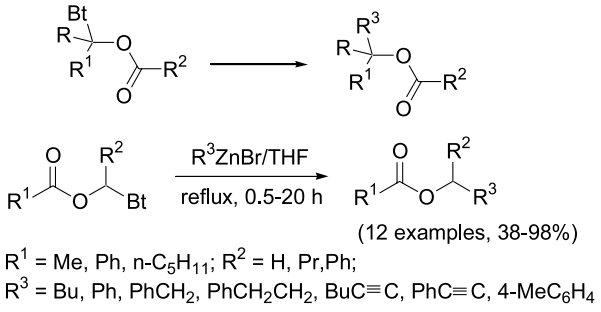
Preparation of ethers by electrophilic substitution at the α-position has been reported: (i) by the formation of organometallic compounds of the type ROCH(Li)R′ by tin–lithium exchange,[99a] (ii) via α-bromoalkyllithium compounds.[99b] The benzotriazole methodology has been successfully applied in a new approach towards the synthesis of α,α-disubstituted methyl ethers. 1-Methoxymethylbenzotriazole undergoes lithiation at the methylene group, which reacts with various electrophiles to yield substituted benzotriazolylmethyl ethers. Further reactions of these compounds with Grignard reagents afford α,α-disubstituted methyl ethers (Scheme 41).[99c]

4.6. Preparation of ethers, aldehydes, enol ethers and acetals

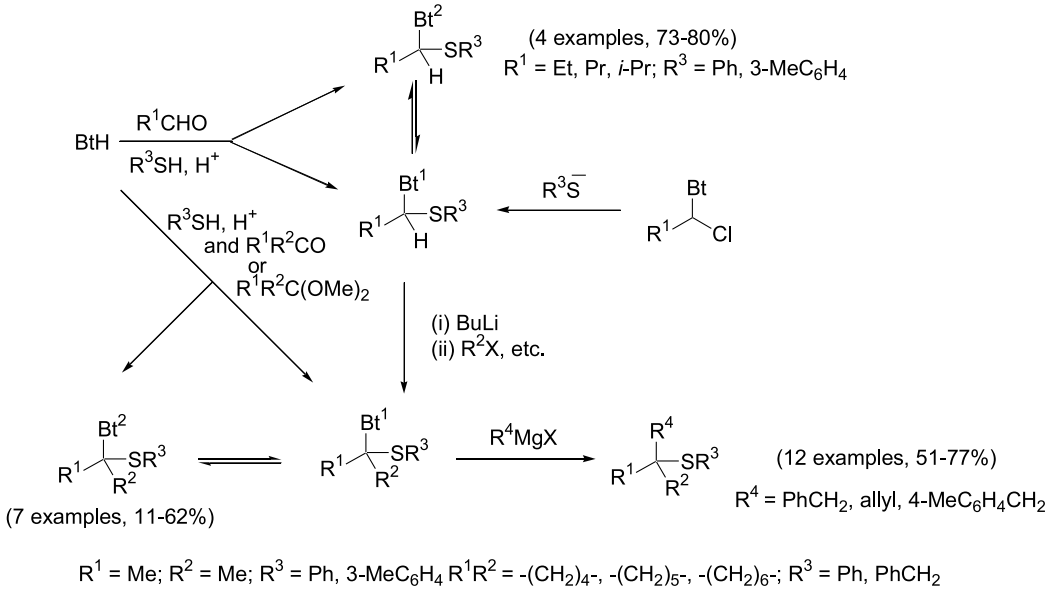
1-(1-Methoxyalkyl)benzotriazoles can be easily converted to the corresponding methyl ethers,[99c] methyl vinyl ethers,[97b] aldehydes and acetals[2,3] as shown in Scheme 42.

4.7. Overview of preparation of ethers

There are several general methods known for the synthesis



Scheme 45.



Scheme 46.

of ethers. However, a convenient synthetic method was not available for the synthesis of aryl alkyl ethers, such as aryl phenethyl ether, where the alkyl group possesses a strong tendency towards elimination and addition of phenol to the olefin does not give the desired product. These problems have been made simpler by benzotriazole methodology. The starting material for this synthesis is α-(benzotriazolyl)alkyl alkyl ether, which can be easily prepared by various methods (Scheme 43), it reacts with Grignard reagents to give a variety of dialkyl and alkyl aryl ethers,[100] some representative examples are shown below.

4.8. Alkoxy-alkylation of vinyl ethers

Addition of acetals to vinyl ethers catalyzed by Lewis acid is known from long ago. Such type of addition catalyzed by trimethylsilyl chloride and tin (II) chloride has been reported under mild conditions.[101a] The more reactive silyl vinyl ethers have also been used instead of alkyl vinyl ethers.[101b] However, in these reactions the acetal protection of the carbonyl group is lost in the product, which may be undesirable. Analogous to acetals are 1-(α-alkoxyalkyl)-benzotriazoles, which are effective in reactions where the corresponding acetals or ketals fail. Addition of 1-(α-alkoxybenzyl)benzotriazoles to vinyl ethers gives an adduct, which on reaction with Grignard reagents, extends the carbon skeleton and produces 1,3-diethers,[101c] a representative example being shown in Scheme 44. This methodology is more efficient for the synthesis of 1,3-diethers than the previous methods.

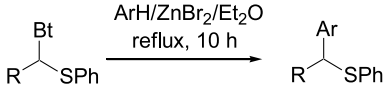
4.9. Acyloxy-alkylation

1-(Benzotriazol-1-yl)alkyl esters, prepared from aldehyde, benzotriazole and thionyl chloride followed by reaction with sodium carboxylates or organozinc reagents give esters with relatively complex alkoxy skeleton. Various types of alkyl or aryl groups could be introduced at the alkoxy part of the ester (Scheme 45).[1,102] Although simple carboxylic esters are prepared by esterification of the corresponding alcohols, benzotriazole methodology is useful in the synthesis of more complex and polyfunctional esters.

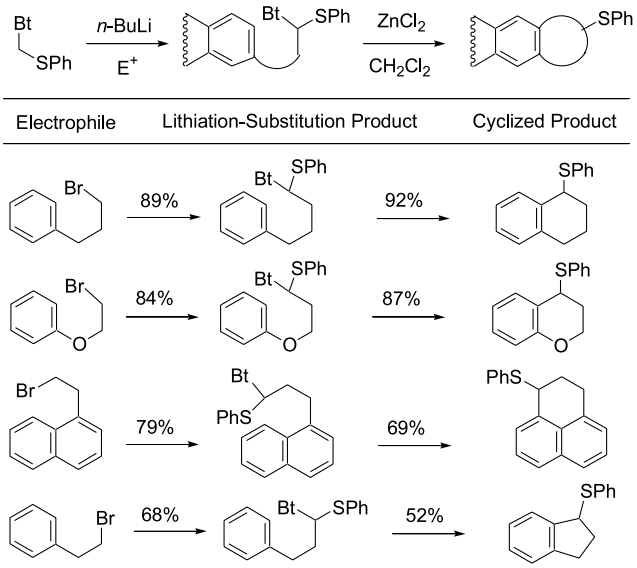
5. Alkylthio-alkylation and silyl-alkylation

5.1. Preparation of thioethers

The preparation of primary and secondary alkyl sulfides by classical methods is satisfactory. However, these methods fail for *tert*-alkyl sulfides for which only few methods are available with moderate yields. This difficulty has been solved by the benzotriazole methodology. Thus, *tert*-alkyl sulfides are conveniently prepared from α-(1*H*-benzotriazol-1-yl)alkyl sulfides by displacement of the 1*H*-benzotriazol-1-yl group with Grignard reagents. The 1-[α-(alkylthio)alkyl] and 1-[α-(arylthio)alkyl]-1*H*-benzotriazole intermediates are easily prepared as shown in Scheme 46.[103]



Scheme 47.



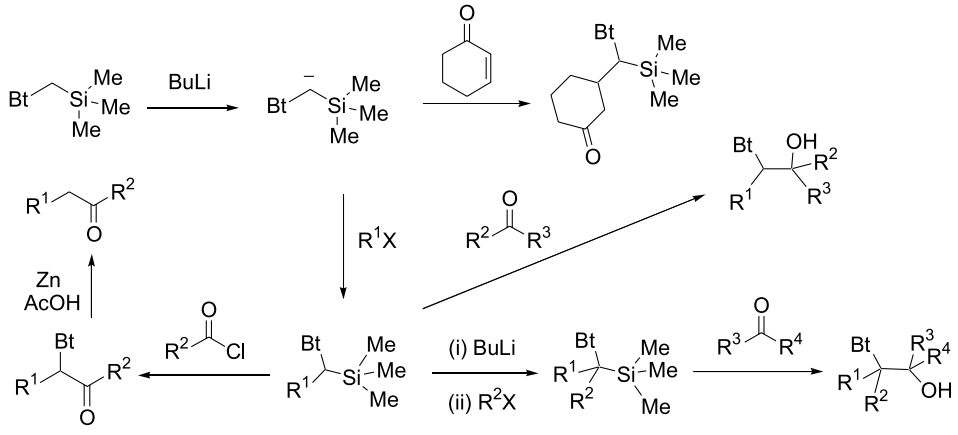
Scheme 48.

5.3. Intramolecular alkylthio-alkylation

Benzotriazol-1-ylphenylthiomethane readily undergoes deprotonation with butyllithium and reacts with a variety of appropriate electrophiles to form derivatives, which upon subsequent treatment with Lewis acids undergo ring closure to afford fused aromatics (Scheme 48).[105] The resistance of the phenylthio group to Lewis acid catalyzed elimination makes this procedure more attractive.

5.4. Silyl-alkylation of acids and ketones

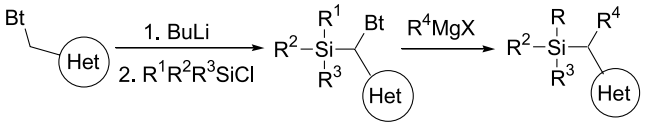
1-(Trimethylsilylmethyl)benzotriazole is readily prepared from benzotriazole and chloromethyltrimethylsilane. This intermediate after lithiation, can be trapped with various electrophiles such as alkyl halides and carbonyl compounds to give the corresponding products in good yields (Scheme 49).[106] Addition of aldehydes and ketones to this lithio derivative gives Peterson olefination products. This



Scheme 49.

5.2. Thio-alkylation of aromatics

1-[α-(Phenylthio)benzyl]- and 1-[(4-methylphenyl)(phenylthio)-methyl] benzotriazole, readily available from benzotriazole, an aldehyde and thiophenol, react with a variety of active aromatic compounds to give the thioalkyl products in moderate to good yields (Scheme 47).[104] The use of benzotriazole methodology in comparison to other thioalkylation reagents is advantageous because of milder reaction conditions, easy preparation of the starting material and its stability.



Scheme 50.

methodology enables the synthesis of a wide range of functionally substituted benzotriazoles, which would be useful in the elaboration of N-substituents in other heterocyclic ring systems.

5.5. Silyl-alkylation of electron rich aromatics and heteroaromatics

Despite the tremendous industrial utility of organosilicon compounds, few examples of α-silylalkylated heterocycles have been reported. This might be due to the relatively low reactivity of halogenoalkylsilanes (as α-silylalkylating reagents) and their limited availability. Lithiation of *N*-(benzotriazol-1-ylmethyl)carbazole or -indole and subsequent reaction with silyl chlorides gives silylated intermediates which are transformed into the corresponding α-silylalkylated heterocycles in good overall yields by displacement of the benzotriazolyl group with Grignard reagents (Scheme 50).[107]

Acknowledgements

We thank Dr. Dennis Hall for helpful suggestions.

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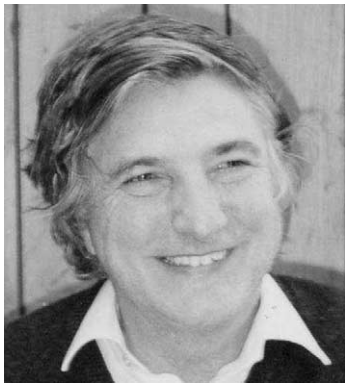
Biographical sketch



Alan R. Katritzky has taught, researched, consulted and published on heterocyclic chemistry, synthetic methods, and QSPR, first in the UK and since 1980 at the University of Florida where he is Kenan Professor of Chemistry and Director of the Center for Heterocyclic Compounds. In 2000 he founded 'Arkivoc' a peer-reviewed journal of organic chemistry completely free electronically to authors and readers (no page charges or access/downloading fees). In its first five years Arkivoc published some 1400 manuscripts (ca. 15,000 pages) to help chemists everywhere but particularly in the developing world (see www.arkat-usa.org).

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Justiciosides E–G, triterpenoidal glycosides with an unusual skeleton from *Justicia betonica*

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Abstract—Three new triterpenoidal glucosides, justiciosides E, F and G, were isolated from the aerial portion of *Justicia betonica*. Their structures were established through chemical and spectroscopic analyses, and showed an unusual A-nor-B-homo oleanan-12-ene skeleton type for the aglycone moiety as A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol 28-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol 28-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, and 11α-methoxy-A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol 28-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside, respectively.

1. Introduction

Justicia betonica (Acanthaceae; Thai name: Tri-Cha-Va, Hang-Kra-Rok) is an ornamental plant, commonly grown in Northeast of Thailand. No ethno-pharmacological use of this plant has been reported in Thai traditional medicine but its aerial parts are used in Indian traditional medicine as an anti-diarrhea as well as an anti-inflammatory agent.

In a previous paper, we reported the isolation and structural elucidation of triterpenoidal glycosides, justicioside A–D,[1] from the aerial portion. Further investigations of the same plant afforded three new triterpenoidal glycosides, which have an unprecedented skeleton for the aglycone moiety (A-nor-B-homo-olean-12-ene skeleton type). Their structures were elucidated on the basis of chemical and spectroscopic evidence. The present paper deals with the isolation and structural elucidation of these compounds.

2. Results and discussion

The ethanolic extract of the aerial portion was suspended in H_2O and partitioned with Et_2O. The aqueous layer was subjected to a column of highly porous copolymer of styrene and divinylbenzene, and eluted with H_2O, 60% aqueous MeOH, MeOH and Me_2CO, successively. The fraction elute with 60% aqueous MeOH was repeatedly subjected to columns of silica gel, as well as RP-18 and preparative HPLC-ODS to provide justiciosides E (**1**), F (**2**) and G (**3**).

Justicioside E (**1**) was obtained as an amorphous powder. Its molecular formula was determined as $C_{42}H_{68}O_{13}$ by HR-FAB mass spectrometric analyses. The ^{13}C NMR spectral data showed the presence of two sugar units (anomeric carbons at δ_C 103.6 and 106.1) in addition to 30 carbon signals for the aglycone moiety. The six tertiary methyl groups (δ_H 0.84×2, 0.96, 1.10, 1.12, and 1.38) and one trisubstituted olefinic proton (δ_H 5.66, d, $J=2.3$ Hz) observed in the ^1H NMR spectrum, coupled with the information from the ^{13}C NMR spectrum (six sp^3 carbon at δ_C 16.0, 16.4, 23.7, 25.9, 27.4 and 33.3 and two sp^2 olefinic carbons at δ_C 127.9 and 145.4) suggested that the aglycone processes an olean-12-ene skeleton.[2] Enzymatic hydrolysis of **1** with crude hesperidinase gave a novel aglycone (**1a**) with a molecular formula $C_{30}H_{48}O_3$, and D-glucose, identified by TLC and comparison of its optical rotation with an authentic sample. DEPT experiments indicated that **1a** has six methyl carbons, ten methylene carbons, seven

Keywords: *Justicia betonica*; Acanthaceae; Triterpenoidal glycoside; A-nor-B-homo olean-12-ene.
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methine carbons and seven quaternary carbons (Table 1). The chemical shifts of **1a** were related to those of olean-12-ene-1β,3β,11α,28-tetraol (**4**), previously reported from our paper.[1] By comparison of the ^{13}C NMR spectral data of **1a** and **4**, the carbon resonances of **1a** attributable to the D and E-rings, and three methyl groups (δ_C 23.7, 25.8, and 33.3) as well as the methylene carbon (δ_C 68.5) on these rings were essentially the same as those of **4**. The remaining signals indicated that A and B-rings of **1a** were different from **4**. In addition, the signals of an exocyclic methylene group (δ_C 110.2 and 148.9) were observed in **1a**. They were assigned to C-10 (δ_C 148.9) and C-25 (δ_C 110.2) from the observation in the HMBC spectrum of correlations between (i) two exocyclic protons (δ_H 5.34 and 5.46) and C-1 (δ_C 45.7) and C-9 (δ_C 57.1), (ii) H-11 (δ_H 4.57) and C-9 (δ_C 57.1), C-10 (δ_C 148.9), C-12 (δ_C 127.8) and C-13 (δ_C 145.7), and (iii) H-2 (δ_H 2.25) and C-10 (δ_C 148.9) as illustrated in Figure 1. From this evidence, A and B-rings of **1a** were changed to cyclopentane (A-nor) and cycloheptane (B-homo) rings, respectively, relative to **4**. Moreover, the germinal coupling of two methelene protons (CH_2-2, δ_H 2.12 and 2.25) with $J=19.5$ Hz was in agreement with the coupling constant of a pentacyclic ring. The absolute configurations of the hydroxyl groups at C-3 and C-11 positions were determined as 3β and 11α on the basis of the modified Mosher's method,[3] applied on the (*R*)- and (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters, in which the significant $\Delta\delta_H$ values ($\delta_{S\text{-MTPA-ester}}-\delta_{R\text{-MTPA-ester}}$) for the protons near to the derivatized chiral centers C-3, and C-11 were calculated (Fig. 2). The results were consistent

Table 1. ^{1}H and ^{13}C NMR spectral data for justicane (**1a**, in C_5D_5N)

Position	DEPT	δ_C	δ_H
1	CH	45.7	2.67 (1H, m)
2	CH_2	36.3	2.25 (1H, dd, $J=19.5$, 10.3 Hz) 2.12 (1H, dd, $J=19.5$, 8.1 Hz)
3	CH	79.6	3.92 (1H, dd, $J=10.3$, 6.8 Hz)
4	C	44.1	
5	CH	52.2	1.59 (1H, dd, $J=8.8$, 3.9 Hz)
6	CH_2	20.6	1.24 (1H, m), 1.15 (1H, m)
7	CH_2	35.7	1.57 (1H, m), 1.48 (1H, m)
8	C	42.5	
9	CH	57.1	2.71 (1H, d, $J=9.5$ Hz)
10	C	148.9	
11	CH	67.9	4.57 (1H, dd, $J=9.5$, 2.9 Hz)
12	CH	127.8	5.72 (1H, d, $J=2.9$ Hz)
13	C	145.7	
14	C	43.1	
15	CH_2	27.4	2.00 (1H, m), 1.32 (1H, m)
16	CH_2	23.3	1.98 (1H, m), 1.55 (1H, m)
17	C	37.6	
18	CH	43.0	2.41 (1H, dd, $J=13.7$, 3.9 Hz)
19	CH_2	46.5	1.90 (1H, d, $J=13.7$ Hz), 1.22 (1H, m)
20	C	31.2	
21	CH_2	34.6	1.27 (1H, m), 1.25 (1H, m)
22	CH_2	31.5	2.02 (1H, dd, $J=13.7$, 3.7 Hz), 1.66 (1H, m)
23	CH_3	27.4	1.13 (3H, s)
24	CH_3	16.0	0.96 (3H, s)
25	CH_2	110.2	5.46 (1H, s), 5.34 (1H, s)
26	CH_3	16.4	1.05 (3H, s)
27	CH_3	25.8	1.44 (3H, s)
28	CH_2	68.5	3.85 (1H, d, $J=10.5$ Hz), 3.60 (1H, d, $J=10.5$ Hz)
29	CH_3	33.3	0.91 (3H, s)
30	CH_3	23.7	0.93 (3H, s)

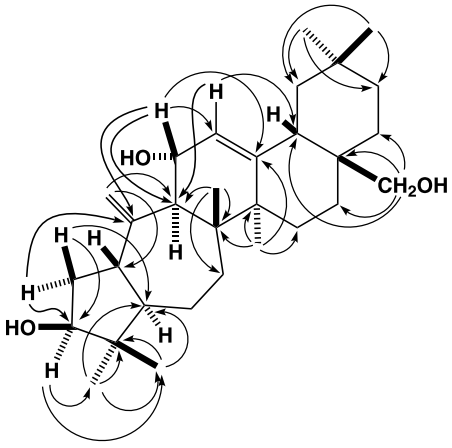


Figure 1. Significant HMBC correlations of **1a**.

with the observation of the NOE correlations between (i) H-3 (δ 3.92) and CH_3-23 (δ 1.13) to suggest the β-position of the C-3 hydroxyl group, and (ii) H-11 (δ_H 4.57) and CH_3-26 (δ_H 1.05) to establish the α-position of the C-11 hydroxyl group (Fig. 3). Furthermore, the coupling constant between H-9 (δ_H 2.71) and H-11 (δ_H 4.57) ($J=9.5$ Hz) provided the more confirmation of the 11α-hydroxy-position.[1,4] The relative configurations at C-1 and C-5 were deduced from NOE experiments. The significant correlations were found between (i) H-1 (δ 2.67) and CH_3-26 (δ 1.05) to suggest the *S*-configuration of C-1, and (ii) H-3 (δ 3.92) and H-5 (δ 1.59) to establish the *R*-configuration of C-5. Based on the results, the structure **1a** was

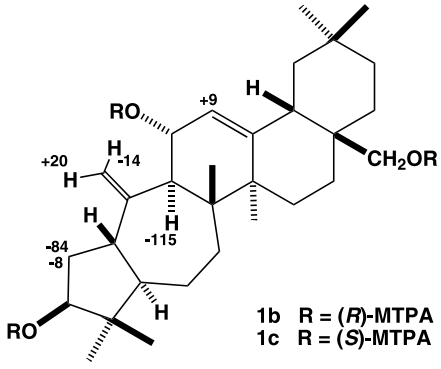


Figure 2. Results with the modified Mosher's method for **1a**. The $\Delta\delta$ values are in Hz ($\delta_S-\delta_R$ at 400 MHz).

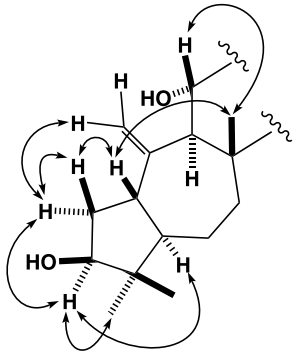
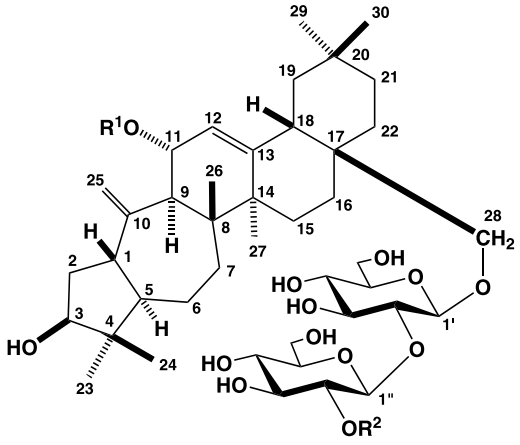
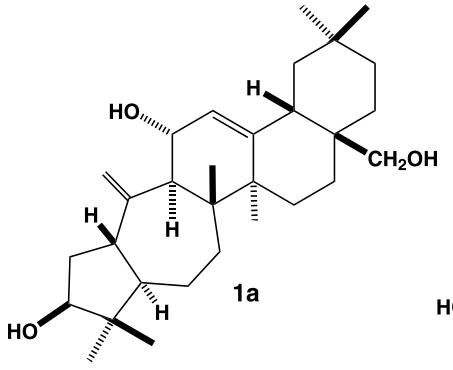
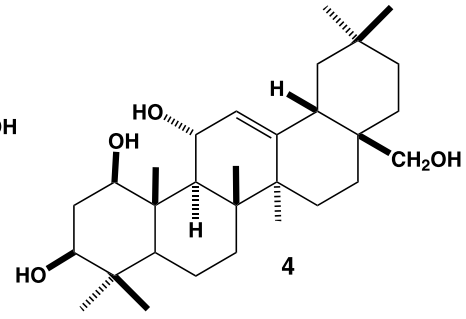


Figure 3. Selected NOE correlations and partial structure of **1a**.



	R^1	R^2
1	H	H
2	H	β-D-Glc
3	Me	β-D-Glc

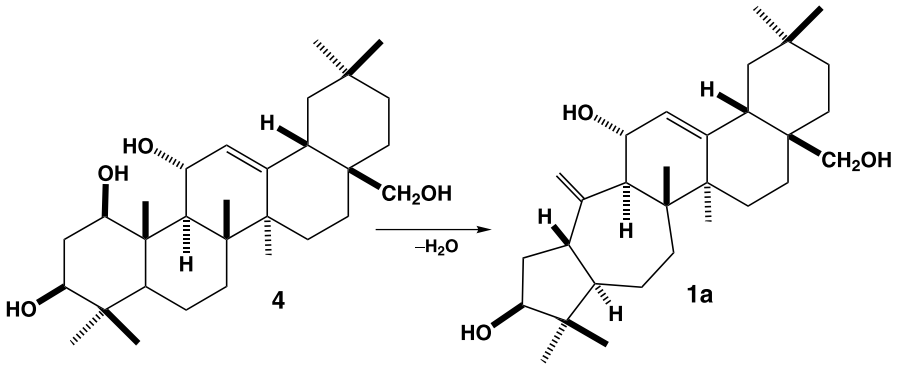




characterized as A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol.

Comparison of the ^{13}C NMR spectral data of **1** with those of **1a** revealed glycosylation shifts for C-28 ($\Delta\delta_C$ +7.9) and C-17 ($\Delta\delta_C$ −0.6) on going from **1a** to **1**, indicating that the sugar moiety was linked to C-28. The sugar sequence was identified to be a β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl unit by comparison of the chemical shifts with those reported.[1,5] The negative ion FAB-MS of **1** exhibited significant fragments at *m/z* 617 $[M-162]^-$, and 455 $[M-162-162]^-$. Consequently, structure **1** was characterized as A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol 28-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside.

Justicioside F (**2**) was isolated as an amorphous powder, and determined as $C_{48}H_{78}O_{18}$ by HR-FAB mass spectrometric analyses. The NMR spectral data were very similar to those of justicioside E (**1**), except for the additional signals of a β-D-glucopyranosyl unit. This unit was assigned to be attached to C-2″ of the inner sugar since the chemical shifts of C-2″ (δ_C 85.5), C-1″ (δ_C 103.2) and C-3″ (δ_C 77.7) changed by +8.6, −2.9 and −0.5 ppm,[1] respectively. Enzymatic hydrolysis of compound **2** with crude hesperidinase provided aglycone **1a** and D-glucose, identified by TLC and comparison of the optical rotation with an authentic sample. Besides, the negative ion FAB-MS showed characteristic fragment ions of a linear sugar unit at *m/z* 941 $[M-H]^-$, 779 $[M-Glc]^-$, 617 $[M-Glc-Glc]^-$, 455 $[M-Glc-Glc-Glc]^-$. Consequently, the structure of **2** was elucidated as A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol 28-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside.



Scheme 1. Possible route of formation of **1a**.

Justicioside G (**3**) was obtained as an amorphous powder. Its molecular formula, $C_{49}H_{80}O_{18}$, was determined by HR-FAB mass spectrometric analyses. Negative ion FAB-MS exhibited fragment ions at *m/z* 955 $[M-H]^-$, 793 $[M-Glc]^-$, 631 $[M-Glc-Glc]^-$; 469 $[M-Glc-Glc-Glc]^-$. The NMR spectral data revealed that **3** contained the same sugar moiety as **2** with a different aglycone moiety, which had the additional signal due to the methoxyl group in the spectra (δ_H 3.29 in the ^1H NMR spectrum and δ_C 56.1 in the ^{13}C NMR spectrum). This methoxyl group was located at C-11 of the aglycone because the significant changed of C-9, C-11, C-12 and C-13 by −3.1, +9.7, −5.1 and +3.6, respectively, when compared to **2**.[1,4] It was concluded thus compound **3** was an 11α-methoxy derivative of **2**. Accordingly, **3** was elucidated as 11α-methoxy-A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol 28-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside.

Justicosides E (**1**), F (**2**) and G (**3**) are triterpenoidal glycosides, which have an unusual A-nor-B-homo oleanan-12-ene type for the aglycone moiety. This skeleton type has been reported for the first time. The formation of this skeleton may be derived from olean-12-ene-1β,3β,11α,28-tetraol (**4**), through a rearrangement as shown in Scheme 1.

3. Experimental

3.1. General

^1H, ^{13}C and 2D NMR spectra were recorded using a JEOL JNM α-400 spectrometer (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR). The NMR data were measured with in C_5D_5N tetramethylsilane (TMS) as internal standard. The negative-ion mode FAB-MS spectra were recorded on a JEOL JMS-SX 102 spectrometer. Optical rotations were determined on a Union PM-1 digital polarimeter.

For column chromatography, silica gel G (Scharlau GE0049, 70-230 mesh ASTM), YMC-gel ODS (50 μm, YMC) and highly porous copolymer resin of styrene and divinylbenzene (Mitsubishi Chem. Ind. Co. Ltd) were used. HPLC (Waters 515 HPLC pump) was carried on a column of ODS (150×20 mm i.d., YMC) with a Shimadzu refractive index (RID-6A) detector.

3.2. Plant material

The aerial portion of *Justicia betonica* L. was collected from Kalasin Province, Thailand, in November, 2002, and identified by Mr. Bamrung Tavinchiua of the Department of Pharmaceutical Botany and Pharmacognosy, Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand. A voucher sample (KKU-0045) is kept in the Herbarium of the Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand.

3.3. Extraction and isolation

The dried aerial portion (1.8 kg) of *J. betonica* was extracted with hot EtOH–H_2O (95:5, v/v) under reflux 4 times (each 8 L, 3 h, 70 °C). The EtOH extract was concentrated to dryness (256.6 g) and partitioned between Et_2O and H_2O, with the aqueous soluble applied to a column of highly porous copolymer resin of styrene and divinylbenzene, and eluted with H_2O, 60% aqueous MeOH, MeOH and Me_2CO, successively. The fraction eluted with MeOH (17.5 g) was applied to a silica gel column using solvent systems EtOAc–MeOH (9:1, 5 L), EtOAc–MeOH–H_2O (40:10:1, 5 L) and EtOAc–MeOH–H_2O (70:30:3, 3.5 L) to give ten fractions. Fraction 6 (2.9 g) was applied to a column of ODS using a gradient system [40% aqueous MeOH (1 L) to MeOH (1 L)] to afford six fractions. Fraction 6-3 was purified by preparative HPLC-ODS using solvent system 37% aqueous MeCN to provide compounds **1** (26.5 mg) and **3** (44.3 mg). Fraction 7 (3.8 g) was similarly applied to a column of ODS using a gradient system [40% aqueous MeOH (1 L) to MeOH (1 L)] to give eight fractions. Fraction 7-2 was

Table 2. ^{13}C NMR spectral data for justicosides E–G (**1–3**, in C_5D_5N)

Position	1	2	3
1	45.7	45.7	45.5
2	36.3	36.2	36.3
3	79.6	79.6	79.5
4	44.1	44.1	44.1
5	52.2	52.2	52.1
6	20.6	20.6	20.6
7	35.5	35.5	35.5
8	42.3	42.3	42.3
9	57.1	57.1	54.0
10	148.8	148.8	147.7
11	67.9	68.0	77.7
12	127.9	127.9	122.8
13	145.4	145.4	149.0
14	43.5	43.2	43.1
15	27.8	27.8	27.8
16	22.3	22.5	22.6
17	37.0	37.0	36.9
18	43.1	43.2	43.2
19	46.1	46.1	46.2
20	31.0	31.0	31.0
21	34.4	34.3	34.3
22	32.1	31.9	31.8
23	27.4	27.4	27.4
24	16.0	16.0	16.1
25	110.1	110.2	109.6
26	16.4	16.5	16.5
27	25.9	25.9	25.7
28	76.4	76.7	76.6
29	33.3	33.2	33.2
30	23.7	23.7	23.8
MeO-11			56.1
Glc-1′	103.6	103.5	103.5
2′	83.0	83.1	83.2
3′	77.8	77.7	77.7
4′	71.5	71.0	71.0
5′	78.0	77.8	77.9
6′	62.6	62.5	62.5
Glc-1″	106.1	103.2	103.2
2″	76.9	85.5	85.5
3″	78.2	77.7	77.7
4″	71.4	70.6	70.6
5″	78.4	77.8	77.9
6″	62.6	62.4	62.4
Glc-1‴		106.2	106.3
2‴		76.3	76.3
3‴		78.3	78.3
4‴		71.3	71.3
5‴		78.9	79.0
6‴		62.7	62.8

purified by preparative HPLC-ODS using solvent system 33% aqueous MeCN to give compound **2** (105.6 mg).

3.3.1. Justicioside E (1). Amorphous powder, $[\alpha]_D^{27}$ −5.8° (MeOH, *c* 1.90); ^{1}H NMR (C_5D_5N): aglycone moiety δ 5.66 (1H, d, *J*=2.3 Hz, H-12), 5.43 (1H, s, H-25a), 5.34 (1H, s, H-25b), 4.63 (1H, dd, *J*=8.0, 2.3 Hz, H-11), 3.86 (1H, d, *J*=9.5 Hz, H-28a), 3.77 (1H, d, *J*=9.5 Hz, H-28b), 2.65 (1H, d, *J*=9.5 Hz, H-9), 1.38 (3H, s, H-27), 1.12 (3H, s, H-23), 1.10 (3H, s, H-26), 0.96 (3H, s, H-24), 0.84 (6H, s, H-29,30), sugar moiety δ 5.35 (1H, d, *J*=7.6 Hz, H-1″), 4.89 (1H, d, *J*=7.3 Hz, H-1′); ^{13}C NMR (C_5D_5N): Table 2; Negative mode FAB-MS *m/z* 779 $[M-H]^-$, 617 $[M-Glc]^-$, 455 $[M-Glc-Glc]^-$; Negative HR-FAB-MS, *m/z*: 779.4572 $[M-H]^-$ (calcd for $C_{42}H_{67}O_{13}$, 779.4581).

3.3.2. Justicioside F (2). Amorphous powder, $[\alpha]_D^{27}$ −15.0° (MeOH, *c* 2.79); ^{1}H NMR (C_5D_5N): aglycone moiety δ_H 5.69 (1H, d, *J*=2.0 Hz, H-12), 5.42 (1H, s, H-25a), 5.34 (1H, s, H-25b), 4.61 (1H, dd, *J*=8.1, 2.0 Hz, H-11), 3.84 (1H, d, *J*=9.3 Hz, H-28a), 3.76 (1H, d, *J*=9.3 Hz, H-28b), 2.67 (1H, d, *J*=9.5 Hz, H-9), 1.33 (3H, s, H-27), 1.11 (6H, s, H-23,26), 0.97 (3H, s, H-24), 0.84 (6H, s, H-29,30), sugar moiety δ 5.43 (1H, d, *J*=7.6 Hz, H-1″), 5.31 (1H, d, *J*=7.6 Hz, H-1‴), 4.87 (1H, d, *J*=7.6 Hz, H-1′); ^{13}C NMR (C_5D_5N): Table 2; Negative mode FAB-MS *m/z* 941 $[M-H]^-$, 779 $[M-Glc]^-$, 617 $[M-Glc-Glc]^-$, 455 $[M-Glc-Glc-Glc]^-$; Negative HR-FAB-MS, *m/z*: 941.5109 $[M-H]^-$ (calcd for $C_{48}H_{77}O_{18}$, 941.5109).

3.3.3. Enzymatic hydrolysis. Justicioside E (**1**, 18 mg) was dissolved in 0.5 mL of MeOH. A solution of crude hesperidinase (100 mg in 20 mL of H_2O) was added in the experiment. After stirring at 37 °C for 1 week, the mixture was extracted with EtOAc, concentrated to dryness, and then purified by prep. HPLC-ODS using 90% aqueous MeOH as solvent system to give **1a** (6 mg). The aqueous layer was concentrated to dryness and applied to a silica gel column [EtOAc–MeOH–H_2O (40:10:1)], affording D-glucose (5 mg) in comparison of its optical rotation with an authentic sample. By the same method, justicioside F (**2**, 40 mg) afforded **1a** (17 mg) and D-glucose (12 mg).

3.3.4. A-nor-B-homo-oleanan-10,12-diene-3β,11α,28-triol (1a). Amorphous powder, $[\alpha]_D^{27}$ −24.5° (MeOH, *c* 1.1.); ^{1}H and ^{13}C NMR (C_5D_5N): Table 1; Negative HR-FAB-MS, *m/z*: 455.3520 $[M-H]^-$ (calcd for $C_{30}H_{47}O_3$, 455.3525).

3.3.5. Preparation of the (*R*)- and (*S*)-MTPA esters from 1a. A solution of **1a** (2.5 mg) in 1 mL of dehydrated CH_2Cl_2 was reacted with (*R*)-MTPA (42 mg) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (30 mg) and 4-dimethylaminopyridine (DMAP) (22 mg), the mixture being occasionally stirred at room temperature for 30 min. After the addition of 1 mL of CH_2Cl_2, the solution was successively washed with H_2O (1 mL), 5% HCl (1 mL), $NaHCO_3$-saturated H_2O (1 mL), and brine (1 mL), successively. The organic layer was dried over Na_2SO_4 and then evaporated under reduce pressure. The residue was purified by preparative TLC [silica gel (0.25 mm thickness, and developed with $CHCl_3$–Me_2CO (19:1) and eluted with $CHCl_3$–MeOH (9:1)] to furnish the ester, **1b** (3.0 mg). Through a similar procedure, **1c** (2.2 mg) by use of (*S*)-MTPA (40 mg), EDC (29 mg), and DMPA (18 mg). (*R*)-MTPA ester (**1b**): colorless syrup, important ^{1}H NMR data ($CDCl_3$, 400 MHz): δ 5.26 (1H, s, H-25a), 5.22 (1H, d, *J*=2.7 Hz, H-12), 5.18 (1H, s, H-25b), 2.54 (1H, d, *J*=10.2 Hz, H-9), 2.50 (1H, dd, *J*=20.0, 10.7 Hz, H-2a), 1.85 (1H, dd, *J*=20.0, 6.8 Hz, H-2b); Positive HR-FAB-MS, *m/z*: 1127.4718 $[M+Na]^+$ (calcd for $C_{60}H_{69}O_9F_9Na$, 1127.4695). (*S*)-MTPA ester (**1c**): colorless syrup, important ^{1}H NMR data ($CDCl_3$, 400 MHz): δ 5.31 (1H, s, H-25a), 5.24 (1H, d, *J*=2.7 Hz, H-12), 5.14 (1H, s, H-25b), 2.25 (1H, d, *J*=9.8 Hz, H-9), 2.27 (1H, dd, *J*=20.0, 10.7 Hz, H-2a), 1.83 (1H, dd, *J*=20.0, 7.6 Hz, H-2b); Positive HR-FAB-MS, *m/z*: 1127.4712 $[M+Na]^+$ (calcd for $C_{60}H_{69}O_9F_9Na$, 1127.4695).

3.3.6. Justicioside G (3). Amorphous powder, $[\alpha]_D^{27}$ −9.9° (MeOH, *c* 2.83); ^{1}H NMR (C_5D_5N): aglycone moiety δ_H 5.65 (1H, d, *J*=2.3 Hz, H-12), 5.37 (1H, s, H-25a), 5.23 (1H, s, H-25b), 3.87 (1H, d, *J*=9.3 Hz, H-28a), 3.72 (1H, d, *J*=9.3 Hz, H-28b), 3.29 (3H, s, MeO-11), 2.61 (1H, d, *J*=9.8 Hz, H-9), 1.36 (3H, s, H-27), 1.11 (3H, s, H-23), 1.07 (3H, s, H-26), 0.97 (3H, s, H-24), 0.88 (3H, s, H-30), 0.85 (3H, s, H-29), sugar moiety δ 5.43 (1H, d, *J*=7.6 Hz, H-1″), 5.30 (1H, d, *J*=7.6 Hz, H-1‴), 4.87 (1H, d, *J*=7.6 Hz, H-1′); ^{13}C NMR (C_5D_5N): Table 2; Negative mode FAB-MS *m/z* 955 $[M-H]^-$, 793 $[M-Glc]^-$, 631 $[M-Glc-Glc]^-$; 469 $[M-Glc-Glc-Glc]^-$; Negative HR-FAB-MS, *m/z*: 955.5271 $[M-H]^-$ (calcd for $C_{49}H_{79}O_{18}$, 955.5266).

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Asymmetric palladium-catalyzed annulation of benzene-1,2-diol and racemic secondary propargylic carbonates bearing two different substituents

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Abstract—The palladium-catalyzed cyclization of benzene-1,2-diol with various racemic secondary propargyl carbonates having no acetylenic hydrogen in the presence of (*R*)-Binap as the chiral ligand afforded the two regioisomers of the corresponding 2,3-dihydro-1,4-dioxin derivatives in quite good yields, and also in enantioselectivities going from 40 to 97%. The cyclization of benzene-1,2-diol with methyl (*R*)-1-methyl-3-phenylpro-2-yn-1-yl carbonate in the presence of dppb as the achiral ligand afforded 2-benzylidene-3-methyl-2,3-dihydro-1,4-benzodioxine as the major product with 15% ee. The use of (*R*)-Binap as the chiral ligand afforded the (+) cyclized compound in 45% ee, when the (−) enantiomer was obtained with 77% ee in the presence of (*S*)-Binap. All the results suggest that in this case the enantioselective step is the diastereoselective protonation of the palladium–carbene intermediates.

1. Introduction

The 1,4-benzodioxin and 1,4-benzodioxan subunits are present in some natural compounds displaying interesting biological properties.[1–5] For example, some 2-substituted 1,4-benzodioxanes exhibit antihyperglycemic properties;[6] others act as inhibitors of 5-lipoxygenase,[7] or can be used as α- or β-blocking agents or in antidepression or anti-hypertension therapy.[8–12] Due to these interesting properties, the synthesis of compounds containing this structure has been the subject of increasing research during the last few years. Moreover, these compounds are also interesting precursors for further synthetic transformations.[13–16]

If the synthesis of 1,4-benzodioxin structures is now well documented in the literature,[13,17–25] the synthetic routes to 2-alkylidene-2,3-dihydro-1,4-benzodioxines are less studied, and the published procedures often required a tedious multistep sequence.[26–32]

Recently two very facile methods for the synthesis of these structures in quite good yields have been developed. Kundu and colleagues.[33,34] described the palladium(II)–copper catalyzed condensation of aryl halides and mono-prop-2-ynilated catechol. We reported also the palladium(0)-catalyzed condensation of catechol with various propargylic carbonates leading regio- and stereoselectively to 2,3-dihydro-2-ylidene-1,4-benzodioxines.[35,36] Moreover, performing the condensation in the presence of a chiral palladium catalyst allowed a very easy access to enantiomerically enriched derivatives with enantioselectivies up to 97%.[37,38] The plausible mechanism for this cyclization process is shown in Scheme 1. The first step is the anti S_N2' attack of the palladium(0) complex on the propargylic carbonate affording the σ-allenyl palladium complex **A**,[39] in equilibrium with the η^3-propargyl palladium complex **B**. Selective attack of the monoanion of benzene-1,2-diol to the central carbon of this η^3-propargyl complex gave the σ-alkyl complex **C** in equilibrium with the carbenic complex **D**. This complex **D** was converted by intramolecular proton transfer to the σ-alkyl complex **E**, which is in equilibrium with the η^3-allyl complex **F**. Internal attack of the nucleophile on one of the termini of this η^3-allylic complex **F** afforded the corresponding benzodioxin derivatives **G** (attack 1) or **H** (attack 2), respectively. In order to apply this synthetic route in an asymmetric way, we

Keywords: Asymmetric catalysis; Palladium; Annulation; 2,3-Benzodioxin.
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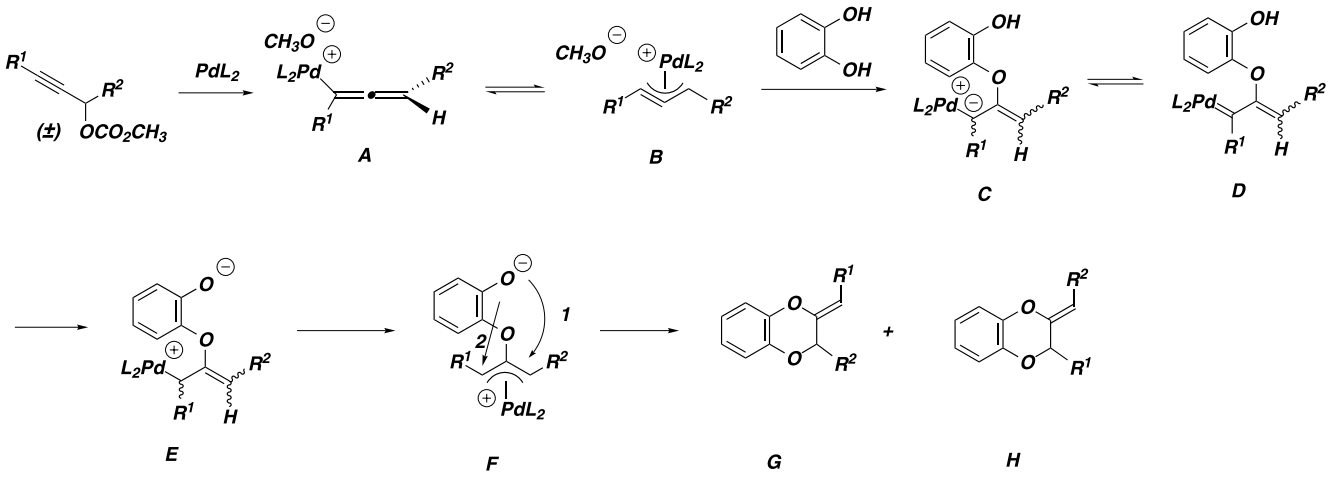


Scheme 1.

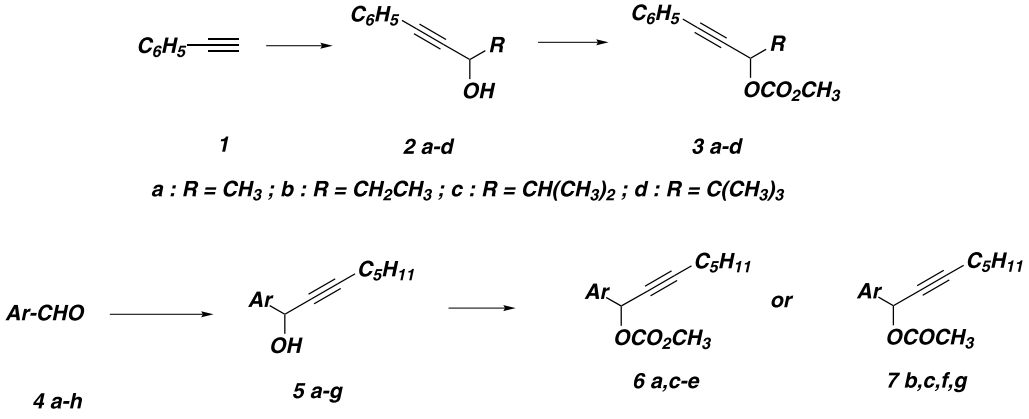
postulated that the enantioselective step was the attack of the nucleophile on the η^3-allyl intermediate. According to the results of the literature,[40] we expected that this η^3-allyl intermediate **E** must have two identical substituents at one of the termini of the η^3-allyl complex, allowing an easy racemization of this complex, or two identical substituents at the two termini of the η^3-allyl complex. We obtained effectively high enantioselectivities, up to 97%, in our palladium catalyzed annulation in these two cases.[38]

However we have also shown that the benzodioxin structures were obtained in quite high enantioselectivity even when the two substituents at the two termini of the η^3-allyl complex were completely different.[41] In this paper we describe in details our results in this field and propose a mechanism for this enantioselective heteroannulation.

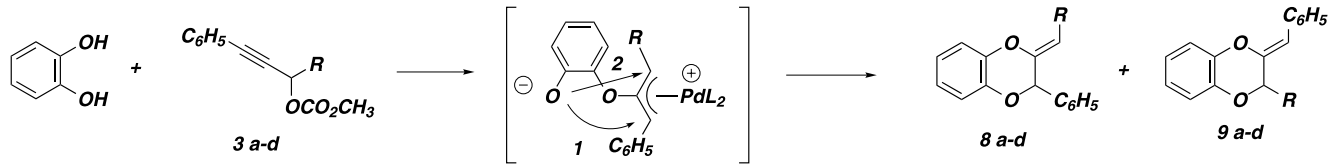
2. Results and discussion

In order to study the influence of both the alkyl and the aryl substituents on the regio-, stereo- and enantioselectivities of this cyclization, we prepared the corresponding propargylic carbonates **3a–d**, **6a**, **6c–e**, and acetates **7b**, **7c**, **7f**, and **7g** (Scheme 2). Reaction of propargylic alcohols **2a–d** with methyl chloroformate in CH_2Cl_2 in the presence of pyridine and dimethylaminopyridine gave the corresponding carbonates **3a–d** in quite good yields. Condensation of the lithium derivative of hept-1-yne with the corresponding aromatic aldehyde in THF afforded the propargylic alcohols **5a–g**. Reaction of methyl chloroformate with alcohols **5a**, and **5c–e**, in CH_2Cl_2 in the presence of pyridine and dimethylaminopyridine afforded the corresponding propargylic carbonates **6a**, and **6c–e**, in moderate chemical yields. Since the carbonates derived from propargylic alcohols **5b**, **5f**, and **5g**, were unstable, we prepared the corresponding acetates **7b**, **7f**, and **7g**, together with acetate **7c**.

The palladium-catalyzed condensation of carbonates **3a–d** with benzene-1,2-diol was conducted at rt in THF as the solvent, $Pd_2(dba)_3$ associated with dppb as the catalyst (Scheme 3). The results summarized in Table 1 showed that the cyclized products **8** and **9** were obtained in high chemical yields for R = CH_3 and CH_2CH_3 (Table 1, entries 1 and 3), in moderate yield for R = $CH(CH_3)_2$ (Table 1, entry 5), when no reaction occurred when the alkyl substituent was a *tert*-butyl group. For R = CH_3, the major regioisomer **9a** (95%)) occurred from the attack of the phenate on the termini of the η^3-allylpalladium complex bearing the alkyl substituent; this is in quite good agreement with the



Scheme 2.



Scheme 3.

Table 1. Palladium-catalyzed condensation of benzene-1,2-diol with propargylic carbonates **3a–c**[a]

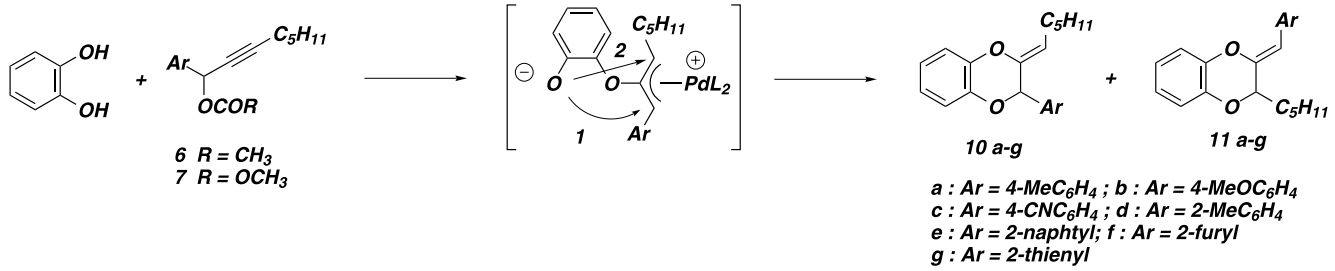
Entry	Carbonate **3**	Phosphine	Yield (%) of (**8**+**9**)[b]	% **8**/% **9**[c]	ee (%) **8**[d]	ee (%) **9**[d]
1	**3a**	dppb	90	5:95		
2	**3a**	(*R*)-Binap	70	20/80	nd	70
3	**3b**	dppb	90	14/86		
4	**3b**	(*R*)-Binap	95	32/68	nd	85
5	**3c**	dppb	66	60/40		
6	**3c**	(*R*)-Binap	70	68/32	93	83

[a] Conditions: [benzene-1,2-diol]/[**3**]/[$Pd_2(dba)_3$]/[phosphine]=48:40:1:4; 25 °C; THF as the solvent.
[b] After column chromatography.
[c] Determined by GC.
[d] Determined by HPLC using a chiral column Chiralpak AD (25 cm×4.6 mm) using hexane/2-propanol as the eluent; nd means that no separation could be observed whatever the conditions used.

previous published results.[36] Increasing the steric bulk of the substituent R and going from -CH_3 or -C_2H_5 to –$CH(CH_3)_2$ reversed the regioselectivity of the cyclization, the regioisomer **8c** being predominantly obtained in this last case. The stereochemistry at the double bond for the two regioisomers was *Z*, as shown using NOE NMR experiments. Irradiation of the signal of the methyl group for **9a** or of the proton on the carbon near the oxygen for **9b** and **9c** showed an enhancement of 6, 8, and 14% of the signal of the ethylenic proton; for compounds **8b** and **8c**, irradiation of the benzylic proton showed an enhancement of the signal of the ethylenic proton of 2 and 7%, respectively.

The use of (*R*)-Binap as the ligand gave quite similar chemical yields; the observed regioselectivity of the cyclization was lower using carbonates **3a** (Table 1, entry 2) and **3b** (Table 1, entry 4), when the reverse selectivity was also observed for **3c** (Table 1, entry 6). The enantioselectivities of the cyclized products **9a** and **9b** were 70 and 85%, respectively (Table 1, entries 2 and 4); unfortunately, the two enantiomers of the minor regioisomers **8a** and **8b** could not be separated, whatever the conditions used. The enantiomeric excesses of the two regioisomers **8c** and **9c** were 93 and 83% ee, respectively (Table 1, entry 6). We also studied the influence of the amount of carbonate used on the enantioselectivity in the cyclization of catechol and carbonate **3c**; we always obtained the same results using 1.2 or 2 equiv of carbonate **3c**.

Then we turned our attention on the influence of the nature of the aromatic ring on both the regio- and the enantioselectivity of the cyclization (Scheme 4). We have previously shown that propargylic carbonate **6a** and acetate **7b**, bearing an electron-donating group on the ring, afforded a 25:75 and 38:62 mixture of regioisomers **10a/11a** and **10b/11b** in 96 and 88% chemical yield, respectively (Table 2, entries 1 and 3), while carbonate **6c** or acetate **7c**, bearing an electron-withdrawing group, gave almost exclusively the regioisomer **11c** in 96 and 56% chemical yield, respectively (Table 2, entries 5 and 6); in the case of acetate **7c** the chemical yield was increased to 84% when the reaction was performed at reflux (Table 2, entry 7). Carbonates **6d** and **6e**, bearing a 2-methylphenyl and a naphthyl substituent, gave also a mixture of the two regioisomers **10d–e** and **11d–e** in quite good yields (65 and 93%, respectively), the last one being the major isomer (94 and 79%, respectively) (Table 2, entries 9 and 11). The palladium-catalyzed cyclisation of acetates **7f** and **7g** gave the corresponding 2-alkylidene-2,3-dihydro-1,4-benzodioxines in moderate



Scheme 4.

Table 2. Palladium-catalyzed condensation of benzene-1,2-diol with propargylic carbonates **6** and acetates **7**[a]

Entry	Propargylic compound	Phosphine	Yield (%) of **10**+**11**[b]	% **10**/% **11**[c]	ee (%) **10**[d]	ee (%) **11**[d]
1	**6a**	dppb	96	25/75		
2	**6a**	(*R*)-Binap	84	24/76	nd	86
3	**7b**	dppb	88	38/62		
4	**7b**	(*R*)-Binap	35	39/61	78	80
5	**6c**	dppb	96	0/100		
6	**7c**	dppb	56	0/100		
7	**7c**	dppb/reflux	84	0/100		
8	**7c**	(*R*)-Binap	49	10/90	52	85
9	**6d**	dppb	65	6/94		
10	**6d**	(*R*)-Binap	77	63/37	40	97
11	**6e**	dppb	93	21/79		
12	**6e**	(*R*)-Binap	74	42/58	76	64
13	**7f**	dppb	34	4/96		
14	**7f**	(*R*)-Binap	30	3/97	nd	85
15	**7g**	dppb	45	7/93		
16	**7g**	(*R*)-Binap	49	8/92	88	90

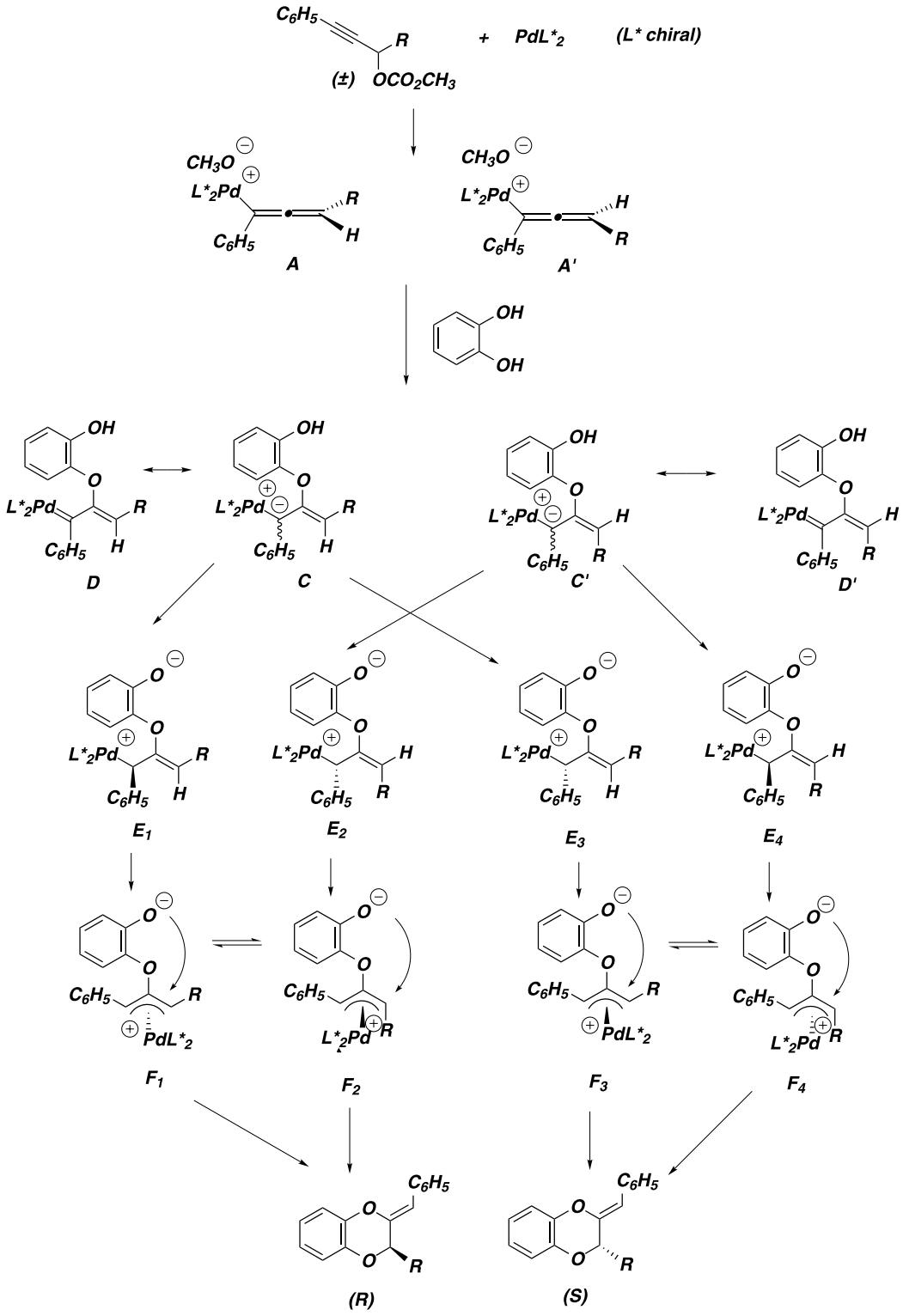
[a] Conditions: [benzene-1,2-diol]/[**3**]/[$Pd_2(dba)_3$]/[phosphine]=48:40:1:4; 25 °C; THF as the solvent.
[b] After column chromatography.
[c] Determined by GC.
[d] Determined by HPLC using a chiral column Chiralpak AD (25 cm×4.6 mm) using hexane/2-propanol as the eluent; nd means that no separation could be observed whatever the conditions used.

chemical yields (34 and 45%, respectively) (Table 2, entries 13 and 15); the major regioisomer was compound **11** (96% **11f** and 93% **11g**, respectively). As described previously, the attack occurred predominantly on the terminus of the π-allyl bearing the alkyl substituent, the regioisomer **11** being the predominant one; however the ratio of the two regioisomers depends strongly on the nature of the aryl ring. The different regioselectivities observed in the cyclization of carbonates **6a** and **6d** could be due probably to steric effects. It is to be noticed that the stereochemistry at the double bond for the two regioisomers was again *Z*, as shown using NOE NMR experiments.

When the cyclization was performed in the presence of (*R*)-Binap as the chiral ligand the ratios of the two regioisomers obtained were generally quite similar, except for carbonate **6d**, where a reversal of the regioselectivity was observed, the regioisomer **10d** being now the major one. In each case, the enantiomeric excess of the regioisomer **11** could be determined, when the separation of the enantiomers for regioisomers **10a** and **10f** was unsuccessful. Enantioselectivities in the range 80–90% ee were obtained when the phenyl ring is *para*-substituted with a methyl, a methoxy, or a cyano group, or when this ring was a heteoatomic one (Table 2, entries 2, 4, 8, 14, and 16); the presence of a methyl group at the *o*-position gave a higher ee (up to 97%) (Table 1, entry 10), whereas the naphtyl group lowered this enantioselectivity (64% ee) (Table 2, entry 12). The highest enantioselectivity obtained for regioisomer **10** was 88% using heterocyclic acetate **7g** (Table 2, entry 16); acetate **7b** and carbonate **6e** afforded the corresponding regioisomers **10b** and **10e** with 78 and 76% ee, respectively (Table 2, entries 4 and 12), whereas acetate **7c** and carbonate **6d** gave lower enantioselectivities (52 and 40% ee, respectively) (Table 2, entries 8 and 10).

All these results (one major isomer, high enantioselectivities for the two regioisomers) could not be explained using the model shown in Scheme 1. Since the palladium intermediate **F** bears two different substituents at the two termini of the η^3-allyl complex, the enantioselective step could not be the attack of the nucleophile on this η^3-allyl intermediate. A possible mechanism that could be invoked is the epimerization of this η^3-allyl complex **F** via a nucleophilic substitution of PdL_n by another PdL_n molecule with inversion of configuration. Although such a mechanism has been proposed by different groups in the case of intermolecular palladium-catalyzed alkylation reactions,[42–51] we postulated a quite different mechanism in our case (Scheme 5).

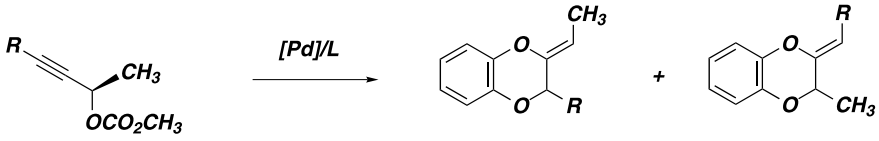
The first step is the formation of the two diastereoisomeric σ-allenyl complexes **A** and **A′** via a S_N2' mechanism from the propargylic carbonate and the palladium(0) complex. These σ-allenyl complexes are in equilibrium with the corresponding diastereoisomeric η^3-propargylic palladium complexes **B** and **B′** (not shown here). Attack of the monoanion of benzene-1,2-diol on the central atom of these σ-allenyl complexes gave the diastereoisomeric σ-alkyl complexes **C** and **C′** in equilibrium with the diastereoisomeric carbenic complexes **D** and **D′**. Since this anion attacked probably on the less hindered site, the major diastereoisomers will be isomers **C′** and **D′**. Protonation of these intermediates **C** and **C′** (or of the corresponding carbene complexes **D** and **D′**) gave four diastereoisomeric σ-alkyl complexes $\mathbf{E_1}$–$\mathbf{E_4}$, in equilibrium with the corresponding diastereoisomeric η^3-allyl complexes $\mathbf{F_1}$–$\mathbf{F_4}$. If interconversion occurred readily between complexes $\mathbf{F_1}$ and $\mathbf{F_2}$, and complexes $\mathbf{F_3}$ and $\mathbf{F_4}$, there is no possibility of interconversion between the diastereoisomeric complexes $\mathbf{F_1}$ and $\mathbf{F_3}$ or $\mathbf{F_4}$, and $\mathbf{F_2}$ and $\mathbf{F_3}$ or $\mathbf{F_4}$, since the two substituents at the two termini of the η^3-allyl are different. The attack of the nucleophile on the terminus of intermediates $\mathbf{F_1}$ or $\mathbf{F_2}$ bearing the alkyl group afforded the (*R*) cyclized product, whereas the (*S*) enantiomer was obtained from intermediates $\mathbf{F_3}$ and $\mathbf{F_4}$. We postulated that the enantioselection occurred during the step of protonation of the intermediates **C**,**C′** or **D**,**D′**, when the new chiral center was created. For example, the diastereoisomeric complexes $\mathbf{E_1}$ and $\mathbf{E_3}$, and so the η^3-allyl intermediates $\mathbf{F_1}$



Scheme 5.

and $\mathbf{F_3}$, are probably formed in quite different amounts, affording the corresponding cyclized enantiomers also in different amounts. It is the same scheme starting from complexes $\mathbf{E_2}$ and $\mathbf{E_4}$. The proposed mechanism is different from that of Yoshida and colleagues.[52,53] These authors observed a cascade chirality transfer process in the palladium-catalyzed reaction of substituted chiral propargylic carbonates with phenols, affording chiral cyclic carbonates in a highly enantiospecific manner. If their mechanism is a general one, the reaction of a racemic propargylic carbonate such as **3** or **6** will give the cyclized product as a racemate, even in the presence of a chiral ligand, since no racemization of the different intermediates could occur.

In order to have a deeper insight into our possible



(R)-12 R = H
(R)-3a R = C6H5

13 R = H
8a R = C6H5

14 R = H
9a R = C6H5

Scheme 6.

mechanism, we performed the palladium-cyclization of benzene-1,2-diol with two chiral propargylic carbonates (*R*)-**3a** and (*R*)-**12** in the presence of both an achiral ligand (dppb) and a chiral ligand [(*R*)- or (*S*)-Binap] (Scheme 6). Enantiopure carbonate (*R*)-**3a** was obtained from commercial (*R*)-but-3-yn-2-ol in the presence of methyl chloroformate, whereas (*R*)-4-phenylbut-3-yn-2-ol, obtained from (*R*)-but-3-yn-2-ol via a Sonogashira coupling,[54] afforded carbonate (*R*)-**12** under the same conditions. The results are summarized in Table 3. Reaction of enantiopure propargylic carbonate (*R*)-**12** with benzene-1,2-diol in the presence of $Pd_2(dba)_3$ associated with dppb afforded the cyclized products **13** and **14** in a 3:97 ratio (Table 3, entry1); however, compound **14** was obtained as a racemate. When the same condensation was performed in the presence of (*R*)-Binap, compound (−)-**14** was obtained with an enantioselectivity up to 60% (Table 3, entry 2). Using (*S*)-Binap as the chiral ligand afforded compound (+)-**14** with 62% ee (Table 3, entry 3). These results could be explained by a rapid racemization of the intermediate η^3-allyl palladium complex bearing in this case two hydrogens on one of the termini of the η^3-allyl system, the rate of the racemization being fast compared to the rate of the attack of the nucleophile.

The palladium-condensation of enantiopure propargylic carbonate (*R*)-**3a** with catechol in the presence of dppb gave the cyclized products **8a/9a** in a 4:96 ratio, compound **9a** being obtained with an enantioselectivity up to 15% in the (−) enantiomer (Table 3, entry 4). When the cyclization was performed in the presence of (*R*)-Binap, compound **9a** was obtained as the (+) enantiomer with an ee up to 45 and 49%, at 25 and 50 °C, respectively (Table 3, entries 5 and 7). The use of (*S*)-Binap afforded the (−) enantiomer with ee up to 77 and 75% at 25 and 50 °C, respectively (Table 3, entries 6 and 8). We have previously shown that the cyclization of racemic propargylic carbonate **3a** in the presence of (*R*)-Binap gave compound **9a** with 70% ee in the (−) enantiomer (Table 1, entry 2). These results clearly showed that the cyclization occurred via two different mechanisms. The first one is similar to the one proposed by Yoshida and colleagues,[52,53] with a transfer of chirality from the carbonate to the cyclized product; however since we observed only 15% of transfer of chirality, this mechanism is not the major one. The other mechanism is the one proposed in Scheme 5. Using (*R*)- or (*S*)-Binap as the chiral ligand gave, respectively, lower and higher ee in the cyclized product, indicating that (*S*)-Binap/(*R*)-**3a** is a match pair, and (*R*)-Binap/(*R*)-**3a** is a mismatch pair. This quite different behaviour between the two mechanisms could be due to the presence of a propargylic hydroxy function in the carbonates used by Yoshida et al,[52,53] function which could stabilize the η^3-propargylic and η^3-allylic intermediates by complexation, and so allowing the transfer of chirality.

3. Conclusion

In conclusion, we have extended the previous asymmetric palladium-catalyzed annulation of benzene-1,2-diol with racemic secondary propargylic carbonates and acetates bearing two different substituents (≠H), both on the sp carbon and on the carbon bearing the carbonate (or acetate) function. The high enantioselectivities observed could be explained by a highly stereospecific protonation of the

Table 3. Palladium-catalyzed condensation of benzene-1,2-diol with propargylic carbonates (*R*)-**12** and (*R*)-**3a**[a]

Entry	Propargylic carbonate	Phosphine	*T* (°C)	Yield (%) of cyclized products[b]	%**14**/%**13** or %**9a**/%**8a**[c]	ee (%) **9a** or **14**[d]
1	(*R*)-**12**	dppb	25	96	97/3 (**14/13**)	0
2	(*R*)-**12**	(*R*)-Binap	25	80	82/18 (**14/13**)	60 (−)[e]
3	(*R*)-**12**	(*S*)-Binap	5	60	83/17 (**14/13**)	62 (+)[f]
4	(*R*)-**3a**	dppb	25	74	96/4 (**9a/8a**)	15 (−)[g]
5	(*R*)-**3a**	(*R*)-Binap	25	32	90/10 (**9a/8a**)	45 (+)
6	(*R*)-**3a**	(*S*)-Binap	25	25	90/10 (**9a/8a**)	77 (−)
7	(*R*)-**3a**	(*R*)-Binap	50	50	85/15 (**9a/8a**)	49 (+)
8	(*R*)-**3a**	(*S*)-Binap	50	50	83/17 (**9a/8a**)	75 (−)

[a] Conditions: [benzene-1,2-diol]/[propargylic carbonate]/[$Pd_2(dba)_3$]/[phosphine]=48:40:1:4; THF as the solvent.
[b] After column chromatography.
[c] Determined by GC.
[d] Determined by HPLC using a chiral column Chiralpak AD (25 cm×4.6 mm) using hexane/2-propanol as the eluent; nd means that no separation could be observed irrespective of the conditions used.
[e] $[\alpha]_D^{25}=-22.5$ (*c* 1.1, CH_2Cl_2).
[f] $[\alpha]_D^{25}=+19.8$ (*c* 1.1, CH_2Cl_2).
[g] $[\alpha]_D^{25}=-3.6$ (*c* 1, diethyl ether).

intermediate palladium–carbene complexes. The results obtained in the palladium-catalyzed annulation of benzene-1,2-diol with methyl (*R*)-1-methyl-3-phenylpro-2-yn-1-yl carbonate in the presence of an achiral (dppb) or a chiral ligand [(*R*)- or (*S*)-Binap] are in agreement with such a mechanism. Extension of this work to other bisnucleophiles is actually in progress.

4. Experimental

General remarks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were obtained using a Bruker AM 300 spectrometer. Chemical shifts are reported with reference to $SiMe_4$ or $CDCl_3$ as an internal standard. Optical rotations were determined using a Perkin–Elmer 241 polarimeter. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60 F-254, Merck). Compounds were exposed under UV light (254 nm). Column chromatography was carried out using Merck silica gel 60 (40–63 μm). HPLC analysis was performed on a Shimatzu apparatus LC-6A combined with a UV detector SPD-6A. Reactions involving palladium complexes were carried out in a Schlenk tube under an argon atmosphere. Tetrahydrofuran was distilled from sodium/benzophenone and stored under argon.

Propargylic alcohols **2a**, **2b**, **2c**, **2d**, **5a**, **5b**, **5c**, propargylic carbonates **3a**, **6a**, **6c**, and propargylic acetates **7b** and **7c**, have already been described, as well as benzodioxins **10a–c**, and **11a–c**.[36]

4.1. Synthesis of propargylic alcohols

To a solution of hept-1-yne (726 mg, 7.4 mmol) in THF (10 mL) maintained at −30 °C was added a 2.5 M solution of *n*-butyllithium in hexane (3.2 mL, 7.8 mmol) and 1,3-dimethyltetahydro-2-[1]pyrimidinone (1.36 g, 10.4 mmol). After being stirred for 2 h at −30 °C, the aromatic aldehyde (7.4 mmol) was added, and the solution was stirred for 24 h at −10 °C. A saturated aqueous ammonium chloride solution (50 mL) was added, and the mixture was extracted with diethyl ether (3×50 mL). Evaporation of the solvent under reduced pressure gave a residue which was purified by flash-chromatography on silica using the appropriate eluent.

4.1.1. 1-(2-Methylphenyl)oct-2-yn-1-ol 5d. Yield 60%; oil; R_f 0.34 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=7.0 Hz, 3H, CH_3), 1.24–1.42 (m, 4H, CH_2), 1.48–1.58 (m, 2H, CH_2), 2.17 (d, J=5.5 Hz, 1H, OH), 2.24 (dt, J=7.0, 2.0 Hz, 2H, =C–CH_2), 2.43 (s, 3H, CH_3), 5.58 (dt, J=5.5, 2.0 Hz, 1H, CHO), 7.13–7.25 (m, 3H, H_{arom}), 7.62–7.67 (m, 1H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4, 19.2, 19.3, 22.6, 28.7, 31.5, 63.0, 80.1, 87.9, 126.5, 126.8, 128.6, 131.1, 136.3, 139.4. Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 82.94; H, 9.39.

4.1.2. 1-(2-Naphtyl)oct-2-yn-1-ol 5e. Yield 72%; oil; R_f 0.24 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=7.0 Hz, 3H, CH_3), 1.24–1.40 (m, 4H, CH_2), 1.51–1.61 (m, 2H, CH_2), 2.10 (s, 1H, OH), 2.25 (dt, J=7.2, 2.1 Hz, 2H, =C–CH_2), 5.50 (t, J=2.1 Hz, 1H, CHO), 7.46–7.49 (m, 2H, H_{arom}), 7.64 (dd, J=8.6, 1.7 Hz, 1H, H_{arom}), 7.81–7.86 (m, 3H, H_{arom}), 7.97 (s, 1H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.0, 18.8, 22.1, 28.2, 31.1, 64.9, 79.9, 88.0, 124.7, 125.3, 126.2, 127.6, 128.2, 128.3, 133.1, 133.2, 138.6. Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.40; H, 8.05.

4.1.3. 1-(2-Furyl)oct-2-yn-1-ol 5f. Yield 69%; oil; R_f 0.30 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J=7.1 Hz, 3H, CH_3), 1.24–1.44 (m, 4H, CH_2), 1.56 (tt, J=7.1, 7.1 Hz, 2H, CH_2), 2.28 (dt, J=7.1, 2.1 Hz, 2H, =C–CH_2), 2.38 (bs, 1H, OH), 5.40 (t, J=2.1 Hz, 1H, CHO), 6.36 (dd, J=3.2, 1.9 Hz, 1H, =CH–), 6.45 (bd, J=3.2 Hz, 1H, =CH–), 7.42 (dd, J=1.9, 1.0 Hz, 1H, =CH–),); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 19.1, 22.6, 28.5, 31.4, 58.7, 87.4, 107.8, 110.7, 115.0, 143.2, 154.1. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.58; H, 8.42.

4.1.4. 1-(2-Thienyl)oct-2-yn-1-ol 5g. Yield 29%; oil; R_f=0.50 (petroleum ether/ethyl acetate 8:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J=7.0 Hz, 3H, CH_3), 1.29–1.44 (m, 4H, CH_2), 1.55 (tt, J=7.0, 7.0 Hz, 2H, CH_2), 2.26 (dt, J=7.0, 1.9 Hz, 2H, =C–CH_2), 2.50 (bs, 1H, OH), 5.63 (t, J=1.9 Hz, 1H, CHO), 6.95 (dd, J=5.1, 3.6 Hz, 1H, =CH–), 7.14 (bd, J=3.6 Hz, 1H, =CH–), 7.26 (dd, J=5.1, 1.3 Hz, 1H, =CH–); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4, 19.1, 22.6, 28.5, 31.4, 60.8, 79.6, 87.6, 107.8, 125.7, 126.2, 127.1, 146.0.

4.1.5. Synthesis of (*R*)-4-phenylbut-3-yn-2-ol. A suspension of iodobenzene (971 mg, 4.76 mmol), CuI (36.2 mg, 0.2 mmol), $Pd(PPh_3)_2Cl_2$ (70.2 mg, 0.1 mmol), and Et_3N (1 mL, 7.14 mmol), in THF (7 mL) was stirred for 45 min at rt. A solution of (*R*)-but-3-yn-2-ol (350 mg, 5 mmol) in THF (5 mL) was then added dropwise, and the stirring was continued for 5 h at rt. After evaporation of the solvent, the residue was diluted with water (10 mL), and the mixture was extracted with diethyl ether (3×10 mL). The combined organic phases were washed with brine (5 mL), and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded an oil that was purified by flash-chromatography on silica to give 502 mg (yield 62%) of (*R*)-4-phenylbut-3-yn-2-ol. Oil; R_f 0.32 (petroleum ether/CH_2Cl_2 1:2); $[\alpha]_D^{25}=+43.6$ (*c* 0.8, diethyl ether) [Ref. 54 (*S*)-4-phenylbut-3-yn-2-ol: $[\alpha]_D^{25}=-44.8$ (*c* 1.0, Et_2O)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (d, J=6.0 Hz, 3H, CH_3), 2.05 (bs, 1H, OH), 4.68 (q, J=6.0 Hz, 1H, C*H*OH), 7.15–7.25 (m, 3H, H_{arom}), 7.33–7.40 (m, 2H, H_{arom}), in agreement with the literature data.[54]

4.2. Typical procedure for the preparation of propargylic carbonates

To a solution of propargylic alcohol **2a–d**, **6a**, or **6c–e** (17.8 mmol), dimethylaminopyridine (436 mg, 3.6 mmol), pyridine (6.7 mg, 71.4 mmol), in CH_2Cl_2 (40 mL) cooled at 0 °C wad added methyl chloroformate (5.6 mg, 71.4 mmol). After stirring for 24 h at rt, the reaction mixture was poured into a saturated aqueous copper sulfate solution (30 mL), and the aqueous phase was extracted with diethyl ether (3× 30 mL). Evaporation of the solvent under reduced pressure

afforded an oil that was purified by flash-chromatography on silica to give the corresponding propargylic carbonate.

4.2.1. 1-Ethyl-3-phenylprop-2-yn-1-yl methyl carbonate 3b. Yield 77%; oil; R_f 0.64 (petroleum ether/ethyl acetate 7:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, J=7.4 Hz, 3H, CH_3), 1.91 (dq, J=7.4, 6.4 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 5.42 (t, J=6.4 Hz, 1H, CHO), 7.24–7.29 (m, 3H, H_{arom}), 7.39–7.45 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 9.6, 28.6, 55.1, 69.9, 86.2, 86.5, 122.6, 128.7, 132.2, 129.1, 155.4. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.53; H, 6.47. Found: C, 71.29; H, 6.61.

4.2.2. 1-Isopropyl-3-phenylprop-2-yn-1-yl methyl carbonate 3c. Yield 84%; oil; R_f 0.73 (petroleum ether/ethyl acetate 7:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, J=6.8 Hz, 3H, CH_3), 1.15 (d, J=6.6 Hz, 3H, CH_3), 2.25 (m, 1H, C*H*Me_2), 3.82 (s, 3H, OCH_3), 5.30 (d, J=5.7 Hz, 1H, CHO), 7.22–7.29 (m, 3H, H_{arom}), 7.39–7.47 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.9, 18.6, 33.2, 55.3, 74.1, 84.9, 87.3, 122.7, 128.6, 129.0, 132.3, 155.6. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 6.98.

4.2.3. 1-*ter*-Butyl-3-phenylprop-2-yn-1-yl methyl carbonate 3d. Yield 86%; mp 71 °C; R_f 0.65 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (s, 9H, CH_3), 3.83 (s, 3H, OCH_3), 5.18 (s, 1H, CHO), 7.27–7.35 (m, 3H, H_{arom}), 7.41–7.49 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.8, 35.4, 55.2, 70.4, 85.6, 89.5, 122.5, 128.6, 129.2, 132.4, 155.6. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.35; H, 7.08.

4.2.4. Methyl 1-(2-methylphenyl)oct-2-yn-1-yl carbonate 6d. Yield 56%; oil; R_f 0.73 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J=7.0 Hz, 3H, CH_3), 1.27–1.37 (m, 4H, CH_2), 1.50–1.55 (m, 2H, CH_2), 2.35 (dt, J=7.1, 2.0 Hz, 2H, =C–CH_2), 2.43 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.42 (t, J=2.0 Hz, 1H, CHO), 7.16–7.26 (m, 3H, H_{arom}), 7.58–7.62 (m, 2H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 19.2, 19.4, 22.5, 28.4, 31.4, 55.4, 68.7, 78.7, 89.8, 126.6, 128.4, 129.3, 131.1, 135.6, 136.6, 155.4. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.52; H, 8.18.

4.2.5. Methyl 1-(2-naphtyl)oct-2-yn-1-yl carbonate 6e. Yield 46%; oil; R_f 0.56 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, J=7.0 Hz, 3H, CH_3), 1.31–1.49 (m, 4H, CH_2), 1.56–1.65 (m, 2H, CH_2), 2.35 (dt, J=7.0, 2.0 Hz, 2H, =C–CH_2), 3.83 (s, 3H, CH_3), 6.63 (t, J=2.0 Hz, 1H, CHO), 7.84–7.92 (m, 3H, H_{arom}), 7.77 (dd, J=8.7, 2.0 Hz, 1H, H_{arom}), 7.49–7.55 (m, 2H, H_{arom}), 8.12 (s, 1H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4, 19.3, 22.6, 28.5, 31.5, 55.3, 70.9, 78.2, 90.2, 125.5, 126.8, 127.1, 127.6, 128.1, 128.8, 129.0, 133.5, 134.0, 135.0, 155.5. HRMS (EI) calcd for $C_{20}H_{23}O_3$ $[M+H]^+$: 311.1647. Found: 311.1646.

4.2.6. Methyl (*R*)-1-methylprop-2-yn-1-yl carbonate. Yield 82%; oil; R_f 0.72 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{25}=+109$ (c 1, diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (d, J=6.7 Hz, 3H, CH_3), 3.83 (s, 3H, CH_3), 5.57 (q, J=6.7 Hz, 1H, C*H*O), 7.26–7.36 (m, 3H, H_{arom}), 7.42–7.50 (m, 2H, H_{arom}), in agreement with the literature data.[36]

4.2.7. Methyl (*R*)-1-methyl-3-phenylprop-2-yn-1-yl carbonate. Yield 91%; oil; R_f 0.56 (petroleum ether/ethyl acetate 6:1); $[\alpha]_D^{25}=+167.4$ (c 1, diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (d, J=6.7 Hz, 3H, CH_3), 3.83 (s, 3H, CH_3), 5.57 (q, J=6.7 Hz, 1H, C*H*O), 7.26–7.36 (m, 3H, H_{arom}), 7.42–7.50 (m, 2H, H_{arom}), in agreement with the literature data.[36]

4.3. Typical procedure for the preparation of propargylic acetates

To a solution of propargylic alcohol (1.6 mmol), and pyridine (514 mg, 6.5 mmol), in CH_2Cl_2 (10 mL) cooled at 0 °C wad added acetyl chloride (521 mg, 6.5 mmol). After stirring for 24 h at rt, the mixture was poured into a saturated aqueous copper sulfate solution (10 mL), and the aqueous phase was extracted with diethyl ether (3×10 mL). Evaporation of the solvent under reduced pressure afforded an oil that was purified by flash-chromatography on silica to give the corresponding propargylic acetate.

4.3.1. 1-(2-Furyl)oct-2-yn-1-yl acetate 7f. Yield 93%; oil; R_f 0.56 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=7.2 Hz, 3H, CH_3), 1.31–1.38 (m, 4H, CH_2), 1.55 (m, 2H, CH_2), 2.10 (s, 3H, $COCH_3$), 2.26 (dt, J=7.2, 2.1 Hz, 2H, =C–CH_2), 6.36 (dd, J=3.2, 1.7 Hz, 1H, =CH–), 6.49–6.52 (m, 2H, =CH-, CHO), 7.41 (m, 1H, =CH–). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 19.1, 21.3, 22.5, 28.3, 31.4, 59.3, 74.6, 88.0, 110.2, 110.8, 143.7, 150.6, 170.0. Anal. Calcd for $C_{14}H_{19}O_3$ $[M+H]^+$ 235.1334. Found: 235.1335.

4.3.2. 1-(2-Thienyl)oct-2-yn-1-yl acetate 7g. Yield 82%; oil; R_f 0.50 (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=7.0 Hz, 3H, CH_3), 1.30–1.40 (m, 4H, CH_2), 1.53 (tt, J=7.1, 7.1 Hz, 2H, CH_2), 2.03 (s, 3H, $COCH_3$), 2.25 (dt, J=7.1, 1.9 Hz, 2H, =C–CH_2), 6.67 (t, J=1.9 Hz, 1H, CHO), 6.93 (dd, J=5.1, 3.6 Hz, 1H, =CH–), 7.19 (bd, J=3.6 Hz, 1H, =CH–), 7.27 (dd, J=5.1, 1.1 Hz, 1H, =CH–). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 19.1, 21.3, 22.5, 28.4, 31.4, 61.4, 76.8, 88.2, 127.0, 127.1, 127.8, 141.3, 169.9. Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 67.44; H, 7.18.

4.4. Typical procedure for the palladium-catalyzed annulation reaction

A mixture of $Pd_2(dba)_3$ (20.8 mg, 2.2×10^{-2} mmol), and diphosphine (9.1×10^{-2} mmol) in THF (7 mL) was stirred under a nitrogen atmosphere at rt for 30 min. This catalyst solution was added to a mixture of benzene-1,2-diol (100 mg, 0.9 mmol) and the corresponding propargylic carbonate (1.1 mmol), or propargylic acetate (1.1 mmol) in the presence of triethylamine (269 mg, 2.6 mmol). The resulting solution was stirred at rt for 24 h. The solvent was evaporated and the residue was chromatographed over silica with petroleum ether/ethyl acetate as the eluent to afford the corresponding 2,3-dihydro-1,4-benzodioxine.

4.4.1. (3*Z*)-2-Ethylidene-3-phenyl-2,3-dihydro-1,4-benzodioxine (8a) and (2*Z*)-2-benzylidene-3-methyl-2,3-dihydro-1,4-benzodioxine (9a). R_f 0.63 (petroleum ether/ethyl acetate 40:1).

For **8a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, J=6.8 Hz, 3H, CH_3), 4.54 (q, J=6.8 Hz, 1H, =CH–), 5.50 (s, 1H, OCH), 6.89–7.86 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.0, 76.4, 105.4, 120.8, 122.0, 126.4, 127.1, 131.3, 132.9, 133.5, 138.9, 146.7, 147.5, 151.6.

For **9a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (d, J=6.5 Hz, 3H, CH_3), 4.72 (q, J=6.5 Hz, 1H, OCH), 5.72 (s, 1H, =CH–), 6.89–7.86 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.2, 74.9, 109.7, 120.8, 122.0, 126.4, 127.1, 131.3, 132.9, 133.5, 138.9, 146.7, 147.5, 151.6. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.61; H, 5.99.

4.4.2. (2*Z*)-2-Phenyl-3-propylidene-2,3-dihydro-1,4-benzodioxine (8b) and (2*Z*)-2-benzylidene-3-ethyl-2,3-dihydro-1,4-benzodioxine (9b). R_f 0.68 (petroleum ether/ethyl acetate 40:1).

For **8b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, J=7.5 Hz, 3H, CH_3), 2.32 (m, 2H, CH_2), 4.50 (m, 1H, =CH–), 5.49 (s, 1H, OCH), 6.90–7.90 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4, 18.0, 76.4, 112.7, 117.9, 122.3, 122.4, 128.0, 128.7, 128.8, 129.3, 137.2, 143.8, 145.3, 146.0.

For **9b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, J=7.3 Hz, 3H, CH_3), 1.91 (m, 2H, CH_2), 4.50 (m, 1H, OCH), 5.64 (s, 1H, =CH–), 6.90–7.90 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 10.4, 25.0, 76.6, 106.8, 116.6, 118.1, 122.2, 123.1, 127.2, 128.7, 129.3, 134.8, 142.5, 142.6, 146.0. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.13; H, 6.34.

4.4.3. (2*Z*)-2-(2-Methylpropylidene)-3-phenyl-2,3-dihydro-1,4-benzodioxine (8c) and (2*Z*)-2-benzylidene-3-isopropyl-2,3-dihydro-1,4-benzodioxine (9c). R_f=0.80 (petroleum ether/ethyl acetate 40:1).

For **8c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, J=4.9 Hz, 6H, CH_3), 2.91 (m, 1H, C*H*Me$_2$), 4.27 (d, J=9.0 Hz, 1H, =CH–), 5.33 (s, 1H, OCH), 6.72–7.65 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 23.2, 23.4, 24.6, 76.3, 118.4, 116.7, 118.0, 118.4, 122.3, 122.4, 128.0, 128.8, 134.8, 137.3, 143.7, 143.9.

For **9c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, J=6.6 Hz, 6H, CH_3), 1.95 (m, 1H, CH_2), 4.04 (d, J=9.8 Hz, 1H, OCH), 5.46 (s, 1H, =CH–), 6.72–7.65 (m, 9H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.9, 19.0, 29.2, 81.6, 108.4, 116.6, 118.1, 122.1, 123.2, 127.2, 128.7, 129.3, 142.2, 142.8, 143.3, 144.7. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.06; H, 6.78.

4.4.4. (2*Z*)-2-Hexylidene-3-(2-methylphenyl)-2,3-dihydro-1,4-benzodioxine (10d) and (2*Z*)-2-(2-methylbenzylidene)-3-pentyl-2,3-dihydro-1,4-benzodioxine (11d). R_f, 0.46 for **10d** and 0.38 for **11d** (petroleum ether/ethyl acetate 60:1).

For **10d**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (t, J=6.8 Hz, 3H, CH_3), 1.19–1.31 (m, 6H, CH_2), 2.08–2.12 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 4.16 (t, J=7.3 Hz, 1H, =CH–), 5.45 (s, 1H, OCH), 6.77–7.22 (m, 7H, H_{arom}), 7.37–7.40 (m, 1H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4, 20.7, 23.0, 25.6, 31.8, 31.9, 75.4, 104.3, 116.8, 118.0, 122.3, 122.9, 126.2, 127.3, 129.9, 130.4, 133.1, 136.3, 142.5, 142.6, 142.9.

For **11d**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J=6.8 Hz, 3H, CH_3), 1.19–1.31 (m, 6H, CH_2), 1.66–1.81 (m, 2H, CH_2), 2.26 (s, 3H, CH_3), 4.50 (t, J=7.3 Hz, 1H, OCH), 5.63 (s, 1H, =CH–), 6.77–7.22 (m, 7H, H_{arom}), 7.79 (d, J=7.6 Hz, 1H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5, 19.7, 22.8, 24.5, 29.3, 74.0, 110.4, 116.7, 117.9, 122.2, 122.4, 126.7, 128.0, 128.9, 130.8, 135.2, 136.7, 143.4, 144.5, 145.5. Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.56; H, 8.02.

4.4.5. (2*Z*)-2-Hexylidene-3-(2-naphthyl)-2,3-dihydro-1,4-benzodioxine (10e) and (2*Z*)-2-(2-naphthylmethylene)-3-pentyl-2,3-dihydro-1,4-benzodioxine (11e). R_f 0.74 (petroleum ether/ethyl acetate 40:1).

For **10e**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=6.8 Hz, 3H, CH_3), 1.46–1.65 (m, 6H, CH_2), 2.28 (dt, J=7.2, 7.2 Hz, 2H, CH_2), 4.53 (t, J=7.2 Hz, 1H, =CH–), 5.64 (s, 1H, OCH), 6.85–8.13 (m, 11H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 22.5, 22.6, 24.2, 29.0, 76.1, 111.1, 116.4, 117.6, 122.0, 122.1, 125.3, 126.3, 126.4, 127.1, 127.7, 128.3, 133.1, 133.2, 134.4, 143.0, 143.4, 145.2.

For **11e**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=6.8 Hz, 3H, CH_3), 1.25–1.44 (m, 6H, CH_2), 1.75–1.95 (m, 2H, CH_2), 4.61 (dd, J=7.9, 6.2 Hz, 1H, OCH), 5.77 (s, 1H, =CH–), 6.85–8.13 (m, 11H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 22.6, 25.2, 31.5, 31.6, 74.9, 106.4, 116.3, 117.8, 121.9, 122.8, 125.8, 126.1, 127.2, 127.6, 127.8, 127.9, 128.1, 132.1, 132.4, 133.6, 142.2, 142.3, 146.3. Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.29; H, 6.98.

4.4.6. (3*Z*)-2-(2-Furyl)-3-hexylidene-2,3-dihydro-1,4-benzodioxine (10f) and (2*Z*)-2-(2-furylmethylene)-3-pentyl-2,3-dihydro-1,4-benzodioxine (11f). R_f 0.5 (petroleum ether/ethyl acetate 60:1+0.5% Et_3N).

For **10f**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J=6.8 Hz, 3H, CH_3), 1.27–1.36 (m, 4H, CH_2), 1.41–1.58 (m, 2H, CH_2), 1.69–1.86 (m, 2H, CH_2), 4.74 (t, J=7.5 Hz, 1H, =CH–), 5.54 (s, 1H, OCH), 6.45–6.47 (m, 1H, H_{arom}), 6.85 (d, J=3.2 Hz, 1H, H_{arom}), 6.92–7.12 (m, 4H, H_{arom}), 7.35–7.36 (m, 1H, H_{arom}).

For **11f**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J=6.8 Hz, 3H, CH_3), 1.27–1.36 (m, 4H, CH_2), 1.41–1.58 (m, 2H, CH_2), 1.69–1.86 (m, 2H, CH_2), 4.49 (dd, J=8.1, 6.0 Hz, 1H, OCH), 5.68 (s, 1H, =CH–), 6.45–6.47 (m, 1H, H_{arom}), 6.85 (d, J=3.2 Hz, 1H, H_{arom}), 6.92–7.12 (m, 4H, H_{arom}), 7.35–7.36 (m, 1H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4, 22.9, 25.4, 31.7, 31.8, 74.3, 96.8, 109.9, 112.1, 116.6, 118.1, 122.3, 123.2, 141.2, 142.5, 142.7, 145.1, 150.0.

HRMS (EI) calcd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1491. Found: 285.1493.

4.4.7. (2*Z*)-2-Hexylidene-3-(2-thienyl)-2,3-dihydro-1,4-benzodioxine (10g) and (3*Z*)-2-pentyl-3-(2-thienylmethylene)-2,3-dihydro-1,4-benzodioxine (11g). R_f 0.46 (petroleum ether/ethyl acetate 60:1+0.5% Et_3N).

For **10g**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J=6.8 Hz, 3H, CH_3), 1.10–1.18 (m, 4H, CH_2), 1.32–1.55 (m, 2H, CH_2), 1.63–1.85 (m, 2H, CH_2), 4.70 (t, J=7.4 Hz, 1H, =CH–), 5.66 (s, 1H, OCH), 6.84–6.93 (m, 4H, H_{arom}), 7.03 (d, J=3.6 Hz, 1H, H_{arom}), 7.05–7.10 (m, 1H, H_{arom}), 7.18–7.21 (m, 1H, H_{arom}).

For **11g**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J=6.8 Hz, 3H, CH_3), 1.24–1.26 (m, 4H, CH_2), 1.32–1.55 (m, 2H, CH_2), 1.63–1.85 (m, 2H, CH_2), 4.45 (dd, J=7.9, 6.2 Hz, 1H, OCH), 5.87 (s, 1H, =CH–), 6.84–6.93 (m, 4H, H_{arom}), 7.03 (d, J=3.6 Hz, 1H, H_{arom}), 7.05–7.10 (m, 1H, H_{arom}), 7.18–7.21 (m, 1H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.8, 25.3, 27.8, 34.2, 34.3, 76.8, 103.7, 119.2, 120.5, 124.7, 125.6, 128.5, 129.2, 129.3, 139.6, 144.9, 145.1, 146.8. Anal. Calcd for $C_{18}H_{20}O_2S$: C, 71.97; H, 6.71. Found: C, 71.81; H, 6.58.

4.5. Separation of the enantiomers

The enantiomeric excesses of the obtained compounds were determined by HPLC on a chiral column Chiralpak AD (25 cm×4.6 mm).

8a/9a (hexane/2-propanol 98:2): **8a**: non-separated; **9a**: R_t=14.5 min for the (−) enantiomer and 16.2 min for the (+) enantiomer.

8b/9b (hexane/2-propanol 98:2): **8b**: non-separated; **9b**: R_t=15.3 and 17.8 min.

8c/9c (hexane/2-propanol 99:1): **8c**: R_t=10.2 and 20.9 min; **9c**: R_t=32.4 and 35.0 min.

10a/11a (hexane/2-propanol 96:4): **10a**: non-separated; **11a**: R_t=44.8 and 51.7 min.

10b/11b (hexane/2-propanol 96:4): **10b**: R_t=15.6 and 19.8 min; **11b**: R_t=11.8 and 12.3 min.

10c/11c (hexane/2-propanol 96:4): **10c**: R_t=27.7 and 32.6 min; **11c**: R_t=15.8 and 17.4 min.

10d/11d (hexane): **10d**: R_t=24.9 and 32.1 min; **11d**: R_t= 13.8 and 14.8 min.

10e/11e (hexane/2-propanol, 150:1): **10e**: R_t=32.0 and 42.9 min; **11e**: R_t=19.7 and 20.4 min.

10f/11f (hexane/2-propanol 98:2) **10f**: non-separated; **11g**: R_t=13.4 and 14.6 min.

10g/11g (hexane): **10g**: R_t=15.3 and 16.2 min; **11g**: R_t= 29.4 and 38.7 min.

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Highly strained tricyclic molecules: tricyclo[p.q.0.0^{1,f}]alkanes and phosphatricyclo[m.1.0.0^{1,3}]alkanes

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Abstract—We theoretically investigate ring strains of tricyclic molecules or tricyclo[p.q.0.0^{1,f}]alkanes by calculating the strain energies as heat of the homodesmotic reactions. The strain energies are well correlated with the deformation from the tetrahedral configuration of the C_1 atom. We theoretically design less strained tricyclic molecules by replacing some carbon atoms with phosphorus atoms.

1. Introduction

More than 100 years ago, Van't Hoff and LeBel proposed the tetrahedral model to understand the three-dimensional structure of organic compounds. Deviation of bond angles from the tetrahedral angle (Baeyer strain) is expected to have significant effects on chemical and physical properties of molecules. In fact, small ring molecules have been investigated extensively. Among them are included monocyclic molecules (e.g., cyclopropane **1**), and polycyclic molecules containing one fusion bond (e.g., bicyclo[1.1.0]-butane[1] **2** and [1.1.1]propellane[2] **3**). Tricyclo[2.1.0.0^{1,3}]-pentane[3] **4** is an isomer of **3** and a member of difusotricyclic molecules (Fig. 1) after the Gund terminology,[4] where tricyclic systems share a common vertex (C_1) and two fusion bonds. There are a central ring and two side rings in the difusotricyclic molecules. Difusotricyclic molecules composed of small rings have been rarely documented so far. Investigation of difusotricyclic molecules is important to advance the chemistry of small ring molecules. There are interesting questions about the effects of the peculiar features of the difusotricyclic geometry on the strain. There is torsion from the tetrahedral configuration (Scheme 1) giving rise to the Pitzer strain. The dihedral angle ϕ is used for the parameter of the torsion (the torsion angle $=90°-\phi$). Widening of a bond angle θ from the tetrahedral angle 109.5° (Scheme 2)[5] gives rise to the Baeyer strain.

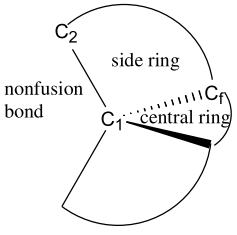
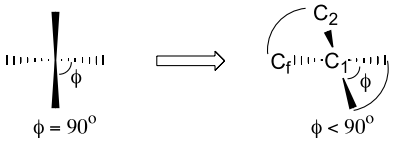
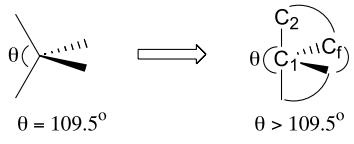


Figure 1. Difusotricyclic molecules, tricyclo[p.q.0.0^{1,f}]alkanes.



Scheme 1.



Scheme 2.

In this paper, we calculate the strain energies of some difusotricyclic hydrocarbons and show the relations of the strain energies with the dihedral angle ϕ, and the bond angle θ. We theoretically design less strained difusotricyclic molecules by replacing some carbon atoms with hetero-atoms to facilitate synthesis, isolation and characterization.

Keywords: Tricyclic molecules; Tricyclic hydrocarbon; Tricyclic phosphorus molecules; Strain energy.
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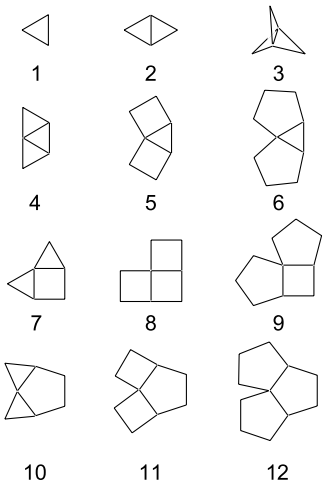
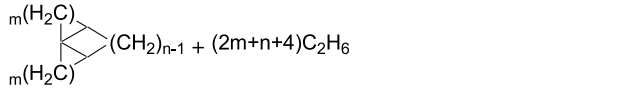
Table 1. Geometrical parameters of **4**–**12** calculated at the B3LYP/6-31G*

	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
C_1C_2 (Å)	1.485, 1.489	1.520	1.519	1.470	1.533	1.534	1.481	1.541	1.544
C_1C_f (Å)	1.456, 1.515	1.530	1.522	1.521	1.571	1.576	1.487	1.563	1.580
θ (°)	197.7	145.4	123.9	177.5	131.8	117.4	158.7	128.1	113.4
ϕ (°)	39.5, 49.1	63.5	77.6	46.7	64.6	80.9	45.2	67.6	83.0



2. Method

The calculations were carried out by using the Gaussian program package.[6] The geometries were optimized at the RHF/6-31G* and the B3LYP/6-31G* levels. The final energies of the B3LYP/6-31G* optimized structures were refined at the Gaussian-3 level, which has been recently proposed and proved to be very accurate and effective.[7] The strain energies were estimated by the homodesmotic reaction (Eq. 1).[8]



(1)

We developed[9] and applied[10] the bond model method to analyze the electronic structures of molecules. The single Slater determinant Ψ for the electronic structure is expanded into electron configurations:

$$\Psi = C_G\Phi_G + \sum C_T\Phi_T + \cdots$$

In the ground configuration (Φ_G), a pair of electrons occupies a bonding orbital of a chemical bond (a nonbonding orbital of an unshared electron pair). Electron delocalization is expressed by mixing an electron-transferred configuration (Φ_T), where an electron shifts from a bonding orbital of one bond to an antibonding orbital of another. The bonding an antibonding orbitals ϕ_i and ϕ_i* of the ith bond are linear combinations of hybrid atomic orbitals χ_{ia} and χ_{ib} on bonded atoms a and b:

$$\phi_i = c_{ia}\chi_{ia} + c_{ib}\chi_{ib}$$

$$\phi_i^* = c_{ia}^*\chi_{ia} + c_{ib}^*\chi_{ib}$$

We use the hybrid orbitals obtained by orthogonalizing the atomic basis functions on each atom. The bond orbitals are obtained by the diagonalization of the 2×2 Fock matrices of the basis of the hybrid orbitals. The hybrid atomic orbitals and therefore the bond orbitals are optimized to give the maximum value of the coefficient (C_G) of the ground configuration. To estimate the interactions between the bond orbitals i and j, we used the interbond energy IBE, which was defined as

$$\mathrm{IBE}_{ij} = P_{ij}(H_{ij} + F_{ij})$$

where P_{ij}, H_{ij}, and F_{ij} are the elements of the density, Fock, and core Hamiltonian matrices, respectively.

3. Results and discussion

3.1. Tricyclo[p.q.0.0^{1,f}]alkanes

The optimised geometry of **4** has no symmetry (C_1).† Selected geometrical parameters of **4**,[3] **5**, **6**, **7**,[3c,d] **8**,[11] **9**,[12] **10**,[13] **11**, and **12**[14] are listed in Table 1 and Figure 2. The lengths of the fusion bonds (C_1C_3, C_1C_4 = 1.456 Å, 1.515 Å) of **4** are different from each other, in agreement with the results of the calculations at the MP2/6-31G* by Wiberg et al.[3a] One is shorter than that of cyclopropane (1.509 Å) whereas the other is longer. The fusion bonds (C_1C_f) of **8** and **12** are longer than the CC bonds of cyclobutane (1.554 Å) and cyclopentane (1.537–1.557 Å), respectively. The nonfusion bonds (e.g., C_1C_2) around the central carbon atom (C_1) are shorter than the bonds in the corresponding monocyclic molecules. The C_2C_3 bonds of the three-membered side ring are longer (1.523, 1.539 Å in **4**, 1.537 Å in **7**, and 1.539 Å in **10**).

The bond angle θ is widened with the decreases in the sizes of the central rings (**10**(158.7°)<**7**(177.5°)<**4**(197.7°)) and the side rings (**6**(123.9°)<**5**(145.4°)<**4**(197.7°)), as

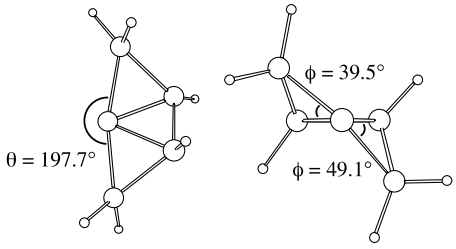


Figure 2. The structure of **4** optimized at the B3LYP/6-31G*.

† The C_2 geometry is a transition state. The energy difference is very small (0.06 kcal/mol) between the C_1 and C_2 geometries.

expected. The torsion increases as the size of the side rings is small. The central rings affect the torsion to a lesser extent. In fact, the dihedral angles (ϕ in Scheme 1) are 39.5–49.1° in **4**, **7** and **10** with the three-membered side rings, 63.5–67.6° in **5**, **8** and **11** with the four-membered side rings, and 77.6–83.0° in **6**, **9** and **12** with the five-membered side rings. The values for each size of the side rings also show that the dihedral angles ϕ change by less than 10° from one another with the size of the central rings.

The strain energies decrease with the increasing size of the rings as expected. We estimated the effects of the difusotricyclic geometry on the strain by comparing the strain energies with the sums of the strain energies (27.4 kcal/mol, 26.1 kcal/mol, and 6.4 kcal/mol) of the composite rings (cyclopropane, cyclobutane, and cyclopentane) as the references. The difusotricyclic geometry significantly strains the molecules (**4**, **7**, **10**) with the three-membered side rings as expected. The difference of the strain energy from the reference energy is of sizable positive values. To our surprise, the difference energies are negative (−6.5 kcal/mol for **6**, −9.6 kcal/mol for **9**, and −6.1 kcal/mol for **12**) for the five-membered side rings.

There is correlation of the calculated strain energy with the dihedral angle ϕ from the tetrahedral configuration of the central carbon (Fig. 3) while the correlation with the bond angle θ (Scheme 2) between the nonfusion bonds is less remarkable (Fig. 4). We studied the origin of the Pitzer strain by using methane as a model. The IBE values (Fig. 5) show that the exchange repulsion significantly increases between the σ_1 and σ_2 bonds closer to each other and between the σ_1 and σ_3 bonds, more than decrease between the σ_1 and σ_4 bonds farther away from each other. The $\sigma_1-\sigma_2$ repulsion corresponds to that between the geminal C_1C_2 and C_1C_f bonds in the difusotricyclic molecules (Scheme 1). The IBE values for the repulsion were calculated and found

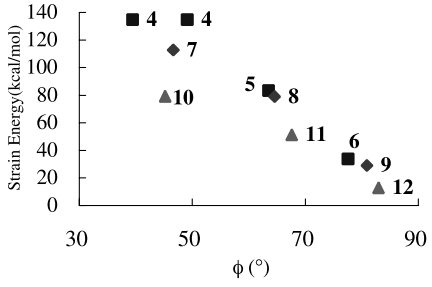


Figure 3. The dependence of the strain energies on the dihedral angles ϕ. There are two values for **4** due to the unsymmetrical geometry.

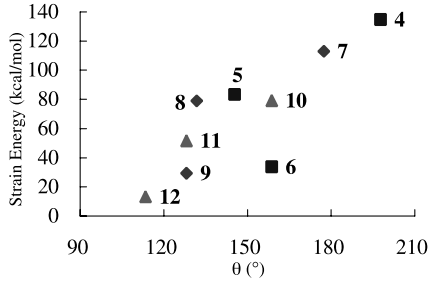


Figure 4. The dependence of the strain energies on the bond angles θ.

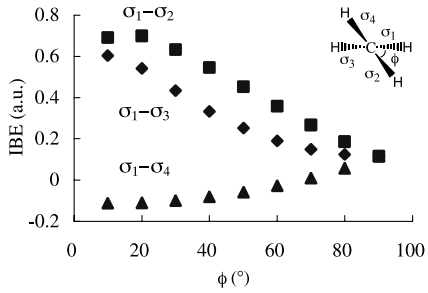


Figure 5. The dependence of interbond energies on the dihedral angles ϕ in methane.

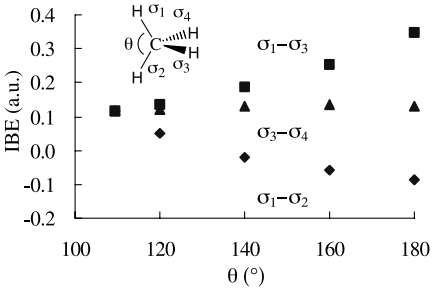


Figure 6. The dependence of interbond energies on the bond angles θ in methane.

to significantly increase with the torsion: **6**(0.2689 au)< **5**(0.4102 au)<**4**(1.2233 au). The geminal repulsions are 0.3026 au[15] in cyclopentane, 0.3504 au in cyclobutane, and 0.9558 au in cyclopropane. The repulsion is stronger in **4** than in cyclopropane and weaker in **6** than in cyclopentane. This can account for the difference of the strain energy from the reference energy (Table 2), that is, the remarkable increment (52.4 kcal/mol) of the strain in **4**, and the decrement (−6.5 kcal/mol) in **6**.

The change in the IBE values with a bond angle in methane is shown in Figure 6. As the bond angle between the σ_1 and σ_2 bonds is widened, the $\sigma_1-\sigma_3$ repulsion increases but the $\sigma_1-\sigma_2$ repulsion decreases as much. This suggests that the bond angle θ is less correlated with the strain energy. The additional (positive or negative) strain by the difusotricyclic geometry is suggested to come mainly from the torsion or the change in the dihedral angle ϕ rather than from the bond angle θ.

The strain energy of **4** (134.7 kcal/mol) in good agreement with the result (137.2 kcal/mol) calculated at the MP2/6-31G* by Wiberg et al.[3d] is higher than **3** (100.4 kcal/mol).[‡] The fusion bonds of **4** (1.456, 1.515 Å) are shorter than the fusion bond of **3** (1.579 Å).[§] One is shorter than that of **2** (1.494 Å), whereas the other is longer.

3.2. Phosphatricyclo[m.1.0.0^{1,3}]alkanes

We theoretically design less strained difusotricyclic molecules by replacing some carbon atoms with

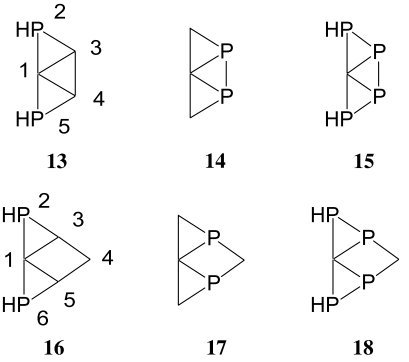
[‡] Experimental and theoretical strain energies of **3** is 98 kcal/mol[2d] and 103 kcal/mol (RHF/6-31G*)[2b] by Wiberg et al.

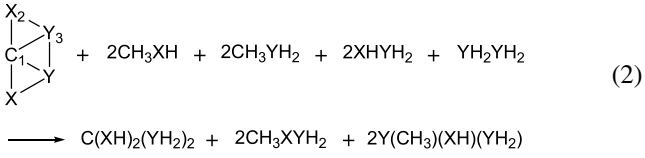
[§] The experimental lengths of the fusion bond of **3** is 1.60 Å by Wiberg et al.[2c]

Table 2. Strain energy (kcal/mol) calculated at the G3B3//B3LYP/6-31G*

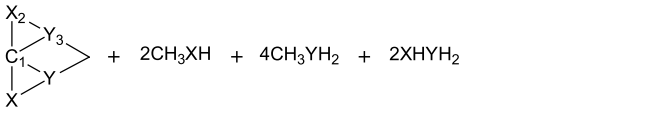
	4	5	6	7	8	9	10	11	12
Strain energies	134.7	83.4	33.8	112.9	78.9	29.3	79.2	51.5	13.1
Reference energies	82.3	79.6	40.3	81.0	78.3	38.9	61.3	58.6	19.2
Difference energies	(+52.4)	(+3.8)	(−6.5)	(+31.9)	(+0.6)	(−9.6)	(+17.9)	(−7.1)	(−6.1)

heteroatoms to facilitate synthesis, isolation and characterization. Phosphirane $(CH_2)_2PH$ has lower strain energy (20.2–24.4 kcal/mol) than cyclopropane (25.8–30.2 kcal/mol).[10b,w,16] The hybrid orbital on P for the ring bond has high p-character since the lone pair orbital on P has high s-character. According to the geminal delocalization theory for the ring strain, the $\sigma-\sigma^*$ interaction between the geminal σ ring bonds are less antibonding or more bonding due to the high p-character.[16] The geminal interaction reduces the strain of the P containing three-membered rings. We expected that strains should be relaxed by introducing phosphorus atoms in the three-membered rings of **4** and **7**. Among them are included 2,5-diphosphatricyclo[2.1.0.0^{1,3}]pentane **13**, 3,4-diphosphatricyclo-[2.1.0.0^{1,3}]pentane **14**, and 2,3,4,5-tetraphospha[2.1.0.0^{1,3}]-pentane **15**, 2,6-diphosphatricyclo[3.1.0.0^{1,3}]pentane **16**, 3,5-diphosphatricyclo[3.1.0.0^{1,3}]pentane **17**, and 2,3,5,6-tetraphosphatricyclo[3.1.0.0^{1,3}]pentane **18**. Introduction of phosphorus atoms into the 3- and 4-positions of **4** shared by the three-membered rings are expected to relax strain more than the other positions. The strain is predicted to decrease in the order of **4**>**13**>**14**>**15**. The introduction of the phosphorus atoms is accompanied by the elongation of the atomic distance between the 2- and 3-positions. The lengthening is also expected to relax the strain, which the bond suffers from as suggested by the long C_2C_3 bond in the three-membered side rings of **4**.





(2)



(3)

The optimized geometries of **13–18** calculated at the B3LYP/6-31G* levels have C_2 symmetry. Selected geometrical parameters of the structures are listed in Table 3 and Figure 7. The C_1X_2 nonfusion bonds on the central atom are shorter than the bonds in the corresponding monocyclic

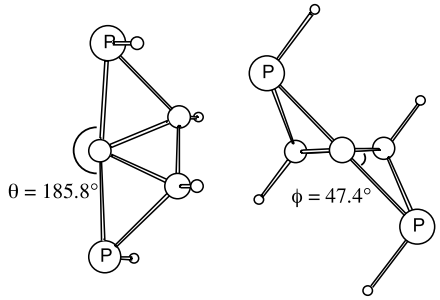


Figure 7. The structure of **13** optimized at the B3LYP/6-31G*.

molecules (1.509 Å in cyclopropane, 1.886 Å in phosphirane, and 1.872 Å in diphosphirane). The X_2Y_3 bonds (1.866 Å in **13**, 1.982 Å in **14**, 2.320 Å in **15**, 1.906 Å in **16**, 1.942 Å in **17**, and 2.287 Å in **18**) of the three-membered side ring are longer than phosphirane (1.886 Å) and diphosphirane (2.235 Å) as are found in the hydrocarbons, **4** and **7**. This suggests that the X_2Y_3 bonds still suffer from the ring strain unique to the difusotricyclic structures. The angle θ between the geminal nonfusion bonds on the central atom is close to 180° in **13** (θ=185.8°) and **16** (171.9°). The torsion from the tetrahedral configuration is reduced by the replacement by phosphorus atoms. The dihedral angles ϕ in **13–15** and **16–18** are larger than those of the corresponding hydrocarbons **4** and **7**.

The strain energies of **13–18** show that the replacement by phosphorus atoms relaxes the strain of the difusotricyclic molecules (Table 4) as was expected. The strain of the difusotricyclic phosphorus molecules with a three-membered central ring decreases in order of (**4**)>**13**>**14**>**15** in

Table 3. Geometrical parameters of **13–18** calculated at the B3LYP/6-31G*

	13	14	15	16	17	18
C_1X_2(Å)	1.821	1.457	1.813	1.822	1.451	1.812
C_1Y_3(Å)	1.497	1.822	1.852	1.517	1.895	1.895
X_2Y_3(Å)	1.866	1.982	2.320	1.906	1.942	2.287
θ (°)	185.8	165.1	167.8	171.9	163.9	163.7
ϕ (°)	47.4	52.8	62.6	54.3	54.2	63.2

Table 4. Strain energy (kcal/mol) calculated at the G3B3//B3LYP/6-31G*

	13	14	15	16	17	18
Strain energies	100.0	84.4	61.3	78.8	86.3	60.4
Reference energies	69.4	56.3	43.1	68.0	57.1	43.9
Difference energies	(+30.6)	(+28.1)	(+18.2)	(+10.8)	(+29.2)	(+16.5)

agreement with the prediction. However, the trends of the strains of the molecules **16**–**18** with a four-membered central ring are different. The molecules **17** and **18** are strained as much as the corresponding molecules **14** and **15** with a three-membered ring, respectively, whereas the molecule **16** is less strained than **13**. The molecule **16** with the phosphorus atoms at the 2- and 6-positions is less strained by 34.1 kcal/mol than the parent hydrocarbon **7**. The decrement in the strain energy is as remarkable as that (34.7 kcal/mol) of **13** from **4**. The phosphorus atoms at the 2- and 5 (6)-positions in the three-membered side rings are similarly effective, irrespective of the size of the central rings. However, the phosphorus atoms at the 3- and 5-positions in the four-membered central ring are less effective than those at the 3- and 4-positions in the three-membered central ring. The decrease (26.6 and 52.5 kcal/mol) in the strain energy from the parent hydrocarbon **7** to **17** and **18** with a four-membered central ring are smaller than those (50.3 and 73.4 kcal/mol) from **4** to **14** and **15** with a three-membered ring. The phosphorus atoms relax the strain of the four-membered rings to lesser extent. In fact, the four-membered ring, 1,3-diphosphetane (15.2 kcal/mol) is a little more strained that the three-membered ring, diphosphirane (14.4 kcal/mol).

There is correlation of the strain energy with the dihedral angle ϕ (Fig. 8) while the correlation with the bond angle θ (Scheme 2) is less remarkable (Fig. 9). These features are

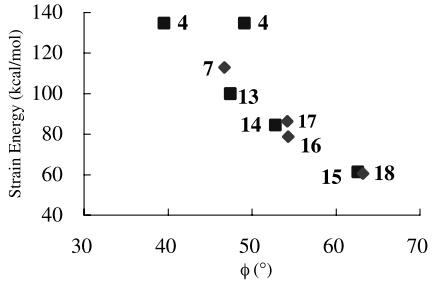


Figure 8. The dependence of the strain energies on the dihedral angles ϕ. There are two values for **4** due to the unsymmetrical geometry.

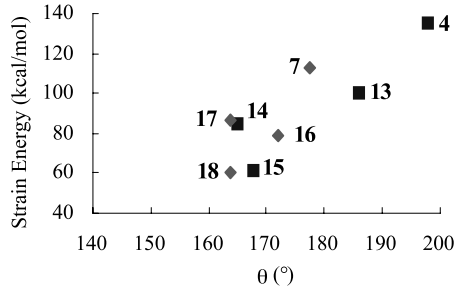


Figure 9. The dependence of the strain energies on the bond angles θ.

similar to those of the hydrocarbons, **4**–**12**. The C_2C_3 bonds of the three-membered side rings in the hydrocarbon are elongated as described. This suggests that the strain decreases with the X_2Y_3 bond length. This was confirmed by the correlation of the strain energy with the bond lengths (Fig. 10).

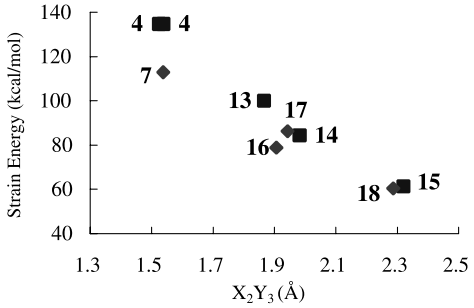


Figure 10. The dependence of the strain energies on the X_2Y_3 bonds. There are two values for **4** due to the unsymmetrical geometry.

4. Conclusion

We investigated the ring strains of the difusotricyclic hydrocarbons, tricyclo[p.q.0.0^{1,f}]alkanes **4**–**12** and designed less strained difusotricyclic molecules **13**–**18** by replacing some carbon atoms with phosphorus atoms.

The effects of the difusotricyclic geometry on the ring strain were found to be enormous. The strain energy (134.7 kcal/mol) of tricyclic[2.1.0.0^{1,3}]pentane **4** composed of only three-membered rings is higher by 34.3 kcal/mol than that of [1.1.1]propellane **3** and by 52.3 kcal/mol than the sum of the strain energies of three cyclopropanes. Compound **4** is strained larger. The geometric effects decrease with the size of the composite rings. The side rings are more effective than the central rings. The effects of the four- and five-membered side rings are small. There are correlations of the strain energy with the deviations from the tetrahedral configuration of the central carbon atom. The correlation is good with the torsion or the dihedral angle ϕ (Scheme 1) between the planes containing the two fusion bonds and the two nonfusion bonds on the central atom, and less remarkable with the bond angle θ (Scheme 2) between the nonfusion bonds.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.066

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Asymmetric synthetic study of macrolactin analogues

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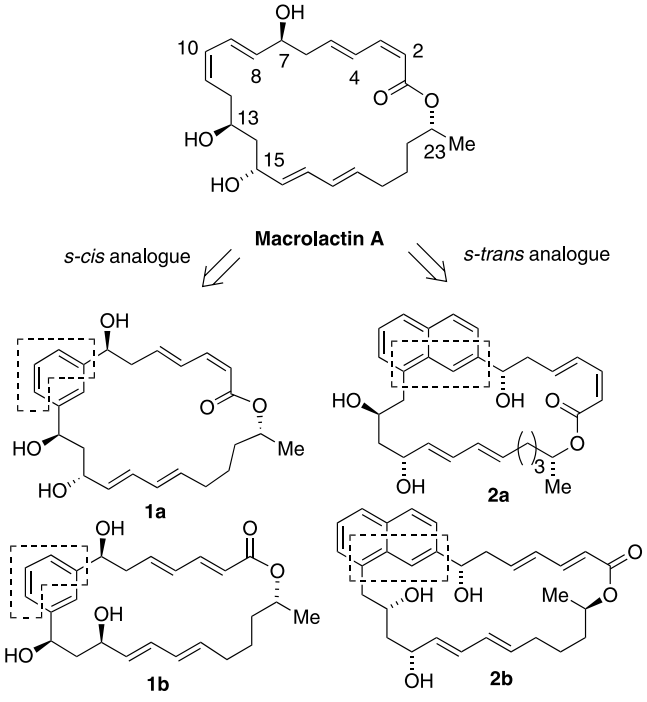
Abstract—We designed two aromatic analogues **1a** and **1b** of macrolactin A with expectation of enhancing biological activity and metabolical stability. As a result of retrosynthetic analysis of these compounds **1a–b**, two synthetic strategies have been examined. The first strategy includes the enantioselective addition of nonadienyl anion, derived from **3**, to aldehyde **4** as a key step. The second one includes epimerization of ynone **7** to (*E*,*E*)-conjugated dienone **31** and subsequent diastereoselective hydride-reduction of **31**. Although the former route furnished no desired target, the latter one was revealed to work well for the synthesis of **1**. Unfortunately, the aimed (2*Z*,4*E*)-analogue **1a** could not be synthesized due to an epimerization of the (2*Z*)-olefin into the (2*E*)-olefin. However, these methods could be applied to the total asymmetric synthesis of the (2*E*,4*E*)-analogue **1b**. Overall, control of all of the four stereocenters was achieved by means of asymmetric and diastereoselective reactions without using any chiral natural sources.

1. Introduction

Macrolactins A–M, which were isolated in 1989[1] and 2001[2] are a family of 24-membered polyene macrolides produced by a deep sea marine bacterium. Though structurally quite diverse, these macrolactins are distinguished by biological activities against various viruses and cancer cell lines. Among them, macrolactin A exhibits a broad spectrum of activity with significant antiviral and cancer cell cytotoxic properties including inhibition of B16–F10 murine melanoma cell replication.[1,2] In addition, this compound features three sets of conjugated dienes and four stereogenic centers in the molecule. Because of its unreliable supply from cell culture as well as its structural characteristics and broad therapeutic potential, macrolactin A has been an attractive target for asymmetric synthesis. Thus far, three total synthesis[3] and novel synthetic studies[4] have been developed, but there are still problems to be solved for therapeutic applications. With an aim of increasing the metabolical stability and identifying requisite substructure of macrolactin A to exhibit biological activity, we planed to replace the (2*Z*,4*E*)- and (8*E*,10*Z*)-dienic moieties by the (2*E*,4*E*)-dienoate and more stable aromatic ring, respectively (Scheme 1). From the point of view that the (8*E*,10*Z*)-dienic moiety should adopt a *s-cis* or *s-trans* form as a major configuration, we designed 1,3-disubstituted benzenes **1a–b** and 1,7-disubstituted naphthalenes **2a–b**,



Scheme 1. Macrolactin A analogues.

Keywords: Macrolactin A; Antibiotics; Antivirus; Asymmetric synthesis; Ynone; Isomerization; (*E*,*E*)-Conjugated dienone.
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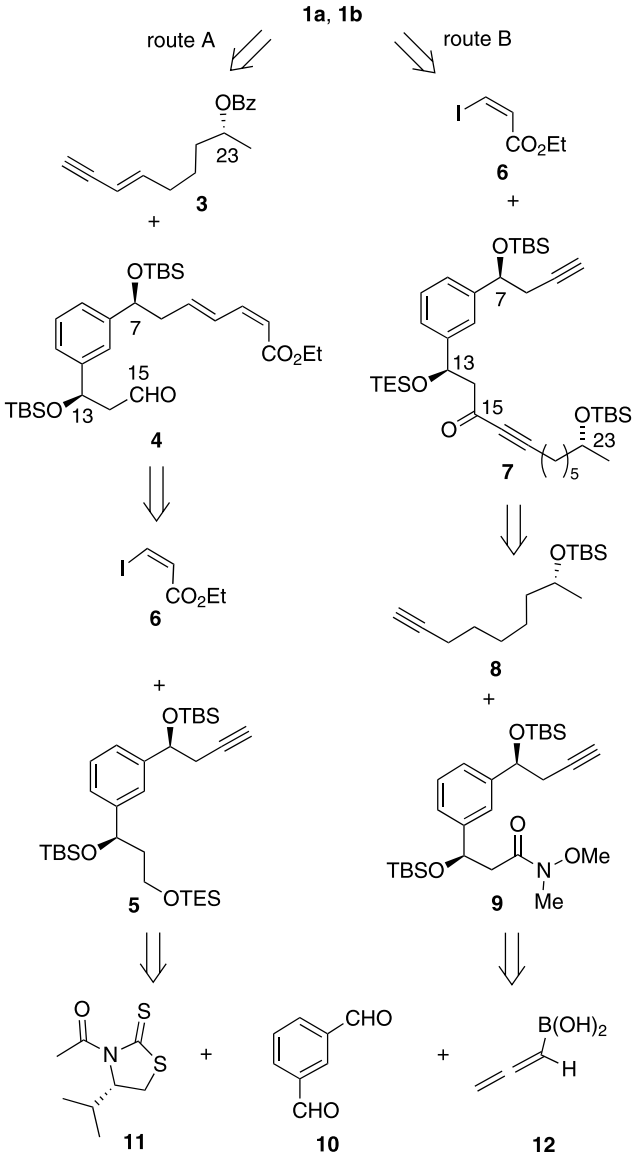
respectively. We first targeted the benzene analogues **1a** and **1b**. While, in both analogues **1a** and **1b**, a rigid phenyl group was introduced instead of the (8*E*,10*Z*)-dienic moiety, only **1b** was replaced the (2*Z*,4*E*)-dienic moiety to the (2*E*,4*E*)-dienic moiety.[5] We have already reported the synthetic studies on macrolactin A and its analogues.[6] Then we describe here the details of an asymmetric total synthesis of a macrolactin analogue **1b** by means of enantioselective and diastereoselective reactions without using any chiral natural sources.

2. Results and discussion

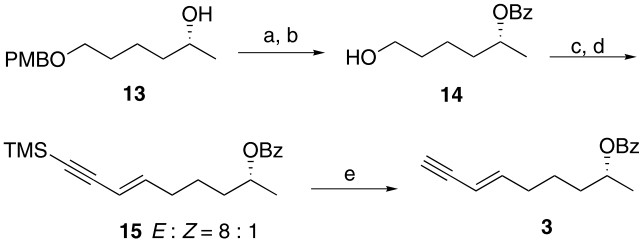
Retrosynthetic analysis. Our retrosynthetic analysis of the macrolactin analogues **1a** and **1b** was described in Scheme 2. This strategy relies on several asymmetric reactions to construct three chiral carbon centers (C7, C13, and C23). In addition, the key step of the strategy is a introduction of the (16*E*,18*E*)-dienyl segment with concurrent formation of the C15 stereogenic center. To investigate the key reaction, we examined two synthetic routes; (1) the asymmetric addition of alkenylzirconocene derived from **3** to aldehyde **4** and (2) the addition of alkynyl anion of **8** to Winreb amide **9** and subsequent epimerization and hydride-reduction of the resulting dienone **7**. Fortunately, these starting materials could be prepared from the same compounds **10**, **11**, and **12**.



Scheme 2. Retrosynthetic analysis of macrolactin analogue **1a**.

2.1. Investigation of the route A using asymmetric addition of alkenylzirconocene to aldehyde 4

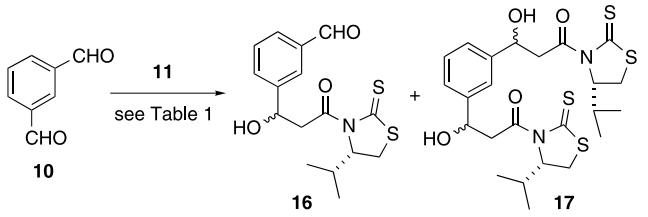
The asymmetric synthesis of **3** and **4**, which were required to examine the enantioselective addition, was conducted as follows. We have already reported the asymmetric synthesis of nonracemic alcohol **13**,[6a] which was obtained in 99% yield with 95%ee according to the Seebach's procedure[7] (Scheme 3). The benzoylation and deprotection of the PMB-group of **13** gave rise to alcohol **14** in 86% yield. The subjection of **14** to oxidation with IBX[8] (2-iodoxybenzoic acid) and subsequent Wittig olefination[9] afforded enyne **15**, which was converted to the desired product **3** by removal of the TMS group. The *E*-configuration of enynes **3** was determined by the coupling constant ($J=14.4$ Hz) between olefinic protons of **3**.



Scheme 3. (a) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, quant; (b) DDQ, CH_2Cl_2–H_2O, 86%; (c) IBX, DMSO–THF, 93%; (d) $Ph_3P^+CH_2CCTMSBr^-$, *n*-BuLi, THF, −25 °C, 91%; (e) TBAF, THF, 86%.

Having the requisite enyne **3** with high enantioselectivity, our attention was directed to the asymmetric synthesis of aldehyde **4**. The synthesis of **4** commenced from the diastereoselective aldol reaction of (*S*)-3-acetyl-4-isopropyl-1,3-thiazolidine-2-thione **11**[10] with dialdehyde **10**. The representative results were shown in Table 1. Although we examined several reaction conditions, the aldol adducts **16** were obtained with moderate diastereoselectivity (53–68% de). The two diastereomers **16** could be separated by column chromatography, but we did not determine the stereochemistry of these adducts. In addition, the side-products **17** were produced as an inseparable mixture of four diastereomers via double aldol reaction together with **16**. Then, we next investigated the aldol reaction of mono-aldehyde **18**, which was prepared in two steps from **10** (Scheme 4). The $TiCl_4$-mediated aldol reaction of **11** with **18** in the presence of *i*-Pr_2NEt proceeded with good diastereoselectivity (88% de) to provide **19** in 80% yield. The relative configuration of **19** was determined to be *R* based on the literature results[10] and the modified MTPA-method.[11] After protection of the hydroxy group of **19**, subjection of the resulting TBS-ether to methanolysis and oxidation gave rise to aldehyde **20**, which was converted to TBS ether **21** stereoselectively by the diastereoselective

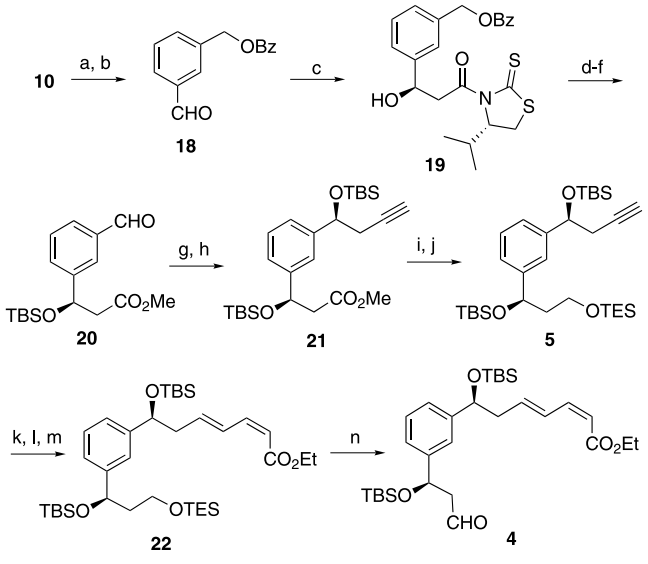
Table 1. Diastereoselective aldol reaction of **10** with **11**



Entry	Reaction conditions	Yield (%)		de of **16** (%)
		16	**17**	
1	$Yb(OTf)_3$, $(i\text{-}Pr)_2NEt$	0	0	—
2	$Sn(OTf)_2$, *N*-ethylpiperazine	23	35	53
3	$TiCl_4$, $(i\text{-}Pr)_2NEt$	39	19	68
4	$TiCl_4$, *N*-ethylpiperazine	42	22	64

propargylation with allenylboronic acid **12** according to the Yamamoto's protocol[12] and TBS protection of the resultant alcohol. The propargylation proceeded with good stereoselectivity (*R*:*S*=10:90) by using (+)-diisopropyl tartrate as a chiral source. After transformation of **21** into TES ether **5** by the reduction and protection, (*Z*,*E*)-dienoester **22** was derived from **5** in moderate yield by the standard three-step sequence: bromination, hydrostanylation,[13] and Stille cross-coupling.[14] The reaction of TES ether **22** with IBX directly gave rise to the desired product **4** in 66% yield.[15]

We examined the final coupling reaction of aldehyde **4** and enyne **3** using the Wipf's protocol[16] (Scheme 5). Although the hydrozirconation of **3** with $Cp_2Zr(H)Cl$ proceeded cleanly, no desired product **23** was obtained by the Me_2Zn-mediated nucleophilic addition of the corresponding alkenylzirconocene with **4**, even in the presence of chiral



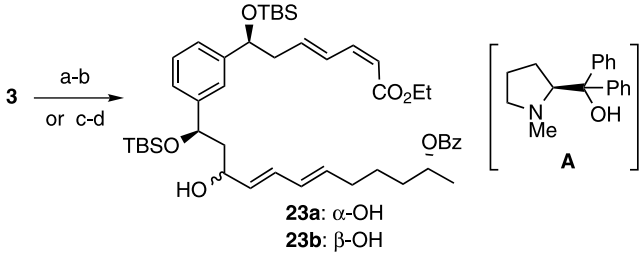
Scheme 4. (a) $NaBH_4$, MeOH, 0 °C, 64%; (b) BzCl, Et_3N, CH_2Cl_2, 0 °C, quant; (c) *N*-acetyl-(*S*)-4-IPTT **11**, $TiCl_4$, $i\text{-}Pr_2NEt$, CH_2Cl_2, −78 °C, 80%, 88%de; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 84%; (e) K_2CO_3, MeOH; (f) IBX, DMSO–THF, 84% (2 steps); (g) $CH_2{=}C{=}CHB(OH)_2$ **12**, (+)-diisopropyl tartrate, MS 4A, toluene, −78 °C, 88%, 80%de; (h) TBSCl, imidazole, DMF, quant; (i) DIBAL, CH_2Cl_2, −78 °C then $NaBH_4$, MeOH, 0 °C 86%; (j) TESCI, imidazole, DMF, quant; (k) BrCN, *n*-BuLi, THF, −78 to −40 °C, 93%; (l) $PdCl_2(PPh_3)_2$, Bu_3SnH, benzene; (m) $Pd_2(dba)_2$, ethyl (*Z*)-3-iodopropenoate **6**, $i\text{-}Pr_2NEt$, DMF, 33% (2 steps); (n) IBX, DMSO–H_2O, 66%.

amino alcohol **A** as a promoter. Then, we next investigated the $CrCl_2/NiCl_2$-mediated cross-coupling[17] of **4** with the alkadienyl iodide, which was easily prepared from **3** via the corresponding alkenylzirconocene. Whereas the cross-coupling reaction successfully occurred, the desired product **23a** was obtained in 28% yield together with the diastereomer **23b** (**23a**:**23b**=1:1). Since we could not improve the stereoselectivity, we turned our attention to the second strategy.

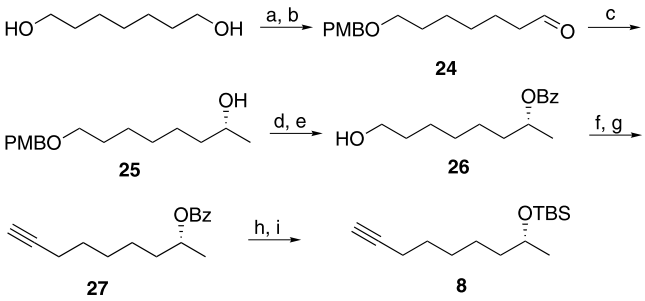
2.2. Investigation of the route B using the addition of alkyne 8 to Winreb amide 9

The strategy involves assembly of three fragments **6**, **8**, and **9** as shown in Scheme 2. Alkyne **8** bearing a stereogenic center (C23), plays a central role in our strategy, serving not only as an ideal nucleophile for joining with the amide **9**, but also as a latent functional group of the (16*E*,18*E*)-conjugated dienone moiety of **1**.

We anticipated that these compounds **8** and **9** could be prepared from **24** and **18** by the same reactions such as asymmetric methylation, asymmetric propargylation of **12**,[6] and diastereoselective aldol condensation of **11**.[7] We commenced from an efficient enantioselective preparation of alkyne **8** (Scheme 6). Synthesis of **8** began with PMB aldehyde **24** derived from 1,7-heptanediol in two steps. This aldehyde **24** was first subjected to the reported asymmetric methylation using Me_2Zn and $Ti(O\text{-}i\text{-}Pr)_4$ in the presence of (+)-TADDOL[7] (20 mol%) to give the desired secondary alcohol **25** in 90% yield with high enantioselectivity (95%ee). The enantioselectivity and absolute configuration were determined by a modified method of the Mosher



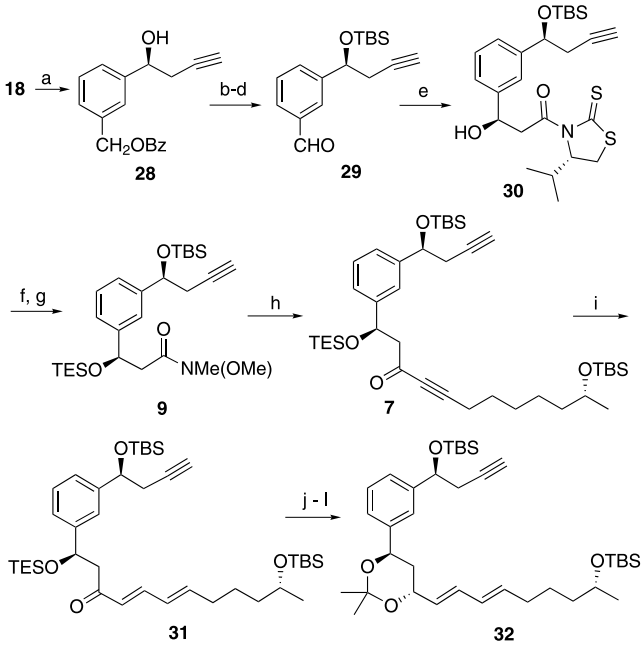
Scheme 5. (a) $Cp_2Zr(H)Cl$, CH_2Cl_2; (b) Me_2Zn, chiral ligand A, **4**, toluene, 25 °C–rt; (c) $Cp_2Zr(H)Cl$, CH_2Cl_2 then NIS, 0 °C, 77%; (d) $CrCl_2$, $NiCl_2$, **4**, DMSO, 56%.



Scheme 6. (a) PMBCI, NAH, THF, 0 °C; (b) IBX, DMSO, THF, 48% (2 steps); (c) Me_2Zn, (+)-TADDOL, Ti(O-*i*-Pr)$_4$, toluene, −25 °C, 90%, 95%ee; (d) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, quant; (e) DDQ, CH_2Cl_2, H_2O, 80%; (f) IBX, DMSO, THF, 95%; (g) $(MeO)_2P(O)CHN_2$, *t*-BuOK, THF, −78 °C→rt, 85%; (h) 3 N KOH/MeOH (1:1), 87%; (i) TBSCl, imidazole, DMF, quant.

protocol.[11] The resulting alcohol **25** was protected as a benzoate before removal of the terminal PMB ether to furnish primary alcohol **26**. Oxidation of **26** to an aldehyde, followed by exposure to the Seyferth–Gilbert reagent,[18] produced alkyne **27** which finally replaced the protecting group from benzoate to *tert*-butyldimethysilyl (TBS) ether to give the desired product **8**.

Having established the synthesis of the C16–C24 fragment **8**, we next sought the construction of **9** from aldehyde **18**. Propargylation of **18** with allenylboronic acid **12** under the same conditions[12] as that of **20** gave chiral alcohol **28** as the single product with moderate enantioselectivity (85% yield, 80%ee) (Scheme 7). Fortunately, the optically pure alcohol **28** (>95%ee) was easily obtained by recrystallization of **28**



Scheme 7. (a) CH_2=C=CHB(OH)$_2$ **12**, (+)-diisopropyl tartrate, MS 4A, toluene, −78 °C, 85%, 80%ee; (b) TBSCl, imidazole, DMF, quant; (c) K_2CO_3, MeOH, 95%; (d) IBX, DMSO, THF, 90%; (e) **11**, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 80%, 92%de; (f) MeONHMe·HCl, Et_3N, CH_2Cl_2 91%; (g) TESCI, pyridine, quant; (h) EtMgBr, **8**, THF, 70%; (i) dppb, toluene, THF; (j) AcOH/THF/H_2O (8:8:1), 40% (2 steps); (k) $Me_4NBH(OAc)_3$, AcOH, MeCN, 89%; (l) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 83%.

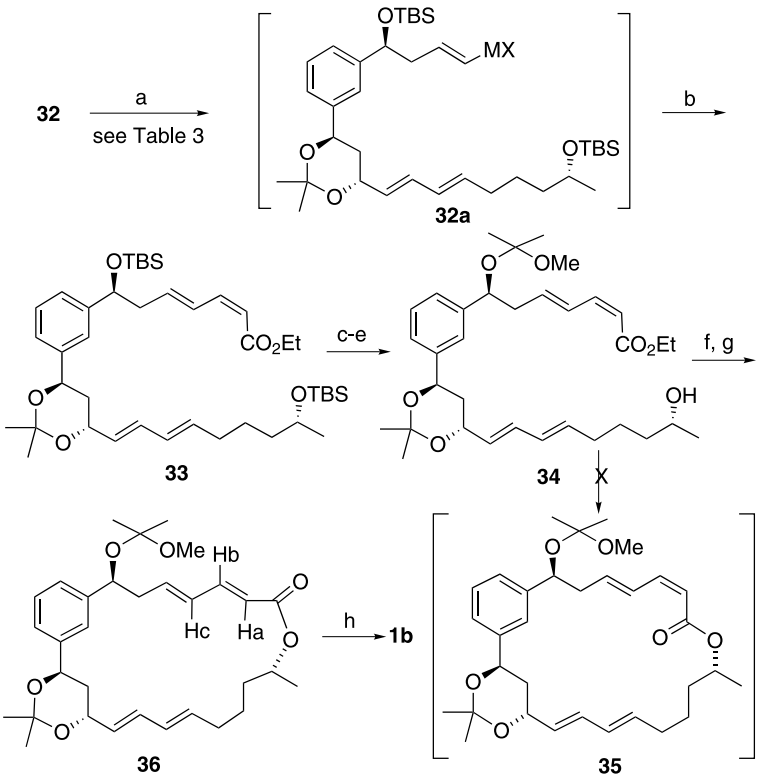
(80%ee) from a mixture of AcOEt and hexane. The enantioselectivity and absolute configuration were determined by a modified method of the Mosher protocol.[11] After protection of the alcohol **28**, hydrolysis of the benzoate afforded the primary alcohol (K_2CO_3, MeOH), which was oxidized with IBX[8] to provide the desired aldehyde **29**. Condensation of **29** with **11** in the presence of $TiCl_4$ (1.1 equiv) and *i*-Pr_2NEt (1.1 equiv) afforded aldol product **30**[10] along with a small amount of its diastereomer (80% yield, 92% de). These products were separated by column chromatography, and major product **30** was treated with *N*-methoxymethylamine, followed by TESCl to yield Weinreb amide **9** in good yield. With the two chiral building blocks now accessible, we investigated the key steps of this strategy, that is, their coupling reaction and stereoselective construction of the (*E*,*E*)-conjugated dienone unit. The coupling reaction of **8** and **9** proceeded smoothly using ethylmagnesium bromide as a base[19] to afforded the desired ynone **7** in good yield. Although the triphenylphosphine-catalyzed isomerization of an ynone to a conjugated dienone has been reported,[20] the desired product could not be obtained in reasonable yield under the standard conditions (Table 2, entry 1). After many experiments as shown in Table 2, use of bis(diphenylphosphino)butane (dppb) in a mixture of toluene and THF (1:1) at room temperature led to the best result to give **31** in 49% yield (entry 5).

Table 2. Phosphine-catalyzed epimerization of ynone **7** to dienone **31**

Entry	Reaction conditions	Yield (%)
1	PPh_3, toluene, 110 °C	31
2	*n*-Bu_3P, toluene, rt	20
3	*n*-Bu_3P, toluene/THF, rt	28
4	dppb, toluene, rt	30
5	dppb, toluene/THF, rt	49

After removal of the TES protecting group, subsequent construction of the fourth stereogenic center was carried out by hydroxyl-directed reduction.[21] Reduction of the resulting alcohol derived from **31** with $Me_4NBH(OAc)_3$ provided the corresponding 1,3-*anti*-diol in 89% yield and 93:7 diastereoselectivity. This 1,3-*anti*-diol was protected as acetonide under the standard conditions to afford **32** as a single isomer. The relative configuration of **32** was determined by the inspection of the ^{13}C chemical shifts of the acetonide methyl groups of **32**,[1b] that is, both signals of two methyl groups appeared at 25 ppm (δ: 25.1 and 25.5). This phenomena strongly indicates that acetonide **32** possesses the 1,3-*anti* configuration.

We finally examined the cross-coupling reaction of acetonide **32** and iodide **6** (Scheme 8 and Table 3). At first, the Pd-mediated cross-coupling was examined in the same manner[13,14] as that of **5**, but the desired product **33** was obtained only in a miserable yield (entry 1). Therefore, we undertook the exploration of other cross-coupling reactions. Whereas the desired product **33** was obtained under neither Negishi[22] nor Denmark[23] reaction conditions, the Cu-catalyzed reaction of **32a** (MX=Bu_3Sn) with **6** proceeded smoothly to give **33** in 58% yield from **32** (entries 2–4).[24] Although the reaction of **33** under acidic conditions gave a mixture of mono-TBS adducts, the C7 TBS group of **33**



Scheme 8. (a) Conditions A; (b) conditions B; (c) TBAF, THF, 0 °C, 92%; (d) CH_2=CMe(OMe), PPTS, CH_2Cl_2, −40 °C, 82%; (e) TBAF, AcOH (1:1), THF, 89%; (f) 3 N KOH, THF, EtOH, 60 °C; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 40% (3 steps); (h) PPTS; MeOH, 61%.

Table 3. Transition metal-catalyzed cross-coupling reaction of **32** and **6a**,**b**

Entry	Conditions A	Conditions B	Yield (%)
1	BrCN, BuLi; Bu_3SnH, $PdCl_2(PPh)_3$	**6**, $Pd(dba)_2$	32
2	$Cp_2Zr(H)Cl$; $ZnCl_2$	**6**, $PdCl_2(PPh_3)_2$, DIBAL	0
3	$(HMe_2Si)_2O$, *t*-Bu_3P-Pt(DVDS)	**6**, TBAF, $Pd(dba)_2$	0
4	BrCN, BuLi; Bu_3SnH, $PdCl_2(PPh)_3$	**6**, CuTC	58

could be removed regioselectively with TBAF, which was followed by protection/deprotection manipulation to furnish the desired alcohol **34** as the single isomer. After hydrolysis of **34**, lactonization of the resulting (2*Z*,4*E*)-carboxylic acid (J_{Ha-Hb}=11.3 Hz) by a modified Yamaguchi's method[25] did not provide the desired (2*Z*,4*E*)-lactone **35** at all, and gave unexpected (2*E*,4*E*)-lactone **36** as the single isomer (J_{Ha-Hb}=15.3 Hz).[26] From the fact that McClure et al.[3c] succeeded in a total synthesis of macrolactin A by the same procedure, the replacement of the (8*E*,10*Z*)-dienic moiety to the aromatic ring seems to prohibit the macrocyclization into the (2*Z*,4*E*)-lactone. Finally, global deprotection of the methoxyisopropylidene acetal and acetonide of **36** afforded the macrolactin A analogue **1b** in 61% yield.

3. Conclusion

The synthesis of **1b** was thus completed in 23 steps in the longest linear sequence, while another aimed compound **1a** could not be synthesized. This strategy features the following reactions: (1) three asymmetric reactions to generate the chiral centers, (2) isomerization of ynone to (*E*,*E*)-conjugated dienone, (3) the Cu-catalyzed cross-coupling reaction to construct the (*Z*,*E*)-conjugated dienoate. The biological activities of the synthetic intermediates and **1b**, prepared in this study, are now investigated in order to establish structure–activity relationship of macrolactin A. These results will be reported in the future.

4. Experimental

4.1. General information

Melting points are uncorrected. IR spectra were obtained using a JASCO FTIR-410 spectrometer. ^1H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were obtained using a JEOL JNM-LA-500 spectrometer using TMS as an internal standard. Optical rotations were measured with a JASCO DIP-360 polarimeter. Nominal (MS) and high resolution mass spectra (HRMS) were measured with a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Column chromatography was carried out using Merck Kieselgel 60. Dry solvents purchased from Kanto Chemicals were used in all reactions.

4.1.1. (2*R*)-6-Hydroxyhexan-2-yl Benzoate (14). To a solution of (2*R*)-6-(4-methoxybenzyloxy)-2-hexanol **13**[6a] (2.80 g, 11.7 mmol), triethylamine (3.28 mL, 23.5 mmol), and DMAP (72.0 mg, 0.580 mmol) in CH_2Cl_2 (40 mL) was added benzoyl chloride (1.78 mL, 15.3 mmol) at 0 °C. The whole mixture was stirred at ambient temperature for 1 h, before quenching with a saturated sodium bicarbonate solution. The organic layer was extracted with ether three times. The combined extracts were washed with water and brine, dried over magnesium sulfate, and then concentrated under reduced pressure. The crude mixture was purified on silica gel (elution: 5:1 hexane/ethyl acetate) to give the benzoate (3.52 g, 85%) as a colorless oil. To a mixture of the benzoate (3.52 g, 10.5 mmol), CH_2Cl_2 (36 mL), and H_2O (2 mL) was added DDQ (3.04 g, 13.4 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 2 h, before quenching with a saturated sodium bicarbonate solution. The mixture was diluted with ether and then filtered through a pad of Celite. The combined filtrates were condensed and purified by column chromatography on silica gel (elution: 2:1 hexane/ethyl acetate) to furnish **14** (1.90 g, 81%) as a colorless oil. $[\alpha]_D^{26}=28.1$ ($c=1.25$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, 2H, $J=7.6$ Hz), 7.54 (dd, 1H, $J=7.6$, 7.6 Hz), 7.43 (dd, 2H, $J=7.6$, 7.6 Hz), 5.17 (m, 1H), 3.63 (m, 2H), 1.77 (m, 1H), 1.63 (m, 4H), 1.47 (m, 2H), 1.34 (d, 3H, $J=6.4$ Hz); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 166.3, 132.7, 130.7, 129.5, 128.3, 71.5, 62.5, 35.7, 32.4, 21.6, 19.9; IR ($CHCl_3$): 3515, 3020, 1708, 1280 cm^{-1}; MS (EI) *m/z* (relative intensity) 222 (M^+, 82), 91 (100); HRMS (EI^+) calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1252.

4.1.2. (2*R*,6*E*)-9-(Trimethylsilyl)non-6-en-8-yn-2-yl benzoate (15). To a solution of **14** (1.00 g, 4.50 mmol) in a 2:1 mixture of DMSO and THF (45 mL) was added IBX (1.89 g, 6.75 mmol), and the mixture was stirred at room temperature for 30 min. After being quenched with a saturated sodium bicarbonate solution, the aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give the aldehyde (893 mg, 90%) as a colorless oil. A magnetically stirred slurry of (3-(trimethylsilyl)prop-2-ynyl)triphenylphosphinium bromide (2.07 g, 4.55 mmol) in dry THF (10 mL) was cooled to −78 °C under an argon atmosphere. A 1.58 M solution of *n*-butyllithium (3.10 mL, 4.55 mmol) in *n*-hexane was added dropwise over a 1 min period, and this mixture was stirred at −78 °C for 5 min. During this time, the color of the reaction mixture changed from pale yellow to brown. Subsequently, a solution of the prepared aldehyde (836 mg, 3.80 mmol) in THF (10 mL) was added to the mixture over a 1 min period. The resulting mixture was stirred at −78 °C for 12 h and then allowed to warm to ambient temperature. Stirring was continued for an additional 2 h, and then the reaction mixture was quenched with water. Extraction of the mixture with dichloromethane, washing of the combined extracts with brine, drying, and removal of solvents afforded the crude product, which was purified by SiO_2 column chromatography (elution: 15:1 hexane/ethyl acetate) to furnish **15** (532 mg, 44%). $[\alpha]_D^{23}=22.1$ ($c=1.04$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.85 (d, 2H, $J=7.9$ Hz), 7.36 (dd, 1H, $J=7.9$, 7.9 Hz), 7.25 (dd, 2H, $J=7.9$, 7.9 Hz), 6.00 (dt, 1H, $J=15.9$, 7.0 Hz), 5.34 (d, 1H, $J=15.9$ Hz), 4.98 (m, 1H), 1.96 (m, 2H), 1.58–1.29 (m, 4H), 1.15 (d, 3H, $J=6.1$ Hz), 0.00 (s, 9H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 166.1, 145.3, 132.8, 130.8, 129.5, 128.3, 110.2, 103.9, 92.9, 71.3, 35.5, 32.8, 24.5, 20.1, 0.0; IR ($CHCl_3$): 2957, 2139, 1710 cm^{-1}; MS (CI) *m/z* (relative intensity) 314 (M^+, 6), 242 (56), 91 (100); HRMS (CI^+) calcd for $C_{19}H_{26}O_2Si$ (M^+) 314.1702, found 314.1706.

4.1.3. (2*R*,6*E*)-Nona-6-en-8-yn-2-yl benzoate (3). To a solution of **15** (504 mg, 1.60 mmol) in THF (12 mL) was added a 1.0 M solution of tetra-*n*-butylammonium fluoride (3.20 mL, 3.20 mmol) in THF at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, before being diluted with diethyl ether. The reaction mixture was quenched with a saturated ammonium chloride solution and then the whole was poured into a saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried, concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 10:1 hexane/ethyl acetate) to give **3** as a colorless oil (321 mg, 64%) $[\alpha]_D^{24}=24.3$ ($c=1.47$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.90 (d, 1H, $J=7.6$ Hz), 7.41 (dd, 1H, $J=7.6$, 7.6 Hz), 7.30 (dd, 2H, $J=7.9$, 7.9 Hz), 6.09 (dt, 1H, $J=15.3$, 7.0 Hz), 5.34 (d, 1H, $J=15.3$ Hz), 5.03 (m, 1H), 2.66 (s, 1H), 2.01 (m, 2H), 1.64–1.30 (m, 4H), 1.20 (d, 3H, $J=6.4$ Hz); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 166.0, 145.9, 132.7, 130.7, 129.4, 128.2, 109.0, 82.3, 75.9, 71.2, 35.3, 32.6, 24.3, 20.0; IR ($CHCl_3$): 3021, 1709, 1279 cm^{-1}; MS (CI) *m/z* (relative intensity) 242 (M^+, 36), 91 (100); HRMS (CI^+) calcd for $C_{16}H_{18}O_2$ (M^+) 242.1307, found 242.1309.

4.1.4. 3-[1-Hydroxy-3-((4*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-oxopropyl]benzaldehyde (16). (Table 1, entry 2): To a fleshly dried tin(II) triflate (451 mg, 1.08 mmol) were successively added a solution of **11** (200 mg, 0.983 mmol) in CH_2Cl_2 (2.5 mL) and *N*-ethylpiperazine (0.148 mL, 1.08 mmol) at −40 °C under an argon atmosphere. After the mixture was stirred for 4 h, a solution of **10** (132 mg, 0.938 mmol) in CH_2Cl_2 (2.5 mL) was added to the mixture at −78 °C, and the whole was stirred for 2 h. The mixture was poured into a mixture of a phosphate buffer solution (pH 7.0, 200 mL) and ethyl acetate with vigorous stirring. The organic layer was washed with brine, dried, concentrated in vacuo. The crude products were purified by SiO_2 column chromatography (elution: 2:1 hexane/ethyl acetate) to give two diastereomers of **16** (60.0 mg, 18% and 18.0 mg, 5.4%) and **17** (190 mg, 35%). (Entry 3): To a solution of **11** (275 mg, 1.34 mmol) in CH_2Cl_2 (7 mL) were successively added titanium(IV) chloride (0.162 mL, 1.48 mmol) and diisopropylethylamine (0.256 mL, 1.48 mmol) at −40 °C under an argon atmosphere. After the mixture was stirred at this temperature for 2 h, a solution of **10** (181 mg, 1.34 mmol) in dry CH_2Cl_2 (7 mL) was added to the mixture at −78 °C, and the mixture was stirred at −78 °C for 30 min. The mixture was poured into a mixture of aqueous phosphate buffer solution (pH 7.0, 200 mL) and ethyl acetate with vigorous stirring. The organic layer was washed with brine, dried, concentrated in vacuo. The crude products were purified by SiO_2 column chromatography (elution: 2:1 hexane/ethyl acetate) to give two diastereomers of **16**

(139 mg, 33% and 26.0 mg, 6.2%) and **17** (136 mg, 19%). (Entry 4): To a solution of **11** (100 mg, 0.492 mmol) in CH_2Cl_2 (2.5 mL) were successively added titanium(IV) chloride (0.059 mL, 0.54 mmol) and *N*-ethylpiperazine (0.074 mL, 0.54 mmol) at −40 °C under an argon atmosphere. The same procedure described above gave two diastereomers of **16** (57.1 mg, 34% and 12.5 mg, 7.5%) and **17** (58.4 mg, 22%). Less polar isomer of **16**; $[\alpha]_D^{23}=+315$ ($c=1.09$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.6 (s, 1H), 7.93 (s, 1H), 7.82 (d, 1H, $J=7.6$ Hz), 7.69 (d, 1H, $J=7.6$ Hz), 7.54 (dd, 1H, $J=7.6$, 7.6 Hz), 5.35 (d, 1H, $J=8.9$ Hz), 5.16 (t, 1H, $J=7.1$ Hz), 3.90 (dd, 1H, $J=17.4$, 2.7 Hz), 3.55–3.49 (m, 2H), 3.38 (br, 1H), 3.05 (d, 1H, $J=11.6$ Hz), 2.38 (m, 1H), 1.07 (d, 3H, $J=6.7$ Hz), 1.00 (d, 3H, $J=6.7$ Hz); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 203.0, 192.2, 172.2, 143.6, 136.6, 131.8, 129.2, 128.9, 127.1, 71.4, 69.5, 46.9, 30.8, 30.7, 19.0, 17.8; IR ($CHCl_3$): 3575, 1698, 1604, 1361, 1311 cm^{-1}; MS (FAB) *m/z* (relative intensity) 338 (MH^+, 30), 162 (88), 154 (100), 136 (77); HRMS (FAB^+) calcd for $C_{16}H_{20}NO_3S_2$ (MH^+) 338.0885, found 338.0894. Polar isomer of **16**; $[\alpha]_D^{24}=+208$ ($c=1.93$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.0 (s, 1H), 7.92 (s, 1H), 7.82 (d, 1H, $J=7.6$ Hz), 7.69 (d, 1H, $J=7.6$ Hz), 7.54 (dd, 1H, $J=7.6$, 7.6 Hz), 5.22 (m, 2H), 3.84 (m, 2H), 3.57 (m, 2H), 3.07 (d, 1H, $J=11.6$ Hz), 2.38 (m, 1H), 1.08 (d, 3H, $J=6.7$ Hz), 1.00 (d, 3H, $J=6.7$ Hz); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 203.2, 192.3, 172.8, 143.7, 136.7, 132.0, 129.3, 129.1, 127.3, 71.3, 70.0, 46.7, 30.7, 30.6, 19.0, 17.8; IR ($CHCl_3$): 3549, 1699 cm^{-1}; MS (FAB) *m/z* (relative intensity) 338 (MH^+, 17), 162 (100); HRMS (FAB^+) calcd for $C_{16}H_{20}NO_3S_2$ (MH^+) 338.0885, found 338.0888.

4.1.5. 3-Formylbenzyl benzoate (18). To a solution of **10** (19.0 g, 0.142 mol) in ethanol (420 mL) was added sodium borohydride (1.33 g, 35.4 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. After the solvent was removed, ethyl acetate and water were added to the residue. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 1:1 hexane/ethyl acetate) to furnish the desired aldehyde (12.1 g, 63%) as a colorless oil along with diol (5.97 g, 30%). To a solution of the aldehyde (1.00 g, 7.34 mmol) in CH_2Cl_2 (25 mL) were successively added triethylamine (2.04 mL, 14.7 mmol) and benzoyl chloride (1.11 mL, 9.55 mmol) at 0 °C. After being stirred at ambient temperature for 1 h, the mixture was quenched with a saturated sodium bicarbonate solution, and the resultant mixture was extracted with ether. The combined extracts were washed with water and brine, dried, concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give **18** (1.54 g, 87%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ:9.97 (s, 1H), 8.04 (d, 2H, $J=7.0$ Hz), 7.92 (s, 1H), 7.79 (d, 1H, $J=7.6$ Hz), 7.66 (d, 1H, $J=7.6$ Hz), 7.49 (m, 1H), 7.37 (t, 2H, $J=7.8$ Hz), 5.37 (s, 2H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 192.0, 166.2, 137.4, 136.7, 133.9, 133.3, 129.8, 129.7, 129.5, 129.4, 129.0, 128.5, 65.7; IR ($CHCl_3$): 1693, 1605, 1451, 1372 cm^{-1}; MS (EI) *m/z* (relative intensity) 240 (M^+, 1), 105 (100); HRMS (EI^+) calcd for $C_{15}H_{12}O_3$ (M^+) 240.0786, found 240.0788.

4.1.6. 3-((1*R*)-1-Hydroxy-3-((4*S*)-isopropyl-2-thioxothiazolidin-3-yl)-3-oxopropyl)benzyl benzoate (19). To a solution of **11** (100 mg, 0.492 mmol) in CH_2Cl_2 (2.5 mL) were successively added titanium(IV) chloride (0.059 mL, 0.54 mmol) and diisopropylethylamine (0.092 mL, 0.54 mmol) at −40 °C under an argon atmosphere. After the mixture was stirred at −40 °C for 2 h, a solution of **18** (107 mg, 0.447 mmol) in CH_2Cl_2 (2.5 mL) was added to this mixture at −78 °C, and the whole was stirred for 30 min. The same work-up procedure described for **16** gave the desired product **19** (150 mg, 76%) along with the minor diastereomer (9.0 mg, 4.5%). **19**: $[\alpha]_D^{23}=+210$ ($c=1.20$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, 2H, $J=7.6$ Hz), 7.55 (t, 1H, $J=7.3$ Hz), 7.48 (s, 1H), 7.43 (t, 2H, $J=7.6$ Hz), 7.37 (m, 3H), 5.36 (s, 2H), 5.29 (d, 1H, $J=8.6$ Hz), 5.11 (t, 1H, $J=7.0$ Hz), 3.80 (dd, 1H, $J=17.4$, 2.44 Hz), 3.60 (dd, 1H, $J=17.6$, 9.3 Hz), 3.45 (dd, 1H, $J=11.3$, 7.9 Hz), 3.34 (s, 1H), 2.99 (d, 1H, $J=11.6$ Hz), 2.35 (m, 1H), 1.04 (d, 3H, $J=6.7$ Hz), 0.97 (d, 3H, $J=6.7$ Hz); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 203.1, 172.4, 166.4, 142.9, 136.3, 133.0, 130.0, 129.7, 128.8, 128.4, 127.4, 125.7, 125.5, 71.4, 69.9, 66.5, 46.7, 30.7, 30.6, 18.9, 17.6; IR ($CHCl_3$): 1713, 1274 cm^{-1}; MS (EI) *m/z* (relative intensity) 443 (M^+, 0.3), 105 (100); HRMS (EI^+) calcd for $C_{23}H_{25}NO_4S_2$ (M^+) 443.1225, found 443.1222.

4.1.7. Methyl (3*R*)-3-(3-formylphenyl)-3-(*tert*-butyldimethylsillyloxy)propanoate (20). To a solution of **19** (57.0 mg, 0.128 mmol) in CH_2Cl_2 (1.3 mL) were added 2,6-lutidine (0.045 mL, 0.39 mmol) and TBSOTf (0.044 mL, 0.19 mmol) at 0 °C, and the whole mixture was stirred at room temperature for 30 min. After being quenched with a saturated sodium bicarbonate solution, the mixture was extracted with ether. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give TBS ether as a colorless oil (60.0 mg, 84%). To a solution of the obtained TBS ether (60.0 mg, 0.107 mmol) in methanol (4.3 mL) was added K_2CO_3 (32.6 mg, 0.236 mmol) at room temperature, and the whole was stirred at room temperature for 2 h. After the solvent was removed, ethyl acetate and water were added to the residue, and the separated organic extract was concentrated in vacuo. To a solution of the obtained residue in a 2/1 mixture of DMSO and THF (1.2 mL) was added IBX (58.0 mg, 0.207 mmol), and the whole was stirred at room temperature for 30 min. After being quenched with a saturated sodium bicarbonate solution, the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give aldehyde (28.0 mg, 84% in 2 steps) as a colorless oil. $[\alpha]_D^{23}=+61.6$ ($c=1.09$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ:10.0 (s, 1H), 7.87 (s, 1H), 7.79 (d, 1H, $J=7.6$ Hz), 7.64 (d, 1H, $J=7.6$ Hz), 7.51 (dd, 1H, $J=7.6$, 7.6 Hz), 5.24 (dd, 1H, $J=4.2$, 9.2 Hz), 3.67 (s, 3H), 2.75 (dd, 1H, $J=14.7$, 9.2 Hz), 2.58 (dd, 1H, $J=14.7$, 4.2 Hz), 0.85 (s, 9H), 0.04 (sm, 3H), −0.16 (s, 3H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 192.2, 171.1, 145.3, 136.6, 131.9, 129.1, 129.0, 127.0, 71.6, 51.7, 46.0, 25.6, 18.0, −4.7, −5.3; IR ($CHCl_3$): 2254, 1734, 1700 cm^{-1}; MS (FAB) *m/z* (relative

intensity) 323 (MH^+, 15), 265 (100); HRMS (FAB^+) calcd for $C_{17}H_{27}O_4Si$ (MH^+) 323.1679, found 323.1659.

4.1.8. Methyl (3*R*)-3-(*tert*-butyldimethylsillyloxy)-3-[3-((1*S*)-1-(*tert*-butyldimethylsillyloxy)-3-butynyl)phenyl]-propanoate (21). To a solution of the chiral boron reagent, prepared from **12** (0.148 mmol) according to the literature procedure,[12] was added **20** (24.0 mg, 0.0744 mmol) at −78 °C, and the mixture was allowed to stand at −78 °C for 20 h. After being quenched with a 1.0 M hydrochloric acid solution, the mixture was extracted with ether two times. The combined extracts were washed with water and brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 3:1 hexane/ether) to give alcohol (23.3 mg, 88%, 80% de) as a colorless oil. $[\alpha]_D^{28}=+32.7$ ($c=1.09$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.25 (m, 4H), 5.14 (dd, 1H, $J=3.4$, 9.5 Hz), 4.86 (m, 1H), 3.67 (s, 3H), 2.71 (dd, 1H, $J=14.7$, 9.5 Hz), 2.62 (m, 1H), 2.54 (dd, 1H, $J=14.7$, 3.4 Hz), 2.42 (m, 1H), 2.04 (s, 1H), 0.83 (s, 9H), 0.00 (s, 3H), −0.21 (s, 3H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 171.5, 144.3, 142.6, 128.5, 125.4, 124.9, 123.2, 80.5, 72.3, 72.2, 71.0, 51.6, 46.2, 29.5, 25.6, 18.0, −4.7, −5.3; IR ($CHCl_3$): 3307, 1733 cm^{-1}; MS (FAB) *m/z* (relative intensity) 363 (MH^+, 9), 305 (100); HRMS (FAB^+) calcd for $C_{20}H_{31}O_4Si$ (MH^+) 363.1992, found 363.1976. To a solution of the obtained alcohol (1.04 g, 2.88 mmol) in DMF (28 mL) were added imidazole (587 mg, 8.63 mmol) and TBSCl (867 mg, 5.75 mmol) at room temperature, and the whole was stirred at room temperature for 4 h. After being quenched with a saturated sodium bicarbonate solution, the mixture was extracted with ether. The extract was washed with water and brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 10:1 hexane/ethyl acetate) to give **21** (1.28 g, quantitative yield) as a colorless oil. $[\alpha]_D^{28}=+23.0$ ($c=1.09$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.27–7.20 (m, 4H), 5.12 (m, 1H), 4.78 (m, 1H), 3.66 (s, 3H), 2.71 (m, 1H), 2.59–2.43 (m, 3H), 1.90 (s, 1H), 0.86 (s, 9H), 0.82 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H), −0.10 (s, 3H), −0.20 (s, 3H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 171.5, 144.1, 143.9, 128.1, 125.1, 123.6, 123.4, 81.5, 73.8, 72.2, 69.9, 51.5, 46.2, 30.9, 25.7, 25.6, 18.2, 18.0, −4.6, −4.7, −4.9, −5.3; IR ($CHCl_3$): 2955, 2857, 1734 cm^{-1}; MS (EI) *m/z* (relative intensity) 476 (M^+, 0.3), 419 (100); HRMS (EI^+) calcd for $C_{26}H_{44}O_4Si_2$ (M^+) 476.2778, found 476.2780.

4.1.9. 1-((1*S*)-1-(*tert*-Butyldimethylsillyloxy)-3-butynyl)-3-[(1*R*)-1-(*tert*-butyldimethylsillyloxy)-3-(triethylsillyl-oxy)propyl]benzene (5). To a stirred solution of **21** (1.28 g, 2.68 mmol) in CH_2Cl_2 (15 mL) was added a 0.93 M solution of DIBAL (11.5 mL, 10.7 mmol) in *n*-hexane at −78 °C under an argon atmosphere, and this mixture was stirred for 1 h. After being quenched with water, the mixture was extracted with three portions of dichloromethane. The combined extracts were washed with brine, drying, and concentrated in vacuo. The crude product was then dissolved in methanol (27 mL), and sodium borohydride (405 mg, 107 mmol) was added to the mixture. After the whole was stirred at ambient temperature for 1 h, the solvent was removed and ethyl acetate and water were added to the residue. The organic layer was washed with water and brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give alcohol (1.03 g, 86%). $[\alpha]_D^{27}=+26.2$ ($c=1.09$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.25 (m, 4H), 5.03 (m, 1H), 4.88 (m, 1H), 3.78 (m, 2H), 2.70–2.51 (m, 3H), 2.01 (m, 3H), 0.96 (s, 9H), 0.95 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.00 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 144.2, 143.9, 128.0, 125.0, 124.8, 123.5, 81.5, 74.6, 73.8, 69.9, 60.3, 42.0, 30.9, 25.8, 25.7, 18.2, 18.1, −4.6, −4.7, −4.9, −5.2; IR ($CHCl_3$): 3308, 2955, 2932 cm^{-1}; MS (FAB) *m/z* (relative intensity) 449 (MH^+, 2), 317 (25), 73 (100); HRMS (FAB^+) calcd for $C_{25}H_{45}O_3Si_2$ (MH^+) 449.2907, found 449.2858. To a solution of the obtained alcohol (200 mg, 0.446 mmol) in DMF (4.5 mL) were added imidazole (91.0 mg, 1.33 mmol) and TESCl (0.150 mL, 0.891 mmol) at room temperature, and the mixture was stirred at room temperature for 5 h. After being quenched with a saturated sodium bicarbonate solution, the mixture was extracted with ether. The extract was washed with water and brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 15:1 hexane/ethyl acetate) to give **5** (250 mg, quantitative yield) as a colorless oil. $[\alpha]_D^{27}=+9.7$ ($c=0.97$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.25 (m, 4H), 4.75 (m, 2H), 3.63 (m, 1H), 3.52 (m, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 1.85 (m, 2H), 1.73 (m, 1H), 0.90 (t, 9H, $J=7.9$ Hz), 0.81 (s, 9H), 0.80 (s, 9H), 0.51 (q, 6H, $J=7.9$ Hz), −0.03 (s, 3H), −0.05 (s, 3H), −0.16 (s, 3H), −0.24 (s, 3H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 145.4, 143.8, 127.9, 125.1, 124.5, 123.6, 81.7, 73.9, 71.9, 69.8, 59.4, 44.0, 30.9, 25.9, 25.8, 18.3, 18.2, 6.8, 4.5, −4.6, −4.7, −5.0, −5.1; IR ($CHCl_3$): 2955, 2879 cm^{-1}; MS (EI) *m/z* (relative intensity) 562 (M^+, 1.5), 505 (70), 477 (78), 75 (100); HRMS (EI^+) calcd for $C_{31}H_{58}O_3Si_3$ (M^+) 562.3694, found 562.3687.

4.1.10. Ethyl (7*S*,2*Z*,4*E*)-7-(*tert*-butyldimethylsillyloxy)-7-[3-((1*R*)-1-(*tert*-butyldimethylsillyloxy)-3-triethylsillyl-oxypropyl)phenyl]hepta-2,4-dienoate (22). To a solution of **5** (882 mg, 1.57 mmol) in THF (15.6 mL) was added a 1.58 M solution of *n*-butyllithium (1.49 mL, 2.35 mmol) in *n*-hexane. After the solution was stirred at −78 °C for 1 h, a 1 M solution of cyanogen bromide (3.10 mL, 3.10 mmol) in THF was added to the mixture. The reaction mixture was stirred at −78 °C for an additional hour, before warming to −40 °C. The mixture was then poured into a 1 M solution of sodium hydroxide and the mixture was extracted with diethyl ether. The combined organic extracts were filtered through a pad of Celite. The filtrate was concentrated in vacuo and the crude product was purified by SiO_2 column chromatography (elution: 40:1 hexane/ethyl acetate) to give bromoalkyne (939 mg, 93%) as a colorless oil. To a benzene solution (14.6 mL) of the obtained bromoalkyne (939 mg, 1.46 mmol) was added bis(triphenylphosphine)palladium(II)-chloride (51.3 mg, 0.5 mol%), which was followed by the slow addition of tri-*n*-butyltinhydride (0.620 mL, 3.21 mmol) over a 5 min period. The resulting mixture was stirred at room temperature for 30 min. After the solvent was removed, the crude vinyl stannane was dissolved in DMF (11 mL) and to the solution were successively added (*Z*)-3-iodopropenoate (372 mg, 1.64 mmol), $Pd_2(dba)_2$ (626 mg, 0.109 mmol), and diisopropylethylamine (0.284 mL, 1.65 mmol). The whole was

stirred at room temperature for 1 h before being quenched with a saturated sodium bicarbonate solution. The mixture was extracted with ether, and the extract was washed with water and brine, dried, and then concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 10:1 hexane/ethyl acetate) to give the desired product **22** (315 mg, 33% in 2 steps) as a colorless oil. $[\alpha]_D^{34}=+14$ ($c=0.97$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ:7.34 (dd, 1H, $J=11.3$, 14.7 Hz), 7.28–7.11 (m, 4H), 6.48 (dd, 1H, $J=11.3$, 11.3 Hz), 5.98 (dt, 1H, $J=14.7$, 7.9 Hz), 5.55 (d, 1H, $J=11.3$ Hz), 4.78 (dd, 1H, $J=7.9$, 4.3 Hz), 4.68 (m, 1H), 4.16 (q, 2H, $J=7.0$ Hz), 3.70 (m, 1H), 3.56 (m, 1H), 2.57 (m, 1H), 2.50 (m, 1H), 1.89 (m, 1H), 1.78 (m, 1H), 1.27 (t, 3H, $J=7.0$ Hz), 0.90 (t, 9H, $J=$ 7.9 Hz), 0.81 (s, 9H), 0.80 (s, 9H), 0.51 (q, 6H, $J=7.9$ Hz), −0.03 (s, 3H), −0.05 (s, 3H), −0.16 (s, 3H), −0.19 (s, 3H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 166.3, 145.5, 144.9, 144.5, 141.4, 128.9, 127.9, 124.9, 124.5, 123.5, 116.0, 74.9, 71.8, 59.7, 59.3, 44.4, 44.0, 25.8, 25.7, 18.2, 18.1, 14.2, 6.8, 4.5, −4.6, −4.7, −5.0, −5.1; IR ($CHCl_3$): 2955, 2360 cm^{-1}; MS (CI) *m/z* (relative intensity) 663 (MH^+, 4), 605 (10), 399 (72), 133 (100); HRMS (CI^+) calcd for $C_{36}H_{67}O_5Si_3$ (MH^+) 663.4296, found 663.4283.

4.1.11. Ethyl (7*S*,2*Z*,4*E*)-7-*tert*-Butyldimethylsillyloxy-7-[3-((1*R*)-1-*tert*-butyldimethylsillyloxy-2-formylethyl)-phenyl]hepta-2,4-dienoate (4). To a solution of **22** (250 mg, 0.377 mmol) in a mixture of DMSO, THF, and H_2O (2.6/1.3/0.02 mL) was added IBX (232 mg, 0.829 mmol), and the mixture was stirred at room temperature for 1 h before being quenched with a saturated sodium bicarbonate solution. The mixture was extracted with diethyl ether, and the combined extracts were washed with brine, dried, and concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give **4** as a colorless oil (136 mg, 66%). $[\alpha]_D^{28}=+26$ ($c=0.97$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ:9.77 (s, 1H), 7.36 (dd, 1H, $J=11.3$, 14.5 Hz), 7.30–7.17 (m, 4H), 6.50 (dd, 1H, $J=11.3$, 11.3 Hz), 5.99 (m, 1H), 5.56 (d, 1H, $J=11.3$ Hz), 5.20 (m, 1H), 4.73 (m, 1H), 4.17 (q, 2H, $J=6.7$ Hz), 2.85 (m, 1H), 2.62–2.41 (m, 3H), 1.28 (t, 3H, $J=6.7$ Hz), 0.86 (s, 18H), 0.04 (s, 3H), 0.01 (s, 3H), −0.26 (s, 3H), −0.27 (s, 3H); ^{13}C NMR ($J=126$ Hz, $CDCl_3$) δ: 201.1, 166.3, 144.9, 144.7, 143.5, 140.9, 129.1, 128.4, 125.1, 124.6, 123.2, 116.1, 74.6, 70.8, 59.8, 53.8, 44.3, 25.7, 25.6, 18.1, 18.0, 14.2, −4.6, −4.7, −5.0, −5.2; IR ($CHCl_3$): 2955, 2931, 2857, 1717, 1638 cm^{-1}; MS (CI) *m/z* (relative intensity) 547 (MH^+, 12), 489 (20), 283 (100); HRMS (CI^+) calcd for $C_{30}H_{51}O_5Si_2$ (MH^+) 547.3275, found 547.3284.

4.1.12. 7-(4-Methoxyphenylmethoxy)heptanal (24). To a suspension of sodium hydride (1.80 g, 75.6 mmol) in DMF (200 mL) was added 1,7-heptanediol (10.0 g, 75.6 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at room temperature for 30 min. To the resulting solution was slowly added 4-methoxybenzyl chloride (10.3 mL, 75.6 mmol) at −20 °C, and the whole was stirred overnight at 0 °C. After being quenched with water, the mixture was extracted with ether. The extract was washed with brine, dried, and then concentrated in vacuo. The crude residue was purified by SiO_2 column chromatography (elution: 2:1 hexane/ethyl acetate) to give PMB alcohol (9.37 g, 50%) as a colorless oil; ^1H NMR ($CDCl_3$) δ: 7.26 (d, 2H, $J=8.2$ Hz), 6.87 (d, 2H, $J=8.2$ Hz), 4.43 (s, 2H), 3.80 (s, 3H), 3.63 (m, 2H), 3.43 (t, 2H, $J=6.4$ Hz), 1.63–1.53 (m, 4H), 1.40–1.30 (m, 6H), 1.20 (br, 1H); ^{13}C NMR ($CDCl_3$) δ: 159.0, 130.6, 129.1, 113.6, 72.4, 70.0, 62.8, 55.1, 32.6, 29.6, 29.1, 26.1, 25.6; IR ($CHCl_3$): 3623, 3443, 3008, 2963, 2860, 1612, 1513, 1462, 1248, 1090, 1035, 777 cm^{-1}; MS (EI) *m/z* (relative intensity) 252 (M^+,10), 137 (97), 121 (100), 107 (16), 91 (14); HRMS (EI^+) calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1719. To a solution of oxalyl chloride (4.05 mL, 46.4 mmol) in CH_2Cl_2 (40 mL) were successively added a solution of DMSO (3.8 mL, 54 mmol) in CH_2Cl_2 (50 mL) at −50 °C and a solution of the obtained alcohol (9.00 g, 35.6 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After being stirred for 1.5 h, the mixture was quenched with triethylamine (15 mL) at −78 °C, and the whole mixture was allowed to warm to 0 °C. The mixture was then quenched with water at 0 °C, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give **24** (8.32 g, 93%) as a colorless oil; ^1H NMR ($CDCl_3$) δ: 9.76 (s, 1H), 7.25 (d, 2H, $J=$ 8.5 Hz), 6.88 (d, 2H, $J=8.5$ Hz), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, 2H, $J=6.6$ Hz), 2.42 (t, 2H, $J=7.4$ Hz), 1.67–1.56 (m, 4H), 1.43–1.29 (m, 4H); ^{13} C NMR ($CDCl_3$) δ: 202.6, 158.9, 130.6, 129.1, 113.6, 72.4, 69.8, 55.1, 43.7, 29.4, 28.8, 25.9, 21.9; IR ($CHCl_3$): 3007, 2938, 2860, 1722, 1612, 1247, 1224, 1091, 1035 cm^{-1}; MS (EI) *m/z* (relative intensity) 250 (M^+,3.2), 137 (30), 121 (100), 91 (10); HRMS (EI^+) calcd for $C_{15}H_{22}O_3$ (M^+) 250.1569, found 250.1564.

4.1.13. (2*R*)-8-(4-Methoxyphenylmethoxy)octan-2-ol (25). (+)-TADDOL (1.01 g, 2.16 mmol) was placed in a dry Schlenk tube under an argon atmosphere. To this, Ti(O-*i*-Pr)$_4$ (0.764 mL, 2.59 mmol) and toluene (16 mL) were successively added, and the mixture was stirred at room temperature for 5 h. After toluene and 2-propanol were removed in vacuo, toluene (32 mL) and Ti(O-*i*-Pr)$_4$ (5.57 mL, 21.6 mmol) were added to the yellow residue at room temperature. After being cooled to −25 °C, to the resulting mixture were added a solution of **24** (2.40 g, 10.8 mmol) in toluene (24 mL) and then a 1.0 M solution of Me_2Zn (21.6 mL, 21.6 mmol) in *n*-hexane, and the mixture was stirred at the same temperature for 12 h. After being quenched with an ammonium chloride solution, the mixture was filtrated through a pad of Celite. The filtrate was washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 2:1 hexane/ethyl acetate) to furnish **25** (2.58 g, 90%, 95%ee) as a colorless oil; $[\alpha]_D^{22}=3.60$ ($c=1.05$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.26 (d, 2H, $J=8.2$ Hz), 6.88 (d, 2H, $J=8.2$ Hz), 4.43 (s, 2H), 3.81 (s, 3H), 3.78 (m, 1H), 3.43 (t, 2H, $J=6.7$ Hz), 1.64–1.55 (m, 2H), 1.50–1.25 (m, 8H), 1.18 (d, 3H, $J=6.1$ Hz); ^{13}C NMR ($CDCl_3$) δ: 159.0, 130.7, 129.2, 113.7, 72.5, 70.1, 68.0, 52.2, 39.2, 29.6, 29.4, 26.1, 25.7, 23.4; IR ($CHCl_3$): 3454, 3009, 2934, 2860, 1513, 1462, 1248, 1232, 1093 cm^{-1}; MS (EI) *m/z* (relative intensity) 266 (M^+,3.0), 137 (45), 121 (100), 91 (10); HRMS (EI^+) calcd for $C_{16}H_{26}O_3$ (M^+) 266.1882, found 266.1892. The enantiomeric excess of **25** was determined by HPLC analysis. Chiral column; eluent; flow rate; retention

times for each compounds are as follows: Daicel Chiralcel OD, 3% 2-propanol in hexane, 1.2 mL/min, (*R*) (major) 20.5 min, (*S*) (minor) 21.7 min.

4.1.14. Determination of the absolute configuration of 25. The absolute configuration of **25** was determined by ^{1}H NMR methods previously described by Kusumi et al.[11] The ^{1}H NMR chemical shifts of (+) and (−)-MTPA esters of **25** are as follows: (+)-MTPA ester; ^{1}H NMR ($CDCl_3$) δ: 7.53 (m, 2H), 7.37 (m, 3H), 7.23 (d, 2H, J=8.5 Hz), 6.87 (d, 2H, J=8.5 Hz), 5.14 (m, 1H), 4.40 (s, 2H), 3.80 (s, 3H), 3.56 (s, 3H), 3.35 (t, 2H, J=6.4 Hz), 1.67–1.48 (m, 10H), 1.32 (d, 3H, J=6.1 Hz), (−)-MTPA ester; ^{1}H NMR ($CDCl_3$) δ: 7.53 (m, 2H), 7.37 (m, 3H), 7.23 (d, 2H, J=8.5 Hz), 6.87 (d, 2H, J=8.5 Hz), 5.14 (m, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.42 (t, 2H, J=6.4 Hz), 1.48–1.33 (m, 10H), 1.24 (d, 3H, J=6.1 Hz).

4.1.15. (7*R*)-7-Benzoyloxyoctanol (26). To a solution of **25** (3.29 g, 12.2 mmol) in CH_2Cl_2 (20 mL) were successively added triethylamine (3.67 mL, 24.4 mmol), DMAP (74.5 mg, 0.610 mmol), and benzoyl chloride at 0 °C. The whole mixture was stirred at ambient temperature for 20 h. After being quenched with a saturated sodium bicarbonate solution, the mixture was extracted with ether. The organic layer was washed with water and brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 10:1 hexane/ethyl acetate) to give benzoate (3.98 g, quantitative yield) as a pale yellow oil; $[\alpha]_D^{22}$=19.0 (c=1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.04 (d, 2H, J=7.4 Hz), 7.55 (dd, 1H, J=7.4, 7.4 Hz), 7.43 (dd, 2H, J=7.4, 7.4 Hz), 7.25 (d, 2H, J=8.2 Hz), 6.87 (d, 2H, J=8.2 Hz), 5.15 (m, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.42 (t, 2H, J=6.7 Hz), 1.74–1.70 (m, 1H), 1.65–1.55 (m, 3H), 1.40–1.30 (m, 6H), 1.33 (d, 3H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 166.1, 158.9, 132.6, 130.8, 129.4, 129.1, 128.2, 113.6, 72.4, 71.5, 69.9, 55.1, 35.9, 29.6, 29.2, 26.0, 25.3, 19.9; IR ($CHCl_3$): 3007, 2937, 2860, 1708, 1512, 1280, 1248, 1108 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 371 (MH^+,5.0), 241 (11), 121 (100); HRMS (CI^+) calcd for $C_{23}H_{31}O_4$ (MH^+) 371.2222, found 371.2210. To a solution of the obtained benzoate (1.24 g, 3.35 mmol) in a mixture of CH_2Cl_2 and H_2O (34 mL and 2 mL) was added DDQ (850 mg, 3.74 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. After being quenched with a saturated sodium bicarbonate solution, the reaction mixture was diluted with ether and filtered through a pad of Celite. The combined filtrates were concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to furnish **26** (790 mg, 80%) as a colorless oil; $[\alpha]_D^{22}$=26.4 (c=0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.04 (d, 2H, J=7.4 Hz), 7.55 (dd, 1H, J=7.4, 7.4 Hz), 7.43 (dd, 2H, J=7.4, 7.4 Hz), 5.15 (dt, 1H, J=6.4, 8.9 Hz), 3.62 (t, 2H, J=6.4 Hz), 1.80–1.70 (m, 1H), 1.65–1.60 (m, 1H), 1.60–1.53 (m, 2H), 1.45–1.35 (m, 6H), 1.33 (d, 3H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ: 166.2, 132.6, 130.7, 129.3, 128.2, 71.5, 62.6, 35.8, 32.5, 29.1, 25.5, 25.3, 19.9; IR ($CHCl_3$): 3481, 2936, 2861, 1708, 1281, 1117 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 251 (MH^+,75), 123 (4.0); HRMS (CI^+) calcd for $C_{15}H_{23}O_3$ (MH^+) 251.1647, found 251.1658.

4.1.16. (8*R*)-8-Benzoyloxy-1-nonyne (27). To a solution of **26** (4.70 g, 18.8 mmol) in a 2/1 mixture of DMSO and THF (180 mL) was added IBX (7.90 g, 28.1 mmol), and the mixture was stirred at room temperature for 30 min. After being poured into a saturated sodium bicarbonate solution, the whole was extracted with ether. The combined extracts were washed, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give aldehyde (4.40 g, 95%) as a colorless oil; $[\alpha]_D^{18}$=29.6 (c=0.960, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 9.73 (s, 1H), 8.04 (d, 2H, J=7.4 Hz), 7.55 (dd, 1H, J=7.4, 7.4 Hz), 7.43 (dd, 2H, J=7.4, 7.4 Hz), 5.15 (m, 1H), 2.40 (m, 2H), 1.80–1.70 (m, 1H), 1.66–1.58 (m, 3H), 1.45–1.35 (m, 4H), 1.33 (d, 3H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ: 202.3, 165.9, 132.5, 130.6, 129.2, 128.0, 71.2, 43.5, 35.6, 28.7, 25.0, 21.7, 19.8; IR ($CHCl_3$): 3028, 2939, 2863, 1715, 1453, 1281, 1116 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 249 (MH^+, 100), 127 (45), 123 (40), 109 (27); HRMS (EI^+) calcd for $C_{15}H_{21}O_3$ (MH^+) 249.1491, found 249.1497. A magnetically stirred slurry of potassium *tert*-butoxide (3.97 g, 35.4 mmol) in THF (40 mL) was cooled to −78 °C under an argon atmosphere. To this mixture was added a solution of dimethyl (diazomethyl)phosphonate (6.31 g, 35.4 mmol) in THF (50 mL) dropwise over a 1 min period, and the resulting mixture was stirred for 5 min. During this time, the color of the reaction mixture changed from pale yellow to brown. Subsequently, to the mixture was added a solution of the obtained aldehyde (4.40 g, 17.7 mmol) in THF (40 mL) over a 1 min period. The resulting solution was stirred at −78 °C for 24 h and then allowed to warm to ambient temperature. Stirring was continued for an additional 4 h, and then the reaction mixture was quenched with water. The mixture was extracted with three portions of dichloromethane, and the combined extracts were washing with brine, drying, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 10:1 hexane/ethyl acetate) to furnish **27** (3.70 g, 85%). $[\alpha]_D^{23}$=34.4 (c=1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.03 (d, 2H, J=7.4 Hz), 7.55 (dd, 1H, J=7.4, 7.4 Hz), 7.44 (dd, 2H, J=7.4, 7.4 Hz), 5.15 (m, 1H), 2.18 (m, 2H), 1.93 (s, 1H), 1.80–1.70 (m, 1H), 1.66–1.58 (m, 1H), 1.58–1.49 (m, 2H), 1.50–1.35 (m, 4H), 1.34 (d, 3H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ: 166.2, 132.7, 130.8, 129.5, 128.3, 84.5, 71.5, 68.2, 35.9, 28.5, 28.3, 24.9, 20.1, 18.3; IR ($CDCl_3$): 3307, 2940, 2963, 1709, 1453, 1281, 1120 cm^{-1}; MS (CI) *m*/*z* (relative intensity) 245 (MH^+, 100), 227 (16), 123 (73), 105 (67); HRMS (EI^+) calcd for $C_{16}H_{21}O_2$ (MH^+) 245.1542, found 245.1535.

4.1.17. (8*R*)-8-(*tert*-Butyldimethylsilyloxy)-1-nonyne (8). To a solution of **27** (3.00 g, 12.3 mmol) in methanol (80 mL) was added a 3 N potassium hydroxide solution (80 mL) and the whole was stirred at room temperature for 3 h. After being concentrated in vacuo, the mixture was extracted with ether. The extracts were washed with water and brine, drying, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 2:1 hexane/ether) to give alcohol (1.43 g, 87%) as a colorless oil; $[\alpha]_D^{19}$=7.9 (c=0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 3.80 (m, 1H), 2.20 (m, 2H), 1.97 (s, 1H), 1.66 (br, 1H), 1.60–1.50 (m, 2H), 1.50–1.38 (m, 5H), 1.38–1.28 (m, 1H), 1.19 (d, 3H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$) δ: 84.5, 68.2, 67.9, 39.1, 28.7, 28.4, 25.2, 23.5, 18.3; IR

($CHCl_3$): 3610, 3306, 3008, 2936, 2861 cm^{-1}; MS (EI) *m/z* (relative intensity) 140 (M^+, 100), 96 (17); HRMS (EI^+) calcd for $C_9H_{17}O$ (M^+) 140.1201, found 140.1212. To a solution of the obtained alcohol (700 mg, 4.99 mmol) in DMF (50 mL) were added imidazole (1.02 g, 14.9 mmol) and TBSCl (1.50 g, 9.98 mmol) at room temperature. The whole was stirred at room temperature for 2 h. After being quenched with a saturated sodium bicarbonate solution, the mixture was extracted with ether. The combined extracts were washed with water and brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 20:1 hexane/ethyl acetate) to give the desired product **8** (1.26 g, quantitative yield) as a colorless oil; $[\alpha]_D^{19}=11.2$ ($c=1.04$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 3.73 (m, 1H), 2.13 (m, 2H), 1.88 (s, 1H), 1.54–1.44 (m, 2H), 1.44–1.28 (m, 5H), 1.28–1.18 (m, 1H), 1.07 (d, 3H, $J=6.4$ Hz), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 84.6, 77.2, 76.9, 76.7, 68.5, 68.1, 39.5, 28.8, 28.5, 25.9, 25.2, 23.8, 18.3, 18.1, −4.4, −4.7; IR ($CHCl_3$):3306, 2933, 2858 cm^{-1}; MS (CI) *m/z* (relative intensity) 255 (MH^+, 100), 140 (11), 96 (17); HRMS (CI^+) calcd for $C_{15}H_{31}OSi$ (MH^+) 255.2144, found 255.2149.

4.1.18. (1*S*)-1-(3-Benzoyloxymethylphenyl)-3-butyn-1-ol (28). By using the same procedure described for **21**, the aldehyde **18** (7.00 g, 29.1 mmol) was transformed into the crude product **28**, which was purified by SiO_2 column chromatography (elution: 3:1 hexane/ether) to give a recovered starting material (2.10 g, 29%) and **28** (4.75 g, 56%, 80%ee) as colorless crystals. The enantiomeric excess of the product was improved from 80 to 99%ee by recrystallization from hexane/ethyl acetate. The ee was determined by ^1H NMR analysis of (+)- and (−)-MTPA esters of **28**; mp 70–72 °C; $[\alpha]_D^{23}=30.9$ ($c=1.11$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ:8.05 (d, 2H, $J=7.3$ Hz), 7.54 (dd, 1H, $J=7.3$, 7.3 Hz), 7.49–7.32 (m, 6H), 5.33 (s, 2H), 4.87 (m, 1H), 2.79 (m, 1H), 2.63 (m, 2H), 2.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 166.4, 143.0, 136.2, 133.0, 129.9, 129.6, 128.7, 128.3, 127.6, 125.7, 125.5, 80.5, 72.0, 71.0, 66.5, 29.3; IR ($CHCl_3$): 3595, 3306, 3023, 2360, 1715, 1603, 1452, 1376, 1274 cm^{-1}; MS (EI) *m/z* (relative intensity) 280 (M^+, 37), 231 (35), 129 (20), 73 (100); Anal. calcd for $C_{15}H_{21}O_3$: C, 77.12; H, 5.75. found: C, 77.36; H, 5.90.

4.1.19. Determination of the absolute configuration of 28. The absolute configuration was determined by ^1H NMR analysis of (+)- and (−)-MTPA esters of **28**: (+)-MTPA ester; ^1H NMR ($CDCl_3$) δ: 8.06 (d, 2H, $J=7.6$ Hz), 7.58 (dd, 1H, $J=7.3$ Hz), 7.46–7.20 (m, 11H), 6.09 (dd, 1H, $J=8.1$, 5.0 Hz), 5.28 (m, 1H), 3.62 (s, 3H), 2.85 (ddd, 1H, $J=16.9$, 8.2, 2.4 Hz), 2.74 (ddd, 1H, $J=17.2$, 5.0, 2.6 Hz), 2.02 (t, 1H, $J=2.4$ Hz), (−)-MTPA ester; ^1H NMR ($CDCl_3$) δ: 8.06 (d, 2H, $J=7.3$ Hz), 7.57 (dd, 1H, $J=7.3$ Hz), 7.47–7.30 (m, 11H), 6.14 (t, 1H, $J=6.6$ Hz), 5.36 (m, 1H), 3.46 (s, 3H), 2.82 (ddd, 1H, $J=17.2$, 7.3, 2.3 Hz), 2.73 (ddd, 1H, $J=16.9$, 6.0, 2.8 Hz), 1.90 (t, 1H, $J=2.4$ Hz).

4.1.20. 3-[(1*S*)-1-(*tert*-Butyldimethylsilyloxy)but-3-ynyl]-benzaldehyde (29). To a solution of **28** (4.80 g, 17.0 mmol) in DMF (170 mL) were added imidazole (2.30 mg, 34.0 mmol) and TBSCl (3.80 g, 25.0 mmol) at room temperature, and the whole was stirred at room temperature for 2 h. After the usual workup, the obtained crude product was purified by SiO_2 column chromatography (elution: 20:1 hexane/ethyl acetate) to give TBS ether (6.07 g, quantitative yield) as a colorless oil; $[\alpha]_D^{26}=17.0$ ($c=1.48$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ:8.08 (d, 2H, $J=7.3$ Hz), 7.56 (dd, 1H, $J=7.3$, 7.3 Hz), 7.47–7.41 (m, 3H), 7.37–7.30 (m, 3H), 5.37 (m, 2H), 4.84 (t, 1H, $J=6.4$ Hz), 2.59 (ddd, 1H, $J=16.5$, 6.4, 2.3 Hz), 2.49 (ddd, 1H, $J=16.5$, 6.4, 2.3 Hz), 1.94 (t, 1H, $J=2.3$ Hz), 0.87 (s, 9H), 0.08 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 166.5, 144.5, 135.9, 133.1, 130.2, 129.8, 128.4, 128.3, 127.2, 125.8, 125.6, 81.4, 73.5, 70.1, 66.6, 30.9, 25.7, 18.2, −4.9, −5.0; IR ($CHCl_3$); 3308, 2931, 2857, 1715, 1603, 1455, 1274, 1199, 1110 cm^{-1}; MS (FAB) *m/z* (relative intensity) 395 (MH^+, 14), 231 (35), 73 (100); HRMS (FAB^+) calcd for $C_{24}H_{31}O_3Si$ (MH^+) 395.2042, found 395.2049. To a solution of the obtained TBS ether (6.07 g, 15.3 mmol) in methanol (150 mL) was added potassium carbonate (20.0 g, 153 mmol) at room temperature, and the mixture was stirred for 1 h. After evaporation and washing with water of the reaction mixture, the obtained product was dissolved in a 2/1 mixture of DMSO and THF (120 mL) and to this mixture was added IBX (4.40 g, 15.7 mmol). The crude product obtained by the usual workup was purified by SiO_2 column chromatography (elution: 5:1 hexane/ethyl acetate) to give aldehyde **29** (3.44 g, 86% in two steps) as a colorless oil; $[\alpha]_D^{20}=33.5$ ($c=1.08$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 10.0 (s, 1H), 7.87 (s, 1H), 7.77 (d, 1H, $J=7.6$ Hz), 7.65 (d, 1H, $J=7.6$ Hz), 7.50 (dd, 1H, $J=7.6$, 7.6 Hz), 4.89 (t, 1H, $J=6.4$ Hz), 2.59 (ddd, 1H, $J=16.5$, 6.4, 2.3 Hz), 2.49 (ddd, 1H, $J=16.5$, 6.4, 2.3 Hz), 1.95 (t, 1H, $J=2.3$ Hz), 0.88 (s, 9H), 0.08 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 192.1, 144.9, 136.3, 131.9, 128.9, 128.8, 127.1, 80.7, 73.0, 70.5, 30.7, 25.7, 18.1, −4.9, −5.0; IR ($CHCl_3$):3307, 2955, 2932, 2889, 2858, 1698, 1215, 1103 cm^{-1}; MS (FAB) *m/z* (relative intensity) 289 (MH^+, 12), 249 (55), 231 (45), 97 (32), 73 (100); HRMS (FAB^+) calcd for $C_{17}H_{25}O_2Si$ (MH^+) 289.1624, found 289.1622.

4.1.21. (4*S*)-*N*-[(3*R*)-3-[3-((1*S*)-1-*tert*-Butyldimethylsilyloxy-3-butynyl)phenyl]-3-hydroxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (30). According to the procedure described for **16**, the same reaction of aldehyde **29** (2.68 g, 9.33 mmol), **11** (2.09 g, 10.3 mmol), titanium(IV) chloride (1.23 mL, 11.2 mmol), and diisopropylethylamine (1.93 mL, 11.2 mmol) provided the desired product **30** (3.45 g, 74%) along with the minor diastereomer (142 mg, 3.1%) after purification by SiO_2 column chromatography (elution: 3:1 hexane/ethyl acetate); **30**: $[\alpha]_D^{17}=+213$ ($c=1.09$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ:7.31 (m, 4H), 5.27 (m, 1H), 5.14 (t, 1H, $J=7.0$ Hz), 4.82 (t, 1H, $J=6.4$ Hz), 3.80 (m, 1H), 3.52 (m, 2H), 3.14–3.00 (m, 1H), 2.58 (ddd, 1H, $J=16.6$, 6.4, 2.6 Hz), 2.48 (ddd, 1H, $J=16.6$, 6.4, 2.6 Hz), 2.38 (m, 1H), 1.96 (t, 1H, $J=2.6$ Hz), 1.07 (d, 1H, $J=6.7$ Hz), 1.00 (d, 1H, $J=7.0$ Hz), 0.88 (s, 9H), 0.07 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 203.0, 172.6, 144.3, 142.3, 128.4, 125.3, 124.8, 123.5, 81.6, 73.6, 71.4, 70.1, 47.0, 30.9, 30.8, 30.7, 25.8, 19.0, 18.2, 17.8, −4.8, −5.0; IR ($CHCl_3$): 3570, 3307, 2959, 2857, 1681, 1468, 1362, 1311, 1256, 1167, 1093 cm^{-1}; MS (FAB) *m/z* (relative intensity) 492 (MH^+, 1.2), 162 (83), 73 (100); HRMS (FAB^+) calcd for $C_{25}H_{38}O_3NSiS_2$ (MH^+) 492.2062, found 492.2047.

4.1.22. Determination of the absolute configuration of 30. The absolute configuration of **30** was determined by ^{1}H NMR analysis of (+)- and (−)-MTPA esters derived from **30** in 4 steps: (+)-MTPA ester; ^{1}H NMR ($CDCl_3$) δ: 7.39–7.28 (m, 9H), 6.18 (dd, 1H, J=8.9, 4.9 Hz), 4.80 (t, 1H, J=6.3 Hz), 3.51 (m, 2H), 3.42 (s, 3H), 2.57 (ddd, 1H, J=16.5, 7.0, 2.8 Hz), 2.46 (ddd, 1H, J=16.6, 5.9, 2.6 Hz), 2.19 (m, 1H), 1.96 (m, 1H), 1.92 (t, 1H, J=2.6 Hz), 0.89 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.01 (s, 6H), −0.11 (s, 3H), (−)-MTPA ester; ^{1}H NMR ($CDCl_3$) δ: 7.37–7.12 (m, 9H), 6.11 (dd, 1H, J=8.7, 5.3 Hz), 4.77 (dd, 1H, J=7.0, 5.8 Hz), 3.68 (m, 1H), 3.58 (m, 1H), 3.50 (s, 3H), 2.55 (ddd, 1H, J=16.5, 7.0, 2.8 Hz), 2.43 (ddd, 1H, J=16.6, 5.9, 2.6 Hz), 2.21 (m, 1H), 2.00 (m, 1H), 1.93 (t, 1H, J=2.6 Hz), 0.90 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.03 (s, 6H), −0.11 (s, 3H).

4.1.23. (3*R*)-3-[3-[(1*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-butynyl]phenyl]-*N*-methoxy-*N*-methyl-3-triethylsilyloxypropionamide (9). A mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (7.01 g, 72.7 mmol) and triethylamine (9.69 mL, 72.7 mmol) in CH_2Cl_2 (70 mL) was stirred at room temperature for 1 h. The reaction mixture was added to a solution of **30** in CH_2Cl_2 (18 mL) at room temperature and the whole mixture was stirred for 21 h. After being poured into a 5% hydrochloric acid solution at 0 °C, the mixture was extracted with ethyl acetate. The extracts were washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 1:1 to 1:2 hexane/ethyl acetate) to furnish Weinreb amide (2.30 g, 91%) as a colorless oil; $[\alpha]_D^{17}$=+22 (c=0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.42–7.24 (m, 4H), 5.15 (m, 1H), 4.83 (t, 1H, J=6.4 Hz), 4.30 (br, 1H), 3.61 (s, 3H), 3.20 (s, 3H), 2.90–2.70 (m, 2H), 2.58 (ddd, 1H, J=16.6, 6.4, 2.6 Hz), 2.48 (ddd, 1H, J=16.6, 6.4, 2.6 Hz), 1.95 (t, 1H, J=2.6 Hz), 0.89 (s, 9H), 0.08 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 173.1, 144.0, 142.9, 128.1, 124.9, 124.6, 123.2, 81.6, 73.6, 70.1, 70.0, 69.9, 61.1, 40.3, 31.8, 30.9, 25.7, 18.1, −4.8, −5.0; IR ($CHCl_3$): 3480, 3307, 3008, 2933, 2889, 2858, 1640, 1468, 1422, 1390, 1255, 1105 cm^{-1}; MS (FAB) m/z (relative intensity) 392 (MH^+, 18), 374 (100), 332 (33), 73 (68); HRMS (FAB^+) calcd for $C_{21}H_{34}O_4NSi$ (MH^+) 392.2257, found 392.2264. To a solution of the Weinreb amide in pyridine (20 mL) was added triethylsilylchloride (1.08 mL, 6.46 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with toluene (20 mL) and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 10:1 hexane/ethyl acetate) to give **9** (2.90 g, quantitative yield) as a colorless oil; $[\alpha]_D^{18}$=+25.8 (c=1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.42–7.24 (m, 4H), 5.26 (dd, 1H, J=8.6, 4.6 Hz), 4.81 (t, 1H, J=6.3 Hz), 3.61 (s, 3H), 3.16 (s, 3H), 3.04 (m, 1H), 2.61–2.43 (m, 3H), 1.93 (t, 1H, J=2.1 Hz), 0.88 (s, 9H), 0.84 (t, 9H, J=8.1 Hz), 0.52 (q, 6H, J=8.1 Hz), 0.08 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 171.6, 144.7, 143.9, 128.0, 125.0, 124.8, 123.4, 81.4, 73.7, 71.7, 69.8, 61.1, 43.0, 31.7, 30.7, 25.6, 18.1, 6.5, 4.5, −4.9, −5.2; IR ($CHCl_3$): 3308, 3003, 2956, 2879, 2360, 1649, 1466, 1388, 1254, 1079 cm^{-1}; MS (FAB) m/z (relative intensity) 506 (MH^+, 6.5), 476 (58), 374 (73), 115 (42), 73 (100); HRMS (FAB^+) calcd for $C_{27}H_{48}O_4NSi_2$ (MH^+) 506.3122, found 506.3107.

4.1.24. (1*R*,11*R*)-11-(*tert*-Butyldimethylsilyloxy)-1-[3-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)-3-butynyl]phenyl]-1-triethylsilyloxy-4-dodecyn-3-one (7). To a solution of alkyne **8** (172 mg, 0.676 mmol) in THF (1.5 mL) was added a 1.0 M solution of ethylmagnesium bromide (0.66 mL, 0.66 mmol) in THF at 0 °C and the mixture was stirred at room temperature for 30 min. To this mixture was added a solution of **17** (260 mg, 0.442 mmol) in THF (2.0 mL) over a 5 min period, and the whole mixture was stirred at room temperature for 2 h. After being quenched with water, the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 20:1–5:1 hexane/ethyl acetate) to furnish **7** (240 mg, 70%) as a colorless oil; $[\alpha]_D^{22}$=+3.10 (c=1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.34–7.23 (m, 4H), 5.27 (dd, 1H, J=8.9, 4.3 Hz), 4.80 (t, 1H, J=6.4 Hz), 3.77 (m, 1H), 3.02 (dd, 1H, J=8.9, 14.9 Hz), 2.70 (dd, J=4.3, 14.9 Hz), 2.57 (ddd, 1H, J=16.6, 6.4, 2.4 Hz), 2.47 (ddd, 1H, J=16.6, 6.4, 2.4 Hz), 2.36 (t, 2H, J=7.0 Hz), 1.94 (t, 1H, J=2.4 Hz), 1.45–1.33 (m, 5H), 1.34–1.22 (m, 3H), 1.12 (d, 3H, J=6.1 Hz), 0.88 (s, 9H), 0.88 (s, 9H), 0.83 (t, 9H, J=7.9 Hz), 0.51 (q, 6H, J=7.9 Hz), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 185.5, 144.1, 144.0, 128.2, 125.1, 125.0, 123.5, 94.7, 81.4, 81.3, 73.7, 71.3, 69.9, 68.4, 56.4, 39.4, 30.8, 28.9, 27.6, 25.8, 25.7, 25.1, 23.7, 18.9, 18.1, 18.0, 6.6, 4.6, −4.5, −4.8, −4.9, −5.1; IR ($CHCl_3$): 3308, 2955, 2933, 2881, 2858, 2213, 1668, 1466, 1255, 1217, 1100, 1080, 837 cm^{-1}; MS (FAB) m/z (relative intensity) 697 (MH^-, 20), 565 (32), 153 (64), 131 (100); HRMS (FAB^-) calcd for $C_{40}H_{69}O_4Si_3$ (MH^-) 697.4504, found 697.4517.

4.1.25. (1*R*,4*E*,6*E*,11*R*)-11-(*tert*-Butyldimethylsilyloxy)-1-[3-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)-3-butynyl]-phenyl]-1-triethylsilyloxy-4,6-dodecadien-3-one (31). (Entry 1): To a solution of ynone **7** (46.0 mg, 0.658 mmol) in toluene (0.3 mL) was added triphenylphosphine (17.2 mg, 0.0658 mmol) and the mixture was stirred at 100 °C for 6 h. After removal of solvent under reduced pressure, purification on silica gel (elution: 30:1 hexane/ethyl acetate) furnished **31** as a colorless oil (14.5 mg, 31%). (Entry 2): To a solution of ynone **7** (50.0 mg, 0.0715 mmol) in toluene (0.35 mL) was added tri-*n*-butylphosphine (0.018 mL, 0.072 mmol) and the mixture was stirred at room temperature for 1 h. The same work-up described above furnished **31** as a colorless oil (10.0 mg, 20%). (Entry 3): To a solution of ynone **7** (80.0 mg, 0.114 mmol) in THF–toluene (0.25–0.25 mL) was added tri-*n*-butylphosphine (0.0030 mL, 0.011 mmol) and the mixture was stirred at room temperature for 5 h. The same work-up described above furnished **31** as a colorless oil (22.6 mg, 28%). (Entry 4): To a solution of ynone **7** (34.0 mg, 0.0486 mmol) in toluene (0.24 mL) was added 1,4-bis(diphenylphosphino)butane (41.5 mg, 0.097 mmol) and the mixture was stirred at room temperature for 1 h. The same work-up described above furnished **31** as a colorless oil (10.5 mg, 30%). (Entry 5): To a solution of ynone **7** (570 mg, 0.815 mmol) in a 1/1 mixture of THF and toluene (4 mL) was added 1,4-bis(diphenylphosphino)butane (69.5 mg, 0.163 mmol), and the mixture was stirred at room temperature for 6 h. The same work-up described above furnished **31** as a colorless oil (280 mg, 49%) along

with the recovered starting material **7** (170 mg, 30%). $[\alpha]_D^{22}=+35.5$ ($c=1.09$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.44–7.18 (m, 4H), 7.11 (dd, 1H, $J=15.6$, 9.8 Hz), 6.16 (m, 2H), 6.06 (d, 1H, $J=15.6$ Hz), 5.21 (dd, 1H, $J=8.4$, 4.1 Hz), 4.80 (t, 1H, $J=6.3$ Hz), 3.78 (m, 1H), 3.10 (dd, 1H, $J=8.4$, 14.7 Hz), 2.70 (dd, $J=4.1$, 14.7 Hz), 2.57 (ddd, 1H, $J=16.7$, 6.3, 2.6 Hz), 2.47 (ddd, 1H, $J=16.7$, 6.4, 2.6 Hz), 2.18 (m, 2H), 1.93 (t, 1H, $J=2.6$ Hz), 1.62–1.46 (m, 1H), 1.47–1.35 (m, 3H), 1.12 (d, 3H, $J=6.1$ Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.81 (t, 9H, $J=7.9$ Hz), 0.48 (q, 6H, $J=7.9$ Hz), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 198.8, 145.7, 144.8, 144.0, 143.8, 129.1, 128.1, 125.0, 124.9, 123.5, 81.6, 73.8, 71.2, 69.8, 68.3, 51.2, 39.0, 33.1, 30.8, 25.8, 25.7, 24.8, 23.8, 18.2, 18.0, 6.6, 4.6, −4.5, −4.8, −5.1; IR ($CHCl_3$): 3307, 2956, 2932, 2880, 2858, 1633, 1592, 1467, 1364, 1255, 1101, 1004, 939, 909, 837 cm^{-1}; MS (FAB) *m/z* (relative intensity) 697 (MH^-, 6.5), 565 (13), 153 (100), 131 (93); HRMS (FAB^-) calcd for $C_{40}H_{69}O_4Si_3$ (MH^-) 697.4504, found 697.4512.

4.1.26. (4*R*,6*R*)-4-[3-[(1*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-butynyl]phenyl]-6-[(1*E*,3*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)nona-1,3-dienyl]-2,2-dimethyl-1,3-dioxane (32). Dienone **31** (630 mg, 0.901 mmol) was dissolved in a mixture of AcOH/THF/H_2O (8:8:1, 10 mL), and the solution was stirred at room temperature for 24 h. After being quenched with a saturated sodium bicarbonate solution, the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 3:1 hexane/ethyl acetate) to give alcohol (440 mg, 83%) as a colorless oil; $[\alpha]_D^{20}=+12$ ($c=0.96$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.34–7.19 (m, 4H), 7.11 (dd, 1H, $J=15.6$, 9.8 Hz), 6.15 (m, 2H), 6.03 (d, 1H, $J=15.6$ Hz), 5.16 (m, 1H), 4.79 (t, 1H, $J=6.4$ Hz), 3.73 (m, 1H), 2.90 (m, 2H), 2.53 (ddd, 1H, $J=16.7$, 6.3, 2.6 Hz), 2.43 (ddd, 1H, $J=16.7$, 6.4, 2.6 Hz), 2.15 (m, 2H), 1.91 (t, 1H, $J=2.6$ Hz), 1.62–1.46 (m, 1H), 1.47–1.35 (m, 3H), 1.08 (d, 3H, $J=6.1$ Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 200.6, 146.7, 144.5, 144.2, 142.9, 128.8, 128.3, 127.9, 125.0, 124.7, 123.2, 81.6, 73.6, 70.0, 69.9, 68.2, 48.4, 39.0, 33.1, 30.9, 25.8, 25.7, 24.7, 23.7, 18.1, 18.0, −4.5, −4.9, −5.0; IR ($CHCl_3$): 3672, 3510, 3307, 2955, 2932, 2858, 1633, 1593, 1467, 1362, 1255, 1105, 1002, 937, 909, 837 cm^{-1}; MS (FAB) *m/z* (relative intensity) 607 ($M+Na^+$, 28), 73 (100); HRMS (FAB^+) calcd for $C_{34}H_{56}NaO_4Si_2$ ($M+Na^+$) 607.3615, found 607.3621. To a solution of tetramethylammonium triacetoxyborohydride (1.42 g, 6.01 mmol) in acetonitrile (3 mL) was added acetic acid (3 mL), and the mixture was stirred at room temperature for 30 min. To the cooled mixture at −40 °C was added a solution of the obtained alcohol (440 mg, 0.752 mmol) in acetonitrile (2.2 mL) via cannula. After being stirred at −40 °C for 18 h, the mixture was quenched with a 0.5 N sodium potassium tartrate solution and then diluted with chloroform. The aqueous layer was extracted with chloroform and the combined extracts were washed with a saturated sodium bicarbonate solution and brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 2:1 hexane/ethyl acetate) to give alcohols as a diastereomixture (374 mg, 85%); $[\alpha]_D^{22}=22.1$ ($c=1.00$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.43–7.19 (m, 4H), 6.19 (dd, 1H, $J=15.3$, 10.4 Hz), 6.03 (dd, 1H, $J=14.8$, 10.4 Hz), 5.66 (m, 2H), 5.03 (m, 1H), 4.82 (t, 1H, $J=6.1$ Hz), 4.37 (m, 1H), 3.78 (m, 1H), 3.14 (br, 1H), 2.62 (br, 1H), 2.58 (ddd, 1H, $J=16.6$, 6.1, 2.6 Hz), 2.47 (ddd, 1H, $J=16.6$, 6.1, 2.6 Hz), 2.07 (m, 2H), 2.00–1.90 (m, 2H), 1.94 (t, 1H, $J=2.6$ Hz), 1.52–1.32 (m, 4H), 1.11 (d, 3H, $J=6.1$ Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 144.2, 144.1, 135.6, 132.6, 130.9, 129.4, 128.3, 124.9, 124.7, 123.2, 81.6, 73.7, 71.7, 70.1, 70.0, 68.4, 44.5, 39.1, 32.6, 30.9, 25.8, 25.7, 25.3, 23.7, 18.2, 18.1, −4.5, −4.8, −4.9, −5.0; IR ($CHCl_3$): 3601, 3503, 3307, 2931, 2858, 1467, 1378, 1255, 1105, 992, 909, 837 cm^{-1}; MS (FAB) *m/z* (relative intensity) 609 ($M+Na^+$, 18), 249 (8), 73 (100); HRMS (FAB^+) calcd for $C_{34}H_{58}NaO_4Si_2$ ($M+Na^+$) 609.3771, found 609.3766. To a solution of the obtained diol (370 mg, 0.640 mmol) in dichloromethane (6.0 mL) were successively added 2,2-dimethoxypropane (0.784 mL, 6.40 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate at 0 °C and the reaction mixture was stirred for 1 h. After being poured into a saturated sodium bicarbonate solution, the aqueous layer was extracted with diethyl ether. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 20:1 hexane/ethyl acetate) to furnish a major diastereomer **32** (288 mg, 74%) as a colorless oil along with a minor diastereomer (21.4 mg, 5.6%). **32**; $[\alpha]_D^{21}=3.0$ ($c=0.70$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.43–7.19 (m, 4H), 6.22 (dd, 1H, $J=15.3$, 10.4 Hz), 6.04 (dd, 1H, $J=14.8$, 10.4 Hz), 5.68 (m, 2H), 4.93 (m, 1H), 4.83 (t, 1H, $J=6.1$ Hz), 4.52 (m, 1H), 3.77 (m, 1H), 2.57 (ddd, 1H, $J=16.6$, 6.1, 2.6 Hz), 2.47 (ddd, 1H, $J=16.6$, 6.1, 2.6 Hz), 2.10–2.00 (m, 4H), 1.96 (t, 1H, $J=2.6$ Hz), 1.52–1.32 (m, 4H), 1.47 (s, 3H), 1.46 (s, 3H), 1.11 (d, 3H, $J=6.1$ Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 144.1, 142.4, 135.6, 131.4, 130.7, 129.6, 128.1, 124.9, 124.8, 123.4, 100.7, 81.8, 73.6, 69.9, 68.4, 68.3, 67.7, 39.3, 39.2, 32.6, 31.0, 25.9, 25.8, 25.6, 25.4, 25.1, 23.9, 18.2, 18.1, −4.3, −4.7, −4.8, −4.9; IR ($CHCl_3$): 3307, 2931, 2858, 1467, 1378, 1255, 1105, 992, 909, 837 cm^{-1}; MS (FAB) *m/z* (relative intensity) 649 ($M+Na^+$, 3.0), 587 (4.0), 176 (8.2), 73 (100); HRMS (FAB^+) calcd for $C_{37}H_{62}NaO_4Si_2$ ($M+Na^+$) 649.4084, found 649.4077.

4.1.27. (2*Z*,4*E*,7*S*)-7-*tert*-Butyldimethylsilyloxy-7-[3-[(4*R*,6*R*)-6-[(1*E*,3*E*,8*R*)-8-(*tert*-butyldimethylsilyloxy)nona-1,3-dienyl]-2,2-dimethyl-1,3-dioxan-4-yl]]phenylhepta-2,4-dienoic acid ethyl ester (33). (Entry 1): To a cooled solution of alkyne **32** (100 mg, 0.159 mmol) in THF (1.9 mL) was added a 1.58 M solution *n*-butyllithium in *n*-hexane (0.190 mmol, 0.120 mL). The solution was stirred at −78 °C for 1 h, before being quenched with a solution of cyanogen bromide in THF (0.190 mmol, 0.190 mL). The reaction mixture was stirred at −78 °C for an additional hour and then allowed to warm to −40 °C. The reaction mixture was then poured into a sodium hydroxide solution (1 M) and extracted with diethyl ether. The combined organic layers were dried and filtered through a pad of Celite. After concentration in vacuo, the crude bromoalkyne (87.0 mg, 0.123 mmol) was dissolved in benzene (1.4 mL).

The addition of bis(triphenylphosphine)palladium(II)-chloride (5.4 mg, 0.5 mol%) to the solution was followed by a slow addition of tri-*n*-butyltinhydride (0.066 mL, 0.34 mmol) over 5 min. The solution was stirred at room temperature for 30 min before removal of the solvent under reduced pressure. The crude vinyl stannane was dissolved in DMF (0.43 mL) and to the solution were added (*Z*)-3-iodopropenoate (15.0 mg, 0.0664 mmol), $Pd_2(dba)_2$ (3.1 mg, 0.0039 mmol), and diisopropylethylamine (0.011 mL, 0.064 mmol). The whole was stirred at room temperature for 1 h before being quenched with a saturated sodium bicarbonate solution. The organic layer was extracted with ether. The extract was washed with water and brine, dried, condensed in vacuo. The residue was purified by SiO_2 column chromatography (elution: 10:1 hexane/ethyl acetate) to give **33** as a colorless oil (15.6 mg, 32% in 3 steps). (Entry 4): To a cooled solution of alkyne **32** (110 mg, 0.159 mmol) in THF (1.7 mL) was added a 1.58 M solution of *n*-butyllithium (0.190 mmol, 0.120 mL) in *n*-hexane, and the mixture was stirred at −78 °C for 1 h. After a 1 M solution of cyanogen bromide (0.190 mmol, 0.190 mL) in THF was added to the mixture, the reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to −40 °C over a 10 min period. The mixture was poured into a 1 M sodium hydroxide solution and the resulting mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried, and filtered through a pad of Celite. The solvent was removed under reduced pressure to provide a crude product, which was dissolved in benzene (1.4 mL). To the mixture was added bis(triphenylphosphine)palladium(II)chloride (6.1 mg, 0.5 mol%), which was followed by a slow addition of tri-*n*-butyltinhydride (0.060 mL, 0.31 mmol) over a 5 min period. After the mixture was stirred at room temperature for 30 min and concentrated in vacuo, the obtained vinylstannane was dissolved in NMP (1.4 mL). To the mixture were successively added (*Z*)-3-iodopropenoate (38.4 mg, 0.170 mmol) and copper (I) 2-thiophenecarboxylate (40.5 mg, 0.212 mmol) at 0 °C. The reaction mixture was then diluted with ether and filtered through a plug of alumina to remove copper salts and tri-*n*-butyltin thiophene-2-carboxylate. The combined filtrates were washed with brine, dried, and the concentrated in vacuo. Several drops of triethylamine were added to the residue before purification by SiO_2 column chromatography (elution: 100:1:0.5 to 100:20:0.5 hexane/ethyl acetate/triethylamine) to give **33** as a colorless oil (72.6 mg, 58%). $[\alpha]_D^{23}=1.50$ ($c=1.75$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.38 (dd, 1H, $J=11.3$, 11.3 Hz), 7.33–7.10 (m, 4H), 6.51 (dd, 1H, $J=11.3$, 11.3 Hz), 6.21 (dd, 1H, $J=15.1$, 10.5 Hz), 6.03 (m, 2H), 5.68 (m, 2H), 5.57 (d, 1H, $J=11.3$ Hz), 4.91 (m, 1H), 4.72 (m, 1H), 4.52 (m, 1H), 4.17 (q, 2H, $J=7.0$ Hz), 3.76 (m, 1H), 2.53 (m, 2H), 2.03 (m, 4H), 1.48 (s, 3H), 1.46 (s, 3H), 1.44–1.31 (m, 4H), 1.28 (t, 3H, $J=7.0$ Hz), 1.10 (d, 3H, $J=6.1$ Hz), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), −0.01 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 166.5, 145.1, 145.0, 142.6, 141.7, 135.7, 131.4, 130.8, 129.7, 129.0, 128.3, 124.7, 124.6, 123.4, 116.1, 100.7, 74.7, 68.4, 68.3, 67.8, 59.8, 44.5, 39.4, 39.2, 32.6, 25.9, 25.7, 25.6, 25.4, 25.1, 23.8, 18.1, 18.0, 14.2, −4.5, −4.7, −4.8, −5.0; IR ($CHCl_3$): 2955, 2931, 2857, 1706, 1638, 1602, 1467, 1378, 1255, 1231, 1074, 996, 904, 836 cm^{-1}; MS (FAB) *m/z* (relative intensity) 749 ($M+Na^+$, 5.0), 587 (10), 247 (9.2), 73 (100); HRMS (FAB^+) calcd for $C_{42}H_{70}NaO_6Si_2$ ($M+Na^+$) 749.4609, found 749.4615.

4.1.28. (2*Z*,4*E*,7*S*)-7-[3-[(4*R*,6*R*)-6-[(1*E*,3*E*,8*R*)-8-Hydroxynona-1,3-dienyl]-2,2-dimethyl-1,3-dioxan-4-yl]]-phenyl-7-(1-methoxy-1-methylethoxy)hepta-2,4-dienoic acid ethyl ester (34). To a solution of **33** (76.0 mg, 105 μmol) in THF (1.0 mL) was added a 1 M solution of tetra-*n*-butylammonium fluoride (0.21 mL, 0.21 mmol) in THF at 0 °C, and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with a mixture of ether and a saturated ammonium chloride solution and then the resulting mixture was poured into a saturated sodium bicarbonate solution. The mixture was extracted with diethyl ether several times. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 4:1 hexane/ethyl acetate) to give alcohol (58.9 mg, 92%) as a colorless oil; $[\alpha]_D^{26}=+8.60$ ($c=1.01$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ:7.48 (dd, 1H, $J=11.3$, 11.3 Hz), 7.41–7.21 (m, 4H), 6.54 (dd, 1H, $J=11.3$, 11.3 Hz), 6.22 (dd, 1H, $J=15.3$, 10.4 Hz), 6.05 (m, 2H), 5.69 (m, 2H), 5.60 (d, 1H, $J=11.3$ Hz), 4.93 (m, 1H), 4.79 (m, 1H), 4.53 (m, 1H), 4.17 (q, 2H, $J=7.3$ Hz), 3.78 (m, 1H), 2.65 (m, 2H), 2.14 (br, 1H), 2.06 (m, 4H), 1.48 (s, 6H), 1.45–1.32 (m, 4H), 1.29 (t, 3H, $J=7.3$ Hz), 1.11 (d, 3H, $J=5.8$ Hz), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 166.5, 144.5, 144.1, 142.9, 140.3, 135.7, 131.5, 130.6, 129.6, 129.5, 128.7, 125.5, 124.9, 123.4, 116.7, 100.8, 73.6, 68.4, 68.3, 67.8, 59.9, 42.6, 39.4, 39.1, 32.6, 25.8, 25.5, 25.3, 25.0, 23.8, 18.0, 14.2, −4.5, −4.8; IR ($CHCl_3$): 3686, 3026, 2993, 2932, 2858, 1705, 1603, 1466, 1377, 1193, 994 cm^{-1}; MS (FAB) *m/z* (relative intensity) 635 ($M+Na^+$, 64), 211 (11), 176 (12), 91 (12), 73 (100); HRMS (FAB^+) calcd for $C_{36}H_{56}NaO_6Si$ ($M+Na^+$) 635.3744, found 635.3738. To a cooled solution of the obtained alcohol (58.9 mg, 96.2 μmol) in dichloromethane (1.0 mL) were added 2-methoxypropene (18.4 μL, 193 μmol) and a catalytic amount of pyridinium *p*-toluenesulfonate at 0 °C and the mixture was stirred for 1 h. After being poured into a saturated sodium bicarbonate solution, the mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 85:15:0.5 hexane/ethyl acetate/triethylamine) to furnish ether (53.2 mg, 82%) as a colorless oil; $[\alpha]_D^{31}=+7.3$ ($c=0.74$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ:7.36 (dd, 1H, $J=11.3$, 11.3 Hz), 7.30–7.11 (m, 4H), 6.48 (dd, 1H, $J=11.3$, 11.3 Hz), 6.22 (dd, 1H, $J=15.1$, 10.5 Hz), 6.04 (dd, 1H, $J=15.0$, 10.5 Hz), 5.94 (m, 1H), 5.69 (m, 2H), 5.56 (d, 1H, $J=11.3$ Hz), 4.92 (m, 1H), 4.76 (t, 1H, $J=6.6$ Hz), 4.52 (m, 1H), 4.17 (q, 2H, $J=7.2$ Hz), 3.78 (m, 1H), 3.08 (s, 3H), 2.66 (ddd, 1H, $J=14.2$, 7.3, 7.2 Hz), 2.55 (ddd, 1H, $J=14.2$, 6.9, 6.6 Hz), 2.04 (m, 4H), 1.48 (s, 3H), 1.47 (s, 3H), 1.44–1.31 (m, 4H), 1.38 (s, 3H), 1.28 (t, 3H, $J=7.2$ Hz), 1.12 (s, 3H), 1.11 (d, 3H, $J=6.1$ Hz), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 166.5, 144.8, 144.5, 142.6, 141.1, 135.7, 131.4, 130.7, 129.6, 129.0, 128.4, 125.3, 124.6, 124.0, 116.2, 101.1, 100.7, 72.8, 68.4, 68.3, 67.7, 59.8, 49.3, 42.6, 39.4, 39.1, 32.6, 26.0, 25.8, 25.5, 25.3, 25.1, 25.0, 23.8, 18.1, 14.2, −4.5, −4.8; IR ($CHCl_3$): 2994, 2933, 2850, 1707, 1634, 1603, 1459, 1378, 1233, 1217, 1199, 1073, 1014, 995 cm^{-1}; MS (FAB) *m/z* (relative

intensity) 707 ($M+Na^+$, 28), 176 (13), 173 (8.0), 73 (100); HRMS (FAB^+) calcd for $C_{40}H_{64}NaO_7Si$ ($M+Na^+$) 707.4319, found 707.4311. To a solution of the obtained ether (53.2 mg, 78.6 μmol) in THF (0.8 mL) was added a 1/1 mixture of tetra-*n*-butylammonium fluoride and acetic acid (1.2 mL) at room temperature. After being stirred for 24 h and poured into a saturated sodium bicarbonate solution, the mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried, and then concentrated in vacuo. The residue was purified by SiO_2 column chromatography (elution: 80:20:0.5 hexane/ethyl acetate/triethylamine) to give **34** (40.0 mg, 89%) as a colorless oil; $[\alpha]_D^{31}=+11$ ($c=0.74$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ:7.35 (dd, 1H, $J=11.3$, 11.3 Hz), 7.30–7.11 (m, 4H), 6.48 (dd, 1H, $J=11.3$, 11.3 Hz), 6.22 (dd, 1H, $J=15.3$, 10.4 Hz), 6.05 (dd, 1H, $J=15.3$, 10.4 Hz), 5.94 (m, 1H), 5.69 (m, 2H), 5.56 (d, 1H, $J=11.3$ Hz), 4.92 (m, 1H), 4.76 (t, 1H, $J=6.4$ Hz), 4.52 (m, 1H), 4.17 (q, 2H, $J=7.2$ Hz), 3.79 (m, 1H), 3.08 (s, 3H), 2.66 (ddd, 1H, $J=14.1$, 7.1, 7.1 Hz), 2.55 (ddd, 1H, $J=14.1$, 6.9, 6.7 Hz), 2.06 (m, 4H), 1.49 (s, 3H), 1.49 (s, 3H), 1.44–1.31 (m, 4H), 1.40 (s, 3H), 1.28 (t, 3H, $J=7.2$ Hz), 1.19 (d, 3H, $J=6.1$ Hz), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 166.5, 144.8, 144.5, 142.6, 141.1, 135.3, 131.3, 130.9, 129.9, 129.0, 128.4, 125.3, 124.6, 124.0, 116.2, 101.2, 100.7, 72.8, 68.3, 68.0, 67.7, 59.8, 49.3, 42.6, 39.4, 38.7, 32.5, 26.0, 25.5, 25.3, 25.1, 25.0, 23.5, 14.2; IR ($CHCl_3$): 3700, 2995, 2935, 2354, 1708, 1641, 1603, 1378, 1187, 1066, 1034, 994, 908 cm^{-1}; MS (FAB) *m/z* (relative intensity) 593 ($M+Na^+$, 33), 176 (14), 173 (6.2), 73 (100); HRMS (FAB^+) calcd for $C_{34}H_{50}NaO_7$ ($M+Na^+$) 593.3454, found 593.3449.

4.1.29. (2*R*,4*R*,5*E*,7*E*,12*R*,15*E*,17*E*,20*S*)-2,4-Dihydroxy-20-(1-methoxy-1-methylethoxy)-13-oxabicyclo[19.3.1]-pentacosa-1(25),5,7,15,17,21,23-heptaen-14-one dimethylacetal (36). A solution of ester **34** (35.0 mg, 61.3 μmol) in a 1/1/1 mixture of THF, ethanol, and 3 N KOH (0.6 mL) was heated to 60 °C for 2 h. After the solvent was evaporated under reduced pressure, diethyl ether and a saturated ammonium chloride solution were added to the residue. The resulting mixture was extracted with diethyl ether. The combined extracts were dried and filtered through a pad of Celite. Triethylamine was added to the filtrates before evaporation of the solvents. To a solution of the triethylamine salt in THF (0.6 mL) was added 2,4,6-trichlorobenzoyl chloride (30.0 mg, 122 μmol) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. After removal of the solvents, DMAP (45.0 mg, 368 μmol) was added to a solution of the obtained residue in toluene (6.0 mL) at room temperature. The mixture was stirred for 1 h. After the solvent was removed under reduced pressure, the residue was purified by SiO_2 column chromatography (elution: 85:15:0.5 hexane/ethyl acetate/triethylamine) to give **36** (14.0 mg, 44% in 3 steps); $[\alpha]_D^{31}=+63$ ($c=0.90$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.44–7.28 (m, 3H), 7.05 (dd, 1H, $J=11.1$, 11.1 Hz), 6.84 (s, 1H), 6.22–5.91 (m, 3H), 5.74 (d, 1H, $J=15.9$ Hz), 5.70 (m, 1H), 5.70 (m, 1H), 5.60 (m, 1H), 5.51 (m, 1H), 4.90 (m, 2H), 4.66 (dd, 1H, $J=9.8$, 4.0 Hz), 4.53 (m, 1H), 3.15 (s, 3H), 2.55 (m, 2H), 2.11 (m, 2H), 1.93 (t, 2H, $J=7.2$ Hz), 1.48 (s, 6H), 1.44–1.31 (m, 4H), 1.40 (s, 3H), 1.20 (d, 3H, $J=6.4$ Hz), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 166.5, 144.1, 143.4, 142.2, 139.5, 134.6, 131.3, 131.2, 130.7, 130.0, 129.2, 124.4, 124.3, 124.0, 120.5, 101.2, 100.5, 73.0, 70.4, 67.9, 67.8, 49.2, 41.9, 39.5, 34.1, 31.3, 26.4, 26.1, 25.7, 24.9, 23.5, 19.6; IR ($CHCl_3$): 3002, 2935, 2870, 2366, 2340, 1701, 1640, 1615, 1445, 1379, 1249, 1201, 1151, 1111, 1074, 1034, 996, 908, 739 cm^{-1}; MS (FAB) *m/z* (relative intensity) 547 ($M+Na^+$, 38), 176 (10), 73 (100); HRMS (FAB^+) calcd for $C_{32}H_{44}NaO_6$ ($M+Na^+$) 547.3036, found 547.3032.

4.1.30. (2*R*,4*R*,5*E*,7*E*,12*R*,15*E*,17*E*,20*S*)-2,4,20-Trihydroxy-13-oxabicyclo[19.3.1]pentacosa-1(25),5,7,15,17,21,23-heptaen-14-one (1b). The lactone **36** (9.0 mg, 17 μmol) was dissolved in wet methanol (0.3 mL) and the mixture was treated with a catalytic amount of PPTS. After being stirred at room temperature for 1 h, the mixture was concentrated in vacuo and the resulting residue was purified by SiO_2 column chromatography (elution: 1:2 hexane/ethyl acetate) to give **1b** (4.3 mg, 61%) as a white amorphous; $[\alpha]_D^{23}=93$ ($c=0.40$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.45–7.30 (m, 2H), 7.19 (m, 2H), 7.08 (dd, 1H, $J=15.3$, 11.0 Hz), 6.15 (m, 2H), 6.02 (m, 1H), 5.93 (m, 1H), 5.72 (d, 1H, $J=15.3$ Hz), 5.61 (m, 2H), 5.03 (m, 1H), 4.97 (m, 1H), 4.92 (dd, 1H, $J=6.7$, 2.4 Hz), 4.41 (m, 1H), 3.56 (br, 1H), 2.79 (m, 1H), 2.69 (br, 1H), 2.62 (m, 1H), 2.21 (br, 1H), 2.09 (m, 2H), 1.98 (m, 2H), 1.55–1.37 (m, 4H), 1.22 (d, 3H, $J=6.4$ Hz); ^{13}C NMR ($CDCl_3$) δ: 166.7, 143.9, 137.7, 134.6, 132.6, 131.7, 130.7, 130.3, 129.2, 129.0, 128.4, 124.9, 124.8, 123.7, 121.1, 73.4, 71.7, 70.5, 70.4, 44.1, 41.8, 34.4, 31.5, 24.1, 19.9; IR ($CHCl_3$): 3559, 3156, 2254, 1794, 1697, 1642, 1466, 1381, 1096, 991 cm^{-1}; MS (FAB) *m/z* (relative intensity) 435 ($M+Na^+$, 10), 281 (10), 207 (10), 176 (19), 147 (32), 73 (93), 55 (100); HRMS (FAB^+) calcd for $C_{25}H_{32}NaO_5$ ($M+Na^+$) 435.2147, found 435.2154.

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Reaction of 3-phenylisoxazole with alkyllithiums

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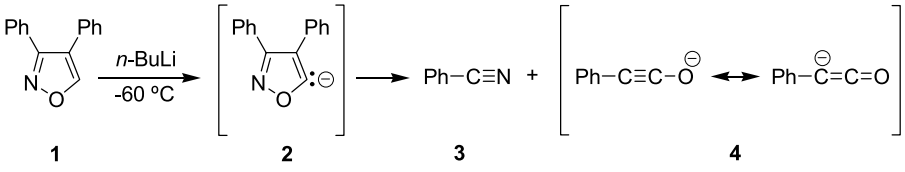
Abstract—Alkyllithiums react with 3-phenylisoxazole giving C_5–H abstraction followed either mainly by ring fragmentation to benzonitrile and ethynolate ion (in the case of *t*-BuLi) or (less hindered alkyllithiums: *n*-BuLi, EtLi, MeLi) also by formation of alkylated enaminones. Appreciable amounts of 2-alkyl-4,6-diphenylpyrimidines have also been isolated for certain alkyllithiums (EtLi and MeLi). This is at variance with the reported behaviour with hindered lithium amides (LTMP) for which only C_5–H abstraction followed by ring fragmentation was described. The mechanistic significance of the observed results is discussed.

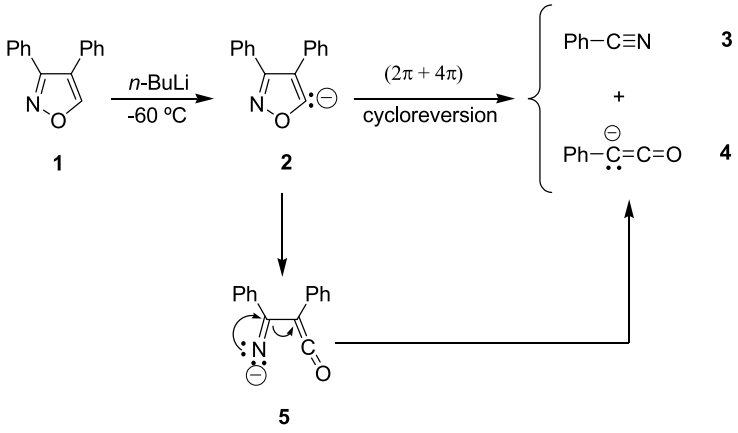
1. Introduction

Reaction of 3,4-diphenylisoxazole with strong bases (lithium dialkylamides or *n*-BuLi) is known to give the C_5–H abstraction followed by ring fragmentation of the formed anion with formation of benzonitrile and a ynolate ion, as depicted in Scheme 1.

As for the fragmentation reaction, it was not clear whether a pericyclic [$(2\pi+4\pi)$ cycloreversion] or a stepwise



Scheme 1.



Scheme 2.

Keywords: 3-Phenylisoxazole ring-fragmentation; Alkyllithiums; Enaminones; Pyrimidines.
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mechanism (via lithium iminoketene intermediate **5**) was involved (Scheme 2).[1]

A similar reaction was carried out starting from 3-phenylisoxazole (**6**), but using a very hindered lithium amide (LTMP) (Scheme 3).[1]

We have repeated the reaction of 3-phenylisoxazole using *t*-butyllithium, observing apparently the same behaviour, as it can be deduced by the formation of *t*-butyl phenyl ketone (**10**) as the main (86% yield) isolated product after quenching with aqueous NH_4Cl (Scheme 4).

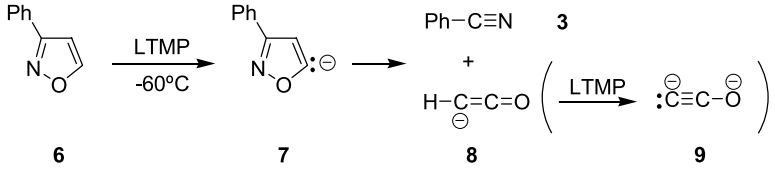
The above ketone **10**, in fact, is just what one could have expected as the ultimate product (under the used quenching conditions) by C_5–H abstraction and subsequent fragmentation, followed by further reaction of the formed benzonitrile with *t*-BuLi and final hydrolysis of the lithium imine intermediate (Scheme 5).

On the other hand, concerning the reaction with *t*-BuLi, full investigation of the reaction products revealed the formation also of the enaminone **11** as the minor product (Scheme 4).

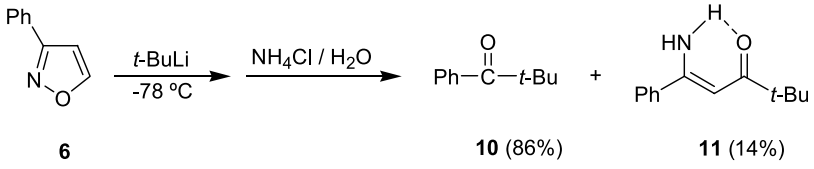
We repeated the reaction with *n*-BuLi, observing an increasing formation of enaminone (Scheme 6 and Table 1).

Quenching the reaction mixture with aqueous NH_4Cl allowed, in fact, isolation of comparable amounts of valerophenone **12** (indicative of ring fragmentation) and 1-amino-1-phenyl-1-hepten-3-one **13**, together with its *N*-acetyl derivative **14**, presumably formed by further reaction with ketene from ynolate ion **8**.

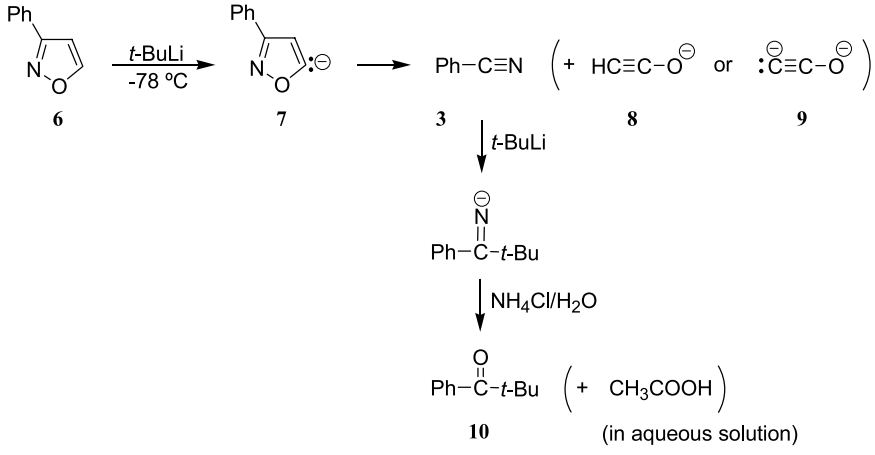
Formation of enaminones from isoxazoles using alkyllithiums is unprecedented. In general, in fact, they are obtained from isoxazoles by selective reductive cleavage of O–N bond by a number of reducing agents (e.g. by catalytic



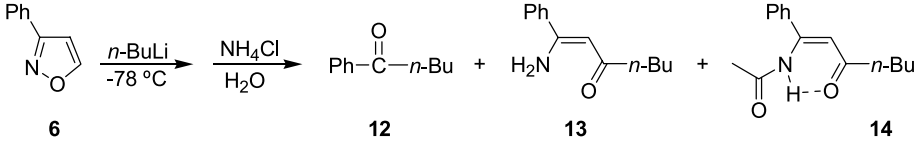
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

Table 1. Percentages of products[a] formed in the reaction of 3-phenylisoxazole (**6**) and *n*-BuLi

Substrate: *n*-BuLi	Time (h)	Valerophenone (**12**)	(*Z*)-1-Amino-1-phenyl-1-hep-ten-3-one (**13**)	*N*-[(*Z*)-3-oxo-1-phenylhept-1-enyl]acetamide (**14**)
1:2	1	50	40	10
1:3	1	45	45	10
1:5	8	37	43	20

[a] % Determined by ^{1}H NMR spectra recorded on reaction crudes.

hydrogenation).[2–4] The latter is also a rather common reaction so that the isoxazoles are just considered masked forms of enaminones (as well as of the related beta-dicarbonyl compounds).

Novelty is also represented by the particular enaminones that are formed by this way (Schemes 4 and 6). At variance with the reductive methods, in fact, simultaneous formation of a new C–C bond occurs, so that, by using different alkyllithiums, variously elongated enaminones could be directly obtained in this case.

Formation of enaminones seems also to be very interesting in relation to the mechanism of fragmentation of isoxazole anions (both **2** and **7**), suggesting a stepwise rather than a pericyclic mechanism.

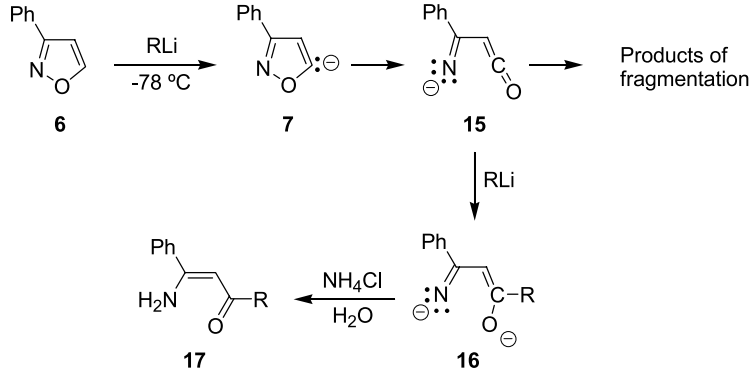
Enaminones **17** (Scheme 7), in fact, could just be the ultimate products of further reaction of the lithium iminoketene **15** (i.e. the postulated intermediate of the stepwise mechanism of fragmentation) with a second molecule of RLi, as reported in Scheme 7.

However, a completely different mechanism of formation of enaminones cannot in principle be excluded.

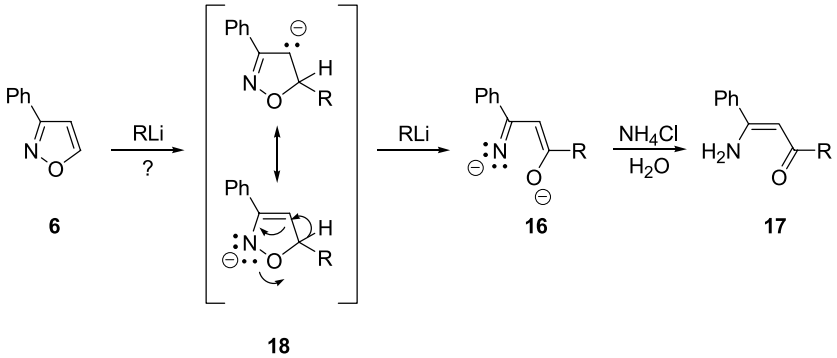
In this case, enaminone would be formed by direct nucleophilic addition of RLi onto the position 5 of isoxazole, as hypothesized in Scheme 8.

Yet, formation of enaminone by this way under the used conditions can be ruled out on the basis of the following experiments.

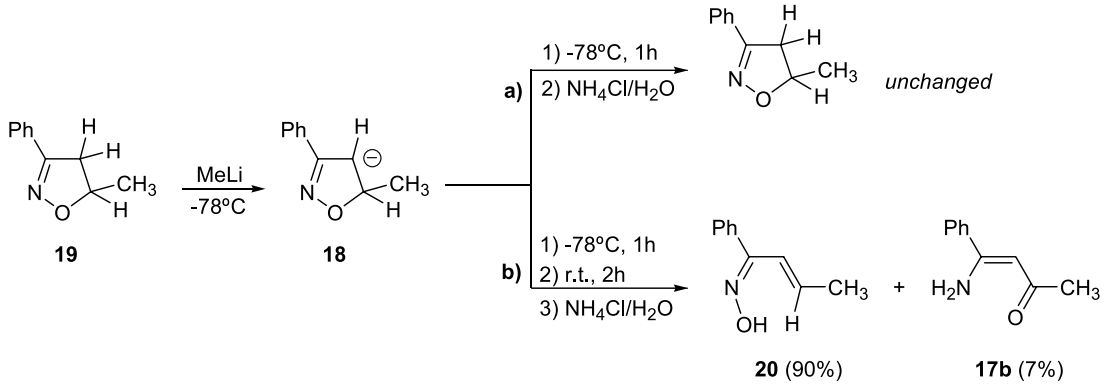
Independent generation of **18** (R=Me) by treating 3-phenyl-5-methylisoxazoline[5] **19** with MeLi under conditions strictly similar (−78 °C; MeLi/substrate=3:1; 1 h) to those used in reactions of 3-phenylisoxazole with MeLi and subsequent quenching with aq. NH_4Cl indicated, in fact, no formation of enaminone, the starting isoxazoline being recovered substantially unchanged (Scheme 9, route a). At variance, by the same treatment of 3-phenylisoxazole, ca. 40% of enaminone **17b** and related product *N*-acetylenaminone **22b** are instead formed (Table 2).



Scheme 7.



Scheme 8.



Scheme 9.

Table 2. Percentages of products[a] formed in the reaction of 3-phenylisoxazole (**6**) and EtLi or MeLi

Substrate: EtLi	Time (h)	Propiophenone (**21a**)	(*Z*)-1-Amino-1-phenyl-1-penten-3-one (**17a**)	*N*-[(*Z*)-3-Oxo-1-phenylpent-1-enyl]-acetamide (**22a**)	2-Ethyl-4,6-diphenyl-pyrimidine (**23a**)
1:3	1	40	40	5	7
Substrate: MeLi	**Time (h)**	**Acetophenone (21b)**	**(*Z*)-1-Amino-1-phenyl-1-buten-3-one (17b)**	***N*-[(*Z*)-3-Oxo-1-phenylbut-1-enyl]-acetamide (22b)**	**2-Methyl-4,6-diphenyl-pyrimidine (23b)**
1:3	15′	73	8	—	19
1:3	1	61	28	—	11
1:3	8	50	30	10	10

[a] % Determined by ^{1}H NMR spectra recorded on reaction crudes.

Thus, under our conditions, the main (or the only) mechanism for formation of enaminone should be the one depicted in Scheme 7, which also means, as said, a stepwise mechanism of isoxazole ring fragmentation.

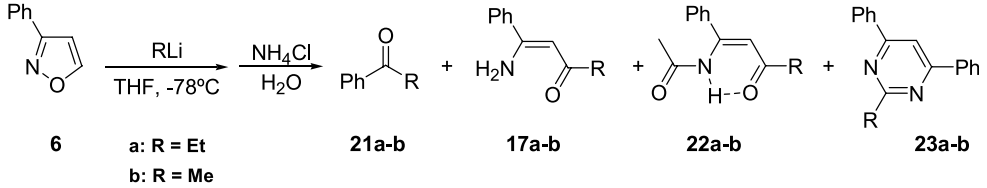
It must be pointed out, however, that little amounts of enaminone can actually be generated also from **18**, but this requires higher temperatures. By allowing, in fact, the reaction mixture containing **18** (from 3-phenyl-5-methyl-isoxazoline and MeLi) to warm to room temperature (two more hours), 7% of enaminone **17b** together with 90% of an unsaturated oxime **20** (already described as the product formed from **18** at higher temperatures)[6] are isolated (Scheme 9, route b).

On the other hand, concerning the reactions of MeLi (and EtLi) with 3-phenylisoxazole, an additional product of reaction [2-ethyl-4,6-diphenylpyrimidine (**23a**) and 2-methyl-4,6-diphenylpyrimidine (**23b**) from EtLi and MeLi, respectively] is also formed (Scheme 10 and Table 2).

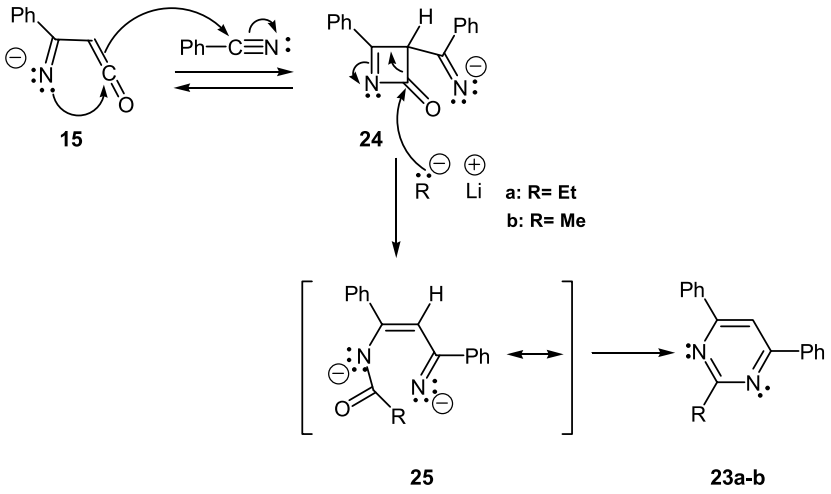
A possible mechanism for formation of 2-alkyl-4,6-diphenylpyrimidines is proposed in Scheme 11, in which 1-azetin-4-one **24**, originated from benzonitrile and, once again, the iminoketene anion **15**, is hypothesized as the key reaction intermediate. Iminoketenes (and by obvious extension also iminoketene anions **15**) could be, in fact, precursors of azetinones.[7] Furthermore, the actual existence of some 1-azetin-4-ones has previously also been evidenced.[8]

Subsequent nucleophilic attack by RLi should then cause the azetinone ring-opening (by C–C rather than C–N bond breaking possibly because of the resonance stabilization of the open intermediate formed by this way), and, finally, a new ring-closing with aromatization to give the observed pyrimidine **23a**-**b**.

Accordingly, the fact that the relative amount of pyrimidine decreases from MeLi to EtLi and that no pyrimidine is observed for both *n*-BuLi and *t*-BuLi should reflect, as expected, an increasing difficulty in the nucleophilic attack of RLi onto azetinone intermediate **24** on going from less to more hindered alkyllithiums. Further investigations are in progress on this point.



Scheme 10.



Scheme 11.

In conclusion, the reaction of 3-phenylisoxazole (and likely of other isoxazoles similarly 'protected' at the position 3) with *t*-BuLi could be an alternative way (with respect to the reported use of LTMP)[1] for accomplishing, in a substantially clean manner, the C_5–H abstraction and subsequent ring fragmentation. By this way benzonitrile (further reacting with *t*-BuLi) and ethynolate ion (a potentially starting material, in turn, in the synthesis of other interesting products, e.g. β-lactams)[9,10] are formed.

However, with *t*-BuLi itself, and to a much greater extent with other less hindered alkyllithiums (*n*-BuLi, EtLi, MeLi), an interesting and unprecedented reaction is also observed. In the latter case, no ring fragmentation but only O–N bond-breaking takes place, with direct formation of elongated enaminones (useful starting molecules, again, for the construction of various other structures).[11–13] Depending on RLi, appreciable amounts of compounds (*N*-acetyl-enaminones and pyrimidines) due to a further interaction of the primary products of both reactions are also isolated.

Apart from some synthetic utility, direct formation of alkylated enaminones **11** and **17** as well as of alkylated pyrimidines **23a** and **23b** seems to be interesting especially from a mechanistic point of view. In particular, it provides useful indications concerning the not previously defined mechanism of the base-induced ring-fragmentation of 3-arylisoxazoles (and by extension, of 3,4-diarylisoxazoles), supporting a stepwise rather than a synchronous mechanism of reaction.

Wider investigations are in progress aimed to extend the reaction to other alkyllithiums and isoxazoles, as well as to possibly optimize the reaction conditions in order to more selectively favour each of the reaction products.

2. Experimental

2.1. General methods

Melting points taken on Electrothermal apparatus were uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 300 MHz spectrometer and chemical shifts are reported in parts per million (δ). Absolute values of the coupling constant are reported. FT-IR spectra were recorded on a Perkin–Elmer 681 spectrometer. GC analyses were performed by using a HP1 column (methyl siloxane; 30 m × 0.32 mm × 0.25 μm film thickness) on a HP 6890 model, Series II. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator, the spots on the TLC were observed under ultraviolet light or were visualized with I_2 vapour. Chromatography was conducted by using silica gel with an average particle size of 60 μm, a particle size distribution 40–63 μm and 230–400 ASTM. GC–MS analyses were performed on a HP 5995C model and microanalyses on an Elemental Analyzer 1106-Carlo Erba-instrument.

2.2. Materials

3-Phenylisoxazole (**6**) has been synthesized from benzonitrile oxide and the enolate ion of acetaldehyde.[14] 3-Phenyl-5-methyl-2-isoxazoline has been synthesized from benzonitrile oxide and propene.[5]

Tetrahydrofuran (THF) from commercial source was purified by distillation (twice) from sodium wire under nitrogen. Standardized 2.5 M *n*-butyllithium in hexane, 0.5 M ethyllithium in cyclohexane/toluene, 1.6 M methyllithium in diethyl ether and 1.7 M *t*-butyllithium in pentane were purchased from Aldrich Chemical Co. Titration of *n*-butyllithium and *t*-butyllithium was performed by using *N*-pivaloyl-*o*-toluidine.[15] All other chemicals and solvents were commercial grade further purified by distillation or crystallization prior to use. 2,2-Dimethyl-1-phenylpropan-1-one (pivalophenone) (**10**), 1-phenylpentan-1-one (valerophenone) (**12**), 1-phenylpropanone (propiophenone) (**21a**) and 1-phenylethanone (acetophenone) (**21b**) isolated as products of the reaction mentioned above had analytical and spectroscopic data identical to those ones commercially available.

2.3. Reaction of 3-phenylisoxazole (6) with *t*-BuLi

0.90 M *t*-Butyllithium in hexane (1.4 mL, 1.26 mmol) was

added to a solution of the isoxazole (61 mg, 0.42 mmol) in THF (2 mL) at −78 °C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and one dropping funnels. The brown reaction mixture kept at −78 °C was stirred for 1 h and then quenched by adding aq. NH_4Cl. The two phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=7:3) of the residue afforded the products indicated in the Scheme 4: **10** (86% yield, 59 mg) and **11** (14% yield, 12 mg).

2.3.1. (*Z*)-1-Amino-4,4-dimethyl-1-phenylpent-1-en-3-one (11).[16] 14% Yield (12 mg of yellow oil) ^{1}H NMR ($CDCl_3$, δ): 1.21 (9H, s); 4.90–5.30 (1H, bs, NH: exchanges with D_2O); 5.63 (1H, s); 7.41–7.49 (3H, m, aromatic protons); 7.53–7.57 (2H, m, aromatic protons); 9.80–10.15 (1H, bs, NH: exchanges with D_2O). GC–MS (70 eV) *m*/*z* (rel. int.): 203 (M^+, 9), 160 (4), 147 (17), 146 (100), 128 (2), 117 (7), 104 (11), 103 (19), 91 (13), 77 (6), 41 (4).

2.4. Reaction of 3-phenylisoxazole (6) with *n*-BuLi: general procedure

The amount of 3-phenylisoxazole, *n*-BuLi and solvent indicated below refer to a ratio substrate/*n*-BuLi 1:1. See Table 1 for other substrate/*n*-BuLi ratios.

A 2.21 M solution of *n*-butyllithium in hexane (0.187 mL, 0.414 mmol) was added to a solution of the isoxazole (60 mg, 0.414 mmol) in THF (2 mL) at −78 °C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and two dropping funnels. The brown reaction mixture kept at −78 °C was stirred for the time indicated on Table 1 and then quenched by adding aq. NH_4Cl. The two phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic extracts combined were dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=7:3) of the residue afforded the products indicated in Table 1.

2.4.1. (*Z*)-1-Amino-1-phenyl-1-hepten-3-one (13). 40–45% Yield. Yellow oil; FT-IR (neat): 3488, 3246, 2993, 2956, 2929, 2857, 1717 (w), 1620, 1594, 1573, 1487, 1465, 1379, 1325, 1302, 1154, 1108, 1000, 898 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 0.89–0.94 (3H, t, J=7.3 Hz); 1.29–1.42 (2H, sextet, J=7.3 Hz); 1.57–1.60 (2H, quintet, J=7.3 Hz); 2.34–2.40 (2H, t, J=7.3 Hz); 5.20–5.40 (1H, bs, NH: exchanges with D_2O); 5.43 (1H, s); 7.35–7.47 (3H, m, aromatic protons); 7.52–7.56 (2H, m, aromatic protons); 9.75–10.15 (1H, bs, NH: exchanges with D_2O). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.22, 22.88, 28.34, 42.91, 94.91, 126.51, 129.12, 130.71, 137.60, 161.21, 200.96. GC–MS (70 eV) *m*/*z* (rel. int.): 203 (M^+, 10), 161 (42), 160 (31), 147 (11), 146 (100), 119 (23), 117 (8), 104 (15), 103 (21), 91 (14), 77 (7). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.85; H, 8.37; N, 6.90. Found: C, 76.83; H, 8.39; N, 6.89.

2.4.2. *N*-[(*Z*)-3-Oxo-1-phenylhept-1-enyl]acetamide (14). 10–20% Yield. Yellow oil. FT-IR (neat): 3324, 3061, 3029, 2957, 2927, 2855, 1723, 1642, 1593, 1574, 1493, 1466, 1367, 1282, 1224, 1140, 1076, 1000, 762, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 0.90–0.96 (3H, t, J=7.3 Hz); 1.28–1.43 (2H, sextet, J=7.3 Hz); 1.57–1.68 (2H, quintet, J=7.3 Hz); 2.16 (3H, s, CH_3CO); 2.46–2.53 (2H, t, J=7.3 Hz); 5.60 (1H, s); 7.34–7.41 (5H, m, aromatic protons); 11.70–11.90 (1H, bs, NH: exchanges with D_2O). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.12, 22.61, 25.20, 27.03, 43.85, 108.35, 126.26, 127.52, 128.25, 128.95, 129.90, 136.02, 154.22, 169.16, 203.28. GC–MS (70 eV) *m*/*z* (rel. int.): 245 (M^+, 1), 227 (1), 202 (4), 198 (6), 188 (14), 174 (2), 161 (14), 160 (100), 146 (58), 129 (2), 119 (6), 104 (10), 103 (10), 91 (6), 77 (5), 43 (9). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.75; N, 5.71. Found: C, 73.48; H, 7.77; N, 5.70.

2.5. Reaction of 3-phenylisoxazole (6) with EtLi

0.5 M Ethyllithium in cyclohexane/toluene (16.56 mL, 8.28 mmol) was added to a solution of the 3-phenylisoxazole (400 mg, 2.76 mmol) in THF (15 mL) at −78°C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and a dropping funnel. The brown reaction mixture kept at −78 °C was stirred for 3 h. Then, quenched by adding aq. NH_4Cl. The two phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic extracts were combined, dried with anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl ether =8:2 to 5:5) of the residue afforded the products indicated on Table 2.

2.5.1. (*Z*)-1-Amino-1-phenyl-1-penten-3-one (17a).[17] 40% Yield. Yellow oil. FT-IR (neat): 3358, 3176, 3062, 2969, 2928, 2851, 1720 (w), 1611, 1572, 1529, 1487, 1412, 1293, 1157, 1038, 759, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 1.12–1.17 (3H, t, J=7.5 Hz); 2.37–2.46 (2H, q, J=7.5 Hz); 5.10–5.40 (1H, bs, NH: exchanges with D_2O); 5.44 (1H, s); 7.38–7.49 (3H, m, aromatic protons); 7.50–7.57 (2H, m, aromatic protons); 9.70–10.15 (1H, bs, NH: exchanges with D_2O). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 9.96, 35.96, 94.45, 126.55, 129.14, 130.74, 137.65, 161.19, 201.46. GC–MS (70 eV) *m*/*z* (rel. int.): 175 (M^+, 32), 147 (18), 146 (100), 117 (12), 104 (19), 103 (30), 91 (19), 77 (11), 65 (5), 51 (5). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 7.99. Found: C, 75.41; H, 7.45; N, 8.00.

2.5.2. *N*-[(*Z*)-3-Oxo-1-phenylpent-1-enyl]acetamide (22a). 5% Yield. Yellow oil. The product was not isolated due to the rather small quantity that was formed, and so not fully characterized. Its formation was detected by GC–MS analysis of the reaction crude. GC–MS (70 eV) *m*/*z* (rel. int.): 217 (M^+, 100), 190 (15), 189 (71), 161 (37), 133 (9), 105 (20), 103 (9), 80 (8), 77 (10), 66 (10), 59 (6), 43 (5).

2.5.3. 2-Ethyl-4,6-diphenylpyrimidine (23a). 7% Yield FT-IR (neat): 3062, 3030, 2924, 2853, 1574, 1533, 1496, 1463, 1365, 761, 691 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 1.46–1.53 (3H, t, J=7.6 Hz); 3.08–3.18 (2H, q, J=7.6 Hz); 7.46–7.55 (6H, m, phenyl protons); 7.90 (1H, s, pyrimidine proton); 8.13–8.17 (4H, m, phenyl protons). GC–MS (70 eV) *m*/*z* (rel. int.): 260 (M^+, 95), 259 (100), 232 (16), 231 (9), 129

(7), 128 (6), 104 (13), 102 (16), 77 (9), 76 (7). Anal. Calcd for $C_{17}H_{14}N_2$: C, 83.08; H, 6.15; N, 10.77. Found: C, 83.05; H, 6.16; N, 10.75.

2.6. Reaction of 3-phenylisoxazole (6) with MeLi: general procedure

The amount of 3-phenylisoxazole, MeLi and solvent indicated below refer to a ratio substrate/MeLi 1:3. See Table 2 for other substrate/MeLi ratios).

1.6 M Methyllithium in diethyl ether (2.72 mL, 4.34 mmol) was added to a solution of the 3-phenylisoxazole (210 mg, 1.45 mmol) in THF (7 mL) at −78 °C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and a dropping funnel. The brown reaction mixture kept at −78 °C was stirred for the time indicated on Table 2. Then, quenched by adding aq. NH_4Cl. The two phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl ether =8:2 to 5:5) of the residue afforded the products indicated in Table 2.

2.6.1. (*Z*)-1-Amino-1-phenyl-1-buten-3-one (17b).[18] 30% yield. Yellow oil; FT-IR (neat): 3489, 3406 (w), 3060, 3030, 2929, 2855, 1718 (m-w), 1624, 1593, 1566, 1487, 1360, 1290, 1128, 974 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.16 (3H, s); 5.05–5.30 (1H, bs, NH: exchanges with D_2O); 5.45 (1H, s); 7.40–7.50 (3H, m, aromatic protons); 7.52–7.60 (2H, m, aromatic protons); 9.80–10.10 (1H, bs, NH: exchanges with D_2O). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 30.05, 95.45, 126.46, 129.18, 130.80, 137.50, 161.11, 197.81. GC–MS (70 eV) *m/z* (rel. int.): 161 (M^+, 46), 160 (27), 147 (11), 146 (100), 117 (9), 104 (19), 103 (35), 91 (16), 77 (12), 65 (5), 43 (10). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.53; H, 6.83; N, 8.70. Found: 74.54; H, 6.81; N, 8.69.

2.6.2. *N*-[(*Z*)-3-Oxo-1-phenylbut-1-enyl]acetamide (22b).[19] 3–10% Yield. Yellow oil. FT-IR (neat): 3421, 3030, 2928, 2856, 1713, 1631, 1591, 1570, 1492, 1458, 1366, 1337, 1289, 1176, 1101, 963 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.17 (3H, s); 2.25 (3H, s); 5.61 (1H, s); 7.32–7.44 (5H, m, aromatic protons); 11.70–11.85 (1H, bs, NH: exchanges with D_2O). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.37, 22.91, 108.55, 127.51, 128.25, 129.31, 129.95, 131.23, 135.90, 154.44, 169.12, 200.23. GC–MS (70 eV) *m/z* (rel. int.): 203 (M^+, 2), 185 (5), 161 (12), 160 (100), 146 (49), 117 (4), 104 (8), 103 (10), 91 (6), 77 (7), 51 (3), 43 (18). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.93; H, 6.40; N, 6.90. Found: C, 70.95; H, 6.39; N, 6.89.

2.6.3. 2-Methyl-4,6-diphenylpyrimidine (23b).[20–22] 19% Yield. Mp 90–92 °C (lit.[22] 91–92 °C, lit.[20–21] 96–97 °C), white crystals. FT-IR (neat): 3035, 2928, 2855, 1586, 1576, 1533, 1496, 1449, 1370, 1075, 874 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.87 (3H, s); 7.40–7.55 (6H, m, phenyl protons); 7.89 (1H, s, pyrimidine proton); 8.10–8.20 (4H, m, phenyl protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 26.73, 110.32, 127.49, 128.94, 129.16, 129.25, 130.85, 137.76, 165.13, 168.82. GC–MS (70 eV) *m/z* (rel. int.): 246 (M^+, 100), 245 (10), 231 (3), 206 (11), 205 (69), 204 (70), 178 (7), 128 (6), 103 (10), 102 (58), 77 (11), 76 (14), 51 (7). Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.93; H, 5.69; N, 11.38. Found: C, 82.91; H, 5.70; N, 11.37.

The structure of 2-methyl-4,6-diphenylpyrimidine (**23b**) was also been established by direct comparison with the authentic sample supplied by SPECS and BioSPECS B.V.[23]

2.7. Reaction of 3-phenyl-5-methyl-2-isoxazoline (19)[5] with MeLi

Route a. A 1.6 M solution of MeLi in diethyl ether (1.8 mL, 2.868 mmol) was added to a solution of the isoxazoline **19** (154 mg, 0.956 mmol) in THF (4 mL) at −78°C under nitrogen, using a nitrogen-flushed three necked flask equipped with a magnetic stirrer and a nitrogen inlet. The yellow reaction mixture kept at −78 °C was stirred for one hour and then quenched by adding aq. NH_4Cl. The two phases were separated and the aqueous layer was extracted three times with ethyl acetate. The organic extracts combined were dried with anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. The crude mixture afforded unreacted 3-phenyl-5-methyl-2-isoxazoline **19**.

Route b. A 1.6 M solution of MeLi in diethyl ether (1.234 mL, 1.974 mmol) was added to a solution of the isoxazoline **19** (106 mg, 0.658 mmol) in THF (3 mL) at −78 °C under nitrogen, using a nitrogen-flushed three necked flask equipped with a magnetic stirrer and a nitrogen inlet. The yellow reaction mixture was stirred for 2 h at −78 °C and then was allowed to reach room temperature in two hours. After this time the reaction was quenched by adding aq. NH_4Cl. The two phases were separated and the aqueous layer was extracted three times with ethyl acetate. The organic extracts combined were dried with anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=8:2) of the residue afforded (*E*)-1-phenylbut-2-en-1-one oxime **20** (90%) and (*Z*)-1-amino-1-phenyl-1-buten-3-one **17b** (7%).

2.7.1. (*E*)-1-phenyl-2-buten-1-one oxime (20).[24] 90% Yield. Mp 89–91 °C (lit[23] 88.5 °C), white crystals. FT-IR (KBr): 3260, 3054, 3024, 2913, 2853, 1640, 1497, 1444, 1332, 1089, 957, 765, 699 cm^{-1}.^1H NMR ($CDCl_3$, δ): 1.89 (3H, d, J_3=6.9 Hz, J_4=1.6 Hz); 6.00–6.13 (1H, m); 6.93–7.00 (1H, dq, J_3=15.95 Hz, J_4=1.6 Hz); 7.35–7.47 (5H, m, aromatic protons); 9.00–10.00 (1H, bs, OH: exchanges with D_2O). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 19.2, 121.1, 126.8, 128.5, 128.9, 129.2, 135.3, 139.2, 157.8. GC–MS (70 eV) *m/z* (rel. int.): 161 (M^+, 22), 146 (100), 144 (41), 130 (13), 128 (17), 115 (21), 104 (27), 91 (13), 77 (46), 51 (17).

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Investigations concerning the organolanthanide and group 3 metallocene-catalyzed cyclization–functionalization of nitrogen-containing dienes

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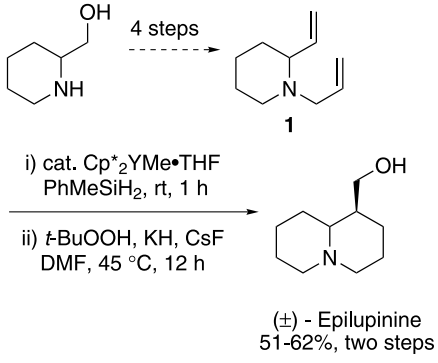
Abstract—Organolanthanide catalyzed cyclization–silylation of nitrogen-containing polyunsaturated systems allows access to core structures commonly found in naturally occurring alkaloids. Nitrogen-containing dienes with various substitution patterns were investigated. The method was most successful for substrates with terminal alkenes. Cyclization upon pendant 1,1-disubstituted olefins was not realized under various conditions. Interestingly, sterically hindered sulfonamides, which were previously believed to render the catalyst inactive, were actually compatible with the catalyst, thus affording the cyclized products after prolonged reaction times. Variations using fused ring systems were also investigated.

1. Introduction

Carbon–carbon bond-forming reactions remain of great importance to synthetic organic chemists. To this end, organolanthanide metallocenes have demonstrated their synthetic utility in the diastereoselective construction of carbocycles from relatively simple acyclic polyunsaturated precursors.[1] Our research utilizing these catalysts has been focused on the selective cyclization–functionalization of dienes,[2] enynes,[3] and dienynes.[4] During the course of our studies, the process was found to be tolerant of tertiary amines, thus providing opportunities for the incorporation of nitrogen atoms within the unsaturated substrate. Successful cyclization–silylations were realized with nitrogen-containing dienes[2c,d] and enynes.[3b] Extension of this method to nitrogen-containing heteroaromatic dienes was effected, demonstrating 'aryl-directed' regioselectivity.[2f] Furthermore, oxidation[5] of the resultant organosilane affords the corresponding amino alcohol, a structural motif commonly found in naturally occurring alkaloids. As a testament to the synthetic utility of the cyclization–silylation–oxidation sequence, diene (**1**) was efficiently cyclized and transformed to (±)-epilupinine (Scheme 1). Remarkably, none of the trans isomers could be observed by NMR. The high diastereoselectivity associated with this process was thought to result from the avoidance of interactions between the catalyst and the piperidine ring during the intramolecular insertion of the more hindered vinyl group of the diene.[2d]



Scheme 1. The synthesis of (±)-epilupinine.

Owing to our successes in constructing relatively complex nitrogen heterocycles selectively from simple polyunsaturated systems, we sought to investigate the scope of the organolanthanide-catalyzed cyclization of nitrogen-containing dienes. The requisite dienes could be easily assembled from commercially available starting materials permitting

Keywords: Organolanthanide-catalyzed; Lanthanide; Organolutetium; Catalysis; Nitrogen heterocycle; Cyclization–silylation reaction.
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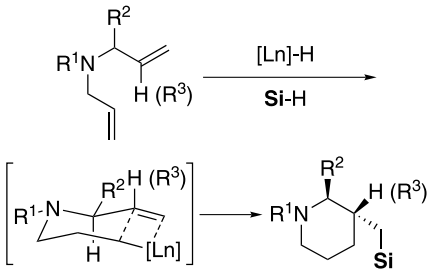


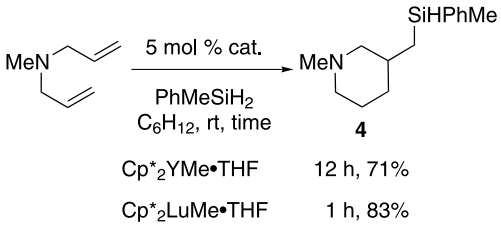
Scheme 2. Variations of nitrogen-containing dienes.

various substitution patterns on the diene to be investigated (Scheme 2). Given the increased steric demands of the cyclization precursors, the potential for the lanthanide to chelate to the initial organometallic intermediate is of greater concern. High diastereoselectivity in the cyclization event was anticipated based on previous studies within our laboratories. Successful application of our protocol would allow ready access to a variety of heterocyclic systems that are widespread in nature.

2. Results and discussion

2.1. Cyclization–functionalization of aminodienes

At the outset of our studies, diallylmethylamine was surveyed for reactivity with $Cp^*_2YMe\cdot THF$ (**2**) and $Cp^*_2LuMe\cdot THF$ (**3**) under a variety of conditions. Investigations commenced with a screening of catalysts, silanes, and solvents to determine the optimal reaction conditions to effect the desired cyclization (Eq. 1). Methylphenylsilane was found to be the required terminator in the reaction to allow the second olefin insertion to occur. Employing phenylsilane resulted in the premature trapping of the initially generated organometallic intermediate, thus affording uncyclized products. Catalyst **2** was effective at providing the desired piperidine **4** in 71% yield after 12 h. However, by simply changing the metal from yttrium to lutetium, the same reaction was completed in 1 h with an increase in yield (83%).

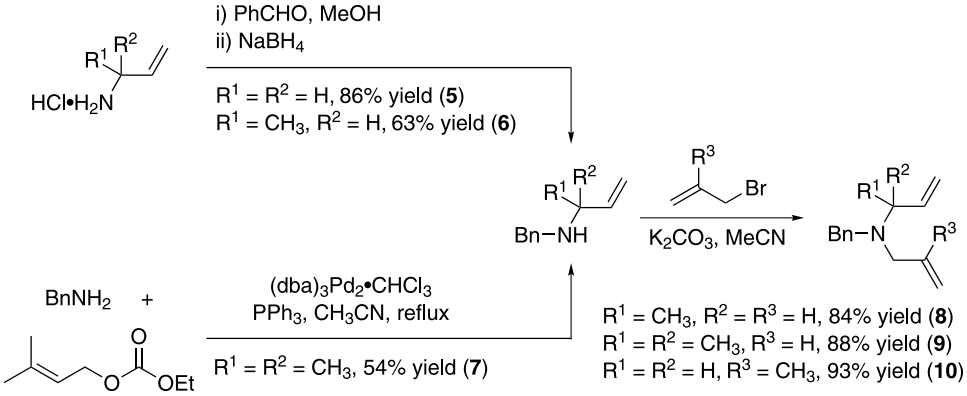


(1)

Extension of this method to nitrogen-containing dienes with various substitution patterns was investigated. Secondary acyclic allylamine derivatives were synthesized by reductive amination with the corresponding aryl aldehyde (**5** and **6**) or *N*-alkylation procedures (**7**).[6] Tertiary amines (**8**–**10**) were assembled by alkylation with the corresponding allyl bromide (Scheme 3).

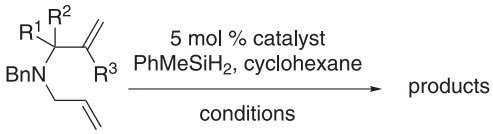
Generally, the catalytic reactions of these more substituted diallylamine derivatives were run at higher temperatures and for longer reaction times in comparison to the cyclization–functionalization of 1,6-heptadiene (Table 1). Under the optimized reaction conditions, substrates containing monosubstitution at the allylic position (**8**) provided a complete reaction within one hour (entry 1, Table 1). Although this is a positive result, a less sterically hindered catalyst is preferred to expand the scope of this method to highly substituted olefins. Unfortunately, attempts at employing $[Cp_2^{TMS}Lu(\mu\text{-}Me)]_2$, a catalyst that provides a more open coordination sphere, resulted in a complex mixture of products (entry 2, Table 1). The progress of the reaction could be complicated by Lewis acid–Lewis base interactions between the lanthanide catalyst and the amine moiety.

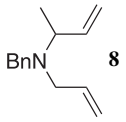
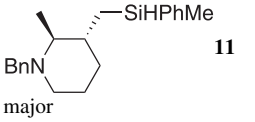
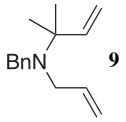
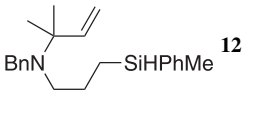
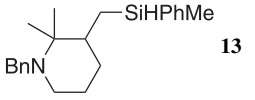
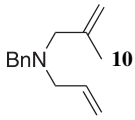
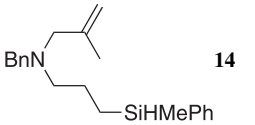
Increasing the steric bulk surrounding nitrogen required fine-tuning of the catalyst to achieve the desired cyclization. Aminodiene **9** failed to cyclize under the reaction conditions established for substrate **8** (entry 3, Table 1). Pleasingly, geminal substitution at the allylic position could be tolerated by employing a less hindered metallocene to accommodate the increased steric demands of the substrate (entry 4, Table 1). The cyclization of diene **9** was successfully realized by utilizing $[Cp_2^{TMS}Lu(\mu\text{-}Me)]_2$, a precatalyst that has a more open coordination sphere because of the smaller ligands surrounding the metal center. Although catalysts based upon



Scheme 3. Synthesis of acyclic diallylamine substrates.

Table 1. Cyclization–silylation of aminodienes **8–10**



Entry	Substrate	Catalyst	Temperature	Time	Results	Products
1	 **8**	$Cp^*_2LuMe\cdot THF$	rt	1 h	Complete reaction, mixture of four diastereomers[a]	 **11** major
2		$[Cp_2^{TMS}Lu(\mu\text{-}Me)]_2$	rt	1 h	Incomplete reaction[b]	—
3	 **9**	$Cp^*_2LuMe\cdot THF$	100 °C	1.5 h	84% Uncyclized product	 **12**
4		$[Cp_2^{TMS}Lu(\mu\text{-}Me)]_2$	100 °C	12 h	77% Cyclized product	 **13**
5	 **10**	$[Cp_2^{TMS}Lu(\mu\text{-}Me)]_2$	50 °C	>24 h	30% Uncyclized product	 **14**

[a] Upon oxidation of the crude silane, the resultant alcohol was obtained in 89:11 ds, 39% yield.
[b] Very low conversion after 24 h (<10%) with uncyclized material as the only product as determined by ^{1}H NMR spectroscopy.

the Cp^{TMS} ligand were ineffective at cyclizing diene **8**, we postulate that geminal substitution α to nitrogen suppresses Lewis base chelation with the more accessible lanthanide. Thus, by sterically shielding the nitrogen, intramolecular olefin insertion is preferred and the desired piperidine **13** can be readily accessed.

Pendant 1,1-disubstituted olefins (**10**) were not effective in the cyclization event under a variety of conditions (entry 5, Table 1). The steric demand of the olefin requires that the catalyst be based upon a more open ligand framework (e.g., Cp^{TMS}, Me_2SiCp^{TMS}, $Me_2SiCp^{t\text{-}Bu}$). Presumably, in the cyclization event, intramolecular olefin coordination precedes olefin insertion. Such an intermediate has been observed by Casey and coworkers and has been used to explain the high diastereoselectivity associated with cyclization reactions.[7] Thus, more 'open' catalysts are necessary to accommodate more substituted alkenes. Unfortunately, by providing a more accessible metal atom, the Lewis basic nitrogen atom competes effectively with the carbon–carbon

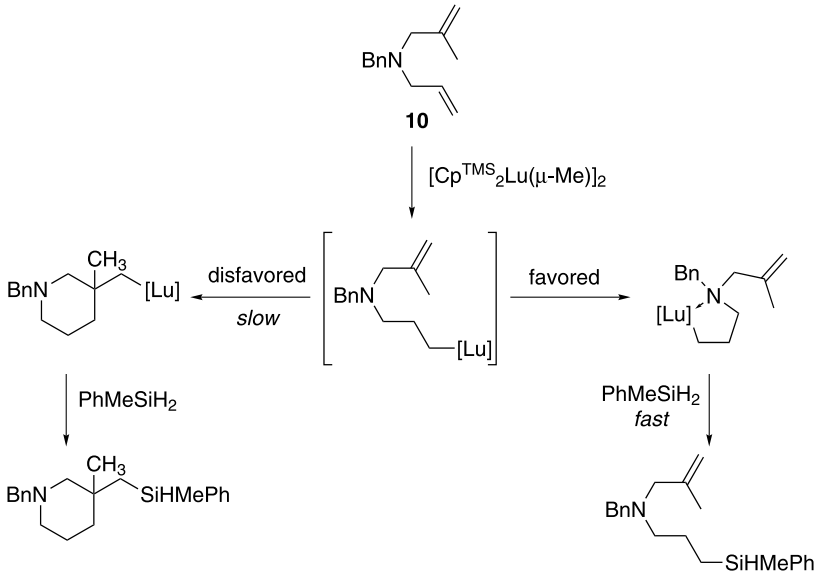
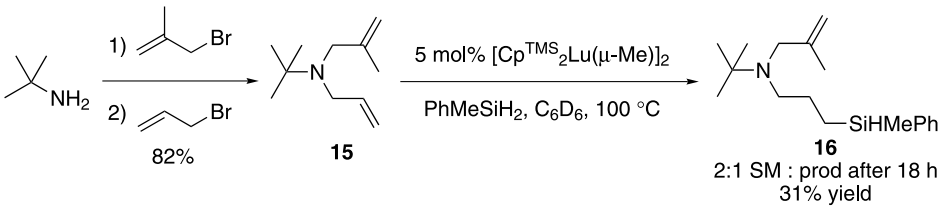


Figure 1. Proposed pathways for the reaction of **10** with $[Cp_2^{TMS}Lu(\mu\text{-}Me)]_2$.

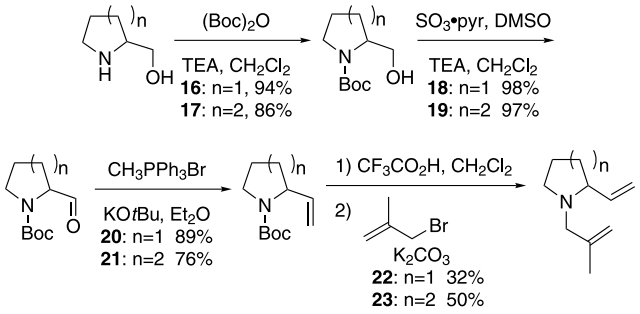


Scheme 4. Synthesis and catalytic reaction of **15**.

double bond for coordination with the Lewis acidic lanthanide. As such, formation of a five-membered chelate via binding between the nitrogen and the lutetium atoms of the hydrometalated olefin intermediate interferes with intramolecular olefin insertion, thus affording uncyclized silanes (Fig. 1).[3b]

In efforts to favor cyclization onto 1,1-disubstituted olefins, several methods were employed. Investigations commenced with applying steric variations to inhibit the intramolecular coordination. Successful cyclization of substrates containing geminal substitution α to nitrogen encouraged us to investigate the use of *tert*-butyl protecting groups as opposed to benzyl. Presumably, intramolecular chelation is disfavored in the presence of the steric hindrance surrounding nitrogen. Diallylamine derivative **15** was assembled by sequential alkylation of *tert*-butylamine with the appropriate electrophiles. Unfortunately, all attempts at cyclization failed to afford the desired cyclized product (Scheme 4).

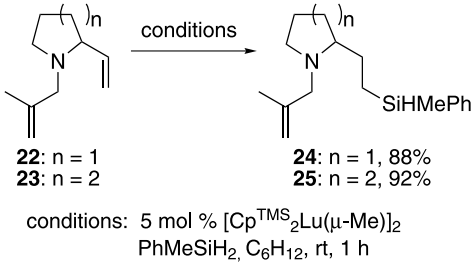
Another structural variation incorporated the diallylamine motif onto a ring. Dienes based upon the pyrrolidine and piperidine systems have similarities with the polyunsaturated precursor of epilupinine, which was known to undergo facile cyclization. Commercially available 2-pyrrolidinemethanol and 2-piperdinemethanol were converted to the BOC protected amino alcohols **16** and **17** in 94 and 86% yields, respectively, by treatment with di-*tert*-butyl dicarbonate in the presence of triethylamine.[8] Parikh–Doering oxidation (SO_3·pyr, DMSO) of the alcohols afforded aldehydes **18** and **19** efficiently after 2 h at 0 °C.[9] Wittig olefination using 2 equiv of both freshly prepared potassium *tert*-butoxide and methyltriphenylphosphonium bromide provided the corresponding alkenes in excellent yields.[10] The amines were deprotected by exposure to trifluoroacetic acid in CH_2Cl_2 and the crude trifluoroacetic acid amine salts were allylated using 3-bromo-2-methylpropene in the presence of excess potassium carbonate in MeCN at room



Scheme 5. Synthesis of cyclic dienes **22** and **23**.

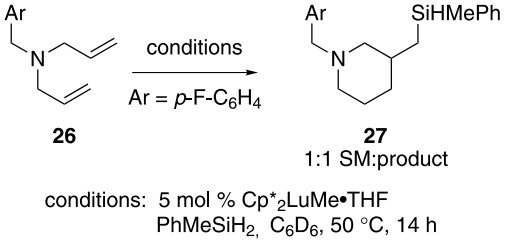
temperature.[11] The desired volatile dienes **22** and **23** were isolated after column chromatography and careful distillation in 32 and 50% yields, respectively, over two steps (Scheme 5).

Over a range of reaction conditions, dienes **22** and **23** failed to afford the desired fused bicycle, providing instead silanes **24** and **25**, respectively (Eq. 2). Interestingly, the initial olefin insertion occurs under milder reaction conditions than previously employed for the cyclization of acyclic substrates. Perhaps unfavorable interactions with the pyrrolidine or piperidine hamper intramolecular coordination of the lanthanide and the nitrogen atoms, thereby facilitating premature termination of the organometallic intermediate.



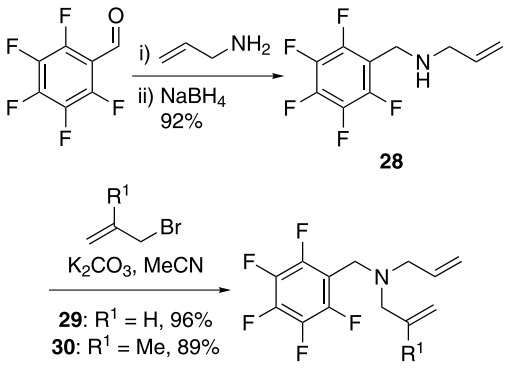
(2)

Based on the above results, the basicity of the nitrogen would have to be attenuated by inductive methods. Unfortunately, conventional electron-withdrawing nitrogen protecting groups (e.g., amide, carbamate, sulfonamide) are not compatible with the highly Lewis acidic lanthanide metal center because of the presence of the Lewis basic oxygens. Previous studies directed at enhancing the rate of the termination step demonstrated that perfluorinated silanes were compatible with the lanthanide metallocenes.[12] In an attempt to reduce the basicity of the nitrogen, fluorine atoms were incorporated onto the benzyl protecting group. To test the compatibility of incorporating a fluorine atom on the substrate, *p*-fluorobenzyldiallylamine (**26**) was assembled in 93% yield by reductive amination of diallylamine and *p*-fluorobenzaldehyde. Gratifyingly, *p*-fluorobenzyldiallylamine was cyclized using catalyst **3**, albeit in low yield and under harsher reaction conditions (Eq. 3).



(3)

To induce a greater electron withdrawing effect, pentafluorobenzyldiallylamine substrates were investigated.



Scheme 6. Synthesis of **29** and **30**.

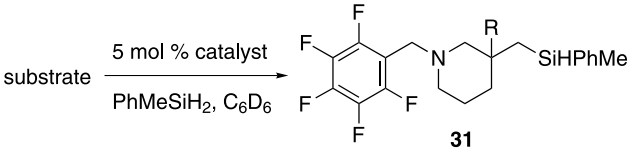
Substrates were easily synthesized by reductive amination of allylamine and pentafluorobenzaldehyde and subsequent alkylation with the appropriate allyl bromide (Scheme 6).

To our delight, the catalytic reaction of **29** with 5 mol% $[Cp_2^{TMS}Y(\mu\text{-Me})]_2$, a catalyst with smaller ligands and a larger metal, successfully afforded the desired cyclized product (Table 2). Utilizing a catalyst that had both smaller ligands and a larger metal center provided two handles for tuning the catalyst. Unfortunately, variations in both the handles did not provide positive results. Reactions with pendant 1,1-disubstituted olefins remained elusive.

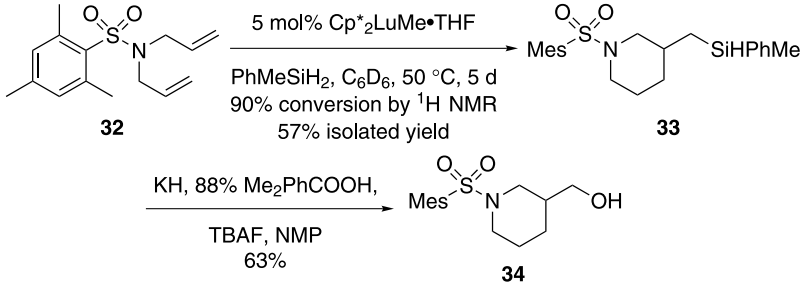
The failures encountered above led us to reevaluate the protecting group on nitrogen. Mesityl sulfonamides are electron-withdrawing and highly sterically encumbered. As such, the ortho methyl groups were expected to provide sufficient steric shielding of the oxygens from coordinating to the lanthanide metal center. After an extended period of time, diallylmesitylsulfonamide **32**, assembled from the reaction of diallylamine and mesitylsulfonyl chloride, did indeed cyclize, despite previous beliefs that polar nitrogen protecting groups would deactivate group 3 metallocenes (Scheme 7). Upon oxidation of the purified silane, primary alcohol **34** was isolated in 63% yield. The structure of **34** was confirmed by X-ray structure determination. Unfortunately, attempts at extending this method to 1,1-disubstituted olefins were unsuccessful.

Despite our best efforts to reduce the ability of nitrogen to chelate to the catalyst, cyclization onto 1,1-disubstituted alkenes was not realized. Therefore, we sought to take advantage of the electron-donating ability of nitrogen to enhance olefin reactivity. The exciting possibility exists to utilize enamine moieties in the cyclization reaction. We reasoned that the enamine moiety would provide added electron density to allow the Lewis acid-driven reaction with the pendant organometallic. Marks and co-workers have shown that enamines can be generated in the intramolecular hydroamination of *N*-allyl-4-pentyn-1-amine.[13] This newly formed pyrrolidine can be envisioned to undergo a C–C bond-forming cyclization reaction. To test this hypothesis, enamine **35** was synthesized by the alkylation of 2,3,3-trimethylindoline.[14] Geminal substitution at the benzylic position was necessary to avoid isomerization of the exocyclic double bond to give the aromatic indole. Unfortunately, subjecting the substrate to the catalytic conditions did not provide the desired tricyclic compound. However, it is surprising that hydrosilylation of the isolated olefin was possible in the presence of the enamine moiety (Eq. 4).

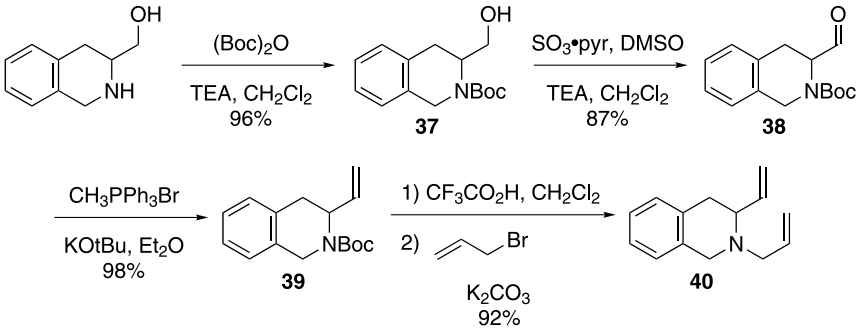
Table 2. Catalytic reactions with **29** and **30**



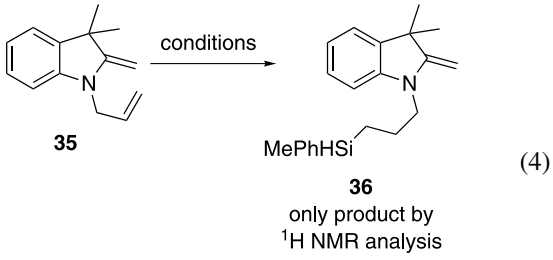
Substrate	Catalyst	Temperature	Time	Results
29	$[Cp_2^{TMS}Y(\mu\text{-Me})]_2$	50 °C	8 h	97% cyclized, 3% uncyclized
30	$[Cp_2^{TMS}Lu(\mu\text{-Me})]_2$	0–100 °C	4–12 h	NR
30	$[Cp_2^{TMS}Y(\mu\text{-Me})]_2$	50 °C	12 h	NR



Scheme 7. Reaction of *N*-sulfonamide **32**.



Scheme 8. Synthesis of diene **40**.

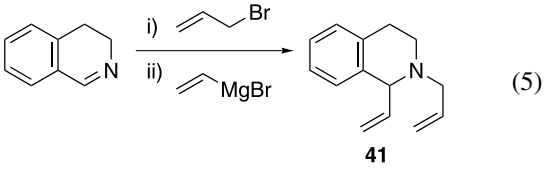


(4)

conditions: 5 mol % $[Cp^{TMS}{}_2Lu(\mu\text{-}Me)]_2$
$PhMeSiH_2$, C_6D_6, 100 °C, 3 days

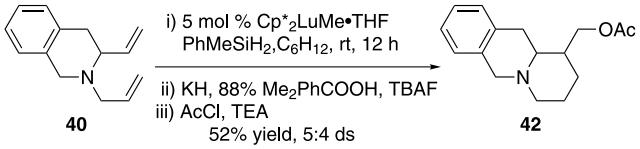
Other nitrogen heterocyclic scaffolds were investigated. Diallylamines based upon isoquinoline systems provided interesting results. Substrate **40**, bearing vinyl substitution at the 3-position, was synthesized in the same fashion as substrates **22** and **23** (Scheme 8).

Isoquinoline **41** with the vinyl moiety at the pseudobenzylic position was synthesized from known 3,4-dihydroisoquinoline (Eq. 5). The imine was treated with allyl bromide to generate the *N*-allyl iminium ion in situ, which was reacted with vinylmagnesium bromide to provide the desired diene.

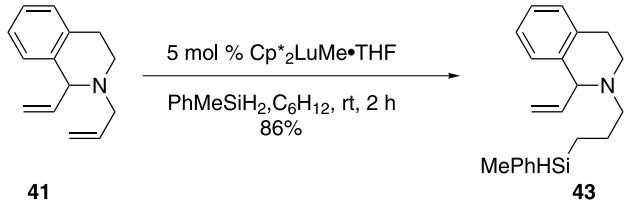


(5)

Isoquinoline **40** underwent efficient cyclization, and after oxidation of the C–Si bond and esterification, the resulting acetate was obtained in 52% yield over three steps in a 5:4 diastereomeric ratio (Eq. 6). Surprisingly, **41** failed to undergo cyclization under a variety of conditions (Eq. 7). It is possible that the vinyl moiety adopts a pseudo-axial orientation to minimize steric interactions with the aryl ring. This perturbation forces the initially generated organometallic to proceed through a transition state that is less chair-like during the insertion step, thus slowing the reaction and providing an opportunity for premature silylation.

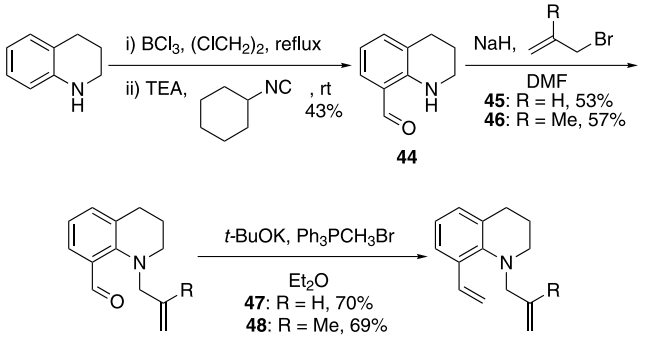


(6)

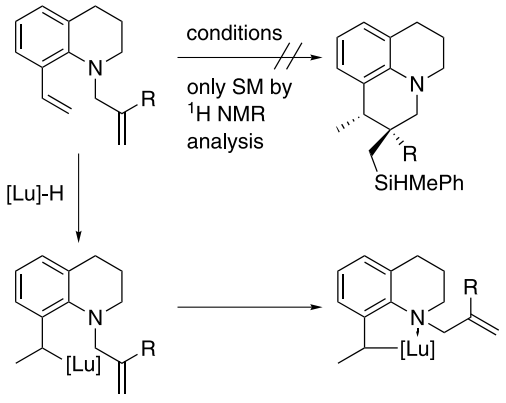


(7)

The final substrates investigated were those that would demonstrate aryl-directed regioselectivity.[2f,15] The substrates were constructed starting with known aldehyde **44**. Aldehyde **44** was synthesized by directed aryl substitution of 1,2,3,4-tetrahydroquinoline.[16] Subsequent *N*-alkylation and Wittig olefination provided the desired dienes **47** and **48** in moderate yields (Scheme 9).



Scheme 9. Synthesis of dienes **47** and **48**.



Scheme 10. Catalytic reaction of **47** and **48**.

Upon subjection to the catalytic reaction conditions (5 mol% $[Cp_2^{TMS}Lu(\mu\text{-}Me)]_2$, $PhMeSiH_2$, C_6D_6) the diene systems failed to react. The lack of reactivity could be explained by the formation of a 5-membered chelate with the adjacent nitrogen, resulting in deactivation of the organolanthanide (Scheme 10).

3. Conclusions

The group 3 metallocene-catalyzed cyclization–silylation of various nitrogen-containing dienes was investigated. The process was limited to monosubstituted olefins. Cyclization onto 1,1-disubstituted olefins was not achieved under a variety of conditions. Studies directed at reducing the basicity of the nitrogen atom revealed that mesityl sulfonamides are compatible with an organolutetium catalyst and that a successful cyclization can be realized. In the case of fused cyclic systems, intramolecular insertion is sensitive to substitution upon the ring. Additionally, enamines do not react with the lanthanide catalysts, while allowing the hydrosilylation of pendant alkenes. Finally, aryl-directive effects were not effective in promoting the cyclization of non-heteroaromatic containing dienes.

4. Experimental

4.1. Materials and methods

All catalytic experiments were performed in a nitrogen-filled glovebox or in a sealed reaction vessel initially prepared in the glovebox. The organolanthanide complexes were prepared according to literature procedures.[17] Et_2O and THF were distilled from sodium/benzophenone ketyl immediately before use. Cyclohexane and d_6-benzene were distilled from sodium/benzophenone ketyl and stored in a glovebox. Triethylamine and dichloromethane were distilled from CaH_2 prior to use. Acetonitrile and *N*-methylpyrrolidinone (NMP) were dried and stored over 4 Å molecular sieves. Phenylsilane, phenylmethylsilane, and toluene were distilled from sodium metal, sparged with argon, freeze-pump-thaw-degassed, and transferred into and stored in a glovebox. Potassium carbonate was dried and stored in a drying oven. Potassium hydride was purchased as a 35% dispersion in mineral oil. The white solid was isolated after several washings with dry hexanes using Schlenk techniques. All products synthesized were found to be >95% pure by capillary GC analysis unless otherwise indicated. All substrates for catalytic reactions were vacuum-transferred from CaH_2 into a Schlenk flask and freeze-pump-thaw degassed prior to exposure to the catalyst. Analytical thin-layer chromatography (TLC) was performed on silica gel (60F–254) plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography was performed on silica gel (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^1H, ^{13}C, and ^{19}F, spectra were recorded on a 500 MHz spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane (δ 0.00), chloroform (δ 7.26), or benzene (δ 7.16) for ^1H and either chloroform (δ 77.0) or benzene (δ 128.0) for ^{13}C.

4.1.1. *N*-Methylpiperidine-3-methylphenylsilylmethane (4) (representative procedure for the cyclization–silylation of an aminodiene with organolanthanide catalysts). In a sealed tube initially prepared in the glovebox, $Cp^*_2LuMe\cdot THF$ (10 mg, 5.0 mol%) was dissolved in cyclohexane (1.0 mL). To this solution was added diallylmethylamine (42 mg, 0.37 mmol) and methylphenylsilane (55 mg, 0.45 mmol). The reaction was stirred at room temperature for 1 h. GC analysis of the crude reaction mixture indicated that the reaction was complete. The clear, colorless solution was diluted with diethyl ether and filtered through a small plug of silica to remove the catalyst. The resulting solution was concentrated by rotary evaporation. The crude product was purified by flash chromatography to provide a mixture of diastereomers of the title compound as a clear, colorless oil in 83% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H), 7.35–7.32 (m, 2H), 6.95 (t, $J=7.0$ Hz, 1H), 4.44–4.41 (m, 1H), 2.78–2.71 (m, 2H), 2.20 (app. d, $J=3.0$ Hz, 3H), 1.80–1.75 (m, 3H), 1.60–1.48 (m, 3H), 0.85–0.70 (m, 3H), 0.34 (app. dd, $J=1.9$, 3.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 134.2, 129.2, 127.8, 65.1, 64.9, 55.9, 46.6, 39.6, 33.4, 33.2, 33.0, 25.7, 19.3, 19.3, −5.0, −5.1; IR (neat) 3023, 2928, 1442 cm^{-1}; LRMS (CI) *m/z* 232 (100), 218 (73); Anal. Calcd for $C_{14}H_{23}NSi$: C, 72.04; H, 9.93; Found: C, 71.95; H, 9.90.

4.1.2. *N*-Allyl-*N*-benzylmethallylamine (8). *N*-Benzylmethallylamine was synthesized by a published procedure.[18] To *N*-benzylmethallylamine (0.808 g, 5.01 mmol) in 10.0 mL of MeCN was added K_2CO_3 (1.38 g, 10.0 mmol) in one portion. The suspension was stirred for 0.5 h before adding allyl bromide (0.786 g, 6.50 mmol). The suspension was stirred overnight at room temperature. The solvent was removed in vacuo, and the crude residue was dissolved in 5 mL of Et_2O and washed with 2 mL of H_2O. The organic layer was separated, dried with $MgSO_4$, and filtered. The resulting clear solution was reduced in vacuo. The diene was purified by flash chromatography to provide the title compound as a clear, colorless oil in 88% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, $J=7.1$ Hz, 2H), 7.28 (t, $J=7.4$ Hz, 2H), 7.20–7.22 (m, 1H), 5.78–5.92 (m, 2H), 5.05–5.19 (m, 4H), 3.62 (d, $J=14.1$ Hz, 1H), 3.54 (d, $J=14.1$ Hz, 1H), 3.34–3.40 (m, 1H), 3.06 (ddd, $J=27.7$, 14.4, 8.3–Hz, 2H), 1.13 (d, $J=3.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 140.3, 137.3, 128.5, 128.1, 116.4, 115.3, 56.1, 53.5, 52.6, 15.2; IR (neat) 3052, 2931, 1243 cm^{-1}; LRMS (CI) *m/z* 201 (100), 104 (87); Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; Found: C, 83.65; H, 9.33.

4.1.3. *N*-Allyl-*N*-benzyl-α,α-dimethylallylamine (9). *N*-Benzyl-α,α-dimethylallylamine was synthesized by a published procedure.[6] To *N*-benzyl-α,α-dimethylallylamine (0.527 g, 3.01 mmol) in 6.00 mL of MeCN was added K_2CO_3 (0.829 g, 6.00 mmol) in one portion. The suspension was stirred for 0.5 h before adding allyl bromide (0.527 g, 0.393 mL, 3.90 mmol). The suspension was stirred overnight at room temperature. The solvent was removed in vacuo, and the crude residue was dissolved in 5 mL of Et_2O and washed with 2 mL of H_2O. The organic layer was separated, dried with $MgSO_4$, and filtered. The resulting solution was reduced in vacuo. The diene was purified by

flash chromatography to provide the title compound as a clear, colorless oil in 92% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J=7.4 Hz, 2H), 7.25 (m, 2H), 7.17 (t, J=7.3 Hz, 1H), 5.99 (dd, J=10.8, 17.6 Hz, 1H), 5.70–5.84 (m, 1H), 5.07 (d, J=17.6 Hz, 1H), 5.01 (dd, J=0.8, 10.8 Hz, 1H), 4.96 (dd, J=1.6, 17.2 Hz, 1H), 4.87 (dd, J=1.3, 10.1 Hz, 1H), 4.68 (s, 2H), 3.20 (d, J=6.4 Hz, 2H), 4.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 142.7, 138.7, 128.1, 127.9, 126.2, 115.0, 111.7, 59.6, 53.0, 52.9, 24.5; IR (neat) 3051, 2963, 1435 cm^{-1}; LRMS (CI) *m/z* 215 (100), 200 (67), 104 (83); Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83; Found: C, 83.80; H, 9.70.

4.1.4. 1-(*N*-Allyl-*N*-benzylamino)-2-methyl-2-propene (10). *N*-Benzylallylamine was synthesized by a published procedure. To *N*-benzylallylamine (1.87 g, 10.0 mmol) in 20.0 mL of MeCN was added K_2CO_3 (2.76 g, 20.0 mmol) in one portion. The suspension stirred for 0.5 h before adding 3-bromo-2-methyl-1-propene (1.74 g, 1.30 mL, 12.9 mmol). The suspension was stirred overnight at room temperature. The solvent was removed in vacuo, and the crude residue was dissolved in 10 mL of Et_2O and washed with 5 mL of H_2O. The organic layer was separated, dried with $MgSO_4$, filtered, and reduced in vacuo. The diene was purified by flash chromatography to provide the title compound as a clear, colorless oil in 93% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.34 (m, 2H), 7.27–7.30 (m, 2H), 7.12–7.22 (m, 1H), 5.78–5.92 (m, 1H), 5.18 (dd, J=1.6, 17.2 Hz, 1H), 5.11 (dd, J=1.3, 10.2 Hz, 1H), 4.92–4.93 (m, 1H), 4.83–4.84 (m, 1H), 3.51 (d, J=4.5 Hz, 2H), 2.98–3.01 (m, 2H), 2.91–2.96 (m, 2H), 1.73–1.75 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 139.2, 136.1, 128.7, 128.1, 126.7, 116.8, 112.5, 60.5, 37.7, 56.3, 20.7; IR (neat) 3042, 2946, 1454 cm^{-1}; LRMS (CI) *m/z* 201 (100), 160 (63), 104 (87); Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; Found: C, 83.06; H, 9.06.

4.1.5. *trans*-*N*-Benzylpiperidine-2-methyl-3-methylphenylsilylmethane (11). The title compound was prepared according to the general procedure for the preparation of **21** using 5 mol% of Cp*$_2$LuMe·THF at room temperature in a glovebox. The reaction was complete after 1 h as indicated by GC analysis. Workup and purification by flash chromatography gave the title compound as a mixture of diastereomers in 84% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.60 (m, 2H), 7.20–7.35 (m, 8H), 4.38–4.41 (m, 1H), 3.79–3.85 (m, 1H), 3.30–3.34 (m, 1H), 2.59–2.66 (m, 1H), 2.24–2.29 (m, 1H), 2.09–2.15 (m, 1H), 1.76–1.83 (m, 1H), 1.48–1.63 (m, 2H), 1.34–1.48 (m, 1H), 1.19–1.32 (m, 1H), 1.08–1.15 (m, 4H), 0.78–0.90 (m, 1H), 0.31–0.34 (m, 3H); ^{13}C NMR (125–MHz, $CDCl_3$) δ 140.0, 134.3, 129.1, 128.9, 128.1, 127.8, 126.6, 61.7, 61.7, 58.6, 50.3, 50.2, 38.1, 38.0, 30.6, 23.7, 23.6, 18.4, 18.2, 15.0, –4.7, –5.1; IR (neat) 3048, 2928, 2116, 1442 cm^{-1}; LRMS (CI) *m/z* 322 (100), 218 (73); Anal. Calcd for $C_{21}H_{29}NSi$: C, 77.96; H, 9.03; Found: C, 77.43; H, 8.95. Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.47 (m, 2H), 7.28–7.34 (m, 7H), 7.22–7.26 (m, 1H), 4.30–4.32 (m, 1H), 3.61–3.66 (m, 1H), 3.41–3.44 (m, 1H), 2.78–2.82 (m, 1H), 2.29–2.35 (m, 1H), 2.19–2.27 (m, 1H), 1.70–1.85 (m, 1H), 1.51–1.62 (m, 4H), 1.38–1.45 (m, 1H), 1.23–1.32 (m, 1H), 0.99–1.02 (m, 2H), 0.82–0.94 (m, 1H), 0.25–0.27 (m, 3H).

4.1.6. 3-(*N*-Allyl-*N*-α,α-dimethylallyl)amino-3-methylphenylsilylpropane (12). The title compound was prepared according to the general procedure for the preparation of **4** using 5 mol% of Cp*$_2$LuMe·THF at 100 °C in a sealed tube. The reaction was complete after 1.5 h as indicated by ^{1}H NMR analysis. Workup and purification by flash chromatography gave the title compound in 84% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.41 (m, 2H), 7.29–7.34 (m, 5H), 7.23–7.27 (m, 2H), 7.09–7.13 (m, 1H), 4.93–5.99 (m, 1H), 4.97–5.04 (m, 2H), 4.20–4.23 (m, 1H), 3.64 (s, 2H), 2.52 (dd, J=6.1, 7.4 Hz, 2H), 1.25–1.28 (m, 2H), 0.99 (s, 6H), 0.61–0.64 (m, 2H), 1.17–1.19 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 143.5, 136.7, 134.3, 129.2, 127.9, 127.8, 127.8, 126.1, 111.4, 59.6, 54.9, 54.5, 25.4, 24.2, 10.9, −5.8; IR (neat) 3032, 2967, 2119, 1461 cm^{-1}; LRMS (CI) *m/z* 337 (42), 336 (100), 240 (73); Anal. Calcd for $C_{22}H_{31}NSi$: C, 78.27; H, 9.26; Found: C, 78.14; H, 9.21.

4.1.7. *N*-Benzylpiperidine-2,2-dimethyl-3-methylphenylsilylmethane (13). The title compound was prepared according to the general procedure for the preparation of **4** using 5 mol% of $[Cp_2^{TMS}LuMe]_2$ at 100 °C in a sealed tube. The reaction was complete after 12 h as indicated by ^{1}H NMR analysis. Workup and purification by flash chromatography gave the title compound as a mixture of diastereomers in 84% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.56 (m, 2H), 7.27–7.36 (m, 6H), 7.23–7.27 (m, 1H), 7.13–7.20 (m, 1H), 4.40–4.43 (m, 1H), 3.82–3.89 (m, 1H), 3.08–3.13 (m, 1H), 2.39–2.48 (m, 1H), 2.24–2.32 (m, 1H), 1.50–1.72 (m, 2H), 1.32–1.48 (m, 4H), 1.18–1.31 (m, 2H), 1.03–1.17 (m, 1H), 0.93 (s, 3H), 0.58–0.71 (m, 1H), 0.35–0.37 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 137.0, 134.3, 134.3, 129.2, 128.2, 128.0, 128.0, 127.9, 126.3, 57.9, 54.3, 54.2, 47.0, 47.0, 42.7, 42.6, 31.6, 29.1, 28.9, 26.9, 25.5, 25.4, 25.3, 22.6, 16.2, 16.1, −4.6, −5.5; IR (neat) 3047, 2954, 2119, 1435 cm^{-1}; LRMS (CI) *m/z* 337 (100), 218 (73); Anal. Calcd for $C_{22}H_{31}NSi$: C, 78.27; H, 9.26; Found: C, 78.43; H, 9.06.

4.1.8. 1-(*N*-Allyl-*N*-*tert*-butylamino)-2-methyl-2-propene (16). *N*-(*tert*-Butylamino)-2-methyl-2-propene was synthesized by a published procedure.[6] To *N*-(*tert*-butylamino)-2-methyl-2-propene (0.382 g, 3.00 mmol) in 6.00 mL of MeCN was added K_2CO_3 (0.829 g, 6.00 mmol) in one portion. The suspension was stirred for 0.5 h before adding 3-bromo-2-methyl-1-propene (0.526 g, 0.393 mL, 3.90 mmol). The suspension was stirred overnight at room temperature. The solvent was removed in vacuo, and the crude residue was dissolved in 5 mL of Et_2O and washed with 3 mL of H_2O. The organic layer was separated, dried with $MgSO_4$, filtered, and reduced in vacuo. The diene was purified by flash chromatography to provide the title compound as a clear, colorless oil in 82% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84–5.92 (m, 1H), 5.01–5.07 (m, 1H), 4.92–4.95 (m, 2H), 4.75 (dd, J=1.2, 2.5 Hz, 1H), 3.15 (d, J=6.2 Hz, 1H), 3.00 (s, 3H), 1.70 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 139.5, 114.3, 110.8, 55.3, 54.8, 52.4, 27.5,

20.5; IR (neat) 3052, 2921, 1435 cm^{-1}; LRMS (CI) *m/z* 167 (100), 110 (89); Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; Found: C, 79.04; H, 12.57.

4.1.9. *N*-(*tert*-Butylcarbonyl)-2-pyrrolidinemethanol (16). To a solution of 2-pyrrolidinemethanol (0.910 g, 9.00 mmol) in CH_2Cl_2 (45.0 mL) was added triethylamine (3.31g, 4.60 mL, 32.7 mmol) via syringe followed by di(*tert*-butyl)dicarbonate (2.36 g, 10.8 mmol) in one portion The reaction stirred for 1 h after which the resulting yellow solution was poured into 50 mL of water. The layers were separated, and the organic layer was washed with 2×10 mL of water. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude orange oil was purified by flash column chromatography to afford the title compound as a white solid in 94% yield; R_f 0.33 (1:1 EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 4.70 (br s, 1H), 3.96 (br s, 1H), 3.60 (br s, 2H), 3.39–3.52 (m, 1H), 3.23–3.39 (m, 1H), 1.94–2.12 (m, 1H), 1.68–1.94 (m, 2H), 1.57–1.68 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 80.1, 67.4, 64.8, 55.3, 47.5, 28.6, 28.4, 24.0; IR (neat) 3268, 3054, 2963, 1694, 1442 cm^{-1}; LRMS (CI) *m/z* 200 (23), 99 (74), 57 (100); Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 6.96; Found: C, 59.65; H, 7.02.

4.1.10. *N*-(*tert*-Butylcarbonyl)-2-piperidinemethanol (17). The title compound was synthesized from 2-piperidinemethanol according to the procedure for the preparation of **16**. The title compound was isolated as a white solid in 88% yield; R_f 0.32 (1:1 EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 4.22–4.35 (m, 1H), 3.86–4.01 (m, 1H), 3.72–3.85 (m, 1H), 3.55–3.66 (m, 1H), 2.86 (br t, $J=$ 12.2, 1H), 2.42 (br s, 1H), 1.65–1.79 (m, 1H), 1.53–1.65 (m, 4H), 1.36–1.52 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 79.7, 61.5, 52.5, 39.9, 28.4, 25.2, 25.1, 19.5; IR (neat) 3204, 3016, 2926, 1694, 1472 cm^{-1}; LRMS (CI) *m/z* 214 (14), 128 (74), 57 (100); Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 6.51; Found: C, 61.47; H, 6.56.

4.1.11. *N*-(*tert*-Butylcarbonyl)-2-pyrrolidinecarbaldehyde (18). To a solution of **16** (0.910 g, 9.00 mmol) in CH_2Cl_2 (45.0 mL) at 0 °C was added triethylamine via syringe followed by $SO_3\cdot$pyr in DMSO via cannula. The reaction was stirred at 0 °C for 1 h. The reaction mixture was partitioned between 100 mL of 2:1 hexanes/diethyl ether and 20 mL of saturated $NaHCO_3$. The aqueous layer was extracted with 2×20 mL of 2:1 hexanes/diethyl ether. The organic layers were combined and washed with 20 mL of 1 M NaH_2PO_4 and 20 mL of saturated NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. Flash column chromatography of the crude material afforded the title compound as a mixture of rotamers in 98% yield; R_f 0.23 (20:80 EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H, minor rotamer), 9.46 (s, 1H, major rotamer), 4.20 (br s, 1H, minor rotamer), 4.03–4.06 (br s, 1H, major rotamer), 3.50–3.56 (m, 2H, minor rotamer), 3.44–3.50 (m, 2H, major rotamer), 1.80–2.05 (m, 8H), 1.48 (s, 9H, minor rotamer), 1.43 (s, 9H, major rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 200.3, 153.9, 80.5, 80.1, 64.9, 64.8, 46.8, 46.6, 28.3, 28.2, 27.9, 26.6, 24.6, 23.9; IR (neat) 3056, 2983, 1694, 1673 cm^{-1}; LRMS (CI) *m/z* 199 (36), 126 (54); Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; Found: C, 60.15; H, 8.72.

4.1.12. *N*-(*tert*-Butylcarbonyl)-2-piperidinecarbaldehyde (19). The title compound was synthesized from **17** according to the procedure for the preparation of **18**. The title compound was isolated as a mixture of rotamers in 97% yield; R_f 0.22 (20:80 EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 9.59 (br s, 1H), 4.38–4.71 (m, 1H), 3.78–4.10 (br m, 1H), 2.73–3.82 (br m, 1H), 2.11–2.21 (m, 1H), 1.57–1.71(m, 3H), 1.30–1.71 (m, 10H), 1.26 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 158.6, 80.3, 75.1, 65.3, 61.5, 60.6, 43.0, 41.9, 28.4, 28.3, 25.3, 24.7, 23.5, 20.9, 19.2; IR (neat) 2983, 1694, 1681, 1210 cm^{-1}; LRMS (CI) *m/z* 213 (43), 140 (83), 57 (100); Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; Found: C, 61.87; H, 8.89.

4.1.13. *N*-(*tert*-Butylcarbonyl)-2-vinylpyrrolidine (20). To a suspension of freshly prepared potassium *tert*-butoxide (2.22 g, 19.8 mmol) in 60 mL of diethyl ether was added methyltriphenylphosphonium bromide (7.08 g, 19.8 mmol) in two portions. The bright yellow mixture was heated at reflux for 1 h. The yellow mixture was allowed to cool to room temperature. A solution of **18** (1.99 g, 10.0 mmol) in 20 mL of Et_2O was added via cannula to the mixture. The yellow suspension was stirred overnight at room temperature. The reaction was quenched with 20 mL of water and the layers were separated. The aqueous layer was extracted with 2×20 mL of Et_2O. The organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The resulting solids were triturated with cold petroleum ether (40–60) and the organic extracts were reduced in vacuo. The crude residue was purified by flash column chromatography to afford the title compound as a mixture of rotamers in 89% yield; R_f 0.30 (30:70 EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (br s, 1H), 5.05 (br s, 2H), 4.20–4.40 (br m, 1H), 3.40 (br s, 2H), 1.95–2.10 (br s, 1H), 1.79–1.90 (m, 2H), 1.69–1.73 (m, 1H), 1.44 (br s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 138.9, 138.5, 113.6, 78.9, 59.1, 46.4, 46.0, 31.9, 31.3, 28.4, 23.3, 22.6, 14.0; IR (neat) 3052, 2928, 1694, 1242 cm^{-1}; LRMS (CI) *m/z* 197 (43), 104 (72), 57 (100); Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; Found: C, 67.06; H, 9.78.

4.1.14. *N*-(*tert*-Butylcarbonyl)-2-vinylpiperidine (21). The title compound was synthesized from **19** according to the procedure for the preparation of **20**. The title compound was isolated as a clear, colorless oil in 76% yield; R_f 0.28 (30:70 EtOAc/Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.72–5.76 (m, 1H), 5.17 (ddd, $J=1.4$, 1.6, 10.7 Hz, 1H), 5.11 (dt, $J=1.5$, 17.4 Hz, 1H), 4.78 (br s, 1H), 3.90–4.00 (m, 1H), 2.82–2.90 (m, 1H), 1.68–1.81 (m, 2H), 1.56–1.65 (m, 2H), 1.48 (s, 9H), 1.30–1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 136.9, 115.4, 79.2, 52.4, 39.7, 28.9, 28.4, 25.5, 19.4; IR (neat) 3061, 2936, 1694, 1230 cm^{-1}; LRMS (CI) *m/z* 197 (63), 104 (87), 57 (100); Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; Found: C, 68.15; H, 10.13.

4.1.15. *N*-(2-Methyl-2-propenyl)-2-vinylpyrrolidine (22). To a solution of **20** (1.97 g, 10.0 mmol) in 100 mL of CH_2Cl_2 was added 10 mL of trifluoroacetic acid via syringe. The solution was stirred for 30 min at room temperature.

The solvent was removed in vacuo, and the brown residue was dissolved in tetrahydrofuran. To the resulting solution was added K_2CO_3 (1.38 g, 10.0 mmol) in one portion. The suspension was stirred for 0.5 h before adding 3-bromo-2-methyl-1-propene (1.35 g, 1.01 mL, 10.0 mmol). The suspension was heated to reflux and was stirred for 12 h. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with 2×10 mL of Et_2O. The organic layers were combined, dried with $MgSO_4$, and filtered. The solvent was removed by careful distillation at ambient pressure. The crude residue was purified by flash chromatography followed by Kugelrohr distillation at 120 °C to provide the title compound as a clear, colorless oil in 32% yield; R_f 0.22 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddd, $J=8.1$, 10.1, 17.2 Hz, 1H), 5.13 (ddd, $J=0.6$, 1.9, 17.2 Hz, 1H), 5.06 (dd, $J=2.0$, 10.1 Hz, 1H), 4.86 (t, $J=0.8$ Hz, 1H), 4.77 (q, $J=1.3$, 2.6 Hz, 1H), 3.32 (d, $J=13.0$ Hz, 1H), 3.03 (dt, $J=2.8$, 9.2 Hz, 1H), 2.67 (dd, $J=8.1$, 16.2 Hz, 1H), 4.49 (d, $J=13.1$ Hz, 1H), 2.01 (dd, $J=8.8$, 17.8 Hz, 1H), 1.90–1.97 (m, 1H), 1.65–1.80 (m, 2H), 1.74 (d, $J=0.5$ Hz, 3H), 1.56–1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 141.3, 116.0, 111.5, 68.8, 61.0, 53.5, 31.6, 22.2, 21.0; IR (neat) 3057, 2926 cm^{-1}; LRMS (CI) *m/z* 151 (79), 124 (100); Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; Found: C, 79.35; H, 11.26.

4.1.16. *N*-(2-Methyl-2-propenyl)-2-vinylpiperidine (23). The title compound was synthesized from **21** according to the procedure for the preparation of **22**. The title compound was isolated as a clear, colorless oil in 50% yield; R_f 0.28 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddd, $J=8.5$, 10.2, 17.3 Hz, 1H), 5.10 (dd, $J=1.9$, 17.3 Hz, 1H), 5.02 (dd, $J=1.9$, 10.2 Hz, 1H), 4.83 (d, $J=0.6$ Hz, 1H), 4.78 (q, $J=1.3$ Hz, 1 H), 3.36 (d, $J=13.5$ Hz, 1H), 2.83–2.87 (m, 1H), 2.51–2.56 (m, 1H), 2.39 (d, $J=13.5$ Hz, 1H), 1.75 (dt, $J=2.8$, 11.5 Hz, 1H), 1.70 (s, 3H), 1.60–1.69 (m, 1H), 1.56–1.60 (m, 2H), 1.39–1.51 (m, 2H), 1.24–1.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 142.6, 115.2, 111.9, 67.1, 62.4, 52.0, 33.7, 25.9, 24.0, 20.9; IR (neat) 3072, 2925 cm^{-1}; LRMS (CI) *m/z* 165 (63), 136 (100); Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; Found: C, 80.07; H, 11.57.

4.1.17. Pyrrolidine 24. The title compound was prepared according to the general procedure for the preparation of **4** using 5 mol% of $[Cp_2^{TMS}LuMe]_2$ at room temperature in a glovebox. The reaction was complete after 1 h as indicated by GC analysis. Workup and purification by flash chromatography gave the title compound in 88% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.59 (m, 2H), 7.31–7.39 (m, 3H), 4.82–4.87 (m, 1H), 4.73–4.78 (m, 1H), 4.32–4.38 (m, 1H), 3.21–3.27 (m, 1H), 2.95–3.01 (m, 1H), 2.52–2.59 (m, 1H), 2.19–2.27 (m, 1H), 1.98–2.05 (m, 1H),1.84–1.92 (m, 1H), 1.60–1.78 (m, 7H), 1.42–1.50 (m, 1H), 1.38–1.48 (m, 1H), 0.82–0.97 (m, 1H), 0.69–0.82 (m, 1H), 0.33 (s, 3H).

4.1.18. Piperidine 25. The title compound was prepared according to the general procedure for the preparation of **4** using 5 mol% of $[Cp_2^{TMS}LuMe]_2$ at room temperature in a glovebox. The reaction was complete after 1 h as indicated by GC analysis. Workup and purification by flash chromatography gave the title compound in 92% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.52 (m, 2H), 7.32–7.39 (m, 3H), 4.82 (br s, 1H), 4.78 (br s, 1H), 4.32–4.35 (m, 1H), 3.18–3.25 (m, 1H), 2.72–2.78 (m, 1H), 2.48–2.53 (m, 1H), 2.11–2.17 (m, 1H), 1.90–1.96 (m, 1H),1.70 (s, 3H), 1.58–1.67 (m, 1H), 1.38–1.58 (m, 6H), 1.22–1.32 (m, 1H), 0.82–0.98 (m, 1H), 0.70–0.82 (m, 1H), 0.30–0.32 (m, 3H).

4.1.19. *p*-Fluorobenzyldiallylamine (26). (General procedure for the reductive amination of an aldehyde). To a solution of *p*-fluorobenzaldehyde (0.621 g, 5.00 mmol) in 25.0 mL of methanol was added diallylamine (0.486 g, 0.617 mL, 5 mmol) via syringe. After stirring for one hour at room temperature, the reaction was cooled to 0 °C and $NaBH_4$ (0.284 g, 7.50 mmol) was added in three portions to the solution. The resulting suspension was warmed to room temperature and stirred for an additional 8 h. The reaction mixture was diluted with 10 mL of Et_2O and washed with 2×5 mL of water. The organic layer was dried with Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography to afford the title compound in 92% yield; R_f 0.27 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.29 (m, 2H), 6.98 (t, $J=8.7$ Hz, 2H), 5.82–5.90 (m, 2H), 5.12–5.20 (m, 4H), 3.53 (s, 2H), 3.03–3.06 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3 ($J_{C-F}=2$ Hz), 135.2, 135.6, 130.7, 130.6, 117.8, 115.3 ($J_{C-F}=0.2$ Hz), 57.1, 56.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.8; IR (neat) 3047, 2920 cm^{-1}; LRMS (CI) *m/z* 205 (57), 164 (100); Anal. Calcd for $C_{13}H_{16}FN$: C, 76.06; H, 7.86; Found: C, 75.98; H, 7.78.

4.1.20. *N*-(*p*-Fluorobenzyl)-piperidine-3-methylphenylsilylmethane (27). The title compound was prepared according to the general procedure for the preparation of **4** using 5 mol% of $Cp^*_2LuMe\cdot THF$ at 50 °C in a sealed tube. The reaction was stopped at a 50% conversion after 14 h as indicated by ^{1}H NMR analysis. Workup and purification by flash chromatography gave the title compound in 19% yield; R_f 0.25 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.54 (m, 4H), 7.25–7.28 (m, 5H), 4.63–4.65 (m, 1H), 3.37–3.40 (m, 2H), 2.78–2.83 (m, 1H), 2.55–2.63 (m, 1H), 1.78–1.99 (m, 2H), 1.68–1.77 (m, 2H), 1.47–1.53 (m, 2H), 0.78–0.92 (m, 2H), 0.76–0.78 (m, 1H), 0.28–0.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 ($J_{C-F}=1.7$ Hz), 135.2, 135.6, 130.7, 130.6, 117.8, 115.3 ($J_{C-F}=0.2$ Hz), 65.1, 64.9, 55.9, 46.6, 39.6, 33.4, 33.2, 33.0, 25.7, 19.3, 19.3, −5.0, −5.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.8; IR (neat) 3052, 2942, 2117, 1447 cm^{-1}; LRMS (CI) *m/z* 327 (100), 262 (63); Anal. Calcd for $C_{20}H_{26}FNSi$: C, 73.35; H, 8.00; Found: C, 73.50; H, 7.88.

4.1.21. Pentafluorobenzyldiallylamine (29). Pentafluorobenzylallylamine was prepared from allylamine (0.571 g, 10.0 mmol) and pentafluorobenzaldehyde (1.96 g, 10.0 mmol) according to the general procedure for the reductive amination of an aldehyde. The crude oil was purified by flash column chromatography to afford the secondary amine in 92% yield. The secondary amine was alkylated acccording to the procedure for the preparation of **8** to afford the title compound as a clear, colorless oil in 96% yield; R_f 0.24 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 5.81–5.86 (m, 2H), 5.21 (dd, J=0.8, 17.2 Hz, 2H), 5.14 (ddd, J=1.1, 1.7, 10.2 Hz, 2H), 3.69 (s, 2H), 3.10 (d, J=6.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 117.8, 56.7, 44.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −142.2 (dd, J=9.4, 23.5 Hz), −156.2 (t, J=21.1 Hz), −163.3 (ddd, J=9.4, 14.1, 23.5 Hz); IR (neat) 3024, 2958, 1442 cm^{-1}; LRMS (CI) m/z 277 (100), 212 (57); Anal. Calcd for $C_{13}H_{12}F_5N$: C, 56.32; H, 4.36; Found: C, 56.30; H, 4.44.

4.1.22. 1-(*N*-Allyl-*N*-pentafluorobenzylamino)-2-methyl-2-propene (30). Pentafluorobenzylallylamine was prepared from allylamine (0.571g, 10.0 mmol) and pentafluorobenzaldehyde (1.96 g, 10.0 mmol) according to the general procedure for the reductive amination of an aldehyde. The crude oil was purified by flash column chromatography to afford the secondary amine in 92% yield. The secondary amine was alkylated acccording to the procedure for the preparation of **8** to afford the title compund as a clear, colorless oil in 89% yield; R_f 0.24 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78–5.85 (m, 1H), 5.20 (dd, J=1.6, 17.2 Hz, 1H), 5.13 (dd, J=1.3, 10.1 Hz, 1H), 4.90 (s, 1H), 4.85 (s, 1H), 3.67 (s, 2H), 3.01 (d, J=6.3 Hz, 2H), 2.94 (s, 2H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 135.5, 117.5, 113.0, 60.7, 56.5, 44.8, 20.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −142.2 (dd, J=7.1, 21.2 Hz), −156.3 (t, J=21.2 Hz), −163.3–−163.2 (m); IR (neat) 3024, 2914, 1456 cm^{-1}; LRMS (CI) m/z 291 (100), 104 (87); Anal. Calcd for $C_{14}H_{14}F_5N$: C, 57.53; H, 4.84; Found: C, 57.42; H, 4.92.

4.1.23. (*N*-Pentafluorobenzyl)-piperidine-3-methylphenylsilylmethane (31). The title compound was prepared according to the general procedure for the preparation of **4** using 5 mol% of $[Cp_2^{TMS}YMe]_2$ at 50 °C in a sealed tube. The reaction was complete after 8 h as indicated by ^{1}H NMR analysis. Workup and purification by flash chromatography gave the title compound in 97% yield; R_f 0.23 (10:90 MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.51 (m, 2H), 7.24–7.37 (m, 3H), 4.37–4.40 (m, 1H), 3.69 (br s, 2 H), 2.70–2.81 (m, 2H), 1.90–2.00 (m, 1H), 1.65–1.78 (m, 3H), 1.51–1.60 (m, 1H), 1.40–1.51 (m, 1H), 0.68–0.90 (m, 3H), 0.32–0.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 134.2, 129.3, 127.9, 61.7, 61.6, 52.9, 52.9, 49.0, 33.3, 33.2, 32.9, 25.4, 19.3, 19.2, −4.9, −5.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −142.4 (m), −156.5 (m), −163.5 (m); IR (neat) 3048, 2928, 2116, 1442 cm^{-1}; LRMS (CI) m/z 399 (100), 384 (83), 334 (45); Anal. Calcd for $C_{20}H_{22}F_5NSi$: C, 60.13; H, 5.55; Found: C, 59.98; H, 5.60.

4.1.24. *N*, *N*-Diallylmesitylsulfonamide (32). To diallylamine in CH_2Cl_2 at 0 °C was added triethylamine. The solution was stirred for 30 min before adding a solution of 2-mesitylenesulfonyl chloride in CH_2Cl_2 dropwise via cannula. The clear solution became cloudy and the mixture was warmed to room temperature over two hours. The reaction was quenched with 15 mL of water and the organic layer was separated. The aqueous layer was washed with 3×5 mL of CH_2Cl_2. The organic layers were combined and washed with 15 mL of saturated NaCl. The layers were separated and the organic layer was dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography to afford the title compound as a viscous oil in 93% yield; R_f 0.17 (5:95 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (d, J=0.5 Hz, 2H), 5.59–5.70 (m, 2H), 5.18 (t, J=1.2 Hz, 2H), 5.12 (dd, J=1.4, 1.8 Hz, 2H), 3.77 (d, J=6.4 Hz, 4H), 2.61 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 140.1, 133.1, 132.6, 131.9, 119.3, 47.9, 22.8, 20.9; IR (neat) 3048, 2928, 2116, 1442 cm^{-1}; LRMS (CI) m/z 279 (100), 239 (62); Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; Found: C, 64.59; H, 7.64.

4.1.25. (*N*-Mesitylsulfonyl)-piperidine-3-methanol (34). (*N*-Mesitylsulfonyl)-piperidine-3-methylphenylsilylmethane (**33**) was prepared according to the general procedure for the preparation of **4** using 5 mol% of $Cp^*_2LuMe\cdot THF$ at 50 °C in a sealed tube. The reaction was complete after five days as indicated by ^{1}H NMR analysis. Workup and purification by flash chromatography afforded silane **33** in 57% yield. The silane was oxidized according to a published method.[5k] To a suspension of KH (0.021 g, 0.54 mmol) in 0.7 mL of NMP was added cumene hydroperoxide (0.074 mL, 88% solution, 0.43 mmol). After 20 min, the silane **33** (0.043 g, 0.11 mmol) in 0.7 mL of NMP was added dropwise via cannula followed by tetrabutylammonium fluoride (0.056 g, 0.22 mmol). After stirring the mixture for 12 h at room temperature; 1.4 mL of saturated $Na_2S_2O_3$ was added and the mixture was stirred for an additional 30 min at room temperature. The mixture was then extracted with 3×1 mL of *t*-BuOMe. The combined organic layers were washed with 1×2 mL of saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to yield the title compound in 63% yield. The structure of the compound was confirmed by X-ray crystallography; R_f 0.22 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 2H), 3.49–3.55 (m, 3H), 3.35–3.42 (m, 1H), 2.83–2.90 (m, 1H), 2.68 (dd, J=9.3, 12.3 Hz, 1H), 2.61 (s, 6H), 2.29 (s, 3H), 1.72–1.85 (m, 3H), 1.50–1.60 (m, 1H), 1.38 (br s, 1H), 1.13–1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 140.4, 131.9, 65.0, 47.0, 45.0, 38.0, 26.7, 23.9, 22.8, 20.9; IR (KBr) 3304, 3075, 2925, 1226 cm^{-1}; Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; Found: C, 60.65; H, 7.70.

4.1.26. *N*-(*tert*-Butylcarbonyl)-3-isoquinolinemethanol (37). The title compound was synthesized from 3-isoquinolinemethanol according to the procedure for the preparation of **16**. The title compound was isolated as a viscous oil in 96% yield; R_f 0.28 (1:1 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10–7.20 (m, 4H), 4.69 (br s, 1H), 4.49 (br s, 1H), 4.31 (d, J=16.5 Hz, 1H), 3.51 (br s, 2H), 3.03 (dd, J=6.0, 15.9 Hz, 1H), 2.80 (d, J=15.5 Hz, 1H), 1.74 (br s, 1H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 129.0, 127.3, 126.9, 126.8, 126.5, 80.82, 64.8, 52.4, 44.5, 30.6, 28.9, 21.4, 14.6; IR (neat) 3249, 3052, 2963, 1210, 1435 cm^{-1}; LRMS (CI) m/z 262 (64), 205 (78), 57 (100); Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; Found: C, 68.59; H, 7.93.

4.1.27. *N*-(*tert*-Butylcarbonyl)-3-isoquinolinecarbaldehyde (38). The title compound was synthesized from **37** according to the procedure for the preparation of **18**. The title compound was isolated as a mixture of rotamers in 87% yield; R_f 0.20 (20:80 EtOAc/Hexane); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 9.49 (d, $J=21.2$ Hz, 1H), 7.09–7.19 (m, 4H), 4.82, (br s, 0.5H), 4.70 (s, 0.5H), 4.68 (s, 0.5H), 4.51–4.59 (m, 1H), 4.46 (br s, 0.5H), 3.21–3.24 (m, 0.5H), 3.10 (br s, 1H), 1.53 (br s, 5H), 1.51, (br s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 200.3, 128.4, 127.7, 127.3, 127.1, 127.0, 126.9, 126.3, 126.2, 81.2, 60.4, 60.3, 59.1, 45.0, 44.3, 29.3, 28.3, 14.2; IR (neat) 3048, 2928, 1694, 1221 cm^{-1}; LRMS (CI) *m/z* 261 (4), 231 (56), 57 (100); Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; Found: C, 69.07; H, 7.40.

4.1.28. *N*-(*tert*-Butylcarbonyl)-3-vinylisoquinoline (39). The title compound was synthesized from **38** according to the procedure for the preparation of **20**. The title compound was isolated as a clear, colorless oil in 98% yield; R_f 0.28 (30:70 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09–7.26 (m, 4H), 5.66 (ddd, $J=5.2$, 10.5, 17.2 Hz, 1H), 5.00–5.07 (m, 2H), 4.97, (br s, 1H), 4.74 (d, $J=16.7$ Hz, 1H), 4.32 (d, $J=16.7$ Hz, 1H), 3.13 (dd, $J=5.9$, 15.9 Hz, 1H), 2.80 (dd, $J=1.8$, 15.7 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 136.9, 133.3, 132.9, 128.6, 126.5, 126.2, 126.0, 115.8, 79.9, 51.4, 43.4, 33.4, 28.5; IR (neat) 2976, 2861, 1694 cm^{-1}; LRMS (CI) *m/z* 259 (15), 203 (48), 57 (100); Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; Found: C, 73.99; H, 8.32.

4.1.29. *N*-Allyl-3-vinylisoquinoline (40). The title compound was synthesized from **39** according to the procedure for the preparation of **22**. The title compound was isolated as a clear, colorless oil in 92% yield; R_f 0.23 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08–7.12 (m, 4H), 5.88–5.96 (m, 1H), 5.78–5.85 (m, 1H), 5.16–5.31 (m, 4H), 4.06 (d, $J=8.5$ Hz, 1H), 3.87 (d, $J=8.5$ Hz, 1H), 3.09–3.14 (m, 1H), 3.05 (ddd, $J=0.8$, 7.4, 14.0 Hz, 1H), 2.88–2.94 (m, 1H), 2.79–2.84 (m, 1H), 2.55–2.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 136.3, 135.6, 134.7, 128.7, 128.2, 126.2, 125.5, 118.1, 117.5, 66.6, 57.6, 46.2, 28.9; IR (neat) 3048, 2934 cm^{-1}; LRMS (CI) *m/z* 199 (100), 104 (87); Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; Found: C, 84.63; H, 8.92.

4.1.30. *N*-Allyl-1-vinylisoquinoline (41). To 3,4-dihydroisoquinoline (0.394 g, 3.0 mmol) in 15.0 mL of THF was added an excess of allyl bromide (3.0 mL). The mixture was stirred for 2 h before adding vinylmagnesium bromide (6.0 mL, 1.0 M in THF, 6.0 mmol) via syringe. The mixture was refluxed for one hour. The mixture was cooled to room temperature, quenched with 5 mL of water, and the layers were separated. The aqueous layer was extracted with $3\times$ 2 mL of Et_2O. The combined organic extracts were washed with 3×10 mL of saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was purified by flash column chromatography to afford the title compound as a clear, colorless oil in 78% yield; R_f 0.27 (10:90 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06–7.14 (m, 4H), 5.87–5.97 (m, 1H), 5.77–5.86 (m, 1H), 5.17–5.30 (m, 4H), 4.06 (d, $J=8.5$ Hz, 1H), 3.47 (ddd, $J=$ 1.4, 5.4, 13.9 Hz, 1H), 3.09–3.14 (m, 1H), 3.05 (ddd, $J=$ 0.8, 7.4, 14.0 Hz, 1H), 2.88–2.94 (m, 1H), 2.79–2.84 (m, 1H), 2.55–2.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 136.3, 135.6, 134.7, 128.7, 128.2, 126.2, 125.5, 118.1, 117.5, 66.6, 57.6, 46.2, 28.9; IR (neat) 3032, 2928 cm^{-1}; LRMS (CI) *m/z* 199 (100), 185 (24), 158 (45); Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; Found: C, 84.23; H, 8.67.

4.1.31. Acetate 42. In a sealed tube initially prepared in the glovebox, $Cp^*_2LuMe\cdot THF$ (10 mg, 5.0 mol%) was dissolved in cyclohexane (1.0 mL). To this solution was added *N*-allyl-3-vinylisoquinoline (74 mg, 0.37 mmol) and methylphenylsilane (55 mg, 0.45 mmol). The reaction was stirred at room temperature for 12 h. GC analysis of the crude reaction mixture indicated that the reaction was complete. The clear, colorless solution was diluted with diethyl ether and filtered through a small plug of silica to remove the catalyst and concentrated by rotary evaporation. The crude product was oxidized according to the procedure for the preparation of **51**. The resulting crude alcohol was dissolved in 2.5 mL of CH_2Cl_2 and to the clear solution was added triethylamine (0.14 g, 0.19 mL, 1.4 mmol). After stirring at room temperature for 10 min, acetyl chloride (0.11 g, 0.10 mL, 1.4 mmol) was added dropwise via syringe. The solution was stirred for 15 min, after which the reaction was complete as determined by TLC analysis. The reaction was quenched with 2 mL of water and the layers were separated. The aqueous layer was extracted with 2×1 mL of CH_2Cl_2. The combined organic extracts were washed with 1×3 mL of saturated NaCl solution, dried with Na_2SO_4, filtered, and concentrated in vacuo. GC analysis of the crude acetate indicated that the fused nitrogen heterocycle was a 5:4 mixture of diastereomers. The crude oil was purified by flash column chromatography to afford the title compound as a mixture of diastereomers in 52% overall yield; R_f 0.23 (5:95 EtOAc/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.32 (m, 4H), 4.33 (dd, $J=5.6$, 11.0 Hz, 1H), 4.13 (dd, $J=5.6$, 11.0 Hz, 1H), 3.71 (d, $J=15.1$ Hz, 1H), 3.42 (d, $J=13.5$ Hz, 1H), 2.59–2.68 (m, 2H), 2.22–2.28 (m, 1H), 2.01 (s, 2H), 1.68–1.79 (m, 2H), 1.58–1.66 (m, 1H), 1.42–1.48 (m, 1H), 1.34–1.40 (m, 1H) 1.10–1.12 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 139.9, 128.7, 128.1, 126.7, 66.7, 58.5, 54.8, 48.3, 40.0, 23.7, 22.7, 21.0; IR (neat) 3025, 2928, 1635, 1220 cm^{-1}; HRMS calcd for $C_{16}H_{21}NO_2$: 259.1572, found: 259.1669; LRMS (CI) *m/z* 259 (69), 217 (100).

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Reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one. One-pot synthesis of 5*H*-imidazo[2,1-*b*][1,3]oxazine derivatives

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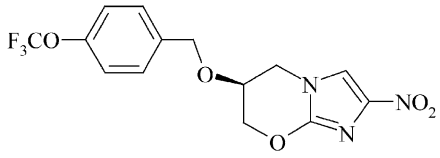
Abstract—The reactive 1:1 intermediate produced in the reaction between alkyl or aryl isocyanides and dialkyl acetylenedicarboxylates was trapped by 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one to yield highly functionalized 2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazine derivatives in fairly good yields.

1. Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[2] The interest in fused bicyclic 5–6 systems with one ring junction nitrogen atom and two extra heteroatoms, one nitrogen in the five-membered ring and one oxygen in the six-membered ring, 1:1, stems from the appearance of saturated and partially saturated imidazo[2,1-*b*][1,3]oxazine ring systems in biologically active compounds. Derivatives containing the imidazo[2,1-*b*][1,3]oxazine ring system have been shown to possess antimicrobial activity. For example, PA-824, PA-822, PA-653, PA-647, PA-601, and PA-602, are all members of bicyclic nitroimidazopyran family, drugs related to nitroimidazoles that have been studied as potent antituberculous compounds against a disease that kills one person every 15 s across the globe. The most promising compound in this series, PA-824, {4-[((3*S*)-6-nitro-(2*H*,3*H*,4*H*-imidazolo[2,1-*b*]1,3-oxazaperhydroin-3-yloxy))-methyl]phenoxy}trifluoromethane (**1**) has a novel mechanism of action against mycobacterium tuberculosis and *Helobacter pylori* comparable with that of isoniazid.[3–7]



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Only a few synthetic methods have been reported for the preparation of imidazo[2,1-*b*][1,3]oxazine ring systems.[8–11] As part of our current studies on the development of new routes in heterocyclic synthesis,[12–15] in this paper we wish to report a facile synthesis of functionalized imidazo[2,1-*b*]-[1,3]oxazines.

2. Results and discussion

Alkyl- or aryl isocyanides **2** and dialkyl acetylenedicarboxylates **3** in the presence of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one **4** undergo a smooth 1:1:1 addition reaction in acetone at room temperature, to produce 5*H*-imidazo-[2,1-*b*][1,3]oxazine derivatives **5** in 65–87% yields (Scheme 1).

The structures of compounds **5a–f** were deduced from their elemental analyses, their IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **5a** displayed the molecular ion (M^{+}) peak at 487 *m*/*z*, which is consistent with the 1:1:1 adduct of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one, dimethyl acetylenedicarboxylate, and cyclohexyl isocyanide. Any initial fragmentation involved the loss of ester moieties. The ^{1}H NMR spectrum of **5a**

Keywords: Isocyanides; Acetylenic esters; 4,5-Diphenyl-1,3-dihydro-2*H*-imidazol-2-one; Three-component reactions; 2,3-Diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazines.
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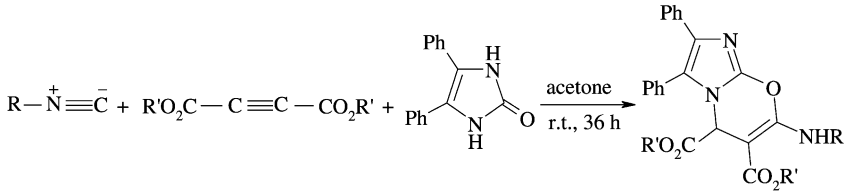


2 3 4 5

2	R
a	Cyclohexyl
b	2,6-$Me_2C_6H_3$
c	^{t}Bu

3	R'
a	Me
b	Et
c	^{t}Bu

5	R	R'	% Yield
a	Cyclohexyl	Me	87
b	Cyclohexyl	Et	84
c	Cyclohexyl	^{t}Bu	79
d	2,6-$Me_2C_6H_3$	Me	70
e	2,6-$Me_2C_6H_3$	Et	69
f	^{t}Bu	Et	65

Scheme 1.

exhibited three sharp lines readily recognized as arising from methoxy ($\delta=3.49$ and 3.69 ppm) and methine ($\delta=5.38$ ppm) protons. A fairly broad doublet ($\delta=8.72$ ppm and $^3J_{HH}=8.0$ Hz) is observed for the NH group because of coupling with the adjacent methine proton of the cyclohexyl moiety, along with characteristic multiplets for the 21 protons of the cyclohexyl and aromatic moieties. The proton decoupled ^{13}C NMR spectrum of **5a** showed 24 distinct resonances in agreement with the proposed structure. Partial assignment of these resonances is given in Section 4.

The ^{1}H and ^{13}C NMR spectra of compounds **5b–f** are similar to those of **5a**, except for the alkylamino and ester groups, which exhibit characteristic signals with appropriate chemical shifts (see Section 4).

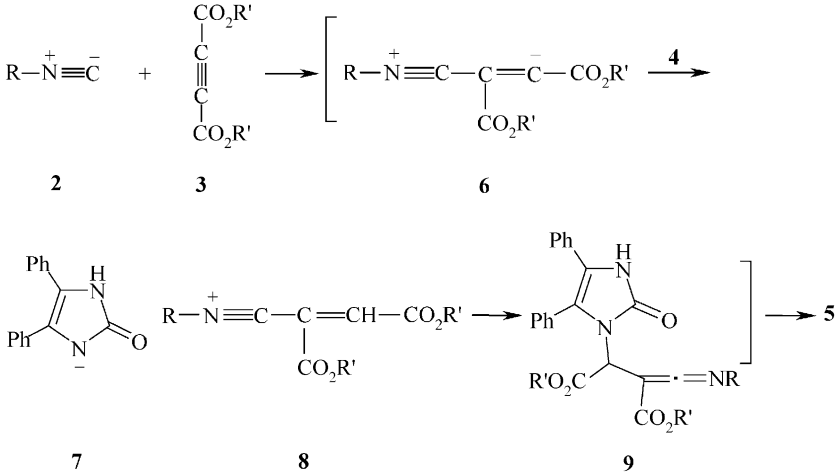
Although we have not established the mechanism of the reaction between isocyanides and acetylenic esters in the presence of compound **4** in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,[16–20] it is reasonable to assume that the functionalized imidazo[2,1-*b*]-[1,3]oxazines **5** apparently result from initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct **6** by compound **4**, followed by attack of the anion of the NH-acid **7** on the positively charged ion **8** to form ketenimine **9**. Intermediate ketenimine **9** can isomerize under the reaction condition employed to produce the fused heterocyclic system **5**.

3. Conclusion

In summary, the reaction between alkyl or aryl isocyanides and dialkyl acetylenedicarboxylates in the presence of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one provides a simple one-pot entry into the synthesis of polyfunctional imidazo[2,1-*b*][1,3]oxazine derivatives of potential synthetic and pharmaceutical interest. The present method carries the advantage of being performed under neutral conditions and requiring no activation or modification of the educts.

4. Experimental

Dimethyl-, diethyl-, and di-*tert*-butyl acetylenedicarboxylates, *tert*-butyl-, 2,6-dimethylphenyl-, and cyclohexyl isocyanides were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification.



2 3 6 7 8 9

Scheme 2.

4,5-Diphenyl-1,3-dihydro-2*H*-imidazol-2-one **4** was prepared according to the literature procedure.[21] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

4.1. General procedure

To a magnetically stirred solution of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one, **4** (0.236 g, 1 mmol) and the appropriate acetylenedicarboxylate (1 mmol) in acetone (6 mL), was added dropwise a mixture of the appropriate isocyanide (1 mmol) in acetone (2 mL) at −5 °C for 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 36 h. The solvent was removed under reduced pressure and the product was purified by column chromatography using hexane–ethyl acetate (2:1) as eluent. The solvent was removed under reduced pressure and the product was obtained.

4.1.1. Dimethyl 7-(cyclohexylamino)-2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (5a). Colorless crystals, mp 180–183 °C (from 1:1 hexane–ethyl acetate), yield 0.42 g, 87%. IR (KBr) (ν_{max}/cm^{-1}): 3267 (NH), 1749 and 1680 (C=O), 1614, 1560, 1440, 1307, 1086, 912, 732. MS, *m*/*z* (%): 488 (M^++1, 41), 487 (M^+, 23), 428 (81), 346 (11), 314 (7), 252 (100), 236 (16), 170 (93), 138 (14), 104 (30), 83 (86), 55 (89). Anal. Calcd for $C_{28}H_{29}N_3O_5$ (487.56): C, 68.98; H, 6.00; N, 8.62. Found: C, 68.8; H, 6.1; N, 8.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.05–2.20 [10H, m, CH(C*H*$_2$)$_5$], 3.49 and 3.69 (6H, 2s, 2CH$_3$), 4.05 (1H, m, NHC*H*), 5.38 (1H, s, NCH), 7.00–7.21 (3H, m, 3CH), 7.30–7.37 (2H, m, 2CH), 7.42–7.50 (5H, m, 5CH), 8.72 (1H, d, J=8.0 Hz, N*H*CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.05, 24.07, 25.01, 33.28, and 33.44 (5CH$_2$), 49.76, 50.92, 52.09, and 52.37 (NHCH, NCH, and 2OCH$_3$), 68.76 (NOC=*C*), 123.44 (C), 126.79, 126.83, 128.22, 129.28, and 129.31 (5CH), 129.34 (C), 130.98 (CH), 133.77, 133.93, 145.55, and 159.27 (4C), 168.27 and 170.35 (2C=O).

4.1.2. Diethyl 7-(cyclohexylamino)-2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (5b). Colorless crystals, mp 170–172 °C (from 1:1 hexane–ethyl acetate), yield 0.43 g, 84%. IR (KBr) (ν_{max}/cm^{-1}): 3255 (NH), 1734 and 1674 (C=O), 1609, 1564, 1433, 1369, 1308, 1259, 1204, 1155, 1086, 1020, 771, 702. MS, *m*/*z* (%): 515 (M^+, 7), 464 (54), 442 (66), 410 (6), 360 (10), 302 (100), 280 (15), 236 (13), 198 (40), 165 (22), 105 (38), 83 (36), 77 (15), 55 (58). Anal. Calcd for $C_{30}H_{33}N_3O_5$ (515.61): C, 69.88; H, 6.45; N, 8.15. Found: C, 69.9; H, 6.6; N, 8.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.02 and 1.21 (6H, 2t, J=7.1 Hz, 2OCH$_2$C*H*$_3$), 1.10–2.05 [10H, m, CH(C*H*$_2$)$_5$], 3.65–4.08 [3H, 2dq (*AB*X$_3$ system, ^3J=7.1 Hz, ^2J=10.7 Hz) and 1 m, OC*H*$_A$*H*$_B$CH$_3$ and NHC*H*], 4.10 and 4.26 (2H, 2dq, *AB*X$_3$ system, ^3J=7.1 Hz, ^2J=10.2 Hz, OC*H*$_A$*H*$_B$CH$_3$), 5.37 (1H, s, NCH), 7.05–7.27 (3H, m, 3CH), 7.34–7.40 (2H, m, 2CH), 7.43–7.55 (5H, m, 5CH), 8.71 (1H, d, J=8.0 Hz, N*H*CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.38 and 14.06 (2OCH$_2$*C*H$_3$), 24.06, 24.09, 24.95, 33.20, and 33.43 (5CH$_2$), 49.62 and 52.29 (NHCH and NCH), 59.50 and 61.28 (2 OCH$_2$CH$_3$), 68.82 (NOC=*C*), 123.34 (C), 126.77, 126.82, 128.20, 129.16 and 129.31 (5CH), 129.34 (C), 130.92 (CH), 133.80, 133.90, 145.56, and 159.09 (4C), 167.83 and 170.08 (2C=O).

4.1.3. Di-*tert*-butyl 7-(cyclohexylamino)-2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (5c). Colorless crystals, mp 109–110 °C (from 1:1 hexane–ethyl acetate), yield 0.45 g, 79%. IR (KBr) (ν_{max}/cm^{-1}): 3260 (NH), 1722 and 1668 (C=O), 1605, 1556, 1429, 1259, 1149, 1082, 771, 692. MS, *m*/*z* (%): 571 (M^+, 3), 552 (5), 540 (4), 485 (4), 470 (4), 454 (6), 414 (6), 236 (11), 142 (9), 105 (13), 83 (20), 57 (100). Anal. Calcd for $C_{34}H_{41}N_3O_5$ (571.72): C, 71.43; H, 7.23; N, 7.35. Found: C, 71.4; H, 7.3; N, 7.4%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.21 and 1.45 [18H, 2s, 2C(CH$_3$)$_3$], 1.19–2.25 [10H, m, CH(C*H*$_2$)$_5$], 4.07 [1H, m, C*H*(CH$_2$)$_5$], 5.28 (1H, s, NCH), 7.09–7.24 (3H, m, 3CH), 7.33–7.41 (2H, m, 2CH), 7.44–7.50 (5H, m, 5CH), 8.51 (1H, d, J=8.0 Hz, N*H*CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.64, 24.67, and 25.41 (3CH$_2$), 27.63 and 28.45 [2OC(*C*H$_3$)$_3$], 33.74 and 33.95 (2CH$_2$), 50.03 and 53.60 (NHCH and NCH), 70.66 (NOC=*C*), 80.04 and 81.95 [2 O*C*(CH$_3$)$_3$], 123.14 (C), 126.65, 126.95, 128.06, 128.67, and 128.86 (5CH), 129.26 (C), and 130.67 (CH), 133.65, 133.72, 145.93, and 158.68 (4C), 168.89 and 171.09 (2C=O).

4.1.4. Dimethyl 7-(2,6-dimethylphenylamino)-2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (5d). Colorless crystals, mp 190–195 °C (from 1:1 hexane–ethyl acetate), yield 0.35 g, 70%. IR (KBr) (ν_{max}/cm^{-1}): 3236 (NH), 1744 and 1672 (C=O), 1622, 1554, 1440, 1416, 1304, 1254, 1084, 769, 702. MS, *m*/*z* (%): 509 (M^+, 2), 450 (4), 395 (3), 371 (3), 274 (15), 214 (6), 105 (37), 57 (44), 43 (100). Anal. Calcd for $C_{30}H_{27}N_3O_5$ (509.56): C, 70.71; H, 5.34; N, 8.25. Found: C, 70.7; H, 5.4; N, 8.3%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.30 (6H, s, 2Ar-CH$_3$), 3.51 and 3.77 (6H, 2s, 2OCH$_3$), 5.45 (1H, s, NCH), 7.10–7.23 (6H, m, 6CH), 7.30–7.53 (7H, m, 7CH), 9.98 (1H, br. s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 18.12 (Ar-*C*H$_3$), 51.31, 52.34, and 52.55 (NCH and 2OCH$_3$), 70.33 (NOC=*C*), 123.47 (C), 126.84, 126.86, 127.99, 128.26, 128.61, 129.32, and 129.36 (7CH), 129.38 (C), 130.99 (CH), 133.17, 133.63, 134.18, 136.28, 145.29, and 159.17 (6C), 168.47 and 170.26 (2C=O).

4.1.5. Diethyl 7-(2,6-dimethylphenylamino)-2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (5e). Colorless crystals, mp 170–172 °C (from 1:1 hexane–ethyl acetate), yield 0.37 g, 69%. IR (KBr) (ν_{max}/cm^{-1}): 3231 (NH), 1740 and 1666 (C=O), 1622, 1597, 1555, 1418, 1298, 1250, 1188, 1072, 770, 698. MS, *m*/*z* (%): 537 (M^+, 10), 464 (66), 302 (100), 228 (12), 200 (14), 172 (16), 144 (20), 105 (29), 77 (11). Anal. Calcd for $C_{32}H_{31}N_3O_5$ (537.62): C, 71.49; H, 5.81; N, 7.82. Found: C, 71.6; H, 5.8; N, 7.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.10 and 1.33 (6H, 2t, J=7.1 Hz, 2OCH$_2$C*H*$_3$), 2.37 (6H, s, 2Ar-CH$_3$), 3.97 and 4.04 (2H, 2dq, *AB*X$_3$ system, ^3J=7.1 Hz, ^2J=

10.8 Hz, $OCH_AH_BCH_3$), 4.24 and 4.36 (2H, 2dq, ABX_3 system, $^3J=7.1$ Hz, $^2J=10.1$ Hz, $OCH_AH_BCH_3$), 5.52 (1H, s, NCH), 7.15–7.24 (6H, m, 6CH), 7.37–7.53 (7H, m, 7CH), 10.08 (1H, br. s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.83 and 14.45 ($2OCH_2CH_3$), 18.48 (Ar-CH_3), 52.78 (NCH), 60.20 and 61.64 (2 OCH_2CH_3), 70.62 (NOC=C), 123.32 (C), 126.72, 126.75, 127.70, 128.07, 128.38, 129.02, and 129.08 (7CH), 129.17 (C), 130.87 (CH), 133.11, 133.53, 133.99, 136.11, 145.13, and 158.68 (6C), 167.74 and 169.54 (2C=O).

4.1.6. Diethyl 7-(*tert*-butylamino)-2,3-diphenyl-5*H*-imidazo[2,1-*b*][1,3]oxazine-5,6-dicarboxylate (5f). Colorless crystals, mp 166–170 °C (from 1:1 hexane–ethyl acetate), yield 0.31 g, 65%. IR (KBr) (ν_{max}/cm^{-1}): 3261 (NH), 1744 and 1672 (C=O), 1614, 1558, 1427, 1303, 1202, 1078, 1026, 910, 735. MS, *m/z* (%): 489 (M^+, 2), 469 (3), 433 (12), 360 (7), 314 (5), 236 (39), 198 (15), 104 (19), 57 (100). Anal. Calcd for $C_{28}H_{31}N_3O_5$ (489.57): C, 68.69; H, 6.38; N, 8.58. Found: C, 68.8; H, 6.4; N, 8.6%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.08 and 1.27 (6H, 2t, $J=7.1$ Hz, $2OCH_2CH_3$), 1.58 [9H, s, $C(CH_3)_3$], 3.95 and 4.01 (2H, 2dq, ABX_3 system, $^3J=7.1$ Hz, $^2J=10.8$ Hz, $OCH_AH_BCH_3$), 4.14 and 4.28 (2H, 2dq, ABX_3 system, $^3J=7.1$ Hz, $^2J=10.8$ Hz, $OCH_AH_BCH_3$), 5.44 (1H, s, NCH), 7.17–7.26 (3H, m, 3CH), 7.35–7.38 (2H, m, 2CH), 7.45–7.53 (5H, m, 5CH), 8.95 (1H, br. s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.83 and 14.49 ($2OCH_2CH_3$), 30.42 [$C(CH_3)_3$], 52.48 and 53.59 [NCH and $C(CH_3)_3$], 59.80 and 61.54 (2 OCH_2CH_3), 69.95 (NOC=C), 123.27 (C), 126.69, 126.94, 128.09, 128.91, and 129.02 (5CH), 129.17 (C), 130.81 (CH), 133.62, 133.92, 145.14, and 160.33 (4C), 167.64 and 169.68 (2C=O).

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Synthesis, stereochemical and conformational properties of *trans*-2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-one oxime ethers

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Abstract—A convenient synthesis and structural characterization of (*Z*)- and (*E*)-*trans*-2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-one oxime ethers has been achieved. By analysis of vicinal interproton coupling constants, it is believed that *trans*-2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-ones which exist predominantly in the diequatorial half-chair or sofa conformation was found to exist predominantly in the diaxial orientation upon conversion to the corresponding oxime ether derivatives.

1. Introduction

2,3-Dihydro-4*H*-1-benzopyran-4-ones (chroman-4-ones) are widely distributed in nature.[1] 2-Arylchroman-4-ones (flavanones) and 3-arylchroman-4-ones (isoflavanones) are ubiquitous in the plant kingdom and many exhibit interesting and useful biological activities.[1] Chroman-4-ones are also important synthetic intermediates for chromans, chromenes, chromanols and chromanone oximes which themselves possess diverse pharmacological properties such as β-blockade, anticonvulsant, antiestrogen and antimicrobial.[2–5]

1,2,4-Triazole constitute an important class of nitrogen heterocycles and is essential structural features of many of the potent azole antifungals.[6] As part of our studies concerning the chemistry of azolylchroman structure, we are now developing a program for the design and the preparation of compounds **1** as conformationally constrained analogs of oxiconazole **2** and potential inhibitors of lanosterol 14α-demethylase.[4,5] Our own interest has been focused on the synthesis of *trans*-2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-one oxime ethers **3**. It is speculated that the chroman ring having the 2-methyl group on opposite side of triazole (*trans* position) in compounds **3** might be a mimetic of B and C rings or D ring and 17-alkyl side chain of the lanosterol **4** (Fig. 1), and that the 2-methyl group and the 3-triazolyl residue of **3** fill the positions of the 13-methyl and 14-methyl groups of lanosterol, respectively.[5] This paper describes synthesis, structural characterization and conformational analysis of 2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-one oxime ethers **3** as potential antifungal agents.

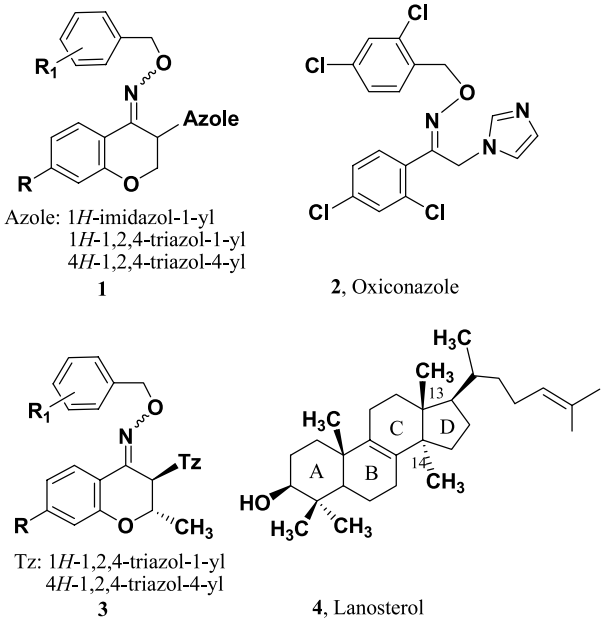

Figure 1.

Keywords: 1,2,4-Triazole; 2,3-Dihydro-4*H*-1-benzopyran-4-one (chroman-4-one); (*Z*)- and (*E*)-Oxime ethers; Conformation.
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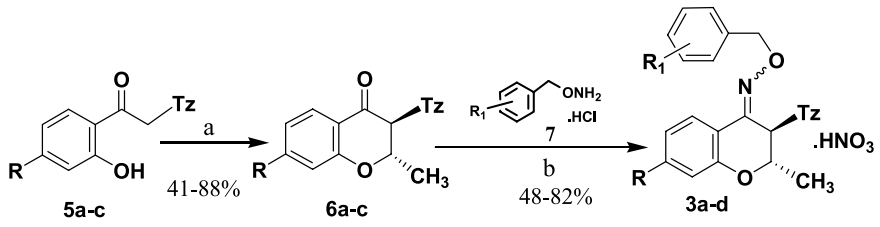
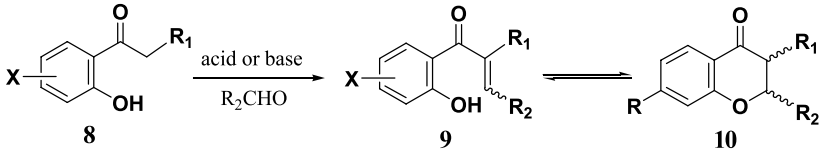


Scheme 1. Synthesis of (±)-(*Z*)- and (*E*)-*trans*-2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-one oxime ethers **3**. Reagents and conditions: (a) CH_3CHO, AcOH, 90 °C; (b), MeOH, rt and then HNO_3.



Scheme 2.

2. Results and discussion

Our synthetic pathway providing access to **3** is outlined in Scheme 1. A convenient method for the preparation of **6** was the ring closure of 2-triazolyl-2′-hydroxyacetophenones **5**.[7] Ring closure of compounds **5** with acetaldehyde in acetic acid at 90 °C gave the corresponding chroman-4-one derivatives **6** predominantly in the *trans* configuration, according to the large ^{1}H NMR coupling constant (J=11.6–12.0 Hz). In all cases, the work-up of the crude product led to the practically pure *trans* derivatives in good yields. Theoretically, the product of condensation between a 2′-hydroxyacetophenone derivative **8** and an aldehyde (Scheme 2) is an equilibrium mixture composed of (*E*)- and (*Z*)-chalcones **9** and *cis*- and *trans*-2,3-disubstituted chroman-4-ones **10**.[8] The equilibrium position between the four potential products in Scheme 2 depends on several factors such as the catalyst and solvent employed, and the steric and electronic characteristics of X, R_1 and R_2 and the pendant substituents within the latter.[9] It is rare to find examples in which the chromanones **6** are the sole products of the reaction and thus to isolate pure samples **6** without using chromatography. The oxime ethers **3** could directly be obtained from the corresponding ketones. Thus, treatment of ketones **6** with *O*-(arylmethyl)hydroxylamine hydrochloride **7** in methanol in the presence of K_2CO_3 at room temperature afforded a mixture of (*Z*)- and (*E*)-oxime ethers, predominantly in the *Z* configuration, which was established by ^{1}H NMR spectral data. In particular, the *syn* relationship between the oxime ether oxygen and the hydrogen at the C-5 [(*E*)-isomer] or the hydrogen at the C-3 [(*Z*)-isomer] of chroman ring may be confirmed by the fact that the protons, in this type of spatial arrangement, resonate at a lower field with respect to the same type of protons of the corresponding isomers.[4,5] This fact is due to the paramagnetic effect of the proximal oxime ether oxygen. A priori one may consider species A and B as the limiting reactive intermediates (Fig. 2). Collapse of A and B leads directly to the (*Z*)- and (*E*)-oxime ethers by elimination of water assisted by the nitrogen lone pair. Jencks[10] has convincingly showed that in oximation, the addition of hydroxylamine is fast and the rate-determining step is the acid-catalyzed dehydration of the intermediate. Since A and B are formed in a fast reaction, the predominance of (*Z*)-isomer may arise from: (1) a faster rate of collapse at A, (2) comparable rates of collapse but predominance of A at equilibrium, or (3) an equilibration of oxime ethers after formation that favors *Z*.

All described compounds, ketone **6** and oxime ether **3**, which possess two chiral center on their chroman ring on C-2 and C-3 positions, are racemates.

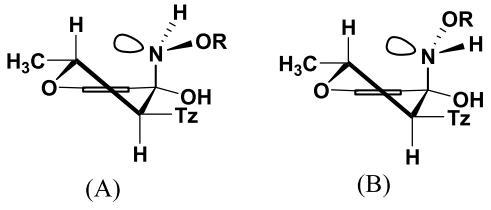


Figure 2.

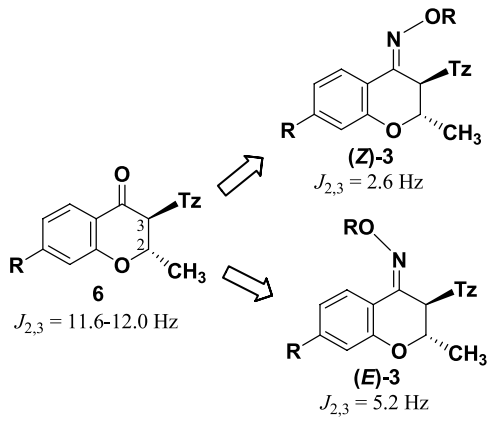


Figure 3. $J_{2,3}$ coupling constants of compounds **6**, (*Z*)-**3** and (*E*)-**3**.

Examination of the ^{1}H NMR coupling constant information of oxime derivatives **3** and ketones **6** clearly demonstrates that formation of (*Z*)- or (*E*)-oxime ethers results in a remarkable decrease in the $J_{2,3}$ coupling constants of chroman ring (Fig. 3). These results suggest that the dihedral angle between H–C(2) and H–C(3) in oxime derivatives is small. As previously discussed by Clark-Lewis et al.,[11] variation in vicinal coupling constants may be due to changes in conformational equilibria. In general, half-chair or sofa conformation is favoured for chroman ring, and principally arises from the restricted rotation imposed by the benzene ring.[12–14] AM1 calculation were performed with HyperChem software.[15] Starting geometries were constructed by the Model Builder function of the program setting the torsion angles for the theoretical values of the two half-chair or sofa conformations of the chroman ring in which triazole ring and methyl group occupy diaxial or diequatorial position. AM1 semiemprical energy calculations showed that the energy difference between the two conformers is small, therefore, the two conformers may exist in equilibrium. This question was studied by NMR. NMR-spectroscopy is the method of choice to address the conformational aspects of the chroman ring in solution, and it has been widely applied in analogous studies.[12–14,16] In the case of chroman-4-one derivatives, $J_{2,3}$ coupling constants is informative. Thus, relatively larg $J_{2,3}$ value (11.6–12.0 Hz) in compound **6** confirms the preferred pseudo-axial conformation of H-2 and H-3 (Fig. 4). The small $J_{2,3}$ value (2.6–5.2 Hz) in oxime derivatives **3** suggests a preference for the conformation in which H-2 and H-3 are in pseudo-equatorial orientation (Fig. 4).

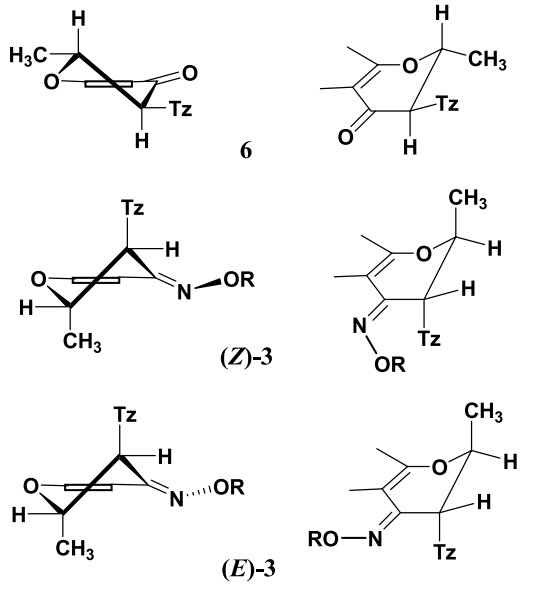


Figure 4. Preferential half-chair and sofa conformations in ketones **6** and in oxime derivatives (*Z*)-**3** and (*E*)-**3**.

In order to evaluate the reasons for the axial preference in oxime derivatives, it is necessary to describe those factors which influence the conformational equilibrium. Several factors have been invoked to explain this preference. The first is a minimization of dipole–dipole repulsion between polar bonds. It would appear, however, that this factor, if operative, is not determinant since the parent ketones **6** exist predominantly in the diequatorial conformation. The second is a hyperconjugative interaction related to the generalized anomeric effect. The increase in axial preference for the 2-substituent in the oxime over the ketone derives from the hyperconjugative interaction identified by Lessard[17–20] and Tronchet.[21] The interaction is viewed as a π–σ^*_{C-N} donation which is only capable of stabilizing the axial conformation (Fig. 5). Because of mixing of $\pi_{C=N}$ and n_o orbitals, the oximes are believed to be more effective than the C=O bond and a vinylogous anomeric-type effect[22,23] exists in oxime derivatives. Furthermore, another effect, different from those described above, has been identified. In (*Z*)-oxime derivatives the coupling constant drops markedly with respect to (*E*)-oxime derivatives (Fig. 3). According to the relation between the triazole ring and oxime oxygen atom in (*Z*)-oxime derivatives we suggested that an 1,3-allylic strain[24] might be responsible for the added stability of the diaxial conformer in (*Z*)-oxime derivatives (*Z*)-**3** (Fig. 6).

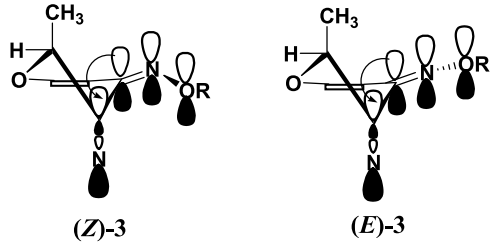


Figure 5. Preferential stabilization of the diaxial conformation of oxime derivatives (*Z*)-**3** and (*E*)-**3** by vinylogous anomeric effect.

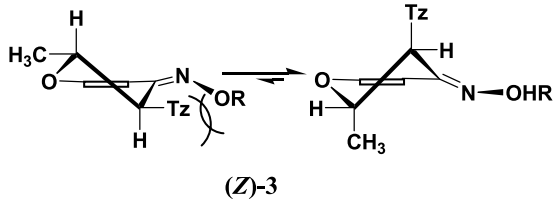


Figure 6. Preferential stabilization of the diaxial conformation of (*Z*)-oxime derivatives (*Z*)-**3** by 1,3-allylic strain.

In our previous reports,[5,7] we prepared both non-2-methyl substituted triazolylchromanones **11** and chromanone oxime derivatives **12** and found similar behavior (Fig. 7). The comparison of oxime derivatives **3** and **12** demonstrated that the pseudo-axial preference for triazolylchroman-4-one oxime derivatives is a general phenomenon and the preference is of sufficient magnitude to force 2-methyl substituent into a pseudo-axial position in compounds **3**.

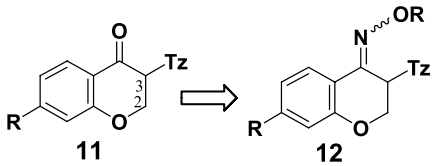


Figure 7. $J_{2,3}$ coupling constants of compounds **11** and **12**.

Table 1. In vitro antifungal activity of oxime ethers **3**: MIC_s in μg/mL

Microorganism	(*Z*)-**3a**	(*E*)-**3a**	(*Z*)-**3b**	(*E*)-**3b**	(*Z*)-**3c**	(*Z*)-**3d**	Fluconazole
C. albicans ATCC 10231	8	16	8	8	>64	16	8
C. albicans PTCC 5027	32	32	64	32	>64	32	16
A. niger ATCC 16401	64	8	64	4	>64	64	16

Compounds (*Z*)-**3a–d** and (*E*)-**3a**,**b** were tested in vitro by using the method of two-fold serial dilution technique[25] against *Candida albicans* (ATCC 10231 and PTCC 5027) and *Aspergillus niger* (ATCC 16401), the most important fungal pathogens. Table 1 shows the antifungal activity of the oxime ethers **3** and fluconazole, taken as the reference drug. The MIC (minimum inhibitory concentration) values of the test derivatives against *C. albicans* indicate that most compounds possessed a comparable activity with respect to fluconazole. (*Z*)-isomers [(*Z*)-**3a–d**] did not show significant antifungal activity against *A. niger*. In contrast, (*E*)-isomers [(*E*)-**3a**,**b**] possessed a comparable or better activity with respect to reference drug.

3. Conclusion

In conclusion, a convenient synthesis and structural characterization of (*Z*)- and *trans*-2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-one oxime ethers has been achieved. By analysis of vicinal coupling constants it is believed that *trans*-2,3-dihydro-2-methyl-3-(1,2,4-triazolyl)-4*H*-1-benzopyran-4-ones exist predominantly in the diequatorial half-chair or sofa conformation. Formation of the oxime ethers results in a remarkable conformational inversion for chroman system and those compounds exist predominantly in the diaxial half-chair or sofa conformation. The origin of this preference is suggested to derive primarily from vinylogous anomeric-type effect.

4. Experimental

Chemicals and all solvents used in this study were purchased from Merck AG and Aldrich Chemical. The desired 2-(1,2,4-triazolyl)-2′-hydroxyacetophenones **5** and *O*-(arylmethyl)hydroxylamine. HCl **7** were prepared according to the literature.[5,7] All melting points were determined with a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR Magna 550 spectrophotometer. ^{1}H NMR spectra were measured using a Bruker FT-80 or Varian 400 Unity plus spectrometer, and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. Yields are of purified product and were not optimized.

4.1. General procedure for the synthesis of *trans*-3-triazolyl-2-methylchroman-4-ones (6)

A solution of the appropriate precursor **5** (4.9 mmol) and acetaldehyde (3.0 mL) in glacial acetic acid (50 mL) was heated at 90 °C for 12–14 h. The solvent was evaporated under reduced pressure and the residue dissolved in $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallized from ethanol.

4.1.1. *trans*-2,3-Dihydro-3-(1*H*-1,2,4-triazol-1-yl)-2-methyl-4*H*-1-benzopyran-4-one (6a). White crystals; yield 41%; mp 95–96 °C; ν_{max} (KBr) 1695, 1641, 1511, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, 3H, J=6.0 Hz, CH_3), 5.09 (dq, 1H, J=12.0, 6.0 Hz, H-2), 5.13 (d, 1H, J=12.0 Hz, H-3), 7.07 (dd, 1H, J=8.0, 1.6 Hz, H-8), 7.13 (dt, 1H, J=8.0, 1.6 Hz, H-6), 7.59 (dt, 1H, J=8.0, 2.0 Hz, H-7), 7.94 (dd, 1H, J=8.0, 2.0 Hz, H-5), 8.10 (s, 1H, triazole H), 8.36 (s, 1H, triazole H). MS (*m*/*z*, %) 229 (M^+, 3), 120 (63), 92 (100), 65 (47), 43 (98). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.80; H, 4.74; N, 18.21.

4.1.2. *trans*-2,3-Dihydro-3-(4*H*-1,2,4-triazol-4-yl)-2-methyl-4*H*-1-benzopyran-4-one (6b). Pale yellow crystals; yield 88%; mp 191–194 °C; ν_{max} (KBr) 1701, 1614, 1527, 1480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, 3H, J=6.0 Hz, CH_3), 4.75 (dq, 1H, J=11.6, 6.4 Hz, H-2), 5.03 (d, 1H, J=11.6 Hz, H-3), 7.08 (dd, 1H, J=8.0, 1.2 Hz, H-8), 7.15 (dt, 1H, J=8.0, 1.2 Hz, H-6), 7.62 (dt, 1H, J=8.0, 1.6 Hz, H-7), 7.94 (dd, 1H, J=7.6, 1.6 Hz, H-5), 8.22 (s, 2H, triazole H). MS (*m*/*z*, %) 229 (M^+, 92), 120 (100), 92 (73). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.75; H, 4.89; N, 18.19.

4.1.3. *trans*-7-Chloro-2,3-dihydro-3-(4*H*-1,2,4-triazol-4-yl)-2-methyl-4*H*-1-benzopyran-4-one (6c). Pale yellow crystals; yield 75%; mp 190–193 °C; ν_{max} (KBr) 1699, 1600, 1426, 1201, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, 3H, J=5.6 Hz, CH_3), 4.77 (dq, 1H, J=12.0, 5.6 Hz, H-2), 5.03 (d, 1H, J=12.0 Hz, H-3), 7.13 (m, 2H, H-6 and H-8), 7.87 (d, 1H, J=8.0 Hz, H-5), 8.19 (s, 2H, triazole H). Anal. Calcd for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94. Found: C, 54.79; H, 3.81; N, 15.79.

4.2. General procedure for the synthesis of (*Z*)- and (*E*)-*trans*-3-(1*H*-1,2,4-triazol-1-yl)-2-methylchroman-4-one oxime ethers [(*Z*)- and (*E*)-3a,b]

A mixture of **6** (2.0 mmol), *O*-(arylmethyl)hydroxylamine hydrochloride **7** (5.0 mmol) and K_2CO_3 (0.27 g, 2.0 mmol) in methanol (10 mL) was stirred at room temperature for 3–7 days. Water (100 mL) was added and the mixture extracted with $CHCl_3$. The organic layer was washed (H_2O), dried (Na_2SO_4) and evaporated. The (*Z*)- and (*E*)-isomers were separated by preparative TLC (silica gel) eluting with $CHCl_3$–MeOH. The desired compounds were dissolved in ethanol or 2-propanol and treated with 70% HNO_3. The precipitate was filtered and washed with Et_2O to give corresponding (*Z*)- and (*E*)-isomers.

4.2.1. (*Z*)-*trans*-2,3-Dihydro-3-(1*H*-1,2,4-triazol-1-yl)-2-methyl-4*H*-1-benzopyran-4-one *O*-(4-chlorophenylmethyl)oxime nitrate [(*Z*)-3a]. White microcrystalline powder; yield 66%; mp 149–150 °C; ν_{max} (KBr) 1614,

1492, 1460, 1396, 1328, 1228 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 1.07 (d, 3H, $J=6.4$ Hz, CH_3), 4.52 (dq, 1H, $J=6.4$, 2.6 Hz, H-2), 5.14 (s, 2H, CH_2), 6.10 (d, 1H, $J=$ 2.6 Hz, H-3), 6.90–7.48 (m, 7H, H-6, H-7, H-8 and aromatic H), 7.80 (dd, 1H, $J=8.0$, 1.8 Hz, H-5), 7.96 (s, 1H, triazole H), 8.65 (s, 1H, triazole H). MS (*m/z*, %) 368 (M^+, 2), 175 (11), 125 (100), 85 (87), 69 (37). Anal. Calcd for $C_{19}H_{17}ClN_4O_2 \cdot HNO_3$: C, 52.85; H, 4.20; N, 16.22. Found: C, 53.05; H, 4.20; N, 16.19.

4.2.2. (*E*)-*trans*-2,3-Dihydro-3-(1*H*-1,2,4-triazol-1-yl)-2-methyl-4*H*-1-benzopyran-4-one *O*-(4-chlorophenylmethyl)oxime nitrate [(*E*)-3a]. White microcrystalline powder; yield 16%; mp 138–139 °C; ν_{max} (KBr) 1602, 1464, 1419, 1388, 1294, 987 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 1.25 (d, 3H, $J=6.4$ Hz, CH_3), 5.10 (dq, 1H, $J=6.4$, 5.2 Hz, H-2), 5.20 (s, 2H, CH_2), 5.37 (d, 1H, $J=$ 5.2 Hz, H-3), 6.90–7.54 (m, 7H, H-6, H-7, H-8 and aromatic H), 8.04 (s, 1H, triazole H), 8.48 (d, 1H, $J=7.2$ Hz, H-5), 8.56 (s, 1H, triazole H). Anal. Calcd for $C_{19}H_{17}ClN_4O_2 \cdot HNO_3$: C, 52.85; H, 4.20; N, 16.22. Found: C, 53.17; H, 4.16; N, 16.24.

4.2.3. (*Z*)-*trans*-2,3-Dihydro-3-(1*H*-1,2,4-triazol-1-yl)-2-methyl-4*H*-1-benzopyran-4-one *O*-(2,4-dichlorophenylmethyl)oxime nitrate [(*Z*)-3b]. Pale yellow microcrystalline powder; yield 44%; mp 148–150 °C; ν_{max} (KBr) 1618,1595, 1460, 1400, 1326, 1305, 1039 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 1.07 (d, 3H, $J=6.4$ Hz, CH_3), 4.53 (dq, 1H, $J=6.4$, 2.6 Hz, H-2), 5.21 (s, 2H, CH_2), 6.10 (d, 1H, $J=2.6$ Hz, H-3), 6.90–7.65 (m, 6H, H-6, H-7, H-8 and aromatic H), 7.80 (dd, 1H, $J=8.0$, 2.0 Hz, H-5), 7.99 (s, 1H, triazole H), 8.70 (s, 1H, triazole H). MS (*m/z*, %) 402 (M^+, 17), 228 (34), 175 (100), 161 (61), 159 (76), 115 (26), 89 (30). Anal. Calcd for $C_{19}H_{16}Cl_2N_4O_2 \cdot HNO_3$: C, 48.94; H, 3.67; N, 15.02. Found: C, 48.92; H, 3.88; N, 15.00.

4.2.4. (*E*)-*trans*-2,3-Dihydro-3-(1*H*-1,2,4-triazol-1-yl)-2-methyl-4*H*-1-benzopyran-4-one *O*-(2,4-dichlorophenylmethyl)oxime nitrate [(*E*)-3b]. White microcrystalline powder; yield 24%; mp 128–130 °C; ^1H NMR (80 MHz, DMSO-d_6) δ 1.24 (d, 3H, $J=6.4$ Hz, CH_3), 5.09 (dq, 1H, $J=6.4$, 5.2 Hz, H-2), 5.27 (s, 2H, CH_2), 5.35 (d, 1H, $J=$ 5.2 Hz, H-3), 6.97–7.66 (m, 6H, H-6, H-7, H-8 and aromatic H), 8.02 (s, 1H, triazole H), 8.46 (d, 1H, $J=7.2$ Hz, H-5), 8.55 (s, 1H, triazole H). Anal. Calcd for $C_{19}H_{16}Cl_2N_4O_2 \cdot HNO_3$: C, 48.94; H, 3.67; N, 15.02. Found: C, 48.99; H, 3.78; N, 15.12.

4.3. General procedure for the synthesis of (*Z*)-*trans*-3-(4*H*-1,2,4-triazol-4-yl)-2-methylchroman-4-one oxime ethers [(*Z*)-3c,d]

A mixture of **6b** or **6c** (2.0 mmol), *O*-(arylmethyl)hydroxylamine hydrochloride **7** (5.0 mmol) and K_2CO_3 (0.27 g, 2.0 mmol) in methanol (10 mL) was stirred at room temperature for 3–7 days. Water (100 mL) was added and extracted with $CHCl_3$. The organic layer was washed (H_2O), dried (Na_2SO_4) and evaporated. The viscous oily residue was dissolved in ethanol or 2-propanol and treated with 70% HNO_3. The precipitate was filtered and washed with Et_2O to give corresponding (*Z*)-**3**.

4.3.1. (*Z*)-*trans*-2,3-Dihydro-3-(4*H*-1,2,4-triazol-4-yl)-2-methyl-4*H*-1-benzopyran-4-one *O*-(2,4-dichlorophenylmethyl)oxime nitrate [(*Z*)-3c]. Pale yellow microcrystalline powder; yield 57%; mp 125–127 °C; ν_{max} (KBr) 1595, 1564, 1454, 1419, 1338, 1064, 1033 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 1.12 (d, 3H, $J=6.4$ Hz, CH_3), 4.61 (dq, 1H, $J=6.4$, 2.6 Hz, H-2), 5.25 (s, 2H, CH_2), 6.13 (d, 1H, $J=2.6$ Hz, H-3), 6.99–7.67 (m, 6H, H-6, H-7, H-8 and aromatic H), 7.81 (dd, 1H, $J=8.0$, 2.2 Hz, H-5), 8.92 (s, 2H, triazole H). MS (*m/z*, %) 404, 402 (M^+, 10,12), 228 (5), 175 (50), 161 (61), 159 (100), 145 (20), 63 (10). Anal. Calcd for $C_{19}H_{16}C_{l2}N_4O_2 \cdot HNO_3$: C, 48.94; H, 3.67; N, 15.02. Found: C, 48.75; H, 3.67; N, 15.23.

4.3.2. (*Z*)-*trans*-7-Chloro-2,3-dihydro-3-(4*H*-1,2,4-triazol-4-yl)-2-methyl-4*H*-1-benzopyran-4-one *O*-(2,4-dichlorophenylmethyl)oxime nitrate [(*Z*)-3d]. White microcrystalline powder; yield 48%; mp 118–120 °C; ν_{max} (KBr) 1602, 1562, 1477, 1450, 1398, 1346, 1213, 1056 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 1.10 (d, 3H, $J=6.4$ Hz, CH_3), 4.69 (dq, 1H, $J=6.4$, 2.6 Hz, H-2), 5.25 (s, 2H, CH_2), 6.12 (d, 1H, $J=2.6$ Hz, H-3), 7.03–7.70 (m, 5H, H-6, H-8 and aromatic H), 7.82 (d, 1H, $J=8.0$ Hz, H-5), 8.89 (s, 2H, triazole H). MS (*m/z*, %) 438 (M^+, 2), 228 (8), 210 (22), 209 (82), 159 (100), 115 (57). Anal. Calcd for $C_{19}H_{15}C_{l3}N_4O_2 \cdot HNO_3$: C, 45.58; H, 3.22; N, 13.99. Found: C, 45.56; H, 3.07; N, 14.27.

4.4. Biological test

For antifungal assays, the compounds were dissolved in DMSO (1 mL) and the solution was diluted with distilled water (9 mL). Further progressive double dilutions with test medium gave the required concentrations of 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25 and 0.125 μg/mL. The minimum inhibitory concentration (MIC) was determined by using the method of two-fold serial dilution technique.[25] Compounds were tested for their in vitro growth inhibitory activity against *Candida albicans* and *Aspergillus niger*. All tested microorganisms were first incubated at 35 °C on Sabouraud dextrose broth for 18 h. Testing was performed in Sabouraud dextrose broth at pH 7.0. Inoculum size was 0.5×10^3 CFU/mL. Reading of MICs were taken after 48 h at 35 °C. The MIC was defined as the lowest concentration of substance at which there was no growth.

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Clerodane diterpenoids from *Microglossa angolensis*

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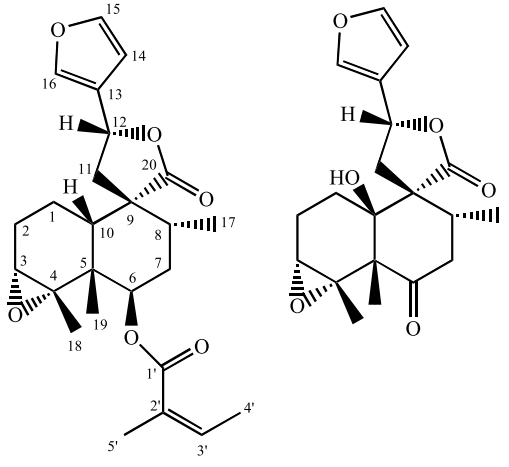
Abstract—Two new diterpenoids, 6β-(2-methylbut-2(*Z*)-enoyl)-3α,4α,15,16-bis-epoxy-8β,10βH-*ent*-cleroda-13(16),14-dien-20,12-olide and 10β-hydroxy-6-oxo-3α,4α,15,16-bis-epoxy-8βH-cleroda-13(16),14-dien-20,12-olide, together with the known β-amyrin, spinasterol, 5,7-dihydroxy-3,8,3′,4′-tetramethoxyflavone and 5,7-dihydroxy-3,8,3′,4′,5′-pentamethoxyflavone have been isolated from the aerial parts of *Microglossa angolensis* Oliv. et Hiern (Compositae). The structures were elucidated on the basis of spectral studies and comparison with published data.

1. Introduction

Clerodane diterpenoids are obtained mainly from the plant families Compositae, Euphorbiaceae and Labiatae, and can possess various structural modifications including rearranged clerodanes, *seco*-clerodanes, *trans*-clerodanes and *cis*-clerodanes. Previous studies have revealed that plants of the genus *Microglossa* (family: Compositae, tribe: Astereae, subtribe: Conyzinae), with about 10 species distributed from South to tropical Africa and eastern Asia, mainly produce terpenoids.[1–4]

According to the literature *Microglossa angolensis* Oliv. et Hiern is identical with *Conyza pyrrhopappa* Sch. Bip. ex A. Rich[5] and the latter is also identical with *Microglossa pyrrhopappa* A. Rich.[2] Nine rearranged clerodanes, six *seco*-clerodanes, seven *cis*-clerodanes and four alicyclic diterpenes have been isolated from *M. pyrrhopappa* A. Rich.[2]

In our continuing search for new substances from Cameroonian medicinal plants,[6] we now report the isolation and structural elucidation of two novel *cis*-clerodane diterpenoids from *M. angolensis* Oliv. et Hiern, an erect undershrub of 60–120 cm high[5] which is used traditionally to treat malaria and gastric troubles in Africa and Madagascar.[7] The novel diterpenes, 6β-(2-methylbut-2(*Z*)-enoyl)-3α,4α,15,16-bis-epoxy-8β,10βH-*ent*-cleroda-13(16),14-dien-20,12-olide (**1**) and 10β-hydroxy-6-oxo-3α,4α,15,16-bis-epoxy-8βH-cleroda-13(16),14-dien-20,12-olide (**2**) were isolated from the aerial parts of *M. angolensis* and their structures elucidated by spectroscopic analysis. The known compounds, β-amyrin,[8] spinasterol,[9] 5,7-dihydroxy-3,8,3′,4′-tetramethoxyflavone[10] and 5,7-dihydroxy-3,8,3′,4′,5′-pentamethoxyflavone[11] were also isolated.



1 **2**

2. Results and discussion

The methylene chloride extract of *M. angolensis* was separated on silica gel column chromatography to give several fractions which were each further purified by

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sephadex LH-20 permeation, open column chromatography, preparative TLC or re-crystallization, to afford compounds **1** and **2** together with β-amyrin,[8] spinasterol,[9] 5,7-dihydroxy-3,8,3′,4′-tetramethoxyflavone[10] and 5,7-dihydroxy-3,8,3′,4′,5′-pentamethoxyflavone.[11]

The molecular formula of compound **1** was shown to be $C_{25}H_{32}O_6$ (10° of unsaturation) on the basis of HRCIMS, IR and NMR data. The IR spectrum displayed absorption bands attributable to a γ-lactone (1757 cm^{-1}), carbonyl (1707 cm^{-1}) and furan (873 cm^{-1}). A methylbutenoyl moiety and a diterpene framework of the clerodane type containing a decalin system were suggested from ^1H and ^{13}C NMR spectroscopic analysis.

The ^1H NMR spectrum exhibited resonances for the 2-methylbut-2-enoyl moiety at δ 1.95 (3H, dq, $J=1.4$, 1.4 Hz), 2.04 (3H, dq, $J=1.4$, 7.1 Hz), and 6.06 (1H, qq, $J=1.4$, 7.1 Hz) (see Table 1). This was confirmed in the ^{13}C NMR spectrum with signals at δ 166.7, 137.5, 128.2, 20.4 and 15.8 (see Table 1).

In the ^1H NMR spectrum a triplet at δ 5.35 (H-12) and a multiplet (instead of a pair of double doublets as observed with closely related diterpenes)[2,12] of two protons at δ 2.47 (2H-11) were suggestive of a 20,12-olide. Furthermore, a β-substituted furan moiety was present as indicated by the typical signals at δ 7.48 (H-16), 7.46 (H-15) and 6.41 (H-14). Since compound **1** has 10° of unsaturation, **1** may also contain one epoxide ring. These proposals are supported by the presence of a lactone carbonyl singlet at δ 176.0 (C-20) and a doublet at δ 70.6 (C-12) in the ^{13}C NMR spectrum. Furthermore, the expected signals indicative of a β-substituted furan ring were present [δ 124.7 (C-13, s), 108.1 (C-14, d), 139.6 (C-16, d) and 144.0 (C-15, d)], as well as signals at δ 60.8 (C-3, d), 71.1 (C-6, d) and 61.5 (C-4, s).

The proton sequence of the aliphatic rings was established using ^1H–^1H COSY and gradient HMQC experiments while the HMBC spectrum permitted the construction of the skeleton of **1**. In the HMBC spectrum, cross peaks were observed between H-12 (δ 5.35) and C-20 (δ 176.0), C-9 (δ 51.8), C-13 (δ 124.7), C-14 (δ 108.1) and C-16 (δ 139.6). Cross peaks were also observed between H-6 (δ 5.80) and C-19 (δ 22.7), C-10 (δ 50.4), C-8 (δ 31.8), C-4 (δ 61.5) and C-1′ (δ 166.7). The latter indicated that the 2-methylbut-2-enoyl moiety was attached to carbon C-6 (δ 71.1) and, therefore, if a clerodane skeleton is assumed, supported the presence of a 3,4-epoxy group.

The stereochemistry of the carbon atoms was deduced from NOE difference spectra with NOE's between H-3/H-1 (δ 1.81) (1.9%), H-3/H-2 (δ 1.80) (1.9%), H-3/H-18 (2.8%), H-18/H-19 (3.1%), H-19/H-8 (1.9%), H-19/H-10 (2.6%), H-10/H-11 (1.7%), H-10/H-12 (1.3%), H-11/H-12 (2.2%), H-6/H-7 (δ 2.34) (2.5%), and H-7 (δ 2.34)/H-17 (1.1%). These observed NOE contacts thus required a β-orientation of C-11, C-18, C-19 with respect to the 2-methylbut-2-enoyl group. The *cis*-decalin structure and the 8α-orientation of the secondary methyl followed from the interaction between H-19 and H-10 and H-8, respectively. Also the effect of H-18 on H-19 and H-3 indicated a 3α,4α-epoxide group.

Table 1. ^{13}C NMR (100.6 MHz, $CDCl_3$) (δ; multiplicity) and ^1H NMR (400.13 MHz, $CDCl_3$) (δ; multiplicity; *J*) data of **1** and **2**

N°	**1**		**2**	
	C	H	C	H
1	21.9; t	1.81; overlapped m 1.46; m	29.6; t	2.15; overlapped m 2.01; m
2	25.3; t	2.20; m 1.80; overlapped m	20.5; t	2.15; overlapped m 2.03; overlapped m
3	60.8; d	2.98; br s	59.6; d	3.05; br s
4	61.5; s		60.1; s	
5	40.6; s		55.4; s	
6	71.1; d	5.80; t; 6.1	210.4; s	
7	33.0; t	2.34; ddd; 6.1, 10.5, 14.4 1.67; overlapped m	43.8; t	2.88; dd; 13.3, 15.4 2.35; dd; 4.6, 15.4
8	31.8; d	2.18; m	33.7; d	2.12; m
9	51.8; s		57.0; s	
10	50.4; d	1.61; overlapped m	73.8; s	
11	46.5; t	2.47; m	40.2; t	3.36; dd; 7.2, 13.0 2.03; overlapped m
12	70.6; d	5.35; t; 7.6	73.0; d	5.50; t; 7.2
13	124.7; s		125.0; s	
14	108.1; d	6.41; t; 1.0	107.9; d	6.40; t; 1.2
15	144.0; d	7.46; t; 1.0	144.1; d	7.45; br s
16	139.6; d	7.48; br s	139.4; d	7.45; br s
17	17.2; q	1.07; d; 6.7	17.6; q	1.14; d; 6.8
18	22.7; q	1.34; s	22.4; q	1.46; s
19	24.0; q	1.41; s	20.6; q	1.44; s
20	176.0; s		176.4; s	
1′	166.7; s			
2′	128.2; s			
3′	137.5; d	6.05; qq; 1.4, 7.1		
4′	15.8; q	2.04; dq; 1.4, 7.1		
5′	20.4; q	1.95; dq; 1.4, 1.4[a]		

[a] $J_{5',4'}=J_{5',3'}=1.4$ Hz.

The 2-methylbut-2-enoyl group was identified as angelate by comparison of data with those of closely related diterpenes.[2] On the basis of the spectroscopic and physical evidence, compound **1** was, therefore, the novel *cis*-furoclerodane 6β-(2-methylbut-2(*Z*)-enoyl)-3α,4α,15,16-bis-epoxy-8β,10βH-*ent*-cleroda-13(16),14-dien-20,12-olide. It should be noted that the 10β-hydroxy derivative has been isolated.[2]

Compound **2** was assigned the molecular formula $C_{20}H_{24}O_6$ as confirmed by HRCIMS, IR and NMR data. In the IR spectrum, absorption bands at 3480, 1740, 1708 and 874 cm^{-1} indicated the presence of hydroxyl, γ-lactone, carbonyl and furan, respectively. ^1H and ^{13}C NMR spectral data of **2** (data given in Table 1) suggested the presence of a furoclerodane 20,12-olide group. Again a 3,4-epoxide was present as indicated by a broad singlet at δ 3.05 (H-3) in the ^1H NMR spectrum. ^{13}C NMR data also supported the 3,4-epoxy group (C-3, δ 59.6, d; C-4, δ 60.1, s).

1D and 2D-NMR data allowed the assignment of nearly all the signals and led to several sequences, which together with the molecular formula, agreed with the presence of 6-keto (δ_C 210.4, s) and 10-hydroxy (δ_C 73.8, s) functions.

NOE contacts were observed between H-3/H-1 (δ 2.15) (1.4%), H-3/H-2 (δ 2.03) (1.1%), H-3/H-18 (2.7%), H-18/H-11 (δ 3.36) (0.9%), H-19/H-8 (0.8%), H-19/H-11 (δ 3.36) (1.0%), H-11 (δ 3.36)/H-12 (3.2%) and H-7 (δ 2.88)/H-1 (δ 2.15) (2.4%), and comparison of the NMR data for **2** with those of closely related diterpenes[2,12] required a *cis*-decalin system with a β-orientation of the hydroxyl group at C-10, and of C-11, C-18, C-19, H-3, H-8 and H-12.

The novel compound **2** was thus identified as 10β-hydroxy-6-oxo-3α,4α,15,16-bis-epoxy-8βH-cleroda-13(16),14-dien-20,12-olide. The corresponding 6β-hydroxy and 6β-angelate derivatives have been isolated previously.[2]

3. Experimental

3.1. General

Melting points (uncorr.) were determined on a Kofler apparatus. Optical rotations were measured on a AA Series Automatic Polarimeter Polaar-2000 at 22 °C. ^1H NMR (400.13 MHz) and ^{13}C NMR (100.6 MHz) with DEPT program were recorded at room temperature in $CDCl_3$, unless otherwise stated, using a Bruker DPX 400 spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) with the solvent signals, δ_H 7.26 and δ_C 77.0 as reference relative to TMS (δ=0) as internal standard, while the coupling constants (*J* values) are given in Hertz (Hz). COSY, HMQC and HMBC experiments were recorded with gradient enhancements using sine shape gradient pulses. The IR spectra were recorded with a JASCO FT-IR-410 spectrophotometer and the UV spectra recorded with a Shimadzu UV-3101 PC spectrophotometer. CIMS, HRCIMS spectra were recorded with a JEOL JMS-700 spectrometer. Column chromatography was run on Merck silica gel 60 and gel permeation on sephadex LH-20, while TLC were carried out either on silica gel GF_{254} pre-coated plates (analytical TLC) or on silica gel 60 PF_{254} containing gypsum (preparative TLC), with detection accomplished by spraying with 50% H_2SO_4 followed by heating at 100 °C, or by visualizing with an UV lamp at 254 and 366 nm.

3.2. Plant material

The aerial parts of *M. angolensis* Oliv. et Hiern were collected at Dschang, West province, Cameroon, in September 2003. Authentication was confirmed by Mr François Nana, a botanist of the Cameroon National Herbarium, Yaoundé. A voucher specimen (BUD 0630) has been deposited at the Botany Department, University of Dschang.

3.3. Extraction and isolation

The air dried powdered material (2.5 kg) was extracted by percolation with CH_2Cl_2 for three days at room temperature. Removal of the solvent under reduced pressure provided 70 g of a greenish organic extract. A portion (60 g) was subjected to CC on silica gel (70–230 mesh) and gradient elution performed with mixtures of hexane and ethyl acetate. Fifty-five fractions of 250 ml each were collected and combined on the basis of their TLC profiles to give 6 major fractions: I (18 g, hexane–EtOAc 100:0 and 19:1), II (8 g, hexane–EtOAc 19:1), III (4 g, hexane–EtOAc 9:1 and 4:1), IV (2.6 g, hexane–EtOAc 7:3), V (10 g, hexane–EtOAc 7:3 and 1:1) and VI (8.7 g, EtOAc). Further purification of these fractions was achieved separately by silica column chromatography by gradient elution with hexane–EtOAc. Fraction I yielded only straight chain fatty alcohols, while fraction II gave β-amyrin (70 mg) and other fatty alcohols. Fraction III afforded spinasterol (120 mg). Fraction IV yielded 6β-(2-methylbut-2(*Z*)-enoyl)-3α,4α,15,16-bis-epoxy-8β,10βH-*ent*-cleroda-13(16),14-dien-20,12-olide (**1**) (14 mg). Fraction V afforded 10β-hydroxy-6-oxo-3α,4α,15,16-bis-epoxy-8βH-cleroda-13(16),14-dien-20,12-olide (**2**) (106 mg) and a mixture of two flavones (42 mg) which were separated by preparative TLC (eluent: CH_2Cl_2–MeOH, 98:2) to give 5,7-dihydroxy-3,8,3′,4′-tetramethoxyflavone (10 mg) and 5,7-dihydroxy-3,8,3′,4′,5′-pentamethoxyflavone (6 mg). The last fraction (VI) yielded straight chain fatty acids and a complex mixture. For the individual fractions an additional purification by CC on LH-20 gel eluted with CH_2Cl_2–MeOH (1:1) was required to obtain analytically pure samples (this removed the last traces of chlorophylls).

3.3.1. 6β-(2-Methylbut-2(*Z*)-enoyl)-3α,4α,15,16-bis-epoxy-8β,10βH-*ent*-cleroda-13(16),14-dien-20,12-olide (1). White pellets (EtOAc), mp 140–141°, $[\alpha]_D^{22}$ +37° ($CHCl_3$; *c* 0.11); IR (KBr) ν_{max} cm^{-1}: 1757 (γ-lactone), 1707 (C=C–C=O), 1454, 1354, 1231, 1155, 1079, 977, 894, 873 (furan), 796; ^1H NMR ($CDCl_3$, 400.13 MHz) see Table 1; ^{13}C NMR ($CDCl_3$, 100.6 MHz) see Table 1. HRCIMS *m/z* 429.2275 $[M+H]^+$ (calcd for $C_{25}H_{33}O_6$, 429.2277); CIMS (*iso*-butane), 200 eV, *m/z* (rel. int.): 429 $[M+H]^+$ (35), 329 $[M+H-C_5H_8O_2]^+$ (100).

3.3.2. 10β-Hydroxy-6-oxo-3α,4α,15,16-bis-epoxy-8βH-cleroda-13(16),14-dien-20,12-olide (2). White powder

(MeOH), mp 176–177°, $[\alpha]_D^{22}-67°$ ($CHCl_3$; *c* 0.10); IR (KBr) ν_{max} cm^{-1}: 3480 (OH), 1740 (γ-lactone), 1708 (C═O), 1508, 1377, 1342, 1186, 1156, 1023, 968, 942, 874 cm^{-1} (furan), 805; ^1H NMR ($CDCl_3$, 400.13 MHz) see Table 1; ^{13}C NMR ($CDCl_3$, 100.6 MHz) see Table 1. HRCIMS *m/z* 361.1650 $[M+H]^+$ (calcd for $C_{20}H_{25}O_6$, 361.1651); CIMS (*iso*-butane), 200 eV, *m/z* 361$[M+H]^+$ (100), 343 $[M+H–H_2O]^+$ (87), 297 (25), 221 (20), 141(15).

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Synthesis of functionalised azecine and azonine derivatives via an enolate assisted aza Claisen rearrangement

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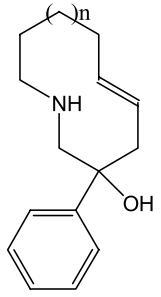
Abstract—This paper describes the synthesis of functionalised azecine and azonine derivatives incorporating the adrenaline motif. In a key step, an enolate assisted aza Claisen rearrangement was employed to interconvert from 6- and 5-membered heterocycles to their corresponding 10- and 9-membered lactams.

1. Introduction

Medium ring heterocycles have, in the past, proven difficult to synthesise via mechanisms involving ring closure making them an under-exploited resource in terms of their chemical and pharmacological application. There is a sound basis for their appeal in pharmacological research; they are of moderate size giving rise to their potential as ligands for receptors, and they offer semi-restricted conformational flexibility allowing considerable scope for selective binding with a range of functional groups. In this connection, we were interested in substituted medium-sized aza ring systems incorporating an imprint of the adrenaline motif as potentially selective signalling agents at adrenergic receptors, in particular the α_{1B} receptor. Such agents could be effective therapeutics, for example, as hypotensives.

A constitutively active Cys^{128}Phe mutant of the α_{1B}-adreno ceptor has previously been reported to act, in the absence of ligand, as a signalling specific ceptor, activating a single biochemical-signalling pathway.[1] This observation suggested that a ligand with a greater affinity for this mutant receptor over the wild-type α_{1B}-adrenoceptor might increase the equilibrium concentration of this activated conformation of the wild-type receptor.

From modelling studies based on a restricted range of phenethylamine and imidazoline ligands, the 10- and 9-membered aza-heterocycles **1** and **2**, respectively, were predicted to selectively bind to the abovementioned mutant receptor over the wild type. This paper now reports concise syntheses of these systems.



1 – n = 1
2 – n = 0

2. Synthesis

The approach to both ring systems involved a ring interconversion strategy from 6- and 5-membered ring precursors (**14** and **15**) via an enolate assisted aza Claisen rearrangement[2] to give the racemic 10- and 9- membered ring compounds (**16** and **17**). This is an adaptation of the approach first described by Suh et al. for the 10-membered ring system.[3,4]

The first step in the synthesis in the overall approach to the target molecules was the straightforward *N*-benzylation of the appropriate lactam **3** or **4** with benzyl bromide in the presence of sodium hydride (step a, Scheme 1).

Keywords: Aza Claisen; Azecine; Azonine; 9-Membered rings; 10-Membered rings; Adrenaline.
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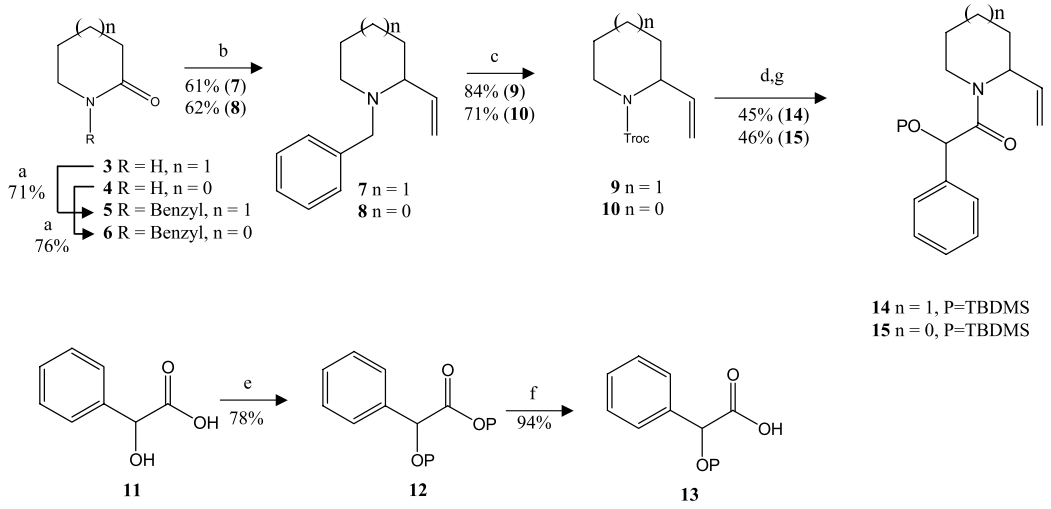
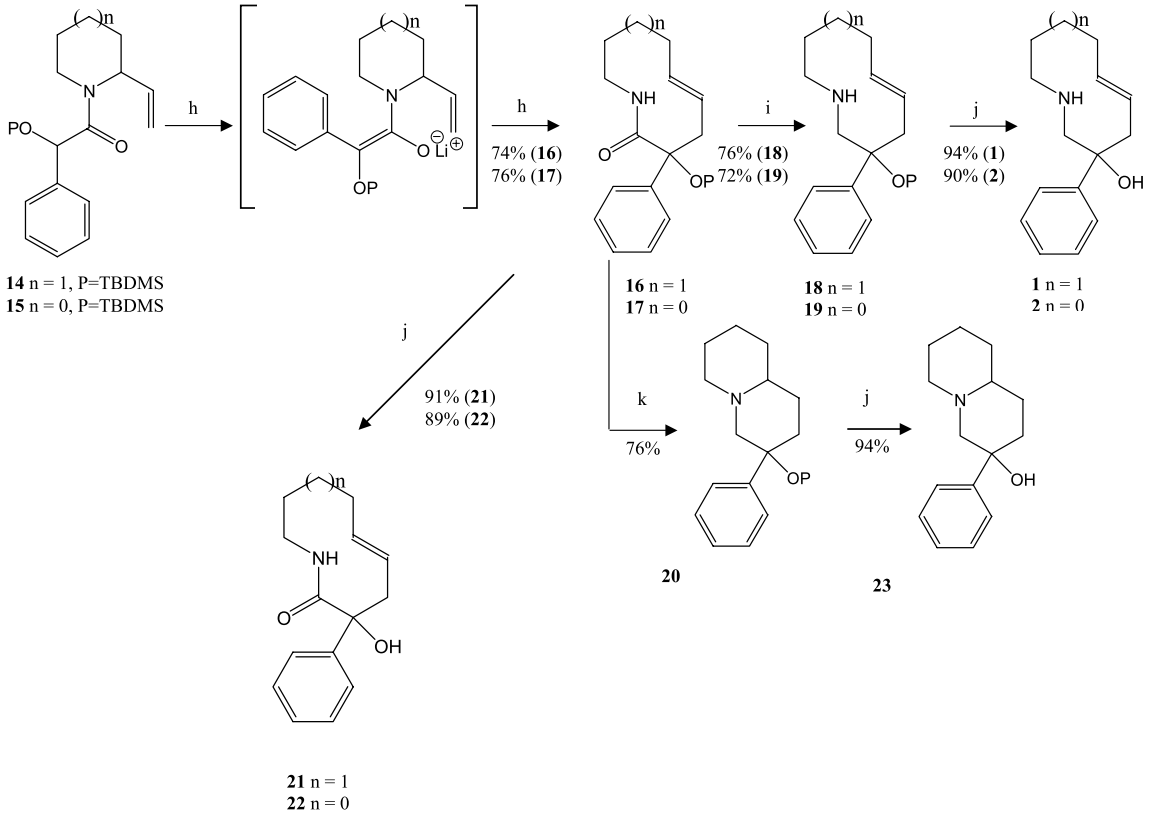


Scheme 1. Reagents: (a) i—NaH, ii—benzyl bromide, THF; (b) i—$LiAlH_4$ 1/2 equiv, ii—Vinyl MgBr, THF; (c) TrocCl, Na_2CO_3, acetonitrile, (reflux); (d) Zn/CH_3COOH; (e) TBDMSOTf, 2,6-lutidine/acetonitrile, (−78 °C); (f) Na_2CO_3, water/MeOH; (g) **13**, EDCI/DMAP/acetonitrile.

The resulting *N*-benzyl derivatives **5** and **6** were then treated with one half equivalent of $LiAlH_4$ as well as the Grignard reagent, vinyl magnesium bromide, to afford the 2-vinyl substituted compounds **7** and **8** (step b, Scheme 1). We also investigated an alternative route to **7** and **8** employing a palladium catalysed intramolecular cyclisation of allylbenzotriazole derivatives.[5] However, this route required an extra step and was not amenable to increased reaction scales.

The benzyl groups in **7** and **8** were then substituted with 2,2,2-trichloroethylformate (Troc) groups using 2,2,2-trichloroethyl chloroformate in acetonitrile in the presence of Na_2CO_3. This step eliminated the necessity of hydrogenation to remove the benzyl group, which would compromise the vinylic double bond, and also gave rise to carbamates **9** and **10**, which could be readily deprotected under relatively mild conditions ($Zn°/CH_3COOH$/room temperature). The resulting unstable secondary bases 2-vinylpiperidine[6] or 2-vinylpyrrolidine[7] were not isolated or characterised but were used directly in the subsequent step.

The next step involved the coupling of the resulting crude free bases with α-*tert*-butyldimethylsilyloxy-α-phenylethanoic acid (**13**), which was synthesised in turn from the bis



Scheme 2. Reagents: (h) i—LHMDS, ii—water, toluene; (i) Red-Al, THF; (j) TBAF, THF and (k) **16**, $LiAlH_4$, THF.

O-protection of mandelic acid (**11**, step e), to form **12**, followed by the subsequent hydrolysis of the silyl ester group to give **13**. Coupling of **13** with **9** or **10** in the presence of EDCI and 4-*N*,*N*-dimethylaminopyridine (DMAP) afforded the α-silyloxyamides **14** and **15** (step g, Scheme 1).

The base-induced (lithium hexamethyldisilazide, LHMDS) aza Claisen rearrangement (Scheme 2) of **14** and **15** then proceeded smoothly in refluxing toluene to give the medium-sized lactams **16** and **17**, respectively, in good yield. Computer-based molecular modelling using the computer program Spartan '02[8] (AM1)[9] suggested that the newly formed annular double bond would be more stable in the *E* configuration than its *Z* counterpart by 4.2 kcal mol^{-1}, and the observed coupling constants between the olefinic protons of **16** and **17** (15.5 Hz in both cases) in the ^{1}H NMR verify that the double bond formed in the rearrangement is in fact generated with an *E* configuration.

The presence of the double bond in both **16** and **17** rendered the reduction of the lactams problematic; reductants such as diborane, for example, have the capability of adding across the double bond.[10] With this in mind, $LiAlH_4$ was used in an attempt to reduce **16** to its corresponding silyl protected phenethylamine **18**. However, while the reduction of the amide carbonyl in **16** in the presence of $LiAlH_4$ was successful, intramolecular cyclisation occurred to give only **20** in good yield (76%) and none of the desired reduced product (**18**) with the double bond intact was isolated (Scheme 2).

The above problem was overcome through the use of sodium bis(2-methoxyethoxy) aluminium hydride (Red-Al®). In the absence of lithium ions, the reduction of the amide carbonyls in **16** and **17** proceeded in good yield (76 and 72%) without destroying the double bond.

While TBDMS groups may be removed with Brönsted acids, molecular models of **18** and **19** suggested that protonation of the double bond may lead to an intraannular ring closure similar to that observed in the presence of $LiAlH_4$. Furthermore, the tertiary alcohol formed in the reaction would be extremely susceptible to acid-catalysed dehydration. For this reason, tetrabutylammonium fluoride in tetrahydrofuran was used to deprotect the TBDMS groups to afford the target compounds **1** and **2**. This system has proved to have several advantages; it was high yielding, involved an easy work-up, and both the double bond and the tertiary hydroxyl group remained intact.

For comparative purposes, the amides, **21** and **22**, and the base **23**, were also prepared for pharmacological testing (Scheme 2).

3. Molecular modelling

Molecular modelling (Spartan '02[8], PM3[12]) of the lithium salt of the enolate ion generated in the aza Claisen rearrangement of **14** and **15** suggested that both molecules are able to adopt a conformation in which the bulky TBDMS groups do not sterically impede the rearrangement. The presence of the lithium ion, which is positioned almost equidistant between the two oxygen atoms, causes the enolate double bond to adopt a *Z* configuration (Fig. 1), which is approximately 10 kcal mol^{-1} more favourable than the *E* configuration of the enolate double bond in the presence of the lithium ion.

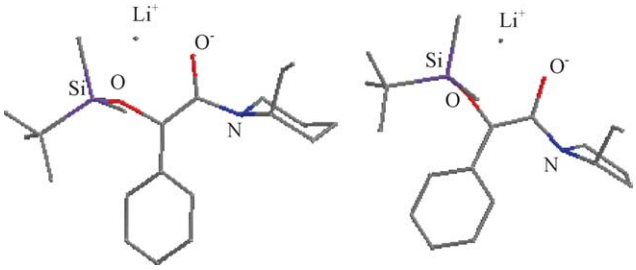


Figure 1. PM3-generated local minima of the lithium enolate salts of **14** (left) and **15**.

The transition state (Fig. 2) for the rearrangement of **14**, adopts a chair–chair conformation similar to that implied for the systems investigated by Suh et al.[4]

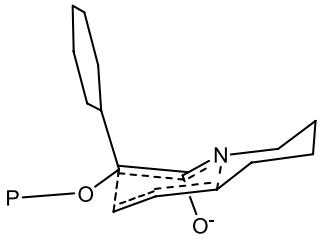


Figure 2. Transition state for the aza Claisen rearrangement of **14**.

4. Future work

We are currently investigating the extension of the current project to incorporate catechol derivatives in the aryl moiety to more closely mimic adrenaline. The pharmacological activities of these compounds and those discussed here will be reported separately.

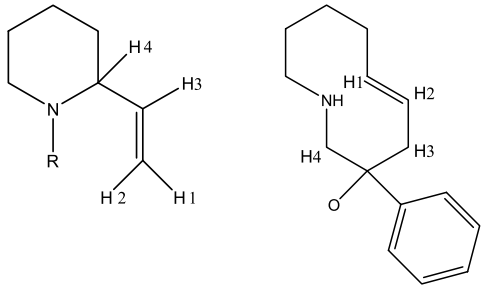
5. Experimental

5.1. General

All starting materials were used without further purification with the exception of zinc powder which was activated as described below, and EDCI which was dehydrated under high vacuum for twelve hours prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium in the presence of benzophenone. Acetonitrile and toluene were freshly distilled over calcium hydride prior to use. Reaction flasks were air dried in an oven at 70 °C and purged with argon or nitrogen where appropriate. The term petroleum spirit refers to petroleum spirit within the boiling range of 40–60 °C. Column chromatography was performed with the indicated solvents freshly distilled over molecular sieves (4 Å). Column chromatography was performed using silica gel 60 (230–400 mesh, Merck) or neutral alumina (activated Brockmann 1, standard grade ~150 mesh, 58 Å, Aldrich). Reactions were followed with thin layer chromatography (0.25 mm aluminium backed silica gel plates) using

analytical grade solvents. Chromatographic solvent mixtures are quoted as volume ratios. Organic solvents were dried over anhydrous sodium sulfate (except where indicated in the text) and the solvent was removed under reduced pressure with a Büchi rotary evaporator. All compounds were judged to be greater than 95% purity by ^{1}H NMR and TLC analysis. High-resolution electrospray mass spectra were recorded on a Q-TOF2 high-resolution electrospray mass spectrometer and the low resolution CI mass spectrum on a Shimadzu QP-5000 mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR spectrometer running at 299.5 MHz for ^{1}H spectra and 74.99 MHz for ^{13}C spectra. All spectra were run in $CDCl_3$ with 1% tetramethylsilane (TMS) and all ^{1}H NMR spectra are referenced to TMS. ^{1}H NMR spectral data are reported in the order of chemical shift, multiplicity, (s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; tt, triplet of triplets; m, multiplet), coupling constant(s) in hertz (Hz) and number of protons. ^{13}C spectra are referenced to the central deuterated solvent peak. The melting point (mp) determination was recorded on a Reichert melting point apparatus and is reported uncorrected.

For identification purposes, the numbering of protons for ^{1}H NMR chemical shift assignments is set out below.



5.2. Computational studies

Computational studies were carried out on a Silicon Graphics Fuel processor running at 600 MHz with 1523 Mb of random access memory (RAM). Minimisations involving lithium were carried out using the PM3[12] force field while others were performed using AM1[9] running on the computer program Spartan'02.[8]

5.3. Activation of zinc powder

Zinc powder (5.01 g, 78.2 mmol) was suspended in 0.1 M HCl, (20 mL) and the mixture stirred at room temperature for 1 min. The mixture was then filtered and the solid washed with distilled water, then ethanol and finally diethyl ether. The air-dried zinc powder was then stored in a vacuum desiccator over silica gel desiccant until used.

5.4. Synthetic procedures

5.4.1. *N*-Benzyl-2-piperidone (5).[11] To a stirred solution of 2-piperidone (2.5 g, 25.3 mmol) in anhydrous THF (50 mL) over an ice bath, was added a suspension of sodium hydride in paraffin oil (60%, 1.1 g, 28.7 mmol). The mixture was stirred for 30 min at 0 °C and benzyl bromide (3.2 mL, 4.53 g, 26.5 mmol) was then injected slowly over 10 min through a rubber septum. The reaction mixture was allowed to warm to room temperature and was stirred for a further 3 h. The solvent was evaporated in vacuo and the residue partitioned between dichloromethane (100 mL) and water (100 mL). The organic phase was washed several times with water, dried and evaporated. The residue was purified by column chromatography (silica gel, petroleum spirit–ethyl acetate, 1:1), to afford **5**[11] as a colourless oil (3.39 g, 17.9 mmol, 71%). ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 4H), 2.20 (t, J=8 Hz, 2H), 3.21 (t, J=8 Hz, 2H), 4.45 (s, 2H), 7.10–7.20, (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.1, 26.9, 32.6, 42.8, 49.6, 128.0, 128.6, 127.1, 136.5, 169.3.

5.4.2. *N*-Benzylpyrrolidin-2-one (6).[13] In a similar manner to that described above for the synthesis of **5**, pyrrolidin-2-one (2.5 g, 29.4 mmol), NaH (60% suspension in paraffin, 1.24 g, 32.4 mmol) and benzyl bromide (5.03 g, 29.4 mmol) yielded **6**[13] as a colourless oil (3.91 g, 22.4 mmol, 76%); ^{1}H NMR ($CDCl_3$) δ 2.03 (quintet, J=7 Hz, 2H), 2.25 (t, J=7 Hz, 2H), 3.40 (t, J=7 Hz, 2H), 4.48 (s, 2H), 7.08–7.18, (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.9, 32.9, 46.0, 49.4, 128.1, 128.6, 127.2, 136.7, 173.3.

5.4.3. *N*-Benzyl-2-vinylpiperidine (7).[5] To a stirred solution of **5** (1.50 g, 7.94 mmol) in anhydrous THF (50 mL) over an ice bath, was added $LiAlH_4$ (0.166 g, 4.36 mmol). The mixture was allowed to stir at 0 °C for 1 h and vinyl magnesium bromide (1 M solution in THF, 24 mL, 24 mmol) was injected through a rubber septum. The mixture was maintained at 0 °C for 10 h and then allowed to warm to room temperature. The reaction mixture was stirred for a further 12 h at room temperature. Methanol (20 mL) was then added slowly to quench unreacted Grignard reagent. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (100 mL) and water (50 mL). Both fractions were filtered over a celite pad and the solid washed several times with warm dichloromethane. The combined organic fractions were dried and the solvent removed under reduced pressure. The resulting brown oily residue was purified by column chromatography (silica gel, ethyl acetate–petroleum spirit, 1:50) to yield **7**[5] as a colourless oil (0.973 g, 4.84 mmol, 61%). ^{1}H NMR ($CDCl_3$) δ 1.25–1.98 (m, 7H), 2.64–2.71 (m, 1H), 2.78–2.84 (m, 1H, H4), 3.05 (d, J=13.5 Hz, 1H, benzyl), 4.08 (d, J=13.5 Hz, 1H, benzyl), 5.10 (dd, J=1.7, 10 Hz, 1H, H1), 5.19 (d, J=17 Hz, 1H, H2), 5.90 (ddd, J=1.7, 10, 17 Hz, 1H, H3), 7.20–7.31 (m, 5H, HAr); ^{13}C NMR ($CDCl_3$) δ 23.9, 26.4, 32.0, 52.1, 58.3, 67.8, 115.6, 127.3, 128.5, 128.9, 135.5, 137.6.

5.4.4. *N*-Benzyl-2-vinylpyrrolidine (8).[14] In a similar manner to that described above for the synthesis of **7**, *N*-benzyl-pyrrolidin-2-one (2.6 g, 14.9 mmol), $LiAlH_4$ (0.310 g, 0.817 mmol) and 1 M vinyl magnesium bromide in THF (45 mL, 45 mmol) yielded **8**[14] as a colourless oil (1.72 g, 9.21 mmol, 62%). ^{1}H NMR ($CDCl_3$) δ 1.62–1.72 (m, 3H), 1.82–2.02 (m, 1H), 2.11 (q, J=9 Hz, 1H), 2.78 (q, J=8 Hz, 1H), 2.91 (t, J=7 Hz, 1H, H4), 3.06 (d, J=12.5 Hz, 1H, benzyl), 4.03 (d, J=12.5 Hz, 1H, benzyl), 5.13 (dd, J=1.4, 10 Hz, 1H, H1), 5.17 (d, J=17 Hz, 1H, H2), 5.79 (ddd, J=17, 10, 1.5 Hz, 1H, H3), 7.20–7.30 (m, 5H,

HAr); ($CDCl_3$) δ 22.0, 31.5, 53.1, 58.1, 68.4, 116.5, 126.7, 128.1, 129.1, 139.8, 141.0.

5.4.5. 2,2,2-Trichloroethyl 2-vinylpiperidine-1-carboxylate (9). To a stirred solution of **7** (1.30 g, 6.47 mmol) and a suspension of anhydrous K_2CO_3 (1.30 g, 9.41 mmol) in anhydrous acetonitrile (50 mL) at room temperature, under a nitrogen atmosphere was added dropwise, 2,2,2-trichloroethyl chloroformate (1.4 g, 6.61 mmol). The mixture was heated to reflux and stirred for 2 h. The solvent was evaporated in vacuo and the residue partitioned between dichloromethane (100 mL) and water (100 mL). The organic phase was washed several times with water, dried and evaporated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate–petroleum spirit, 1:50), yielding **9** as a colourless oil (1.58 g, 5.55 mmol, 84%). ^{1}H NMR ($CDCl_3$) δ 1.41–2.13 (m, 7H), 2.95 (m, 1H), 4.02 (m, 1H, H4), 4.82 (bs, 2H, CH_2CCl_3), 5.11 (ddd, J=17.2, 2.2, 1.2 Hz, 1H, H2), 5.19 (ddd, J=10.5, 2.2, 1.2 Hz, 1H, H1), 5.78 (ddd, J=17.2, 10.5, 4.5 Hz, 1H, H3); ^{13}C NMR ($CDCl_3$) δ 23.6, 25.8, 31.4, 44.2, 53.8, 74.8, 77.2, 115.7, 139.0, 154.8; HRMS (ES +ve) calcd for $C_{10}H_{14}^{35}Cl_3NO_2$+H: 286.0163; found: 286.0169.

5.4.6. 2,2,2-Trichloroethyl 2-vinylpyrrolidine-1-carboxylate (10). In a similar manner to that described above for the synthesis of **9**, *N*-benzyl-2-vinylpyrrolidine (1.25 g, 6.68 mmol), 2,2,2-trichloroethyl chloroformate (1.52 g, 7.20 mmol) and K_2CO_3 (1.30 g, 9.41 mmol) yielded **10** as a colourless oil (1.41 g, 5.21 mmol, 71%) ^{1}H NMR ($CDCl_3$) δ 1.45–1.82 (m, 5H), 2.85 (m, 1H), 3.98 (m, 1H, H4), 4.85 (bs, 2H, CH_2CCl_3), 5.13 (ddd, J=17.5, 2.2, 1.2 Hz, 1H, H2), 5.21 (ddd, J=10.5, 2.2, 1.2 Hz, 1H, H1), 5.82 (ddd, J=17.5, 10.5, 4.5 Hz, 1H, H3); ^{13}C NMR ($CDCl_3$) δ 23.2, 33.5, 48.3, 57.9, 75.5, 77.9, 115.8, 137.8, 155.1; HRMS (ES +ve) calcd for $C_9H_{12}^{35}Cl_3NO_2$+H: 272.0006; found: 271.9998.

5.4.7. *tert*-Butyldimethylsilyl 2-*tert*-butyldimethylsilyloxy 2-phenylethanoate (12). To a stirred solution of **11**, (1.00 g, 6.67 mmol) in acetonitrile at −78 °C was added 2,6-lutidine (1.43 g, 13.3 mmol) and *tert*-butyldimethylsilyl triflate (3.52 g, 13.3 mmol). The mixture was stirred for 3 h at −78 °C. The solvent was then removed under reduced pressure and the residue partitioned between dichloromethane (50 mL) and water (50 mL). The organic fraction was dried and the solvent removed unde reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate–petroleum spirit, 1:50), yielding **12** as a colourless oil (1.98 g, 5.20 mmol, 78%). ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H, OSiCH_3), 0.08 (s, 6H, COOSiCH_3), 1.08 (s, 18H, Bu^t), 5.34 (s, 1H, C*H*OSi), 7.12–7.26, (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −6.9, −5.7, 17.2, 18.1, 25.8, 25.9, 84.3, 127.6, 128.8, 129.6, 135.0, 179.0; HRMS (ES +ve) calcd for $C_{20}H_{36}O_3Si_2$+ H: 381.2276; found: 381.2281.

5.4.8. 2-*tert*-Butyldimethylsilyloxy-2-phenylethanoic acid (13). A solution of **12** (0.50 g, 1.32 mmol) in a 1 M solution of K_2CO_3 in methanol–water (1:1, 100 mL) was stirred at reflux for 1 h. The volume was then reduced to approximately 30 mL under vacuum at 40 °C. The pH was then slowly lowered to pH 5 with aqueous HCl (0.5 M) and the mixture extracted with dichloromethane (3×30 mL). The solvent was evaporated under reduced pressure to yield a white solid, which was recrystallised from dichloromethane/diethyl ether to yield **13** as a white crystalline solid (0.330 g, 1.24 mmol, 94%); mp 98–100 °C; ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H, SiCH_3), 1.05 (s, 9H, Bu^t), 5.38 (s, 1H, C*H*OSi), 7.12–7.26, (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −5.8, 18.2, 25.8, 83.5, 127.7, 128.7, 129.5, 135.8, 178.7; HRMS (ES, −ve) calcd for $C_{14}H_{22}O_3Si$–H: 265.1265; found: 265.1269.

5.4.9. 2-(*tert*-Butyldimethylsilyloxy)-2-phenyl-1-(2-vinylpiperidin-1-yl)ethan-1-one (14). To a stirred solution of **9** (1.81 g, 6.32 mmol) in glacial acetic acid (5 mL) was added freshly activated Zn (0.5 g, 7.94 mmol). The vigorously bubbling reaction was stirred at room temperature for 3 h under argon. Water (30 mL) was added and the pH of the solution was made basic (pH 9) with aqueous sodium carbonate (1 M). The mixture was extracted with dichloromethane (50 mL) and the organic phase dried with anhydrous sodium carbonate. The dichloromethane was removed under a slight vacuum, and the residue dissolved in anhydrous acetonitrile. To this was added EDCI (1.25 g, 6.52 mmol), DMAP (0.8 g, 6.55 mmol) and **13** (1.60 g, 6.01 mmol). The reaction mixture was stirred for 24 h at room temperature under argon. The solvent was then removed in vacuo and the residue partitioned between dichloromethane (50 mL) and water (50 mL). The organic phase was dried and evaporated and the residue purified on a chromatographic column (neutral alumina, petroleum spirit–ethyl acetate 50:1) yielding **14** as a colourless oil (1.02 g, 2.84 mmol, 45%). ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H, SiCH_3), 1.03 (s, 9H, Bu^t), 1.41–2.13 (m, 7H), 3.05 (m, 1H), 3.95 (m, 1H, H4), 5.13 (ddd, J=17.2, 2.2, 1.2 Hz, 1H, H2), 5.22 (ddd, J=10.5, 2.2, 1.2 Hz, 1H, H1), 5.45, (s, 1H, C*H*OSi), 5.83 (ddd, J=17.2, 10.5, 4.5 Hz, 1H, H3), 7.19–7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −6.1, 17.6, 23.6, 25.8, 25.8, 31.4, 43.1, 52.9, 80.4, 115.9, 127.6, 129.0, 129.6, 136.7, 138.0, 172.7; HRMS (ES +ve) calcd for $C_{21}H_{33}NO_2Si$+H: 360.2353; found: 360.2349.

5.4.10. 2-(*tert*-Butyldimethylsilyloxy)-2-phenyl-1-(2-vinylpyrrolidin-1-yl)ethan-1-one (15). In a similar manner to that described above for the synthesis of **14**, **10** (1.32 g, 4.63 mmol), Zn (powder, 0.5 g, 7.94 mmol), EDCI (0.90 g, 4.71 mmol), DMAP (0.58 g, 4.75 mmol) and **13** (1.20 g, 4.51 mmol) yielded **15** as a colourless oil (0.737 g, 2.13 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H, SiCH_3), 1.01 (s, 9H, Bu^t), 1.61–2.13 (m, 5H), 3.15 (m, 1H), 4.03 (m, 1H, H4), 5.14 (ddd, J=17.2, 2.2, 1.2 Hz, 1H, H2), 5.22 (ddd, J=10.5, 2.2, 1.2 Hz, 1H, H1), 5.45, (s, 1H, C*H*OSi), 5.80 (ddd, J=17.2, 10.5, 4.5 Hz, 1H, H3), 7.19–7.31 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −5.8, 17.6, 23.3, 25.9, 33.3, 47.1, 55.8, 81.5, 115.8, 127.6, 129.3, 129.8, 136.5, 137.7, 172.3; HRMS (ES +ve) for $C_{20}H_{31}NO_2Si$+ H: 346.2197; found: 346.2191.

5.4.11. (*E*)-3-(*tert*-Butyldimethylsilyloxy)-3,4,7,8,9,10-hexahydro-3-phenylazecin-2(1*H*)-one (16). To a stirred solution of **14** (0.301 g, 0.833 mmol) in refluxing anhydrous toluene under argon, was added a 1 M solution of lithium hexamethyldisilazide (LHMDS) in toluene, (1.4 mL, 1.4 mmol) through a rubber septum. The reaction was stirred at reflux for 3 h. Water (1 mL) was then added and the solvent removed under reduced pressure. The residue

was purified using column chromatography (neutral alumina, dichloromethane–ethylacetate–petroleum spirit, 0.5:1:1) yielding **16** as a thick pale yellow oil (0.223 g, 0.617 mmol, 74%) ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H, SiC*H*$_3$), 0.99 (s, 9H, Bu^t), 1.33 (tt, J=10, 3.5 Hz, 1H), 1.41–2.18 (m, 8H), 2.52 (dd, J=10, 3.5 Hz, 1H, H3), 2.77, (dd, J=10, 3.5 Hz, 1H, H3′), 5.18 (ddd, J=15.5, 10.5, 4 Hz, 1H, H1), 5.35 (ddd, J=15.5, 10.5, 4 Hz, 1H, H2), 7.20–7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −5.8, 18.4, 25.8, 27.4, 28.1, 36.3, 43.1, 43.8, 84.5, 127.8, 129.0, 129.3, 130.1, 134.0, 139.0, 175.3; HRMS (ES +ve) calcd for $C_{21}H_{33}NO_2Si$+H: 360.2353; found: 360.2349.

5.4.12. (*E*)-3-(*tert*-Butyldimethylsilyloxy)-1,3,6,7,8,9-hexahydro-3-phenyl-2*H*-azonin-2-one (17). In a similar manner to that described above for the synthesis of **16**, **15** (0.281 g, 0.812 mmol) and (LHMDS), (1.4 mL, 1.4 mmol) yielded **17** as a thick colourless oil, (0.213 g, 6.17 mmol, 76%) ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H, SiC*H*$_3$), 0.99 (s, 9H, Bu^t), 1.41–2.18 (m, 6H), 2.52 (dd, J=10, 3.5 Hz, 1H, H3), 2.77 (dd, J=10, 3.5 Hz, 1H, H3′), 5.18 (ddd, J=15.5, 10.5, 4 Hz, 1H, H1), 5.35 (ddd, J=15.5, 10.5, 4 Hz, 1H, H2), 7.20–7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −5.7, 17.7, 27.6, 28.2, 36.5, 43.1, 43.5, 84.8, 128.0, 129.1, 129.7, 130.3, 134.2, 139.2, 175.2; HRMS (ES +ve) calcd for $C_{20}H_{31}NO_2Si$ + H: 346.2197; found: 346.2198.

5.4.13. (*E*)-3-(*tert*-Butyldimethylsilyloxy)-1,2,3,4,7,8,9,10-octahydro-3-phenylazecine (18). To a stirred solution of **16** (0.120 g, 0.333 mmol) in anhydrous THF (15 mL) at 0 °C, was added drop wise a 70% solution of sodium bis(2-methoxyethoxy) aluminium hydride in toluene (Red-Al®) (0.124 g, 0.733 mmol) through a rubber septum. The reaction mixture was heated to reflux and stirred for 3 h under an atmosphere of nitrogen gas. The reaction was quenched with iced water (10 mL) followed by cold aqueous 1 M NaOH (30 mL) the mixture was then filtered over a bed of celite and the solid residue washed several times with hot chloroform. The two-phased supernatant was partitioned in a separating funnel and the organic phase was collected, dried and the solvent removed in vacuo. The resulting dark yellow residue was purified by column chromatography (neutral alumina, methanol–dichloromethane–concd NH_4OH, 1:10:0.01) yielding **18** as a colourless oil (0.0874 g, 0.253 mmol, 76%); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 1.02 (s, 9H), 1.32 (tt, J=10, 3.5 Hz, 1H), 1.38–2.03 (m, 8H), 2.54 (dd, J=10, 3.5 Hz, 1H), 2.68 (d, J=12 Hz, 1H) 2.81, (dd, J=10, 3.5 Hz, 1H) 3.11 (d, J=12 Hz, 1H), 5.13 (ddd, J=17, 10.5, 4 Hz, 1H), 5.28 (ddd, J=17, 10.5, 4 Hz, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.1, 18.8, 25.8, 27.2, 28.5, 36.3, 43.9, 45.2, 64.0, 74.5, 126.0, 126.2, 128.5, 130.3, 133.1, 150.0; HRMS (ES) for $C_{21}H_{35}NOSi$+H: 346.2561; found: 346.2568.

5.4.14. (*E*)-3-(*tert*-Butyldimethylsilyloxy)-2,3,6,7,8,9-hexahydro-3-phenyl-1*H*-azonine (19). In a similar manner to that described above for the synthesis of **18**, **16** (0.11 g, 0.318 mmol) and Red-Al (70% solution in toluene, (0.120 g, 0.709 mmol) yielded **19** as a colourless oil (0.076 g, 0.23 mmol, 72%); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 1.02 (s, 9H), 1.32–2.03 (m, 6H), 2.54 (dd, J=10, 3.5 Hz, 1H), 2.68 (d, J=12 Hz, 1H) 2.81, (dd, J=10, 3.5 Hz, 1H) 3.11 (d, J=12 Hz, 1H), 5.13 (ddd, J=17, 10.5, 4 Hz, 1H), 5.28 (ddd, J=17, 10.5, 4 Hz, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.1, 18.7, 25.8, 32.6, 34.3, 44.9, 45.1, 63.9, 74.3, 125.8, 126.2, 128.0, 128.2, 129.1, 149.9; HRMS (ES) for $C_{20}H_{33}NOSi$+H: 332.2404; found: 332.2391.

5.4.15. (*E*)-1,2,3,4,7,8,9,10-Octahydro-3-phenylazecin-3-ol (1). To a stirred solution of **18** (0.080 g, 0.22 mmol) in anhydrous THF (5 mL) was added a 1 M solution of tetrabutyl ammonium fluoride (TBAF) (0.3 mL, 0.3 mmol). The reaction was heated to reflux and stirred under nitrogen for 3 h. The solvent was then removed under reduced pressure and the residue placed under high vacuum for several hours at 40 °C. The residue was then partitioned between dichloromethane (10 mL) and water (30 mL). The organic phase was washed several times with water (30 mL) until the ^{1}H NMR spectrum of a representative sample of the dried organic phase indicated the absence of any tetrabutyl ammonium salts. The organic phase was collected and dried and the solvent removed under reduced pressure yielding pure **1** as a colourless waxy glass (0.0493 g, 0.213 mmol, 94%). ^{1}H NMR ($CDCl_3$) δ 1.31 (tt, J=10, 3.5 Hz, 1H), 1.38–2.13 (m, 8H), 2.51 (dd, J=10, 3.5 Hz, 1H), 2.65 (d, J=12 Hz, 1H) 2.78, (dd, J=10, 3.5 Hz, 1H) 3.13 (d, J=12 Hz, 1H), 5.10 (ddd, J=17, 10.5, 4 Hz, 1H), 5.28 (ddd, J=17, 10.5, 4 Hz, 1H), 5.40 (bs, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.7, 28.4, 36.4, 43.8, 44.2, 63.0, 80.2, 126.1, 126.3, 128.2, 130.4, 133.1, 149.9; HRMS (ES +ve) calcd for $C_{15}H_{21}NO$+ H: 232.1696; found: 232.1688.

5.4.16. (*E*)-2,3,6,7,8,9-Hexahydro-3-phenyl-1*H*-azonin-3-ol (2). In a similar manner to that described above for the synthesis of **1**, **19** (0.061 g, 0.184 mmol) and TBAF (1 M THF solution, 0.3 mL, 0.3 mmol) yielded **2** as a colourless waxy glass; (0.0360 g, 0.165 mmol, 90%). ^{1}H NMR ($CDCl_3$) δ 1.42–2.23 (m, 7H), 2.53 (dd, J=10, 3.5 Hz, 1H), 2.65 (d, J=12 Hz, 1H) 2.82, (dd, J=10, 3.5 Hz, 1H) 3.18 (d, J=12 Hz, 1H), 5.10 (ddd, J=17, 10.5, 4 Hz, 1H), 5.28 (ddd, J=17, 10.5, 4 Hz, 1H), 5.67 (bs, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 32.2, 34.4, 44.1, 44.9, 63.3, 78.0, 126.0, 126.2, 128.4, 128.8, 129.9, 149.9. HRMS (ES) for $C_{14}H_{19}NO$+H: 218.1539; found: 218.1531.

5.4.17. (*E*)-3,4,7,8,9,10-Hexahydro-3-hydroxy-3-phenylazecin-2(1*H*)-one (21). In a similar manner to that described above for the synthesis of **1**, **16** (0.082 g, 0.228 mmol) and TBAF (1 M THF solution, 0.3 mL, 0.3 mmol) yielded **21** as a cream coloured waxy glass (0.051 g, 0.207 mmol, 91%). ^{1}H NMR ($CDCl_3$) δ 1.33 (tt, J=10, 3.5 Hz, 1H), 1.38–2.13 (m, 7H), 2.53 (dd, J=10, 3.5 Hz, 1H), 2.81, (dd, J=10, 3.5 Hz, 1H), 5.10 (ddd, J=15, 10, 4 Hz, 1H), 5.28 (ddd, J=15, 10, 4 Hz, 1H), 5.62 (bs, 1H), 7.10–7.25 (m, 5H), 7.50 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 27.3, 28.0, 36.3, 42.4, 43.9, 88.2, 127.7, 129.3, 129.7, 130.1, 133.8, 139.0, 175.7; HRMS (ES +ve) calcd for $C_{15}H_{19}NO_2$+H: 246.1489; found: 246.1481.

5.4.18. (*E*)-1,3,6,7,8,9-Hexahydro-3-hydroxy-3-phenyl-2*H*-azonin-2-one (22). In a similar manner to that described above for the synthesis of **1**, **17** (0.075 g, 0.217 mmol) and tetrabutyl ammonium fluoride (1 M THF solution, 0.3 mL, 0.3 mmol) yielded **22** as a cream coloured waxy glass

(0.045 g, 0.194 mmol, 89%). ^{1}H NMR ($CDCl_3$) δ 1.55–2.23 (m, 6H), 2.53 (dd, $J=10$, 3.5 Hz, 1H), 2.81, (dd, $J=10$, 3.5 Hz, 1H), 5.15 (ddd, $J=15$, 10, 3.5 Hz, 1H), 5.38 (ddd, $J=15$, 10, 3.5 Hz, 1H), 5.62 (bs, 1H), 7.10–7.25 (m, 5H) 7.43 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 31.76, 34.21, 42.38, 46.34, 87.91, 127.32, 127.72, 128.65, 129.31, 129.78, 139.13, 175.38; HRMS (ES) for $C_{14}H_{17}NO_2+H$: 232.1332; found: 232.1340.

5.4.19. 1,3,4,6,7,8,9,9a-Octahydro-3-(*tert*-butyldimethylsilyloxy)-3-phenyl-2*H*-quinolizine (20). To a stirred solution of **16** (0.120 g, 0.333 mmol) in anhydrous THF (15 mL) at 0 °C, was added lithium aluminium hydride (0.032 g, 0.830 mmol). The reaction mixture was heated to reflux and stirred for 3 h under an atmosphere of nitrogen gas. The reaction was quenched with iced water (10 mL) followed by cold aqueous 1 M NaOH (30 mL) the mixture was then filtered over a bed of celite and the solid residue washed several times with hot chloroform. The two-phased supernatant was partitioned in a separating funnel and the organic phase was collected, dried and evaporated. The resulting dark yellow residue was purified by column chromatography (neutral alumina, methanol–dichloromethane–concd NH_4OH, 1:10:0.01) yielding **20** as a colourless oil (0.0874 g, 0.253 mg, 76%); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 1.06 (s, 9H), 1.25–2.45 (m, 13H), 2.56 (d, $J=12$ Hz, 1H), 2.83, (d, $J=12$ Hz, 1H), 7.17–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0, 22.5, 23.8, 25.8, 26.3, 31.5, 37.5, 52.6, 63.1, 64.0, 68.1, 126.1, 128.3, 128.6, 140.6; MS (CI +ve) *m/z* 346 (M+H).

5.4.20. 1,2,3,6,7,8,9,9a-Octahydro-3-phenyl-2*H*-quinolizin-3-ol (23). In a similar manner to that described above for the synthesis of **1**, **20** (0.058 g, 0.161 mmol) and tetrabutyl ammonium fluoride (1 M THF solution, 0.2 mL, 0.2 mmol) yielded **23** as a cream coloured waxy glass (0.035 g, 0.151 mmol, 94%). ^{1}H NMR ($CDCl_3$) δ 1.25–2.45 (m, 13H), 2.53 (d, $J=12$ Hz, 1H), 2.81, (d, $J=12$ Hz, 1H), 4.62 (bs, 1H), 7.17–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.7, 23.6, 26.2, 31.5, 37.5, 52.7, 63.1, 63.6, 71.8, 126.1, 128.3, 128.6, 140.6; HRMS (ES +ve) calcd for $C_{15}H_{21}NO+H$: 232.1696; found: 232.1692.

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Three dimeric anthracene derivatives from the fruits of *Bulbine abyssinica*

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Dedicated to Professor Wolfgang Steglich on the occasion of his 70th birthday

Abstract—From the fruits of *Bulbine abyssinica* three new dimeric anthracene derivatives, (*P*)-8,9,1′,8′-tetrahydroxy-3,3′-dimethyl[10,7′-bianthracene]-1,4,9′,10′-tetraone (trivial name abyquinone A), (10*R*)-1,4,8,1′,8′-pentahydroxy-3,3′-dimethyl-[10,7′-bianthracene]-9,9′,10′(10*H*)-trione (trivial name abyquinone B), and (10*R*)-3′,4′-dihydro-1,4,8,3′,8′,9′-hexahydroxy-3,3′-dimethyl-[10,7′-bianthracene]-9,1′(10*H*,2′*H*)-dione (trivial name abyquinone C) were isolated. Despite their structural differences, these three compounds are connected to each other by the apparently biomimetic conversion of abyquinone C (a preanthraquinonylanthrone with two stereogenic centers) into B (an anthraquinonylanthrone with one stereogenic center) and finally into A (an axially chiral bianthraquinone) under mild conditions, involving a highly efficient center-to-axis chirality transfer. In addition, the known anthraquinones islandicin and chrysophanol were identified. The structures were determined on the basis of spectroscopical evidences, chemical transformations, and quantum chemical CD calculations.

1. Introduction

The genus *Bulbine* (Asphodelaceae) comprises about 40 species,[1] of which *B. abyssinica* and *B. frutescens* are the only ones found in Kenya. While the former is an indigenous species,[2] the latter is widely cultivated for aesthetic purposes.[3] In traditional medicine, *Bulbine* species are used for the treatment of various ailments including infections.[4] In South Africa, *B. asphodeloides* is taken as a styptic, for scrofula, dehydration, and for palpitation,[5] while *B. latifolia* is used to treat rheumatism, diarrhea, and dysentery.[6]

The presence of anthraquinones, including phenylanthraquinones, and isofuranonaphthoquinones in *Bulbine* species has been reported,[3,6–10] and from the roots of *B. abyssinica*, also some anthraquinones have been isolated.[7,9] In this paper, we describe the isolation and characterization of three dimeric anthracene derivatives (**1**, **2**, and **3**), along with two known anthraquinones from the fruits of *B. abyssinica*.

2. Results and discussion

Compound **1** was isolated as a dark-red amorphous powder. The UV (λ_{max} 232, 256, 303, 438, 471, 500, 542 and 582 nm) suggested an anthraquinone chromophore. The presence of four chelated hydroxy protons (δ 17.04, 12.30, 11.95 and 10.51 in the ^{1}H NMR spectrum, see Table 1), four carbonyl resonances (δ 193.4, 186.8, 184.3 and 182.2 in the ^{13}C NMR spectrum), two methyl groups (at δ 2.03 and 2.50 in ^{1}H NMR, 17.3 and 22.5 in ^{13}C NMR), and the molecular ion peak in the EIMS (*m*/*z* 506) showed this compound to be a dimeric anthraquinone derivative.[11,12]

From the NMR (Table 1) spectra, one half of the molecule was established to be a 9,10-anthraquinone derivative, viz a chrysophanol moiety, exhibiting two broad ^{1}H NMR singlets at δ 7.14 and 7.72, assigned to H-2′ and H-4′, respectively, and with a methyl group (δ 2.50) located at

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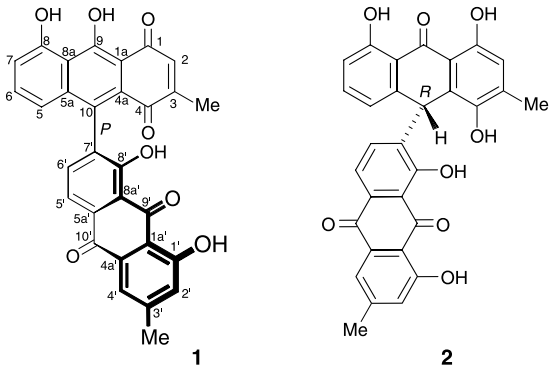
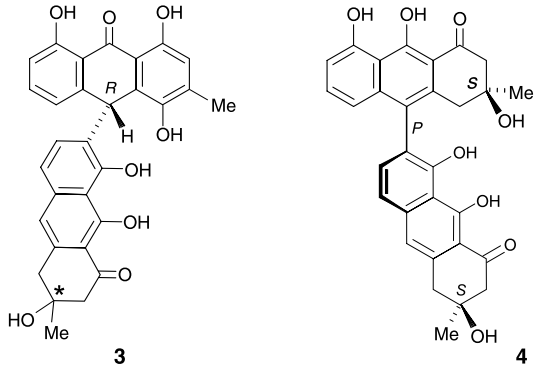




C-3′. Two *ortho*-coupled ($J=8.0$ Hz) protons at δ 7.95 and 7.43 were attributed to H-5′ and H-6′, respectively, with C-7′ of the chrysophanol moiety being substituted.

For the other half of the molecule, the ^{1}H NMR signals at δ 17.04 and 10.51 (for two chelated hydroxy protons) and the ^{13}C NMR signals at δ 182.2 and 186.8 for two carbonyl groups) suggested the presence of a 1,4-anthraquinone skeleton.[11,12] The long-wavelength UV absorption maxima (λ_{max} 500, 542 and 582 nm) in compound **1** were in agreement with the presence of such a moiety.[11,12] In the 1,4-anthraquinone part an AMX spin system at δ 6.93 (dd, $J=1.5$, 8.0 Hz), 7.51 (t, $J=8.0$ Hz), and 7.10 (dd, $J=1.5$, 8.0 Hz) was assigned to H-5, H-6 and H-7, respectively. A one-proton quartet ($J=1.2$ Hz) was assigned to H-2, which showed a long-range coupling with Me-3 (δ 2.03, d, $J=$ 1.2 Hz). This assignment was confirmed by a NOESY correlation between H-2 and Me-3. This left C-10 of the 8,9-dihydroxy-3-methyl-1,4-anthraquinone moiety to be the point of attachment to the chrysophanol moiety, thus suggesting a 10,7′-linkage in compound **1**. This connection was confirmed by an HMBC correlation of H-6′ with C-10 and a NOESY interaction between H-5 and H-6′. From these data the new natural product was characterized as 8,9,1′,8′-tetrahydroxy-3,3′-dimethyl[10,7′-bianthracene]-1,4,9′,10′-tetraone, for which the trivial name abyquinone A (**1**) was suggested. The compound was optically active indicating the presence of a non-racemic axially chiral biaryl. In the CD spectrum of **1**, a positive Cotton effect at 276 nm and a negative one at 301 nm, that is, nearly opposite to those reported for the *P*-configured dimeric preanthraquinone peroxisomicine A_1 (**4**),[13] indicated abyquinone A (**1**) to have the opposite stereoarray at the chiral axis, so that, due to the formalism of the CIP denotation, a *P*-configured axis was expected for **1**, too.

In order to determine the absolute configuration at the chiral axis in a reliable, non-empirical way, quantum chemical CD calculations were performed.[14,15] Arbitrarily starting with the *P*-atropo-enantiomer of abyquinone A (**1**), the molecule was submitted to a conformational analysis using the semiempirical AM1[16] method, resulting in eight optimized minimum geometries within the energetically relevant range of 3 kcal/mol above the global minimum. For each single geometry thus obtained, a CD spectrum was calculated using the semiempirical CNDO/S[17] as well as the OM2[18] Hamiltonian. In both cases the individual spectra were then added and weighted following the Boltzmann statistics, that is, according to the respective heats of formation. The two overall CD spectra thus obtained, were subsequently UV corrected[19] and compared with the experimental CD curve of **1**. Both when following the CNDO/S approach (Fig. 1(a)) and the OM2 method (Fig. 1(b)), a good agreement between the measured spectrum and those predicted for (*P*)-**1** was obtained (Fig. 1, left), whereas the CD curves computed for (*M*)-**1** were virtually opposite as compared to the experimental one (Fig. 1, right). Consequently, the chiral axis of **1** was clearly assigned to be *P*-configured.

The second compound (**2**) was isolated as an amorphous yellow powder. The EIMS ($[M]^+$ at *m/z* 508, $C_{30}H_{20}O_8$), as well as ^{1}H and ^{13}C NMR (Table 1) spectra suggested a bianthracene skeleton. Comparison of the ^{1}H and ^{13}C NMR spectra of **2** with those of **1** (Table 1) showed that one half of the molecule was again a chrysophanol moiety coupled to the second half of the molecule via C-7′.

For that other moiety, the ^{1}H NMR (Table 1) displayed signals for two chelated hydroxy groups (δ 11.95 and 12.35 for OH-1 and OH-8), aromatic protons with an AMX spin system (δ 6.95, dd, $J=1.5$, 8.0 Hz for H-5; 7.41, t, $J=$ 8.0 Hz for H-6; 6.88, dd, $J=1.5$, 8.0 Hz for H-7), an up-field shifted aromatic methyl group (δ 2.26 for CH_3-3), a broad singlet for an aromatic proton (δ 6.79 for H-2), and a methine proton (6.20, s, for H-10) suggesting that this moiety was 1,4,8-trihydroxy-3-methylanthrone, which was connected to the other half of the compound via C-10. The ^{13}C NMR was in agreement with the presence of a carbonyl function (δ 193.1), three hydroxy groups (δ 157.6, 144.5, and 162.9 for C-1, -4, and -8, respectively), and a methine unit (δ 35.8 for C-10) in this half of the molecule. The 10,7′-linkage in this compound was confirmed by HMBC correlations of H-10 with C-6′, -7′, and -8′, and by NOESY interactions of H-10 with H-6′ and OH-8′, thus suggesting **2** to be 1,4,8,1′,8′-pentahydroxy-3,3′-dimethyl-[10,7′-bianthracene]-9,9′,10′(10*H*)-trione, which was henceforth given the trivial name abyquinone B.

The configurational assignment of abyquinone B (**2**) was again achieved by means of the AM1-Boltzmann approach as described above for compound **1**. In this case, the conformational analysis resulted in two conformers within the range of 3 kcal/mol above the global minimum, and the overall CD spectra received with the OM2[18] approach on the SCI (Fig. 2(a)) and the SDCI (Fig. 2(b)) levels led to the unambiguous attribution of the chiral center of **2** to be *R*-configured (Fig. 2, right).

Table 1. ^{1}H and ^{13}C NMR data δ together with HMBC (^{2}J and ^{3}J) correlations of **1**, **2**, and **3**

	1			**2**			**3**		
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C	HMBC	^{1}H	^{13}C	HMBC
1		182.2			157.6			157.5	
1a		108.3			113.2			113.0	
2	6.97 q	134.8	4, 9a	6.79 br s	118.5	1a, 4, 3-Me	6.72 br s	118.2	3, 3-Me
3		152.5			137.4			138.1	
4		186.8			144.5			145.2	
4a		134.0			127.0			127.1	
5	6.93 dd	120.6	6, 8a, 10	6.95 dd	120.0	8a	6.87 dd	120.5	7, 10
5a		138.1			144.4			145.9	
6	7.51 t	134.4	5a, 8	7.41 t	137.1	5a, 8	7.38 t	137.0	5a, 8
7	7.10 dd	116.7	5, 8, 8a	6.88 dd	116.5	5	6.84 dd	116.1	5, 8
8		160.1			162.9			162.9	
8a		116.2			115.5			115.7	
9		170.1			193.1			194.0	
10		132.3		6.20 s	35.8	1a, 4, 4a, 5, 5a, 8a, 6′, 7′, 8′	6.13 s	35.0	1a, 4, 4a, 5, 5a, 8a, 6′, 7′, 8′
1′		163.2			163.0			204.4	
1a′		114.3			113.8			110.7	
2′	7.14 br s	124.7	1a′, 4′	7.12 br s	124.6	4′	2.86 br s	51.6	1a′, 1′
3′		150.2			150.8			71.4	
4′	7.72 br s	121.7	1a′, 2′, 10′	7.60 br s	121.8	1a′, 2′, 4a	3.06 br s	43.5	1a′, 10′
4a′		134.9			133.5			136.5	
5′	7.95 d	120.3	7′, 8a′, 10′	7.59 d	120.5	7′	6.98 d	120.5	7′, 10′
5a′		133.5			132.5			138.7	
6′	7.43 d	137.3	5a′, 8′, 10	7.18 d	136.8	10a′	6.84 d	132.0	5a′, 8′
7′		136.3			138.4			123.6	
8′		160.9			158.4			152.1	
8a′		115.8			116.8			112.9	
9′		193.4			194.2			164.8	
10′		184.3			181.5		6.93 s	118.1	1a′, 4′, 5′, 5a′, 8a′
Me-3	2.03 d	17.3	2, 3, 4	2.26 s	17.5	2, 3, 4	2.18 s	17.5	2
Me-3′	2.50 s	22.5	2′, 3′, 4′	2.55 s	22.4	2′, 3′, 4′	1.4 s	29.4	
OH-1				11.95 s		1, 1a	11.96 s		1, 1a, 2
OH-8	10.51 s			12.35 s		8, 8a	12.36 s		7, 8
OH-9	17.04 s		1a						
OH-1′	11.95 s		1′, 2′	11.87 s		1′, 1a′, 2′			
OH-8′	12.30 s		7′, 8′, 8a′	13.16 s			10.74 s		
OH-9′							16.12 s		

$J_{5,6}=J_{6,7}=J_{5',6'}=8.0$ Hz; $J_{5,7}=1.5$ Hz; in **1** $J_{2,Me\text{-}3}=1.2$ Hz.

Compound **3** was isolated as a yellowish brown amorphous powder. The NMR spectra (Table 1) of this compound, as for **2**, once again suggested the presence of a bianthracene derivative in which one half is a 1,4,8-trihydroxy-3-methylanthrone moiety coupled via C-10. The comparison of the NMR spectra of **3** with those of prechrysophanol (**5**)[20] indicated the substituent at C-10 to be such an anthracenone moiety. The only difference observed was that the AMX system in **5** was now replaced by two *ortho*-coupled doublets at δ 6.98 and 6.84 ($J=8.0$ Hz), which suggested either C-5′ or C-7′ in the preanthraquinone moiety of **3** to be substituted. The latter—and thus a 10,7′-linkage in compound **3**—was confirmed by an HMBC correlation of H-10 with C-6′, -7′, and -8′, and also by NOESY correlations of H-10 with H-6′ and OH-8′. EIMS showed a weak molecular ion peak at *m/z* 512, with a fragment ion at *m/z* 494 as a result of the loss of one molecule of water, which was in agreement with **3** being a bianthracene derivative containing a prechrysophanol moiety. The fragment ions at *m/z* 254 and 240 corresponded to the monomeric portions of **3**, that is, resulting from a cleavage of the 10,7′-linkage, with subsequent loss of water. By these investigations, the constitution of **3** was identified as 3′,4′-dihydro-1,4,8,3′,8′,9′-hexahydroxy-3,3′-dimethyl-[10,7′-bianthracene]-9,1′(10*H*,2′*H*)-dione, for which the trivial name abyquinone C was suggested.

The CD spectrum of abyquinone C (**3**) exhibited Cotton effects very similar to those obtained for abyquinone B (**2**) at 230, 270, and 300 nm. Hence the absolute configuration at C-10, as the chiral center dominating the CD behavior of **3**, should also be *R*, whereas a reliable conclusion about the absolute stereostructure at C-3′, which has a much lower influence on the molecular CD, was not possible at that stage.

For the determination of the absolute configurations of **3** at its two stereogenic centers, C-10 and C-3′, again quantum chemical CD calculations were performed. Since not even the relative configuration of these two chiral centers was known, two independent conformational analyses, for the (10*S*,3′*R*)- and the (10*S*,3′*S*)-diastereomer of **3**, were launched, resulting in both cases in 28 minimum structures within the range of 3 kcal/mol above the global minimum. While both overall simulated CD spectra for (10*S*,3′*R*)-**3** and (10*S*,3′*S*)-**3** behaved virtually oppositely compared with

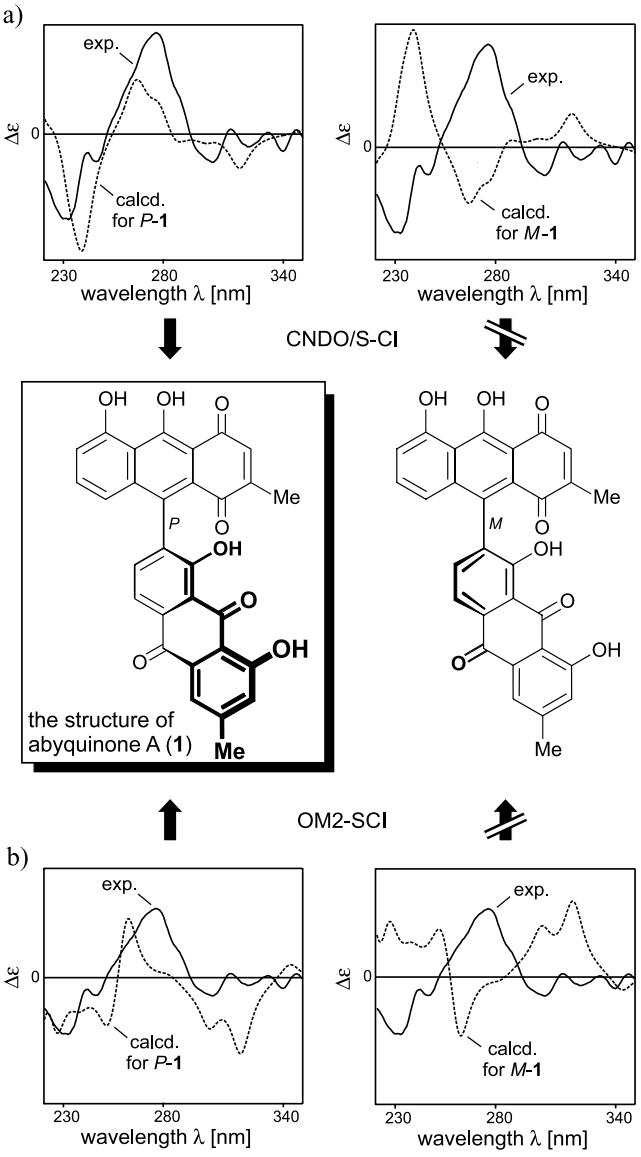
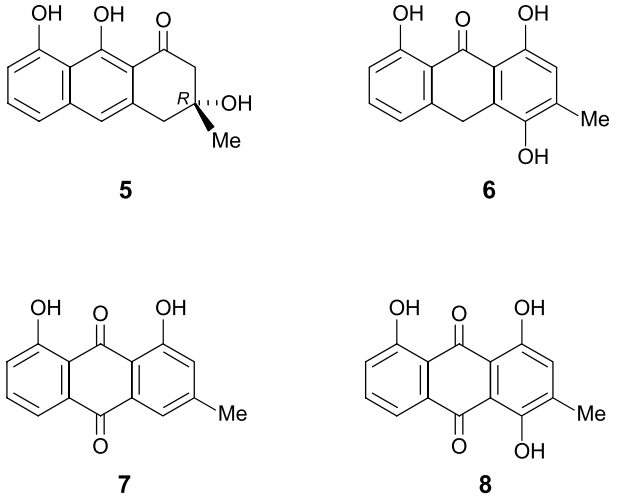


Figure 1. Attribution of the absolute configuration of abyquinone A (**1**) by comparison of the experimental CD spectrum with the spectra calculated for (*P*)-**1** and (*M*)-**1**; (a) using the CNDO/S and (b) the OM2 Hamiltonian.

the experimental curve (Fig. 3, left), a good agreement for the measured CD spectrum with both spectra computed for (10*R*,3′*S*)-**3** and (10*R*,3′*R*)-**3** was obtained (Fig. 3, right), thus, at least, assigning the stereocenter at C-10 to be *R*-configured. This result was in accordance with the above determined *R*-configuration of **2** and the easy transformation of **3** into **2** by dehydration and oxidation (see below).

A closer look at the two calculated CD spectra matching the measured one (Fig. 3, right) suggests that the absolute configuration at C-3′ of abyquinone C (**3**) should be *S*, due to the slightly better agreement of the computed curve for (10*R*,3′*S*)-**3** in the short wavelength area with the experimental one. This, however, can only be regarded as a tendency and remains to be confirmed by chemical or biochemical methods, like by total synthesis,[21] by biosynthetic investigations,[22] or by degradation,[13] which is presently in progress.[23]

Compound **3** appears to originate from the oxidative coupling of the precursors prechrysophanol[24] (**5**) and islandicin anthrone (**6**). In accordance with this assumption, chrysophanol (**7**) and islandicin (**8**) themselves were also isolated and identified along with the new compounds **1**–**3** from the fruits of *B. abyssinica*.



Upon aerial oxidation under basic conditions, compound **3** was converted into **2** and subsequently into **1**. This suggested that compound **3** is the biosynthetic precursor to **1** in the plant, too, whereas **2** is an intermediate. All of the three compounds, **1**, **2**, and **3** were also detected (by TLC) in the crude ethyl acetate extract, clearly indicating that these substances are genuine natural products and not artefacts.

Besides the smooth course of these presumably biomimetic reactions, the stereochemical implications are of particular interest. While the dehydration of **3** to give **2** simply implies the loss of one stereogenic center, with the remaining one being expectedly the same in **3** and **2**, as confirmed by the quantum chemical CD calculations, the formation of **1** from **2** involves the loss of the only stereogenic center and the new formation of a rotationally hindered biaryl axis. This reaction occurs with a remarkable center-to-axis chirality transfer. The direction of the asymmetric induction—(*R*)-**2**→(*P*)-**1**—can be explained in terms of the global minimum structure of **2** shown in Fig. 4 (left), in which the 'Southern' molecular portion is firmly locked in an array with the 'trioxy front' directed above the plane, fixed by a strong hydrogen bond of the proton of OH-4 with the oxygen of OH-8′. This pre-orientation is apparently fully retained during the oxidative conversion of **2** to abyquinone A (**1**), thus leading to a *P*-configuration at the originating chiral axis (Fig. 4, right).

The conversion is likely to be highly efficient in terms of chirality transfer, since the precursors **3** and **2**, as well as the final product **1**, were obtained in enantiomerically pure forms as evidenced by their chromatographic analysis on a chiral phase and by examination of their CD spectra. This chirality transfer, so far undescribed in natural products chemistry, merits further attention for synthetic purposes.[25]

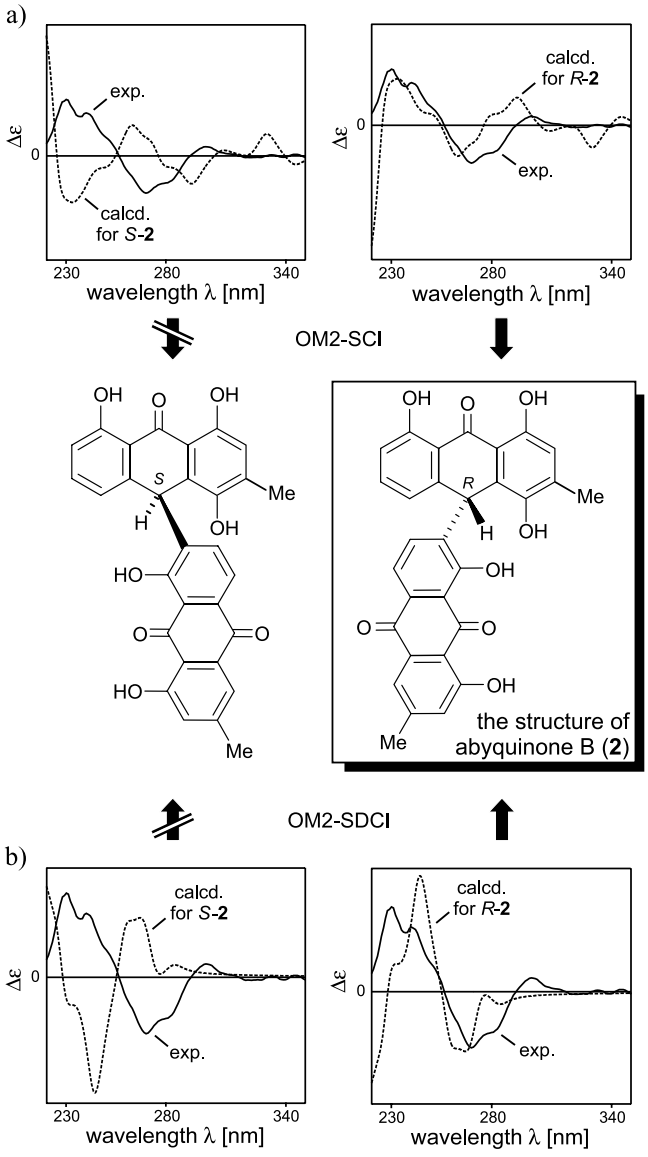


Figure 2. Assignment of the absolute configuration of abyquinone B (**2**) by comparison of the experimental CD spectrum with the spectra calculated for (*S*)-**2** and (*R*)-**2** using the OM2 Hamiltonian (a) with an SCI and (b) using an SDCI calculation.

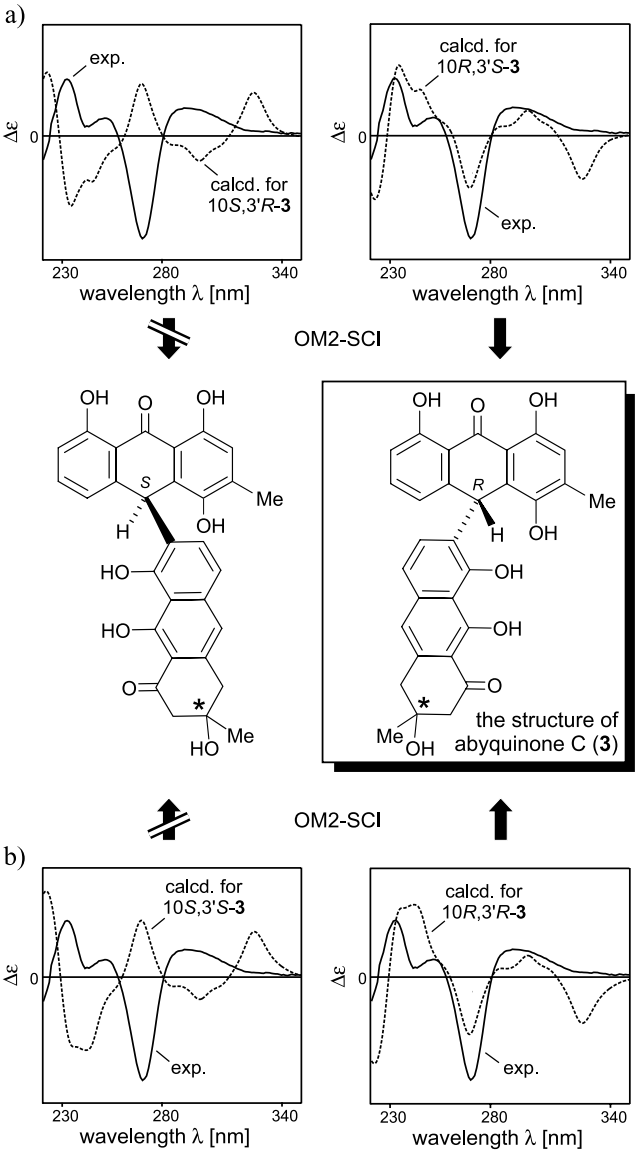


Figure 3. Attribution of the absolute configuration of abyquinone C (**3**) by comparison of the experimental CD spectrum with the spectra calculated for (a) (10*S*,3′*R*)-**3** and (10*R*,3′*S*)-**3** and (b) (10*S*,3′*S*)-**3** and (10*R*,3′*R*)-**3** using in both cases the OM2 Hamiltonian with an SCI calculation.

3. Conclusion

The work described in this paper presents the isolation and structural assignment of a series of three new dimeric anthracene derivatives, abyquinones A, B, and C, by using a combined approach of spectroscopic methodes, chemical transformations, and quantum chemical CD calculations. Accordingly, **2** and **3** have an identical configuration at C-10 (both *R*), whilst in the case of **3** the absolute configuration at C-3′ could not be elucidated with certainty, although the computations suggest the stereogenic center to be *S*-configured. The absolute configuration of the rotationally hindered biaryl axis of **1** was unambiguously assigned as *P*. The results demonstrate the value of combining experimental and computational methods in attaining configurational information and explaining stereochemical behavior otherwise difficult to achieve. Certainly of biosynthetic

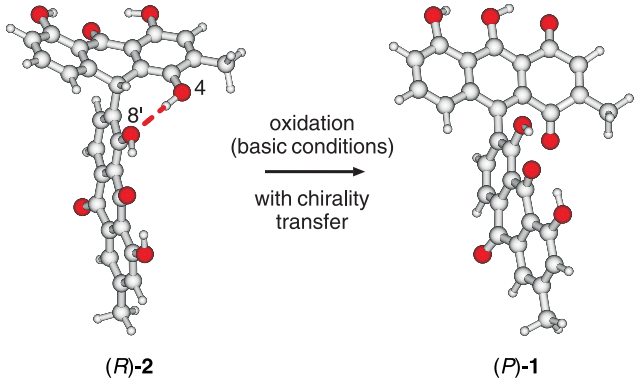


Figure 4. Center-to-axis chirality transfer from abyquinone B (**2**) to abyquinone A (**1**). The *R*-configuration in **2** induces a *P*-configured chiral axis in **1** due to the pre-orientation initiated by the hydrogen bond between OH-4 and OH-8′; both structures shown constitute global AM1 minimum geometries.

relevance, the preanthraquinonylanthrone **3**, upon standing under basic conditions in the presence of air, gives the anthraquinonylanthrone **2**, which is further converted to the axially chiral bianthraquinone **1**, apparently without loss of enantiomeric purity, hinting at a center-to-axis chirality transfer as yet unprecedented for natural products, in particular under so mild conditions.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were taken on a Jasco FT/IR-410 spectrometer. UV spectra were recorded on a Varian Cary 50 probe spectrophotometer. Analytical TLC: Merck pre-coated silica gel 60 F_{254} plates. CC on oxalic acid impregnated silica gel 60 (70–230 mesh). EIMS: direct inlet, 70 eV on a SSQ 710, Finnigan MAT spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) on Bruker spectrometer using TMS as int. standard. HMQC and HMBC spectra were acquired using the standard Bruker software. CD spectra were recorded on a Jasco J-715 spectropolarimeter and optical rotations on a Jasco P-1020 polarimeter (using a sodium D line and a quartz cuvette with 1 cm path length and 1 cm i.d.).

4.2. Plant material

Fruits of *Bulbine abyssinica* were collected near Thika town along the Nairobi-Thika highway in August 1994. The plant was identified at the University Herbarium, Department of Chemistry, University of Nairobi, where a voucher specimen (SGM-AYT-1994-06) has been deposited.

4.3. Extraction and isolation

The dried and ground powder (150 g) of the fruits of *Bulbine abyssinica* was extracted with ethyl acetate by cold percolation. The crude extract (3.5 g) was chromatographed on oxalic acid impregnated silica gel (100 g), eluting with increasing polarities of mixtures of *n*-hexane/dichloromethane and then ethyl acetate/dichloromethane. A total of 23 fractions, each ca. 200 ml, were collected and combined into seven major fractions (A to G).

The methanol soluble portion of fraction C (eluted with 20% dichloromethane in *n*-hexane) was crystallized from dichloromethane/*n*-hexane to give islandicin (3 mg) as red crystals (R_f 0.5 on 5% ethyl acetate in *n*-hexane). PTLC (5% ethyl acetate in *n*-hexane) separation of fraction D (eluted with 30% dichloromethane in *n*-hexane), gave further amounts of islandicin (4 mg) and chrysophanol (16 mg) as a yellow crystalline compound (R_f 0.4 on 5% ethyl acetate in *n*-hexane). Fraction E (eluted with 40% dichloromethane in *n*-hexane) was crystallized from dichloromethane/ *n*-hexane to give compound **1** (55 mg) as a dark red amorphous powder (R_f 0.7, dichloromethane). Fraction F (eluted with 50% dichloromethane in *n*-hexane) showed two spots on TLC (10% ethyl acetate in dichloromethane). PTLC separation (oxalic acid impregnated silica gel, solvent dichloromethane) and subsequent crystallization from dichloromethane/*n*-hexane yielded compound **2** (43 mg) as a yellowish brown powder. Fraction G (eluted with 5% ethyl acetate in dichloromethane) was purified by CC on Sephadex LH 20 (CH_2Cl_2–MeOH; 1:1) to give compound **3** (15 mg).

4.3.1. Abyquinone A (1). Dark red amorphous powder; mp 161 °C (CH_2Cl_2); $\alpha_D^{20} = -248°$ (*c* 0.02, CH_2Cl_2, mean value; the measured α_D values varied from −200 to −300 due to the long-wavelength UV absorbance;[26–28] IR (NaCl): 3452, 1667, 1618, 1427, 1381, 1269, 1132, 1073, 1025, 1004, 965, 885, 754 cm^{-1}; UV/Vis (MeOH): λ_{max} (log ε) = 232 (3.83), 256 (3.60), 303 (3.00), 438 (3.26), 471 (3.20), 500 (3.01), 542 (3.02), 582 (2.60) nm; CD (CH_2Cl_2): $\Delta\varepsilon_{229}$ −12.4, $\Delta\varepsilon_{276}$ 10.5, $\Delta\varepsilon_{301}$ −2.5; ^{1}H NMR (Table 1); ^{13}C NMR (Table 1); EIMS *m/z* (rel. int.): 506 (M^+, 100), 489 (61), 281 (23); HREIMS *m/z* 506.0993 (M^+; calcd for $C_{30}H_{18}O_8$, 506.1002).

4.3.2. Abyquinone B (2). Yellowish brown amorphous powder; mp 184 °C (MeOH); $\alpha_D^{20} = -25.2°$ (*c* 0.02, MeOH); IR (NaCl): 3431, 1662, 1621, 1420, 1379, 1259, 1122, 1069, 1025, 885, 754 cm^{-1}; UV/Vis (MeOH): λ_{max} (log ε) = 232 (3.92), 256 (3.60), 303 (3.00), 438 (3.18), 467 (2.78) nm; CD (CH_2Cl_2): $\Delta\varepsilon_{230}$ 10.1, $\Delta\varepsilon_{237}$ 7.0, $\Delta\varepsilon_{240}$ 7.7, $\Delta\varepsilon_{270}$ −6.7, $\Delta\varepsilon_{300}$ 1.6; ^{1}H NMR (Table 1); ^{13}C NMR (Table 1); EIMS *m/z* (rel. int.): 508 (M^+, 20), 489 (8), 281 (24), 254 (25); HREIMS *m/z* 508.1153 (M^+; calcd for $C_{30}H_{20}O_8$, 508.1158).

4.3.3. Abyquinone C (3). Yellow amorphous powder; mp 193 °C (MeOH); $\alpha_D^{20} = -63.5°$ (*c* 0.1, MeOH); IR (NaCl): 3428, 1633, 1620, 1600, 1485, 1284, 1124, 775 cm^{-1}; UV/Vis (MeOH): λ_{max} (log ε) = 232 (4.09), 276 (3.91), 398 (3.48) nm; CD (MeOH): $\Delta\varepsilon_{194}$ 2.8, $\Delta\varepsilon_{208}$ −2.4, $\Delta\varepsilon_{212}$ −1.5, $\Delta\varepsilon_{218}$ −2.6, $\Delta\varepsilon_{230}$ 1.8, $\Delta\varepsilon_{241}$ −0.1, $\Delta\varepsilon_{251}$ 1.2, $\Delta\varepsilon_{273}$ −4.8, $\Delta\varepsilon_{323}$ 1.1; ^{1}H NMR (Table 1); ^{13}C NMR (Table 1); EIMS *m/z* (rel. int.): 512 (M^+, 3), 494 (6), 493, (7), 474 (16), 254 (100), 240 (67); HREIMS *m/z* 512.1465 (M^+; calcd for $C_{30}H_{24}O_8$, 512.1471).

4.4. Aerial oxidation

Compound **3** (10 mg) was dissolved in 5% methanolic KOH and the mixture was stirred for 2 h at room temperature. The solution was acidified and extracted with dichloromethane. Preparative TLC purification of the organic layer gave compound **1** (trace), **2** (5 mg) and unreacted **3** (3 mg). In a separate experiment compound **3** (5 mg) was completely converted to **1** (3 mg) when the methanolic solution was stirred for 3 d. Compound **2** was also converted to **1** in a similar experiment. The reactions were monitored by TLC and the identity of the products was confirmed by ^{1}H NMR analysis.

4.5. Computational

The conformational analyses were performed on a Linux AMD MP 2400+ workstation by means of the semi-empirical AM1[16] method as implemented in the program

package Gaussian 98,[29] starting from preoptimized geometries generated by the TRIPOS[30] force field as part of the molecular modeling package SYBYL 6.9.[30] The wave functions required for the computation of the rotational strengths for the electronic transitions from the ground state to excited states were obtained by CNDO/S[17] calculations followed by SCI computations including 625 singly occupied configurations and the ground state determinant, and by OM2[18] calculations followed by SCI and SDCI calculations including 900 singly and 400 doubly occupied configurations, respectively, and the ground state determinant. These computations were also carried out with a Linux AMD MP 2400+ workstation using the BDZDO/MCDSPD[31] program package, and by the use of the MNDO99[32] software package. The single CD spectra were summed up and weighted following the Boltzmann statistics, that is, according to the respective heats of formation. The rotational strengths were transformed into $\Delta\varepsilon$ values and for a better visualization superimposed with a Gaussian band shape function.

Acknowledgements

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Oligonucleotides containing 7-propynyl-7-deazaguanine: synthesis and base pair stability

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Abstract—Oligonucleotides incorporating the propynyl derivative of 7-deaza-2′-deoxyguanosine (**1**) were synthesized by solid-phase oligonucleotide synthesis. As building blocks the phosphoramidites **7a**,**b** were prepared. The incorporation of **1** into oligonucleotides exerts a positive effect on the DNA duplex stability. The duplex stabilization by **1** was higher than that of 7-iodo-7-deaza-2′-deoxyguanosine (**2b**). The stabilizing effect of the 7-propynyl group introduced in the 7-deazapurines is similar to that reported for 8-aza-7-deazapurines. From CD spectra it was deduced that the B-DNA structure is not significantly altered by compound **1**.

1. Introduction

Structural modifications on nucleic acids constituents have been examined to increase base pair stability or nucleobase pairing selectivity or to change base pair recognition as well as to increase antiviral or anticancer activity. Such modifications were also applied to oligonucleotides hybridization probes used for diagnostic purposes.[1] The structural perturbation include modifications on the oligonucleotide backbone,[2] the sugar moiety,[3–5] or the nucleobase.[6–11] Among the various groups used for duplex stabilization, the propynyl group gained particular attention.[12–14] Their introduction has been shown to increase duplex stability which can be useful for antisense oligonucleotide application or primer probe interactions.[15–17] Furthermore, it was demonstrated that this modification enhances the mismatch penalties[13,14,18,19] as well as the stability of DNA triplexes.[20,21]

Earlier, the propynyl group was introduced in the 5-position of pyrimidine nucleosides, e.g. in 2′-deoxycytidine[11–13,22,23] and 2′-deoxyuridine.[24–26] Also 8-propynylated 2′-deoxyadenosine and 2′-deoxyguanosine derivatives were studied.[26,27] However, the 8-propynyl residues destabilize duplex DNA and drive the molecule into the *syn* conformation.[28,29] Recently, it was shown that 7-propynyl residues of 8-aza-7-deazapurines are well accommodated in duplex DNA.[30,31] However, longer hex-1-ynyl chains do not show such favourable properties.[32]

Earlier, oligophosphorothioates with propynyl groups substituting the 7-position of 7-deaza-2′-deoxyguanosine (**2a**) have been investigated.[33,34] Nevertheless, oligodeoxyribonucleotides with a natural phosphodiester backbone in which 2′-deoxyguanosine was replaced by compound **1** have not been studied. This manuscript reports on the synthesis and hybridization of such oligodeoxyribonucleotides. For this purpose, an improved synthetic route for compound **1** was developed starting from the 7-iodo nucleoside **2b** which was subsequently converted into phosphoramidite building blocks in an excellent overall yield (67%). Also an amidine protected phosphoramidite was synthesized from which oligonucleotides can be obtained using mild deprotection conditions. Finally, the effect of the propynyl group at the 7-position of 7-deaza-2′-deoxyguanosine (**2a**) and 8-aza-7-deaza-2′-deoxyguanosine (**3a**) on the DNA duplex stability will be compared (Scheme 1).

2. Results and discussion

The synthesis of the 7-deaza-7-propynyl-2′-deoxyguanosine (**1**) was reported earlier using 4-chloro-2-(methylthio)-pyrrolo[2,3-*d*]pyrimidine as a starting material, followed by glycosylation and the exchange of the 2-methylthio group by an amino residue.[33] As the yields of the particular

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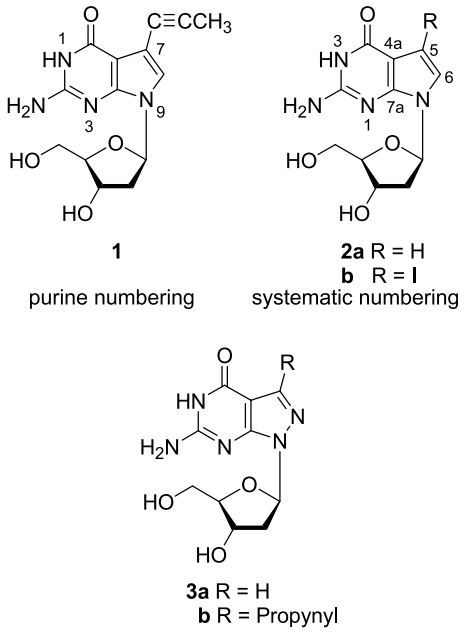
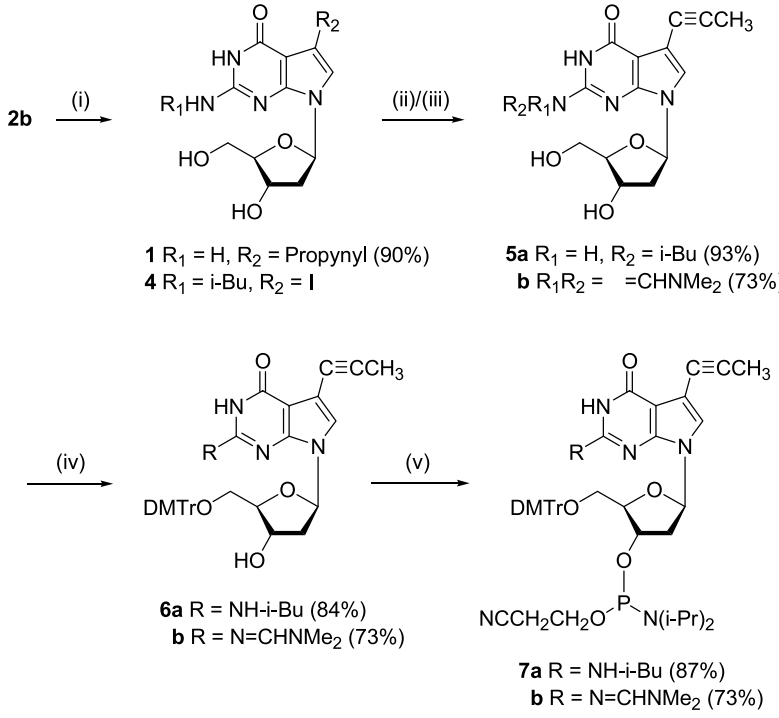


Scheme 1.

steps were moderate or were not mentioned[34] we developed an alternative synthetic route. 7-Iodo-7-deaza-2′-deoxyguanosine (**2b**)[35] was selected as precursor which was subjected to the palladium-catalyzed Sonogashira cross-coupling reaction yielding compound **1**.[36–38] The reaction was carried out in anhydrous DMF in the presence of [$(PPh_3)_4Pd(0)$]/CuI/triethylamine. The solution was saturated with propyne (0 °C) to give the nucleoside **1** in 90% yield (Scheme 2).

Next, the amino group of **1** was blocked with either an isobutyryl residue[39] or a formamidine protecting group. For this purpose, the isobutyryl protected compound **4** was used for the cross-coupling reaction furnishing compound **5a** in 93% yield, and compound **1** was treated with *N*,*N*-dimethylaminoformamide dimethylacetal in MeOH at 40 °C yielding **5b** in 73% yield. The half-life of the isobutyryl protecting group of **5a** was found to be 95 min (at 40 °C, 25% aq. NH_3) while that of the dimethylaminoformamidine residue of **5b** was 7 min. As the formamidine protection results in a lower half-life when compared to the isobutyryl group, mild deprotection conditions can be used when compound **5b** is incorporated. Subsequently, the intermediates **5a**,**b** were converted into the 4,4′-dimethoxytrityl derivatives **6a**,**b** under standard conditions. Phosphitylation of the DMT derivatives **6a**,**b** with 2-cyanoethyl diisopropylphosphoramidochloridite in CH_2Cl_2 in the presence of $(i\text{-}Pr)_2EtN$ furnished the phosphoramidites **7a**,**b** in 86 and 73% yields, respectively (Scheme 2 and Section 3). Structural proof of all compounds was performed by ^1H-, ^{13}C- and ^{31}P NMR spectra (Table 1) as well as by elemental analyses. According to Table 1, the 7-propynyl substituent changes the chemical shift of C(7) of compound **1** and its derivatives. This is due to a positive mesomeric effect of the 7-propynyl-substituent on the pyrrolo[2,3-*d*]pyrimidine system, which is similar in the case of the 7-iodo substituted nucleoside **2b**. As the base pair stability is influenced by the pK_a value the effect of the 7-propynyl residue on the pyrrolo[2,3-*d*]pyrimidine nucleoside was studied; pK_a values of the compound **1** were determined UV-spectrophotometrically. The 7-propynyl group does not change the pK_a values significantly, compound **1** has pK_a values of 1.6 and 10.2 while the non-functionalized nucleoside **2a** shows pK_a values of 1.7 and 10.2; the pK_a values for the 7-iodo nucleoside **2b** are 0.6 and 10.3. The UV-spectra of compound **1** was significantly



Scheme 2. (i) and (ii) [$Pd(0)(PPh_3)_4$], CuI, Et_3N, DMF, propyne, rt, 18 h. (iii) *N*,*N*-dimethylformamide dimethylacetal, MeOH, 40 °C, 30 min. (iv) $(MeO)_2TrCl$, pyridine, rt, 15 h. (v) 2-cyanoethyl-diisopropylphosphoramido chloridite, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, rt, 30 min.

Table 1. ^{13}C NMR chemical shifts of 7-substituted 7-deaza-2′-deoxyguanosines at 298 K[a]

Compound	C(2)[b] C(2)[c]	C(4)[b] C(6)[c]	C(4a)[b] C(5)[c]	C(5)[b] C(7)[c]	C(6)[b] C(8)[c]	C(7a)[b] C(4)[c]	C=O/C=N
1	152.9[d]	157.8	99.3	85.4	120.9	150.0[d]	—
2a	152.5	158.5	100.0	102.0	116.6	150.5	—
2b	152.7	158.0	99.8	54.9	121.6	150.5	—
5a	147.4[d]	155.9	103.4	86.6	123.4	147.0[d]	180.0
6a	147.4[d]	155.9	103.6	85.4	123.3	147.0[d]	180.0
5b	157.4	158.7	102.4	85.6	122.5	156.6	148.8
6b	158.0[d]	158.8	102.5	85.3	122.2	157.4[d]	148.9
	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	C≡C	C≡C
1	82.1	[e]	70.8	87.0	61.8	99.3	73.7
2a	82.2	39.5	70.8	86.8	61.9	—	—
2b	82.2	[e]	70.9	87.1	61.8	—	—
5a	82.6	[e]	70.8	87.3	61.7	100.1	72.9
6a	82.5	[e]	70.4	86.6	64.1	100.2	72.7
5b	82.3	[e]	70.9	87.2	61.9	99.5	73.6
6b	81.9	[e]	70.6	85.6	64.3	99.7	73.5

[a] Measured in (D_6) DMSO.
[b] Systematic numbering.
[c] Purine numbering.
[d] Tentative.
[e] Overlaped in DMSO signal.

different from that of the non-functionalized nucleoside **2a** (**1**: λ_{max}=236 and 271 nm; **2a**: λ_{max}=257 and 281 nm).

Next, the role of the 7-propynyl group on the duplex stability was studied on the duplex 5′-d(TAG GTC AAT ACT) (**8**) 3′-d(ATC CAG TTA TGA) (**9**). Earlier, it was shown that the non-functionalized nucleoside **2a** reduces the stability of the Watson–Crick base pair thereby reducing the duplex stability of **8·9** by about 1 °C per modification (**9·10** and **10·13**). The incorporation of the 7-iodo derivative **2b** increases the duplex stability (**9·11** and **11·14**) to the level of standard duplex **8·9** (Table 2)[32] when compared with that of **2a**. Now, it is shown that the 7-propynyl group is more effective than a halogen substituent for duplex stabilization. The average T_m-increase per modification is around 1.5 °C when the data of the duplex **9·12** and **12·15** containing nucleoside **1** are related to the standard duplex **8·9**. If one relates it to the duplexes **9·10** or **10·13** containing 7-deaza-2′-deoxyguanosine (**2a**) in place of dG, the T_m-increase is around 2.5 °C per modification (Table 2). Also the T_m-values of the duplexes **8·17**, **9·16** and **9·18** containing **1** at various positions clearly indicate a nearest neighbour effect. According to Table 3, the ΔT_m for the 8-aza-7-deaza-7-propynyl-2′-deoxyguanosine (**3b**) is also around 2.5 °C per

Table 2. T_m-values and thermodynamic data of duplexes containing 7-propynyl-7-deaza-2′-deoxyguanosine (**1**)

Duplexes	T_m [°C]	ΔH° [kcal/mol]	ΔS° [cal/mol K]	ΔG°_{310} [kcal/mol]
5′-d(TAG GTC AAT ACT)(**8**)[a] 3′-d(ATC CAG TTA TGA) (**9**)	47	−89	−253	−10.9
5′-d(TA**2a** **2a**TC AAT ACT) (**10**)[a,b] 3′-d(ATC CAG TTA TGA) (**9**)	45	−101	−317	−2.7
5′-d(TA**2b** **2b**TC AAT ACT) (**11**)[a,b] 3′-d(ATC CAG TTA TGA) (**9**)	46	−99	−310	−2.9
5′-d(TA**1** **1**TC AAT ACT) (**12**)[a] 3′-d(ATC CAG TTA TGA) (**9**)	51	−99	−280	−11.7
5′-d(TA**2a** **2a**TC AAT ACT) (**10**)[a,b] 3′-d(ATC CA**2a** TTA T**2a**A) (**13**)	44	−91	−284	−2.9
5′-d(TA**2b** **2b**TC AAT ACT) (**11**)[a,b] 3′-d(ATC CA**2b** TTA T**2b**A) (**14**)	48	−112	−348	−4.12
5′-d(TA**1** **1**TC AAT ACT) (**12**)[a] 3′-d(ATC CA**1** TTA T**1**A) (**15**)	53	110	−314	−12.8
5′-d(TAG **1**TC AAT ACT) (**16**)[c] 3′-d(ATC CAG TTA TGA) (**9**)	52	−91	−284	−12.1
5′-d(TAG GTC AAT ACT)(**8**)[c] 3′-d(ATC CAG TTA T**1**A) (**17**)	51	−88	−247	−11.6
5′-d(TA**1** GTC AAT ACT) (**18**)[c] 3′-d(ATC CAG TTA TGA) (**9**)	50	−86	−241	−11.3
5′-d(TAG GTC AAT ACT) (**8**)[c] 3′-d(ATC CA**1** TTA T**1**A) (**15**)	53	−91	−225	−12.2
5′-d(TA**1** GTC AAT ACT) (**18**)[c] 3′-d(ATC CA**1** TTA T**1**A) (**15**)	52	−85	−237	−11.8
5′-d(TA**1** **1**TC AAT ACT) (**12**)[c] 3′-d(ATC CA**1** TTA TGA) (**19**)	54.5	−95	−264	−12.8

[a] Measured in 0.1 M NaCl, 10 mM $mgCl_2$ and 10 mM Na-cacodylate (pH 7.0) with 7.5 μM single-strand concentration.
[b] Ref. 32.
[c] Measured in 1 M NaCl, 100 mM $mgCl_2$ and 60 mM Na-cacodylate (pH 7.0) with 5 μM single-strand concentration.

Table 3. T_m-values and thermodynamic data of the oligonucleotides containing 7-deaza-7-propynyl-2′-deoxyguanosine (**1**) and 8-aza-7-deaza-7-propynyl -2′-deoxyguanosine (**3**)[a]

Duplexes	T_m [°C]	ΔT_m [°C] per modification	$\Delta G°_{310}$ [kcal/mol]
5′-d(TAG GTC AAT ACT) (**8**) 3′-d(ATC CAG TTA TGA) (**9**)	50	0	−10.9
5′-d(TAG GTC AAT ACT) (**8**) 3′-d(ATC CA**1** TTA TGA) (**20**)	52	2	−11.6
5′-d(TAG GTC AAT ACT) (**8**) 3′-d(ATC CA**3** TTA TGA) (**21**)	53	3	−12.5
5′-d(TA**1** **1**TC AAT ACT) (**12**) 3′-d(ATC CAG TTA TGA) (**9**)	53	1.5	−12.5
5′-d(TA**3** **3**TC AAT ACT) (**22**) 3′-d(ATC CAG TTA TGA) (**9**)	56	3	−14.5
5′-d(TA**1** **1**TC AAT ACT) (**12**) 3′-d(ATC CAG TTA T**1**A) (**17**)	54	1.3	−13.0
5′-d(TA**3** **3**TC AAT ACT) (**22**) 3′-d(ATC CAG TTA T**3**A) (**23**)	58	2.6	−14.0
5′-d(TA**1** **1**TC AAT ACT) (**12**) 3′-d(ATC CA**1** TTA T**1**A) (**15**)	55	1.25	−12.8
5′-d(TA**3** **3**TC AAT ACT) (**22**) 3′-d(ATC CA**3** TTA T**3**A) (**24**)	60	2.5	−14.6

[a] Measured in 1 M NaCl, 100 mM $mgCl_2$ and 60 mM Na-cacodylate (pH 7.0) with 5 μM single-strand concentration.

modification. As the incorporation of 8-aza-7-deaza-2′-deoxyguanosine (**3a**) causes already a T_m-increase of about 1 °C per modification.[40] The final effect of compound **3a** is stronger than that observed for **2a**. Nevertheless, when the T_m data of the propynylated oligonucleotide duplexes are correlated to those of non-propynylated duplexes, the average increase of the T_m-value is very similar (2.5 °C) in both series of heterocycles (pyrrolo[2,3-*d*]pyrimidines and pyrazolo[3,4-*d*]pyrimidines).

The enhancement of duplex stability may be caused by increased molecular polarizability of the nucleobase, the hydrophobic character and coplanarity of the propynyl group to the heterocyclic base which can increase stacking interactions.

Recently, we have performed a single crystal X-ray analysis of the nucleoside **1** (Fig. 1). In the crystalline state, the orientation of the nucleobase related to the sugar moiety of **1** is *anti* [$\chi = -117.2(5)°$], and the sugar moiety shows *S*-type sugar puckering with pseudorotational parameters $P = 152.5°$ and $\tau_m = 41.9°$. The linear propynyl group is almost in plane with the base moiety.[41] As this group is protruding into the major groove it has steric freedom. The conformation in solution was also determined from the vicinal [^{1}H, ^{1}H] NMR coupling constants using the PSEUROT 6.3 program. Here, the favored conformation is *S* (71%, $^2T_3$) which is the actual conformation of the nucleoside residue in B-DNA.

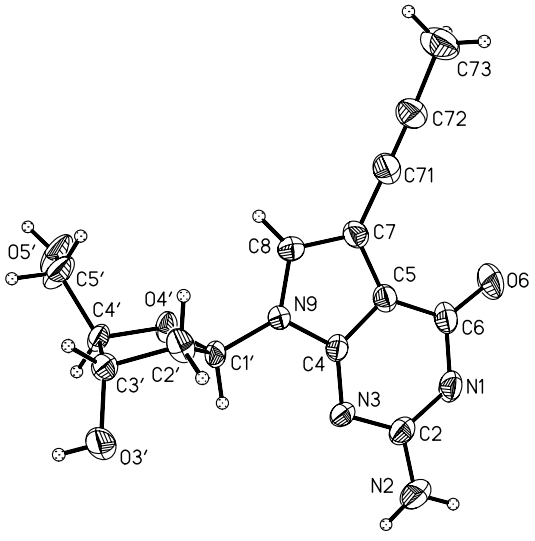


Figure 1. The perspective view of the single crystal X-ray analysis of the 7-deaza-7-propynyl-2′-deoxyguanosine (**1**).

To gain more information on the effect of the 7-propynyl group of **1** on the DNA duplex structure circular dichroism (CD) spectra of the duplexes **16**·**9**, **8**·**15**, **12**·**19**, **12**·**15** containing **1** were measured. The B-DNA structure is perturbated only very little when compound **1** is replacing dG, as it is demonstrated by the CD spectra shown in Figure 2(a). This clearly demonstrates that the B-DNA structure is maintained even with four modified residues (**1**) present in the duplex. Next, the composition of oligonucleotides containing **1** were determined by the enzymatic hydrolysis of the oligonucleotides using snake venom phosphodiesterase followed by alkaline phosphatase. According to the HPLC profile shown in Figure 2(b) compound **1** is much more hydrophobic than 2′-deoxyguanosine as indicated in the composition analysis of the oligonucleotide **12** (see also Section 3).

From the points discussed above it can be concluded that the introduction of the propynyl group in the position-7 of 7-deazapurine 2′-deoxyribonucleoside enhances the DNA duplex stability significantly. The stability increase is attributed to the linear and coplanar nature of the 7-propynyl group towards the heterocyclic base, which increase stacking interactions and makes the major groove hydrophobic by expelling water molecules. The B-DNA structure is not perturbated significantly when compound **1** is replacing dG. These favourable properties can broaden the applications of such modifications into oligonucleotides hybridization probes used for diagnostic purposes or in antisense technology.

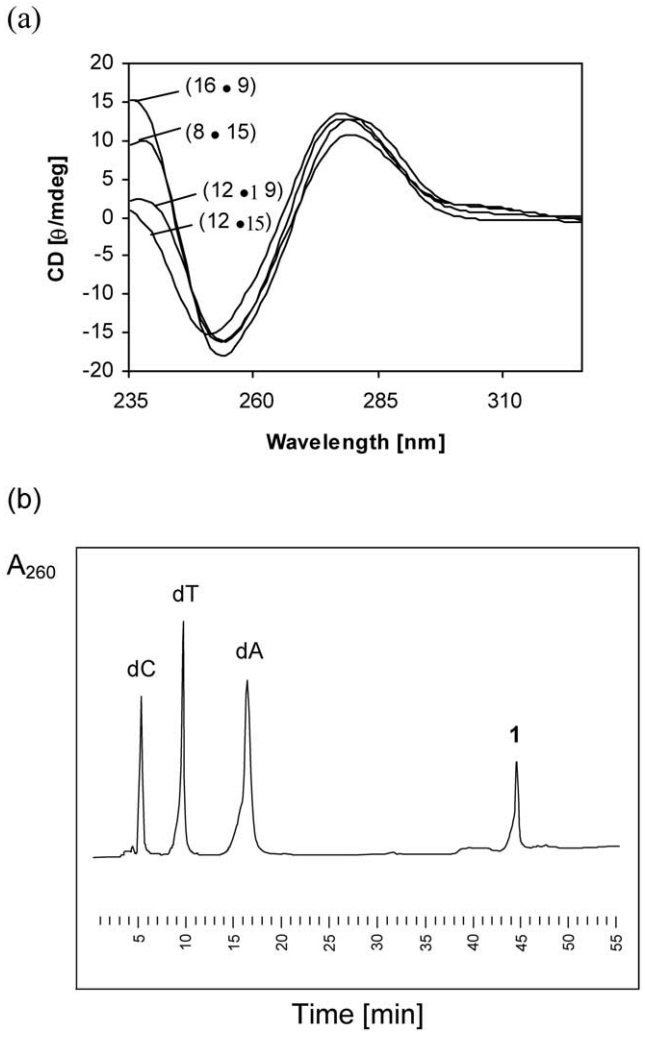


Figure 2. (a) The CD spectra of oligonucleotides containing **1**, measured at 20 °C in buffer as indicated in Table 3. (b) HPLC profile of enzymatic analysis of oligonucleotide **12** containing **1** by phosphodiesterase followed by alkaline phosphatase in 0.1 M Tris–HCl buffer (pH 8.3) at 37 °C.

3. Experimental

3.1. General

All chemicals were purchased from Aldrich, Sigma, or Fluka (Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany). Solvents were of laboratory grade. TLC: aluminum sheets, silica gel 60 F_{254}, 0.2 mm layer (VWR, Germany). Column flash chromatography (FC): silica gel 60 (VWR, Germany) at 0.4 bar; Sample collection with an UltroRac II fractions collector (LKB Instruments, Sweden). UV spectra: U-3200 spectrometer (Hitachi, Tokyo, Japan); λ_{max} (ε) in nm. CD Spectra: Jasco 600 (Jasco, Japan) spectropolarimeter with thermostatically (Lauda RCS-6 bath) controlled 1-cm quartz cuvettes. NMR Spectra: Avance-250 or AMX-500 spectrometers (Bruker, Karlsruhe, Germany), at 250.13 MHz for ^{1}H and ^{13}C; δ in ppm rel. to Me_4Si as internal standard; ^{31}P rel. to ext. 85% H_3PO_4, *J* values in Hz. Elemental analyses were performed by Mikroanalytisches Laboratorium Beller (Göttingen, Germany). The melting temperatures were measured with a Cary-1/3 UV/Vis spectrophotometer (Varian, Australia) equipped with a Cary thermoelectrical controller. The temp. was measured continuously in the reference cell with a Pt-100 resistor, and the thermodynamic data of duplex formation were calculated by the Meltwin 3.0 program.[42]

3.2. Synthesis, purification and characterization of the oligonucleotides

The oligonucleotide syntheses were carried out in an ABI 392-08 DNA synthesizer (Applied Biosystems, Weiterstadt, Germany) at 1-μmol scale using the phosphoramidites **7a**,**b** following the synthesis protocol for 3′-cyanoethyl-phosphoramidites (user manual for the 392 DNA synthesizer Applied Biosystems, Weiterstadt, Germany). The coupling efficiency was always higher than 97%. After cleavage from the solid support, the oligonucleotides were deprotected in 25% aq. ammonia solution for 14–16 h at 60 °C.[43]

Purification of 5′-dimethoxytrityl oligomers was performed by reversed-phase HPLC (RP-18) with the following solvent gradient system [A: 0.1 M (Et_3NH)OAc (pH 7.0)/MeCN 95:5; B: MeCN]: 3 min, 20% B in A, 12 min, 20–50% B in A and 25 min, 20% B in A with a flow rate of 1.0 ml/min. The solution was dried and treated with 2.5% $CHCl_2COOH/CH_2Cl_2$ for 5 min at 0 °C to remove the 4,4′-dimethoxytrityl residues. The detritylated oligomers were purified by reverse phase HPLC with the gradient: 0–20 min, 0–20% B in A with a flow rate of 1.0 ml/min. The oligomers were desalted (RP-18, silica gel) and lypophilized on a Speed Vac evaporator to yield colorless solids which were frozen at −24 °C.

The enzymatic hydrolysis of the oligonucleotides was performed as described by Seela and Becher[10] with snake venom phosphodiesterase (EC 3.1.15.1, *Crotallus adamanteus*) and alkaline phosphatase (EC 3.1.3.1, *Escherichia coli* from *Roche Diagnostics GmbH*, Germany) in 0.1 M Tris–HCl buffer (pH 8.3), which was carried out on reverse phase HPLC by gradient: 20 min A, 20–60 min 50% B in A. Quantification of the constituents was made on the basis of the peak areas, which were divided by the extinction coefficients of the nucleosides [(ε_{260}): dT 8800, dC 7300, dA 15400, **1** 11400]. The molecular masses of the oligonucleotides were determined by MALDI-TOF Biflex-III mass spectrometry (Bruker Saxonia, Leipzig, Germany) with 3-hydroxypicolinic acid (3-HPA) as a matix (Table 4).

3.2.1. 2-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (1). To a soln. of compound **2b** (500 mg, 1.28 mmol)[35] in anhydrous DMF (4 ml), tetrakis(triphenylphosphine)palladium(0) [$(PPh_3)_4Pd(0)$] (116 mg, 0.1 mmol), CuI (68 mg, 0.36 mmol) and triethylamine (240 μl, 1.71 mmol) were added while stirring. The sealed suspension was saturated with propyne at 0 °C and stirred at rt for 24 h. The solvent was evaporated in vacuo, the reaction mixture dissolved in MeOH (2 ml) and adsorbed on silica gel (2 g). The resulting powder was subjected to FC. (silica gel, column 15×3 cm, CH_2Cl_2/MeOH, 95:5). From the main zone compound **1** was isolated as colorless solid (350 mg, 90%) which gave colorless crystals from MeOH.

Table 4. Molecular weight of selected oligonucleotides determined by MALDI-TOF mass spectrometry

Oligonucleotide	MH^+ (calcd)	MH^+ (found)
5′-d(TA**1** **1**TC AAT ACT) (**12**)	3718.4	3719.1
3′-d(ATC CA**1** TTA T**1**A) (**15**)	3718.4	3718.2
5′-d(TAG **1**TC AAT ACT) (**16**)	3682.4	3681.7
3′-d(ATC CAG TTA T**1**A) (**17**)	3682.4	3681
5′-d(TA**1** GTC AAT ACT) (**18**)	3682.4	3681
3′-d(ATC CA**1** TTA TGA) (**19**)	3682.4	3682.4
3′-d(ATC CA**1** TTA T**1**A) (**20**)	3718.4	3718.2

Mp>210 °C. TLC (CH_2Cl_2/MeOH, 9:1)): R_f 0.35. UV (MeOH): λ_{max} 236 (27800), 271 (13200). ^{1}H NMR.[33]

3.2.2. 7-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-3,7-dihydro-2-(isobutyrylamino)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (5a). As described for **1** with compound **4** (400 mg, 0.87 mmol),[44] tetrakis(triphenylphosphine)palladium(0) [$(PPh_3)_4Pd(0)$] (58 mg, 0.05 mmol), CuI (34 mg, 0.18 mmol), triethylamine (0.14 ml, 1.0 mmol) and DMF (3 ml). FC (silica gel, column 15×3 cm, CH_2Cl_2/MeOH, 95:5) afforded compound **5a** as a colorless solid (300 mg, 93%). TLC (CH_2Cl_2/MeOH, 9:1): R_f 0.68. UV (MeOH): λ_{max} 237 (22600), 281 (1600), 296 (16300). ^{1}H NMR ((D_6) DMSO): 1.09 (d, J= 6.7 Hz, 2 CH_3), 2.00 (s, CH_3); 2.14 (m, H_α-C(2′)); 2.36 (m, H_β-C(2′)); 2.73 (m, CH); 3.49 (t, J=2.3, 5.9 Hz, H_2-C(5′)); 3.78 (m, H-C(4′)); 4.30 (m, H-C(3′)); 4.96 (t, J=5.3, 5.3 Hz, OH-C(5′)); 5.26 (d, J=3.4 Hz, OH-C(3′)); 6.35 (dd, J=5.9, 5.9 Hz, H-C(1′)); 7.46 (s, H-C(8)); 11.54 (s, NH); 11.78 (s, NH). Anal. calcd for $C_{18}H_{22}N_4O_5$ (374.39): C 57.75, H 5.92, N 14.96. Found: C 57.48, H 5.92, N 14.62.

3.2.3. 7-(2-Deoxy-5-O-(4,4′-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-3,7-dihydro-2-(isobutyrylamino)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (6a). Compound **5a** (250 mg, 0.67 mmol) was dried by repeated co-evaporation with anhydrous pyridine and then dissolved in pyridine (5 ml). After addition of 4,4′-dimethoxytrityl chloride (338 mg, 1.0 mmol) the soln. was stirred overnight at rt. The reaction was quenched by adding 5% aq. $NaHCO_3$ soln. (25 ml), and the soln. was extracted with CH_2Cl_2 (30 ml). The aq. layer was washed with CH_2Cl_2 (25 ml×3). The combined org. phase was dried over Na_2SO_4 and evaporated. The residue was subjected to FC (silica gel, column 15×3 cm, CH_2Cl_2/acetone, 95:5). The main zone afforded compound **6a** as a colorless solid (379 mg, 84%). TLC (CH_2Cl_2/MeOH, 95:5): R_f 0.41. UV (MeOH): λ_{max} 234 (39400), 281 (1700), 340 (1100). ^{1}H NMR ((D_6) DMSO): 1.10 (d, J=6.4 Hz, 2 CH_3); 2.00 (s, CH_3); 2.21 (m, H_α-C(2′)); 2.42 (m, H_β-C(2′)); 2.75 (m, CH); 3.13 (m, H_2-C(5′)); 3.71, 3.73 (2s, 2 OCH_3); 3.89 (m, H-C(4′)); 4.31 (m, H-C(3′)); 5.30 (s, OH-C(3′)); 6.38 (t, J= 6.5, 6.1 Hz, H-C(1′)); 6.8 (m, Ar 4H); 7.21–7.58 (m, H-C(8) + Ar 9H); 11.57 (s, NH); 11.81 (s, NH). Anal. calcd for $C_{39}H_{40}N_4O_7$ (676.76): C 69.21, H 5.96, N 8.28. Found: C 69.11, H 6.00, N 8.32.

3.2.4. 7-(2-Deoxy-5-O-(4,4′-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-3,7-dihydro-2-(isobutyrylamino)-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one 3′-[2-Cyanoethyl *N*,*N*-diisopropylphosphoramidite] (7a). To a soln. of compound **6a** (200 mg, 0.30 mmol) in anhydrous CH_2Cl_2 (10 ml), *N*,*N*-diisopropylethylamine (DIPEA) (0.1 ml, 0.57 mmol) and 2-cyanoethyl-diisopropylphosphoramido chloridite (0.1 ml, 0.45 mmol) were added under Ar atmosphere. After stirring for 0.5 h, 5% aq. $NaHCO_3$ soln. was added, and it was extracted with CH_2Cl_2 (10 ml×2). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was subjected to FC (silica gel, column 7×1.5 cm, CH_2Cl_2/acetone, 95:5). The main zone afforded compound **7a** as a colorless foam (225 mg, 87%).TLC (CH_2Cl_2/$(CH_3)_2CO$, 9:1): R_f 0.7. ^{31}P NMR ($CDCl_3$): 148.69, 149.19.

3.2.5. 7-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-3,7-dihydro-2-[(*N*,*N*-dimethylamino)methylidene]amino-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (5b). To a soln. of **1** (500 mg, 1.87 mmol) in MeOH (20 ml) was added *N*,*N*-dimethylformamide dimethylacetal (750 µl, 5.6 mmol). The reaction mixture was stirred at 40 °C for 1 h, and the solvent was evaporated to dryness. The resulting residue was applied to FC (silica gel, column 15×3 cm, CH_2Cl_2/MeOH, stepwise gradient, 95:5, 9:1). Compound **5b** was isolated as a colorless solid (430 mg, 73%). TLC (CH_2Cl_2/MeOH, 9:1)): R_f 0.65. UV (MeOH): λ_{max} 231 (17000), 253 (22000), 314 (16800). ^{1}H NMR ((D_6) DMSO): 1.99 (s, CH_3); 2.14 (m, H_α-C(2′)); 2.34 (m, H_β-C(2′)); 3.00, 3.14 (2s, 2 NCH_3); 3.50 (d, J=4.0 Hz, H_2-C(5′)); 3.77 (m, H-C(4′)); 4.31 (m, H-C(3′)); 4.89 (t, J=4.8, 5.0 Hz, OH-C(5′)); 5.22 (d, J=3.3 Hz, OH-C(3′)); 6.40 (t, J=6.5, 7.0 Hz, H-C(1′)); 7.27 (s, H-C(8)); 8.53 (s, N=CH); 11.02(s, NH). Anal. calcd for $C_{17}H_{21}N_5O_4$ (359.38): C 56.82, H 5.89, N 19.49. Found: C 56.58, H 5.75, N 19.55.

3.2.6. 7-(2-Deoxy-5-O-(4,4′-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-3,7-dihydro-2-[(*N*,*N*-dimethylamino)methylidene]amino-4*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one (6b). Compound **5b** (350 mg, 0.97 mmol) was dried by repeated co-evaporation with anhydrous pyridine (4 ml×2) and dissolved in pyridine (4 ml). After addition of 4,4′-dimethoxytrityl chloride (440 mg, 1.3 mmol) the soln. was stirred for 30 min at rt. The reaction was quenched by adding 5% aq. $NaHCO_3$ soln. (25 ml) and it was extracted with CH_2Cl_2 (30 ml). The aq. layer was extracted with CH_2Cl_2 (25 ml×3), the combined org. phase dried over Na_2SO_4 and evaporated. The residue was subjected to FC (silica gel, column 15×3 cm, CH_2Cl_2/acetone, stepwise gradient, 9:1, 8:2, 1:1). The main zone afforded compound **6b** as a colorless solid (470 mg, 73%). TLC (CH_2Cl_2/MeOH, 97:3): R_f 0.38. UV (MeOH): λ_{max} 233 (37400), 313 (1700). ^{1}H NMR ((D_6) DMSO): 1.98 (s, CH_3); 2.16 (m, H_α-C(2′)); 2.42 (m, H_β-C(2′)); 3.01 (s, NCH_3); 3.13 (m, NCH_3 + H_2-C(5′)), 3.73 (s, 2 OCH_3); 3.88 (m, H-C(4′)); 4.30 (m, H-C(3′)); 5.30 (d, J=4.0 Hz, OH-C(3′)); 6.45 (t, J=6.4, 6.5 Hz, H-C(1′)); 6.84 (m, Ar 4H); 7.13–7.38 (m, H-C(8)+Ar 9H); 8.55 (s, N=CH); 11.07 (s, NH). Anal. calcd for $C_{38}H_{39}N_5O_6$ (661.75): C 68.97, H 5.94, N 10.58. Found: C 68.85, H 6.03, N 10.48.

3.2.7. 7-(2-Deoxy-5-O-(4,4′-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl)-5-(prop-1-ynyl)-3,7-dihydro-2-[(*N*,*N*-dimethylamino)methylidene]amino-4*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one 3′-[2-Cyanoethyl *N*,*N*-diisopropylphosphoramidite] (7b). To a soln. of compound

6b (250 mg, 0.38 mmol) in anhydrous CH_2Cl_2 (5 ml), *N*,*N*-diisopropylethylamine (DIPEA) (116 µl, 0.67 mmol) and 2-cyanoethyl-diisopropylphosphoramido chloridite (112 µl, 0.55 mmol) were added under Ar atmosphere. After stirring for 0.5 h, 5% aq. $NaHCO_3$ soln. was added, and it was extracted with CH_2Cl_2 (10 ml×2). The org. layer was dried over Na_2SO_4, filtered and evaporated. The residue was subjected to FC (CH_2Cl_2/acetone, 9:1). The main zone afforded compound **7b** as a colorless foam (240 mg, 73%). TLC (CH_2Cl_2/$(CH_3)_2CO$, 8:2): R_f 0.7. ^{31}P NMR ($CDCl_3$): 149.79, 150.12.

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Synthesis of 2-mesityl-3-methylpyrrole via the Trofimov reaction for a new BODIPY with hindered internal rotation

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Abstract—The reaction of *E*-ethylmesitylketoxime with acetylene in the system KOH/DMSO (the Trofimov reaction) (70–74 °C, 3 h, atmosphere pressure) affords 2-mesityl-3-methylpyrrole (23%), 2-mesityl-3-methyl-1-vinylpyrrole (8%), *Z*- (5%) and *E*- (2%) isomers of *O*-vinylethylmesitylketoxime. Initial ethylmesitylketoxime was prepared in two ways: via very slow oximation of ethylmesitylketone in 30% yield after 8 months, and, more efficiently, by oximation of ethylmesitylketimine hydrochloride derived from bromomesitylene in several steps. 2-Mesityl-3-methylpyrrole was used for the synthesis of 4,4-difluoro-2,6-dimethyl-3,5,8-trimesityl-4-bora-3a,4a-diaza-*s*-indacene with mesityl substituents having hindered internal rotation and preventing π-stacking at high concentrations. The latter factor enables the fluorescence of crystals of the prepared BODIPY, a feature that was not previously documented for such molecules.

1. Introduction

For more than 30 years since their discovery[1] BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) derivatives have enjoyed wide popularity among experts in chemistry,[2] physics,[3] biology[4] and related fields[5] for their exceptional optical properties.

During the practical realization of various devices based on BODIPY dyes, when high concentrations are needed, intermolecular π-stacking can cancel out their advantages such as high fluorescence quantum yields and intensities.[6] To the best of our knowledge, so far, no fluorescent crystals of BODIPY have been reported, although the pigments (solid dyes) based on them, due to their anticipated high brightness and enhanced resistance to photobleaching, might find extensive application. Therefore, the design of new boradiazaindacenes with hindered π-stacking, which is considered as the principal culprit behind the loss of fluorescence in crystalline form, has remained a challenge.

Herein, we describe a synthesis of the first representatives of boradiazaindacenes, which are fluorescent in a crystalline form. The main idea was to develop an approach to structures with bulky mesityl substituents attached to the BODIPY core, distorting overall planarity and thus hampering the π-stacking at high concentrations. Furthermore, the hindered internal rotation of mesityl rings reduces non-radiative relaxation of excited states, hence decreasing fluorescence quantum yields.[7]

2. Results and discussion

As a synthetic target 4,4-difluoro-2,6-dimethyl-3,5,8-trimesityl-4-bora-3a,4a-diaza-*s*-indacene **1** was chosen because its 2,6-methyl groups could additionally hinder internal rotation and force benzene rings out of the molecular plane more efficiently.

The disconnection of **1** (reverse to the synthesis of BODIPY via the reaction of boron trifluoride etherate with dipyrromethenes derived from pyrroles and aldehydes[8]) leads to dipyrromethene **2** and then to 2-mesityl-3-methylpyrrole **3** and 2,4,6-trimethylbenzaldehyde **4** (Scheme 1).

Keywords: 2-Mesitylpyrroles; Oximes; Acetylene; Superbases; BODIPY; Hindered internal rotation; Fluorophores; π-Stacking.
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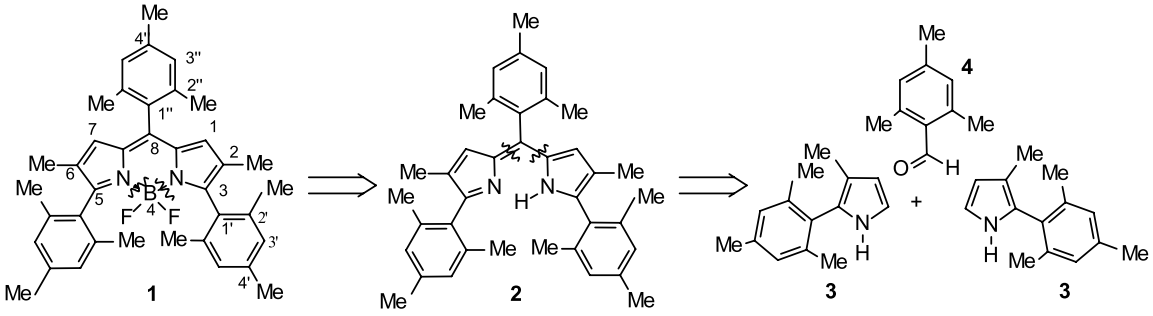
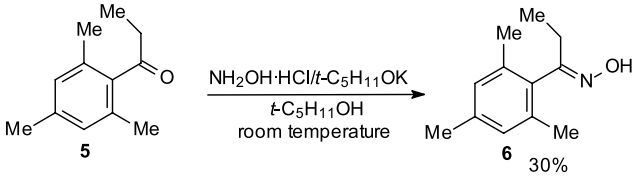


Scheme 1.

To accomplish this synthetic sequence, we had to develop an approach to pyrrole **3**. The Trofimov reaction (reaction of ketoximes with acetylene in superbasic media affording pyrroles and *N*-vinyl pyrroles)[9,10] might be useful for approaching **3** from ethylmesitylketoxime **6**. However, until the present work there were no examples of a successful application of this reaction to highly hindered ketoximes and this exploration could shed light on whether such ketoximes are capable of affording pyrroles upon reaction with acetylene.

Meanwhile, at the very beginning of the study we encountered a serious problem of very low reactivity of ethylmesitylketone **5** towards hydroxylamine. Oximation by refluxing mixtures of ketones and hydroxylamine hydrochloride in pyridine, effective in the synthesis of some hindered oximes,[11] proved to be inefficient in the case of **5** (even when microwave activation was applied) and yielded only trace amounts of **6**. The 'lethargic' oximation, although it gave mesitylmethylketoxime from mesitylmethylketone in 98% yield in 28 days,[12] after application to **5** afforded its oxime **6** (mostly *E*-isomer) only in 30% yield after 8 months (Scheme 2).



Scheme 2.

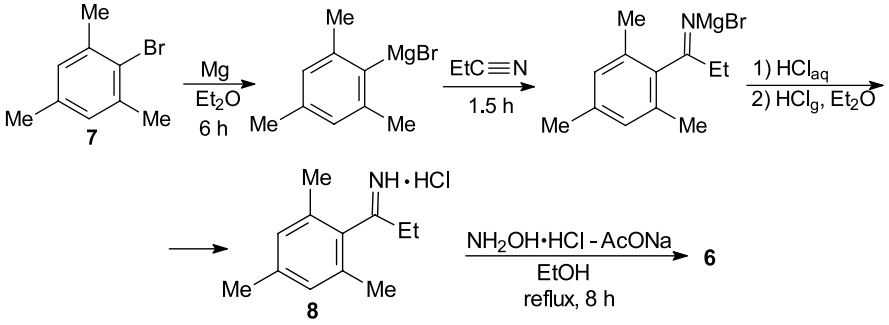
It is obvious that the mesityl group blocks the carbonyl carbon in ketone **5**, and the blockage becomes much more pronounced on passing from mesitylmethylketone to ethylmesitylketone **5**.

To develop a better access to the ketoxime **6** we, therefore, attempted the oximation of ethylmesitylimine hydrochloride **8** similar to that used previously for the synthesis of some other mesityl oximes.[13] This procedure, though multistep, allowed us to approach **6** from bromomesitylene **7** in 39% yield in a matter of 2 days (Scheme 3).

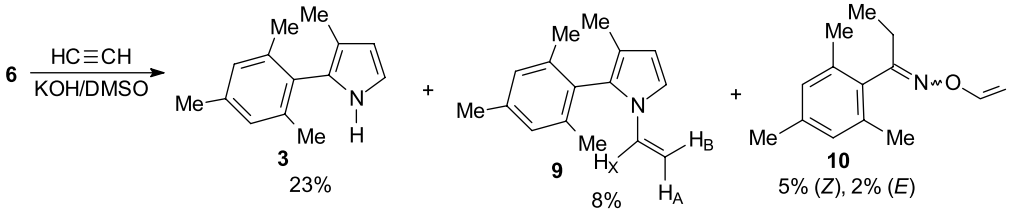
The reaction of the *E*-isomer of oxime **6** with acetylene in the KOH/DMSO superbasic system (70–74 °C, 3 h, atmospheric pressure) gave 2-mesityl-3-methylpyrrole **3** (23%), 2-mesityl-3-methyl-1-vinylpyrrole **9** (8%), *Z*- (5%) and *E*- (2%) isomers of *O*-vinylethylmesitylketoxime **10** (Scheme 4).

A short contact (70 °C, 5 min) of the *E*-isomer of **6** with acetylene in the KOH/DMSO system under increased acetylene pressure (initial pressure 17 atm) led to *O*-vinylketoxime **10** (23%) (*E*–*Z*∼1:2) and pyrrole **3** (12%) (^{1}H NMR).

Interestingly, the *E*-isomer of oxime **6** was transformed mainly to the *Z*-isomer of *O*-vinylketoxime **10**. This is a striking contrast to, for example, methylphenylketoxime, which under similar conditions gave only the *E*-isomer of *O*-vinylmethylphenylketoxime.[14] Heating of the *E*-isomer of the oxime **6** at 80 °C for 1 h in KOH/DMSO system resulted in the formation of 1:1 mixture of its *E*- and *Z*-isomers. Thus, the *E*–*Z* isomerization of **6** occurs under the reaction conditions, and steric hindrances imparted on the oxime hydroxyl by both mesityl and ethyl groups in **6** are similar. The specific behaviour of the oxime **6** can be rationalized assuming twisting of mesityl ring out of the C–C=N–O plane. When twisted, it strongly hinders the C=N (C=O) carbon (as evident from the difficulty of oximation of mesityl ketones) and, on the other hand, makes



Scheme 3.



Scheme 4.

easier the approach of acetylene to the oximate anionic centre generated under superbasic conditions.

The twisted mesityl group might also pre-organize acetylene via either π-stacking or π-hydrogen bonding (Fig. 1),[15] thus making formation of *Z*-isomer of *O*-vinylketoxime **10** entropicaly more favourable.

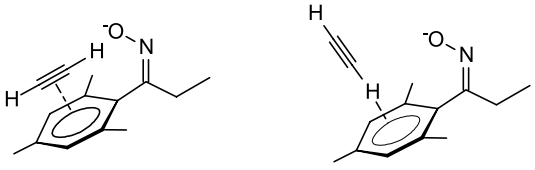


Figure 1.

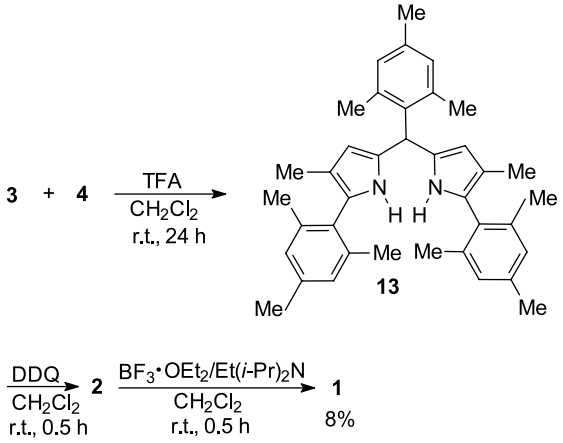
Heating of a DMSO-d_6 solution of *O*-vinylketoxime **10** at 120 °C (5 min) leads to its rearrangement to the pyrrole **3** (yield ~50%, ^{1}H NMR) in the absence of a base, similar to the rearrangement of 5-(1-vinyloxyiminoethyl)[2,2]paracyclophane to the appropriate pyrrole.[16]

The isolation of the *O*-vinylketoxime **10** from the reaction mixture is remarkable because so far only *O*-vinyl (3-indolyl)ketoximes with an α-methylene group (different from that constituting methyl) have been known to be stable under the reaction conditions.[17] Presumably, the stability of the *O*-vinylketoximes with α-methylene group is due to either increased electron donation of R^1 substituent (e.g., 3-indolyl) or a steric effect inhibiting the [1,3] hydrogen shift (Scheme 5) assumed as a key step of the transformation of *O*-vinylketoximes to pyrroles.[10]

Thus, the twisted mesityl group, due to its size, may interfere with the [1,3] hydrogen shift in **10** leading to *O*-vinylhydroxylamine **11** (R^1=Mes, R^2=Me), as well as [3,3]-sigmatropic rearrangement of the latter to iminoaldehyde **12** by impeding redistribution of electron density during the rearrangement.

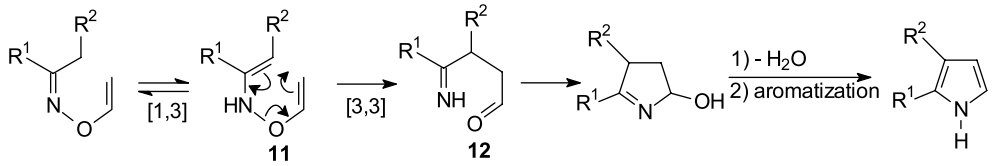
The distinction between the *E*- and *Z*-isomers of oxime **6** and *O*-vinyloxime **10** was made based on the difference in ^{1}H NMR shifts of their methylene protons due to the anisotropic influence of the oxime oxygen.[18] These protons in their *E*-isomers (*syn* disposition to oxime oxygen) are shifted downfield (2.65 and 2.70 ppm for oxime and *O*-vinyloxime, respectively) relative to their *Z*-isomers (2.42 and 2.46 for oxime and *O*-vinyloxime, respectively). As compared to other *N*-vinylpyrroles, the resonance of H_X proton in **9** residing in the shielding cone of the twisted mesityl aromatic ring is shifted considerably upfield (6.27 ppm).

Pyrrole **3** was introduced into the reaction with 2,4,6-trimethylbenzaldehyde **4** catalysed by trifluoroacetic acid (TFA). Generated dipyrromethane **13** was further oxidized in situ with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to dipyrromethene **2**. The reaction of **2** with boron trifluoride etherate in the presence of diisopropylethylamine afforded the target BODIPY **1** in 8% yield.



Interestingly, the bulky mesityl substituent in aldehyde **4** did not block its reaction with pyrrole **3**, although the reaction actually involves attack of secondary 2-pyrrolic nucleophile at the hindered carbonyl carbon in **4**.

The optical absorption of the BODIPY **1**, dissolved in spectrometric grade dichloromethane (DCM), had the S_0–S_1 transition maximum at 543 nm with an extinction coefficient 40,150 $LM^{-1}\,cm^{-1}$. The emission maximum was observed at 559 nm with a fluorescence quantum yield 95% (Rhodamine in ethanol was used as a reference). The fluorescence lifetime was 8.5 ns, which is longer than any



Scheme 5.

reported lifetime for such molecules. Submicrometric crystals of **1** obtained after evaporation of DCM exhibited fluorescence with lifetime of 1.5 ns that is in striking contrast to previously known boradiazaindacenes for which fluorescence in crystals had not been reported. The use of 1,2-dichlorobenzene as a solvent gave slower evaporation and smaller crystallized fluorescent particles with longer lifetimes (3–4 ns). The detailed description of the study of the fluorescent properties of the synthesized BODIPY **1** will be described elsewhere.

3. Conclusion

An approach to a new BODIPY with bulky mesityl substituents preventing the molecule from π-stacking at high concentrations and possessing hindered internal rotation decreasing non-radiative relaxation of excited states was developed. The precursor of the boradiazaindacene **1**, 2-mesityl-3-methylpyrrole **3**, was prepared via the Trofimov reaction. It was demonstrated that the mesityl group imposes less steric hindrance on the nucleophilic addition of ethylmesitylketoxime to acetylene than phenyl group. However, the presence of mesityl in *O*-vinylethylmesitylketoxime inhibits its rearrangement to appropriate pyrrole. This was not the case for most known *O*-vinylketoximes with α-methylene groups.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (400.13 and 100.61 MHz, respectively) and a Bruker ultrashield 300 AC (300.1 and 75.4 MHz, respectively) instruments in $CDCl_3$ using HMDS as an internal standard. IR spectra were recorded on a Bruker IFS 25 instrument. Absorption spectra were obtained using a UV–vis Varian CARY 500 spectrophotometer. Steady-state excitation and emission spectra were measured on a SPEX Fluorolog-3 (Jobin-Yvon). A right-angle configuration was used. Optical density of the samples was less than 0.1 to avoid reabsorption artefacts. The fluorescence decay curves were obtained with a time-correlated single-photon-counting method using a titanium-sapphire laser pumped by an argon ion laser. The Levenberg–Marquardt algorithm was used for non-linear least squares fits.

4.1.1. Ethylmesitylketone (5). The ketone **5** was prepared in 84% yield according to the procedure.[19] Transparent colourless liquid; bp 116–121 °C (5 mm); $n_D^{22}=1.5093$; ^{1}H NMR δ (ppm) 6.80 (s, 2H, H_m), 2.67 (q, 2H, $^3J_{H1H2(Et)}=7.4$ Hz, CH_2Me), 2.25 (s, 3H, Me_p), 2.15 (s, 6H, Me_o), 1.17 (t, 3H, CH_2Me); ^{13}C NMR δ (ppm) 211.4 (C=O), 140.0 (C_i), 138.2 (C_o), 132.5 (C_p), 128.5 (C_m), 38.0 (*C*H_2Me), 21.1 (Me_p), 19.1 (Me_o), 7.7 (CH_2Me); IR (cm^{-1}, film) 2975, 2936, 2878, 2735, 1700, 1611, 1575, 1457, 1413, 1378, 1342, 1297, 1265, 1224, 1156, 1077, 1036, 1014, 961, 930, 851, 801, 740, 723, 592.

4.1.2. Ethylmesitylketimine hydrochloride (8). This protocol represents a modified method.[13] To a stirred solution of mesityl magnesium bromide prepared from magnesium turnings (5.00 g, 205.8 mmol) and bromomesitylene **7** (30.00 g, 150.7 mmol),[20] a mixture of propionitrile (8.25 g, 149.8 mmol) and diethyl ether (10 mL) was added over 30 min and the obtained white suspension was additionally stirred for 1 h at room temperature. After that a 13% solution of hydrochloric acid (100 mL) was added for 1 h to the stirred reaction mixture cooled in a water bath with subsequent stirring for 1 h. The acid was neutralized with a solution of NaOH (14.00 g, 350.1 mmol) in water (30 mL), and from the resultant mixture ethylmesitylketone imine was extracted with diethyl ether (5×40 mL). The combined extracts were dried over K_2CO_3 and evaporated to the volume of 70 mL. Dry hydrogen chloride was passed through the etheral solution to precipitate the ketimine hydrochloride **8** which was collected by filtration and dried. As a result, **8** (15.01 g, 47%) was obtained as a yellowish solid; mp 194–196 °C; ^{1}H NMR δ (ppm) 13.73 (broad s, 1H, NH_E), 13.36 (broad s, 1H, NH_Z), 6.90 (s, 2H, H_m), 3.09 (q, 2H, $^3J_{H1H2(Et)}=7.6$ Hz, CH_2Me), 2.27 (s, 9H, Me_o, Me_p), 1.32 (t, 3H, $^3J_{H1H2(Et)}=7.6$ Hz, CH_2Me); ^{13}C NMR δ (ppm) 196.3 (C=N), 141.3 (C_i), 133.7 (C_o, C_p), 129.4 (C_m), 32.6 (*C*H_2Me), 21.2 (Me_p), 19.9 (Me_o), 10.4 (*C*H_2Me); IR (cm^{-1}, KBr) 3372, 3250-2250, 2017, 1687, 1611, 1556, 1456, 1382, 1297, 1187, 1120, 1020, 909, 854, 717.

4.1.3. Ethylmesitylketoxime (6). This procedure represents a modified protocol.[13] A mixture of **8** (10.00 g, 47.2 mmol), $NH_2OH\cdot HCl$ (6.56 g, 94.5 mmol), CH_3COONa (9.68 g, 118.0 mmol) and 96% ethanol (160 mL) was refluxed for 8 h. After cooling, K_2CO_3 (10.00 g, 72.4 mmol) and water (5 mL) were added to the solution with subsequent stirring for 1 h to neutralize nascent acetic acid. Then diethyl ether (200 mL) was added; the precipitate was filtered off and washed with diethyl ether. The organic solutions were combined and evaporated to dryness in vacuo to give viscous amber coloured liquid (7.37 g, 82%) consisting of the *E*- and *Z*-isomers of ethylmesitylketoxime **6** (*E*–*Z*∼3:1) (^{1}H NMR) and crystallizing in several hours. The *E*-isomer of **6** was isolated by column chromatography (basic Al_2O_3, petroleum ether–diethyl ether).

4.1.4. *E*-isomer of 6. White crystals, mp 80–82 °C; ^{1}H NMR δ (ppm) 9.0 (broad s, 1H, OH), 6.83 (s, 2H, H_m), 2.65 (q, 2H, $^3J_{H1H2(Et)}=7.6$ Hz, CH_2Me), 2.26 (s, 3H, Me_p), 2.18 (s, 6H, Me_o), 0.93 (t, 3H, $^3J_{H1H2(Et)}=7.6$ Hz, CH_2Me); ^{13}C NMR δ (ppm) 162.0 (C=N), 137.6 (C_i), 136.2 (C_o), 132.8 (C_p), 128.3 (C_m), 22.8 (*C*H_2Me), 21.1 (Me_p), 19.8 (Me_o), 9.7 (CH_2Me); IR (cm^{-1}, KBr) 3240, 2968, 2920, 1649, 1612, 1574, 1488, 1458, 1374, 1321, 1302, 1283, 1171, 1071, 1038, 972, 955, 892, 851, 764, 744, 726, 668, 592, 579.

4.1.5. *Z*-isomer of 6. White crystals. ^{1}H NMR δ (ppm) 8.7 (broad s, 1H, OH), 6.86 (s, 2H, H_m), 2.43 (q, 2H, $^3J_{H1H2(Et)}=7.3$ Hz, CH_2Me), 2.26 (s, 3H, Me_p), 2.15 (s, 6H, Me_o), 1.15 (t, 3H, CH_2Me); ^{13}C NMR δ (ppm) 160.3 (C=N), 137.8 (C_i), 134.1 (C_o), 132.1 (C_p), 128.2 (C_m), 28.6 (*C*H_2Me), 21.1 (Me_p), 19.5 (Me_o), 10.3 (CH_2Me)

The 'lethargic' oximation of **5** was carried out similarly to mesitylmethylketone.[12] However, 8 months were required

for the reaction to afford the oxime **6** (mainly *E*-isomer) in only 30% preparative yield.

4.2. 2-Mesityl-3-methylpyrrole (3), 2-mesityl-3-methyl-1-vinylpyrrole (9) and *O*-vinylethylmesitylketoxime (10)

A mixture of ethylmesitylketoxime **6** (1.00 g, 5.2 mmol), fine-powdered $KOH \cdot 0.5H_2O$ (0.34 g, 5.2 mmol) and DMSO (15 mL) was stirred under acetylene atmosphere at 70–74 °C for 3 h. After cooling to room temperature the mixture was diluted with water (10 mL) and extracted with diethyl ether (4×10 mL). The ether extracts were washed with water (4×5 mL) and dried over anhydrous K_2CO_3. The residue obtained after distilling off the solvent was chromatographed on column (basic Al_2O_3, petroleum ether–diethyl ether) to yield 2-mesityl-3-methylpyrrole **3** (23%), 2-mesityl-3-methyl-1-vinylpyrrole **9** (8%), *Z*- (5%) and *E*-(2%) isomers of **10**.

The reaction of oxime **6** with acetylene under high pressure was carried out as follows: ethylmesitylketoxime **6** (0.50 g, 2.6 mmol), $KOH \cdot 0.5H_2O$ (0.34 g, 5.2 mmol) and DMSO (20 mL) were charged in a 250-mL steel rotating autoclave, saturated with acetylene at room temperature (initial acetylene pressure 17 atm), heated to 70 °C and kept at this temperature for 5 min. After cooling and discharge, the reaction mixture was diluted with 40 mL of water and extracted with diethyl ether (5×10 mL). The extracts were washed with water (4×5 mL) and dried over K_2CO_3. After evaporation of the ether, a red liquid (0.50 g) containing (^{1}H NMR) pyrrole **3** (12%) and *O*-vinylketoxime **10** (*E*–*Z*∼1:2) (23%) was obtained.

4.2.1. Compound 3. White crystals, mp 74–76 °C; ^{1}H NMR δ (ppm) 7.65 (broad s, 1H, NH), 6.91 (s, 2H, H_m), 6.73 (t, 1H, J_{H1H4H5}=2.7 Hz, H_5), 6.12 (t, 1H, J_{H1H4H5}=2.7 Hz, H_4), 2.30 (s, 3H, Me_p), 2.03 (s, 6H, Me_o), 1.86 (s, 3H, Me_{Pyr}); ^{13}C NMR δ (ppm) 139.2 (C_p), 137.7 (C_o), 130.1 (C_i), 127.9 (C_m), 126.8 (C_2), 116.2 (C_3), 115.9 (C_5), 109.8 (C_4), 21.1 (Me_p), 20.1 (Me_o), 11.2 (Me_{Pyr}); IR (cm^{-1}, KBr) 3423, 2917, 2868, 1640, 1610, 1582, 1569, 1539, 1509, 1488, 1467, 1452, 1375, 1278, 1249, 1157, 1099, 1081, 1063, 1052, 1000, 897, 852, 821, 745, 719, 689, 631, 570, 554, 531, 494; EIMS: *m*/*z* calculated for $C_{14}H_{17}N$: 199.3, found: 199 (M^+).

4.2.2. Compound 9. A transparent colourless liquid, n_D^{19}=1.6815; ^{1}H NMR δ (ppm) 7.02 (d, 1H, $^3J_{H4H5}$=3.0 Hz, H_5), 6.91 (s, 2H, H_m), 6.27 (dd, 1H, H_X, $^3J_{AX}$=9.0 Hz, $^3J_{BX}$=15.8 Hz), 6.15 (d, 1H, $^3J_{H4H5}$=3.0 Hz, H_4), 4.90 (d, 1H, $^3J_{BX}$=15.8 Hz, H_B), 4.33 (d, 1H, $^3J_{AX}$=9.0 Hz, H_A), 2.31 (s, 3H, Me_p), 1.95 (s, 6H, Me_o), 1.79 (s, 3H, Me_{Pyr}); ^{13}C NMR δ (ppm) 139.7 (C_p), 138.1 (C_o), 131.2 (C_α), 128.9 (C_i), 128.1 (C_2), 127.9 (C_m), 117.4 (C_5), 115.0 (C_3), 111.5 (C_4), 95.2 (C_β), 22.8 (Me_p), 21.2 (Me_o), 14.2 (Me_{Pyr}); IR (cm^{-1}, film) 2922, 2856, 1640, 1613, 1582, 1491, 1472, 1419, 1388, 1370, 1305, 1229, 1201, 1160, 1073, 1034, 1015, 989, 966, 851, 761, 723, 693, 677, 593. EIMS: *m*/*z* calculated for $C_{16}H_{19}N$: 225.3, found: 225 (M^+).

4.2.3. *Z*-isomer of 10. A transparent colourless liquid, n_D^{19}=1.5218; ^{1}H NMR δ (ppm) 6.86 (s, 2H, H_m), 6.80 (dd, 1H, $^3J_{AX}$=6.7 Hz, $^3J_{BX}$=14.1 Hz, H_X), 4.52 (dd, 1H, $^3J_{BX}$=14.1 Hz, $^2J_{AB}$=1.3 Hz, H_B), 4.01 (dd, 1H, $^3J_{AX}$=6.7 Hz, $^2J_{AB}$=1.3 Hz, H_A), 2.46 (q, 2H, $^3J_{H1H2(Et)}$=7.5 Hz, C*H*$_2$Me), 2.27 (s, 3H, Me_p), 2.13 (s, 6H, Me_o), 1.15 (t, 3H, $^3J_{H1H2(Et)}$=7.5 Hz, CH$_2$*Me*); ^{13}C NMR δ (ppm) 163.0 (C=N), 152.5 (C_α), 137.7 (C_p), 133.7 (C_o), 132.4 (C_i), 128.1 (C_m), 87.5 (C_β), 28.8 (CH_2), 21.1 (Me_p), 19.5 (Me_o), 10.4 (CH$_2$*Me*); IR (cm^{-1}, film) 2975, 2922, 1643, 1620, 1576, 1459, 1380, 1306, 1187, 1152, 1088, 1055, 981, 949, 933, 873, 850, 833, 693, 604. Anal. calcd for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45; found: C 77.51, H 8.92, N 6.80.

4.2.4. *E*-isomer of 10. A transparent colourless liquid; ^{1}H NMR δ (ppm) 6.98 (dd, 1H, $^3J_{AX}$=6.8 Hz, $^3J_{BX}$=14.2 Hz, H_X), 6.86 (s, 2H, H_m), 4.58 (dd, 1H, $^3J_{BX}$=14.2 Hz, $^2J_{AB}$=1.4 Hz, H_B), 4.09 (dd, 1H, $^3J_{AX}$=6.8 Hz, $^2J_{AB}$=1.4 Hz, H_A), 2.70 (q, 2H, $^3J_{H1H2(Et)}$=7.6 Hz, C*H*$_2$Me), 2.26 (s, 3H, Me_p), 2.20 (s, 6H, Me_o), 0.96 (s, 3H, CH$_2$*Me*); ^{13}C NMR δ (ppm) 164.6 (C=N), 153.1 (C_α), 138.1 (C_p), 136.0 (C_o), 132.0 (C_i), 128.5 (C_m), 87.4 (C_β), 24.1 (*C*H$_2$Me), 21.1 (Me_p), 19.9 (Me_o), 9.9 (CH$_2$*Me*).

4.3. Thermal *E*–*Z* isomerisation of ethylmesitylketoxime (6)

A mixture of *E*-isomer of **6** (0.05 g, 0.3 mmol), fine-powdered $KOH \cdot 0.5H_2O$ (0.05 g, 0.8 mmol) and DMSO (5 mL) was stirred at 80 °C for 1 h. After cooling, the mixture was neutralized with dry ice, diluted with water (5 mL) and extracted with diethyl ether (3×10 mL). The ether extracts were washed with water (3×3 mL) and dried over K_2CO_3. After evaporation of the ether, a viscous mass (0.04 g) consisting of *E*- and *Z*-isomers of **6** (*E*:*Z*∼1:1) (^{1}H NMR) was obtained.

4.4. Thermal rearrangement of *Z*-isomer of *O*-vinylethylmesitylketoxime (10) into 2-mesityl-3-methylpyrrole (3)

An NMR ampule containing a solution of *Z*-isomer of **10** (∼0.05 g) in DMSO-d_6 (0.5 mL) was heated in the NMR spectrometer at 120 °C for 10 min and kept at this temperature until disappearance of the signals of the vinyl group of **10** (5 min). During the heating the intensity of the *O*-vinyl group signals decreased with a simultaneous increase in the intensity of the signals of pyrrole **3**. In addition to signals of **3** (yield ∼50%, ^{1}H NMR) heating gave rise to unidentified singlets at 9.72 and 7.06 ppm with half intensities of the pyrrole ring protons in **3** and singlet at 2.44 ppm with the threefold intensity of the latter.

4.4.1. 4,4-Difluoro-2,6-dimethyl-3,5,8-trimesityl-4-bora-3a,4a-diaza-*s*-indacene (1). Pyrrole **3** (0.35 g, 1.8 mmol) and 2,4,6-trimethylbenzaldehyde **4** (0.13 g, 0.9 mmol) were dissolved in degassed CH_2Cl_2 (50 mL), then two drops of TFA were added, and the obtained orange solution was stirred for 24 h under argon at room temperature. TLC analysis (SiO_2 on aluminium plates, CH_2Cl_2–petroleum ether=1:1) of the reaction mixture showed the presence of initial pyrrole **3**, so an additional 0.025 g of aldehyde **4** and two drops of TFA were added and stirring was continued for some time until TLC showed no stain of pyrrole **3**. Then DDQ (0.19 g, 0.8 mmol) was added and the reaction mixture was stirred for 0.5 h. After that, diisopropylethylamine

(2 mL, 1.48 g, 11.5 mmol) and boron trifluoride etherate (2 mL, 2.24 g, 15.8 mmol) were added with subsequent stirring of the obtained fluorescent solution for 0.5 h. After evaporation of the solvent at ambient temperature in vacuo the residue (was flash chromatographed under nitrogen on silica (CH_2Cl_2–petroleum ether = 1:3) to afford 0.04 g (8%) of BODIPY **1**. A red powder, it does not melt but decomposes above 280–300 °C; ^{1}H NMR δ (ppm) 7.00 (s, 2H, $H_{3''}$), 6.84 (s, 4H, $H_{3'}$), 6.42 (s, 2H, $H_{1,7}$), 2.40 (s, 3H, $Me_{4''}$), 2.26 (s, 6H, $Me_{2''}$ or $Me_{4'}$), 2.24 (s, 6H, $Me_{4'}$ or $Me_{2''}$), 2.06 (s, 12H, $Me_{2'}$), 1.65 (s, 6H, $Me_{2,6}$); ^{13}C NMR δ (ppm) 157.8, 141.6, 138.3, 137.4 (CH_{arom}), 136.8, 134.2, 131.1, 129.0, 128.5, 128.1 (CH_{arom}), 127.8 (CH_{arom}), 127.0, 29.8 ($Me_{4''}$), 21.4 ($Me_{4'}$), 20.1 ($Me_{2'}$ or $Me_{2''}$), 20.0 ($Me_{2''}$ or $Me_{2'}$), 11.0 ($Me_{2,6}$). EIMS: *m/z* calculated for $C_{38}H_{41}BF_2N_2$: 574.6, found: 526 $[M-BF_2]^+$.

Acknowledgements

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Synthetic applications of aryl radical building blocks for cyclisation onto azoles

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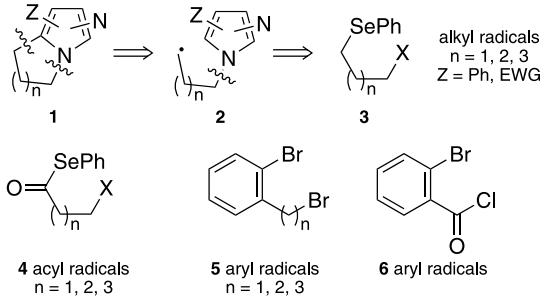
Abstract—2-(2-Bromophenyl)ethyl groups have been used as building blocks in radical cyclisation reactions onto azoles to synthesise tri- and tetra-cyclic heterocycles. 2-(2-Bromophenyl)ethyl methanesulfonate was used to alkylate azoles (imidazoles, pyrroles, indoles and pyrazoles) for the synthesis of the radical precursors. Cyclisations of the intermediate aryl radicals yield new 6-membered rings attached to the azoles. The aryl radicals undergo intramolecular homolytic aromatic substitution onto the azole rings. Tributylgermanium hydride has been used with success to replace the toxic and troublesome tributyltin hydride. Initial studies show that the protocol can be used on solid phase resins. The molecular and crystal structures of methyl 5,6-dihydroimidazo[5,1-*a*]iso-quinoline-1-carboxylate and methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate were determined by X-ray crystallography.

1. Introduction

The use of radical cyclisations for the synthesis of heterocyclic compounds has become commonplace.[1] One of the advances, that has proved most useful, is the cyclisation of radicals onto heteroarenes to yield bi- and tri-cyclic heterocycles. In these reactions, which are mediated by Bu_3SnH and related hydrides, the heteroarene undergoes rearomatisation in the radical cyclisation. With the use of *NH*-heteroarenes, *N*-alkylation provides a facile route for the addition of 'radical' building blocks. These units can then be used for cyclisation onto a range of different *NH*-heteroarenes and also in other radical cyclisations.

Our earlier studies have reported the application of *N*-(ω-phenylselanyl)alkyl **3** and *N*-(ω-bromo)alkyl building blocks for the cyclisation of *N*-(ω-alkyl)-radicals onto pyrroles,[2] imidazoles[2] and pyrazoles[3] with electron withdrawing groups or radical stabilising groups such as phenyl. The protocol is illustrated in Scheme 1; a bicyclic heterocycle (**1**) is synthesised via cyclisation of an intermediate alkyl radical (**2**). The moiety (**3**) is added by *N*-alkylation. Similar methodologies using alkyl radicals have been used in the cyclisation onto other heteroarenes which include indoles[4,5,6] pyrroles,[4] pyridinium salts,[7] 1,2,3-triazoles,[8] and quinolones.[9] More recently, we have shown that acyl radical building blocks (**4**) can be used for cyclisation onto electron deficient pyrroles (pyrroles with electron withdrawing groups).[10]



Scheme 1. Radical building blocks.

The analogous use of these protocols to yield intermediate aryl radicals instead of alkyl radicals can also be envisaged. In this paper we report our studies of the development of the use of components derived from 2-(2-bromophenyl)ethyl groups (Scheme 2, e.g. (**8**)). The cyclisation of the intermediate aryl radicals (**9**) yield new 6-membered rings attached to the azoles (**11**). One of the aims of our study was to develop building blocks to facilitate diversity for use in

Keywords: Aryl radicals; Radical cyclisation; Building blocks; Azoles; Heterocycles.
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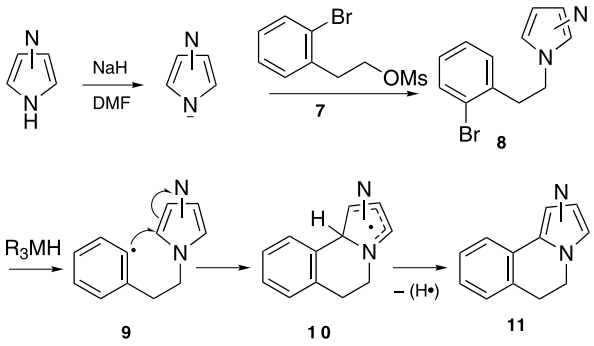


Scheme 2. General protocol for use of 2-(2-bromophenyl)ethyl building blocks for the synthesis of tricyclic heterocycles.

solid phase synthesis and combinatorial chemistry. We also report our further studies of the use of tributylgermanium hydride (Bu_3GeH) as the radical generating reagent in place of the toxic and troublesome tributyltin hydride (Bu_3SnH).[11] Bu_3GeH has a number of advantages over Bu_3SnH which include lower toxicity, better shelf life, ease of work-up and slower rates of H-abstraction by intermediate radicals which helps to facilitate cyclisation over reduction.

Building blocks which yield intermediate aryl radicals for cyclisation onto heteroarenes and other functional groups have been reported. For example, aryl radicals generated from precursors synthesised from 2-bromobenzoyl chloride (**6**) have been used in a number of reactions.[12] The most commonly used aryl radical entity has been pendant *N*-(2-bromophenyl)methyl moieties synthesised using (2-bromo-phenyl)methyl bromide (**5**), $n=1$. Examples of cyclisation using this unit include cyclisation onto indoles,[13,14] pyrroles,[4] pyridones[15] and 5-amino- and 5-hydroxyuracils.[16]

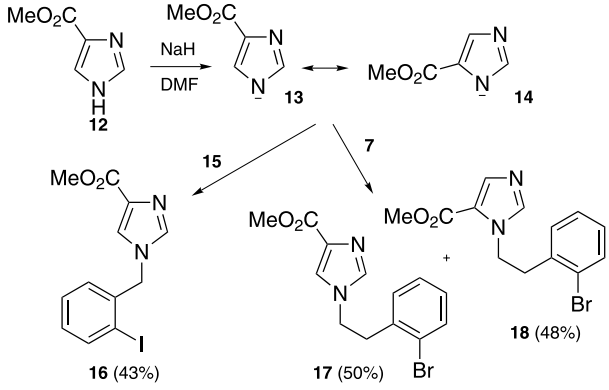
The analogous 2-(2-bromophenyl)ethyl components, which generate new six-membered rings by cyclisation of aryl radicals, have been less commonly used. These units have been attached by *N*-alkylation with 2-(2-bromophenyl)ethyl bromide (**5**), $n=2$. Cyclisation onto indoles,[13] pyridones[15] and 2-quinolones[17] has given high yields. In contrast, the 5-membered ring cyclisations of aryl radicals onto azoles have proven less successful. Cyclisation onto 5-membered ring azoles is less favoured due to the strain of formation of products with two 5-membered rings, one of which is a heteroarene.[2] In our studies on the alkyl radical cyclisation onto imidazoles, 6-membered ring cyclisation gave better yields than 5-membered ring cyclisation, in which reduced uncyclised products were also obtained. We showed using X-ray crystallography that the structure of 6,7-dihydro-5*H*-pyrrolo-[1,2-*c*]imidazole-1-carb-aldehyde is completely planar indicating considerable strain in the new five-membered ring.[2]

Cyclisation onto heteroarenes of aryl radicals generated from pendant 2-(2-bromophenyl)ethyl moieties, attached at atoms other than the nitrogen, have also been reported. Good yields have been reported for cyclisations onto indoles,[13] quinolines[18] and pyridines[19] showing that the 6-membered ring cyclisation is particularly favourable.

2. Discussion

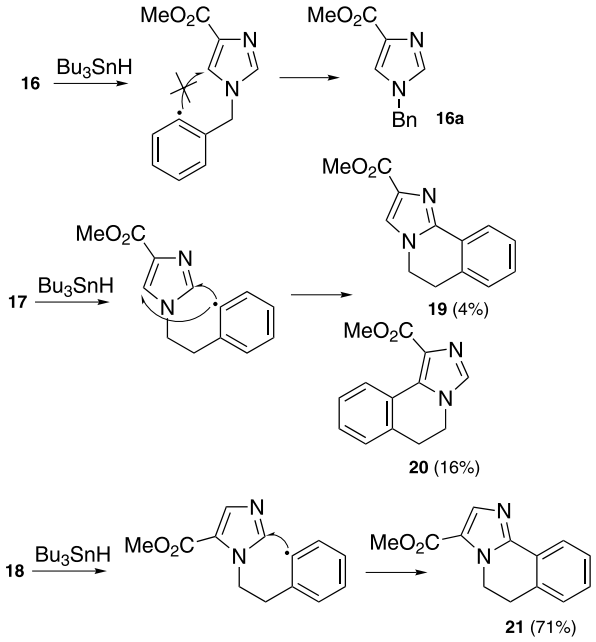
We chose four different representative azole esters for testing the 'building block' protocol. The esters were used in each case to provide a handle for solid phase studies and to facilitate lower electron density on the azole rings. Aryl radicals are nucleophilic and therefore lower electron density on the azole rings would help with cyclisation. We have previously shown that electron withdrawing and/or radical stabilising groups improve cyclisation.[2,3]

The alkylations were carried out by standard procedures using sodium hydride (NaH) in DMF to deprotonate the azoles followed by addition of 2-(2-bromophenyl)ethyl methane-sulfonate (**7**) as shown in Scheme 2. In the alkylation using 1*H*-imidazole-4-carboxylic acid methyl ester (**12**) two products are possible due to the ambident nature of the anion (Scheme 3). Alkylation with 1-iodo-2-(iodomethyl)benzene (**15**) gave only the 4-ester product in moderate yield. This regioselectivity was as expected from studies of alkylation of other imidazoles with electron withdrawing groups (e.g. aldehyde and nitro groups) in the 4/5-position.[2] The nitrogen anion furthest from the ester (as represented by the canonical form (**13**)) is more nucleophilic than the nitrogen anion nearest to the ester (as represented by the canonical form (**14**)) and normally facilitates selective alkylation to yield the product with the substituent in the 4-position (Scheme 3). Steric hindrance may also be a factor in the regioselectivity. Surprisingly, alkylation with 2-(2-bromo-phenyl)ethyl methane-sulfonate (**7**) gave both isomers (**17**) and (**18**). In the alkylation of 3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid ethyl ester which could yield two isomers, only the required isomer was obtained.



Scheme 3. Alkylation of 1*H*-imidazole-4-carboxylic acid methyl ester (**12**).

The radical cyclisations using Bu_3SnH were carried using syringe pump addition in order to maximise the chance of cyclisation. Because of the slower H-abstraction from Bu_3GeH, the reagent was added in one portion at the beginning of the reaction.[11] Initially we compared the cyclisation via a 5-membered ring versus cyclisation via a 6-membered ring in the imidazole system (Scheme 4). The radical reaction between methyl 1-[(2-iodophenyl)methyl]-1*H*-imidazol-4-carboxylate (**16**) and Bu_3SnH or Bu_3GeH gave only the reduced uncyclised methyl 1-benzyl-1*H*-imidazole-4-carboxylate. This is surprising for the Bu_3GeH reaction because the rate of H-abstraction from Bu_3GeH is



Scheme 4. Radical cyclisation onto imidazoles.

ca. 20 times slower than for Bu_3SnH and therefore should favour cyclisation over reduction.

In contrast, reaction of 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-4-carboxylate (**17**) gave a mixture of methyl 5,6-dihydro-imidazo[2,1-*a*]isoquinoline-2-carboxylate (**19**)

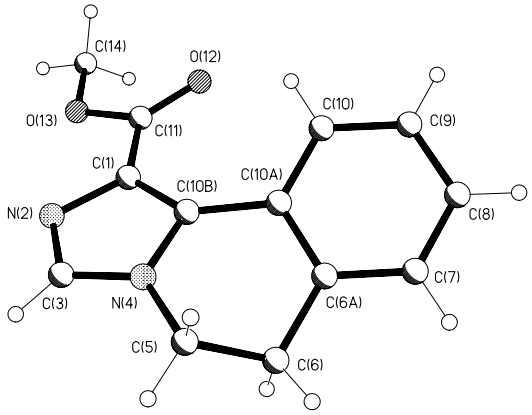


Figure 1. X-ray structure of methyl 5,6-dihydroimidazo[5,1-*a*]isoquinoline-1-carboxylate (**20**) with atom labelling.

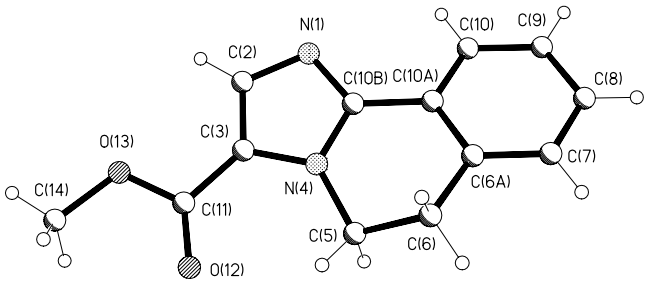


Figure 2. X-ray structure of methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate (**21**) with atom labelling.

(4%) and methyl 5,6-dihydro-imidazo[5,1-*a*]isoquinoline-1-carboxylate (**20**) (16%) with no uncyclised reduced material. These results further illustrate the strain involved in 5-membered ring cyclisation on 5-membered ring azoles. The use of Bu_3GeH and tris-(trimethylsilyl)silane (TTMSS) gave improved yields ((**19**) (19%), (**20**) (38%)] and [(**19**) (30%), (**20**) (30%)), respectively. The latter results illustrate the advantage of both Bu_3GeH and TTMSS over Bu_3SnH in facilitating easier work-up and higher yields. The use of Bu_3GeH along with phenylthiol in a polarity reversal catalysis (PRC)[20] experiment gave only (**20**) in 44% yield. The electrophilic phenylthiyl radical should intercept the nucleophilic aryl radical intermediate at a faster rate than the Bu_3GeH and this may have a bearing on the selectivity.

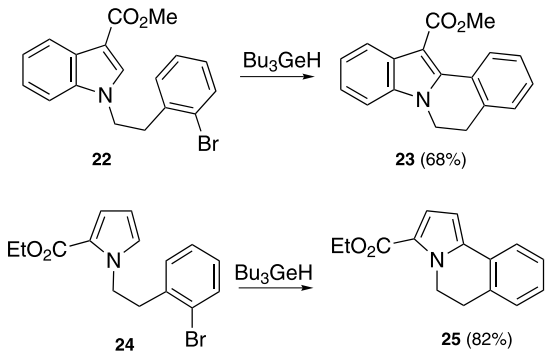
The structures of (**19**) and (**20**) could not be positively distinguished by normal analysis so the structure of (**20**) was confirmed by X-ray crystallography (Fig. 1).

Cyclisation of methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-5-carboxylate (**18**) yielded methyl 5,6-dihydroimidazo-[2,1-*a*]isoquinoline-3-carboxylate (**21**) [Bu_3SnH (71%) and Bu_3GeH (54%)] (Scheme 4). The structure of (**21**) was also confirmed using X-ray crystallography (Fig. 2). The cyclisation of the intermediate aryl radicals derived from (**17**) at both 2-C and 5-C, and from (**18**) at 2-C, is in contrast to the cyclisation of alkyl radicals which only give cyclisation at 5-C.[2] The considerably higher reactivity of aryl radical as compared to alkyl radicals is likely to be the dominant factor in the difference.

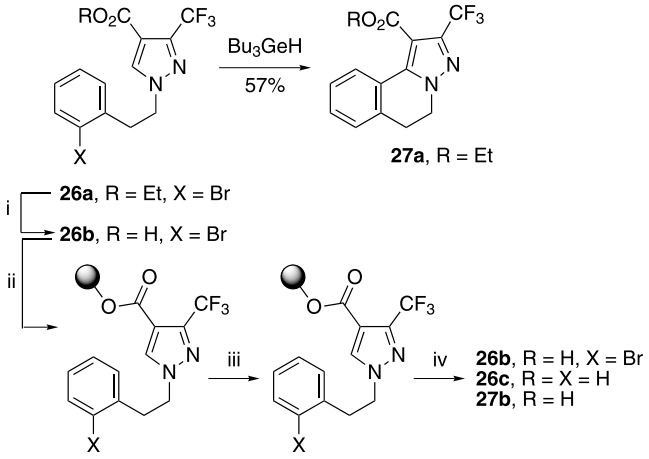
In the radical reactions of the other azoles, the indole (**22**) and the pyrrole (**24**) radical precursors were cyclised in good yields using Bu_3GeH to give methyl 5,6-dihydro-indolo[2,1-*a*]isoquinoline-12-carboxylate (**23**) (68%) and ethyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**25**) (82%), respectively (Scheme 5). The pyrazole precursor (**26a**) was also cyclised in good yield using Bu_3GeH to give ethyl 2-(trifluoromethyl)-5,6-dihydro-pyrazolo-[5,1-*a*]isoquinoline-1-carboxylate (**27a**) with no other products (57%) (Scheme 6).

The overall mechanism of the radical cyclisations is shown in Scheme 2. Formally the mechanisms of these radical reactions are intramolecular aromatic homolytic substitutions, i.e. hydrogen (H·) substituted by the cyclising aryl radicals (**9**) via intermediate aromatic π-radicals (**10**). Related Bu_3SnH and AIBN mediated 'oxidative' cyclisations have also been reported for cyclisations onto arenes by alkyl, vinyl and aryl and heteroaryl radicals. While previous studies have centred on the use of Bu_3SnH as the radical generating reagent, we suggest that similar mechanisms apply for the cyclisations using Bu_3GeH or TTMSS. The mechanism has been an area of debate and we refer readers to our recent publication[21] and a recent review[22] which have extensive discussion. Both publications contain full lists of relevant references.

The pyrazole radical precursor (**26a**) was also used for initial solid phase studies. The ester (**26a**) was hydrolysed to the corresponding carboxylic acid (**26b**) and attached by standard procedures to Wang resin. Cyclisation using standard radical conditions but over a longer time, followed



Scheme 5.



Scheme 6. (i) NaOH, EtOH, reflux, 8 h, 97% (**26b**); (ii) Wang resin (swollen in DCM), DMF, DMAP. DIC, 48 h; (iii) Bu_3GeH or TTMSS, AIBN, toluene, reflux, 30 h; (iv) TFA, DCM (9:1).

by cleavage from the resin with TFA, yielded a mixture of products. The use of Bu_3GeH gave (**27b**) (20%) and unreacted starting acid (**26b**) (70%).

The use of TTMSS gave a better yield of cyclised pyrazole (**27b**) (53%) but also yielded reduced uncyclised (**26c**) (27%). Although the results were disappointing as compared to the solution phase reaction, the results do give further indication that radical chemistry can be used for solid phase synthesis.[23]

3. Experimental

3.1. General

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from $CaCl_2$ and dichloromethane (DCM) was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil and was washed with light petroleum. Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard for ^1H NMR spectra and deuteriochloroform the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and J values in Hertz (Hz). Mass spectra were recorded on a JEOL SX102 mass spectrometer or carried out by the EPSRC Mass Spectrometry Service at University of Wales, Swansea. All mass spectra are electron impact spectra (EI) unless otherwise stated. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F254). Column chromatography was carried out using neutral alumina unless otherwise specified.

Tributylgermanium hydride was prepared using literature procedures.[11,24]

3.1.1. 2-(2-Bromophenyl)ethyl methanesulfonate (7). Methanesulfonyl chloride (0.43 mL, 5.6 mmol) was added to a solution of 2-(bromophenyl)ethyl alcohol (0.5 mL, 3.7 mmol) and triethylamine (1.54 mL, 11.1 mmol) in toluene (30 mL) which was cooled to 0 °C. The reaction mixture was stirred at room temperature for 18 h and then extracted into water and DCM. The DCM layers were combined and dried and evaporated under reduced pressure to afford (**7**) as a pale yellow oil (1.0 g, 3.7 mmol, 99%); ν_{max}(neat) 3057, 3024, 2939, 1594, 1568, 1473, 1442, 1353, 1173, 1038, 1022, 958, 905, 858, 805, 755, 657 cm^{-1}; δ_H 2.88 (3H, s, CH_3), 3.21 (2H, t, $J=6.8$ Hz, CH_2), 4.45 (2H, t, $J=6.8$ Hz, OCH_2), 7.11–7.15 (1H, m, ArH), 7.28–7.29 (2H, m, ArH), 7.55 (1H, d, $J=8.1$ Hz, Ar-3-H); δ_C 35.86 (2-CH_2), 37.2 (CH_3), 68.5 (OCH_2), 124.4 (Ar-2-C), 127.7, 128.9, 131.5 and 132.9 (Ar-3,4,5,6-C), 135.6 (Ar-1-C); *m/z* 278 (M^+, 3), 220 (26), 182 (68), 169 (100), 103 (38), 90 (40), 77 (34%); HRMS: M^+, found: M^+, 277.9611. $C_9H_{11}BrO_3S$ requires 277.9612.

3.1.2. 1-Iodo-2-(iodomethyl)benzene (15). A solution of 1-iodo-2-(chloromethyl)benzene (10.0 g, 39.6 mmol) and sodium iodide (30.0 g, 0.20 mol) in dry acetonitrile (250 mL) was heated under reflux for 18 h. The precipitated sodium chloride was removed by filtration on a Celite® bed and the solution was evaporated under reduced pressure. The residue was triturated with diethyl ether and the solution filtered a second time. The ether solution was evaporated under reduced pressure to afford (**15**) as a dark brown oil (13.48 g, 39.2 mmol, 99%). Found: M^+, 343.8552. $C_7H_6I_2$ requires 343.8559); ν_{max}(neat) 2360, 2342, 1580, 1560, 1464, 1433, 1424, 1273, 1212, 1152, 1012, 827, 757, 644 cm^{-1}; δ_H 4.54 (2H, s, CH_2), 6.92 (1H, dd, $J=7.6$, 7.6 Hz, 5-H), 7.28 (1H, dd, $J=7.6$, 7.6 Hz, 4-H), 7.47 (1H, d, $J=7.6$ Hz, 3-H), 7.80 (1H, d, $J=7.6$ Hz, 6-H); δ_C 12.2 (CH_2), 99.7 (1-C), 129.3, 129.6 and 129.8 (3,4,5-C), 140.23 (6-C), 141.4 (2-C); *m/z* 344 (MH^+, 5), 254 (12), 217 (100), 90 (47%).

3.2. General procedure for alkylation

The azole was added slowly to a suspension of NaH (1.5 equiv) in dry DMF (40 mL). The mixture was stirred and heated at 80 °C for 1 h. A solution of the alkylating

agent (1.5 equiv) in DMF (10 mL) was added drop wise to the reaction mixture which was heated at 80 °C for a further 12 h. The salts were removed by filtration on a Celite® bed and the solution evaporated under reduced pressure to yield the crude product. The crude product was purified by column chromatography using light petroleum/ethyl acetate (1:4) as the eluent.

3.2.1. Methyl 1[(2-iodophenyl)methyl]-1*H*-imidazole-4-carboxylate (16). Colourless oil (43%); ν_{max}(neat)/cm^{-1} 2947, 1718, 1545, 1437, 1380, 1224, 1204, 1119, 1014, 765, 742, 660; δ_H 3.88 (3H, s, CH_3), 5.20 (2H, s, CH_2), 7.02 (1H, dd, J=7.6, 1.2 Hz, Ar-6-H), 7.07 (1H, ddd, J=7.6, 7.6, 1.2 Hz, Ar-4-H), 7.36 (1H, ddd, J=7.6, 7.6, 1.2 Hz, Ar-5-H), 7.59 (1H, s, 2- or 5-H), 7.60 (1H, s, 2- or 5-H), 7.89 (1H, dd, J=7.6, 1.2 Hz, Ar-3-H); δ_C 51.7 (CH_3), 55.86 (CH_2), 98.6 (Ar-2-C), 125.4, 129.1, 129.2 and 130.5 (5-C and Ar-4,5,6-C), 134.1 (4-C), 137.4 (Ar-1-C), 138.4 and 140.2 (2-C and Ar-3-C), 163.2 (C=O); *m/z* 342 (M^+, 27), 311 (12), 284 (13), 217 (100), 183 (46), 121 (15), 90 (43%); HRMS: found: M^+, 341.9860. $C_{12}H_{11}IN_2O_2$ requires 341.9865).

3.2.2. Methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-4-carboxylate (17) and methyl 1-[2-(2-bromophenyl)-ethyl]-1*H*-imidazole-5 carboxylate (18). (**17**), pale yellow oil (50%), ν_{max}(neat) 2948, 1724, 1547, 1472, 1439, 1382, 1225, 1197, 1120, 1029, 997, 757, 660 cm^{-1}; δ_H 3.10 (2H, t, J=7.2 Hz, CH_2), 3.79 (3H, s, OCH_3), 4.16 (2H, t, J=7.2 Hz, NCH_2), 6.88 (1H, dd, J=7.2, 1.6 Hz, Ar-6-H), 7.04 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar-4- or 5-H), 7.11 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar-4- or 5-H), 7.24 (1H, s, 5-H), 7.47–7.50 (2H, m, imidazole 2-H and Ar-3-H); δ_C 37.04 (CH_2), 45.95 (NCH_2), 50.61 (OCH_3), 123.16 (Ar-2-C), 124.11, 126.98, 128.14, 129.97 and 132.18 (5-C and Ar-3,4,5,6-C), 132.84 and 134.93 (4-C and Ar-1-C), 136.89 (imidazole 2-C), 162.19 (C=O); *m/z* 309 (MH^+, 1), 229 (34), 197 (95), 169 (52), 115 (53), 108 (100), 89 (68), 77 (69), 53 (77%). HRMS: found: M^+, 308.0157. $C_{13}H_{13}BrN_2O_2$ requires 308.0160. Further elution yielded the other regioisomer (**18**) as a colourless crystalline powder (48%), mp 92.0–95.9 °C. (Found: C, 50.29; H, 4.05; N, 9.25. $C_{13}H_{13}BrN_2O_2$ requires C, 50.50; H, 4.24; N, 9.06%); ν_{max}(KBr) 3079, 1715, 1539, 1475, 1437, 1362, 1236, 1162, 1108, 1025, 947, 867, 761, 660 cm^{-1}; δ_H 3.22 (2H, t, J=7.0 Hz, CH_2), 3.89 (3H, s, OCH_3), 4.55 (2H, t, J=7.0 Hz, NCH_2), 6.98 (1H, d, J=7.4 Hz, Ar 6-H), 7.10 (1H, ddd, J=7.4, 7.4, 1.9 Hz, Ar-4- or 5-H), 7.17 (1H, ddd, J=7.4, 7.4, 1.9 Hz, Ar-4- or 5-H), 7.28 (1H, s, 4-H), 7.56 (1H, d, J=7.4 Hz, Ar-3-H), 7.73 (1H, s, 2-H); δ_C 37.7 (CH_2), 46.4 (NCH_2), 51.5 (OCH_3), 122.1 (5-C), 124.4 (Ar-2-C), 127.8, 128.7, 131.1 and 133.0 (Ar-3,4,5,6-C), 136.8 (Ar-1-C), 138.0 (4-C), 142.1 (2-C), 160.7 (C=O); *m/z* 309 (MH^+, 1), 277 (2), 229 (100), 197 (15), 182 (8), 169 (25), 103 (18), 89 (13), 77 (29%); HRMS: found: MH^+, 309.0239. $C_{13}H_{13}BrN_2O_2$ requires 309.0238).

3.2.3. Methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-indole-3-carboxylate (22). Colourless crystals (40%), mp 111.7–112.8 °C. (Found: C, 60.84; H, 4.27; N, 3.80. requires C, 60.35; H, 4.50; N, 3.91%); ν_{max}(KBr) 2946, 1696, 1534, 1470, 1442, 1267, 1224, 1162, 1116, 1093, 1026, 747 cm^{-1}; δ_H 3.27 (2H, t, J=7.6 Hz, CH_2), 3.90 (3H, s, OCH_3), 4.40 (2H, t, J=7.6 Hz, NCH_2), 6.93 (1H, dd, J=7.2, 2.0 Hz, 7-H or Ar-6-H), 7.08–7.16 (1H, m), 7.25–7.30 (1H, m), 7.40–7.42 (1H, m), 7.57 (1H, dd, J=7.2, 2.0 Hz, Ar-3-H), 7.70 (1H, s, 2-H), 8.15–8.19 (1H, m, indole 4-H); δ_C 37.1 (CH_2), 46.6 (NCH_2), 51.0 (OCH_3), 107.2 (3-C), 109.9 (7-C), 121.8, 121.9 and 122.8 (4,5,6-C), 124.2 (Ar-2-C), 126.6 (3a-C), 127.8, 128.9, 131.1, 133.1 and 134.2 (2-C and Ar-3,4,5,6-C), 136.4 and 136.8 (7a-C and Ar 1-C), 165.5 (C=O); *m/z* 357 (M^+, 14), 278 (8), 138 (100), 129 (10), 77 (8%); HRMS: found: M^+, 357.0371. $C_{18}H_{16}BrNO_2$ requires 357.0364.

3.2.4. Ethyl 1-[2-(2-bromophenyl)ethyl]-1*H*-pyrrole-2-carboxylate (24). Pale yellow oil (97%); ν_{max}(neat) 3109, 3056, 2979, 2869, 1694, 1567, 1531, 1470, 1415, 1325, 1241, 1171, 1101, 1077, 1027, 917, 738, 657 cm^{-1}; δ_H 1.36 (3H, t, J=7.2 Hz, CH_3), 3.20 (2H, t, J=7.2 Hz, CH_2), 4.30 (2H, q, J=7.2 Hz, OCH_2), 4.52 (2H, t, J=7.2 Hz, NCH_2), 6.02 (1H, dd, J=3.9, 2.5 Hz, 4-H), 6.59 (1H, dd, J=2.5, 1.9 Hz, 3- or 5-H), 6.95 (1H, dd, J=3.9, 1.9 Hz, 3- or 5-H), 7.02–7.16 (3H, m, Ar-4, 5,6-H), 7.53 (1H, dd, J=7.9, 1.2 Hz, Ar-3-H); δ_C 14.5 (CH_3), 37.2 (CH_2), 48.7 (NCH_2), 59.8 (OCH_2), 107.8 (3-C), 118.2 (4-C) 124.4 (Ar-2-C), 128.3 (pyrrole 5-C), 121.6, 126.7, 127.5, 131.3 and 132.7 (2-C, Ar-3,4,5,6-C), 137.7 (Ar-1-C), 161.1 (C=O); *m/z* 321 (M^+, 2), 276 (11), 242 (100), 169 (98), 152 (22), 124 (100), 103 (24), 94 (46), 77 (25%); HRMS: found: M^+, 321.0367. $C_{15}H_{16}BrNO_2$ requires 321.0364.

3.2.5. Ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (26a). Pale yellow oil (85%); ν_{max}(neat) 3135, 3070, 2984, 1732, 1543, 1474, 1443, 1368, 1303, 1223, 1143, 1054, 847, 776, 752 cm^{-1}; δ_H 1.33 (3H, t, J=7.2 Hz, CH_3), 3.32 (2H, t, J=7.2 Hz, CH_2), 4.30 (2H, q, J=7.2 Hz, OCH_2), 4.42 (2H, t, J=7.2 Hz, NCH_2), 6.99 (1H, dd, J=7.4, 1.8 Hz, Ar-6-H), 7.12 (1H, ddd, J=7.5, 7.5, 1.2 Hz, Ar-4- or 5-H), 7.20 (1H, ddd, J=7.5, 7.5, 1.6 Hz, Ar-4- or 5-H), 7.58 (1H, dd, J=7.5, 1.2 Hz, Ar-3-H), 7.74 (1H, s, pyrazole 5-H); δ_C 14.1 (CH_3), 36.8 (CH_2), 52.4 (NCH_2), 60.9 (OCH_2), 113.0 (CF_3), 119.1, 121.7 and 124.3 (3-C, 4-C, Ar-2-C), 127.9, 129.1, 131.1, 133.2 and 135.8 (5-C, Ar-3.4.5.6-C), 136.1 (Ar-1-C), 160.8 (C=O); *m/z* 391 (M^+, 1), 345 (10), 311 (100), 283 (29), 265 (18), 182(100), 169 (48), 103 (78), 77 (51%); HRMS: found: MH^+, 391.0269. $C_{15}H_{14}BrF_3N_2O_2$ requires 391.0269.

3.3. General procedure for radical reactions

Bu_3SnH. A deoxygenated solution of Bu_3SnH (2.2 equiv) in toluene was added drop wise using a syringe pump to a solution of the radical precursor (0.25–1.0 mmol) in anhydrous toluene under reflux under an atmosphere of nitrogen. The radical initiator (AIBN) was added, followed by heating under reflux for the time indicated for each reaction. AIBN (1.2 equiv) was added portion-wise every 45 min. The solution was refluxed for a further set time. The basic products were extracted from the cooled reaction mixture with dilute hydrochloric acid and the acidic extracts washed with light petroleum to remove Bu_3Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14 and extracted with DCM. The organic extracts were dried and evaporated under reduced pressure. The residues were analysed by ^1H NMR spectroscopy and TLC. The crude residues were purified by column chromatography.

Bu_3GeH. The procedure was the same as the procedure for Bu_3SnH radical reactions except that the Bu_3GeH (1.5 equiv) was added in one portion at the beginning of the reaction instead of addition using a syringe pump.

3.3.1. Methyl 1-benzyl-1*H*-imidazole-4-carboxylate (16a). *Bu_3SnH*. Reflux 7 h, methyl 1-benzyl-1*H*-imidazole-4-carboxylate as a colourless oil (**16a**) (33%); ν_{max}(neat) 2363, 1720, 1545, 1440, 1380, 1224, 1119, 997, 713 cm^{-1}; δ_H 3.88 (3H, s, OCH_3), 5.14 (2H, s, CH_2), 7.17–7.20 (2H, m, Ar-H), 7.25–7.26 (1H, m, Ar-H), 7.37–7.41 (2H, m, Ar-H), 7.56 (1H, s, 2- or 5-H), 7.60 (1H, m, 2- or 5-H); δ_C 51.4 (CH_2), 51.73 (OCH_3), 118.6 (4-C), 125.4, 127.6, 128.8 and 129.2 (5-C and Ph-2,3,4-C), 138.1 (2-C), 142.9 (Ph-1-C), 163.2 (C=O); *m/z* 216 (M^+, 10), 185 (5), 158 (8), 128 (4), 91 (100), 77 (8), 65 (18%); HRMS: found: MH^+, 217.0976. $C_{12}H_{12}N_2O_2$ requires 217.0977.

Bu_3GeH. 10 h reflux, methyl 1-benzyl-1*H*-imidazole-4-carboxylate (56%). The TLC and ^1H NMR and IR spectra were identical to an authentic sample.

3.3.2. Methyl 5,6-dihydroimidazo[5,1-*a*]isoquinoline-1-carboxylate (20) and methyl 5,6-dihydroimidazo[2,1-*a*]-isoquinoline-2-carboxylate (19). *Bu_3SnH*. Reflux (5 h addition, 5 h further reflux), (**20**) as crystalline colourless needles (16%), mp 179.0–182.9 °C; ν_{max}(KBr) 3118, 2951, 2368, 1689, 1546, 1469, 1432, 1347, 1217, 1182, 1164, 1107, 939, 769, 655 cm^{-1}; δ_H 3.10 (2H, t, J=6.5 Hz, 6-CH_2), 3.96 (3H, s, OCH_3), 4.17 (2H, t, J=6.5 Hz, NCH_2), 7.27 (1H, dd, J=8.0, 1.0 Hz, 7-H), 7.32 (1H, ddd, J=8.0, 8.0, 1.0 Hz, 8- or 9-H), 7.38 (1H, ddd, J=8.0, 8.0, 1.0 Hz, 8- or 9-H), 7.54 (1H, s, 3-H), 8.74 (1H, dd, J=8.0, 1.0 Hz, 10-H); δ_C 29.6 (5-C), 42.5 (6-C), 51.9 (OCH_3), 125.9 (1-C), 127.6, 127.8, 128.4 and 129.1 (7,8,9,10-C), 128.2, 133.0 and 133.8 (6a,10a,10b-C), 135.5 (3-C), 164.2 (C=O); *m/z* 228 (M^+, 74), 197 (100), 170 (54), 140 (13), 115 (25%); HRMS: found: M^+, 228.0900. $C_{13}H_{12}N_2O_2$ requires 228.0900. The structure was confirmed by X-ray crystallography.

Further elution yielded (**19**) as a pale yellow oil (4%); ν_{max}(neat) 3134, 2953, 2925, 2359, 1723, 1542, 1461, 1437, 1349, 1326, 1258, 1225, 1199, 1181, 1124, 1103, 1006, 808, 777, 737, 718 cm^{-1}; δ_H 3.11 (2H, t, J=7.2 Hz, 6-CH_2), 3.84 (3H, s, OCH_3), 4.15 (2H, t, J=7.2 Hz, NCH_2), 7.17 (1H, dd, J=6.8, 2.0 Hz, 7-H), 7.23–7.30 (2H, m, 8,9-H), 7.58 (1H, s, 3-H), 8.10 (1H, dd, J=7.6, 2.0 Hz, 10-H); δ_C 27.2 (6-C), 42.7 (5-C), 50.8 (OCH_3), 123.5, 124.4, 126.7, 126.8 and 128.3 (3.7,8,9,10-C), (C), 125.1 (2-C), 127.3 and 131.7 (6a,10a-C), 144.0 (10b-C), 162.5 (C=O); *m/z* 228 (M^+, 100), 197 (92), 170 (75), 140 (12), 115 (28), 77 (10%); HRMS: found: M^+, 228.0900. $C_{13}H_{12}N_2O_2$ requires 228.0900. A considerable amount of the two products was also obtained as a mixture after chromatography and was not further separated.

Bu_3GeH. Reflux (10 h), (**20**) (38%), (**19**) (19%).

Bu_3GeH and phenylthiol. Benzenethiol (10 mol%) was added at the beginning of the reaction. Reflux (10 h), (**20**) (44%). ^1H NMR spectroscopic analysis of the crude reaction product showed the presence of starting material and traces of other unidentifiable materials. The yield of unaltered starting material was not recorded.

Tris(trimethylsilyl)silane (TTMSS). The general procedure for Bu_3SnH reactions was used except that TTMSS was used in place of Bu_3SnH. Reflux (5 h addition, 5 h further reflux), (**20**) (30%), (**19**) (30%).

3.3.3. Methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate (21). *Bu_3SnH*. Reflux (5 h addition, 7 h further reflux), colourless crystals (71%), mp 122.0–124.9 °C; ν_{max}(KBr) 2372, 1710, 1509, 1441, 1387, 1337, 1252, 1184, 1108, 1072, 980 cm^{-1}; δ_H 3.17 (2H, t, J=7.2 Hz, 6-CH_2), 3.88 (3H, s, OCH_3), 4.62 (2H, t, J=7.2 Hz, NCH_2), 7.26–7.28 (1H, m), 7.33–7.39 (2H, m), 7.83 (1H, s, 2-H), 8.07 (1H, m, 10-H); δ_C 28.1 (6-C), 42.2 (5-C), 51.5 (OCH_3), 122.1 (3-C), 126.2 (10a-C), 124.7, 127.6, 127.7 and 129.8 (7,8,9,10-C), 133.2 (6a-C), 137.9 (imidazole 2-C), 148.3 (10b-C), 161.0 (C=O); *m/z* 228 (M^+, 100), 213 (8), 197 (42), 183 (7), 169 (17), 140 (13), 128 (17), 115 (35), 84 (29%); HRMS: found: MH^+, 229.0981. ($C_{13}H_{12}N_2O_2$+H) requires 229.0977. The structure was confirmed using X-ray crystallography.

Bu_3GeH. Reflux (10 h), (54%) starting material (**18**) (20%).

3.3.4. Methyl 5,6-dihydroindolo[2,1-*a*]isoquinoline-12-carboxylate (23). *Bu_3GeH*. Clear oil (68%); ν_{max}(neat) 2947, 1698, 1530, 1468, 1455, 1404, 1282, 1224, 1188, 1154, 1110, 1022, 768, 747 cm^{-1}; δ_H 3.15 (2H, t, J=6.5 Hz, 5-CH_2), 3.99 (3H, s, OCH_3), 4.24 (2H, t, J=6.5 Hz, NCH_2), 7.25–7.40 (6H, m), 8.19 (1H, m, 11-H) and 8.53 (1H, dd, J=7.2, 1.8 Hz, 1-H); δ_C 29.7 (5-C), 40.4 (6-C), 51.1 (OCH_3), 103.0 (12-C), 109.1 (8-C), 122.0, 122.4, 122.9, 126.7, 127.7, 129.3 and 129.7 (1, 2, 3, 4, 9, 10, 11-C), 133.2, 134.8, 135.3, 138.0 and 134.0 (4a, 7a, 11a, 12a, 12b-C), 166.4 (C=O); *m/z* 277 (M^+, 100), 246 (92), 217 (38), 188 (30), 108 (14), 77 (9%); HRMS: found: M^+, 277.1104. $C_{18}H_{15}NO_2$ requires 277.1103.

3.3.5. Ethyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (25). *Bu_3GeH*. Clear oil (82%); ν_{max}(neat) 2928, 1694, 1489, 1446, 1260, 1224, 1150, 1105, 1068, 749 cm^{-1}; δ_H 1.37 (3H, t, J=7.1 Hz, CH_3), 3.08 (2H, t, J=6.8 Hz, CH_2), 4.31 (2H, q, J=7.1 Hz, OCH_2), 4.64 (2H, t, J=6.8 Hz, NCH_2), 6.52 (1H, d, J=4.0 Hz, 1-H), 7.02 (1H, d, J=4.0 Hz, 2-H), 7.20–7.28 (3H, m, 7,8,9-H), 7.56 (1H, d, J=7.6 Hz, Ar 10-H); δ_C 14.5 (CH_3), 28.9 (6-CH_2), 42.2 (NCH_2), 59.8 (OCH_2), 104.4 (1-C), 118.2 (2-C), 113.7 and 122.1 (3,10b-C), 123.6, 127.1, 127.4 and 128.4 (7,8,9,10-C), 131.7 (10a-C), 136.0 (6a-C), 161.4 (C=O); *m/z* 241 (M^+, 100), 213 (39), 196 (28), 168 (32), 139 (11), 115 (11), 77 (3%); HRMS: found: M^+, 241.1103. $C_{15}H_{15}NO_2$ requires 241.1103.

3.3.6. Ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline-1-carboxylate (27a). *Bu_3GeH*. Colourless oil (57%); ν_{max}(neat) 2928, 2369, 1717, 1473, 1199, 1142, 1042 cm^{-1}; δ_H 1.39 (3H, t, J=7.2 Hz, CH_3), 3.19 (2H, t, J=6.8 Hz, 6-CH_2), 4.36–4.42 (4H, m, 5-CH_2 and OCH_2), 7.30–7.40 (3H, m, ArH), 8.30–8.32 (1H, m, 10-H); δ_C 13.8 (CH_3), 29.3 (6-CH_2), 47.1 (5-CH_2), 61.4 (OCH_2), 109.0 (1-C), 119.5 (CF_3), 122.1 (2-C), 125.0 and

133.3 (2,6a,10a-C), 127.6, 127.8, 128.1 and 130.2 (7,8,9,10-C), 141.5 (10b-C), 162.6 (C=O); *m/z* 310 (M^+, 43), 282 (10), 265 (100), 238 (14), 140 (5), 104(38), 91 (10), 77 (6%); HRMS: found: M^+, 310.0926. $C_{15}H_{13}F_3N_2O_2$ requires 310.0929.

3.4. Solid phase studies

3.4.1. 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid (26b). Ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**26a**) (1.20 g, 3.1 mmol) was dissolved in ethanol (10 mL) followed by addition of aqueous sodium hydroxide (2 M, 15 mL). The reaction mixture was heated under reflux for 8 h and the progress monitored by TLC. The reaction mixture was cooled and washed with ethyl acetate. The aqueous layer was acidified to pH 3 with hydrochloric acid and extracted with DCM. The organic layers were washed with water, dried and evaporated under reduced pressure to afford (**26b**) as light yellow crystals (1.10 g, 3.0 mmol, 97%); ν_{max}(KBr) 3300, 2953, 2683, 2600, 1697, 1547, 1499, 1438, 1309, 1236, 1191, 1145, 1048, 945, 754 cm^{-1}; δ_H 3.34 (2H, t, J=7.2 Hz, 6-CH_2), 4.45 (2H, t, J=7.2 Hz, NCH_2), 6.97 (1H, dd, J=7.6, 1.6 Hz, Ar 6-H), 7.15 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar 4- or 5-H), 7.20 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar 4- or 5-H), 7.58 (1H, dd, J=7.6, 1.6 Hz, Ar 3-H), 7.75 (1H, s, pyrazole 5-H); δ_C 36.7 (CH_2), 52.7 (NCH_2), 111.6 (CF_3), 118.8 (pyrazole 4-C), 121.5 (pyrazole 3-C), 124.2 (Ar-2-C), 127.9, 129.2, 131.1, 133.2 and 136.8 (5-C, Ar-3,4,5,6-C), 135.9 (Ar 1-C),165.6 (C=O); *m/z* 283 (95), 182 (100), 169 (60), 103 (62), 90 (52), 77 (45), 69 (32%); HRMS: found: MH^+, 362.9956. $C_{13}H_{10}BrF_3N_2O_2$ requires 362.9961.

3.4.2. Synthesis of solid-supported 1-[2-(2-bromophenyl)-ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (28). DCM (8.0 mL) was added to a portion of Wang resin (0.40 g, 0.7 mmol). The resin was allowed to swell for 30 min under an atmosphere of nitrogen. (**26b**) (0.62 g, 1.7 mmol) in DMF (8.0 mL), DMAP (0.25 g, 2.1 mmol) and diisopropylcarbodiimide (DIC) (0.64 mL, 4.1 mmol) were added sequentially. The suspension was shaken for 48 h at room temperature. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents. ν_{max}(KBr) 3458, 3026, 2922, 2370, 1723, 1602, 1508, 1370, 1290, 1211, 1138, 1037, 815, 747, 693 cm^{-1}.

3.4.3. Radical cyclisations of solid-supported 1-[2-(2-bromo-phenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (28). *Use of Bu_3GeH.* Bu_3GeH (0.55 mL, 2.1 mmol) was added to the solid supported pyrazole (**28**) (140 mg, 0.11 mmol) in toluene (10 mL) under reflux. AIBN (0.25 g, 1.5 mmol) was added to the refluxing reaction mixture at equal intervals of 1 h. The reaction mixture was heated under reflux for 30 h. The reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH. The resin was dried at 40 °C under vacuum for 24 h. The products were cleaved from the resin using TFA/DCM (9:1) and a crystalline material was recovered (44 mg). LC-MS analysis of the cleaved sample from the resin showed a mixture of the cyclised adduct 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline-1-carboxylic acid (**27b**) and the starting material (**26b**). The ^1H NMR spectrum of the cleaved sample showed a mixture the cyclised product (**27b**) (20%) and the unreacted starting material (**26b**) (70%). The separation of these products by column chromatography was unsuccessful due to co-elution and therefore products were not fully characterised.

Use of TTMSS. The above procedure was used with TTMSS (1.3 mL, 4.2 mmol), AIBN (0.20 g, 1.2 mmol) and resin-bound pyrazole moiety (**27b**) (111 mg, 0.09 mmol). Cleavage from the resin yielded a brown oil (30 mg) which LC-MS analysis confirmed a mixture of the cyclised adduct (**27b**) and the reduced product (**26c**). ^1H NMR spectral analysis showed a mixture of (**27b**) (53%) and the reduced product (**26c**) (27%) with no other products.

(**27b**): δ_H 3.20 (2H, t, J=6.8 Hz, 6-CH_2), 4.40 (2H, t, J=6.8 Hz, 5-CH_2), 7.16–7.34 (3H, m, ArH), 8.33–8.35 (1H, m, 10-H); δ_C 29.35 (6-CH_2), 47.25 (5-CH_2), 108.0 (1-C), 119.2 (CF_3), 121.9, 124.7 and 133.7 (2,6a,10a-C), 127.7, 128.1, 128.4 and 130.5 (7,8,9,10-C), 142.7 (pyrazole 10b-C), 166.9 (C=O).

(**26c**): δ_H 3.20 (2H, t, J=6.8 Hz, CH_2), 4.40 (2H, m, NCH_2), 7.08 (1H, d, J=7.6 Hz, ArH), 7.16–7.34 (1H, m, ArH), 7.39–7.42 (3H, m, ArH), 7.75 (1H, s, 5-H); δ_C 36.2 (CH_2), 54.8 (NCH_2), 111.7 (CF_3), 118.9 (4-C), 121.6 (3-C), 127.3 (PhCH), 128.6 (PhCH), 128.9 (PhCH), 133.6 (Ph-1-C), 136.7 (5-C), 165.4 (C=O).

3.5. X-ray crystallography

Both sets of data for methyl 5,6-dihydroimidazo[5,1-*a*]-isoquinoline-1-carboxylate (**20**) and methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate (**21**) were collected on a Bruker SMART 1000 diffractometer at 150(2) K using Mo Kα radiation. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using all the data. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were included at calculated positions using a riding model. Data collection and

Table 1. Crystal data for heterocycles **20** and **21**

Identification code	**20**	**21**
Empirical formula	$C_{13}H_{12}N_2O_2$	$C_{13}H_{12}N_2O_2$
Formula weight	228.25	228.25
Crystal system	Triclinic	Monoclinic
a (Å)	7.077(3)	11.9248(13)
b (Å)	7.830(3)	11.9615(13)
c (Å)	9.856(4)	7.6375(8)
α (°)	100.317(6)	90
β (°)	92.468(6)	98.895(2)
γ (°)	93.062(6)	90
U (Å^3)	535.7(3)	1076.3(2)
Z	2	4
Space group	$P\bar{1}$	$P2_1/c$
μ (mm^{-1})	0.098	0.097
Refl. collected	4162	5967
Unique refl. (R_{int})	2332 (0.0314)	1861 (0.0292)
$R1$, $wR2$ [$I>2\sigma(I)$]	0.0701, 0.2164	0.0363, 0.0924
$R1$, $wR2$ (all data)	0.0829, 0.2253	0.0475, 0.0985

refinement parameters are summarized in Table 1. All programs used in structure solution and refinement are included in the SHELXTL package.[25] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre supplementary publication numbers, (**20**) (CCDC 244723) and (**21**) (CCDC 244724).

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Copper-free palladium-catalyzed sonogashira-type coupling of aryl halides and 1-aryl-2-(trimethylsilyl)acetylenes

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Abstract—A one-pot procedure for the direct coupling of 1-aryl-2-trimethylsilylacetylenes with aryl halides to give diaryl acetylenes is reported. The procedure does not involve the use of copper(I) iodide. Improvement in reaction yields has been obtained by replacing conventional oil bath heating with the use of microwave dielectric heating.

1. Introduction

The palladium-catalyzed carbon–carbon bond forming reactions developed through the last decades remain of great value to synthetic organic chemists. One such reaction, the Sonogashira coupling,[1–3] involves the preparation of substituted acetylenes by coupling aryl or vinyl halides with terminal acetylenes in the presence of a palladium catalyst and copper(I) iodide as cocatalyst. Although there are examples of Sonogashira-type couplings without the use of a copper cocatalyst,[4–9] its use together with palladium is by far the most common procedure. Furthermore, copper(I) in itself is known to efficiently mediate the homo- and heterocoupling of terminal acetylenes,[10] being an undesirable side-reaction in several applications of the Sonogashira reaction.

Numerous reports describe the coupling of trimethylsilylacetylene with aryl halides in Sonogashira-type reactions. The C(sp)–Si bond is generally not affected by these reaction conditions. The silyl group can, therefore, if desired, subsequently be removed to furnish a structurally modified terminal alkyne.[2,5] The trimethylsilyl group is thereby used as a protective group, and as recently exemplified within solid-phase synthesis, the functionalized terminal alkyne formed by cleaving off the trimethylsilyl functionality with for example tetrabutylammonium fluoride (TBAF) or aqueous alkali can subsequently be subjected to reactions like the Mannich reaction[11] or a second Sonogashira cross-coupling step.[12]

We have studied the direct coupling of trimethylsilylacetylenes to give disubstituted acetylenes in a one-pot procedure which does not require isolation of the terminal alkyne after deprotection.[13] It has been described that this type of palladium-mediated coupling can be accomplished in the presence of equivalent[14] or catalytic[15] amounts of silver ions. In another recent study, describing the copper-palladium cocatalyzed cross-coupling of (arylethynyl)trimethylsilanes and aryl halides or triflates, it was concluded that catalytic amounts of copper are required for such a coupling reaction to take place.[16] Thus, with the omission of copper(I) chloride in the otherwise successful reaction of 4-acetylphenyl trifluoromethanesulfonate with 1-phenyl-2-trimethylsilylacetylene these authors could not detect any formation of the desired coupling product. In contrast to the use of an either catalytic[17,18] or stoichiometric[19] amount of copper, the result of our work presented here is a procedure for the direct coupling of trimethylsilylacetylenes to give 1,2-diaryl acetylenes in a palladium-catalyzed reaction without the use of a copper cocatalyst and furthermore with a reduction in the reaction time from several hours[16] to only minutes by means of microwave heating. Regarding the use of microwaves,[19–27] it has recently been reported that aryl trimethylsilylacetylenes can be prepared efficiently from trimethylsilylacetylene and an aryl halide using standard Sonogashira coupling conditions and microwave irradiation with much reduced reaction times.[28] Thus, as recently exemplified in a one-pot procedure,[16] combining the introduction of the trimethylsilylethynyl functionality and subsequent coupling with an aryl halide represents a useful tool for the preparation of diarylacetylenes. An example of this class of compounds which has been of great interest to us is the neuroactive compound 2-methyl-6-(phenylethynyl)pyridine (MPEP, **4**, Table 2), found to be a

Keywords: Microwaves; Sonogashira-type coupling; 1-Aryl-2-trimethylsilylacetylenes; Diaryl acetylenes.
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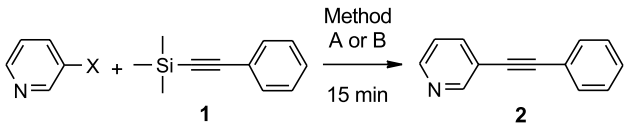
Table 1. Reaction conditions for coupling of 1-phenyl-2-(trimethylsilyl)acetylene (**1**) and 3-halopyridines



Entry	X	Method[a]	Solvent	Catalyst	T (°C)	Base/transf. cat.[b]	Yield (%)
1	Br	A	DMF	$Pd(OAc)_2$	100	A	32
2	Br	B	DMF	$Pd(OAc)_2$	100	B	53[c]
3	Br	A	DMF	$Pd(OAc)_2$	100	B	61[c]
4	Br	A	DMF	$Pd(OAc)_2/(o\text{–tol})_3P$	100	B	71
5	I	A	*n*-Bu_2O	$Pd(OAc)_2$	100	B	16
6	I	A	H_2O/DMF 1:9	$Pd(OAc)_2$	100	C	64
7	I	A	DMF	$Pd(OAc)_2$	100	D	5
8	I	A	DMA	$Pd(OAc)_2$	100	B	80
9	I	A	DMA	$Pd(OAc)_2/(o\text{–tol})_3P$	100	B	80
10	I		DMF	$Pd(OAc)_2$	rt[d]	B	28
11	I	B	DMF	$Pd(OAc)_2$	100	B	62[c]
12	I	A	DMF	$Pd(OAc)_2$	100	B	74[c]
13	I	A	DMF	$Pd(OAc)_2$	140	B	58
14	I	A	DMF	$Pd(OAc)_2$	180[e]	B	37
15	I	A	DMF	$Pd(PPh_3)_2$	100	B	87
16	I	A	DMF	$Pd(OAc)_2/(o\text{–tol})_3P$	100	B	90

[a] Method A: microwave heating, Method B: conventional heating.
[b] A: NaOAc/Bu_4NBr, B: NaOAc/Bu_4NCl, C: K_2CO_3/Bu_4NCl, D: triethylamine.
[c] Average of two determinations (see footnote[†]).
[d] Reaction time 16 h.
[e] Reaction time 4 min.

highly potent and selective antagonist for the metabotropic glutamate receptor subtype mGlu5.[29,30]

2. Results and discussion

Initially, we studied the coupling of 1-phenyl-2-(trimethylsilyl)acetylene (**1**) with 3-bromo- or 3-iodopyridine to identify the optimal reaction conditions (Table 1). Compound **2** was isolated in a moderate 28% yield (entry 10, Table 1) when the reaction (scale 2.50 mmol) was carried out at room temperature overnight in the presence of 5 mol% palladium acetate together with sodium acetate and tetrabutylammonium chloride. Performing this transformation at elevated temperature applying 15 min of microwave irradiation (Method A), resulted in an initial improvement of the reaction to 74% isolated yield of **2** when starting from 3-iodopyridine (entry 12, Table 1).[†]

We found the reaction to be highly reproducible when using a microwave instrument that allows for control and monitoring of temperature as well as giving efficient stirring. For most of our experiments DMF was used as solvent. With its high polarity it absorbs microwaves well, resulting in very rapid heating. Using typically 50 ml of DMF as solvent and irradiation at 450 W, we achieved a temperature increase from room temperature to 100 °C within less than 30 s.

As can be seen from Figure 1, heating the reaction mixture in a hot oil bath (Method B) results in much slower heating and conversion rates, and the rapid heating when applying microwaves may be the explanation for the higher isolated yields obtained in the cases where comparable experiments were carried out.

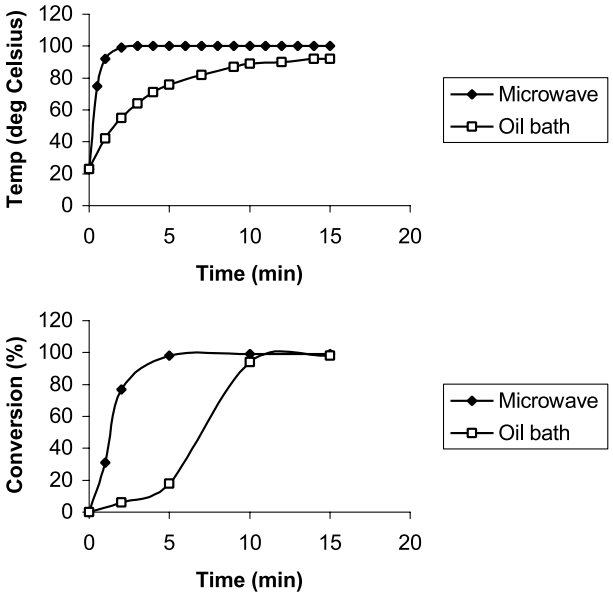


Figure 1. Experiments performed using identical scale (50 ml solvent) and identical reaction flasks and magnetic stirring bars. Upper graph: For MW experiment, a sensor placed in the reaction mixture allows for on-line temperature control and monitoring. For oil bath, values are average of three determinations (maximal deviation two degrees Celsius). Lower graph: Conversion rates (single determination) were calculated from H-NMR spectral data of crude product (desired product/aryl halide).

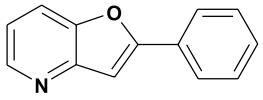
[†] Isolated yields obtained in the repeated microwave experiments: 75 and 73% from 3-iodopyridine (Table 1, entry 12); 61 and 60% from 3-bromopyridine (Table 1, entry 3). For the oil bath experiments, 60 and 64% were obtained from 3-iodopyridine (Table 1, entry 11) and 50 and 56% from 3-bromopyridine (Table 1, entry 2).

Thus, for the synthesis of **2** an average of 74% yield from two determinations (entry 12, Table 1) was obtained in the former case as compared to 62% for two otherwise identical experiments using a pre-heated oil bath (entry 11, Table 1).[†] A similar tendency was found when starting from 3-bromopyridine (entry 2 and 3, Table 1).[†] To this end, it should be noticed that microwave heating is now generally considered as having only thermal effects although some discussion is still active in the literature regarding a specific 'microwave effect'.

We generally used palladium acetate as pre-catalyst but observed in most cases a significantly improved yield when introducing a phosphine ligand. This could be explained by a stabilizing effect of the phosphine ligand on the reactive palladium species, or by a facilitated reduction of the palladium (II) to a palladium(0) species as previously discussed for example the palladium-catalyzed Heck coupling.[31,32] Using either palladium acetate/tri(*o*-tolyl)-phosphine (entry 16, Table 1) or tetrakis(triphenyl-phosphine)palladium (entry 15, Table 1) very high yields of **2** were obtained. Regarding the base, sodium acetate turned out to be superior to aqueous potassium carbonate and, in particular, triethylamine, for which only poor yield was obtained (entry 7, Table 1).

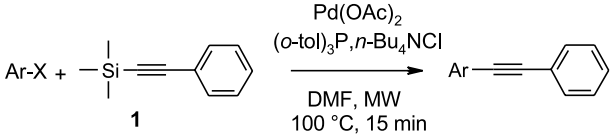
In order to study the scope of this reaction, a number of aryl halides and heteroaryl halides were subjected to this transformation (Table 2). The yields are highly substrate-dependent, and the coupling product was formed only in cases where the aryl halide was sufficiently activated. As could be expected, iodides afforded better results than the corresponding bromides. For the benzoic acid methyl esters, efficient conversion-rates were obtained for the 3- and 2-substituted derivatives, yielding after 15 min at 100 °C compounds **8** and **9** in 84 and 85% yield, respectively. For comparison, the latter result is identical to what has previously been published in the synthesis of **9** from methyl 2-iodobenzoate applying Cu(I) as cocatalyst and stirring two days at room temperature.[33]

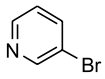
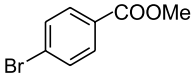
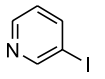
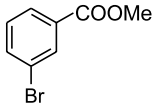
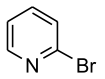
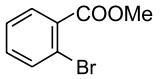
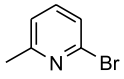
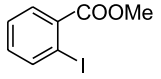
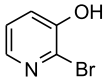
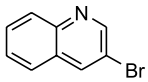
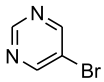
In contrast to the successful reactions using 2- and 3-substituted benzoic acid methyl esters, the corresponding 4-bromosubstituted substrate gave compound **7** in a poor 7% yield from a complex mixture of reaction products. In the reaction of 2-bromo-3-hydroxypyridine, the 3-hydroxy group participates in an intramolecular cyclization and the expected disubstituted acetylenic product was, therefore, not isolated. Instead, the further cyclized 2-phenyl-furo(3,2b)pyrrole **5** was obtained in 33% yield. This result corresponds to what has been reported by Sakamoto et al. for the reaction of 2-iodo-3-hydroxypyridine with phenyl-acetylene.[34]



5

Table 2. Coupling reactions of 1-phenyl-2-trimethylsilyl)acetylene (**1**)



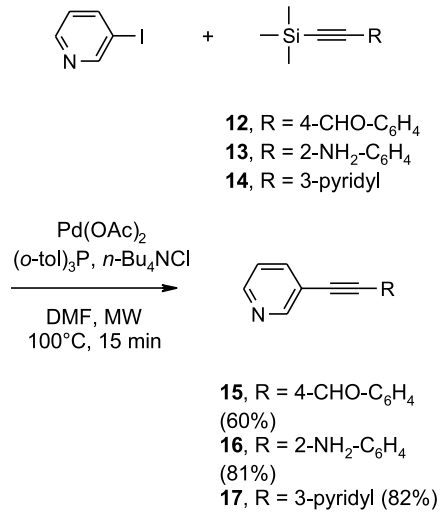
Ar–X	Product, yield (%)[a]	Ar–X	Product, yield (%)[a]
	**2** 71 (61)[b]		**7** (7)
	**2** 90 (74)[b]		**8** 84 (60)
	**3** (39)[c]		**9** 85 (60)
	**4** 50[d] (40)		**9** 85 (70)
	**5** (33)[e]		**10** 44 (37)
	**6** 55 (57)		**11** 84 (60)

[a] Numbers in parentheses are isolated yields obtained without the use of (*o*-tol)$_3$P.
[b] Average of two determinations.
[c] 35% isolated yield obtained with $T=140$ °C.
[d] 2.5 min, 600 W, 120 °C.
[e] From 2-bromo-3-hydroxypyridine further cyclized **5** was obtained.

Furthermore, it should be mentioned that neither phenyl bromide nor phenyl iodide gave the desired product, although trace amounts of diphenylacetylene had apparently been formed in the latter case (TLC). Generally, good results were obtained from heterocyclic aryl halides. The two pyrimidine derivatives **10** and **11** were prepared from their respective bromides. An early study of Sonogashira couplings on iodopyrimidines[35] previously reported the synthesis of **10** in high yield (93%) from 2-iodopyrimidine and phenylacetylene. In contrast, we isolated **10** in 44% yield when starting from the corresponding 2-bromopyrimidine, whereas the more reactive 5-bromopyrimidine gave the novel compound **11** in up to 83% isolated yield. As observed for the pyrimidines, pyridines having the halide positioned meta to the heterocyclic nitrogen atom gave the best results in this reaction (Table 2). It should be noted, that **3** has been reported synthesized from the corresponding heterocyclic triflate using conventional Sonogashira coupling conditions in 68% yield in the presence of copper.[16]

To further broaden the versatility of the reaction we were also interested in introducing functionalized substituents via the alkyne substrate.

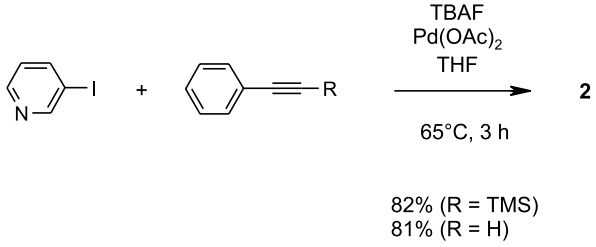
Moreover, using as substrate 4-(trimethylsilylethynyl)-benzaldehyde (**12**) or 2-(trimethylsilylethynyl)aniline (**13**) it was possible to introduce an aldehyde moiety as well as an amino group and obtain the desired coupling products **15** and **16** in 60 and 81% yield, respectively (Scheme 1). Thus, neither of these, respectively, electron-withdrawing and electron-donating functional groups appear to significantly affect the reactivity of the phenylacetylene substrate, suggesting tolerance to a wide range of substituents. Finally, 3,3′-ethynediyl-bis-pyridine (**17**) was synthesized in high yield from **14** whereas an attempt to introduce an aliphatic substituent, using 1-(trimethylsilyl)-1-pentyne, was unsuccessful.



Scheme 1.

We have not investigated the reaction mechanism of this transformation and, as discussed elsewhere,[36] it is not clear whether it takes place via for example, a carbopalladation pathway or via transmetallation between palladium and silicon in analogy with the mechanism recently argued by Itami et al. to explain the palladium-catalyzed coupling of alkenyl silanes with aryl- and vinyl halides in the presence of TBAF.[37]

Fluoride-induced silicon to Pd transmetallation has been invoked in Pd-catalyzed cross-coupling reactions by Hiyama et al.[38] To study this, we carried out a number of experiments in which the coupling of the trimethylsilylacetylene and the aryl halide was carried out in the presence of only TBAF and palladium acetate. Interestingly, **2** could in fact be isolated in good yield from 3-iodopyridine using this procedure (Scheme 2).



Scheme 2.

Despite this result, the same method used on 2- and 5-bromopyrimidine gave low yields of products (8 and 4%, respectively) together with many side-products, and when applied to aldehyde **12**, reaction with 3-iodopyridine gave **15** in 23% isolated yield. Following the addition of TBAF the reaction was in all cases exothermic, and the reaction mixture instantly turned black. In a control experiment, applying an identical procedure, 3-iodopyridine was treated with phenylacetylene (Scheme 2) in the presence of TBAF. This experiment proceeded without the initial development of heat and the reaction mixture did only slowly turn black. Interestingly, the desired product **2** was isolated in similarly high yield (81%) as in the reaction with trimethylsilylacetylene **1**. Thus, on the basis of this control experiment it cannot be concluded whether a transmetallation pathway is operating or if TBAF simply causes desilylation to give phenylacetylene being the actual substrate in the cross-coupling reaction.

In summary, a procedure for diarylacetylene synthesis via the direct coupling of activated aryl- and heteroaryl bromides and iodides with 1-aryl-2-trimethylsilylacetylenes has been developed. It avoids the use of a copper(I) iodide cocatalyst and is carried out by means of microwave heating with short reaction times at elevated temperature.

3. Experimental

3.1. General methods

Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise stated. Melting points were determined in open capillaries and are uncorrected. Microwave irradiation was performed using a MLS-Ethos 1600 instrument or in one case (Table 1, entry 14) by use of a SmithCreator™ instrument. Column chromatography (CC) was performed

using silica gel 60 (0.040–0.063 mm) or prepacked silica gel colums (50 or 70 g). Compounds were visualized on TLC using UV light and $KMnO_4$ spraying reagent. Proton and carbon NMR spectra were recorded on a 400 MHz instrument at 400 and 100 MHz, respectively. Mass spectrometry analyses were obtained using an LC/MSD instrument.

3.1.1. General procedure for the synthesis of 2-(phenylethynyl)arenes. Synthesis of 3-(phenylethynyl)pyridine (2). Method A (microwave heating). 3-Iodopyridine (2.50 mmol, 512 mg), 1-phenyl-2-trimethylsilylacetylene (5.00 mmol, 872 mg), palladium acetate (0.125 mmol, 28.1 mg), Bu_4NCl (2.50 mmol, 695 mg), and sodium acetate (10.0 mmol, 820 mg) in dry DMF (50 ml) were heated under argon in the Ethos 1600 microwave oven for 15 minutes regulating the power (initially 450 W thereafter 40–50 W) in order to keep the temperature constant at 100 °C. After cooling to room temperature, the reaction mixture was added saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to dryness and the residue purified by CC (0–10% EtOAc in hexane) to give **2** as a solid in 75% yield (335 mg); mp 47.8–49.0 °C (lit.[39] mp 50–51 °C). ^{1}H NMR in correspondence with literature;[39] ^{1}H NMR ($CDCl_3$) δ 7.20–7.25 (m, 1H), 7.30–7.36 (m, 3H), 7.51–7.56 (m, 2H), 7.73–7.79 (m, 1H), 8.50–8.55 (m, 1H), 8.75–8.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 86.0, 92.7, 120.4, 122.5, 123.0, 128.4, 128.8, 131.7, 138.4, 148.5, 152.2. MS (ES^+) *m/z* 180 ($[M+1]^+$, 100). HRMS: Calcd for $C_{13}H_{10}N$ 180.0813, found 180.0816.

3.1.2. Method B (conventional heating). These experiments (Table 1) were carried out exactly identical to the above described (method A), except that the reaction mixture was put in a preheated (100 °C) oil bath for 15 min, cooled to room temperature, and worked up as described for method A.

3.1.3. Method C (Synthesis of 2 using tetrabutylammonium fluoride (TBAF) in THF). 3-Iodopyridine (2.87 mmol, 588 mg), 1-phenyl-2-trimethylsilylacetylene (4.30 mmol, 750 mg), and palladium acetate (0.14 mmol, 32.2 mg) in dry THF (3 ml) was dropwise added in a 1 M solution of TBAF in THF (4.30 mmol) and stirred under argon 3 h at 65 °C. After cooling to rt, the reaction mixture was added saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to dryness. Compound **2** was isolated as a dark solid in 82% yield (423 mg) by flash chromatography (0–10% EtOAc in hexane). Compound characterization (^{1}H NMR and MS) showed that the isolated product was identical to **2** as described above for method A.

3.1.4. 2-(Phenylethynyl)pyridine (3). Method A. Oil, 173 mg (39%). ^{1}H and ^{13}C NMR in correspondence with literature;[40,41] ^{1}H NMR ($CDCl_3$) δ 7.18–7.22 (m, 1H), 7.32–7.36 (m, 3H), 7.48–7.52 (m, 1H), 7.57–7.65 (m, 3H), 8.58–8.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 88.6, 89.2, 122.2, 122.7, 127.1, 128.4, 129.0, 132.0, 136.2, 143.4, 150.0. MS (ES^+) *m/z* 180 ($[M+1]^+$, 100).

3.1.5. 2-Methyl-6-(phenylethynyl)pyridine (4). Method A (2.5 min oven setting 600 W, internal temperature 120 °C, 2-bromo-6-methylpyridine (2.9 mmol, 0.50 g), 1-phenyl-2-trimethylsilylacetylene (8.9 mmol, 1.50 g), palladium acetate (0.14 mmol, 32.0 mg), Bu_4NCl (2.9 mmol, 810 mg), and sodium acetate (11.6 mmol, 951 mg) in dry DMF (50 ml)). Isolated as the 1,5-naphthalenedisulfonate salt (crystallized from MeOH—EtOH-Et_2O), 380 mg (47%); mp 296–297 °C. Spectra from corresponding free base: ^{1}H NMR in correspondence with literature;[42] ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 7.05–7.10 (m, 1H), 7.31–7.36 (m, 4H), 7.51–7.62 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.7, 88.9, 89.0, 122.4, 122.6, 124.4, 128.3, 128.5, 128.8, 132.0, 136.4, 142.7, 158.9. MS (ES^+) *m/z* 194 ($[M+1]^+$, 100). Anal. Calcd for $C_{38}H_{30}N_2O_6S_2 \cdot 0.5\ H_2O$: C, 66.75; H, 4.57; N, 4.10; O, 15.20; S, 9.38. Found: C, 66.55; H, 4.53; N, 4.08; O, 15.23; S, 9.32.

3.1.6. 2-phenyl-furo[3,2-b]pyridine (5). Method A (2-bromo-3-hydroxypyridine (5.75 mmol, 1.00 g), 1-phenyl-2-trimethylsilylacetylene (11.5 mmol, 1.98 g), palladium acetate (0.28 mmol, 64.0 mg), Bu_4NCl (5.75 mmol, 1.6 g), and sodium acetate (23.0 mmol, 1.9 g) in dry DMF (50 ml). Reaction temperature 140 °C, 15 min). Solid, 376 mg (33%), mp 91–93 °C (lit.[34] mp 88–89 °C). ^{1}H NMR in correspondence with literature;[34,43] ^{1}H NMR ($CDCl_3$) 7.05–7.49 (m, 5H), 7.72–7.92 (m, 3H), 8.50–8.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 102.2, 118.0, 118.9, 125.4, 129.0, 129.7, 129.8, 146.2, 148.1, 149.2, 159.8. MS (EI^+) *m/z* 195 (M^+, 100). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17; O, 8.20. Found: C, 79.93; H, 4.82; N, 7.16; O, 8.10.

3.1.7. 3-(Phenylethynyl)quinoline (6). Method A (using in addition 10 mol % tri(*o*-tolyl)phosphine). Solid, 316 mg (55%), mp 67–70 °C. ^{1}H NMR ($CDCl_3$) δ 7.20–7.71 (m, 8H), 8.05–8.10 (m, 1H), 8.20 (s, 1H), 8.95 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 86.6, 92.6, 117.4, 122.6, 127.1, 127.2, 127.5, 128.4, 128.8, 129.3, 130.0, 131.7, 138.2, 146.7, 152.0. MS (ES^+) *m/z* 230 ($[M+1]^+$, 100). HRMS: Calcd for $C_{17}H_{12}N$ 230.0970, found 230.0970.

3.1.8. Methyl 4-(phenylethynyl)benzoate (7). Method A. Oil, 40 mg (7%). ^{1}H NMR in correspondence with literature;[44] ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 7.20–7.60 (m, 7H), 7.98–8.02 (m, 2H). MS (EI^+) *m/z* 236 (M^+, 100).

3.1.9. Methyl 3-(phenylethynyl)benzoate (8). Method A (using in addition 10 mol % tri(*o*-tolyl)phosphine). Solid, 498 mg (84%), mp 77.0–78.2 °C (lit.[45] mp 77–79 °C). ^{1}H NMR in correspondence with literature;[46] ^{1}H NMR ($CDCl_3$) 3.93 (s, 3H), 7.34–7.46 (m, 4H), 7.52–7.57 (m, 2H), 7.68–7.72 (m, 1H), 7.97–8.02 (m, 1H), 8.19–8.23 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 52.3, 88.3, 90.3, 122.9, 123.8, 128.4, 128.5, 128.6, 129.2, 130.5, 131.7, 132.8, 135.7, 166.5. MS (EI^+) *m/z* 236 (M^+, 100).

3.1.10. Methyl 2-(phenylethynyl)benzoate (9). Method A (from methyl 2-iodobenzoate, using in addition 10 mol % tri(*o*-tolyl)phosphine). Oil, 505 mg (85%). ^{1}H NMR in correspondence with literature;[47,48] ^{1}H NMR ($CDCl_3$) 3.95 (s, 3H), 7.31–7.65 (m, 8H), 7.92–7.98 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 52.2, 88.2, 94.3, 123.3, 123.7, 127.9, 128.4, 128.5, 130.5, 131.3, 131.7, 131.9, 134.0, 166.7. MS (ES^+) *m/z* 259 ($[M+Na]^+$, 100).

3.1.11. 2-(Phenylethynyl)pyrimidine (10). Method A (using in addition 10 mol % tri(*o*-tolyl)phosphine). Solid, 197 mg (44%), mp 84–86 °C (lit.[35] mp 84–85 °C). ^{1}H NMR ($CDCl_3$) δ 7.15–7.22 (m, 1H), 7.32–7.40 (m, 3H), 7.62–7.69 (m, 2H), 8.71–8.76 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 77.5, 87.9, 119.7, 121.2, 128.7, 129.7, 132.5, 153.2, 157.3. MS (ES^+) *m/z* 181 ($[M+1]^+$, 100). HRMS: Calcd for $C_{12}H_9N_2$ 181.0766, found 181.0766.

3.1.12. 5-(Phenylethynyl)pyrimidine (11). Method A (using in addition 10 mol % tri(*o*-tolyl)phosphine). Solid, 375 mg (83%), mp 51.5–53.5 °C. ^{1}H NMR ($CDCl_3$) δ 7.35–7.42 (m, 3H), 7.53–7.58 (m, 2H), 8.85 (s, 2H), 9.14 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 82.3, 96.3, 119.9, 121.8, 128.6, 129.4, 131.8, 156.7, 158.6. MS (EI^+) *m/z* 180 (M^+, 100). Anal. Calcd for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.54. Found: C, 79.83; H, 4.55; N, 15.30.

3.1.13. 4-(3-Pyridylethynyl)benzaldehyde (15). Method A (using in addition 10 mol % tri(*o*-tolyl)phosphine). Solid, 309 mg (60%); a sample was recrystallized (EtOAc/hexane) for mp and elemental analysis; mp 98.5–99.3 °C. ^{1}H NMR ($CDCl_3$) δ 7.29–7.35 (m, 1H), 7.68–7.73 (m, 2H), 7.82–7.93 (m, 3H), 8.57–8.63 (m, 1H), 8.78–8.83 (m, 1H), 10.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 89.7, 91.6, 119.7, 123.1, 128.7, 129.6, 132.2, 135.8, 138.6, 149.2, 152.4, 191.3. MS (ES^+) *m/z* 208 ($[M+1]^+$, 100). Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 80.81; H, 4.52; N, 6.89.

3.1.14. 2-(3-Pyridylethynyl)aniline (16). Method A (using in addition 10 mol % tri(*o*-tolyl)phosphine). Solid, 394 mg (81%); a sample was recrystallized (EtOAc) for mp and elemental analysis; mp 113.5–115.0 °C (lit.[49] mp 104–106 °C). ^{1}H NMR and ^{13}C NMR in correspondence with literature;[49] ^{1}H NMR ($CDCl_3$) δ 4.32 (br s, 2H), 6.70–6.77 (m, 2H), 7.13–7.20 (m, 1H), 7.24–7.31 (m, 1H), 7.35–7.41 (m, 1H), 7.76–7.82 (m, 1H), 8.50–8.55 (m, 1H), 8.74 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 89.4, 91.2, 107.0, 114.5, 118.0, 120.5, 123.1, 130.3, 132.3, 138.2, 148.0, 148.5, 152.0. MS (ES^+) *m/z* 195 ($[M+1]^+$, 100). Anal. Calcd for $C_{13}H_{10}N_2 \cdot 0.05$ EtOAc: C, 79.81; H, 5.28; N, 14.10. Found: C, 79.86; H, 5.32; N, 14.45.

3.1.15. 3,3′-Ethynediyl-bis-pyridine (17). Method A (using in addition 10 mol % tri(*o*-tolyl)phosphine). Solid, 369 mg (82%); mp 53–56 °C (lit.[50] mp 60–62 °C). ^{1}H NMR ($CDCl_3$) δ 7.26–7.32 (m, 2H), 7.80–7.86 (m, 2H), 8.55–8.60 (m, 2H), 8.78 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 89.2, 119.8, 123.1, 138.5, 149.1, 152.3. MS (ES^+) *m/z* 181 ($[M+1]^+$, 100).

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Gas-phase acidity of sulfonamides: implications for reactivity and prodrug design

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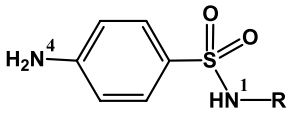
Abstract—A computational study at the density functional theory level was performed on bioactive and model sulfonamides with the aim of determining the factors affecting the acidity of the sulfonamido group. The effects of introducing different substituents at either the *para*-aryl or the N^1-sulfonamide positions were independently analyzed. A linear correlation was found between sulfonamide acidity and the Hammett constants or charge of the SO_2 group of substituents at the *para*-aryl position. Most N^1-substituents were taken from bacteriostatic sulfonamide structures and presented a more complex behavior, possibly due to a conjugation of steric and electronic factors. In the latter situation, sulfonamide acidity and the charge of the SO_2 group were not linearly correlated. Interestingly, the acidity of the sulfonamido group was found to be correlated with the reactivity of sulfa drugs towards acylating agents. The implications for the design of suitable sulfonamide prodrugs are discussed.

1. Introduction

The characterization of sulfonamides as chemotherapics is more than half a century old.[1] Since then, the sulfonamido group—SO_2NH—has been found as a key structural motif shared by a large number of bioactive compounds, spanning a wide variety of biological effects, such as antimicrobial activity, specific enzyme inhibition, hormone regulation, among others.[2] The most popular sulfonamides are *p*-aminobenzensulfonamides, or sulfanilamides (**1**), which are bacteriostatic due to their resemblance to *p*-aminobenzoic acid (PABA, **2**), used by bacteria in the biosynthesis of the folic acid required for their growth.[3]



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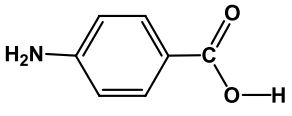

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Most bacteriostatic sulfonamides are characterized by a *p*-aminoaryl moiety and structural diversity has been obtained basically by variation of the R-group linked to the N^1 atom of the sulfonamido group. Generally, this R group is a heterocyclic structure that renders the compound several times more active than the original sulfanilamide (R=–H). In the early days of sulfonamide therapy, experimental studies by Bell et al.[4] Kumler et al.[5,6] and, 20 years later, Seydel,[7] have been devoted to the analysis of stereoelectronic factors that could be related to bacteriostatic activity, paying special attention to the role of the acidity of the sulfonamido group.[4,7] These studies suggested that bacteriostatic activity is favored by decreased sulfonamide acidity (larger ΔG° values), which was confirmed in a very recent theoretical work published by Soriano-Correa and co-workers.[8] Also, distinct therapeutical effects are often associated to different acidity ranges, as illustrated by the higher acidity of antiglaucoma sulfas when compared to their cancerostatic counter parts.[9] Thus, it seems that the acidity of the sulfonamido group, and factors affecting it, are key features ruling the physico-chemical properties that modulate the sulfonamide bioactivity.

Due to the well-known problems of sulfonamide therapy, especially those related to growing bacterial resistance, adverse effects and low bioavailability,[10–12] we have been working on the synthesis of N^1-acyl and N^4-acylsulfanilamides as potential prodrugs of antimalarial sulfonamides. These antimalarials were acylated with amino acids and dipeptides, which are interesting carriers for drug delivery in vivo. Dipeptide carriers have several advantages, since they are non-toxic, non-immunogenic and can trigger the

Keywords: Acylation; Amino acid; Bioactive; Density functional theory; Gas-phase acidity; Peptide; Prodrug; Sulfonamide.
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intestinal oligopeptide transporter, favoring prodrug absorption in the gastro-intestinal tract.[13–16] Also, dipeptide-based prodrugs can be activated by a strictly chemical process, an intramolecular cyclization to a 2,5-diketopiperazine, and, thus, not subject to biological variability.[13,17–19] The development of efficient sulfonamide prodrugs is a priority in medicinal chemistry, since sulfonamides such as sumatriptan (a 5-HT_1 agonist for migraine treatment), acetazolamide (antiglaucoma carbonic anhydrase inhibitor) or nimesulide (anti-inflamatory COX-2 inhibitor) still suffer from several problems related to low bioavailability or serious adverse effects.[10,11,20] Further, N-acylated and amino acid based sulfonamides are emerging as potential antiviral and antitumoral drugs[21,22] and, thus, a detailed description of *N*-acylsulfonamides is mandatory.

In a previous experimental work, we found that sulfanilamide acylation was regiosselective (Scheme 1) and that the degree of regiosselectivity and reactivity depended of the drug employed.[13] This prompted us to perform a brief computational analysis of the geometrical and thermodynamic factors ruling the acylation reactions between amino acid glycine and four sulfanilamides, in order to explain our experimental findings.[13] We now wish to present an extensive computational study of the gas-phase acidity of both bioactive and model sulfonamides, in order to evaluate the relevance of this property on their reactivity towards acylating agents. Implications of the present study for prodrug design will be discussed.

2. Computationals details

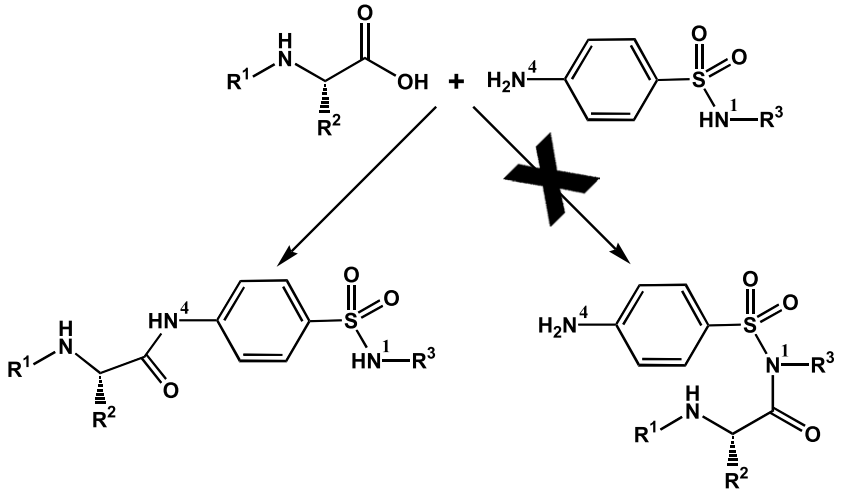
In the present work, the density functional theory based B3LYP three-parameter hybrid method proposed by Becke[23] was used for all the calculations. These computations were performed by means of the GAMESS-US[24] and Gaussian 98[25] suites of programs. The B3LYP method comprises an exchange-correlation functional that mixes the non-local Fock exchange with the gradient-corrected form of Becke[23] and adds the correlation functional proposed by Lee et al.[26] The use of the B3LYP method is known to be an excellent computational choice both to obtain geometric and thermodynamic data.[27–29] In fact, the three *a*, *b* and *c* parameters in this hybrid approach were determined by fitting to experimental thermochemical data which include atomization energies, ionization energies, proton affinities and atomic energies of a large set of molecules.[23] Very recently, several different thermochemical properties have been computed at the B3LYP level of theory and the results obtained compare excellently with available experimental data.[29,30–36]

In the DFT calculations, the geometry optimization runs were performed without symmetry constraints for all compounds considered and the atomic electronic density of all atoms was described by the standard 6-31+G(d) basis set. The calculation of frequencies was performed to ensure that a minimum is located and also to correct total energies by including the Zero-Point Energies, ZPE, as well as translational (H_T), rotational (H_R) and vibrational (H_V) contributions to the enthalpy at $T=298.15$ K. Then, a single-point energy calculation (E_0) was performed at the B3LYP/6-311+G(2d,2p) level of theory on the 6-31+G(d) optimized geometries. The thermally corrected enthalpy of species A is calculated as:

$$H(\mathrm{A}, 298.15\ \mathrm{K}) = E_0(\mathrm{BL}) + \mathrm{ZPE}(\mathrm{BS}) + H_T(\mathrm{BS}) + H_R(\mathrm{BS}) + H_V(\mathrm{BS}) + RT \quad (1)$$

where BL and BS stand for basis large (6-311+G(2d,2p)) and basis small (6-31+G(d)), respectively, and *RT* results from the *PV* term.

From previous experience, the use of this combined strategy, B3LYP/6-311+G(2d,2p)//B3LYP/6-31+G(d) approach, yields identical results to that obtained from full-optimization and frequencies calculations performed at the B3LYP/6-311+G(2d,2p) level,[31–33] i.e. where all terms in equation (1) are computed using the large basis. In these works, the combined approach was tested for several different thermodynamic properties, such as enthalpies of formation, bond dissociation enthalpies, gas-phase acidities



Scheme 1.

and proton or electron affinities. In the present work, the gas-phase acidity was calculated as:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (2)$$

with the enthalpic difference (ΔH°) associated to the reaction SULFA-H$\rightarrow$SULFA$^-$ + H$^+$ given as:

$$\Delta H^\circ = H^\circ(\mathrm{SULFA}^-) + H^\circ(\mathrm{H}^+) - H^\circ(\mathrm{SULFA-H}) \quad (3)$$

This equation may be simplified to

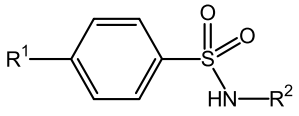
$$\Delta H^\circ = H^\circ(\mathrm{SULFA}^-) - H^\circ(\mathrm{SULFA-H}) + 5/2RT \quad (4)$$

since the enthalpy of the proton is reduced to the sum of the contributions from translational motion ($H_T = 3/2RT$) and from the pV term. The gas-phase acidity computed with the combined strategy (BL and BS basis sets) for *p*-aminobenzenesulfonamide was tested against the gas-phase acidity obtained with the B3LYP/6-311+G(2d,2p) approach; the two results differ by only 0.1 kJ/mol.

3. Results and discussion

3.1. Effects of R^1 and R^2 on sulfonamide acidity

In a previous experimental and theoretical work we found that the acylation of four different *para*-aminobenzenesulfonamides with glycine was regiosselective and governed by a combination of geometrical, thermodynamic and electronic factors.[13] These findings drove us to the present study, where the influence of the sulfonamido group acidity on chemical reactivity and other sulfonamide properties is discussed. We analyzed separately the effects on sulfonamido acidity of: (i) the R^1 group (*para*-aryl substituent) and, (ii) the R^2 group attached to N^1 (**3**). We chose groups that were either present in bioactive sulfonamides or useful to establish structure–activity relationships (SAR).



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In Table 1, a compilation of the most interesting geometric parameters is reported for several different *para*-R^1-benzenesulfonamides, with R^1=H, F, Cl, OH, CN, NH_2, NO_2, CH_3 and OCH_3. The R^1 substituents were chosen in such a way that a wide range of Hammett constants could be spanned, allowing us to analyse the effect of varying substituents from those having large electron withdrawing effects to those with large electron donation capacity. A close inspection of parameters given in Table 1 shows that the length of the N–H bond that may suffer heterolytic cleavage upon acylation with amino acids is unaffected by the electronic effects imposed by the different R^1 groups tested. This is also the case for the S=O bond lengths, which vary between 1.466 and 1.470 Å. This is in clear contrast with the significantly larger variations found for the ring-sulfur bond lengths. Such behavior suggests that only the sulfur atom is largely affected by the presence of different groups attached to the aromatic ring at the *para* position, leaving the oxygen atoms lessly affected. When compared with R^1=H, electron donating groups such as NH_2 lead to an increase in the S=O and S–N bond lengths, and to a decrease in the Ar–S distance. The opposite is found for $R^1=NO_2$, where S=O and S–N bonds are shortened and the Ar–S bond length is enlarged. In all compounds studied, the non-planar O=S=O group is *cis*-oriented with the H–N^1–H′ bonds. The small influence of the R^1 substituent on the sulfonamido group is also noticed from the slight variation in the H–N^1–S–H′ dihedral angle, which varies between 121.7 and 123.8° for $R^1=NH_2$ and $R^1=NO_2$, respectively.

Table 1 also displays the enthalpies of inversion for the different compounds considered, calculated as the difference between the enthalpy at T=298.15 K for the fully-optimized H–N^1–H′ *trans*-oriented geometry and that for the H–N^1–H′ *cis*-oriented species. The values lie in the 2.8–4.9 kJ/mol range, respectively, for NH_2 and NO_2 groups, and are correlated with the calculated S–N bond lengths. Indeed, the shorter S–N bond in the nitro-substituted compound is responsible for a less effective accommodation of the nitrogen atom lone-pair, when compared to its amino-substituted counterpart, thus explaining the different enthalpies of inversion found.

Gas-phase acidities calculated as ΔG° at the B3LYP/6-311+G(2d,2p)//B3LYP/6-31+G(d) level of theory, are also reported in Table 1. This thermodynamic property is a direct measure of the promptness of the sulfonamido group to lose one proton during the acylation reaction. The ΔG° calculated for the nine different R^1-substituted sulfonamides show that, despite the large intramolecular distance between the *para*-substituent and the sulfonamido group, this

Table 1. Selected geometrical parameters, enthalpies of inversion and gas-phase acidities of benzenesulfonamides substituted at the R^1 position computed at the B3LYP//6-311+G(2d,2p)//B3LYP/6-31+G(d) level of theory

R^1 (R^2=H)	Geometrical parameters (Å)				ΔH° (kJ/mol)	ΔG° (kJ/mol)
	d(S=O)	d(Ar–S)	d(S–N)	d(N–H)	Inversion	Acidity
–H	1.468/1.468 (1.488/1.500)	1.797 (1.842)	1.700 (1.582)	1.018 (1.024)	3.6	1402.8
–F	1.468/1.468 (1.488/1.500)	1.794 (1.843)	1.700 (1.580)	1.019 (1.024)	4.4	1391.4
–Cl	1.468/1.468 (1.487/1.499)	1.796 (1.843)	1.699 (1.580)	1.019 (1.024)	4.2	1385.2
–OH	1.469/1.469 (1.489/1.502)	1.788 (1.843)	1.702 (1.580)	1.019 (1.024)	3.6	1407.2
–CN	1.467/1.467 (1.486/1.497)	1.803 (1.840)	1.695 (1.579)	1.019 (1.024)	4.7	1361.1
–NH_2	1.470/1.470 (1.490/1.502)	1.783 (1.841)	1.705 (1.581)	1.019 (1.024)	2.8	1421.9
–NO_2	1.466/1.466 (1.484/1.496)	1.804 (1.834)	1.693 (1.581)	1.018 (1.024)	4.9	1352.2
–CH_3	1.469/1.469 (1.489/1.501)	1.793 (1.841)	1.702 (1.582)	1.019 (1.024)	3.6	1404.3
–OCH_3	1.470/1.469 (1.489/1.502)	1.787 (1.841)	1.703 (1.581)	1.019 (1.024)	3.5	1411.0

Geometrical parameters given in parenthesis refer to the corresponding anionic forms.

property is largely affected by the nature of R^1. This is clearly depicted in Fig. 1(a), where the calculated ΔG° are plotted against the Hammett σ constants for the different R^1 employed.[37] A clear correlation is observed ($r^2=0.94$), showing that the calculated ΔG° strongly depend on the electronic effects of the nine R^1 substituents studied. This dependence is reflected by free energy differences as high as 70 kJ/mol, found between the *para*-amino- and the *para*-nitrobenzenesulfonamides. This is an extremely important finding, since it shows that substitution at R^1 is also responsible for the different acidities that characterize sulfonamide-based drugs.

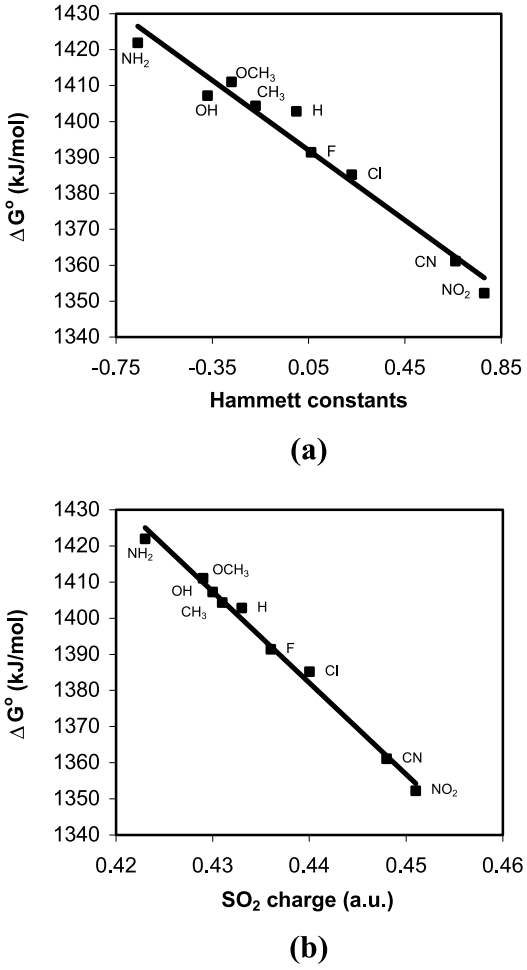


Figure 1. Correlation between calculated gas-phase acidities (as ΔG°) of R^1-**3** compounds and (a) Hammett σ constants for the R^1 substituent; (b) the charge in the SO_2 group.

Depending on the substituent considered, calculated charges at the sulfonamido group and derived from a Natural Population Analysis[38] show larger variations in oxygen and sulfonamido hydrogen atoms than in nitrogen and sulfur. In an earlier work of Bell et al.[4] concerning only N^1-substituted sulfanilamides, **1**, an increase of the compound acidity (which is equivalent to a decrease in ΔG°) was found to cause a decrease in the SO_2 group negative charge and in bacteriostatic activity. The variation of calculated ΔG° with the charge of the SO_2 group is depicted in Fig. 1(b). As it can be seen, the correlation between sulfonamide ΔG° and the atomic populations at the SO_2 group determined by the *para*-substituent of the aromatic ring is now linear ($r^2=0.99$). This shows that direct substitution in the aromatic ring has also a great effect in the charge of the sulfonamido group that is highly correlated with the electronic effects caused by the substituent.

In a recent work, Soriano-Correa et al.[8] suggested that sulfonamide activity was accompanied by a small torsion barrier, i.e. more rigid molecules will be more active. In order to check the rigidity of sulfonamide, the energetics of the rotation of the aromatic ring with respect to the sulfonamido group was calculated for sulfanilamide and is depicted in Fig. 2. At the B3LYP/6-31+G(d) level of theory, the calculated energy barrier is of about 8.5 kJ/mol, slightly lower than for C–C rotation in ethane ($\sim$12 kJ/mol). This suggests almost free rotation around the Ar–S bond, despite the neighboring oxygen atoms of the sulfonamido group. The calculated energy of rotation will be valid for the generality of sulfanilamides since substitution at both R^1 and R^2 positions will not sterically affect the ring-S bond rotation.

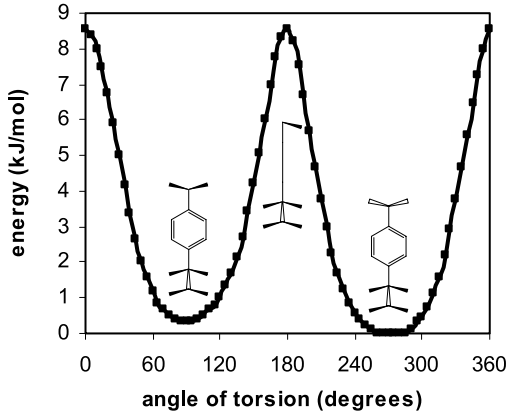
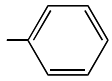
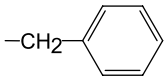
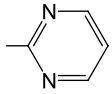
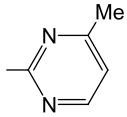
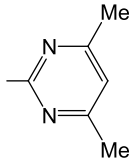
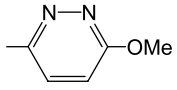
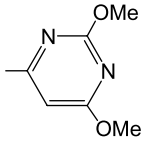
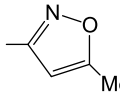
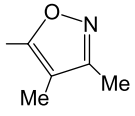
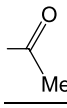


Figure 2. Potential energy surface for the rotation of the phenyl ring around the ring-S axis calculated at the B3LYP/6-31+G(d) level of theory. The x-axis values of 0 and 180° mean that the aromatic ring lies between the SO_2 moiety.

As mentioned above, despite the large distance between R^1 and N^1 positions, the R^1 substituent seems to have a crucial role in the acidities of sulfonamide derivatives. An enhanced effect in the chemical and biological properties that distinguish different sulfonamide-based drugs should be expected if N^1 substitution takes place due to its proximity to the leaving proton. Thus, the role of different R^2 groups attached to the N^1 atom should be equally inspected. In view of this, we analyzed the influence of several different R^2 substituents on the structure of the sulfonamido group, as reported in Table 2. The substituents were chosen taking into account the structures of some sulfonamide-based drugs, with the difference that the *para*-amino group is now absent. In comparison with data from Table 1, larger changes in the internal geometry of the sulfonamido group are now observed, as expected from the closer distance between the substituent group and the sulfur atom. First, if an oxygen atom is placed in a position adjacent to the carbon-sulfonamido nitrogen bond (two last entries in Table 2), the S–N bond length is noticeably increased when

Table 2. Selected geometrical parameters and gas-phase acidities of benzenesulfonamides substituted at the R^2 position computed at the B3LYP//6-311+G(2d,2p)//B3LYP/6-31+G(d) level of theory

R^2 (R^1=H)	Geometrical parameters (Å)					ΔG° (kJ/mol)
	d(S=O)	d(Ar–S)	d(S–N)	d(N–H)	d(N-R^2)	Acidity
–H	1.468/1.468 (1.488/1.500)	1.797 (1.842)	1.700 (1.582)	1.018 (–)	1.018 (1.024)	1402.8
$-NH_2$	1.468/1.473 (1.484/1.500)	1.795 (1.837)	1.730 (1.615)	1.021 (–)	1.411 (1.451)	1415.9
$-NO_2$	1.463/1.457 (1.478/1.478)	1.784 (1.820)	1.768 (1.676)	1.021 (–)	1.403 (1.350)	1289.6
	1.466/1.463 (1.482/1.493)	1.800 (1.830)	1.704 (1.598)	1.017 (–)	1.425 (1.382)	1367.7
	1.469/1.471 (1.485/1.498)	1.800 (1.839)	1.685 (1.579)	1.018 (–)	1.477 (1.449)	1385.8
	1.467/1.461 (1.481/1.484)	1.794 (1.826)	1.711 (1.624)	1.017 (–)	1.390 (1.347)	1360.8
	1.468/1.461 (1.482/1.484)	1.794 (1.827)	1.710 (1.623)	1.016 (–)	1.392 (1.348)	1366.0
	1.468/1.461 (1.482/1.484)	1.795 (1.827)	1.707 (1.621)	1.017 (–)	1.394 (1.350)	1370.3
	1.463/1.465 (1.479/1.495)	1.799 (1.830)	1.708 (1.596)	1.020 (–)	1.415 (1.372)	1354.9
	1.464/1.462 (1.479/1.489)	1.798 (1.825)	1.701 (1.614)	1.017 (–)	1.401 (1.357)	1344.2
	1.463/1.463 (1.481/1.494)	1.798 (1.832)	1.706 (1.594)	1.019 (–)	1.400 (1.370)	1350.2
	1.464/1.462 (1.480/1.489)	1.797 (1.824)	1.725 (1.601)	1.019 (–)	1.393 (1.355)	1332.6
	1.468/1.458 (1.483/1.483)	1.792 (1.827)	1.724 (1.637)	1.016 (–)	1.391 (1.356)	1344.3

Geometrical parameters given in parenthesis refer to the corresponding anionic forms.

compared to that in benzenesulfonamide. Second, in the case of a nitrogen atom placed in a position adjacent to the carbon-sulfonamido nitrogen bond, the S–N bond is less changed if donor groups are attached to the heterocyclic ring. This is easily noticed for sulfadiazine, sulfamerazine and sulfamethazine derivatives, entries 6–8 in Table 2, where a slight increase in the S–N bond is found when on going from the sulfamethazine to the sulfadiazine derivative followed by correspondent slight decrease in the N-R^2 bond length.

For the list of compounds reported in Table 2, the variation of calculated ΔG° with the charge of the SO_2 group is depicted in Fig. 3(a). In this case, the correlation between acidity and charge is not linear, which suggests a rather different influence caused by the substituent in sulfonamide acidity. The variation ΔG°(sulfadiazine) < ΔG°(sulfamerazine) < ΔG°(sulfamethazine) is associated with a negligible decrease in the positive charge calculated for the SO_2 group (0.487; 0.486; 0.483 a.u., respectively). These differences in the SO_2 group charge do not seem to be the only cause for a 6 kJ/mol variation in ΔG° between sulfadiazine and sulfamerazine derivatives, or for 4 kJ/mol between the sulfamerazine and sulfamethazine derivatives,

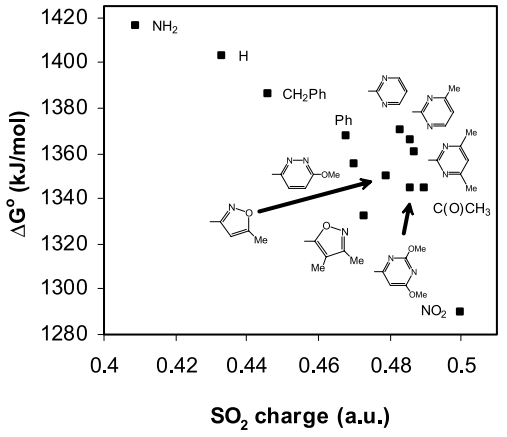


Figure 3. Correlation between calculated gas-phase acidities (as ΔG°) of R^2-**3** compounds and (a) the charge in the SO_2 group; (b) experimental pK_a's of the parent sulfa drugs, as reported in Ref. 4.

since the small charge variation is connected with a larger ΔG° variation. Further, if we consider the sulfamethoxypyridazine and sulfadimethoxine derivatives, both incorporating methoxyl groups attached to the aromatic ring, a ΔG° difference of $\sim$10 kJ/mol is now accompanied by a larger variation in the SO_2 group charges, 0.470 and 0.486 a.u. for sulfamethoxypyridazine and sulfadimethoxine derivatives, respectively. Also important and contrarily to what was found for sulfadiazine and methyl substituted sulfadiazine derivatives, the decrease in ΔG° is now associated with a decrease in the S–N bond length. Finally, the difference between NPA charges in the SO_2 moiety calculated for sulfamethoxypyridazine and sulfadimethoxine derivatives is identical to the difference found for sulfadimethoxine and the NO_2-substituted sulfonamide derivatives that correspond to variations in ΔG° of 10 and 55 kJ/mol, respectively. Thus, and as observed for R^1 substituents, the charge on the SO_2 group cannot be seen as the only factor affecting sulfonamide acidity. Therefore, a conjugation of geometrical and electronic effects determined by the R^1 and R^2 substituents, including delocalization through aromatic rings on either side of the SO_2 group, must underlie sulfonamide reactivity and bioactivity. This should be interpreted as an addition, and not a correction, to the suggestions of Bell et al.[4]

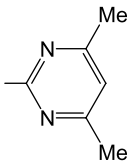
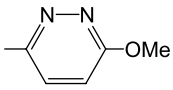
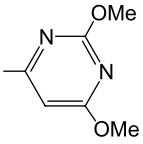
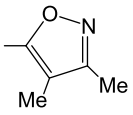
It is noteworthy that the computed acidities herein reported present some correlation with previously published pK_a, as shown in Fig. 3(b). In fact, if we do not consider the phenyl derivative, there is a linear correlation, which gives support to the quality of the computed thermodynamic data reported in the present work. Following conclusions by Bell et al.[4] these data have implications in terms of correlation with bacteriostatic activity. Indeed, computed acidities for compounds considered in Fig. 3(b) are somewhat correlated with the bacteriostatic activities against *E. coli* reported by the same authors (data not shown).[4] However, the correlation is not perfect, as one should expect from the fact that linear correlations have only been found for series of homologous sulfonamides.[4,39,40]

The present work is also relevant for sulfonamide therapeutical properties other than bacteriostatic activity. Aromatic sulfonamides used to treat glaucoma are known to exhert their therapeutical action through inhibition of the human zinc-enzyme carbonic anhydrase II (HCA II). These sulfonamides bind the zinc dication of HCA II through their deprotonated sulfonamide nitrogen, thus $-SO_2NH-$ acidity has an important role on sulfonamide ability to inhibit HCA II. Indeed, recent studies by Remko and co-workers show that the acidity of common sulfa drugs such as acetazolamide, brinzolamide and dorzolamide is correlated with their Zn^{2+}-binding affinity.[41,42]

3.2. Implications of sulfonamide reactivity on prodrug design

As above mentioned, this study was set out to shed some light on the understanding of the N^1 versus N^4 acylation reaction between glycine and four different *para*-aminobenzenesulfonamides, previously reported.[13] In the present notation, acylation at position N^1 means reaction at the sulfonamido group while acylation at the N^4 nitrogen means reaction at the 4-anilino group. Experimentally, sulfamethazine, sulfamethoxypyridazine, sulfadimethoxine and sulfisoxazole were reacted with N^{α}-protected glycine, and both the position and yield of acylation were seen to vary with sulfonamide. The yields of N^4-acylation with N^{α}-Boc-GlyOH were 52%, 43% and 41% for the three first compounds, respectively (Table 3). For sulfisoxazole, high levels of starting materials were recovered, although the formation of several products could be detected. N^{α}-ZGlyOH was also reacted with sulfamethazine and sulfisoxazole, for comparison purposes. Again, reaction with sulfamethazine yielded 41% of the N^4-derivative, whereas reaction with sulfisoxazole yielded a complex mixture from which 8% of the N^1-derivative could be isolated. Thus, it was proposed that sulfisoxazole reacts both at N^1 and N^4 with very low yields for both reactions. These experimental observations seem to be directly correlated with the acidity of these four sulfas. Data on Table 3 show that ΔG° decreases from sulfamethazine to sulfisoxazole, which comes associated with a decrease in N^4-acylation yields. Further, lower ΔG° values are correlated with lower energetic barriers for N^1-acylation. This shows that, as the sulfonamide gets more acidic, the easier becomes the

Table 3. Correlation between gas-phase acidity in the sulfonamido group and published experimental yields of N^4-acylation and enthalpies for N^1-acylation

R^2 ($R^1=NH_2$)	$\Delta G°$ (kJ/mol)[a]	Yield (%) BocGlyOH	Yield (%) ZglyOH	$\Delta H°$ (kJ/mol)[b] sulfa+glycine
	1382.5 (+12.2)[c] 1329.4[d] (−40.9)[e]	52	41	76.1
	1369.8 (+14.9)[c]	43	Not tested	68.5
	1357.1 (+12.9)[c]	41	Not tested	50.3
	1348.9 (+16.3)[c]	Intractable mixture	8[f]	34.4

[a] B3LYP//6-311+G(2d,2p)//B3LYP/6-31+G(d).
[b] B3LYP//6-311+G(d,p)//B3LYP/6-31+G(d).
[c] Difference between $R^1=NH_2$ and $R^1=H$ compounds.
[d] $R^1=NO_2$.
[e] Difference between $R^1=NO_2$ and $R^1=H$ compounds.
[f] N^1-acylation product.

introduction of an amino acid or peptide carrier at the sulfonamido group (N^1).

These findings have obvious implications for the design of peptide-based sulfonamide prodrugs. The higher acidity of the $–SO_2NH–$ group with respect to the $–NH_2$ group reflects the relative stabilities of the corresponding conjugate bases. From the higher stability of SO_2N^- with respect to $–NH^-$, together with the higher steric compression around the N^1 atom, one expects the sulfonamide to behave as a better leaving group from an N^1-acylsulfonamide than from an N^4-acylsulfonamide. Indeed, all N^4-acylsulfonamides derived from N^α-amino acids and dipeptides prepared in our laboratory were found to be useless as prodrugs, since they do not release the parent drug at physiological pH and temperature, with slow release being observed only under harsh conditions (pH 12, 60 °C).[43] Further, irreversible acylation at N^4 blocks the first site of sulfonamide-enzyme interaction that underlies the bacteriostatic action of most sulfa drugs.[1] This reinforces the importance of derivatizing sulfonamides at the $–SO_2NH–$ group to produce suitable prodrugs or novel drugs and, thus, the relevance of acidity studies on this class of compounds.

The difference between calculated $\Delta G°$ for sulfonamide derivatives reported in Table 1 and their parent sulfas listed in Table 3, i.e. $R^1=NH_2$ and $R^1=H$ compounds, is also shown in Table 3. In the case of sulfamethazine, the calculated $\Delta G°$ value for the compound with $R^1=NO_2$ is also given. The differences show that the *para*-amino still increases $\Delta G°$ while the *para*-nitro group decreases its value. Further, when R^2 is not equal to H the differences in acidity are slightly decreased but, importantly, its effects on the final computed acidity follow the same direction as given by the values compiled in Table 1. Thus, the Hammett σ constants may be extremely useful for the future design of sulfa drugs with tailored acidities.

4. Conclusions

This theoretical study was set out to analyze the determinants of sulfonamide acidity and the influence of the latter on sulfonamide reactivity towards acylating agents, such as amino acids. To achieve our purposes, DFT calculations, based on the B3LYP method, were carried out to fully optimize the geometry of all compounds under study and to extract their enthalpies at $T=298.15$ K. These enthalpies were then used to compute gas-phase acidities of the sulfonamides. The main conclusions that can be withdrawn from the present work are:

i. There is a linear correlation between sulfonamide acidity and the Hammett constants of substituents at the *para*-aryl position.
ii. Sulfonamide acidity was found to be linearly correlated with the charge of the SO_2 group in the case of para-aryl substitution in agreement with previously reported works, whereas a conjugation of steric and electronic factors determined by the N^1-substituent seems to govern sulfonamide acidity.
iii. The acidity of the sulfonamido group was found to be correlated with the reactivity of some sulfa drugs towards amino acids as acylating agents.
iv. The dipeptide carrier approach to design the sulfonamide prodrugs will expectedly be more successful with more acidic sulfas.
v. Hammett constants may be useful indicators for the design of sulfonamides with tailored acidities.

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Dibromomethane as one-carbon source in organic synthesis: total synthesis of (±)- and (−)-methylenolactocin

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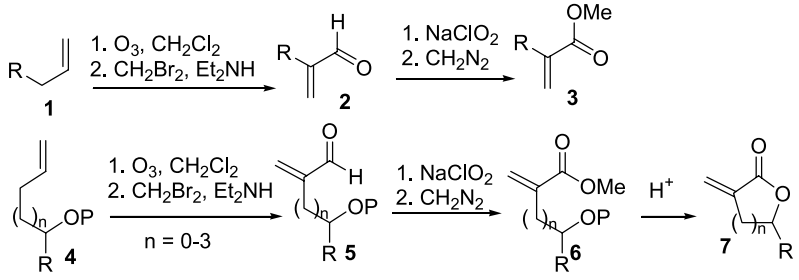
Abstract—A general method was developed to construct monocyclic α-methylene-γ-butyrolactone moiety. The key step is to introduce the α-methylene group by the ozonolysis of mono-substituted alkenes followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH. Application of this key step in the total synthesis of the (±)- and (−)-methylenolactocin was described.

1. Introduction

We have reported that the ozonolysis of mono-substituted alkenes **1** followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH affords α-substituted acroleins **2** in good yields.[1] The α-substituted acroleins **2** were easily oxidized by $NaClO_2$ and then treated with CH_2N_2 to give α-substituted acrylate **3** in excellent yields. Each step in Scheme 1 is mild so that it is suitable to prepare the α-substituted acrylates with labile groups.[2] This methodology was also applied to prepare the α-methylene lactones **7** with different ring size (n=0–3) from the corresponding alkenol **4** (Scheme 1).[3]

The α-methylene-γ-butyrolactone moiety is a core skeleton in many structurally complex natural products.[4] The monocyclic, disubstituted α-methylene-γ-butyrolactones such as (−)-methylenolactocin **8a**,[5] *trans*-nephrosterinic acid **8b**,[6] and (−)-protolichesterinic acid **8c**[7] are noted for their biological activities, being antibacterial,[8a–h] antifungal,[8b] antitumor,[8h] and, in certain cases, growth regulating agents.[8i] The characteristic features of these natural products are described as follows. These structures contain α-methylene, β-carboxylic acid and γ-alkyl groups in different chain length. Both the β- and γ-substituents are *trans* to each other for compounds **8a**, **8b**, and **8c**, while they are *cis* to each other for *cis*-nephrosterinic acid (**8b′**) and alloprotolichesterolic acid (**8c′**) (Fig. 1). All these natural products have been synthesized by different methodologies.[9–12] In order to extend the synthetic applications of our α-methylenation methodology, our effort to the total synthesis of (−)-methylenolactocin is described in this article.



Scheme 1.

Keywords: Ozonides; α-Methylenation; γ-Butyrolactone; (−)-Methylenolactocin; (±)-Methylenolactocin.
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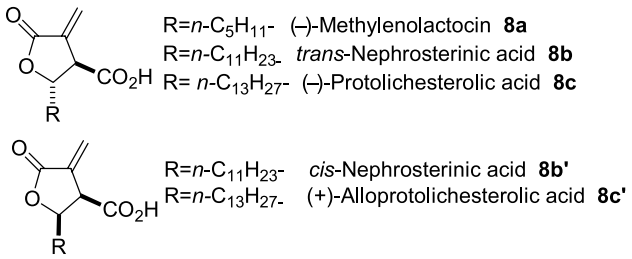


Figure 1. Monocyclic α-methylene-γ-butyrolactone natural products.

2. Results and discussions

2.1. Retrosynthetic analysis of our design in the total synthesis of α-methylene-β-carboxyl-γ-butyrolactone natural products

The retrosynthetic analysis of α-methylene-β-carboxyl-γ-butyrolactone **A** is shown in Figure 2. Several groups reported that structure **A** could be derived from the corresponding *cis*-isomer **B** via epimerization and hydrolysis in the same flask.[9l] The γ-butyrolactone **B** should be easily prepared from alkenol **C** by our methodology as shown in Scheme 1.[1] The stereoselective introduction of the β-stereogenic center of compound **C** from the allylation of the dianion of β-hydroxy ester **D** is a well known procedure in the literature.[13] The β-hydroxy ester **D** should be easily prepared by Reformatsky reaction[14a] from the methyl bromoacetate (**9**) and aldehyde (Fig. 2).

2.2. The total synthesis of the (±)-methylenolactocin (method I)

The known β-hydroxy ester **11** was prepared from methyl bromoacetate (**9**) and *n*-hexanal (**10**) in the presence of activated zinc in 78% yield.[14b] The allylation of β-hydroxy ester **11** following the procedure of Frater[13] gave the *anti*-β-hydroxy ester **12** in 85% yield (Scheme 2). The acetylation of the secondary alcohol **12** gave the corresponding acetate **13** in 96% yield. The ozonolysis of terminal olefin **13** followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH[1] afforded acrolein **14** in 78% yield. The acrolein **14** was oxidized by sodium chlorite in the presence of a chlorine scavenger (i.e., 2-methyl-2-butene) to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give methyl acrylate **15** in 79% yield.[2] Acid-catalyzed cyclization of methyl acrylate **15** in methanol gave *cis*-β,γ-disubstituted lactone **16** in 82% yield. Following the literature procedure,[9l] compound **16** was treated with 6 N HCl in butanone under refluxing for 2 h to give an inseparable mixture of methylenolactocin (**8a**) and butenolide **8a′** in a ratio of 4: 1 in 77% yield. The mole ratio was determined by the ^{1}H NMR integrations of the α-methylene protons (δ 6.47 and 6.02 ppm) of compound **8a** and the γ-methine proton (δ 5.11 ppm) of compound **8a′**. After treatment with CH_2N_2, their methyl esters **17** and **18** are separable and are spectroscopically identical with previously reported samples (Scheme 2).[9j,u]

We failed to avoid the formation of side product **8a′** derived from the double bond isomerization by employing the milder reaction conditions, such as using 4 N HCl or running the reaction at 40 °C. Therefore, if the hydrolysis and epimerization of compound **16** were arranged at the last two steps of the synthetic pathway, we have to face two problems. One is the formation of the minor product **8a′** and the other is the difficulty of separating **8a′** from the methylenolactocin (**8a**). The approach of Method I led us to accomplish the total synthesis of (±)-methylenolactocin in six operation steps in 31% overall yield from β-hydroxy ester **11**. In addition, we learned from this approach that the epimerization should be carried out at the earlier stage of the synthetic pathway in order to improve the efficiency of the synthesis.

2.3. The total synthesis of the (±)-methylenolactocin (method II)

In order to inverse the configuration of the secondary alcohol at the early stage, *anti*-β-hydroxy ester **12** was subjected to the standard Mitsunobu condition.[15] Unfortunately, the desired *p*-nitrobenzoate **19** was formed in poor

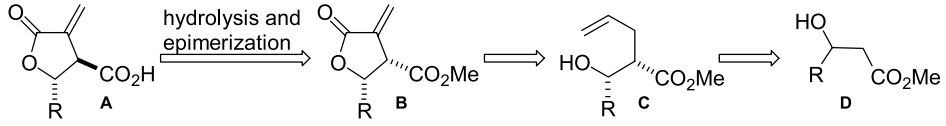
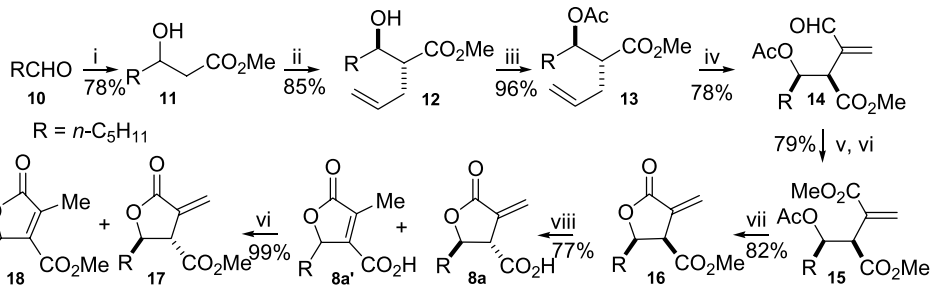


Figure 2. Retrosynthetic analysis of the methylenolactocin and its analogues.



Scheme 2. Reagents and conditions: (i) Zn, $BrCH_2CO_2Me$ (**9**), PhH, reflux, 4 h; (ii) 2.2 equiv LDA; $H_2C{=}CHCH_2Br$, −78 °C, 5 h; (iii) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 2 h; (iv) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv = 5:15), 2 h; (v) $NaClO_2$, *t*-BuOH, $NaH_2PO_4{\cdot}2H_2O$, $MeCH{=}CMe_2$, 8 h; (vi) CH_2N_2; (vi) cat. MeCOCl, MeOH, 24 h; (viii) 6 N HCl, butanone, 2 h.

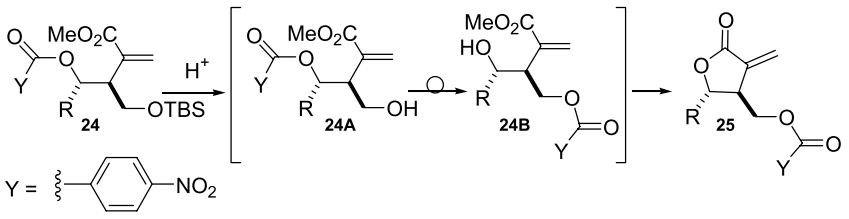
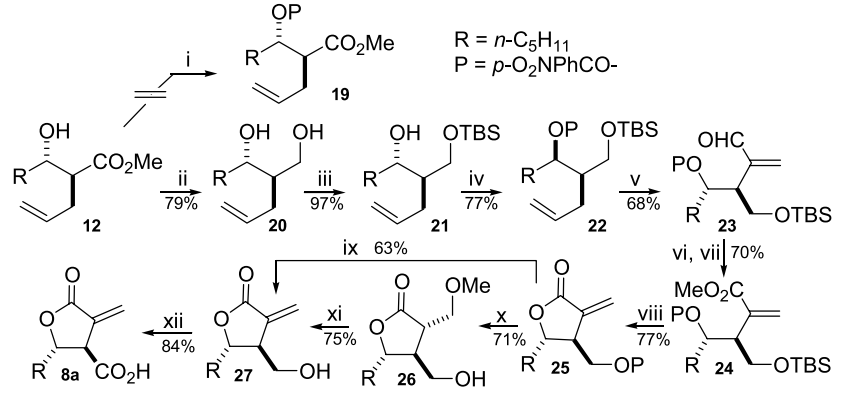


Figure 3. Proposed mechanism for the γ-lactone **25** formation via *p*-nitrobenzoyl group migration intermediate **24B**.

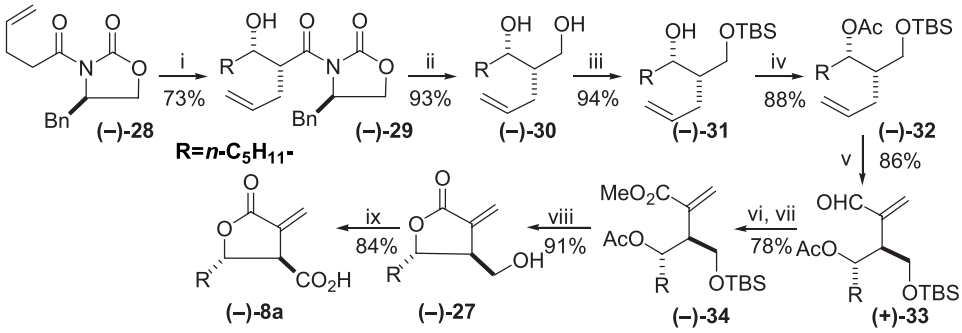
yield and most of the starting material **12** was recovered. The β-hydroxy ester **12** was reduced with Dibal-H to give the corresponding 1,3-diol **20** in 79% yield. The primary alcohol of 1,3-diol **20** was electively protected as *tert*-butyldimethylsilyl ether **21** in 97% yield. The configuration of the secondary alcohol **21** was inversed successfully by Mitsunobu reaction to give the corresponding *p*-nitrobenzoate **22** in 77% yield. The ozonolysis of terminal olefin **22** followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH afforded acrolein **23** in 68% yield. The acrolein **23** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give the methyl acrylate **24** in 70% yield. In the presence of a catalytic amount of HCl in methanol, the methyl acrylate **24** was cyclized to *trans*-β,γ-disubstituted lactone **25** in 77% yield. The possible mechanism for the formation of the lactone **25** from compound **24** was proposed as follows (Fig. 3). The *tert*-butyldimethylsilyl ether of compound **21** was selectively deprotected under acidic condition to give the primary alcohol **24A**. The 1,5-*p*-nitrobenzoyl group migration of the intermediate **24A** before the cyclization gave the lactone **25**. When the *p*-nitrobenzoate **25** was hydrolyzed by ammonium hydroxide in methanol, the corresponding primary alcohol **27** was obtained in 62% yield. Alternatively, when the *p*-nitrobenzoate **25** was treated with K_2CO_3 in methanol, not only the methanolysis, but also the 1,4-addition of methanol occurred to give the α-methoxymethyl lactone **26** in 71% yield. The β-elimination of compound **26** with DBU (i.e. 1,8-diazabicyclo[5.40]undec-7-ene) in refluxing benzene afforded the α-methylene lactone **27** in 75% yield. The primary alcohol on compound **27** was oxidized to the corresponding carboxylic acid by Jones reagent to give the (±)-methylenolactocin **8a** in 84% yield (Scheme 3). The exocyclic double bond of product **8a** was found to be intact during the oxidation process. The approach of Method II led us to accomplish the total synthesis of (±)-methylenolactocin in nine operation steps in 9.6% overall yield from β-hydroxy ester **11**.

2.4. The total synthesis of the optical active (−)-methylenolactocin

In order to prepare the methylenolactocin in optically active form, the optical active 1,3-diol **20** was needed. We began with the Bu_2BOTf-mediated asymmetric aldol reaction between *N*-acyl oxazolidinone (−)-**28**[16] and *n*-hexanal to give *syn*-aldol (−)-**29** in 73% yield (>95:5 diastereoselectivity).[17] *N*-Acyl oxazolidinone (−)-**29** was reduced with $NaBH_4$ to give the corresponding 1,3-diol (−)-**30**. Selective silylation at the primary alcohol of compound (−)-**30** followed by acetylation gave the acetate (−)-**32** in excellent yield. The ozonolysis of terminal olefin (−)-**32** followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH afforded acrolein (+)-**33** in 86% yield. The acrolein (+)-**33** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give the methyl acrylate (−)-**34** in 78% yield. Acid-catalyzed ring closure of acrylate (−)-**34** in methanol gave the corresponding α-methylene-γ-butyrolactone (−)-**27** in 91% yield. We believe that the formation of the lactone (−)-**27** from acrylate (−)-**34** follows the similar mechanism as described in Figure 3. However, under the acidic condition, the corresponding α-methylenelactone-acetate (Y=Me, Fig. 3) intermediate undergoes the transesterification to give the desired (−)-**27** in excellent yield. Finally, compound (−)-**27** was treated with Jones reagent to give the optical active (−)-methylenolactocin ((−)-**8a**) in 84%



Scheme 3. Reagents and conditions: (i) *p*-O_2N–$PhCO_2H$, DEAD, Ph_3P; (ii) Dibal-H, 0 °C to rt, CH_2Cl_2, 2 h; (iii) TBSCl, cat. DMAP, imidazole, CH_2Cl_2, 3 h; (iv) DEAD, Ph_3P, *p*-O_2N–$PhCO_2H$, CH_2Cl_2, 8 h; (v) (a) O_3, CH_2Cl_2, −78 °C, (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv=5:15), 2 h; (vi) $NaClO_2$, *t*-BuOH, $NaH_2PO_4\cdot 2H_2O$, MeOH=CMe_2, 8 h; (vii) CH_2N_2; (viii) cat. MeCOCl, MeOH, 30 min; (ix) NH_4OH (28–30%), MeOH, 0 °C, 2 h; (x) K_2CO_3, MeOH/H_2O (2:1), rt, 20 min; (xi) DBU, PhH, reflux, 5 h; (xii) Jones reagents, 40 °C, acetone, 5 min.



Scheme 4. Reagents and conditions: (i) Bu_2BOTf, Et_3N, n-$C_5H_{11}CHO$ (**10**), −78 to 0 °C, CH_2Cl_2, 2 h; (ii) $NaBH_4$, THF/H_2O (4:1), 2 h; (iii) TBSCl, cat. DMAP, imidazole, CH_2Cl_2, 3 h; (iv) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 1.5 h; (v) (a) O_3, CH_2Cl_2, −78 °C, (b) preheated miture of Et_2NH and CH_2Br_2 (mol equiv=5:15), 2 h; (vi) $NaClO_2$, t-BuOH, $NaH_2PO_4\cdot 2H_2O$, MeCH=CMe_2, 8 h; (vii) CH_2N_2; (viii) cat. MeCOCl, MeOH, 30 min; (ix) Jones reagent, 40 °C, acetone, 5 min.

yield (Scheme 4). We have accomplished the total synthesis of (−)-methylenolactocin in eight operation steps in 29% overall yield from *N*-acyl oxazolidinone (−)-**28**.

3. Conclusions

We have developed an efficient methodology for the synthesis of methylenolactocin in racemic and optically active forms. The characteristics of this synthetic design are to introduce the α-methylene group at the early stage of the synthesis by the ozonolysis of mono-substituted alkene followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH. For the racemic synthesis, the relative stereochemistry of β- and γ-substituents was established by the stereoselective allylation of the dianion of β-hydroxy ester **11**. As for the overall yield and the number of the transformations are concerned, method I should be the most efficient design. However, we cannot solve the problem of the side product **8a′** formation during the hydrolysis. Therefore, the epimerization needed to be operated at the early stage of the synthesis. Guided by this concept, we finished the total synthesis of (±)-methylenolactocin in nine operation steps in 9.6% overall yield from β-hydroxy ester **11**. Based on the success of this approach, we tried to complete the total synthesis of (−)-methylenolactocin ((−)-**8a**). *N*-Acyl oxazolidinone (−)-**28** was used as chiral auxiliary to induce the asymmetric aldol reaction to give *syn*-aldol (−)-**29** in excellent diastereoselectivity. Starting with this chiral alcohol, we have accomplished the total synthesis of (−)-methylenolactocin in eight operation steps in 29% overall yield from (−)-**28**.

4. Experimental

4.1. General

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Thomas–Hoover melting point apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorption was listed. Mass spectra were measured on a VG-Trio-2000GC/MS spectrometer (National Chiao-Tung University) by electronic impact at 70 eV (unless otherwise indicated). High-resolution mass spectroscopy (HRMS) was measured on a Finnigan/Thermo Quest MAT 95XL (National Chung Hsing University) and FAB mass spectra were recorded with 3-nitrobenzyl alcohol matrix using argon or xenon as the target gas.

4.1.1. 3-Hydroxyoctanoic acid methyl ester (11).[14b] A suspension of the activated zinc dust[18] (392 mg, 6 mmol) in 2 mL of anhydrous benzene was heated up to reflux for 10 min. To the refluxing suspension solution was slowly added a mixture of the *n*-hexanal (**10**) (0.55 g, 5.5 mmol) and methyl bromoacetate (**9**) (0.57 mL, 6 mmol) in 10 mL of benzene in a period of 1 h. After 2 h, the reaction mixture was cooled to 0 °C and then added 1 N HCl to work up the reaction and extracted with ether (20 mL×3). The combined organic extract was dried ($MgSO_4$), concentrated, and chromatographed on silica gel column to give the desired β-hydroxy ester **11** (746 mg, 4.3 mmol) in 78% yield as a colorless oil. TLC R_f=0.48 (hexane/EtOAc=3:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94–3.98 (m, 1H, C*H*OH), 3.66 (s, 3H, OMe), 2.95 (br, 1H, OH), 2.36–2.49 (m, 2H, CH_2CO), 1.21–1.42 (m, 8H), 0.85 (t, J=6.7 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1 (4°), 67.8 (3°), 51.4 (1°), 41.1 (2°), 36.4 (2°), 31.5 (2°), 24.9 (2°), 22.3 (2°), 13.7 (1°); IR (CH_2Cl_2): 2931, 2859, 1738, 1438, 1168 cm^{-1}; EI mass (*m*/*z*): 173 (M^+−1, 10), 157 (100), 125 (70), 55 (48), 43 (35); HRMS *m*/*z* calcd for $C_9H_{18}O_3$ 174.1256, found: 174.1259.

4.1.2. (2*R,3*R**)-2-Allyl-3-hydroxyoctanoic acid methyl ester (12).** *n*-Butyllithium (3.95 mL, 6.33 mmol, 1.6 M in hexane) was added to a stirring solution of diisopropylamine (0.89 mL, 6.33 mmol) in THF (10 mL) at −78 °C. To the LDA solution, β-hydroxy ester **11** (0.50 g, 2.87 mmol) in 5 mL of THF was added at −78 °C and stirred at this temperature for 1 h. At −78 °C, a mixture of allyl bromide (0.30 mL, 3.44 mmol) and HMPA (1 mL) in THF (4 mL) was added to the reaction mixture. After stirring at −78 °C for 1 h, the reaction mixture was partitioned between 40% ethyl acetate/petroleum ether and saturated aqueous NH_4Cl. The combined organic phase was dried ($MgSO_4$), concentrated, and chromatographed on silica gel column to afford

product **12** (522 mg, 2.44 mmol) in 85% yield as a colorless oil. TLC R_f=0.55 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66–5.73 (m, 1H, C*H*=CH_2), 4.97–5.06 (m, 2H, CH=CH_2), 3.65 (s, 3H, OMe), 3.64–3.67 (m, 1H, C*H*OH), 2.68–2.75 (br, 1H, OH), 2.47–2.50 (m, C*H*CO), 2.36–2.39 (m, 2H, CH_2CH=CH_2), 1.23–1.42 (m, 8H), 0.84 (t, J=6.9 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.1 (4°), 134.8 (4°), 116.9 (2°), 71.6 (3°), 51.4 (1°), 50.5 (3°), 35.3 (2°), 33.6 (2°), 31.5 (2°), 25.2 (2°), 22.4 (2°), 13.8 (1°); IR (CH_2Cl_2): 3374, 2932, 2859, 1735, 1643, 1438, 1169, 1047 cm^{-1}; EI mass (*m*/*z*): 125 (M^+-89, 100), 113 (21), 55 (82), 43 (70), 41 (91); HRMS *m*/*z* calcd for $C_{12}H_{22}O_3$–OCH_3 183.1385, found: 183.1384.

4.1.3. (2*R,3*R**)-3-Acetoxy-2-allyloctanoic acid methyl ester (13).** To a solution of β-hydroxy ester **12** (500 mg, 2.34 mmol), DMAP (57 mg, 0.47 mmol) and Et_3N (0.49 mL, 3.5 mmol) in CH_2Cl_2 (4.7 mL) was added acetic anhydride (0.33 mL, 3.5 mmol) at rt and stirred it for 2 h. The reaction mixture was concentrated and chromatographed on silica gel column to afford the acetate **13** (574 mg, 2.24 mmol) in 96% yield as a pale yellow oil. TLC R_f=0.75 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70–5.77 (m, 1H, –C*H*=CH_2), 5.01–5.12 (m, 3H, –CH=CH_2 and C*H*OAc), 3.68 (s, 3H, –OCH_3), 2.70–2.75 (m, 1H, C*H*CO), 2.42–2.24 (m, 2H, –CH_2-CH=CH_2), 2.04 (s, 3H, COCH_3), 1.55–1.60 (m, 2H), 1.26–1.30 (m, 6H), 0.88 (t, J=6.8 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7 (4°), 170.2 (4°), 134.8 (3°), 117.0 (2°), 73.5 (3°), 51.5 (1°), 49.1 (3°), 32.3 (2°), 31.6 (2°), 31.5 (2°), 24.7 (2°), 22.4 (2°), 20.9 (1°), 13.9 (1°); IR (CH_2Cl_2): 2955, 2933, 2861, 1743, 1437, 1238 cm^{-1}; EI mass (*m*/*z*): 241 (M^+-15, 35), 227 (32), 181 (100), 149 (47), 55 (48); HRMS *m*/*z* calcd for $C_{13}H_{21}O_4$ 241.1440 (M^+-15), found: 241.1442.

4.2. General procedure to prepare the α-substituted acrolein from terminal alkene

A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar was charged with terminal alkene **13** (650 mg, 2.54 mmol) in CH_2Cl_2 (50 mL). The flask was cooled to −78 °C and ozone was bubbled through the solution. When the solution turned blue, ozone addition was stopped. Nitrogen was passed through the solution until the blue color was discharged. A mixture of Et_2NH (1.4 mL, 12.7 mmol) and CH_2Br_2 (2.7 mL, 38.0 mmol) was heated to 55 °C for 1.5 h to give a yellow solution and then cooled to rt. To a solution of ozonide in CH_2Cl_2 generated above was added a preheated mixture of Et_2NH and CH_2Br_2 at −78 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at rt. The reaction was complete in 1.5 h and the reaction mixture was concentrated. To the crude mixture, ether was added and most of the ammonium salts were precipitated out. After filtration, the filtrate was concentrated, chromatographed on the silica gel column to give the desired acrolein **14** (510 mg, 1.97 mmol) in 78% yield.

4.2.1. (1′*R,2*R**)-2-(1′-Acetoxyhexyl)-3-formylbut-3-enoic acid methyl ester (14).** TLC R_f=0.38 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (s, 1H, C*H*O), 6.69 (s, 1H, C=CH_2), 6.29 (s, 1H, C=CH_2), 5.27 (ddd, J=3.8, 7.6, 8.4 Hz, 1H, C*H*OAc), 4.04 (d, J=7.5 Hz, ^{1}H C*H*CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 2.02 (s, 3H, COCH_3), 1.40–1.55 (m, 2H), 1.17–1.30 (m, 6H), 0.86 (t, J=6.8 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2 (4°), 170.7 (4°), 170.1 (4°), 144.2 (4°), 137.6 (2°), 73.2 (3°), 52.0 (1°), 45.4 (3°), 31.4 (2×2°), 24.6 (2°), 22.3 (2°), 20.8 (2°), 13.8 (1°); IR (CH_2Cl_2): 2955, 2860, 1744, 1696, 1435, 1236, 1024, 734 cm^{-1}; EI mass (*m*/*z*): 271 (M^++1, 1), 211 (40), 170 (42), 128 (100), 96 (52), 86 (38), 55 (13); HRMS *m*/*z* calcd for $C_{14}H_{22}O_5$ 270.1467, found: 270.1468.

4.3. General procedure to prepare the methyl acrylate from the corresponding acrolein

To a solution of acrolein **14** (700 mg, 2.71 mmol), *t*-butyl alcohol (14 mL) and 2-methyl-2-butene (0.9 mL, 570 mg, 8.13 mmol) was added dropwise a solution of sodium chlorite (565 mg, 6.23 mmol) and sodium dihydrogenphosphate dihydrate (835 mg, 5.42 mmol) in 4 mL of water. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue then dissolved in 8 mL of water and this extracted with 30 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 25 mL portions of ether. The combined ether layers were washed with 30 mL of water, dried with Na_2SO_4, concentrated to give the crude carboxylic acid. To a solution of α-substituted acrylic acid was dissolved in 9.5 mL of CH_2Cl_2 was added a solution of CH_2N_2 in ethyl ether at rt. The progress of the reaction should be monitored carefully by TLC. Excess of the CH_2N_2 will cause the further 1,3-dipolar cycloaddition on the double bond. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate **15** (642 mg, 2.14 mmol) as a colorless oil in 79% yield.

4.3.1. (1′*R,2*R**)-2-(1′-Acetoxyhexyl)-3-methylenesuccinic acid dimethyl ester (15).** TLC R_f=0.68 (hexane/EtOAc=2:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.46 (s, 1H, C=CH_2), 5.96 (s, 1H, C=CH_2), 5.32 (ddd, J=3.7, 8.1, 8.1 Hz, 1H, C*H*OAc), 3.99 (d, J=7.9 Hz, 1H, C*H*CO_2Me) 3.79 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.02 (s, 3H, COCH_3), 1.41–1.57 (m, 2H), 1.23–1.30 (m, 6H), 0.86 (t, J=6.8 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (4°), 170.1 (4°), 166.2 (4°), 135.0 (4°), 129.0 (2°), 73.4 (3°), 52.2 (1°), 52.0 (1°), 49.1 (3°), 31.5 (2°), 31.4 (2°), 24.6 (2°), 22.3 (2°), 20.8 (1°), 13.8 (1°); IR (CH_2Cl_2): 2955, 2860, 1746, 1437, 1237, 1023, 733 cm^{-1}; EI mass (*m*/*z*): 269 (M^+-31, 1), 227 (12), 158 (100), 126 (60), 55 (6); HRMS *m*/*z* calcd for $C_{14}H_{21}O_6$ 285.1338 (M^+-15), found: 285.1344.

4.4. General procedure to prepare the γ-butyrolactone from the corresponding acyloxy-acrylate under acidic condition

To a mixture of acetoxy-acrylate **15** (100 mg, 0.29 mmol) in 6 mL of MeOH was added a catalytic amount of acetyl chloride (2 μL, 29 μmol) and stirred at rt for 24 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the α-methylenelactone **16** (62 mg, 0.24 mmol) in 82% yield as a pale yellow oil.

4.4.1. (2*R,3*R**)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid methyl ester (16).**[9u] TLC R_f= 0.57 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.40 (d, J=2.4 Hz, 1H, C=CH_2), 5.82 (d, J=2.4 Hz, 1H, C=CH_2), 4.59–4.64 (m, 1H, C*H*OCO), 4.00 (dt, J=2.2, 7.6 Hz, 1H, C*H*C=CH_2), 3.75 (s, 3H, OMe), 1.29–1.64 (m, 8H), 0.88–0.90 (t, J=6.9 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3 (4°), 168.8 (4°), 133.7 (4°), 124.8 (2°), 78.2 (3°), 52.3 (1°), 49.1 (3°), 31.4 (2°), 31.3 (2°), 25.1 (2°), 22.3 (2°), 13.8 (1°); IR (CH_2Cl_2): 2931, 2861, 1768, 1666, 1437, 1170, 714 cm^{-1}; EI mass (*m*/*z*): 166 (M^+-60, 29), 155 (78), 127 (38), 126 (100), 67 (42); HRMS *m*/*z* calcd for $C_{12}H_{18}O_4$ 226.1205, found: 226.1213.

4.4.2. (2*S,3*R**)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid methyl ester (17)**[9u] **and 4-methyl-5-oxo-2-pentyl-2,5-dihydrofuran-3-carboxylic acid methyl ester (18)**[9j] A solution of methyl ester **16** (113 mg, 0.5 mmol) in butanone (3 mL) containing HCl (6 N, 3 drops) was heated under reflux for 2 h. H_2O (5 mL) was added and the organic solvent was removed. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL) and solvents were evaporated to give an inseparable mixture of methylenolactocin (**8a**) and butenolide **8a**′ (mol ratio is about 4:1). To the crude mixtures in 5 mL of CH_2Cl_2 were added a solution of CH_2N_2 in ether. After stirring at rt for 20 min, the reaction mixture was concentrated, chromatographed on silica gel column to give the methyl ester of the methylenolactocin **17** (72 mg, 0.32 mmol, 64% yield) and its isomer **18** (18 mg, 0.08 mmol, 16%).

Compound **17**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.40 (d, J=2.4 Hz, 1H, C=CH_2), 5.91 (d, J=2.4 Hz, 1H, C=CH_2), 4.79 (q, J=6.0 Hz, 1H, C*H*OCO), 3.80 (s, 3H, OMe), 3.56–3.59 (m, 1H, C*H*C=CH_2), 1.25–1.73 (m, 8H), 0.88–0.91 (m, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7 (4°), 168.2 (4°), 133.2 (4°), 125.0 (2°), 79.0 (3°), 52.8 (1°), 49.9 (3°), 35.7 (2°), 29.6 (2°), 24.4 (2°), 22.4 (2°), 13.8 (1°); IR (CH_2Cl_2): 2927, 2857, 1770, 1740, 1437, 1115, 738 cm^{-1}; EI mass (*m*/*z*): 226 (M^+, 6), 156 (68), 155 (100), 127 (90), 99 (62); HRMS *m*/*z* calcd for $C_{12}H_{18}O_4$ 226.1205, found: 226.1207.

Compound **18**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.09 (m, 1H, C*H*OCO), 3.88 (s, 3H, OMe), 2.18 (d, J=2.0 Hz, 3H, CH_3C=C), 2.04–2.07 (m, 2H), 1.25–1.58 (m, 6H), 0.88 (t, J=6.8 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8 (4°), 162.6 (4°), 147.6 (4°), 137.4 (4°), 81.3 (3°), 52.2 (1°), 32.7 (2°), 31.6 (2°), 24.4 (2°), 22.3 (2°), 13.8 (1°), 10.8 (1°); IR (CH_2Cl_2): 2928, 2859, 1768, 1728, 1438, 1152, 759 cm^{-1}; EI mass (*m*/*z*): 226 (M^+, 4), 197 (48), 156 (100), 99 (28), 67 (30); HRMS *m*/*z* calcd for $C_{12}H_{18}O_4$ 226.1205, found: 226.1206.

4.4.3. (2*S,3*R**)-2-Allyloctane-1,3-diol (20).** To a solution of β-hydroxy ester **12** (1.8 g, 8.40 mmol) in 42 mL of CH_2Cl_2 was added diisobutylaluminium hydride (Dibal-H, 1 M in hexane, 21 mL, 21.0 mmol) at 0 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 h. To the reaction mixture was added 10 mL of ethyl acetate in order to quench the excess of Dibal-H at 0 °C. The reaction mixture was then washed with 30 mL of water. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give diol **20** (1.23 g, 6.61 mmol) in 79% yield as a colorless oil. TLC R_f=0.29 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.87 (m, 1H, –C*H*=CH_2), 5.03–5.12 (m, 2H, –CH=CH_2), 3.91–3.94 (m, 1H, C*H*OH), 3.66–3.70 (m, 2H, –CH_2OH), 2.45 (br s, 1H, OH), 2.20–2.28 (m, 3H, –CH_2CH=CH_2 and C*H*CH$_2$OH), 1.31–1.61 (m, 8H), 0.90 (t, J=6.6 Hz, 3H, –CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.6 (3°), 116.4 (2°), 75.0 (3°), 63.6 (2°), 44.0 (3°), 35.4 (2°), 33.3 (2°), 31.8 (2°), 25.3 (2°), 22.6 (2°), 13.9 (1°); IR (CH_2Cl_2): 3349, 2955, 2859, 1443, 1128, 1026, 733 cm^{-1}; FAB mass (*m*/*z*): 187 (M^++1, 27), 178 (34), 169 (49), 151 (62), 136 (58), 109 (56), 95 (93), 81 (88), 55 (100); HRMS *m*/*z* calcd for $C_{11}H_{22}O_2$ 186.1620, found: 186.1624.

4.4.4. (4*R,5*S**)-4-(*tert*-Butyldimethylsilyloxymethyl)-dec-1-en-5-ol (21).** To a solution of the diol **20** (1.9 g, 10.21 mmol), DMAP (250 mg, 2.04 mmol) and imidazole (765 mg, 11.23 mmol) in 21 mL of CH_2Cl_2 was added *t*-butyldimethylsilyl chloride (1.7 g, 11.2 mmol) at rt and stirred it for 3 h. The reaction is quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give the secondary alcohol **21** (2.81 g, 9.87 mmol) in 97% yield as a pale yellow oil. TLC R_f=0.60 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.73–5.84 (m, 1H, –C*H*=CH_2), 5.02–5.09 (m, 2H, –CH=CH_2), 3.91 (dd, J=3.5, 10.2 Hz, 1H, –CH_2OTBS), 3.66 (dd, J=5.0, 10.2 Hz, 1H, –CH_2OTBS), 3.59–3.64 (m, 1H, –C*H*OH), 3.29 (d, J=6.2 Hz, 1H, OH), 2.14–2.30 (m, 2H, –CH_2CH=CH_2), 1.38–1.51 (m, 3H, C*H*CH$_2$OTBS), 1.20–1.35 (m, 6H), 0.88–0.91 (m, 12H, CH$_2$CH_3 and (CH_3)$_3$CSiMe$_2$), 0.08 (s, 3H, *t*-BuSi(CH_3)$_2$), 0.07 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9 (3°), 116.3 (2°), 74.6 (3°), 64.1 (2°), 43.8 (3°), 35.7 (2°), 33.3 (2°), 32.0 (2°), 25.8 (3×1°), 25.6 (2°), 22.7 (2°), 18.1 (4°), 14.0 (1°), −5.7 (2×1°); IR (CH_2Cl_2): 3464, 2955, 2857, 1470, 1255, 1087, 777 cm^{-1}; FAB mass (*m*/*z*): 301 (M^++1, 61), 283 (23), 154 (100), 136 (99), 95 (62), 81 (58), 73 (90), 55 (65); HRMS *m*/*z* calcd for $C_{17}H_{36}O_2Si$ 300.2485, found: 300.2481.

4.4.5. 4-Nitrobenzoic acid (1*S,2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)-1-pentylpent-4-enyl ester (22).** To a mixture of the secondary alcohol **21** (1.2 g, 5.90 mmol) in 18 mL of THF was added a solution of Ph_3P (2.21 g, 8.43 mmol) and 4-nitrobenzoic acid (1.41 g, 8.43 mmol) in 20 mL of THF at rt under nitrogen. To the resulted solution was added DEAD (40% in toluene, 3.83 mL, 8.43 mmol) by syringe pump dropwise in 1 h at 0 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at rt for 8 h. The reaction mixture was concentrated and chromatographed on silica gel column to give 4-nitrobenzoate **22** (1.46 g, 3.25 mmol) in 77% yield as a pale yellow solid. TLC R_f=0.82 (hexane/EtOAc=10:1); mp 47.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27–8.30 (m, 2H, O_2NPh–*H*), 8.18–8.20 (m, 2H, O_2NPh–*H*), 5.77–5.87 (m, 1H, –C*H*=CH_2), 5.36 (dt, J=5.0, 7.7 Hz, 1H, C*H*OCOAr), 5.02–5.08 (m, 2H, –CH=CH_2), 3.65 (dd, J=4.8, 10.1 Hz, 1H, –CH_2OTBS), 3.57 (dd, J=6.0, 10.1 Hz, 1H, –CH_2OTBS), 2.20–2.27 (m, 2H, –CH_2-CH=CH_2), 1.91–1.95 (m, 1H, –C*H*CH$_2$OTBS), 1.71–1.78

(m, 2H), 1.26–1.30 (m, 6H), 0.85–0.90 (m, 12H, $-CH_2CH_3$ and $(CH_3)_3CSiMe_2$), 0.01 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.01 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2 (4°), 150.5 (4°), 136.7 (3°), 136.2 (4°), 130.6 (2×3°), 123.5 (2×3°), 116.3 (2°), 76.4 (3°), 62.1 (2°), 43.8 (3°), 31.6 (2°), 31.5 (2°), 31.3 (2°), 25.8 (3×1°), 25.3 (2°), 22.4 (2°), 18.1 (4°), 13.9 (1°), −5.6 (2×1°); IR (CH_2Cl_2): 2955, 2857, 1725, 1530, 1274, 1101, 719 cm^{-1}; EI mass (*m*/*z*): 173 (M^++1, 1), 224 (100), 150 (21), 109 (16), 95 (27), 55 (7); HRMS *m*/*z* calcd for $C_{24}H_{39}SiNO_5$ 449.2598, found: 449.2598.

4.4.6. 4-Nitrobenzoic acid (1*S,2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)-3-formyl-1-pentylbut-3-enyl ester (23).** Following the general procedure to prepare the α-substituted acrolein from terminal alkene, compound **23** (873 mg, 1.88 mmol) was prepared from alkene **22** (1.25 g, 2.78 mmol) in 68% yield as a white solid. TLC R_f=0.85 (hexane/EtOAc=3:1); mp 77.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, CHO), 8.26–8.29 (m, 2H, O_2NPh–*H*), 8.10–8.13 (m, 2H, O_2NPh–*H*), 6.59 (s, 1H, C=CH_2), 6.17 (s, 1H, C=CH_2), 5.60 (dt, *J*=4.7, 7.3 Hz, 1H, C*H*OCO), 3.74 (dd, *J*=5.1, 10.2 Hz, 1H, CH_2OTBS), 3.63 (dd, *J*=5.5, 10.2 Hz, 1H, CH_2OTBS), 3.26–3.31 (m, 1H, C*H*C=CH_2), 1.62–1.76 (m, 2H), 1.26–1.36 (m, 6H), 0.84–0.87 (m, 12H, CH_2CH_3 and $(CH_3)_3CSiMe_2$), 0.01 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.02 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.0 (4°), 164.0 (4°), 150.5 (4°), 147.9 (4°), 137.0 (2°), 135.8 (4°), 130.6 (2×3°), 123.5 (2×3°), 75.0 (3°), 62.5 (2°), 41.8 (3°), 32.5 (2°), 31.5 (2°), 25.7 (3×1°), 24.8 (2°), 22.4 (2°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); IR (CH_2Cl_2): 2955, 2857, 1725, 1696, 1273, 1101, 719 cm^{-1}; IR (CH_2Cl_2): 2955, 2857, 1725, 1696, 1273, 1101, 719 cm^{-1}; EI mass (*m*/*z*): 433 (M^+−30, 1), 239 (100), 224 (66), 169 (14), 150 (61), 95 (10), 75 (31), 55 (4); HRMS *m*/*z* calcd for $C_{24}H_{37}SiNO_6$ 463.2390, found: 463.2393.

4.4.7. 4-Nitrobenzoic acid (1*S,2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)-3-methoxycarbonyl-1-pentylbut-3-enyl ester (24).** Following the general procedure to prepare the methyl acrylate from α-substituted acrolein, methyl acrylate **24** (650 mg, 2.14 mmol) was prepared from acrolein **23** (873 mg, 1.88 mmol) in 70% yield as a pale yellow oil. TLC R_f=0.70 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26–8.29 (m, 2H, O_2NPh–*H*), 8.12–8.15 (m, 2H, O_2NPh–*H*), 6.34 (s, 1H, C=CH_2), 5.84 (s, 1H, C=CH_2), 5.56 (dt, *J*=4.2, 7.3 Hz, 1H, C*H*OCOAr), 3.77 (dd, *J*=5.4, 10.2 Hz, 1H, CH_2OTBS), 3.72 (s, 3H, OCH_3), 3.71 (dd, *J*=6.1, 10.2 Hz, 1H, CH_2OTBS), 3.25 (q, *J*=6.0 Hz, 1H, C*H*C=CH_2), 1.66–1.80 (m, 2H), 1.24–1.37 (m, 6H), 0.84–0.90 (m, 12H, CH_2CH_3 and $(CH_3)_3CSiMe_2$), 0.01 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.01 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6 (4°), 164.1 (4°), 150.5 (4°), 138.2 (4°), 136.0 (4°), 130.6 (2×3°), 127.4 (2°), 123.5 (2×3°), 75.4 (3°), 63.0 (2°), 52.0 (1°), 45.9 (3°), 32.5 (2°), 31.6 (2°), 25.8 (3×1°), 24.9 (2°), 22.4 (2°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); IR (CH_2Cl_2): 2954, 2857, 1725, 1530, 1273, 1101, 719 cm^{-1}; EI mass (*m*/*z*): 478 (M^+−15, 1), 269 (100), 224 (48), 150 (35), 89 (19), 55 (2); HRMS *m*/*z* calcd for $C_{25}H_{39}SiNO_7$ 478.2261 (M−CH_3), found: 478.2252.

4.4.8. 4-Nitrobenzoic acid (2*S,3*S**)-4-methylene-5-oxo-2-pentyltetrahydrofuran-3-ylmethyl ester (25).** Following the general procedure to prepare the γ-butyrolactone from the corresponding acyloxy-acrylate under acidic condition, γ-butyrolactone **25** (351 mg, 1.01 mmol) was prepared from acetoxy-acrylate **24** (650 mg, 1.32 mmol) in 77% yield as a pale yellow oil. TLC R_f=0.33 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29–8.31 (m, 2H, O_2NPh–*H*), 8.14–8.16 (m, 2H, O_2NPh–*H*), 6.45 (d, *J*=2.0 Hz, 1H, C=CH_2), 5.78 (d, *J*=2.0 Hz, 1H, C=CH_2), 5.35 (quint, *J*=4.4 Hz, 1H, C*H*OCO), 4.41 (dd, *J*=7.7, 9.6 Hz, 1H, CH_2OCOAr), 4.35 (dd, *J*=2.9, 9.6 Hz, 1H, CH_2OCOAr), 3.46–3.49 (m, 1H, C*H*C=CH_2), 1.66–1.82 (m, 2H), 1.26–1.39 (m, 6H), 0.87 (t, *J*=7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 (4°), 164.2 (4°), 150.8 (4°), 134.9 (4°), 134.1 (4°), 130.7 (2×3°), 124.9 (2°), 123.7 (2×3°), 76.7 (3°), 67.6 (2°), 42.1 (3°), 31.3 (2°), 30.1 (2°), 25.1 (2°), 22.4 (2°), 13.8 (1°); IR (CH_2Cl_2): 2961, 2859, 1766, 1723, 1527, 1269, 1102, 719 cm^{-1}; EI mass (*m*/*z*): 347 (M^+, 1), 150 (100), 104 (22), 92 (8); HRMS *m*/*z* calcd for $C_{18}H_{21}NO_6$ 347.1369, found: 347.1379.

4.4.9. (3*S,4*S**,5*S**)-4-Hydroxymethyl-3-methoxymethyl-5-pentyldihydrofuran-2-one (26).** To a mixture of 4-nitrobenzoate **25** (120 mg, 0.34 mmol) in 1.2 mL of MeOH was added a solution of K_2CO_3 (53 mg, 0.38 mmol) in 0.6 mL of water and stirred at rt for 20 min. The reaction mixture was added 1 mL of water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, concentrated and chromatographed on silica gel column to give hydroxy-lactone **26** (56 mg, 0.24 mmol) in 71% yield as a pale yellow oil. TLC R_f=0.35 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (ddd, *J*=3.5, 8.8, 8.8 Hz, 1H, C*H*OCO), 3.86 (dd, *J*=3.7, 9.5 Hz, 1H), 3.69–3.76 (br m, 1H), 3.60 (dd, *J*=7.6, 11.0 Hz, 1H), .3.51 (dd, *J*=9.0, 9.0 Hz, 1H,), 3.43 (s, 3H, OCH_3), 2.79 (ddd, *J*=3.7, 8.6, 10.4 Hz, 1H, C*H*CO), 2.23–2.30 (m, 1H, C*H*CH_2OH), 1.64–1.73 (m, 2H), 1.26–1.33 (m, 6H), 0.90 (t, *J*=6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3 (4°), 80.4 (3°), 71.3 (2°), 62.7 (2°), 59.2 (1°), 49.4 (3°), 46.4 (3°), 34.6 (2°), 31.5 (2°), 25.3 (2°), 22.4 (2°), 13.9 (1°); IR (CH_2Cl_2): 3462, 2931, 2872, 1757, 1459, 1185, 733 cm^{-1}; EI mass (*m*/*z*): 230 (M^+, 1), 126 (29), 103 (52), 85 (35), 55 (28), 45 (100); HRMS *m*/*z* calcd for $C_{12}H_{22}O_4$ 230.1518, found: 230.1523.

4.4.10. (4*S,5*S**)-4-Hydroxymethyl-3-methylene-5-pentyldihydrofuran-2-one (27).** *Method A* (*from compound* **25**). To a mixture of 4-nitrobenzoate **25** (50 mg, 0.14 mmol) in 0.7 mL of MeOH was added a solution of ammonium water (28–30% in water, 20 μL, 0.16 mmol) at 0 °C and stirred at this temperature for 2 h. The reaction mixture was added 0.3 mL of water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, concentrated and chromatographed on silica gel column to give α-methylenelactone **27** (18 mg, 0.09 mmol) in 63% yield as a pale yellow oil.

Method B (*from compound* **26**). To a solution of compound **26** (13 mg, 56.4 μmol) and DBU (9.5 mg, 62.1 μmol) in 0.7 mL of benzene. The resulting solution was heated to reflux for 5 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the

α-methylenelactone **27** (8.4 mg, 42.3 μmol) in 75% yield as a pale yellow oil. TLC R_f=0.55 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.33 (d, J=2.8 Hz, 1H, C=CH_2), 5.72 (d, J=2.4 Hz, 1H, C=CH_2), 4.40 (ddd, J=4.4, 6.4, 6.4 Hz, 1H, CHOCO), 3.74–3.79 (m, 2H, CH_2OH), 2.85–2.90 (m, 1H, CHCH$_2$OH), 1.65–1.71 (m, 3H), 1.31–1.51 (m, 6H), 0.89 (t, J=7.2 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (4°), 136.2 (4°), 123.4 (2°), 80.9 (3°), 63.8 (2°), 46.8 (3°) 36.0 (2°), 31.4 (2°), 24.6 (2°), 22.4 (2°), 13.9 (1°); IR (CH_2Cl_2): 3459, 2932, 2860, 1748, 1465, 1151, 733 cm^{-1}; FAB mass (*m*/*z*): 199 (M^++1, 16), 181 (10), 154 (23), 136 (27), 91 (40), 81 (39), 55 (100); HRMS *m*/*z* calcd for $C_{11}H_{18}O_3$ 198.1256, found: 198.1248.

4.5. General procedure to prepare the carboxylic acid from the corresponding primary alcohol by Jones reagent

To a solution of primary alcohol **27** (50 mg, 0.25 mmol) in acetone (1 mL) at 40 °C was added Jones reagent dropwise until the orange color persisted and the resulting solution was stirred at this temperature for 5 min. After cooling to 0 °C, the reaction mixture was added isopropanol to quench the excess of Jones reagent. The mixture was partitioned between CH_2Cl_2 and water. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residual oil was chromatographed on silica gel column to give a white solid **8a** (45 mg, 0.21 mmol) in 84% yield.

4.5.1. (2*S,3*R**)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid (8a).** TLC R_f=0.20 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, J=3.1 Hz, 1H, C=CH_2), 6.02 (d, J=2.2 Hz, 1H, C=CH_2), 4.78–4.83 (m, 1H, CHOCO), 3.62–3.64 (m, 1H, CHC=CH$_2$), 1.71–1.78 (m, 2H), 1.26–1.51 (m, 6H), 0.90 (t, J=7.0 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 (4°), 168.6 (4°), 132.5 (4°), 125.8 (2°), 79.2 (3°), 49.4 (3°), 35.4 (2°), 31.1 (2°), 24.2 (2°), 22.2 (2°), 13.7 (1°); IR (CH_2Cl_2): 3462, 2954, 2861, 1743, 1660, 1465, 1257, 1186, 737 cm^{-1}; EI mass (*m*/*z*): 212 (M^+, 2), 183 (24), 141 (100), 123 (21), 113 (61), 81 (9), 55 (24); HRMS *m*/*z* calcd for $C_{11}H_{16}O_4$ 212.1049, found: 212.1053.

4.5.2. (−)-(4*R*)-4-Benzyl-3-pent-4-enoyloxazolidin-2-one ((−)-28).[16] To a stirred solution of 4-pentenoic acid (1.65 g, 16.52 mmol) and Et_3N (2.8 mL, 19.98 mmol) in 48 mL of dry THF, cooled to −78 °C under nitrogen, was added pivaloyl chloride (2.08 g, 17.27 mmol). The mixture was warmed to 0 °C for 60 min, and then recooled to −78 °C. A solution of (4*S*)-(phenylmethyl)-2-oxazolidone (2.66 g, 15.0 mmol) in 42 mL of THF, stirred at −30 °C to −45 °C under nitrogen, was treated dropwise with *n*-BuLi (2.50 M in hexane, 6.6 mL, 16.52 mmol). The resulting solution was cooled to −78 °C and then added, via rapid cannulation, to the above stirred mixture containing the mixed anhydride. The resulting mixture was stirred at −78 °C for 30 min. After warming to 0 °C, the mixture was partitioned between CH_2Cl_2 and pH 7 phosphate buffer. The CH_2Cl_2 phase washed with 5% aqueous $NaHCO_3$ followed by saturated aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The residual oil was chromatographed on silica gel column to give a colorless, viscous oil (−)-**28** (3.45 g, 13.31 mmol) in 88% yield. TLC R_f=0.44 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.35 (m, 5H, Ph–*H*), 5.84–5.94 (m, 1H, CH=CH$_2$), 5.02–5.14 (m, 2H, CH=CH_2), 4.68–4.71 (m, 1H, CHNCO), 4.15–4.22 (m, 2H, CH_2OCO), 3.30 (dd, J=13.4, 3.3 Hz, 1H, PhCH_2), 2.76 (dd, J=13.4, 9.6 Hz, 1H, PhCH_2), 2.98–3.14 (m, 2H, CH_2CH=CH$_2$), 2.49–2.43 (m, 2H, CH_2CO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4 (4°), 153.4 (4°), 136.6 (4°), 135.2 (3°), 129.3 (3°), 128.9 (3°), 127.3 (3°), 115.6 (2°), 66.1 (2°), 55.0 (3°), 37.8 (2°), 34.7 (2°), 28.1 (2°); IR (CH_2Cl_2): 2980, 2872, 1782, 1703, 1389, 1210, 1101, 703 cm^{-1}.

4.5.3. (−)-(2*R*,3*S*,4*R*)-4-Benzyl-3-(3-hydroxy-2-allyloctanoyl)oxazolidin-2-one ((−)-29).[17] To a solution of oxazolidinone (−)-**28** (2.5 g, 9.65 mmol) in 17 mL of CH_2Cl_2 in an ice bath was added Bu_2OTf (1 M in CH_2Cl_2, 11.6 mL, 11.6 mmol) over a 10 min period and then addition of Et_3N (1.75 mL, 12.5 mmol) over a 10 min period. The resulting light yellow solution was stirred at 0 °C for 10 min. The ice bath was replaced with a dry ice/acetone bath (78 °C) and freshly distilled *n*-hexanal (1.4 mL, 11.6 mmol) was added by syringe over a 5 min period. The reaction mixture was stirred at −78 °C for 1 h, warmed to 0 °C for 2 h, and quenched by addition of 2 mL of pH 7 buffer and 2 mL of MeOH. A solution of 1.2 mL of MeOH/30% aqueous H_2O_2 (2:1 by volume) was added dropwise and the biphasic mixture was stirred vigorously at rt for 1 h. The mixture was diluted with 100 mL of water and the layers were separated. The aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude product was chromatographed on silica gel column to give compound (−)-**29** (2.52 g, 7.0 mmol) in 73% yield as a pale yellow oil. TLC R_f=0.38 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.35 (m, 5H, Ph–*H*), 5.83–5.93 (m, 1H, CH=CH$_2$), 5.04–5.15 (m, 2H, CH=CH_2), 4.68–4.74 (m, 1H, CHNCO), 4.13–4.20 (m, 3H, CH_2OCO and O*H*), 3.91–3.94 (m, 1H, CHOH), 3.33 (dd, J=3.2, 13.3 Hz, 1H, PhCH_2), 2.64 (dd, J=10.1, 13.3 Hz, 1H, PhCH_2), 2.57–2.65 (m, 1H, CHCO), 2.46–2.51 (m, 2H, CH_2CH=CH$_2$), 1.49–1.58 (m, 2H), 1.31–1.36 (m, 6H), 0.89 (t, J=6.3 Hz, 3H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3 (4°), 153.4 (4°), 135.4 (4°), 135.3 (3°), 129.3 (3°), 128.9 (3°), 127.2 (3°), 117.1 (2°), 72.0 (3°), 65.9 (2°), 55.5 (3°), 47.1 (3°), 37.9 (2°), 34.0 (2°), 31.6 (2°), 31.5 (2°), 25.6 (2°), 22.5 (2°), 13.9 (1°); $[\alpha]_D^{30}$=−7.0 (c=0.55, $CHCl_3$); IR (CH_2Cl_2): 3524, 2954, 2859, 1779, 1696, 1385, 1208, 1104, 702 cm^{-1}; EI mass (*m*/*z*): 359 (M^+, 4), 341 (24), 270 (46), 259 (77), 178 (100), 117 (66), 91 (48), 83 (40), 55 (48); HRMS *m*/*z* calcd for $C_{21}H_{29}NO_4$ 359.2097, found: 359.2093.

4.5.4. (−)-(2*S*,3*S*)-2-Allyloctane-1,3-diol ((−)-30). To a 0 °C solution of aldol (−)-**29** (100 mg, 0.28 mmol) in 2.4 mL of THF was added dropwise a solution of $NaBH_4$ (43 mg, 1.11 mmol) in 0.6 mL of deionized H_2O. Once addition was complete, the ice bath was removed and the biphasic mixture was stirred vigorously at rt for 2 h. The mixture was then recooled in an ice bath and 5 mL of 1 N HCl was added carefully to quench the excess hydride reagent. The aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic layers was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude

product by silica gel column chromatography gave the diol (−)-**30** (48 mg, 0.26 mmol) in 93% yield as a colorless oil. TLC R_f=0.25 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.81 (m, 1H, C*H*=CH_2), 5.02–5.10 (m, 2H, CH=CH_2), 3.86–3.90 (m, 1H, C*H*OH), 3.80 (dd, J=6.4, 10.8 Hz, 1H, CH_2OH), 3.74 (dd, J=3.8, 10.8 Hz, 1H, CH_2OH), 2.13 (dd, J=7.2, 7.2 Hz, 2H, CH_2CH=CH_2), 1.73–1.78 (m, 1H,), 1.44–1.55 (m, 2H), 1.31–1.32 (br m, 6H), 0.89 (t, J=6.2 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.1 (3°), 116.2 (2°), 74.6 (3°), 64.4 (2°), 44.0 (3°), 33.4 (2°), 31.8 (2°), 29.9 (2°), 25.9 (2°), 22.6 (2°), 14.0 (1°); $[\alpha]_D^{28}=-7.1$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 3419, 2931, 2859, 1416, 1160, 1026, cm^{-1}; FAB mass (*m*/*z*): 187 (M^++1, 27), 178 (45), 169 (53), 151 (68), 136 (57), 109 (65), 95 (97), 81 (94), 55 (100); HRMS *m*/*z* calcd for $C_{11}H_{22}O_2$ 186.1620, found: 186.1613.

4.5.5. (−)-(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-dec-1-en-5-ol ((−)-31). To a solution of the diol (−)-**30** (160 mg, 0.86 mmol), DMAP (21 mg, 0.17 mmol) and imidazole (64.4 mg, 0.94 mmol) in 1.8 mL of CH_2Cl_2 was added *t*-butyldimethylsilyl chloride (142.5 mg, 0.94 mmol) at rt and stirred it for 3 h. The reaction is quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give the silyl ether (−)-**31** (231 mg, 0.81 mmol) in 94% yield as a pale yellow oil. TLC R_f=0.38 (hexane/EtOAc=20:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72–5.83 (m, 1H, C*H*=CH_2), 5.01–5.08 (m, 2H, CH=CH_2), 3.81–3.85 (m, 1H, C*H*OH), 3.78 (dd, J=5.2, 9.8 Hz, 1H, CH_2OTBS), 3.73 (dd, J=3.5, 9.8 Hz, 1H, CH_2OTBS), 3.27 (br d, J=3.7 Hz, 1H, O*H*), 2.14–2.17 (m, 2H, CH_2CH=CH_2), 1.61–1.68 (m, 1H, C*H*CH_2OTBS), 1.47–1.55 (m, 2H), 1.30–1.43 (m, 6H), 0.88–0.91 (m, 12H, CH_2CH_3 and $(CH_3)_3CSiMe_2$), 0.08 (s, 3H, *t*-BuSi(CH_3)$_2$), 0.07 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.3 (3°), 116.1 (2°), 74.9 (3°), 65.4 (2°), 43.8 (3°), 33.8 (2°), 31.9 (2°), 29.3 (2°), 25.9 (2°), 25.8 (3×1°), 22.6 (2°), 18.0 (4°), 14.0 (1°), −5.6 (1°), −5.7 (1°); $[\alpha]_D^{31}=-8.6$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 3447, 2955, 2857, 1471, 1255, 1091, 777 cm^{-1}; FAB mass (*m*/*z*): 301 (M^++1, 7), 283 (7), 154 (27), 136 (40), 95 (21), 91 (23), 81 (24), 73 (100), 55 (42); HRMS *m*/*z* calcd for $C_{17}H_{36}O_2Si$ 300.2485, found: 300.2483.

4.5.6. (−)-Acetic acid (1*S*,2*S*)-2-(*tert*-butyldimethylsilyloxymethyl)-1-pentylpent-4-enyl ester ((−)-32). To a solution of the alcohol (−)-**31** (231 mg, 0.86 mmol), DMAP (21 mg, 0.86 mmol) and Et_3N (0.18 mL, 1.29 mmol) in 1.8 mL of CH_2Cl_2 was added acetic anhydride (0.12 mL, 1.29 mmol) at rt and stirred it for 2 h. The reaction mixture was concentrated and chromatographed on silica gel column to afford the acetate (−)-**32** (260 mg, 0.76 mmol) in 88% yield as a pale yellow oil. TLC R_f=0.50 (hexane/EtOAc=20:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.73–5.84 (m, 1H, C*H*=CH_2), 4.99–5.06 (m, 3H, CH=CH_2 and C*H*OCO), 3.56 (dd, J=5.1, 10.1 Hz, 1H, CH_2OTBS), 3.52 (dd, J=5.6, 10.1 Hz, 1H, CH_2OTBS), 2.12–2.15 (m, 2H, CH_2CH=CH_2), 2.03 (s, 3H, COCH_3), 1.72–1.79 (m, 1H, C*H*CH_2OTBS), 1.55–1.57 (m, 2H), 1.25–1.35 (br m, 6H), 0.86–0.92 (m, 12H, CH_2CH_3 and $(CH_3)_3$-$CSiMe_2$), 0.02 (s, 6H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 (4°), 137.1 (3°), 116.0 (2°), 74.4 (3°), 61.9 (2°), 43.7 (3°), 31.7 (2°), 31.5 (2°), 31.3 (2°), 25.8 (3×1°), 25.2 (2°), 22.5 (2°), 21.2 (1°), 18.2 (4°), 14.0 (1°), −5.6 (2×1°); $[\alpha]_D^{34}=-2.9$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 2955, 2857, 1740, 1471, 1242, 1098, 776 cm^{-1}; FAB mass (*m*/*z*): 343 (M^++1, 9), 307 (52), 154 (99), 136 (100), 107 (65), 91 (55), 81 (29), 73 (83), 55 (43); HRMS *m*/*z* calcd for $C_{19}H_{38}O_3Si$ 342.2590, found: 342.2580.

4.5.7. (+)-(1*S*,2*S*)-2-[2-Acetoxy-1-(*tert*-butyldimethylsilyloxymethyl)heptyl]acrolein ((+)-33). Following the general procedure to prepare the α-substituted acrolein from terminal alkene, compound (+)-**33** (1.07 g, 3.0 mmol) was prepared from alkene (−)-**32** (1.2 g, 3.50 mmol) in 86% yield as a colorless oil. TLC R_f=0.25 (hexane/EtOAc=20:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, C*H*O), 6.53 (s, 1H, C=CH_2), 6.15 (s, 1H, C=CH_2), 5.27–5.31 (m, 1H, C*H*OCO), 3.63 (dd, J=5.5, 10.1 Hz, 1H, CH_2OTBS), 3.56 (dd, J=5.9, 10.1 Hz, 1H, CH_2OTBS), 3.09–3.13 (m, 1H, C*H*–C=CH_2), 1.99 (s, 3H, COCH_3), 1.48–1.51 (m, 2H), 1.25–1.27 (m, 6H), 0.84–0.90 (m, 12H), 0.02 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.02 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.1 (4°), 170.2 (4°), 147.8 (4°), 137.0 (2°), 72.7 (3°), 62.6 (2°), 41.7 (3°), 32.4 (2°), 31.6 (2°), 25.7 (3×1°), 24.8 (2°), 22.4 (2°), 21.0 (1°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); $[\alpha]_D^{32}=+1.4$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 2955, 2858, 1741, 1697, 1471, 1239, 1104, 1022, 777 cm^{-1}; FAB mass (*m*/*z*): 357 (M^++1, 16), 297 (42), 239 (71), 117 (84), 91 (22), 81 (31), 73 (100), 55 (44); HRMS *m*/*z* calcd for $C_{19}H_{36}O_4Si$ 356.2383, found: 356.2391.

4.5.8. (−)-(1*S*,2*S*)-2-[2-Acetoxy-1-(*tert*-butyldimethylsilyloxymethyl)heptyl]acrylic acid methyl ester ((−)-34). Following the general procedure to prepare the methyl acrylate from α-substituted acrolein, methyl acrylate (−)-**34** (910 mg, 2.35 mmol) was prepared from acrolein (+)-**33** (1.07 g, 3.00 mmol) in 78% yield as a colorless oil. TLC R_f=0.70 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.32 (s, 1H, C=CH_2), 5.77 (s, 1H, C=CH_2), 5.24 (ddd, J=5.0, 7.2, 7.2 Hz, 1H, C*H*OCO), 3.76 (s, 3H, OCH_3), 3.68 (dd, J=5.7, 10.1 Hz, 1H, CH_2OTBS), 3.63 (dd, J=6.2, 10.1 Hz, 1H, CH_2OTBS), 3.05–3.09 (m, 1H, C*H*C=CH_2), 1.98 (s, 3H, COCH_3), 1.51–1.62 (m, 2H), 1.22–1.33 (m, 6H), 0.83–0.91 (m, 12H), 0.01 (s, 6H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (4°), 167.7 (4°), 138.1 (4°), 127.3 (2°), 73.1 (3°), 63.0 (2°), 51.9 (1°), 45.7 (3°), 32.4 (2°), 31.6 (2°), 25.8 (3×1°), 24.9 (2°), 22.5 (2°), 21.0 (1°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); $[\alpha]_D^{32}=-2.4$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 2955, 2858, 1739, 1438, 1242, 1104, 777 cm^{-1}; FAB mass (*m*/*z*): 387 (M^++1, 15), 329 (34), 269 (52), 154 (12), 117 (40), 91 (11), 73 (100), 55 (9); HRMS *m*/*z* calcd for $C_{20}H_{38}O_5Si$ 386.2489, found: 386.2493.

4.5.9. (−)-(4*R*,5*S*)-4-Hydroxymethyl-3-methylene-5-pentyldihydrofuran-2-one ((−)-27). To a mixture of acetoxy-acrylate (−)-**34** (50 mg, 0.13 mmol) in 0.3 mL of MeOH was added catalytic amount of acetyl chloride (1 μL, 13 μmol) and stirred at rt for 24 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the α-methylenelactone (−)-**27** (23.4 mg, 0.12 mmol) in 91% yield as a pale yellow oil. TLC R_f=0.55 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.33 (d,

$J=2.8$ Hz, 1H, C=CH_2), 5.72 (d, $J=2.8$ Hz, 1H, C=CH_2), 4.40 (ddd, $J=4.4$, 6.4, 6.4 Hz, 1H, CHOCO), 3.74–3.79 (m, 2H, CH_2–OH), 2.85–2.90 (m, 1H, CHCH$_2$OH), 1.65–1.71 (m, 3H), 1.31–1.51 (m, 6H), 0.89 (t, $J=7.2$ Hz, 3H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (4°), 136.2 (4°), 123.4 (2°), 80.9 (3°), 63.8 (2°), 46.8 (3°) 36.0 (2°), 31.4 (2°), 24.6 (2°), 22.4 (2°), 13.9 (1°); $[\alpha]_D^{30}=-16.2$ ($c=0.52$, $CHCl_3$); IR (CH_2Cl_2): 3459, 2932, 2860, 1748, 1465, 1151, 733 cm^{-1}; FAB mass (*m/z*): 199 ($M^+ +1$, 16), 181 (10), 154 (23), 136 (27), 91 (40), 81 (39), 55 (100); HRMS *m/z* calcd for $C_{11}H_{18}O_3$ 198.1256, found: 198.1248.

4.5.10. (−)-(4*R*,5*S*)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid ((−)-8a). Following the general procedure to prepare the carboxylic acid from the corresponding primary alcohol by Jones reagent, (−)-methylenolactocin ((−)-**8a**) (492 mg, 0.21 mmol) was prepared from primary alcohol (−)-**27** (550 mg, 2.52 mmol) in 84% yield as a white solid. TLC $R_f=0.20$ (hexane/EtOAc=1:1); mp 82.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, $J=3.1$ Hz, 1H, C=CH_2), 6.02 (d, $J=2.2$ Hz, 1H, C=CH_2), 4.78–4.83 (m, 1H, CHOCO), 3.63 (ddd, $J=2.8$, 2.8, 5.6 Hz, 1H, CHC=CH$_2$), 1.71–1.78 (m, 2H), 1.26–1.51 (m, 6H), 0.90 (t, $J=7.0$ Hz, 3H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 (4°), 168.8 (4°), 132.5 (4°), 125.8 (2°), 79.2 (3°), 49.4 (3°), 35.4 (2°), 31.1 (2°), 24.2 (2°), 22.2 (2°), 13.7 (1°); $[\alpha]_D^{32}=-18.8$ ($c=0.31$, $CHCl_3$); IR (CH_2Cl_2): 3462, 2954, 2861, 1743, 1257, 1186, 737 cm^{-1}; EI mass (*m/z*): 212 (M^+, 2), 183 (24), 141 (100), 123 (21), 113 (61), 81 (9), 55 (24); HRMS *m/z* calcd for $C_{11}H_{16}O_4$ 212.1049, found: 212.1053.

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Corrigendum

Corrigendum to "Indium- and Gallium-mediated carbon–carbon bond forming reactions in organic synthesis" [Tetrahedron 60 (2004) 1959]

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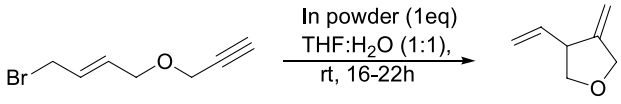
(1) An important paper by Salter et al. (ref: Synlett, 2002, 2068) which describes the indium mediated intramolecular cyclisation of tethered allyl bromides onto terminal alkynes to give unsaturated carbocycles and heterocycles, was omitted inadvertently.



(2) In the key words gallium is spelt incorrectly.

The authors apologise for the errors.

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