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Tetrahedron

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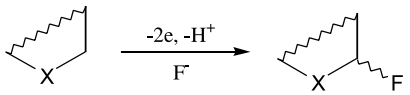
Contents

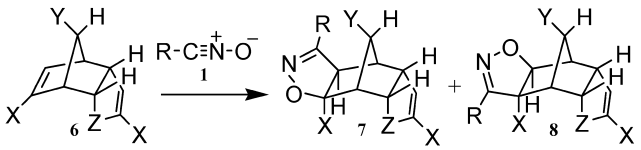
REPORT



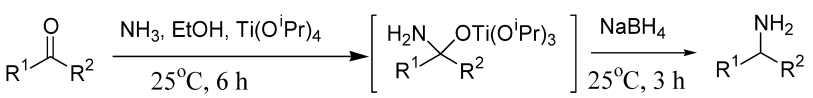
X = O, N, S, Se

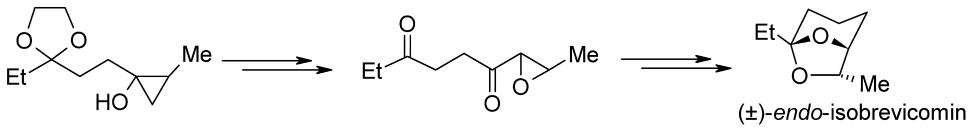
Regio- and stereoselective electrolytic fluorination of various classes of organic compounds have been reviewed. The report contains 140 references.

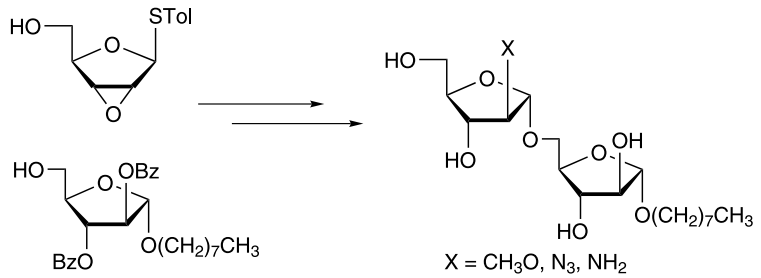
ARTICLES

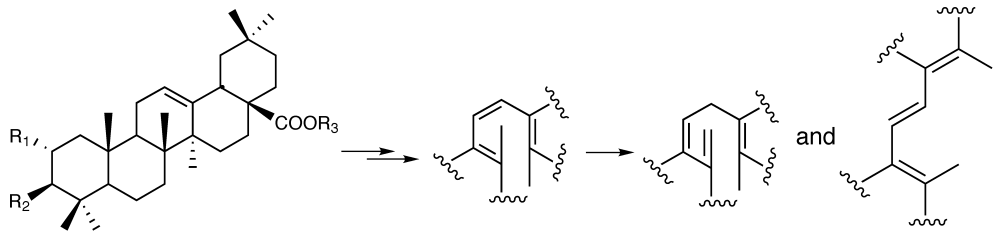


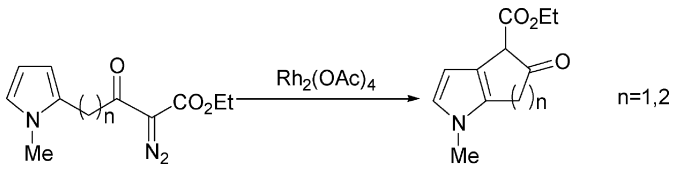
R = Me or Ph; X = Y = H, Z = CH_2; **7**:**8** = ~55:45
R = Me or Ph; X = CO_2Me, Y = H, Z = CH_2; **7**:**8** = >99:1
R = Ph, X = H, Y = OH, Z = CH_2; **7**:**8** = ~55:45
R = Ph, X = Y = H, Z = CO; **7**:**8** = 34:66

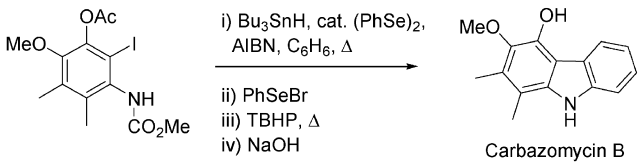




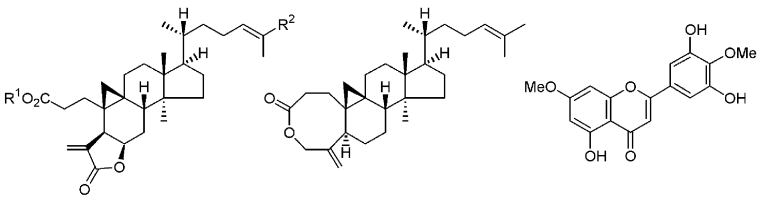




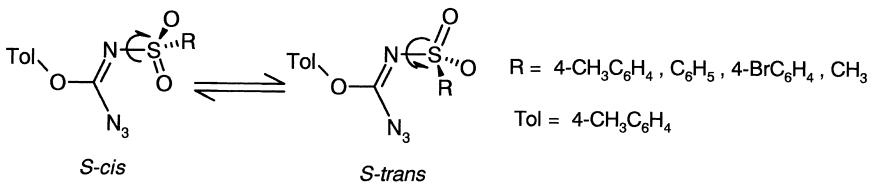


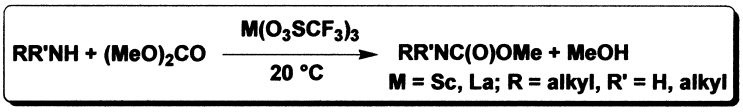


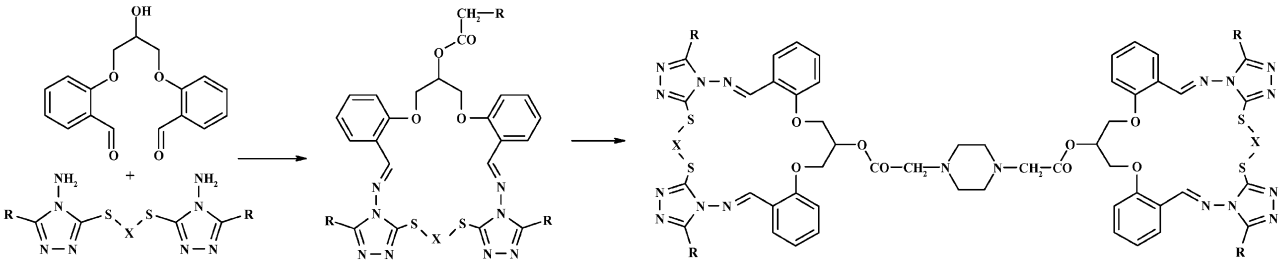
Two new natural cycloartanes **1** and **2**, together with the known **3** and **4** have been isolated from leaves and twigs of *Gardenia tubifera*. In addition, a new flavone **5**, five known flavones and hexacosyl 4′-hydroxy-*trans*-cinnamate were also obtained from the same source. All isolated constituents were evaluated for cytotoxic and anti-HIV-1 activities.

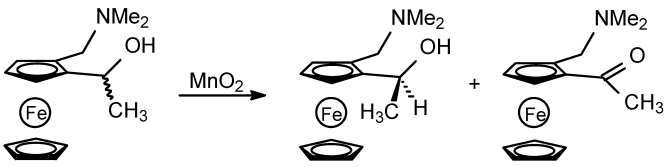


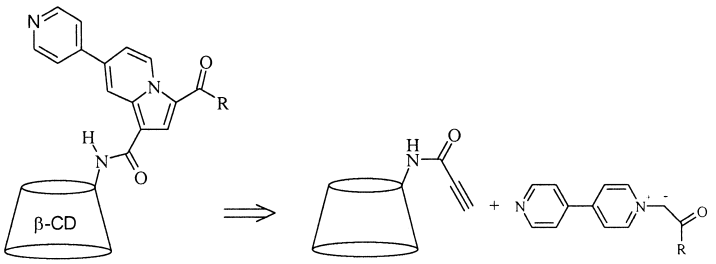
1 $R^1 = R^2 = Me$ **2** **5**
3 $R^1 = H$, $R^2 = CHO$
4 $R^1 = Me$, $R^2 = CHO$

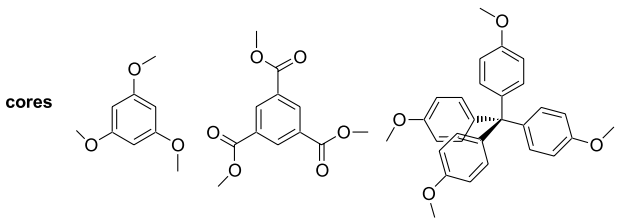


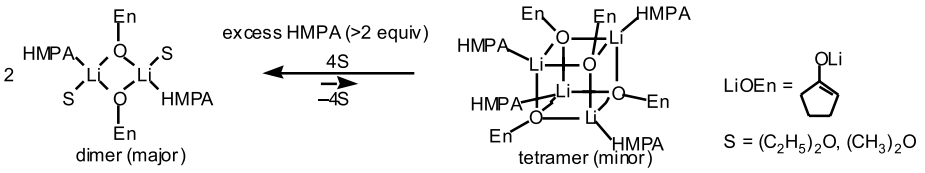


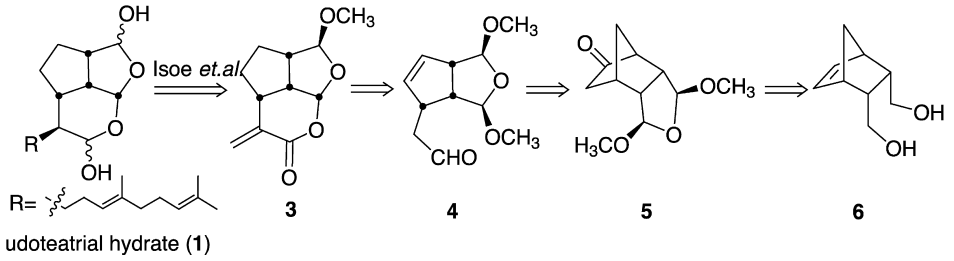




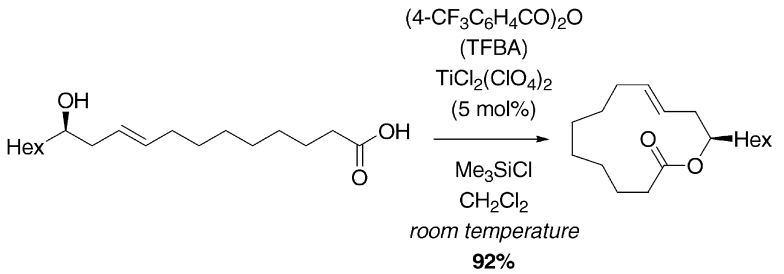


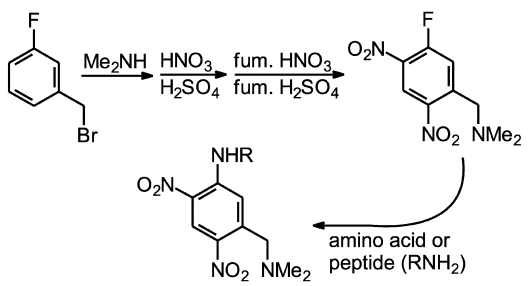


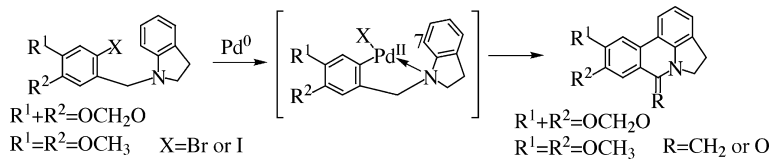


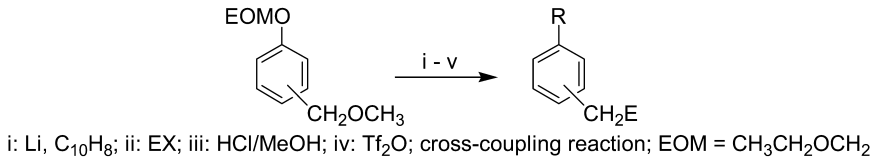


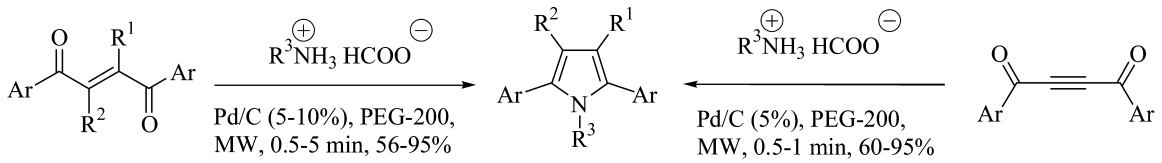
The formal synthesis of antimicrobial diterpene udoteatrial hydrate (**1**) is described in nine steps. Diol **6** used as starting material. The key intermediate **4** was obtained from bicyclic ketone **5** via the key Norrish type I reaction.

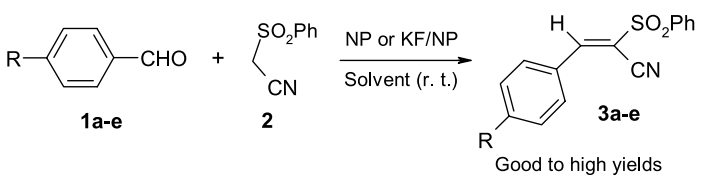


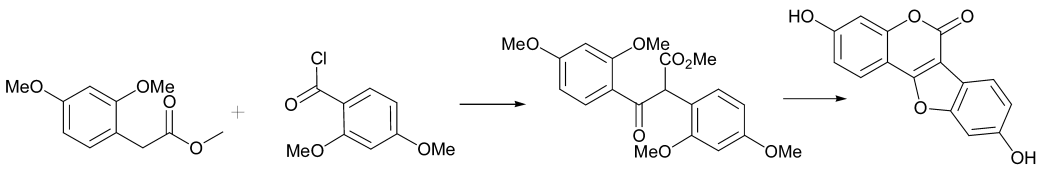


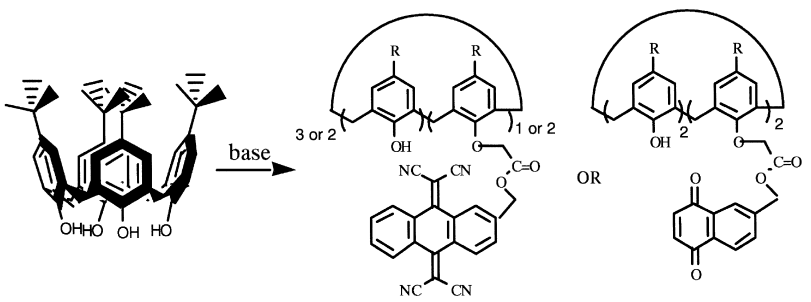


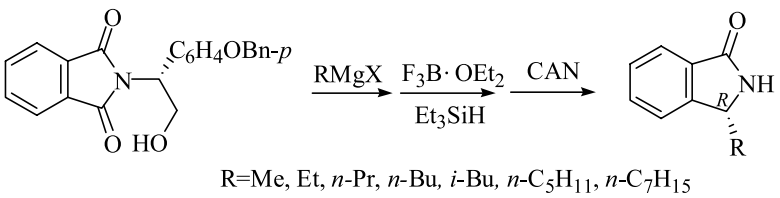




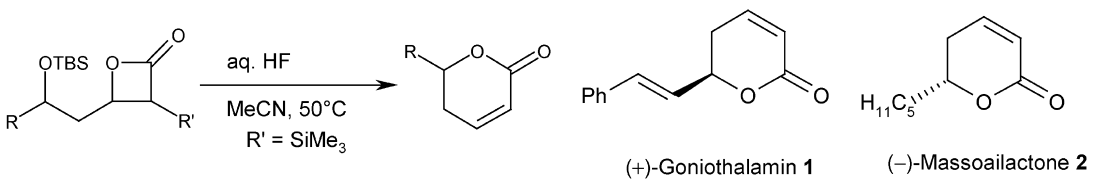




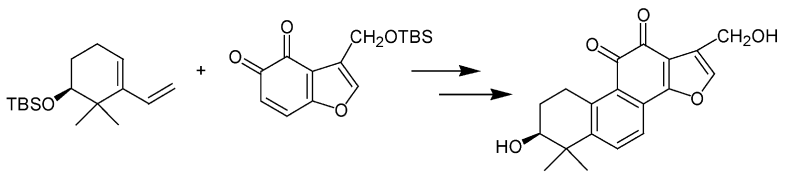


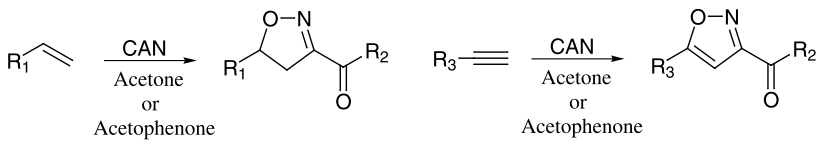


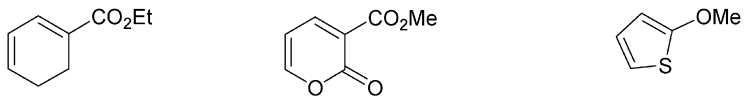
R=Me, Et, *n*-Pr, *n*-Bu, *i*-Bu, *n*-C_5H_{11}, *n*-C_7H_{15}



(+)-Goniothalamin **1** (−)-Massoailactone **2**







1 **2** **3**

Irreversible Diels–Alder cycloaddition of **1**–**3** with acetylenic compound were carried out under micro-wave activation with important specific effect for **2** and **3**.

OTHER CONTENTS

*Corresponding author

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology Abstracts, Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

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Electrolytic fluorination of organic compounds

Kamal M. Dawood*

Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt

Received 26 October 2003

Contents

1. Introduction

Partially fluorinated organic compounds have unique properties that make them suitable for diverse applications in agrochemistry, materials science and in the pharmaceutical industry.[1–10] This is attributed to the high electronegativity of the fluorine atom combined with the relatively similar size of fluorine to hydrogen and the high lipophilicity of the C–F bond.[11] In addition, fluorine can participate in hydrogen bonding interactions as an electron donor.[11] Efficient methods for the synthesis of fluorinated organic compounds are, therefore, becoming increasingly important. The two fundamentally different strategies by which fluorine can be introduced into target molecules are by chemical methods and by electrochemical methods. The chemical methods are as follows.

* Fax: +202-5676501; e-mail addresses: dr_dawood@cu.edu.eg; dr_dawood@yahoo.com

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1.1. Introduction of fluorine by the application of fluorine-containing building blocks[2]

This is an effective methodology for the preparation of complex molecules based on multiple molecular conversions of commercially available fluorinated compounds such as CF_3COCF_3, CF_3COMe, CF_3COOEt and CF_2Br_2. The disadvantages of this method are: (i) the limitation of commercially available fluorinated compounds; (ii) the shortage of monofluorinated precursors, though the incorporation of perfluorinated (e.g., trifluoromethyl and perfluoroalkyl) groups is well developed; and (iii) that fluorinated substrates are always costly.

1.2. Direct fluorination[12–15]

Direct substitution of hydrogen by fluorine generally requires the handling of elemental fluorine, either in a direct reaction with the substrate or in the preparation of fluorinating reagents. The fluorinating reagents are divided into two groups.

(A) *Nucleophilic fluorinating reagents*. Many reagents have been developed to overcome problems such as the poor nucleophilicity of F^-, and lowering the toxicity and increasing the stability of the fluorinating reagents. The most commonly used nucleophilic reagents are HF, BrF_3, XeF_2, SF_4, SiF_4, alkali metal fluorides, AgF, HgF_2, CuF_2, ZnF_2, Et_2NSF_3 (DAST) and $R_3N.nHF$.

(B) *Electrophilic fluorinating reagents*. These reagents have been developed for introducing fluorine at centres of high electron density and, therefore, they offer an interesting alternative when nucleophilic sources of fluorine are inefficient or have failed. The ability of fluorine to behave as an electrophile (F^+) is not easily achieved, since fluorine is the most electronegative element. Ingenious ways for overcoming this problem have been achieved by either withdrawing electronic charge from fluorine through inductive effects or by the presence of an excellent leaving group adjacent to fluorine. Examples of electrophilic fluorinating reagents are F_2, $FClO_3$, CF_3OF, CF_3COOF, $CsSO_4F$ and *N*-fluoropyridinium triflates. The main disadvantages of these methods are: (i) the difficulties in handling the hazardous or troublesome fluorinating reagents; and (ii) the lack of selectivity (regio- and stereoselectivity).

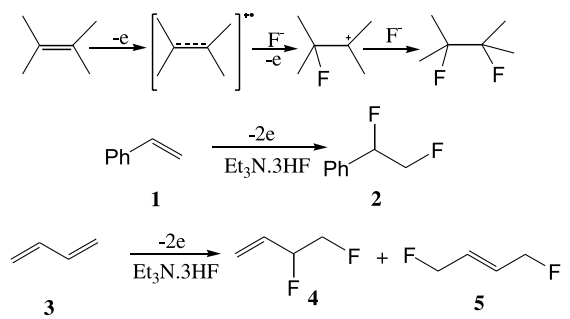
On the contrary, electrolytic fluorination methodology proved to be highly attractive and more promising than the above-mentioned methods and, consequently, it serves as a new tool in fluoro-organic synthesis.[16–19] Compared with the conventional chemical fluorination methods, electrolytic fluorination has the following advantages: (a) hazardous or toxic reagents are not required, the less corrosive fluoride salts compared with the other fluorinating reagents being widely used in electrolytic fluorination; (b) fluorination can be carried out in relatively simple equipment under mild conditions; (c) fluorination processes can be easily controlled by the applied potential, current and electricity; (d) it is a type of green chemistry, where the secondary pollution can be avoided because electricity is used as an oxidising reagent; and (e) it is an economic method, where a fluoride salt can be used as the fluoride ion source and supporting electrolyte and, in addition, some fluoride salts such as $Et_3N{\cdot}3HF$ can be easily recycled by simple distillation. Moreover, electrolytic reactions can be attempted using a simple battery as a power supply and glassware common to any synthetic laboratory.[20] Electrolytic fluorination processes are frequently employed to convert C–H to C–F bonds. Anhydrous HF (AHF) is the most common reagent used in electrolytic perfluorination, where all C–H bonds are converted to C–F bonds. AHF is, however, an extremely hazardous substance due to its low boiling point and high toxicity, in addition to giving poor yields of the electrochemically-perfluorinated products.[21,22] HF combined with organic bases, to form salts such as $Et_3N{\cdot}nHF$ or $Et_4NF{\cdot}nHF$ (n=2–5), have therefore, been widely utilised as the fluorine source and supporting electrolytes for the selective electrolytic partial fluorination of organic compounds.[23,24]

This review article covers the recent remarkable advances in the direct and indirect electrolytic partial fluorination of organic compounds such as olefins, aromatic compounds, carbonyl compounds, heteroatom compounds and heterocycles. Electrolytic perfluorination is also briefly described.

2. Electrolytic partial fluorination of organic compounds

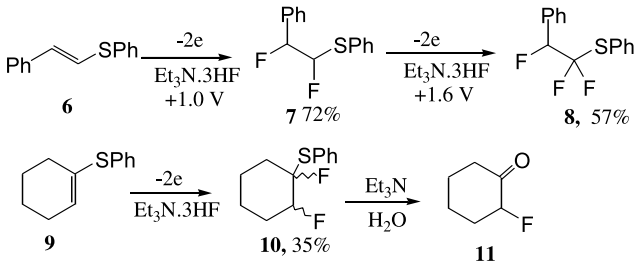
2.1. Direct electrolytic partial fluorination of organic compounds

2.1.1. Olefins. The electrolytic oxidation of double bonds in the presence of fluorinating agents proceeds predominantly through *cis* addition to give the corresponding *vicinal* difluorinated products.[25,26] Electrofluorination of styrene (**1**) in $Et_3N{\cdot}3HF$/MeCN gave the corresponding *vic*-difluorinated product **2** in 51% yield. Butadiene (**3**) gave a 1:2 mixture of the 1,2- and 1,4-adducts **4** and **5**, respectively[25] (Scheme 1).



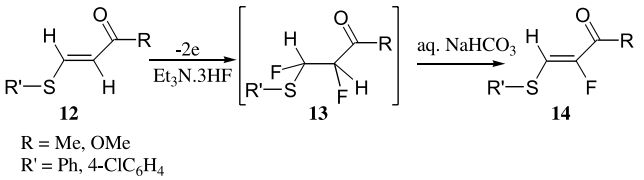
Scheme 1.

Electrolytic fluorination of 2-(phenylthio)styrene (**6**) in $Et_3N{\cdot}3HF$ under constant potential gave the *vic*-difluorinated product **7** which upon further fluorination at higher potential yielded the trifluorinated derivative **8**.[27] Electrofluorination of 1-(phenylthio)cyclohexene (**9**) resulted in the formation of the 1,2-difluoro-1-phenylthiocyclohexane (**10**) which is highly sensitive to acids and bases and could be converted into α-monofluorocyclohexanone (**11**) in the presence of traces of Et_3N,[27] as shown in Scheme 2.



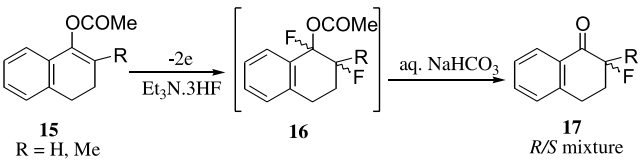
Scheme 2.

Vinyl sulfides **12** bearing carbonyl functions were also electrolytically fluorinated using $Et_3N{\cdot}3HF$ in acetonitrile to give the monofluorinated vinyl sulfides **14** stereoselectively.[28] The latter products were obtained through dehydrofluorination of the adduct intermediate **13** (Scheme 3).



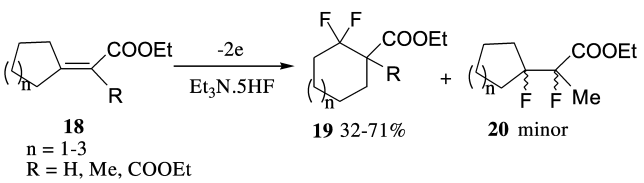
Scheme 3.

Anodic oxidation of 1-acetoxy-3,4-dihydronaphthalene derivatives **15**, in the presence of $Et_3N{\cdot}3HF$, afforded the *vic*-difluorinated intermediates **16**, which were subsequently hydrolysed to give the α-fluoro cyclic ketones **17**,[29] as shown in Scheme 4.



Scheme 4.

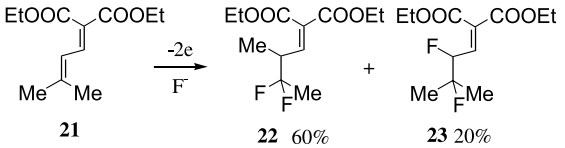
Yoneda and co-workers[30] found that electrolytic oxidation of the cyclic unsaturated esters **18** in $Et_3N{\cdot}5HF$ resulted in fluorination and ring expansion to provide the *gem*-difluoro cycloalkanecarboxylates **19**, (Scheme 5), together with the minor product **20**.



Scheme 5.

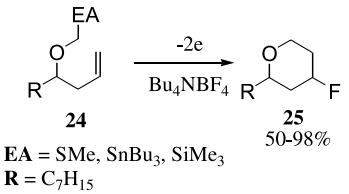
Electrolytic fluorination of the conjugated diene ester **21** occurred at the distal olefin moiety to give a mixture of the *vic*- and *gem*-difluorinated alkene esters **22** and **23**, respectively,[31] as demonstrated in Scheme 6.

Electrolytic fluorination accompanied by C–C bond formation has been achieved using silyl, stannyl or sulfenyl groups as electroauxiliaries (EA).[32–34] Anodic fluorination



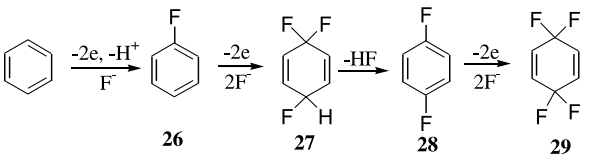
Scheme 6.

of the olefin derivatives **24** using Bu_4NBF_4 resulted in the loss of the electroauxiliaries and intramolecular cyclisation to one of the olefinic carbons and the introduction of fluoride ion to the other carbon to give the corresponding fluoropyran derivatives **25**[32] (Scheme 7).



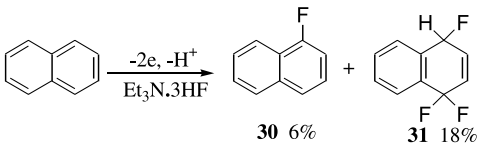
Scheme 7.

2.1.2. Aromatic compounds. Electrochemical fluorination of benzene, in $Et_4NF{\cdot}4HF/MeCN$, afforded mainly monofluorobenzene (**26**) along with traces of 1,4-difluorobenzene (**28**).[35] Further fluorination of fluorobenzene (**26**) gave 3,3,6-trifluorocyclohexadiene (**27**) which undergoes dehydrofluorination to give 1,4-difluorobenzene (**28**). The latter compound was also electrolysed and converted into 3,3,6,6-tetrafluorocyclohexadiene (**29**),[36,37] as shown in Scheme 8. The compounds **28** and **29** could also be obtained as the final products during the electrofluorination of chloro- or bromobenzene.[38,39]



Scheme 8.

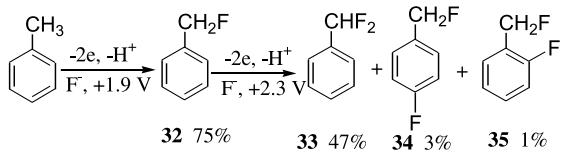
Meures et al.[25] have reported the electrolytic fluorination of naphthalene in $Et_3N{\cdot}3HF$, which gave the corresponding mono- and trifluoro- derivatives **30** and **31** (Scheme 9).



Scheme 9.

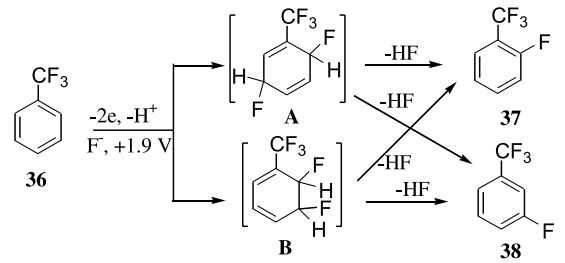
Electrolysis of toluene in the presence of neat liquid $Et_4NF{\cdot}4HF$ was found to be highly regioselective and gave exclusively benzyl fluoride (**32**).[40,41] Further electrolysis of **32** afforded mainly difluoromethylbenzene (**33**), in addition to the ring-fluorinated byproducts **34** and **35**[40] (Scheme 10).

Trifluoromethylbenzene (**36**) was also electrolytically monofluorinated to give a mixture of the 2- and 3-fluoro-1-trifluoromethylbenzenes **37** and **38**, respectively, through



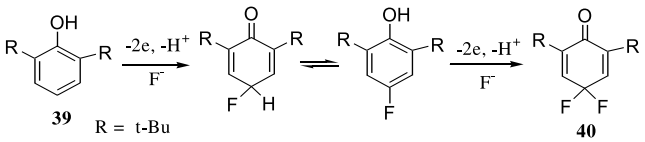
Scheme 10.

the dehydrofluorination of the intermediate adducts **A** or **B**[42] (Scheme 11).



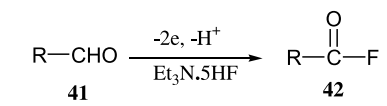
Scheme 11.

In the presence of $Et_3N{\cdot}5HF$ as the electrolyte, electrolytic fluorination of phenols such as **39** successfully afforded the 4,4-difluorocyclohexadien-1-one **40**, according to the reaction mechanism outlined in Scheme 12.[43,44]



Scheme 12.

2.1.3. Carbonyl compounds. Yoneda and co-workers[45–47] reported a series of selective electrolytic fluorinations of aldehydes and ketones also using $Et_3N{\cdot}5HF$ as the electrolyte. The selective displacement of formyl hydrogen by a fluorine atom in the aliphatic aldehydes **41** took place electrolytically to give the corresponding acyl fluorides **42** in good yields.[45,47] The mechanism is depicted in Scheme 13.

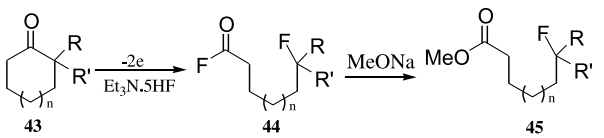


R = n-heptyl, 3-heptyl, c-C_6H_{11}, n-pentyl, t-Bu

Scheme 13.

Selective electrolytic α-bond cleavage between the carbonyl carbon and the substituted α-carbon in the cyclic ketones **43** was attempted in the presence of $Et_3N{\cdot}5HF$ to give the fluoroacyl fluorides **44**, which upon esterification gave the corresponding fluoroacid esters **45**[46,47] (Scheme 14).

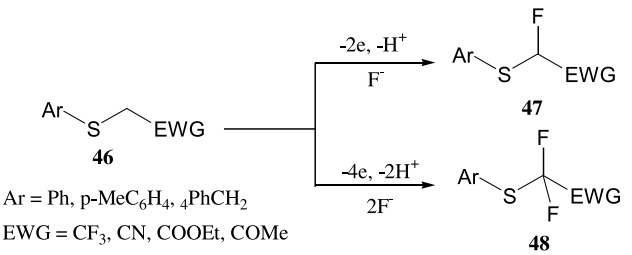
2.1.4. Aryl sulfides. The Fuchigami[48–54] and Laurent[55,56] groups found that the presence of an electron-withdrawing group (EWG) at the α-position to sulfur markedly facilitates the electrolytic α-fluorination of sulfides. In one example, electrolytic oxidation of aryl sulfides **46** in $Et_3N{\cdot}3HF$ or



R = R' = Me; R = Me, R' = Cl; R,R' = -$(CH_2)_4$-

Scheme 14.

$Et_4NF{\cdot}3HF$ affords the corresponding α-monofluorinated sulfides **47** regioselectively (Scheme 15).



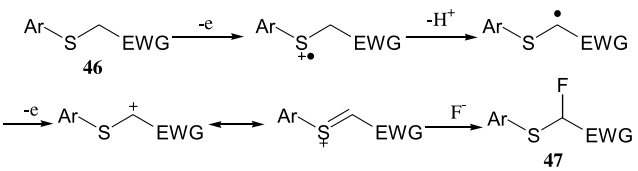
Ar = Ph, p-MeC_6H_4, $_4PhCH_2$

EWG = CF_3, CN, COOEt, COMe

Scheme 15.

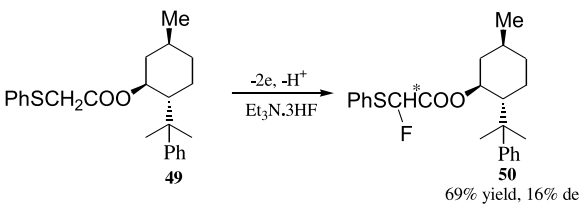
For the sulfides **46**, which have several positions susceptible to substitution by fluorine (Ar=*p*-MeC_6H_4 or $PhCH_2$), a fluorine atom was introduced exclusively α to the EWG and no fluorination of the tolyl or benzyl carbons was observed.[50] α-Fluorination of sulfides devoid of an EWG was also achieved electrolytically.[50,57,58] Passing double amount of the electricity in the fluorination of **46** resulted in the formation of the α,α-difluorinated products **48** (Scheme 15).[53,55–58]

An Electrochemical reaction–Chemical reaction–Electrochemical reaction–Chemical reaction (ECEC) mechanism was proposed for the α-fluorination of thioethers,[54] as shown in Scheme 16.

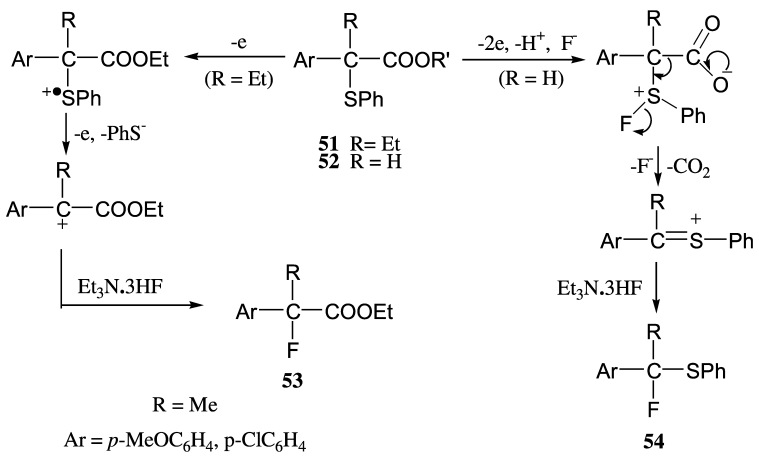


Scheme 16.

The diastereoselective electrolytic fluorination of an α-(phenylthio)acetate having a chiral auxiliary **49**, in the presence of $Et_3N{\cdot}3HF$, was found to give the corresponding fluorinated product **50**,[59] as shown in Scheme 17.



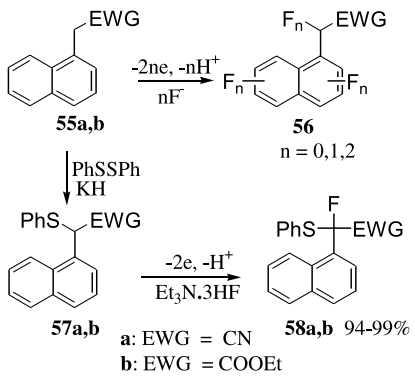
Scheme 17.



Scheme 18.

It is interesting that the electrolytic fluorinations of the α-(phenylthio)esters **51** and α-(phenylthio)acids **52** were reported to give the fluorinated products **53** and **54**, respectively, according to the different mechanisms postulated in Scheme 18.[60]

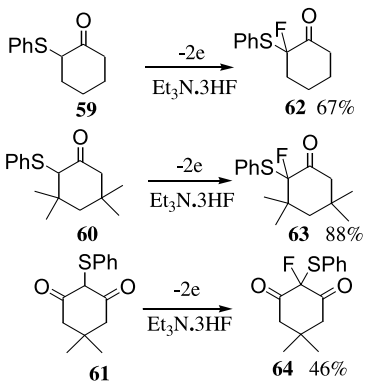
Attempts to electrochemically fluorinate 1-naphthaleneacetonitrile (**55a**) or ethyl 1-naphthaleneacetate (**55b**) met with failure and several polyfluorinated products **56** were detected, in very poor yields, without any selectivity.[61] This was attributed to the high oxidation potentials of **55a**,**b** and consequently they would be difficult to fluorinate electrolytically. Insertion of a phenylthio group at the α position of the naphthalene derivatives **55a**,**b**, however, to give **57a**,**b**, reduced the oxidation potential dramatically and the fluorination then became easy. The compounds **57a**,**b** were, therefore, selectively fluorinated at the α-carbon using $Et_3N{\cdot}3HF$/MeCN to give **58a**,**b** in excellent yields, as shown in Scheme 19.[61]



Scheme 19.

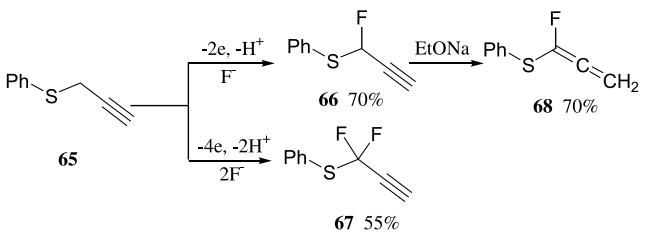
Electrolytic fluorination was extended to the α-(phenylthio)-substituted cyclic ketones **59**–**61** and found to be highly selective, the fluorine atom being selectively inserted at the α position to sulfur to give the corresponding monofluorinated ketones **62**-**64**, respectively, as shown in Scheme 20.[52]

Next, electrolytic fluorination of phenyl propargyl sulfide (**65**) using $Et_4NF{\cdot}4HF$ in dimethoxyethane (DME) was found to be greatly dependent on the amount of electricity



Scheme 20.

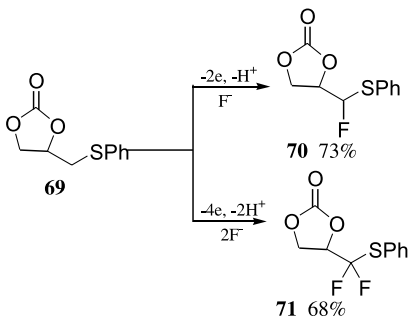
used.[62,63] When twice of the theoretical amount of electricity (4 Far/mol) was passed, the α-monofluorinated sulfide **66** was selectively formed in good yield. Passage of a large excess amount of electricity, however, resulted in the selective formation of α,α-difluoropropargyl sulfide **67**. Treatment of **66** with ethanolic sodium ethoxide solution afforded the corresponding fluoroallene **68** (Scheme 21).[62,63]



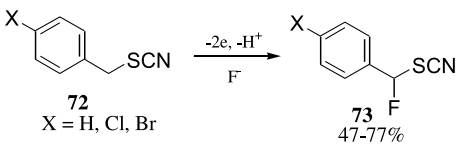
Scheme 21.

Anodic fluorination of 4-phenylthiomethyl-1,3-dioxolan-2-one (**69**) was successfully carried out in $Et_3N{\cdot}3HF$ to provide the corresponding α-mono- or α,α-difluorinated sulfides **70** or **71**, respectively, based on the amount of electricity passed, as shown in Scheme 22.[64]

2.1.5. Benzyl thiocyanates. Benzyl thiocyanates **72** were also fluorinated, using $Et_4NF{\cdot}4HF$, at the benzylic carbon to give the corresponding α-fluorothiocyanates **73** in moderate yields (Scheme 23).[65]

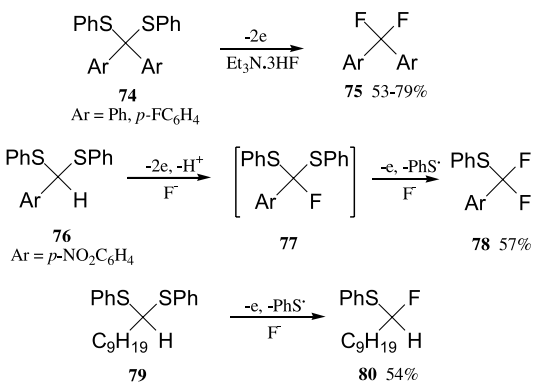


Scheme 22.



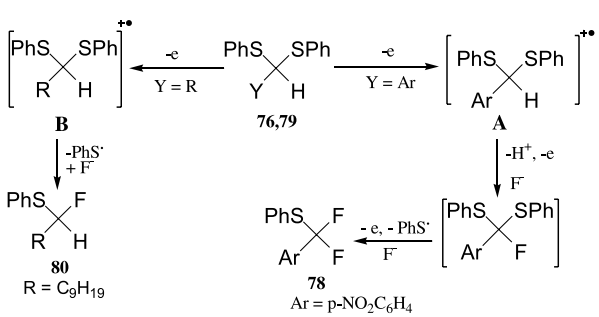
Scheme 23.

2.1.6. Dithioacetals and dithioketals. Electrolytic fluorodesulfurisation of dithioacetals and dithioketals has been reported,[66] and, in his study, electrolysis of the dithioketals **74** in the presence of $Et_3N{\cdot}3HF$ provided the corresponding *gem*-difluoro compounds **75**. Dithioacetals of the aromatic aldehyde **76**, however, afforded via **77** the *gem*-difluorothioether **78** and those of the aliphatic aldehyde **79** gave the monofluorothioether **80**, as shown in Scheme 24.



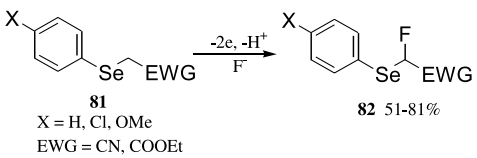
Scheme 24.

It is interesting to note that the electrolytic behaviour of the dithioacetal **76** is quite different from that of the dithioacetal **79**. This can be explained on the basis that deprotonation of the cation radical **A** seems to be easier than that of **B**, since the former α-hydrogen is more acidic than the latter (Scheme 25).[66]



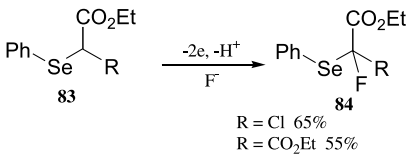
Scheme 25.

2.1.7. Organoselenium compounds. The phenylselenoethers **81** having an activated methylene group gave the corresponding α-monofluorinated derivatives **82** in good yields when electrolysed in the presence of $Et_3N{\cdot}3HF$/MeCN, as shown in Scheme 26.[67,68]



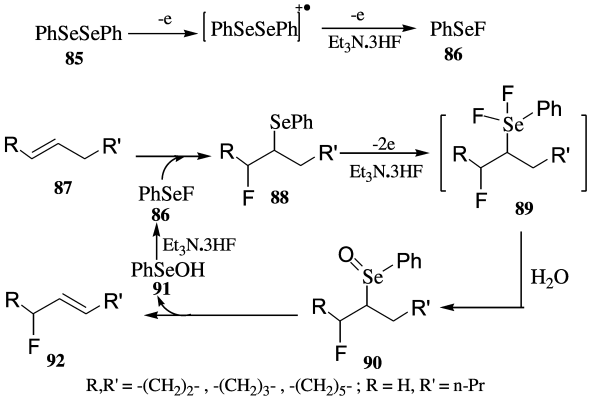
Scheme 26.

Similarly, selenides bearing two EWGs **83** were also electrolytically fluorinated to give the α-fluoroselenides **84** (Scheme 27).[67]



Scheme 27.

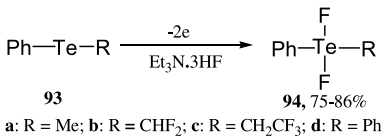
Uneyama et al.[69–72] reported the electrolytic fluorination of diphenyldiselenide (**85**), in the presence of $Et_3N{\cdot}3HF$/CH_2Cl_2, to generate phenylselenyl fluoride (**86**). The latter compound underwent fluoroselenation with the olefins **87** to give the adducts **88**, which were subsequently oxidised via **99** to the selenoxides **90**. *syn*-Elimination of benzeneselenic acid (**91**) from **90** produced the allylic fluorides **92**, as shown in Scheme 28.[69]



Scheme 28.

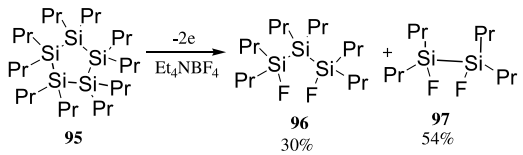
2.1.8. Organotellurium compounds. Electrolytic oxidation of the organotellurium compounds **93a–d** in the presence of fluoride ions using a divided cell resulted in difluorination of the tellurium atom selectively to give **94** in high yields. Even trifluoroethyl telluride **93c**, having an active methylene group, did not give any α-fluorination at carbon, as shown in Scheme 29.[73]

2.1.9. Organosilicon compounds. Electrolytic fluorination of deca-*n*-propylcyclopentasilane (**95**) in the presence of



Scheme 29.

Et_4NBF_4 resulted in ring opining and Si–Si bond cleavage to give the difluorosilane derivatives **96** and **97** (Scheme 30).[74]

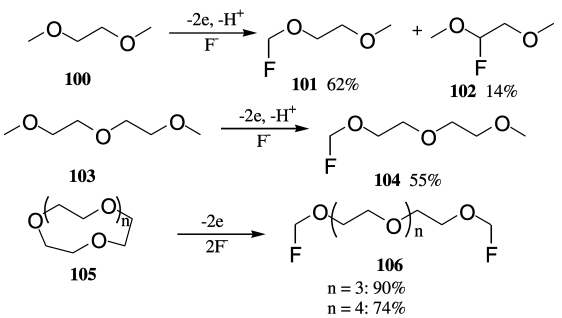


Scheme 30.

2.1.10. Organoantimony compounds. Electrofluorination of triphenylantimony (**98**) was conducted in the presence of the $Et_3N{\cdot}3HF$/MeCN system to give triphenylantimony difluoride (**99**) in excellent yield (Scheme 31).[75]

Scheme 31.

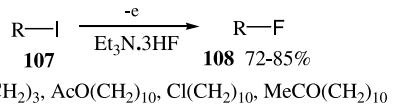
2.1.11. Ethers and cyclic ethers. Anodic fluorinations of ethers and crown ethers were reported by Fuchigami's group.[76,77] They found that electrolytic fluorination of dimethoxyethane (DME) (**100**) in $Et_3N{\cdot}5HF$ or $Et_4NF{\cdot}4HF$ gave a mixture of the two monofluorinated products **101** and **102** (Scheme 32). Similar fluorination of diethyleneglycol dimethylether (**103**) gave solely monofluorination at the terminal carbon, **104**. The crown ethers **105**, however, underwent carbon–carbon bond cleavage preferentially on fluorination to give the α,ω-difluorinated products **106**, as shown in Scheme 32.[76,77]



Scheme 32.

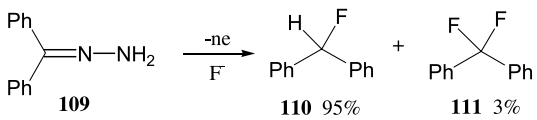
2.1.12. Alkyl iodides. Electrolytic fluorodeiodination of alkyl iodides **107** using $Et_3N{\cdot}nHF$ (n=3–5) proceeds smoothly under mild conditions to give the corresponding alkyl fluorides **108** chemoselectively (Scheme 33).[78]

2.1.13. Hydrazones. Electrolysis of benzophenone hydrazone (**109**), in the presence of $Et_3N{\cdot}3HF/CH_2Cl_2$, was reported to afford mainly diphenylmonofluoromethane



Scheme 33.

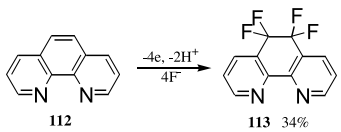
(**110**), in addition to its difluorinated derivative **111** as a byproduct (Scheme 34).[79]



Scheme 34.

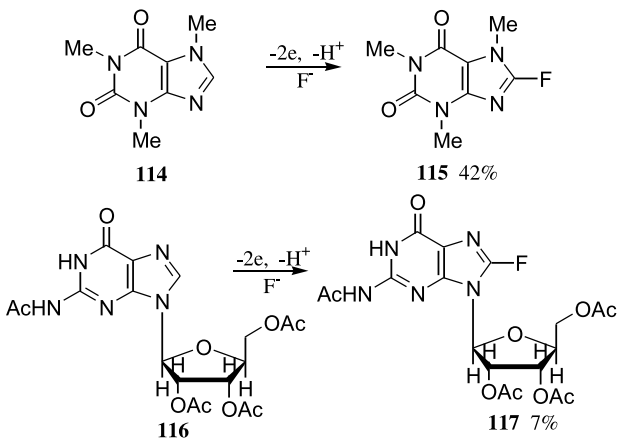
2.1.14. Heterocyclic compounds

2.1.14.1. Nitrogen-containing heterocycles. The electrolysis of 1,10-diazaphenanthrene (**112**) using $Et_3N{\cdot}3HF$ in absence of solvents resulted in the formation of its 5,5,6,6-tetrafluoro derivative **113** (Scheme 35).[25]



Scheme 35.

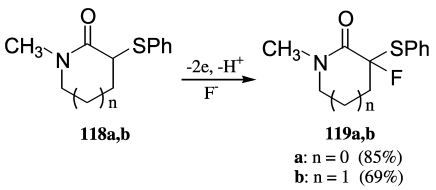
Caffeine (**114**) was fluorinated using $Et_3N{\cdot}3HF$ in acetonitrile to give 8-fluorocaffeine (**115**) in a reasonable yield (Scheme 36).[80,81] When guanosine tetraacetate (**116**) was oxidised under similar electrolytic conditions, 8-fluoroguanosine tetraacetate (**117**) was produced in a very low yield (Scheme 36).[80,81]



Scheme 36.

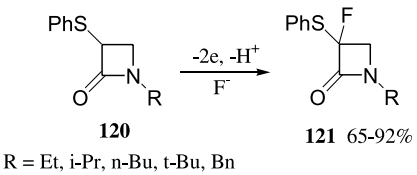
Five- and six-membered lactams **118a**,**b** bearing a phenylthio group were selectively fluorinated at the α position to the sulfur atom, to give the corresponding monofluorinated lactams **119a**,**b**, as shown in (Scheme 37).[82]

Electrolytic fluorination of α-phenylthio-β-lactams **120** in



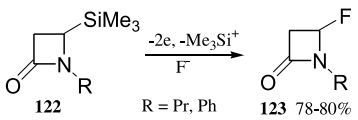
Scheme 37.

$Et_3N{\cdot}3HF$ also led to the formation of the corresponding α-monofluorinated lactams **121** in high yields (Scheme 38).[83]



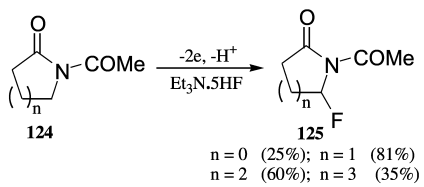
Scheme 38.

Suda et al.[84] have reported the electrolytic fluorodesilylation of (4-trimethylsilyl)azetidin-2-ones **122**, as shown in Scheme 39. In this reaction, the good leaving group (Me_3Si) greatly assisted the regioselective formation of the β-fluoro-β-lactams **123**.



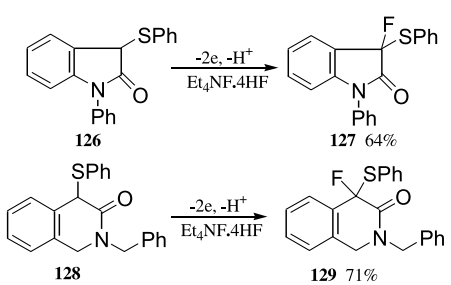
Scheme 39.

The lactams **124** having no sulfenyl or silyl groups in their rings were electrolytically fluorinated using $Et_3N{\cdot}5HF$ by Yoneda's group.[85] In this work, fluorine atom was selectively inserted at the α position to the lactam nitrogen to give the desired products **125**, as outlined in Scheme 40.[85]



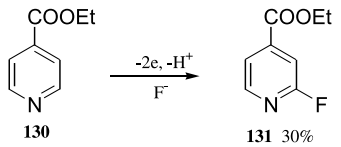
Scheme 40.

The oxindole and tetrahydroisoquinolinone derivatives **126** and **128**, activated with a phenylthio function α to the carbonyl group, were electrochemically fluorinated to give their monofluoro derivatives **127** and **129**, respectively, as depicted in Scheme 41.[86,87]



Scheme 41.

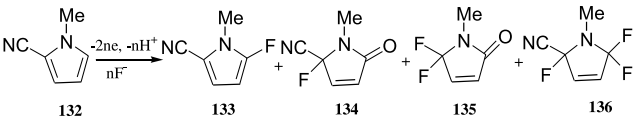
Ethyl 4-pyridinecarboxylate (**130**) underwent electrofluorination using $Et_3N{\cdot}3HF$ to give ethyl 2-fluoro-4-pyridinecarboxylate (**131**) in low yield (Scheme 42).[88]



Scheme 42.

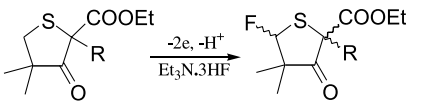
Recently, Tajima et al.[89] have reported that the electrolytic fluorination of 2-cyano-1-methylpyrrole (**132**) provides four ring-fluorinated products **133**–**136** and that the product selectivity was greatly dependent on both the fluoride salts and the solvents, as outlined in Scheme 43.[89]

2.1.14.2. Sulfur-containing heterocycles. Ethyl 2-benzyl-4,4-dimethyl-3-thiolanone-2-carboxylate (**137**) was reported to be electrolysed in $Et_3N{\cdot}3HF$/MeCN to give a mixture of *trans*/*cis* isomers of the highly biologically active 5-fluorothiolanone derivative **138** (Scheme 44).[90]



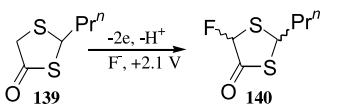
Fluoride salt/Solvent	Yield (%)			
	133	**134**	**135**	**136**
$Et_3N{\cdot}5HF/CH_2Cl_2$	0	12	47	5
$Et_3N{\cdot}4HF/CH_2Cl_2$	0	25	0	0
$Et_3N{\cdot}3HF/CH_2Cl_2$	0	traces	traces	60
$Et_3N{\cdot}2HF/CH_2Cl_2$	19	traces	traces	51
$Et_3N{\cdot}2HF$/MeCN	20	traces	traces	32

Scheme 43.



Scheme 44.

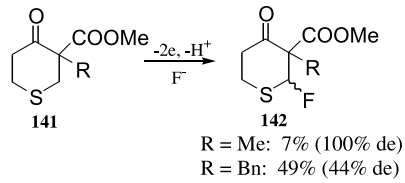
Electrolytic fluorination of 2-(*n*-propyl)-1,3-dithiolan-4-one (**139**) was performed using $Et_4NF{\cdot}4HF$/MeCN to afford a *cis*/*trans* mixture of 5-fluoro-2-(*n*-propyl)-1,3-dithiolan-4-one (**140**) in 72% yield (Scheme 45). The use of $Et_3N{\cdot}3HF$/MeCN also afforded compound **140**, but in very low yield (26%). This was explained on the basis that $Et_4NF{\cdot}4HF$/MeCN is highly stable against anodic oxidation up to 3 V vs. SCE, while $Et_3N{\cdot}3HF$/MeCN discharges around 2 V.[91]



$Et_4NF{\cdot}4HF$/MeCN: 72%; *cis*/*trans* = 48/52
$Et_3N{\cdot}3HF$/MeCN: 26%; *cis*/*trans* = 44/56

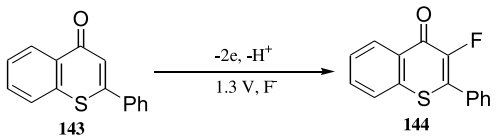
Scheme 45.

The 4-thianones **141** were similarly fluorinated at the 2-position to give the 2-fluoro-4-thianone derivatives **142** with a moderate to high diastereoselectivity (Scheme 46).[92]



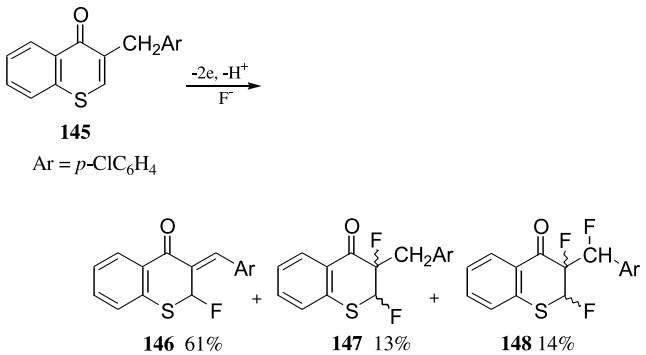
Scheme 46.

Thioflavone (**143**) was electrolytically fluorinated under controlled potential in the presence of $Et_3N{\cdot}3HF$ to afford 3-fluorothioflavone (**144**), as outlined in Scheme 47.[28]



Scheme 47.

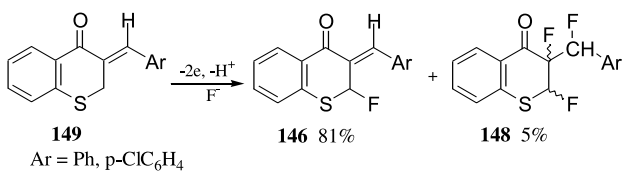
Recently, Dawood et al.[93] the reported that electrolytic fluorination of the homoisothioflavone derivative **145** proceeds in a different manner to that of thioflavone (**143**), in $Et_4NF{\cdot}4HF$/DME affording mainly the 2-fluoro-3-benzylidenethiochromanone derivative **146** in addition to its di- and trifluorinated derivatives **147** and **148**, respectively, as shown in Scheme 48.[93]



Scheme 48.

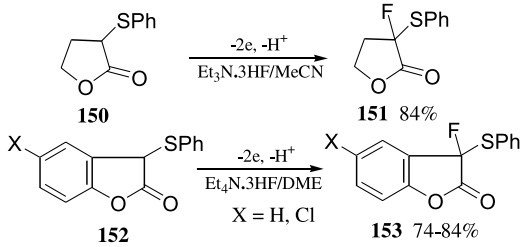
The mono- and trifluorinated thiochromanone derivatives **146** and **148** were alternatively obtained from the direct electrolytic fluorination of 3-arylidenethiochroman-4-ones **149** under similar electrolytic conditions (Scheme 49).[93]

2.1.14.3. Oxygen-containing heterocycles. The electrofluorination of 3-(phenylthio)tetrahydrofuran-2-one (**150**)[52] and 3-(phenylthio)-dihydrobenzofuran-2-one (**152**)[94] was successfully achieved in the presence of the appropriate



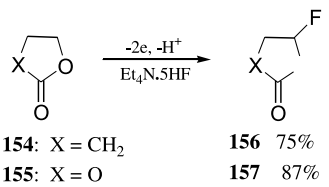
Scheme 49.

fluoride salt to form the corresponding monofluorinated derivatives **151** and **153**, respectively, as shown in Scheme 50.



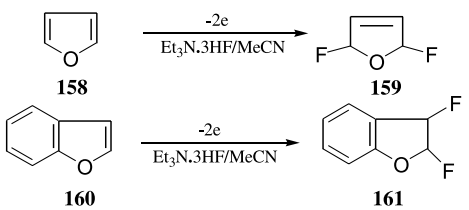
Scheme 50.

The regioselective anodic fluorination of γ-butyrolactone (**154**) and ethylene carbonate (**155**) was attempted using $Et_4NF{\cdot}5HF$ without a solvent to give the corresponding monofluorinated products **156** and **157**, respectively, in good yields (Scheme 51).[95]



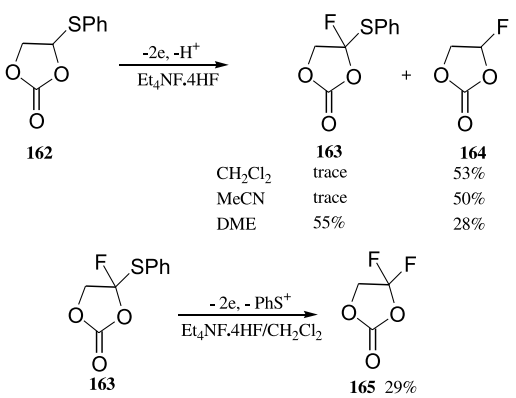
Scheme 51.

Difluorinated products were obtained in the electrolytic fluorination of furan (**158**) and benzofuran (**160**) using $Et_3N{\cdot}3HF$.[25] With furan, 1,4-addition of fluorine took place to give **159**, but 1,2-addition was observed in the fluorination of benzofuran to give **161** (Scheme 52).[25]



Scheme 52.

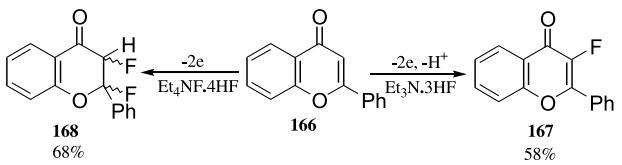
Electrolytic solvents played a significant role in the product selectivity during the fluorination of 4-phenylthio-1,3-dioxolan-2-one (**162**).[96,97] As shown in Scheme 53,



Scheme 53.

fluorodesulfurisation occurred to give 4-fluoro-1,3-dioxolan-2-one (**164**) selectively when CH_2Cl_2 or MeCN were used as the solvents; in dimethoxyethane (DME), however, α-fluorination took place to give **163** preferentially in addition to **164**. Further electrolytic fluorination of **163** in CH_2Cl_2 afforded 4,4-difluoro-1,3-dioxolan-2-one (**165**) (Scheme 53).[96,97]

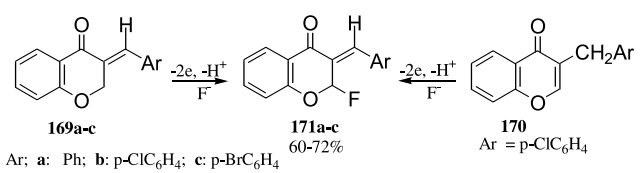
Electrolytic fluorination of flavone (**166**) was found to be dependent on the type of fluoride salts used. In $Et_3N{\cdot}3HF$, it afforded 3-fluoroflavone (**167**), but using $Et_4NF{\cdot}4HF$ led to formation of 2,3-difluoro-2,3-dihydroflavone (**168**) (Scheme 54).[98,99]



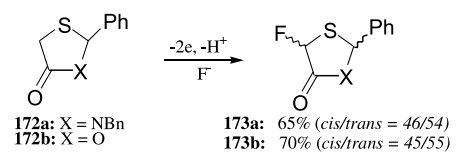
Scheme 54.

Highly regioselective electrolytic direct fluorination at the α-position to the ring-oxygen atom of the chroman-4-one derivatives **169a–c** was successfully performed using $Et_4NF{\cdot}4HF$/DME to give the corresponding 2-fluorochromanones **171a-c**.[100,101] The compound **171b** could also be obtained stereoselectively from an alternative electrofluorination of the homoisoflavone derivative **170**, as shown in Scheme 55.[100,101]

2.1.14.4. Heterocycles containing more than one heteroatom. The highly regioselective electrolytic fluorination of 3-benzyl-2-phenylthiazolidin-4-one (**172a**) was performed in $Et_3N{\cdot}3HF$/MeCN to give the corresponding monofluorinated product **173a** (Scheme 56).[102] When $Et_4NF{\cdot}4HF$/MeCN was used for the fluorination of the oxathiolan-4-one derivative **172b**, the monofluorinated product **173b** was obtained in 70% yield, while $Et_3N{\cdot}3HF$/MeCN resulted in no fluorination (Scheme 56).[103] The latter result was attributed to a severe passivation of the anode when $Et_3N{\cdot}3HF$/MeCN was used, due to the equilibrating existence of free Et_3N,[23] but no passivation was observed in the case of $Et_4NF{\cdot}4HF$/MeCN.[103]

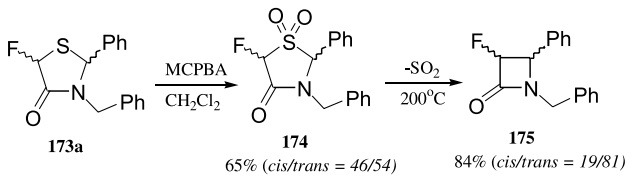


Scheme 55.



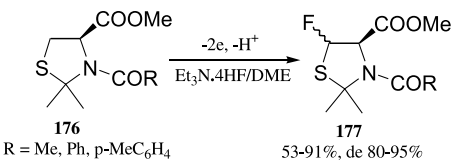
Scheme 56.

Treatment of **173a** with *m*-chloroperbenzoic acid (MCPBA) afforded the fluorosulfone **174** which, under thermolysis at 200 °C, resulted in the formation of the biologically active monofluorinated β-lactam **175** (Scheme 57).[102]



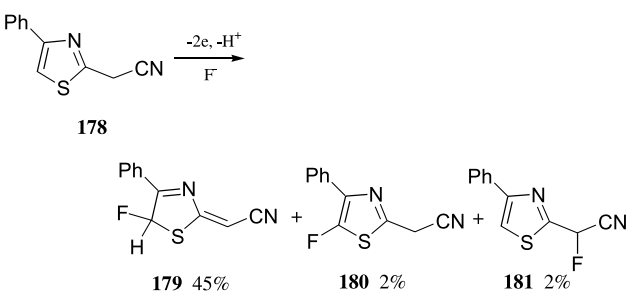
Scheme 57.

The thiazolidines **176** were also diastereoselectively electrolysed in dimethoxyethane using $Et_3N{\cdot}4HF$ to give the monofluorinated products **177** where a fluorine atom was selectively introduced at the α position to the sulfur atom (Scheme 58).[104]



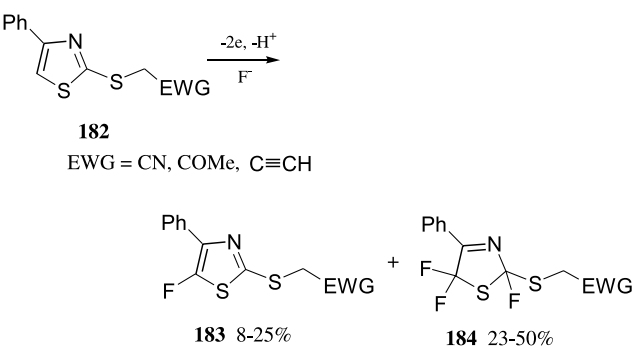
Scheme 58.

Electrolytic fluorination of 4-phenyl-2-thiazolylacetonitrile (**178**) was conducted in $Et_4NF{\cdot}5HF$/DME to give the monofluorinated products **179–181** as shown in Scheme 59.[105]



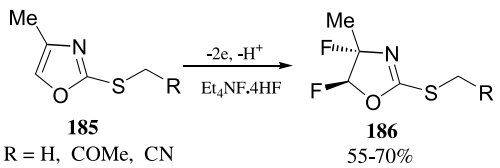
Scheme 59.

Similarly, the thiazolyl sulfides **182** were electrochemically fluorinated at the thiazole ring to give the mono- and trifluorinated derivatives **183** and **184**, respectively (Scheme 60).[106]



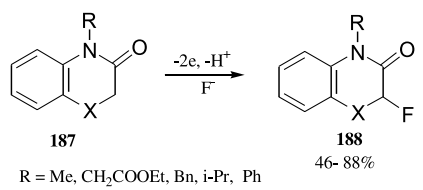
Scheme 60.

Anodic fluorination of 2-alkylthio-4-methyloxazoles **185** was performed using $Et_4NF{\cdot}4HF$ to provide the corresponding 2-alkylthio-4,5-difluoro-4-methyl-2-oxazolines **186**, as shown in Scheme 61.[107]



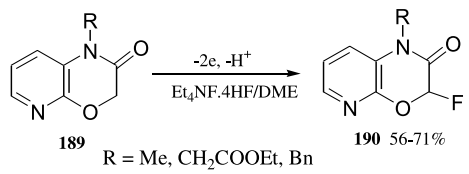
Scheme 61.

Electrofluorination of benzothiazinone derivatives **187** in $Et_3N{\cdot}3HF$/MeCN furnished the corresponding α-fluorinated products **188** (Scheme 62).[82,108,109]



Scheme 62.

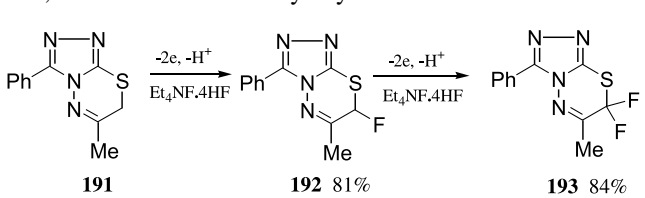
Similar electrolytic fluorination of the pyrido[2,3-*b*]oxazines **189** resulted in the introduction of fluorine atom at the α position to oxygen to give compound **190**, as depicted in Scheme 63.[110]



Scheme 63.

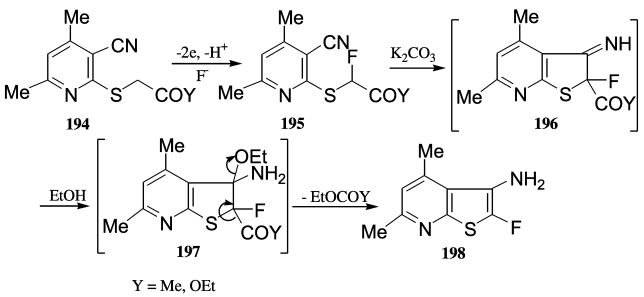
Potentiostatic anodic fluorination of the *s*-triazolo[3,4-*b*]thiadiazine derivative **191** in DME containing $Et_4NF{\cdot}4HF$ using an undivided cell afforded the corresponding 7-monofluorinated product **192**. The 7,7-difluorinated derivative **193** could be obtained by direct anodic fluorination of the 7-monofluoro derivative **192**, as shown in Scheme 64.[111]

2.1.14.5. Fluorination of the side chain of heterocycles. Electrolytic monofluorination of the side chain of various heterocyclic compounds has been systematically studied by Fuchigami's group. The active methylene thio group attached to heterocycles was selectively fluorinated to give the corresponding α-fluorinated products.[112–122] In one example, the 2-pyridyl sulfides **194** were fluorinated in $Et_3N{\cdot}3HF$ to give the corresponding α-fluorinated sulfides **195**, which were readily cyclised into the 2-fluoro-



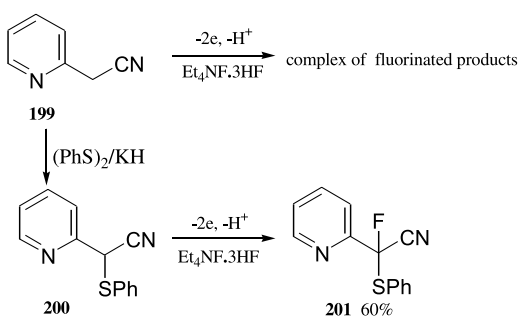
Scheme 64.

thieno[2,3-*b*]pyridine derivative **198** in K_2CO_3/EtOH solution through the intermediates **196** and **197**,[112,113] as shown in Scheme 65.



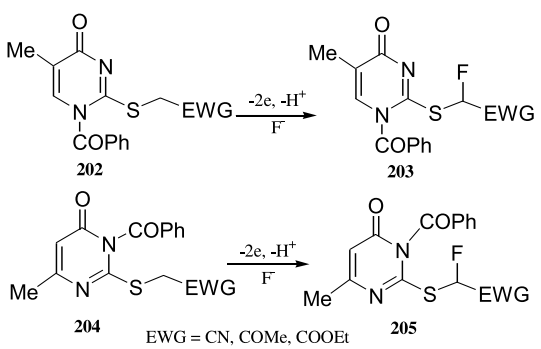
Scheme 65.

In contrast, 2-pyridylacetonitrile (**199**) did not give the desired fluorination. Its α-phenylthiolated derivative **200** proceeded smoothly, however, to give the corresponding α-fluorinated product **201**[61] (Scheme 66).



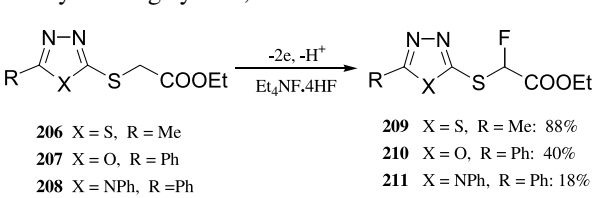
Scheme 66.

The pyrimidyl sulfides **202** and **204** were similarly fluorinated using $Et_4NF{\cdot}4HF$/DME to give **203** and **205**, respectively, in good yields (Scheme 67).[114]



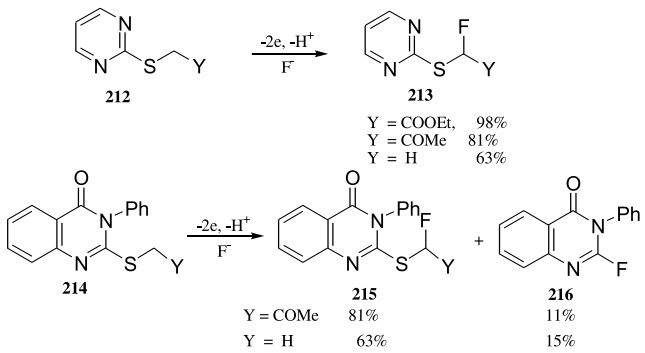
Scheme 67.

Thiadiazolyl, oxadiazolyl and triazolyl sulfides **206-208** were successfully fluorinated to give **209–211**, respectively. The yield of the products was greatly affected by the type of heterocyclic ring system,[115] as shown in Scheme 68.



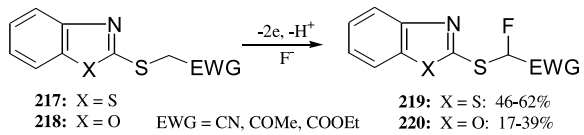
Scheme 68.

Pyrimidyl and quinazolinyl sulfides **212** and **214**, with or without an EWG, were efficiently fluorinated at the position α to the sulfur atom using $Et_4NF{\cdot}4HF$/DME to give the corresponding monofluorinated products **213** and **215**, respectively.[116] It was also noted that *ipso*-fluorodesulfurisation took place during electrofluorination of the quinazoline derivatives **214** to give the 2-fluoroquinazoline **216** as a byproduct[116] (Scheme 69).



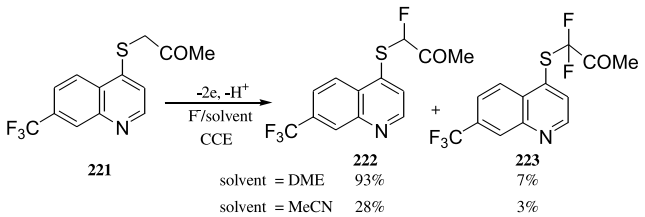
Scheme 69.

Benzothiazolyl[117] and benzoxazolyl[118] sulfides **217** and **218** were also electrolytically fluorinated in $Et_4NF{\cdot}nHF$/DME (n=3, 4) to give the corresponding fluorosulfides **219** and **220**, respectively (Scheme 70).



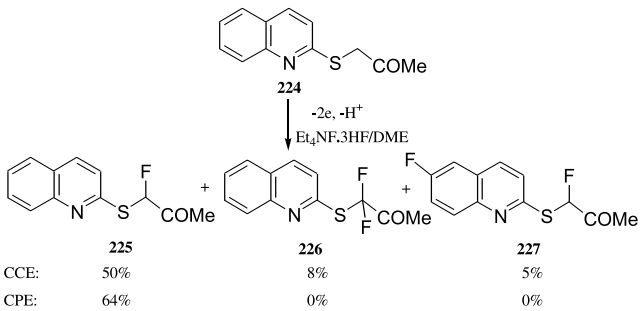
Scheme 70.

Constant current electrolytic (CCE) fluorination of 4-acetonylthio-7-(trifluoromethyl)-quinoline (**221**) in $Et_4NF{\cdot}3HF$ afforded a mixture of the α-mono- and α,α-difluorinated sulfides **222** and **223** in poor to excellent yields depending on the solvents[119] (Scheme 71). When similar conditions were applied for the fluorination of 2-(acetonylthio)quinoline (**224**), its α-monofluorinated product **225** was obtained in addition to two difluorinated byproducts **226** and **227**, as shown in Scheme 72[119] When constant potential electrolysis (CPE) was applied in the fluorination of **224**, however, only the α-fluorinated product **225** was obtained selectively.[119]

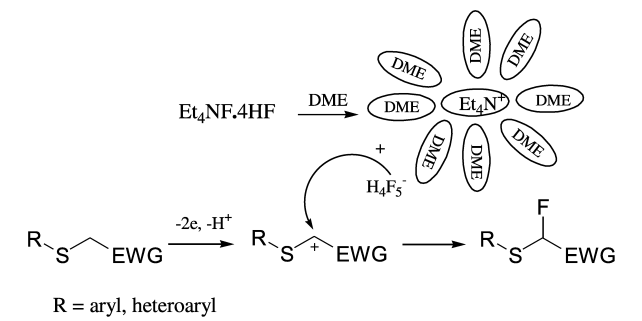


Scheme 71.

The nucleophilicity of fluoride ion in the presence of dimethoxyethane (DME) is much higher than in MeCN or CH_2Cl_2. This is attributed to the ability of DME to solvate the cationic part of the fluoride salt, leaving fluoride anion to easily attack the cationic intermediate of the substrate, as shown in Scheme 73.[118,119]

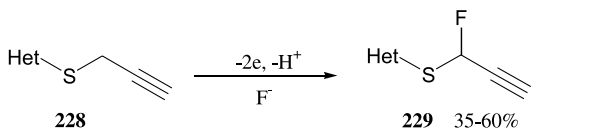


Scheme 72.



Scheme 73.

Heterocyclic propargyl sulfides **228** were also fluorinated electrolytically in $Et_3N{\cdot}3HF$/DME to give the α-fluorinated propargyl sulfides **229** in moderate yields (Scheme 74).[120]



Scheme 74.

The solvent effects on the electrolytic fluorination process of several heterocyclic compounds were comprehensively studied. Dimethoxyethane (DME) was found to be more suitable than other solvents.[121–124]

2.2. Indirect electrolytic partial fluorination of organic compounds

2.2.1. Organosulfur compounds. Occasionally, direct electrolytic fluorination could not proceed well, due to the formation of a polymeric layer at the anode surface (passivation). To solve this problem, organic mediators can be used to be electrochemically oxidised, instead of the substrate, at the anode surface. The hypervalent iodobenzene difluoride **230**, for example, was electrochemically synthesised to act as a mediator in the fluorination of the dithioketal **231**.[125] The role of the mediator **230** is shown in Figure 1 and the selective indirect electrolytic *gem*-difluorodesulfurisation of the dithioketal **231** was successfully carried out using a catalytic amount of *p*-methoxyiodobenzene in the presence of $Et_3N{\cdot}3HF$ to give the corresponding *gem*-difluorinated product **232**.[125]

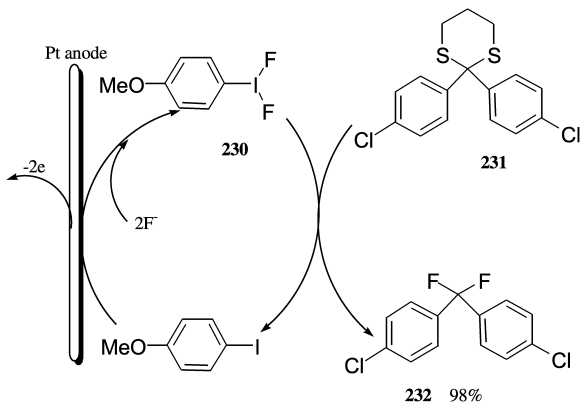
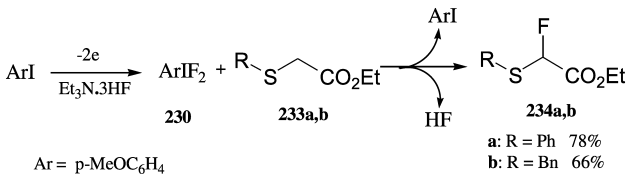


Figure 1.

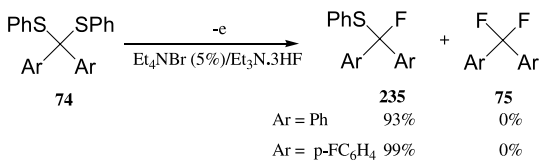
Similarly, the compound **232** could also be obtained in 61% yield using another mediator, *p*-methoxyiodobenzene chlorofluoride, in the electrofluorination of **231**.[126]

The electrolytically-generated hypervalent *p*-methoxyiodobenzene difluoride (**230**) also reacted with the α-(phenylthio)- and α-(benzylthio)acetates **233a**,**b** to provide the corresponding α-fluorinated sulfides **234a**,**b**[127] (Scheme 75).



Scheme 75.

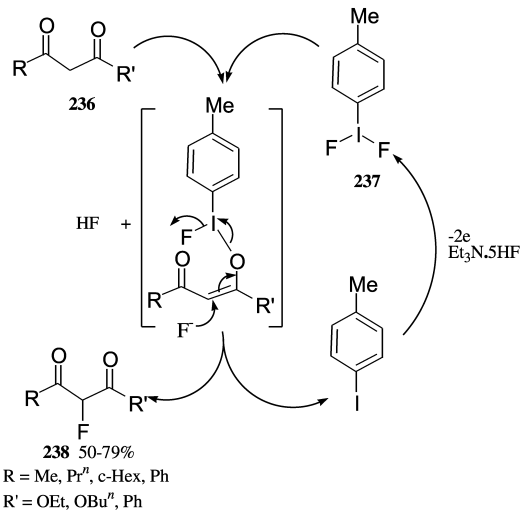
Electrolytic fluorination of the dithioketals **74**, which has been mentioned previously in this review,[66] was repeated indirectly using Et_4NBr as a mediator in $Et_3N{\cdot}3HF$.[128] In this case, the corresponding monofluorothioethers **235** were obtained selectively, but the difluorinated derivatives **75** could not be detected, as shown in Scheme 76.[128]



Scheme 76.

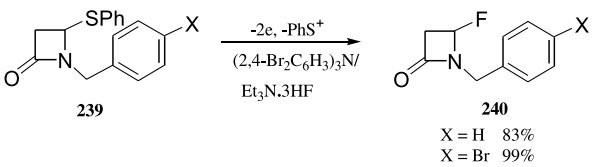
2.2.2. Carbonyl compounds. Selective and indirect introduction of a fluorine atom into the α-position of the β-dicarbonyl compounds **236** was achieved electrolytically using iodotoluene difluoride (**237**) as a mediator.[129,130] The compound **237** was prepared in situ by the electrolytic oxidation of iodotoluene in the presence of $Et_3N{\cdot}5HF$ and was then used for the direct fluorination of **236** to give the desired α-fluoro-β-dicarbonyl compounds **238** in good yields (Scheme 77).[129,130]

2.2.3. Heterocycles. Indirect electrolytic fluorination of the 4-(phenylthio)azetidin-2-ones **239** using a triarylamine as a mediator, in $Et_3N{\cdot}3HF$/MeCN, proceeded smoothly to afford the 4-fluoroazetidin-2-ones **240** in excellent yields[131]



Scheme 77.

(Scheme 78). Triarylamines are known to be efficient electron transfer reagents. A plausible mechanistic pathway for this reaction is outlined in Figure 2.[131]



Scheme 78.

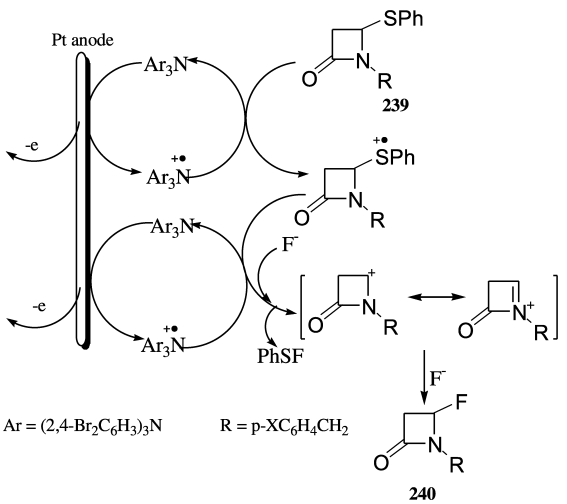
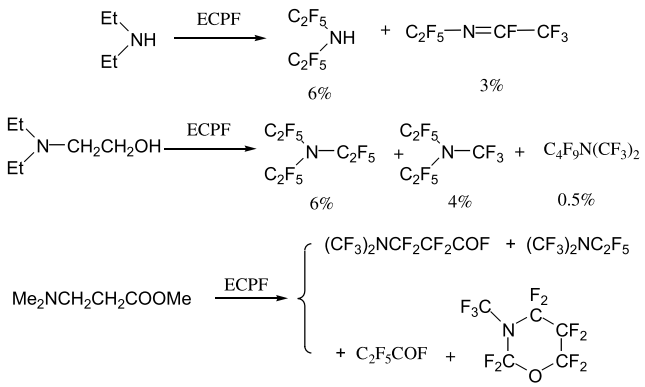


Figure 2.

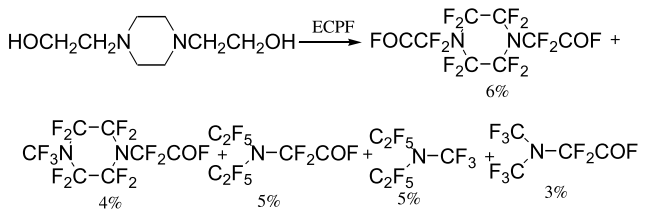
3. Electrolytic perfluorination of organic compounds

Electrochemical perfluorination (ECPF) of organic compounds has been reported by many scientists because some perfluorinated organic compounds are useful as artificial blood and oxygen carriers.[132] Abe et al. reported the electrolytic perfluorination of secondary and tertiary alkylamines,[22,133–135] piperazines[135,136] and morpholines[137] using anhydrous hydrogen fluoride (AHF). In most of these cases, however, the yield of the perfluorinated products was very low and they were usually accompanied

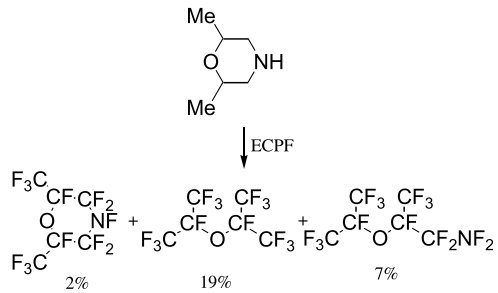
by various cyclised and degraded byproducts, as shown in Schemes 79–81.



Scheme 79.

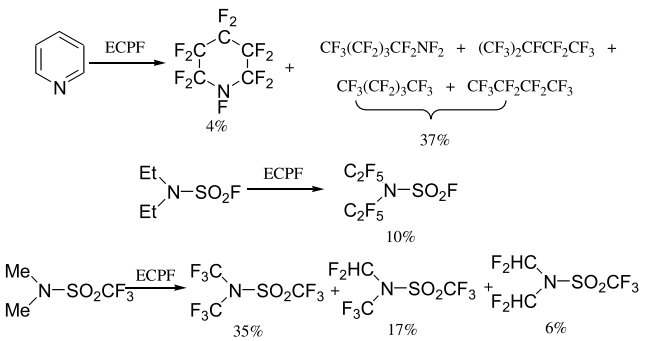


Scheme 80.



Scheme 81.

Ignat'ev et al. have reported the electrolytic perfluorination of pyridine[138] and sulfonamides,[139,140] as shown in Scheme 82.



Scheme 82.

4. Conclusions

In this article, the electrolytic fluorination of various classes of organic compounds during the last decade, using $Et_3N{\cdot}nHF$, $Et_4NF{\cdot}nHF$ (n=2–5) or Bu_4NBF_4 has been reviewed. As is clear throughout this review article, the electrolytic fluorination methodology has proved itself as a widely applicable technique for the synthesis of wide range of fluorinated organic compounds in good to excellent yields, with high selectivity, which are difficult to obtain by the alternative chemical methods. The role of HF combined with organic bases is also clarified to be superior, for selective fluorination, over the use of HF itself, where the latter leads to complete conversion of all C–H to C–F bonds without any selectivity and the products were obtained in very low yields. The highly stable $Et_4NF{\cdot}4HF$ under electrolytic conditions was found to be more suitable for electrolytic fluorination of organic compounds, which have high oxidation potentials. Dimethoxyethane (DME), which has a higher donor number than acetonitrile or dichloromethane, is also an effective electrolytic solvent due to its ability to solvate the cationic part of fluoride salts and leads to increase in the nucleophilicity of the fluoride anion. The electrolytic fluorination process is, therefore, markedly dependent on the type of organic compounds, fluoride salts and solvents.

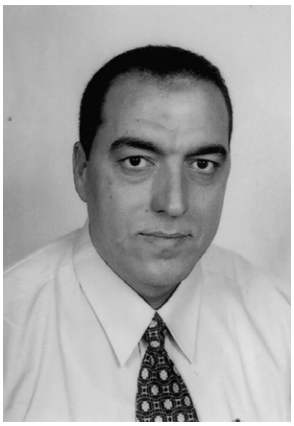
References and notes

1. Resnati, G. *Tetrahedron* **1993**, *49*, 9385.
2. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
3. Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.
4. Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381.
5. Burger, K.; Wucherpfennig, U.; Brunner, E. *Adv. Heterocycl. Chem.* **1994**, *60*, 1.
6. *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kondansha and Elsevier Biomedical: Tokyo, 1982.
7. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991.
8. *Biomedical Frontiers of Fluorine Chemistry*. *ACS Symposium Series 639*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996.
9. Narizuka, S.; Fuchigami, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1293.
10. Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000.
11. Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.
12. Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431.
13. Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563.
14. Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505.
15. Yoneda, N. *Tetrahedron* **1991**, *47*, 5329.
16. Noel, M.; Suryanarayanan, V.; Chellammal, S. *J. Fluorine Chem.* **1997**, *83*, 31.
17. Fuchigami, T.; Higashiya, S.; Hou, Y.; Dawood, K. M. *Rev. Heteroat. Chem.* **1999**, *19*, 67.
18. Fuchigami, T. *Advances in Electron-Transfer Chemistry*; Mariano, P. S., Ed.; JAI: Greenwich, CT, 1999; Vol. 6.
19. Fuchigami, T. In *Organic Electrochemistry*; 4th ed. Lund, H., Hammerich, O., Eds.; Dekker: New York, 2001; pp 1035–1050.
20. Frey, D. A.; Nicholas, W.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317.

21. Meinert, H.; Fackler, R.; Mader, J.; Reuter, P.; Rohlke, W. *J. Fluorine Chem.* **1992**, *59*, 351.
22. Abe, T.; Hayashi, E.; Baba, H. *J. Fluorine Chem.* **2000**, *106*, 35.
23. McClinton, M. A. *Aldrichim. Acta* **1995**, *28*, 31.
24. Yoneda, N. *J. Fluorine Chem.* **2000**, *105*, 205.
25. Meures, J. H. H.; Eilenberg, W. *Tetrahedron* **1991**, *47*, 705.
26. Dmowski, W.; Kozlowski, T. *Electrochim. Acta* **1997**, *42*, 513.
27. Andres, D. F.; Laurent, E. G.; Marquet, B. S.; Benotmane, H.; Bensadat, A. *Tetrahedron* **1995**, *51*, 2605.
28. Andres, D. F.; Dietrich, U.; Laurent, E. G.; Marquet, B. S. *Tetrahedron* **1997**, *53*, 647.
29. Ventalon, F. M.; Faure, R.; Laurent, E. G.; Marquet, B. S. *Tetrahedron: Asymmetry* **1994**, *5*, 1909.
30. Hara, S.; Chen, S. Q.; Toshio, T.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1996**, *37*, 8511.
31. Dinoiu, V.; Fukuhara, T.; Hara, S.; Yoneda, N. *J. Fluorine Chem.* **2000**, *103*, 75.
32. Yoshida, J.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992**, *114*, 7594.
33. Yoshida, J.; Sugawara, M.; Kise, N. *Tetrahedron Lett.* **1996**, *37*, 3157.
34. Yoshida, J.; Sugawara, M.; Tatsumi, M.; Kise, N. *J. Org. Chem.* **1998**, *63*, 5950.
35. Momota, K.; Morita, M.; Matsuda, Y. *Electrochim. Acta* **1993**, *38*, 619.
36. Momota, K.; Morita, M.; Matsuda, Y. *Electrochim. Acta* **1993**, *38*, 1123.
37. Momota, K.; Kato, K.; Morita, M.; Matsuda, Y. *Electrochim. Acta* **1994**, *39*, 41.
38. Momota, K.; Horio, H.; Kato, K.; Morita, M.; Matsuda, Y. *Electrochim. Acta* **1995**, *40*, 233.
39. Morita, M.; Momota, K.; Horio, H.; Kato, K.; Matsuda, Y. *J. Electrochem. Soc. Jpn* **1994**, *62*, 1196.
40. Momota, K.; Mukai, K.; Kato, K.; Morita, M. *Electrochim. Acta* **1998**, *43*, 2503.
41. Tajima, T.; Ishii, H.; Fuchigami, T. *Electrochem. Commun.* **2002**, *4*, 589.
42. Momota, K.; Kato, K.; Morita, M.; Matsuda, Y. *Electrochim. Acta* **1994**, *39*, 681.
43. Fukuhara, T.; Sawaguchi, M.; Yoneda, N. *Electrochem. Commun.* **2000**, *2*, 259.
44. Sawaguchi, M.; Fukuhara, T.; Yoneda, N. *J. Electroanal. Chem.* **2001**, *507*, 66.
45. Yoneda, N.; Chen, S. Q.; Hatakeyama, T.; Hara, S.; Fukuhara, T. *Chem. Lett.* **1994**, 849.
46. Hara, S.; Chen, S. Q.; Hatakeyama, T.; Fukuhara, T.; Sekiguchi, M.; Yoneda, N. *Tetrahedron Lett.* **1995**, *36*, 6511.
47. Chen, S. Q.; Hatakeyama, T.; Fukuhara, T.; Hara, S.; Yoneda, N. *Electrochim. Acta* **1997**, *42*, 1951.
48. Konno, A.; Nakagawa, K.; Fuchigami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1027.
49. Fuchigami, T.; Yano, H.; Konno, A. *J. Org. Chem.* **1991**, *56*, 6731.
50. Fuchigami, T.; Konno, A.; Nakagawa, K.; Shimojo, M. *J. Org. Chem.* **1994**, *59*, 5937.
51. Konno, A.; Fuchigami, T. *J. Appl. Electrochem.* **1995**, *25*, 173.
52. Fuchigami, T.; Shimojo, M.; Konno, A. *J. Org. Chem.* **1995**, *60*, 3459.
53. Konno, A.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 8579.
54. Fuchigami, T.; Yamamoto, K.; Konno, A. *Tetrahedron* **1991**, *47*, 625.
55. Brigaud, T.; Laurent, E. *Tetrahedron Lett.* **1990**, *31*, 2287.
56. Brigaud, T.; Laurent, A.; Laurent, E. *Phosphorus, Sulfur, Silicon* **1991**, *59*, 447.
57. Baroux, P.; Tardivel, R.; Simonet, J. *Tetrahedron Lett.* **1995**, *36*, 3851.
58. Baroux, P.; Tardivel, R.; Simonet, J. *J. Electrochem. Soc.* **1997**, *144*, 841.
59. Narizuka, S.; Koshiyama, H.; Konno, A.; Fuchigami, T. *J. Fluorine Chem.* **1995**, *73*, 121.
60. Laurent, E.; Marquet, B.; Roze, C.; Ventalon, F. *J. Fluorine Chem.* **1998**, *87*, 215.
61. Higashiya, S.; Sato, T.; Fuchigami, T. *J. Fluorine Chem.* **1998**, *87*, 203.
62. Riyadh, S. M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2001**, *42*, 3009.
63. Riyadh, S. M.; Ishii, H.; Fuchigami, T. *Tetrahedron* **2002**, *58*, 5877.
64. Suzuki, K.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2001**, *42*, 4861.
65. Hou, Y.; Higashiya, S.; Fuchigami, T. *Electrochim. Acta* **2000**, *45*, 3005.
66. Yoshiyama, T.; Fuchigami, T. *Chem. Lett.* **1992**, 1995.
67. Fuchigami, T.; Hayashi, T.; Konno, A. *Tetrahedron Lett.* **1992**, *33*, 3161.
68. Surowiec, K.; Fuchigami, T. *Tetrahedron Lett.* **1992**, *33*, 1065.
69. Uneyama, K.; Asai, H.; Dan-Oh, Y.; Matta, H. *Electrochim. Acta* **1997**, *42*, 2005.
70. Uneyama, K. *J. Fluorine Chem.* **2000**, *105*, 209.
71. Uneyama, K. *J. Organomet. Chem.* **2000**, *611*, 158.
72. Uneyama, K.; Hiraoka, S.; Amii, H. *J. Fluorine Chem.* **2000**, *102*, 215.
73. Fuchigami, T.; Fujita, T.; Konno, A. *Tetrahedron Lett.* **1994**, *35*, 4153.
74. Becker, J. Y.; Shakkour, E.; West, R. *Tetrahedron Lett.* **1992**, *33*, 5633.
75. Fuchigami, T.; Miyazaki, M. *Electrochim. Acta* **1997**, *42*, 1979.
76. Hou, Y.; Fuchigami, T. *Tetrahedron Lett.* **1999**, *40*, 7819.
77. Ishii, H.; Hou, Y.; Fuchigami, T. *Tetrahedron* **2000**, *56*, 8877.
78. Sawaguchi, M.; Ayuba, S.; Nakamura, Y.; Fukuhara, T.; Hara, S.; Yoneda, N. *Synlett* **2000**, 999.
79. Fuchigami, T.; Sano, M.; Iio, K. *J. Electroanal. Chem.* **1994**, *369*, 255.
80. Sono, M.; Toyoda, N.; Shizuri, Y.; Tori, M. *Tetrahedron Lett.* **1994**, *35*, 9237.
81. Sono, M.; Toyoda, N.; Shimizu, K.; Noda, E.; Shizuri, Y.; Tori, M. *Chem. Pharm. Bull.* **1996**, *44*, 1141.
82. Konno, A.; Naito, W.; Fuchigami, T. *Tetrahedron Lett.* **1992**, *33*, 7017.
83. Narizuka, S.; Fuchigami, T. *J. Org. Chem.* **1993**, *58*, 4200.
84. Suda, K.; Hotoda, H.; Aoyagi, M.; Takanami, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1327.
85. Sawaguchi, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *Isr. J. Chem.* **1999**, *39*, 151.
86. Hou, Y.; Higashiya, S.; Fuchigami, T. *Synlett* **1997**, 655.
87. Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 8773.
88. Konno, A.; Shimojo, M.; Fuchigami, T. *J. Fluorine Chem.* **1998**, *87*, 137.

89. Tajima, T.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2001**, *42*, 4857.
90. Narizuka, S.; Fuchigami, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1293.
91. Fuchigami, T.; Narizuka, S.; Konno, A.; Momota, K. *Electrochim. Acta* **1998**, *43*, 1985.
92. Narizuka, S.; Konno, A.; Matsuyama, H.; Fuchigami, T. *J. Electrochem. Soc. Jpn* **1993**, *61*, 868. C.A. 119: 270959f.
93. Dawood, K. M.; Ishii, H.; Fuchigami, T. *J. Org. Chem.* **2001**, *66*, 7030.
94. Higashiya, S.; Dawood, K. M.; Fuchigami, T. *J. Fluorine Chem.* **1999**, *99*, 189.
95. Hasegawa, M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2002**, *43*, 1503.
96. Ishii, H.; Yamada, N.; Fuchigami, T. *Chem. Commun.* **2000**, 1617.
97. Ishii, H.; Yamada, N.; Fuchigami, T. *Tetrahedron* **2001**, *57*, 9067.
98. Hou, Y.; Higashiya, S.; Fuchigami, T. *Synlett* **1998**, 973.
99. Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1999**, *64*, 3346.
100. Dawood, K. M.; Fuchigami, T. *Tetrahedron Lett.* **2001**, *42*, 2513.
101. Dawood, K. M.; Fuchigami, T. *J. Org. Chem.* **2001**, *66*, 7691.
102. Fuchigami, T.; Narizuka, S.; Konno, A. *J. Org. Chem.* **1992**, *57*, 3755.
103. Higashiya, S.; Narizuka, S.; Konno, A.; Maeda, T.; Momota, K.; Fuchigami, T. *J. Org. Chem.* **1999**, *64*, 133.
104. Baba, D.; Ishii, H.; Higashiya, S.; Fujisawa, K.; Fuchigami, T. *J. Org. Chem.* **2001**, *66*, 7020.
105. Riyadh, S. M.; Fuchigami, T. *Heterocycles* **2003**, *60*, 15.
106. Riyadh, S. M.; Fuchigami, T. *J. Org. Chem.* **2002**, *67*, 9379.
107. Riyadh, S. M.; Ishii, H.; Fuchigami, T. *Tetrahedron* **2002**, *58*, 9273.
108. Konno, A.; Naito, W.; Fuchigami, T. *Acta Chim. Scand.* **1999**, *53*, 887.
109. Shaaban, M. R.; Fuchigami, T. *Synlett* **2001**, 1644.
110. Shaaban, M. R.; Fuchigami, T. *Tetrahedron Lett.* **2002**, *43*, 273.
111. Iwayasu, N.; Shaaban, M. R.; Fuchigami, T. *Heterocycles* **2002**, *57*, 623.
112. Erian, A. W.; Konno, A.; Fuchigami, T. *Tetrahedron Lett.* **1994**, *35*, 7245.
113. Erian, A. W.; Konno, A.; Fuchigami, T. *J. Org. Chem.* **1995**, *60*, 7654.
114. Shaaban, M. R.; Ishii, H.; Fuchigami, T. *J. Org. Chem.* **2000**, *65*, 8685.
115. Shaaban, M. R.; Ishii, H.; Fuchigami, T. *J. Org. Chem.* **2001**, *66*, 5633.
116. Dawood, K. M.; Higashiya, S.; Hou, Y.; Fuchigami, T. *J. Org. Chem.* **1999**, *64*, 7935.
117. Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 9173.
118. Dawood, K. M.; Higashiya, S.; Hou, Y.; Fuchigami, T. *J. Fluorine Chem.* **1999**, *93*, 159.
119. Dawood, K. M.; Fuchigami, T. *J. Org. Chem.* **1999**, *64*, 138.
120. Riyadh, S. M.; Ishii, H.; Fuchigami, T. *Tetrahedron* **2001**, *57*, 8817.
121. Hou, Y.; Fuchigami, T. *Electrochem. Commun.* **1999**, *1*, 445.
122. Hou, Y.; Fuchigami, T. *J. Electrochem. Soc.* **2000**, *147*, 4567.
123. Suryanarayanan, V.; Noel, M. *J. Fluorine Chem.* **1998**, *91*, 153.
124. Suryanarayanan, V.; Noel, M. *J. Fluorine Chem.* **1998**, *92*, 177.
125. Fuchigami, T.; Fujita, T. *J. Org. Chem.* **1994**, *59*, 7190.
126. Fujita, T.; Fuchigami, T. *Tetrahedron Lett.* **1996**, *37*, 4725.
127. Fuchigami, T.; Fujita, T.; Higashiya, S.; Konno, A. *J. Chin. Chem. Soc.* **1998**, *45*, 131.
128. Fuchigami, T.; Sano, M. *J. Electroanal. Chem.* **1996**, *414*, 81.
129. Hara, S.; Sekiguchi, M.; Ohmori, A.; Fukuhara, T.; Yoneda, N. *Chem. Commun.* **1996**, 1899.
130. Hara, S.; Hatakeyama, T.; Chen, S. Q.; Ishii, K.; Yoshida, M.; Sawaguchi, M.; Fukuhara, T.; Yoneda, N. *J. Fluorine Chem.* **1998**, *87*, 189.
131. Fuchigami, T.; Tetsu, M.; Tajima, T.; Ishii, H. *Synlett* **2001**, 1269.
132. Lowe, K. C. *J. Fluorine Chem.* **2001**, *109*, 59.
133. Abe, T.; Hayashi, E.; Fukaya, H.; Hayakawa, Y.; Baba, H.; Ishikawa, S.; Asauto, K. *J. Fluorine Chem.* **1992**, *57*, 101.
134. Abe, T.; Fukaya, H.; Hayashi, E.; Ono, T.; Nishida, M.; Soloshonok, I.; Okuhara, K. *J. Fluorine Chem.* **1999**, *97*, 229.
135. Abe, T.; Soloshonok, I.; Baba, H.; Sekiya, A. *J. Fluorine Chem.* **1999**, *99*, 51.
136. Abe, T.; Baba, H.; Fukaya, H.; Tamura, M.; Sekiya, A. *J. Fluorine Chem.* **2003**, *119*, 27.
137. Abe, T.; Fukaya, H.; Ono, T.; Hayashi, E.; Soloshonok, I.; Okuhara, K. *J. Fluorine Chem.* **1998**, *87*, 193.
138. Sartori, P.; Velayutham, D.; Ignat'ev, N.; Noel, M. *J. Fluorine Chem.* **1998**, *87*, 31.
139. Ignat'ev, N.; Datsenko, S. D.; Yagupolskii, L. M.; Dimitrov, A.; Radeck, W.; Rudiger, St. *J. Fluorine Chem.* **1995**, *74*, 181.
140. Sartori, P.; Ignat'ev, N.; Datsenko, S. *J. Fluorine Chem.* **1995**, *75*, 157.

Biographical sketch



Kamal M. Dawood was born in 1965 in Kafr-Elsheikh, Egypt. He graduated from Cairo University, Egypt in 1987 then he joined Professor Ahmad M. Farag's research group to carry out his MSc and PhD studies under the supervision of Professor Farag, Cairo University. He received his PhD in 1995 in the applications of hydrazonoyl halides in heterocyclic chemistry. Then he was appointed as a Lecturer of Organic Chemistry at Cairo University and continued his research work on the topics of regioselectivity and reaction mechanisms of cycloaddition reactions of nitrilimines. In 1997 he was awarded the UNESCO Fellowship for one year at Tokyo Institute of Technology (TIT) and collaborated with Professor Toshio Fuchigami at TIT in the field of 'Electrochemical Partial Fluorination of Heterocyclic Compounds'. In 1999, he was awarded the JSPS (Japan Society for Promotion of Science) Fellowship for two years and worked again with Professor Fuchigami at TIT in the same field. During his stay at TIT he published ten articles in JOC, TL and JFC. In 2001 he returned back to Cairo and promoted to Assoc. Professor in 2002. In 2002 he received the Cairo University Award in Chemistry. In Aug. 2003 he was awarded the Alexander von Humboldt Fellowship at Hannover University with Professor Andreas Kirschning in the field of polymer-supported palladium catalysed hydrogenation of organic compounds.

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Selectivities in the 1,3-dipolar cycloaddition of nitrile oxides to dicyclopentadiene and its derivatives

Irishi N. N. Namboothiri,[a,*] Namrata Rastogi,[a] Bishwajit Ganguly,[b,*] Shaikh M. Mobin[c] and Miriam Cojocaru[d]

[a]*Department of Chemistry, Indian Institute of Technology, Bombay, Mumbai 400 076, India*
[b]*Analytical Science Division, Central Salt and Marine Chemicals Research Institute, Bhavnagar Gujarat 364 002, India*
[c]*National Single Crystal X-ray Diffraction Facility, Indian Institute of Technology, Bombay, Mumbai 400 076, India*
[d]*Department of Chemistry, Bar-Ilan University, Ramat Gan 52900, Israel*

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Dedicated to Professor S. N. Balasubrahmanyam on the occasion of his 72nd birthday

Abstract—The 1,3-dipolar cycloaddition of nitrile oxides, generated from aldoximes and nitroalkanes, to dicyclopentadiene proceeds with complete chemo- and stereoselectivity. The approach of the dipole takes place exclusively from the *exo*-face of the bicycloheptane moiety providing a mixture of regioisomers in approximately 55:45 ratio. On the other hand, nitrile oxide cycloaddition to dimethyldicyclopentadiene dicarboxylate (Thiele's ester), besides exhibiting chemo- and stereoselectivity as in the case of dicyclopentadiene, exhibits complete regioselectivity as well providing a single isomer in good yield. The Influence of remote substituents, including sterically 'sterile' ones, on the regioselectivity has also been investigated using 8-hydroxy and 1-keto derivatives of dicyclopentadiene. These experimental observations have been investigated through gas phase and solvent model MO calculations on the transition state geometries at semiempirical (PM3) and hybrid ab initio-DFT levels of theory. The Computational methods employed in this study were rigorously tested by performing model calculations on well-established experimental observations.

1. Introduction

1,3-Dipolar cycloadditions offer convenient one-step routes for the construction of a variety of five-membered heterocycles.[1,2] In particular, cycloaddition of nitrile oxides to olefins are of considerable interest as the resulting isoxazolines are versatile intermediates in the synthesis of a variety of natural products.[3,4] Recently, isoxazolines fused to bicyclic frameworks have been subjected to molybdenum mediated N–O bond cleavage to afford stereoselectively substituted cyclopentane rings.[5] Achievement of a high degree of selectivity is, therefore, of paramount importance for further expanding the scope and exploiting the potential of this elegant synthetic strategy.

Regioselectivity in the addition of nitrile oxides **1** to unsymmetrical acyclic[6,7] and simple cyclic[8] dipolarophiles **2** has been investigated experimentally[6,8] and theoretically.[7,8] For instance, addition of nitrile oxide **1** to methyl acrylate **2** (X=CO_2Me) provides 5-isoxazoline **3a** in overwhelming predominance, compared to its regioisomer, 4-isoxazoline **3b** (ratio ~95:5).[6,7] As for stereochemistry, π face selection[9,10] in the addition of nitrile oxides to various dipolarophiles such as norbornene,[11] 2,3-dioxabicyclo[2.2.2]octane,[12] *cis*-3,4-dichlorocyclobutene,[13] α-chiral alkenes[14] etc. has been investigated.[15] In the case of norbornene **4** (X=H), the approach of the dipole preferentially takes place from the *exo* face.[11] Further, in the case of unsymmetrically substituted norbornenes **4** (X=hexyl, $SiMe_3$, CO_2Et) formation of single stereo- and regioisomers has been observed, i.e. the *exo* isomer **5** in which oxygen of the dipole is attached to the more substituted center of the dipolarophile.[16] A handful of other reports on the inter-[13] and intramolecular[14] cycloadditions of nitrile oxides to bicyclic systems, viz. norbornenes[17,18] and norbornadienes[18,19,20] also reflected this feature. However, in the intermolecular reactions of norbornadienes[18,19] and in presence of sterically demanding groups on the *exo* face of norbornenes,[17,18] formation of considerable amount of *endo* isomers is observed.

Keywords: Nitrile oxide; 1,3-Dipolar cycloaddition; Dicyclopentadiene; Thiele's ester.
* Corresponding authors. Tel.: +91-22-2576-7196; fax: +91-22-2576-7152 (I.N.N.N.); Tel.: +91-278-256-7760 ext. 750; fax: +91-278-256-7562 (B.G.);
e-mail addresses: irishi@iitb.ac.in; gang_12@rediffmail.com

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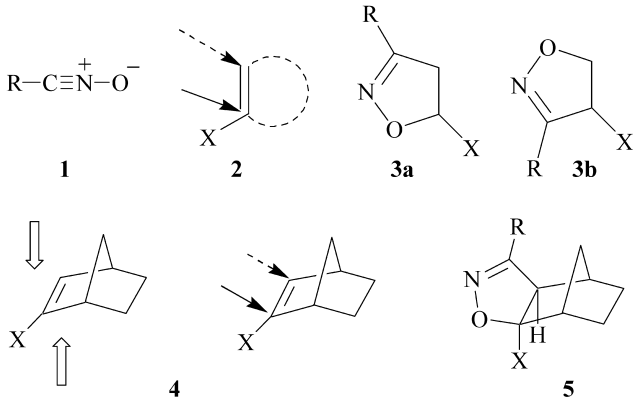


Although nitrile oxide cycloadditions to dienes (e.g., norbornadienes, vide supra) and polyenes (e.g., fulvene)[21] have been reported in the literature, to our knowledge, selectivities in the cycloaddition of nitrile oxides to systems possessing multiple π-faces has not been investigated.[22,23] Herein, we report the remarkable selectivities observed in the cycloaddition of nitrile oxides to representative tricyclic systems.

2. Results and discussion

Dicyclopentadiene **6a** and its derivatives, viz. dicarboxylate, Thiele's ester, **6b**,[24] alcohol **6c**[25] and enone **6d**[25,26] were chosen as the dipolarophiles as three degrees of differentiation, viz. chemo, stereo and regio, in their cycloaddition with suitable dipoles such as nitrile oxides would be possible (Fig. 1). Although norbornene has been shown to be much more reactive than cyclopentene in the cycloaddition with nitrile oxides (vide infra),[27] the dipole could, in principle, react with the C2–C3 double bond or C5–C6 double bond exhibiting chemoselectivity. The approach of the dipole could take place from the ββ-face, βα-face, αβ-face or αα-face. Furthermore, formation of two regioisomers in which the dipole oxygen is bonded to C2 or C3/C5 or C6 is also a possibility for every cycloaddition. Therefore, there is a statistical possibility of formation of 8 monocycloadducts and 16 biscycloadducts taking the total number of products expected to 24.

The dipoles, acetonitrile oxide **1a** and benzonitrile oxide **1b**, were generated from two different precursors, viz. aldoximes[28] (Scheme 1, path A) and nitroalkanes (Scheme 1, path B),[29,30] in order to probe whether or not the selectivities are influenced by the method by which the dipole is generated (Tables 1 and 2). The ^{1}H and ^{13}C NMR spectra of the products formed from dicyclopentadiene **6a** indicated the formation of mixtures of two monocycloadducts **7a/8a** and **7b/8b**, respectively, in ~55:45 ratio (Table 1).[31]

In contrast to the behavior of dicyclopentadiene **6a**, the reaction of its dicarboxylate, Thiele's ester, **6b** with acetonitrile oxide **1a** and benzonitrile oxide **1b** provided single monocycloadducts **7c** and **7d**, respectively (Table 2).[32]

Further examination of Tables 1 and 2 indicates that the isomer ratios of the cycloadducts formed in the nitrile oxide cycloaddition to dicyclopentadiene **6a** and its dicarboxylate **6b** are independent of the method of generation of nitrile oxide **1**[33] However, it has been observed that in our hands path B (nitroalkane, BOC_2O, DMAP, THF; Scheme 1, see Section 5)[30] is superior for the generation of acetonitrile oxide **1a** (Table 1, entry 2 and Table 2, entry 2) over path A, method A (aldoxime, NCS, Et_3N, CH_2Cl_2; see also Table 1, entry 1 and Table 2, entry 1) and path A, method B (aldoxime, NaOCl, Et_3N, CH_2Cl_2). On the other hand, path A, method B (aldoxime, NaOCl, Et_3N, CH_2Cl_2) turned out to be better for the generation of benzonitrile oxide **1b** (Table 1, entry 3 and Table 2, entry 3) as compared to path B (Table 1, entry 4 and Table 2, entry 4).

In view of the above, only **1b**, generated via path A, method B, has been employed for the subsequent cycloaddition with alcohol **6c** and enone **6d**. A mixture of isomers **7e/8e**, similar to that observed in the case of dicyclopentadiene **6a**, has been isolated when *syn*-alcohol **6c** was reacted with benzonitrile oxide **1b** (Table 3, entry 1). Finally, the enone **6d**, when treated with benzonitrile oxide **1b**, provided a mixture of isomers **7f** and **8f** in 34:66 ratio (Table 3, entry 2).

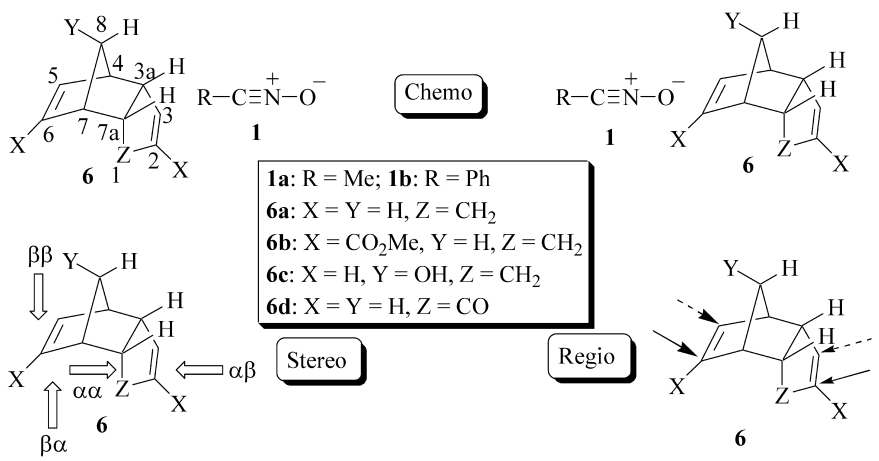
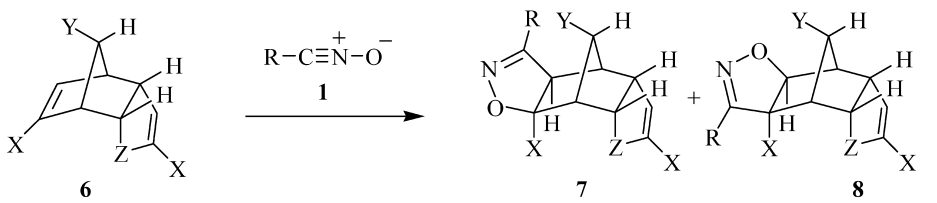


Figure 1. Chemo-, stereo- and regioselectivity in the cycloaddition of nitrile oxides **1** to dicyclopentadiene moiety **6**.



Path A, Method A: Aldoxime, NCS, Et_3N, CH_2Cl_2
Path A, Method B: Aldoxime, NaOCl, Et_3N, CH_2Cl_2
Path B: Nitroalkane, BOC_2O, DMAP, THF

7, 8a: R = Me, X = Y = H, Z = CH_2;
b: R = Ph, X = Y = H, Z = CH_2;
c: R = Me, X = CO_2Me, Y = H, Z = CH_2
d: R = Ph, X = CO_2Me, Y = H, Z = CH_2;
e: R = Ph, X = H, Y = OH, Z = CH_2;
f: R = Ph, X = Y = H, Z = CO

Scheme 1. 1,3-Dipolar cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a** and its derivatives **6b**–**d**.

The ^1H and ^{13}C NMR spectra of all the products revealed the preferential reactivity of the bicycloheptenyl (C5–C6) double bond in **6a**–**d** vis-à-vis the cyclopentenyl (C2–C3) double bond. There is no evidence for the formation of the cycloadduct arising from reaction of the cyclopentenyl (C2–C3) double bond with the nitrile oxides. This is broadly consistent with the reactivity of dicyclopentadiene **6a**[18] and Thiele's ester **6b**[34] although evidence to the contrary also exists in the literature.[35,36] In any event, the lower reactivity amounting to inertness of the *endo*-oriented cyclopentenyl (C2–C3) double bond in the dipolar cycloaddition is attributable to the preferential entry of the approaching dipole from the *exo* face of the bicycloheptane skeleton.

Having confirmed the chemoselectivity in the dipolar cycloaddition, the stereo and regio preferences observed in the cycloaddition had to be ascertained. It is evident from ^1H NMR spectra that all the cycloadditions follow the '*exo* rule'[37] of Alder and Stein providing exclusively the *exo*-cycloadducts. This is also in accord with the formation of *exo*-cycloadducts as the exclusive or predominant products in the cycloaddition of nitrile oxides to norbornenes[11,17,18,38] and norbornadienes.[18,19,20]

Reaction of dicyclopentadiene **6a** with nitrile oxides **1a** and **1b** proceeds with high stereoselectivity providing exclusively the *exo* cycloadducts (Table 1). The protons H^a (X^a=H^a) and H^b in the cycloadducts appear as doublets (J=8.25 Hz) coupled only with each other, but not with H^c or H^d) indicating their *endo* orientation (Fig. 2). However, unlike the case of Thiele's ester **6b** where single regioisomer **7c** or **7d** is formed (vide infra), regioselectivity in the case of **6a** is low, as expected, providing a mixture of regioisomers **7a/8a** and **7b/8b** in ~55:45 ratio (Table 1). In the major isomer **7a** of **7a/8a** pair, the ^1H NMR chemical shift values for the key resonances viz. the two *endo* hydrogens and the Me are δ 4.36, 2.97 and 1.80, respectively. The corresponding values for the minor isomer **8a** are δ 4.28, 2.92 and 1.83, respectively. In the **7b/8b** pair, the *endo* hydrogens appear at δ 4.66 and 3.63 for the major isomer **7b** and at δ 4.58 and 3.58 for the minor isomer **8b**. This was confirmed by NOESY experiment in that, in **7b**, besides the positive NOE between H^b and the aromatic protons, the key positive NOE between H^a and the *endo*-methylene protons as well as between H^b and the olefinic proton H-3 were discernible.

Quite remarkably, a single stereo- and regioisomer **7c** or **7d** is formed from Thiele's ester **6b** in its reaction with nitrile oxide **1a** or **1b** (Table 2). That H^b in **7c** (δ 3.43) and in **7d** (δ 4.00) is *endo* oriented (Fig. 2) is evident from the fact that it appears either as a singlet (in **7c** no coupling with H^c) or shows only very weak coupling (~2 Hz) with H^c (dihedral angle of close to 90° between H^b and H^c). As for the regiochemistry, the regioisomer **7c** or **7d** in which the oxygen of the nitrile oxide bonded to the more substituted (ester-bearing) olefinic carbon C6 is preferentially formed. This is consistent with the reactivity of aceto- and benzonitrile oxides with methyl acrylate[6,7] as well as with unsymmetrically substituted norbornenes.[16] The ^{13}C-SEFT (APT) spectra show that the carbons attached to the oxygen in the isoxazoline rings of **7c** and **7d** appearing at δ 93.1 and 94.7, respectively, are quaternary carbons. The above assignment is further confirmed by NOESY experiment. For instance, H^b in **7d** has a positive NOE with H^c, the olefinic proton H-3 and the aromatic protons (presumably the *ortho* protons). This, taken together with the absence of any NOE between H^b and H^d, confirms structure **7d** and, therefore, by analogy, structure **7c** for the cycloadducts.

Table 1. 1,3-Dipolar cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a**

Entry	1	Path	Yield[a] (%)	7:8[b]
1	**1a**	A (A)[c]	57	53:47
2	**1a**	B	84	53:47
3	**1b**	A (B)[c]	86	54:46
4	**1b**	B	52	53:47

[a] Isolated yield after column chromatography.
[b] Obtained by ^1H NMR (400 MHz) integration of the crude product.
[c] Method in parenthesis.

Table 2. 1,3-Dipolar cycloaddition of nitrile oxides **1** to Thiele's ester **6b**

Entry	1	Path	Yield[a] (%)	7:8[b]
1	**1a**	A (A)[c]	52	>99:1
2	**1a**	B	72	>99:1
3	**1b**	A (B)[c]	73	>99:1
4	**1b**	B	50	>99:1

[a] Isolated yield after column chromatography.
[b] Obtained by ^1H NMR (400 MHz) integration of the crude product.
[c] Method in parenthesis.

Table 3. 1,3-Dipolar cycloaddition of nitrile oxides **1** to alcohol **6c** and enone **6d**

Entry	1	6	Path	Yield[a] (%)	7:8[b]
1	**1b**	**6c**	A (B)[c]	70	55:45
2	**1b**	**6d**	A (B)[c]	68	34:66

[a] Isolated yield after column chromatography.
[b] Obtained by ^{1}H NMR (400 MHz) integration of the crude product.
[c] Method in parenthesis.

Subsequently, the influence of remote substituents on the reactivity of the bicycloheptenyl double bond has been investigated using *syn*-alcohol **6c** and enone **6d** (Table 3, entries 1 and 2). Interestingly enough, despite the presence of a hydroxy group syn to the bicycloheptenyl (C5–C6) double bond, the behavior of alcohol **6c** is analogous to that of **6a**. A mixture of regioisomers **7e** and **8e** (**7e/8e**=55:45) is formed when **6c** reacts with benzonitrile oxide **1b** (Table 3, entry 1). When the *endo*-methylene group in dicyclopentadiene **6a** is replaced by a carbonyl group (as in **6d**), substantial alteration in the ratio of the regioisomers (**7f/8f**=34:66) arising from the reaction of the bicycloheptenyl double bond (in **6d**) is observed (Table 3, entry 2). Comparison of the reactivity of **6a** and **6d** indicates that the reversal in the regioselectivity is attributable to electronic effects (vide infra) as the *exo* face of the bicycloheptenyl double bond in both **6a** and **6d** experiences similar steric environment.

The structure and stereochemistry of the pairs of cycloadducts **7e/8e** and **7f/8f** were confirmed as described in the case of the cycloadducts arising from dicyclopentadiene **6a** and Thiele's ester **6b**. The structure of **8f** has been further established by single crystal X-ray crystallography (Fig. 3).[39]

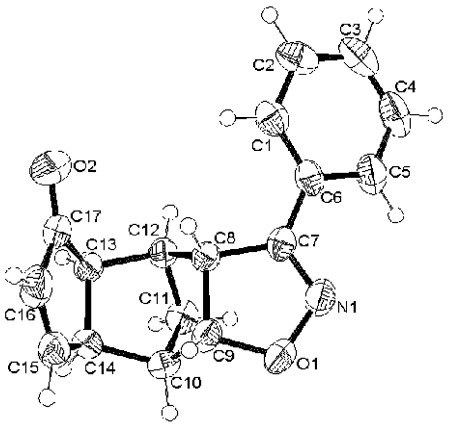


Figure 3. X-ray crystal structure of **8f**.[39]

3. Theoretical calculations

In order to probe the selectivities observed during the 1,3-dipolar cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a** and Thiele's ester **6b** and other derivatives **6c–d**, TS energy calculations were carried out at semiempirical (PM3) and hybrid ab initio-DFT levels of theory. All the TS geometries were optimized at PM3 level and characterized with one imaginary frequency.[40] Single point calculations were performed using B3LYP/6-31G* level of theory at PM3 TS geometries.[41] Solvent corrections[42] were modeled with aqueous model[43] and organic solvent (THF).[44] It may be noted that THF was used in the generation of nitrile oxides **1** from nitroalkanes and its subsequent cycloaddition with **6a** and **6b**. Solvent continuum model, IPCM was employed to calculate the energies in presence of THF.[42,43]

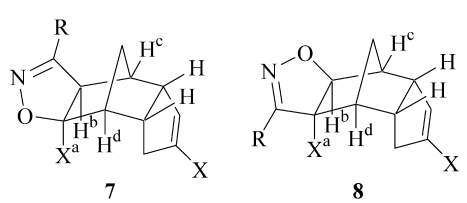


Figure 2.

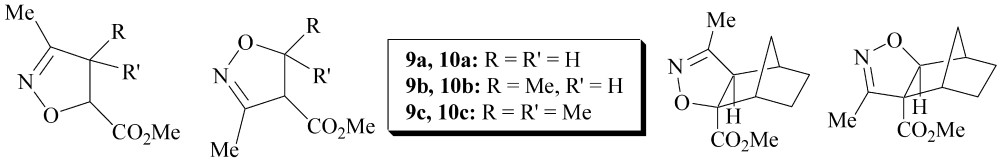
Though aqueous model has been used to examine the selectivity in all the cases at both the levels of theory, THF has been employed only with B3LYP/6-31G*//PM3 basis set. The reliability of these calculations for predicting the selectivities observed in the 1,3-dipolar cycloaddition were first examined by performing model calculations as described below.

The relative reactivities of cyclopentene and norbornene with acetonitrile oxide **1a** were first examined. As mentioned earlier, norbornene has been shown to be much more reactive than cyclopentene in their cycloaddition with nitrile oxides by Huisgen and co-workers (vide infra).[27] In addition, we have examined the regioselectivity in the cycloaddition of nitrile oxide **1a** to methylacrylate, β-methyl methylacrylate and β,β-dimethyl methylacrylate that has earlier been investigated by Huisgen and Houk.[6,7]

Our calculated results on the relative reactivities of ethylene, cyclopentadiene and norbornene with acetonitrile oxide **1a** showed good qualitative agreement with Huisgen's results. Transition states were located for the cycloaddition of acetonitrile oxide **1a** with ethylene, cyclopentene and norbornene, at PM3 level and the relative activation barriers calculated at B3LYP/6-31G*//RHF/PM3 level were 12.2, 17.1 and 11.1 kcal mol^{-1}, respectively. The corresponding rate constants k (sec^{-1}) calculated using Arrhenius equation are 0.00224, 0.000193 and 0.00388, respectively. The relative rate constants for the cycloaddition of cyclopentene and norbornene with respect to ethylene (0.086 and 1.73, respectively) clearly indicate the preferential reactivity of norbornene towards nitrile oxide **1a** visà-vis cyclopentene. The fact that the cyclopentene moiety in **6** is *endo* fused to the norbornene moiety further diminishes the reactivity of the former and, therefore, points to the observed chemoselectivity.

As far as our model calculations on the regioselectivity are concerned, results obtained at semi-empirical (PM3) and hybrid ab initio-DFT levels of theory, for the cycloaddition of nitrile oxide **1a** to methylacrylate, β-methyl methylacrylate and β,β-dimethyl methylacrylate, by locating the transition states (TS's) of cycloadducts, viz. 5-isoxazoline **9** and 4-isoxazoline **10**, concurred well with the observed experimental results[6,7] (see Table 4).

Table 4. Semi-empirical (PM3) and hybrid ab initio/DFT (B3LYP/6-31G*) level calculated relative TS energy differences in kcal/mol for the cycloaddition of acetonitrile oxide **1a** with substituted acrylates



9 **10** **11** **12**

Row/col	1	2	3	4	5	6	7	8	9
	Method	**9a**	**10a**	**9b**	**10b**	**9c**	**10c**	**11**	**12**
1	RHF/PM3 (A)	0.0	0.3	0.9	0.0	1.4	0.0	0.2	0.0
2	PM3 SM5.4 (B)[a]	0.0	1.6	0.0	0.1	0.1	0.0	0.0	1.8
3	B3LYP/6-31G*//PM3 (C)	0.0	2.0	2.7	0.0	8.6	0.0	0.0	2.5
4	B3LYP/6-31G*//PM3 SM5.4 (D)[a]	0.0	3.4	1.8	0.0	6.9	0.0	0.0	4.2
5	B3LYP/6-31G*//PM3 (E)[b]	0.0	2.2	2.7	0.0	8.2	0.0	0.0	2.6

[a] Aqueous model.
[b] THF model.

The gas phase and solvent model calculations at semi-empirical (PM3) and hybrid ab initio/DFT levels of theory predicted the predominant formation of 5-isoxazoline **9a** over 4-isoxazoline **10a** (Table 4, cols 2 and 3) in the cycloaddition of methylacrylate with acetonitrile oxide **1a** (experimental ratio[6] **9a**:**10a**=95:5). The selectivity is reversed in the cycloaddition of acetonitrile oxide **1a** with β-methyl methylacrylate in that the 4-isoxazoline **10b** is the major isomer (cols 4 and 5, experimental ratio[6] **9b**:**10b**=36:64). Further methyl substitution at the β-position of acrylate, i.e. β,β-dimethyl methylacrylate, leads to exclusive formation of 4-isoxazoline **10c** (cols 6 and 7, experimental ratio[6] **9c**:**10c**=0:100). The regio and stereoselectivity observed in the cycloaddition of acetonitrile oxide **1a** to norbornene carboxylate **4** (X=CO_2Me)[16] is also qualitatively supported by our calculations at various levels of theory (cols 8 and 9, experimental ratio, X=CO_2Et,[16] **11**:**12**=100:0).

Having established the efficacy of our approach to satisfactorily predict the selectivities observed in the previous experimental studies,[6,16] we turned to the chemo-, stereo- and regioselectivities observed in our laboratories in the cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a**, its dicarboxylate, Thiele's ester, **6b**, and other derivatives **6c–d** and the results are summarized in Table 5. Since the experimental results provided no evidence for the formation of any bis-cycloadducts, they were excluded from calculations. Further, the relative TS energies corresponding to βα- and αα-approach of the dipole **1a** towards both **6a** and **6b** and the corresponding approaches of the dipole **1b** towards dipolarophile **6d** were found to be prohibitively high and, therefore, were omitted from Table 5 for simplicity. The analysis of PM3 TS geometries suggested that the computed TS's for addition of dipole **1a** to dipolarophiles **6a** and **6b** and those for the addition of dipole **1b** to dipolarophile **6d** are concerted and slightly asynchronous in nature.[45]

The gas phase and aqueous model calculations at semi-empirical level for the cycloaddition of **1a** to dicyclopentadiene **6a** (Table 5, entry 1), though favor the ββ-approach of the dipole **1a** over the αβ and other approaches, make no distinction between the TS's leading to two regioisomers **7** and **8**. However, calculations at higher level, i.e. B3LYP/6-31G* (including gas phase, aqueous and THF model, Table 5, entry 2), predicted the marginal preference for the formation of isomer **7** over isomer **8**, as observed experimentally (**7a**:**8a**=53:47).

As for the cycloaddition of nitrile oxide **1a** to Thiele's ester **6b**, calculations at semi-empirical level (PM3, gas phase and aqueous model, Table 5, entry 3) showed the marginal preference for the approach of nitrile oxide **1a** towards the C2–C3 double bond (αβ-approach) of Thiele's ester **6b**. However, the ββ-approach of the dipole **1a** in which the dipole oxygen is bonded to the ester-bearing carbon C6 of **6b** is preferred over the ββ-approach in which the dipole C is bonded to C6 by 0.6 and 1.4 kcal mol^{-1}, respectively. Higher level (B3LYP/6-31G*) calculated results very

Table 5. Semi-empirical (PM3) and B3LYP/6-31G* calculated relative transition state energy differences for the cycloaddition of **1a** with **6a** and **6b** and **1b** with **6d** in kcal/mol[a]

Entry	Computational level	6	ββ(XC,O)[b] **7**	ββ(XC,C)[c] **8**	αβ(XC,O)	αβ(XC,C)
1	RHF/PM3	**6a**	0.0 (0.0)	0.0 (0.0)	0.7 (0.7)	0.7 (0.8)
2	B3LYP/6-31G*//PM3	**6a**	0.0 (0.0, 0.0)	0.1 (0.05, 0.1)	6.1 (6.0, 5.9)	6.0 (5.9, 6.0)
3	RHF/PM3	**6b**	0.4 (0.2)	1.0 (1.6)	0.9 (0.0)	0.0 (1.7)
4	B3LYP/6-31G*//PM3	**6b**	0.0 (0.0, 0.0)	3.0 (4.0, 3.4)	3.9 (3.2, 3.6)	6.7 (8.8, 7.1)
5	RHF/PM3	**6d**	0.4 (0.0)	0.0 (0.9)	1.1 (0.5)	0.4 (2.3)
6	B3LYP/6-31G*//PM3	**6d**	0.5 (0.0, 0.3)	0.0 (0.5, 0.0)	6.9 (6.0, 6.4)	2.3 (3.6, 2.8)

[a] Solvent calculated (aqueous model, THF model) energy differences in parentheses.
[b] (XC,O): dipole oxygen forms bond with C–X.
[c] (XC,C): dipole carbon forms bond with C–X.

clearly predicted the formation of the experimentally observed product **7c** over **8c** and the products arising from αβ-approach of the dipole **1a** (Table 5, entry 4). Furthermore, upon incorporating the solvent model (aqueous and THF) at B3LYP/6-31G* level, the calculated results show even larger preference for the formation of experimentally observed product **7c** (**7c**:**8c**=>99:1).

In the case of **6d**, PM3 and B3LYP/6-31G* calculated results predicted the preferential approach of nitrile oxide **1b** towards the ββ-face of C5–C6 double bond over the αβ-face of C2–C3 double bond. The regioselectivity obtained from our calculations is in agreement with our experimental results. Aqueous model, however, altered the preference in favor of ββ(XC,O) approach, and can be understood on the basis of the dipole moment of the transition states. The calculated dipole moment of the TS corresponding to ββ(XC,O) approach is relatively higher and gets more stabilized in the polar solvent. However, the calculations performed in THF are in accordance with gas phase results. The overall calculated results suggest that the hybrid ab initio/DFT (B3LYP) levels predict more accurately the experimental observations. It has been found that for 1,3-dipolar cycloadditions, B3LYP calculations often give comparable or slightly better results than other high level MP2, CASSCF or CCSD(T) calculations.[46] The perturbation MO treatment of cycloaddition reactivity pioneered by Sustmann[47] has generally been applied to explain the regioselectivity qualitatively of 1,3-dipolar cycloadditions.[48] Such frontier molecular orbital analysis performed for **6a**, **6b** and **6d** does not provide any clear picture towards the origin of regioselectivity in these cases. However, turning to the Mulliken population analysis, the charges calculated for **6b** and **6d** at B3LYP/6-31G* shows that the C6 carbon of **6b** bears a positive charge (0.100), while C5 has a negative charge of (−0.118) and in the case of **6d**, C6 carries slightly more negative charge (−0.111) in comparison to C5 (−0.106). This result explains the regioselectivity observed for **6b** qualitatively, where the negative end of the dipole **1a** (oxygen) is attached to the C6 carbon of **6b** and the positive end of the dipole **1a** (carbon) is attached to C5 of **6b**. The difference in the charge between C5 and C6 is smaller in the case of **6d**, and leads to a mixture of regioisomers. Mayo et al. have performed similar charge analysis to rationalize the regioselectivity observed for the 1,3-dipolar cycloaddition of nitrile oxides with unsymmetrically substituted norbornenes.[16]

The above calculated results for the cycloaddition of nitrile oxide **1** to dicyclopentadiene **6a** and its derivatives **6b–d** have shown that the norbornene units of **6a–d** are comparatively more reactive than cyclopentene units as predicted and observed in the case of isolated norbornenes and cyclopentenes.[27] Regioselectivities predicted and observed for the addition of nitrile oxide **1a** to Thiele's ester **6b** are in accordance with the norbornene esters.[16] Overall, it appears that the reactivity of norbornene units in **6a–d** are not perturbed in presence of cyclopentene units.

4. Summary and conclusions

The 1,3-dipolar cycloaddition of nitrile oxides to representative systems possessing multiple π-faces, viz. dicyclopentadiene and its derivatives, has been investigated. The greater reactivity of bicycloheptenyl double bond vis-à-vis cyclopentenyl double bond in the dicyclopentadienyl moiety towards the nitrile oxide dipole is amply evident from the exclusive formation of the *exo*-cycloadduct arising from approach of the dipole from the *exo* face of the bicycloheptenyl double bond. Furthermore, in the case of substituted dicyclopentadienes, viz. the dicarboxylate (Thiele's ester), the exclusive regioisomer is the one in which the dipole oxygen is attached to the carbon bearing the substituent. Influence of remote substituents, including sterically 'sterile' ones, on the regioselectivity has also been demonstrated. The combination of semi-empirical (PM3) and hybrid ab initio/DFT (B3LYP) methods was used to predict the chemo-, stereo- and regioselectivity of dicyclopentadienes and its derivatives. These more economical methods have successfully predicted the selectivity in the 1,3-dipolar cycloadditions of nitrile oxide to model systems as well as complex real systems. Regioselectivities observed in these cases were rationalized on the basis of Mulliken population analysis. The commonly used frontier molecular orbital analysis failed to predict the regio-selectivity in these cases at the levels of theory employed.

5. Experimental

5.1. General

The melting points are uncorrected. IR spectra were recorded on an Impact 400/Nicolet FT spectrometer. NMR spectra (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY) were recorded on a JEOL-400, AMX-400 or VXR-300S spectrometer with TMS as the internal standard. High resolution mass spectra (CI in methane or *i*-butane) were recorded at 60–70 eV on a VG-Fisons 'Autospec' spectrometer. X-ray data were collected on a MACH3S-CAAD4/NONIUS diffractometer.

5.2. Procedure for the generation of acetonitrile oxide 1a from acetaldoxime and its reaction with 6 (path A, method A)

To a stirred solution of **6** (0.5 mmol) and *N*-chlorosuccinimide (134 mg, 1 mmol, 2 equiv.) in CH_2Cl_2 (10 ml) at 0 °C under N_2 was added acetaldoxime (59 mg, 1 mmol, 2 equiv.) followed by Et_3N (22 mg, 0.22 mmol, 0.44 equiv.). The reaction mixture was stirred at rt overnight (12 h). The reaction mixture was then diluted with CH_2Cl_2 (20 ml), washed with 5% HCl (20 ml), brine (20 ml), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to ^{1}H NMR (400 MHz) analysis in order to determine the isomeric purity/composition and then purified by silica gel column chromatography by eluting with ethylacetate/pet. ether.

5.3. Procedure for the generation of benzonitrile oxide 1b from benzaldoxime and its reaction with 6 (path A, method B)

To a stirred solution of **6** (0.5 mmol), oxime (1 mmol, 2 equiv.) and few drops of Et_3N in CH_2Cl_2 (10 ml) at 0 °C

was added dropwise 4% NaOCl solution (10 ml, excess). The cooling bath was removed and the reaction mixture, while stirring continued, was allowed to warm to rt overnight (12 h). The layers were separated, the organic layer was washed with 5% HCl (20 ml), brine (20 ml), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to ^1H NMR (400 MHz) analysis as before and then purified by silica gel column chromatography by eluting with ethylacetate/pet. ether.

5.4. Procedure for the generation of nitrile oxide 1 from nitroalkane (nitroethane or nitrophenylmethane) and its reaction with 6 (path B)

To a stirred solution of **6** (0.5 mmol) and nitroalkane (1 mmol, 2 equiv.) in THF (10 ml) under N_2 was added DMAP (12 mg, 0.1 mmol, 20 mol%) followed by BOC_2O (327 mg, 1.5 mmol, 3 equiv.). The reaction mixture was stirred at rt overnight (12 h). The reaction mixture was then diluted with water (20 ml) and extracted with ether (3×15 ml). The combined organic layer was washed with 5% HCl (20 ml), brine (20 ml), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to ^1H NMR (400 MHz) analysis as before and then purified by silica gel column chromatography by eluting with ethylacetate/pet. ether.

5.4.1. Cycloaddition of acetonitrile oxide 1a with dicyclopentadiene 6a. Total yield of cycloadducts 3-methyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno [5,6-*d*]isoxazole **7a** +3-methyl-4,4a,5,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **8a** (inseparable mixture; **7a**:**8a**=53:47): path A, method A: 57%, path B: 84% (see also Table 1, entries 1 and 2); colorless crystalline solid; mp 60–62 °C; IR (KBr) cm^{-1} 2960 (s), 1453 (s), 1262 (s); ^1H NMR ($CDCl_3$) δ 1.30 (d, J=9.2 Hz, 1H), 1.45 (d, J=9.2 Hz, 1H), 1.80, 1.83 (d, J=0.8 Hz, 3H), 2.05–2.32 (m, 3H), 2.38 (m, 1H), 2.45–2.60 (m, 1H), 2.92, 2.97 (d, J=8.3 Hz, 1H), 3.08 (m, 1H), 4.28, 4.36 (d, J=8.3 Hz, 1H), 5.45–5.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.6, 11.8, 31.5, 32.4, 34.6, 35.0, 39.3, 40.7, 41.3, 42.9, 45.5, 47.3, 50.2, 51.6, 53.4, 56.6, 81.6, 84.0, 130.5, 131.2 (×2), 131.8, 156.2, 156.4; MS (CI, CH_4) *m/e* (rel intensity) 190 (MH^+, 12) 189 (M^+, 42), 169 (80), 168 (100), 141 (96), 131 (62), 115 (78); HRMS calcd for $C_{12}H_{15}NO$ (M^+) 189.1154, found:189.1164.

5.4.2. Cycloaddition of benzonitrile oxide 1b with dicyclopentadiene 6a. Total yield of cycloadducts 3-phenyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno [5,6-*d*]isoxazole **7b** +3-phenyl-4,4a,5,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **8b** (**7b**:**8b**=54:46): path A, method B: 86%, path B: 52% (see also Table 1, entries 3 and 4).

3-Phenyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **7b** (major isomer). Separated from the **7b/8b** mixture by fractional crystallization from ethanol; colorless crystalline solid; mp 85–87 °C; IR (KBr) cm^{-1} 2962 (s), 1600 (m), 1461 (s); ^1H NMR ($CDCl_3$) δ 1.40 (d, J=10.3 Hz, 1H), 1.60 (d, J=10.3 Hz, 1H), 2.30 (m, 2H), 2.60 (m, 3H), 3.20 (m, 1H), 3.63 (d, J=8.4 Hz, 1H), 4.66 (d, J=8.4 Hz, 1H), 5.68 (m, 1H), 5.78 (m, 1H), 7.36 (m, 3H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 31.4, 35.2, 39.3, 42.4, 47.5, 51.8, 52.9, 83.3, 126.6, 128.5, 129.1, 129.5, 131.1, 132.1, 157.6; MS (CI, CH_4) *m/e* (rel intensity) 251 (M^+, 100), 183 (22), 157 (19), 156 (17), 155 (19), 117 (15), 105 (18), 91 (18); HRMS calcd for $C_{17}H_{17}NO$ (M^+): 251.1310, found: 251.1314.

3-Phenyl-4,4a,5,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **8b** (minor isomer). Colorless crystalline solid; mp 95–96 °C; IR (KBr) cm^{-1} 2960 (s), 1604 (m), 1459 (s), 1348 (s); ^1H NMR ($CDCl_3$) δ 1.40 (d, J=10.3 Hz, 1H), 1.60 (d, J=10.3 Hz, 1H), 2.40 (m, 2H), 2.60 (m, 2H), 2.75 (d, J=5.6 Hz, 1H), 3.20 (m, 1H), 3.58 (d, J=8.4 Hz, 1H), 4.58 (d, J=8.4 Hz, 1H), 5.70 (m, 2H), 7.36 (m, 3H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 32.6, 34.6, 40.8, 44.0, 45.7, 49.5, 50.2, 85.7, 126.6, 128.5, 129.2, 129.4, 130.6, 131.2, 157.3; MS (CI, CH_4) *m/e* (rel intensity) 251 (M^+, 100), 183 (26), 155 (33), 141 (17), 115 (15), 105 (16); HRMS calcd for $C_{17}H_{17}NO$ (M^+): 251.1310, found: 251.1290.

5.4.3. Cycloaddition of acetonitrile oxide 1a with dimethyldicyclopentadiene dicarboxylate 6b. Yield of cycloadduct dimethyl 3-methyl-3a,4,4a,7,7a,8-hexahydro-8a*H*-4,8-methanoindeno-[5,6-*d*]isoxazole-6,8a-dicarboxylate **7c**: path A, method A: 52%, path B: 72% (see also Table 2, entries 1 and 2); colorless crystalline solid; mp 175–177 °C; IR (KBr) cm^{-1} 2960 (s), 1737 (s), 1716 (s), 1314 (m), 1262 (s); ^1H NMR ($CDCl_3$) δ 1.48 (d, J=11.0 Hz, 1H), 1.79 (d, J=11.0 Hz, 1H), 1.94 (s, 3H), 2.34 (m, 1H), 2.48 (m, 1H), 2.62 (d, J=5.1 Hz, 1H), 2.82 (m, 1H), 2.88 (d, J=4.4 Hz, 1H), 3.37 (m, 1H), 3.43 (s, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 6.60 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.7, 30.3, 37.4, 40.1, 42.9, 49.1, 51.4 (×2), 52.4, 56.7, 93.1, 137.8, 141.5, 156.6, 164.6, 168.5; MS (CI, CH_4) *m/e* (rel intensity) 306 (MH^+, 5), 305 (M^+, 1), 274 (8), 246 (7), 232 (8), 214 (11), 204 (15), 183 (100), 173 (14), 172 (26), 151 (75), 117 (23); HRMS calcd for $C_{16}H_{20}NO_5$ (MH^+): 306.1342, found: 306.1360.

5.4.4. Cycloaddition of benzonitrile oxide 1b with dimethyldicyclopentadiene dicarboxylate 6b. Yield of cycloadduct 3-phenyl-3a,4,4a,7,7a,8-hexahydro-8a*H*-4,8-methanoindeno-[5,6-*d*]isoxazole-6,8a-dicarboxylate **7d**: path A, method B: 73%, path B: 50% (see also Table 2, entries 3 and 4); colorless crystalline solid; mp 160–161 °C; IR (KBr) cm^{-1} 2939 (s), 1738 (s), 1716 (s); ^1H NMR ($CDCl_3$) δ 1.50 (d, J=10.6 Hz, 1H), 1.89 (d, J=10.6 Hz, 1H), 2.40 (m, 1H), 2.52 (m, 1H), 2.78 (dd, J=5.1 and 2.2 Hz, 1H), 2.88 (m, 1H), 2.98 (d, J=4.4 Hz, 1H), 3.39 (m, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 4.0 (d, J=2.2 Hz, 1H), 6.74 (d, J=1.8 Hz, 1H), 7.40 (m, 3H), 7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.3, 37.5, 40.1, 44.1, 49.2, 51.5 (×2), 52.5, 53.2, 94.7, 127.0, 128.3, 128.7, 130.2, 137.9, 141.5, 158.1, 164.7, 168.3; MS (CI, CH_4) *m/e* (rel intensity) 367 (M^+, 23), 331 (24), 308 (10), 280 (24), 232 (12), 183 (100), 151 (49); HRMS calcd for $C_{21}H_{21}NO_5$ (M^+) 367.1420, found: 367.1420.

5.4.5. Cycloaddition of benzonitrile oxide 1b with dicyclopentadien-8-ol 6c. 3-Phenyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazol-9-ol **7e** (major isomer) +3-phenyl-4,4a,5,7a,8,8ahexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazol-9-ol **8e** (minor isomer): Total

yield (inseparable mixture, **7e**:**8e**=55:45) 70% (see also Table 3, entry 1); colorless crystalline solid; mp 140–142 °C; IR (KBr) cm^{-1} 3399 (b), 2976 (s), 1658 (s), 1351 (s), 1038 (s); ^1H NMR ($CDCl_3$) δ 1.55 (m, 2H), 2.45 (m, 1H), 2.65 (m, 1H), 2.81 (m, 1H), 3.36 (m, 1H), 3.39, 3.48 (d, J=8.4 Hz, 1H), 4.43, 4.49 (d, J=8.4 Hz, 1H), 4.83 (m, 1H), 5.87–5.95 (m, 1H), 6.02–6.05 (m, 1H), 7.40–7.48 (m, 3H), 7.60–7.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 35.2, 35.7, 42.4, 43.0, 45.5, 46.6, 49.5, 50.6, 51.0, 51.1, 52.2, 52.6, 75.6, 76.8, 83.5, 85.0, 126.7, 126.8, 128.72, 128.74, 129.0 (×2), 129.9 (×2), 133.6, 134.9, 137.1, 137.4, 157.3, 157.6; MS (CI, *i*-butane) *m*/*e* (rel intensity) 268 (MH^+, 61), 267 (M^+, 100), 250 (13); HRMS calcd for $C_{17}H_{17}NO_2$ (M^+): 267.1259, found 267.1236.

5.4.6. Cycloaddition of benzonitrile oxide 1b with dicyclopentadien-1-one 6d. Total yield of cycloadducts (**7f**:**8f**=34:66) 68% (see also Table 3, entry 2).

3-Phenyl-3a,4,4a,7a,8,8a-hexahydro-5*H*-4,8-methanoindeno[5,6-*d*]isoxazol-5-one (major isomer) **8f**. Separated from the mixture by fractional crystallization from ethanol, colorless crystalline solid; mp 210–211 °C; IR (KBr) cm^{-1} 2976 (m), 1697 (s), 1351 (w), 1274 (m), 1184 (w), 1076 (w), 890 (m); ^1H NMR ($CDCl_3$) δ 1.70 (ABq, J=11.0 Hz, 2H), 2.77 (t, J=6.1 Hz, 1H), 2.95 (d, J=4.9 Hz, 2H), 3.36 (m, 1H), 3.44 (d, J=8.5 Hz, 1H), 4.44 (d, J=8.5 Hz, 1H), 6.21 (m, 1H), 7.39–7.40 (m, 3H), 7.68 (m, 2H), 7.73 (dd, J=6.1, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 36.5, 43.6, 45.2, 46.5, 50.7, 52.3, 84.2, 126.7, 128.2, 128.69, 129.9, 135.9, 156.9, 164.4, 209.6; MS (CI, *i*-butane) *m*/*e* (rel intensity) 266 (MH^+, 265 (M^+, 100), 172 (79), 144 (12), 143 (15), 128 (8), 117 (9), 93 (54), 76 (14); HRMS calcd for $C_{17}H_{15}NO_2$ (M^+): 265.1103, found 265.1106.

3-Phenyl-3a,4,4a,7a,8,8a-hexahydro-7*H*-4,8-methanoindeno[5,6-*d*]isoxazol-7-one (minor isomer) **7f**. Colorless crystalline solid; mp 158–160 °C; IR (KBr) cm^{-1} 2970 (m), 1697 (s), 1345 (w), 1095 (w); ^1H NMR ($CDCl_3$) δ 1.70 (ABq, J=11.0 Hz, 2H), 2.78 (m, 2H), 3.18 (d, J=4.9 Hz, 1H), 3.35 (m, 2H), 4.52 (d, J=8.5 Hz, 1H), 6.25 (m, 1H), 7.41 (m, 3H), 7.67 (m, 2H), 7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 36.3, 42.0, 47.1, 48.3, 48.9, 50.7, 52.0, 52.8, 83.3, 126.6, 128.5, 128.72, 129.9, 136.5, 157.1, 163.5, 208.5; MS (CI, *i*-butane) *m*/*e* (rel intensity) 266 (MH^+, 59), 265 (M^+, 100), 86 (23); HRMS calcd for $C_{17}H_{15}NO_2$ (M^+): 265.1103, found 265.1117.

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References and notes

1. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.
2. For selected reviews: (a). In *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984. (b) Namboothiri, I. N. N.; Hassner, A. *Topics in current chemistry: stereoselective intramolecular 1,3-dipolar cycloadditions*; Metz, P., Ed.; Springer: Germany, 2001; Vol. 216, pp 1–49. (c) Karlsson, S.; Hogberg, H.-E. *Org. Prep. Proc. Int.* **2001**, *33*, 103. (d) Fisera, L.; Ondrus, V.; Kuban, J.; Micuch, P.; Blanarikova, I.; Jäger, V. *J. Heterocycl. Chem.* **2000**, *37*, 551. (e) Huisgen, R. *Chem. Pharm. Bull.* **2000**, *48*, 757. (f) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
3. For reviews: (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Torssell, K. B. G. *Nitrile oxides, nitrones and nitronates in organic synthesis*; VCH: New York, 1988. (c) Grundmann, C.; Grünanger, P. *The nitrile oxides*. Springer: Berlin, 1971. (d) Hassner, A.; Murthy, K. S. K.; Maurya, R.; Dehaen, W.; Friedman, O. *J. Heterocycl. Chem.* **1994**, *31*, 687. (e) Litvinovskaya, R. P.; Khripach, V. A. *Russ. Chem. Rev.* **2001**, *70*, 405. (f) Caramella, P.; Grünanger, P. In *1,3-Dipolar cycloaddition chemistry*; Padwa, A. Ed.; Wiley: New York; Vol. 1; Chapter 3. (g) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Ed.; Wiley: New York; Vol. 2; Chapter 2. (h) Padwa, A.; Schoffstall, A. M. Intramolecular 1,3-dipolar cycloaddition chemistry. In *Advances in cycloaddition*. Curran, D. P., Ed.; JAI: Greenwich, 1990; pp 1–89.
4. For applications to natural product synthesis: (a). *Tetrahedron symposia-inprint*; Oppolzer, W., Ed.;, 1985; Vol. 41. p 3447. (b) Jäger, V.; Müller, R.; Leibold, T.; Hein, M.; Schwarz, M.; Fengler, M.; Jaroskova, L.; Pärzel, M.; Le Roy, P.-Y. *Bull. Soc. Chim. Belg.* **1994**, *103*, 491. (c) Brieger, G.; Bennet, J. N. *Chem. Rev.* **1980**, *80*, 63. (d) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905. (e) Kotyatkina, A. I.; Zhabinsky, V. N.; Khripach, V. A. *Russ. Chem. Rev.* **2001**, *70*, 641. (f) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719.
5. Tam, W.; Tranmer, G. K. *Org. Lett.* **2002**, *4*, 4101.
6. (a) Christl, M.; Huisgen, R. *Tetrahedron Lett.* **1968**, 5209. (b) Christl, M.; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3275. (c) Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, *106*, 3345.
7. (a) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403. (b) Houk, K. N.; Sims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (c) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.
8. (a) Beltrame, P.; Beltrame, P. L.; Caramella, P.; Cellerino, G.; Fantechi, R. *Tetrahedron Lett.* **1975**, 3543. (b) Bianchi, G.; De Micheli, C.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1518.
9. (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (c) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. (d) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.
10. For recent reviews on π-facial selectivity: (a) *Chem. Rev.* **1999**, *99*(5): Special issue on π-face selection (b) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278. (c) Marchand, A. P.; Coxon, J. M. *Acc. Chem. Res.* **2002**, *35*, 271.
11. Fliege, W.; Huisgen, R. *Justus Liebigs Ann. Chem.* **1973**, 2038.
12. Gandolfi, R.; Tonoletti, G.; Rastelli, A.; Bagatti, M. *J. Org. Chem.* **1993**, *58*, 6038.
13. Bianchi, G.; De Micheli, C.; Gamba, A.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 137.
14. (a) Houk, K. N.; Moses, S. R.; Wu, Y. D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (b) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.*

1984, *49*, 2762. (c) Jäger, V.; Schohe, R. *Tetrahedron Lett.* **1983**, *24*, 5501.
15. For recent examples of diastereofacial selective 1,3-dipolar cycloadditions (a) Garcia Ruano, J. L.; Bercial, F.; Gonzalez, G.; Martin Castro, A. M.; Martin, M. R. *Tetrahedron: Asymmetry* **2002**, *13*, 1993. (b) Melsa, P.; Mazal, C. *Collect. Czech. Chem. Commun.* **2002**, *67*, 353. (c) Garcia Ruano, J. L.; Alonso de Diego, S. A.; Blanco, D.; Martin Castro, A. M.; Martin, M. R.; Rodriguez Ramos, J. H. *Org. Lett.* **2001**, *3*, 3173. (d) Garcia Ruano, J. L.; Fraile, A.; Martin, M. R. *Tetrahedron* **1999**, *55*, 14491. (e) Padwa, A.; Prein, M. *Tetrahedron* **1998**, *5*, 6957. (f) Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362.
16. Mayo, P.; Hecnar, T.; Tam, W. *Tetrahedron* **2001**, *57*, 5931.
17. (a) Arjona, O.; de Dios, A.; de la Pradilla, R. F.; Mallo, A.; Plumet, A. *Tetrahedron* **1990**, *46*, 8179. (b) Arjona, O.; Dominguez, C.; de la Pradilla, R. F.; Mallo, A.; Manzano, C.; Plumet, J. *J. Org. Chem.* **1989**, *54*, 5883.
18. Tanaka, K.; Masuda, H.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn* **1986**, *59*, 3901.
19. (a) Micheli, C. D.; Gandolfi, R.; Oberti, R. *J. Org. Chem.* **1980**, *45*, 1209. (b) Taniguchi, H.; Ikeda, T.; Yoshida, Y.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2694.
20. (a) Yip, C.; Handerson, S.; Jordan, R.; Tam, W. *Org. Lett.* **1999**, *1*, 791. (b) Yip, C.; Handerson, S.; Trammer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 276.
21. Houk, K. N.; Luskus, L. J.; Bhacca, N. S. *J. Am. Chem. Soc.* **1970**, *92*, 6392.
22. Addition of trifluoroacetonitrile oxide to dicyclopentadiene has been found to give a mixture of isomers, but no attempts have been made to characterize the isomers; the *endo* cyclopentenyl double bond was hydrogenated making the two regioisomers indistinguishable: see Ref. 18.
23. For addition of azido and azomethine oxide groups to dicyclopentadiene, see (a) Nagibina, N. N.; Sidorova, L. P.; Klyuev, N. A.; Charushin, V. N.; Chupakhin, O. N. *Russ. J. Org. Chem.* **1997**, *33*, 1468. (b) Plenkiewicz, J. *Bull. Acad. Polym. Sci., Ser. Sci. Chim.* **1977**, *CA87*, 68248.
24. (a) Thiele, J. *Chem. Ber.* **1900**, *33*, 666. (b) Thiele, J. *Chem. Ber.* **1901**, *34*, 68. (c) Peters, D. *J. Chem. Soc.* **1959**, 1761. (d) Dunn, G. L.; Donohue, J. K. *Tetrahedron Lett.* **1968**, 3485. (e) Minter, D. E.; Marchand, A. P.; Lu, S.-P. *Magn. Reson. Chem.* **1990**, *28*, 623. (f) Marchand, A. P.; Namboothiri, I. N. N.; Lewis, S. B. *Tetrahedron* **1998**, *54*, 12691.
25. (a) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70. (b) Cookson, R. C.; Hudec, J.; Williams, R. O. *J.C.S. Chem. Commun.* **1967**, 1382. (c) Dilling, W. L. *Chem. Rev.* **1966**, 373.
26. Ogino, T.; Awano, K. *Bull. Chem. Soc. Jpn* **1986**, *59*, 2811.
27. For instance, the relative addition constants k for norbornene and cyclopentene in their cycloadditions with benzonitrile oxide are 15.3 and 0.21, respectively. Ethylene (k=1) was taken as the standard dipolarophile, see: Bast, K.; Christl, M.; Huisgen, R.; Mack, W. *Chem. Ber.* **1973**, *106*, 3312.
28. (a) Grundmann, C.; Dean, J. M. *J. Org. Chem.* **1965**, *30*, 2809. (b) See also Ref. 2b for recent references.
29. (a) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (b) Shimizu, T.; Hayashi, T.; Shibafuchi, H.; Teramura, K. *Bull. Chem. Soc. Jpn* **1986**, *59*, 2827.
30. Basel, Y.; Hassner, A. *Synthesis* **1997**, 309.
31. While the isomer **7b** was isolated in pure form from **7b/8b** mixture by fractional crystallization from ethanol, attempts to separate isomers **7a** and **8a** were not successful (see Section 5).
32. Selective formation of one of the several possible thermally allowed pericyclic reaction products was called periselectivity: see Ref. 7c.
33. Presence of excess nitrile oxide precursors (up to 4 equiv. of oxime or nitroalkane) and/or excess reagents did not alter the isomer ratios. In presence of excess dipolarophile, on the other hand, the reaction remained incomplete, but the isomer ratio remained unchanged. However, best yields were obtained when nitrile oxides **1** were generated in presence of the dipolarophile.
34. For e.g. the bicycloheptenyl double bond in Thiele's ester **6b** undergoes hydrogenation much faster compared to the cyclopentenyl double bond: see Alder, K.; Stein, G. *Annales* **1931**, *485*, 223.
35. For e.g. both the double bonds in dicyclopentadiene **6a** are epoxidised at the same rate: see Turner, R. B.; Meador, W. R.; Winkler, R. E. *J. Am. Chem. Soc.* **1957**, *79*, 4116.
36. (a) Dols, P. P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1993**, *49*, 11373. (b) Marchand, A. P.; Sorokin, V. D.; Rajagopal, D.; Bott, S. G. *Tetrahedron* **1994**, *50*, 9933.
37. (a) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510. (b) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537.
38. The torsional effects and steric hindrance exerted by the 5-*endo* H's were blamed for the *exo* preference: see Ref. 11.
39. Selected X-ray crystallographic data for **8f** ($C_{17}H_{15}NO_2$): Space group: monoclinic P 21/n; a=9.45(12) Å; b=13.629(10) Å; c=10.865(8) Å; V=1304.3(2) Å3; Z=4, D_{calc}=1.351 g cm^{-3}; μ=0.089 mm^{-1}; R_1=0.0521; R_w=0.0890. Complete crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 211238. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
40. (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
41. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Boresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. GAUSSIAN 94, Rev. B.2, Gaussian Inc., Pittsburgh, PA, 1995.
42. For a recent report on the solvent effect in 1,3-dipolar cycloadditions, see: Hu, Y.; Houk, K. N. *Tetrahedron* **2000**, *56*, 8239, and the references cited therein.
43. Chambers, C. C.; Hawkins, C. J.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Phys.* **1996**, *100*, 16385.
44. Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098.
45. For discussion on the mechanism of 1,3-dipolar cycloadditions: (a) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291. (b) Ref. 7a. (c) Poppinger, D. *Aust. J. Chem.* **1976**, *29*, 465. (d) Komornicki, A.; Goddard, J.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1980**, *102*, 1763. (e) Hiberty, P. C.; Ohanessian, G.; Schlegel, H. B. *J. Am. Chem. Soc.* **1983**, *105*, 719. (f) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650. (g) Liuch, J. M.; Bertran, J. *Tetrahedron* **1982**, *38*, 1847. (h) Liuch, J. M.; Bertran, J. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1419. (i) Harcourt, R. D.; Little, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 41. (j) Weingarten, M. D.; Prein,

M.; Price, T.; Snyder, J. P.; Padwa, A. *J. Org. Chem.* **2001**, *1997*, 62.

46. (a) Binkley, J. S.; Pople, J. A. *Int. J. Quantum Chem.* **1975**, *9*, 229. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem. Symp.* **1976**, *10*, 1. (c) Roos, B. O. *Adv. Chem. Phys.* **1987**, *69*, 399. (d) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. *Chem. Phys. Lett.* **1989**, *157*, 479. (e) Nguyen, M. T.; Chandra, A. K.; Sakai, S.; Morokuma, K. *J. Org. Chem.* **1999**, *64*, 65.
47. (a) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717. (b) Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838.
48. (a) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (b) Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1976**, *98*, 6397. (c) Houk, K. N.; Caramella, P.; Munchausen, L. L.; Chang, Y.-M.; Battaglia, A.; Sims, J.; Kaufman, D. C. *J. Electron Spectrosc. Related Phenom.* **1977**, *10*, 441. (d) Houk, K. N.; Yamaguchi, K. *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 407.

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Chemoselective reductive alkylation of ammonia with carbonyl compounds: synthesis of primary and symmetrical secondary amines

Bruhaspathy Miriyala,[a] Sukanta Bhattacharyya[b,*] and John S. Williamson[a]

[a]*Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677, USA*
[b]*Department of Chemistry, Argonaut Technologies, 1101 Chess Drive, Foster City, CA 94404, USA*

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Abstract—An efficient, general procedure for highly chemoselective reductive mono-alkylation of ammonia with ketones is reported. Treatment of ketones with ammonia in ethanol and titanium(IV) isopropoxide, followed by in situ sodium borohydride reduction, and a straightforward workup afforded primary amines in good to excellent yields. Reductive alkylation of ammonia with aldehydes, on the other hand, afforded the corresponding symmetrical secondary amines selectively.

1. Introduction

Synthesis of amines is an objective of high priority from the perspective of drug discovery.[1] Amines and their carboxamide derivatives are the most prevalent structural moieties present in the registered drugs globally and constitute more than two thirds of the comprehensive medicinal chemistry database.[2] Reductive amination[3] of carbonyl compounds is a very important and powerful tool for chemists to target the synthesis of structurally diverse primary, secondary and tertiary amines. The sequence proceeds through the formation of an imine or iminium intermediate upon reaction of a carbonyl compound with ammonia, primary amine or secondary amine followed by in situ reduction to an amine of higher order. Catalytic hydrogenation[3a,4] has remained one of the commonly applied methods for carrying out this transformation, which is, however, incompatible with a number of otherwise reducible functional groups such as nitro, cyano and 'C–C' multiple bonds. Among the borohydride reagents, sodium cyanoborohydride[3c,d,5] and sodium triacetoxyborohydride[3e,6] have found significant applications. However, these reagents are not without limitations[3g,6] in terms of functional group tolerance and side reactions. In order to further improve the scope and selectivity in reductive amination reactions, several other reducing systems including pyridine–borane,[7] and variously modified zinc borohydride,[8] sodium borohydride,[9] organosilanes,[10] and organotin hydrides[11] have been described. Apart from hydride-based reagents, development of a Hantzsch dihydropyridine system has been recently reported.[12]

Though many of the reported protocols for reductive amination reactions work well for the preparation of tertiary amines, synthesis of primary and secondary amines is compromised[3,5,6] by over-alkylation reactions in many cases. This is particularly true for reductive alkylation of ammonia with aldehydes and ketones.[13] In this case, the primary amine initially formed continues to undergo further reductive alkylation with the carbonyl compound still present in the reaction mixture. Thus, formation of variable amounts of secondary and tertiary amines along with the desired primary amines is common, thereby making the reaction less useful. A variety of ammonia equivalents such as tritylamine, diallylamine, allylamine and carbamates have been developed[14] to address this problem. However, the reaction sequence routinely involves an additional step to obtain the targeted primary amines in their unprotected form. Development of a direct, chemoselective route for reductive alkylation of ammonia, therefore, remains a challenge.

In the context of our ongoing investigations on titanium(IV) isopropoxide[15,16] mediated reductive amination reactions, we report herein a full account[17] of our efforts on the reductive alkylation of ammonia with carbonyl compounds using the $Ti(O^iPr)_4$–$NaBH_4$ reagent system. In these investigations, primary amines were obtained exclusively from reactions with ketones, and the reaction conditions have been found compatible with various acid-labile groups

Keywords: Reductive amination; Ammonia; Ketones; Aldehydes.
* Corresponding author. Tel.: +1-650-655-4229; fax: +1-650-655-4329; e-mail address: sbhattacharyya@argotech.com

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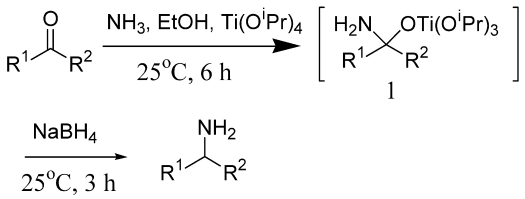


Scheme 1. Primary amines from ketones.

such as N-Boc, carbamate, acetal and ketal. The reactions with aldehydes, on the other hand, afforded a general, chemoselective synthesis of symmetrical secondary amines. To our knowledge, this is the first report for the selective formation of symmetrical secondary amines from reductive amination reactions using highly reactive partners such as ammonia and aldehydes.[18] Syntheses of secondary amines are particularly significant in view of their potential as versatile pharmacophores, ligands and synthetic intermediates.[19]

2. Results and discussion

2.1. Reductive alkylation of ammonia with ketones

The initial experiments for the reductive amination of ketones were performed using a mixture of ammonium chloride and triethylamine in anhydrous ethanol as the source of ammonia. A 2-fold molar excess of ammonium chloride–triethylamine was utilized with respect to the ketones. Though the method avoids the use of gaseous ammonia, the reactions were slow with many ketonic substrates and could not be improved by using up to 5-fold excess of ammonium chloride and triethylamine. There are numerous reports in the literature[3g] that reductive amination reactions using ammonium salts often fail due to their poor solubility in common organic solvents used for such reactions. As an alternative approach, we reasoned that a better transformation might be achieved using a commercially available ethanol solution of ammonia. Treatment of an excess of ammonia–ethanol solution (5 equiv.) with ketones as the limiting reagent in the presence of titanium(IV) isopropoxide, followed by sodium borohydride reduction offered clean conversion at room temperature, affording only the desired primary amines. The primary amines were not contaminated with any secondary and tertiary amine resulting from overalkylation reactions. The reaction may proceed[5c,15,20] through the titanium(IV) complex **1** (Scheme 1) which is either reduced directly or via a transient imine species.

As evaluated on a structurally diverse set of ketones, the scope and utility of the protocol proved to be quite general. The results are summarized in Table 1. A mixture of

Table 1. Synthesis of primary amines from ketones

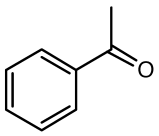
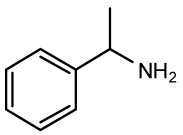
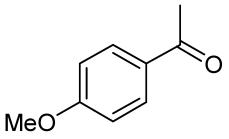
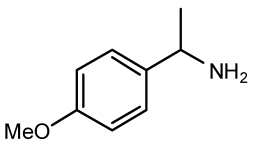
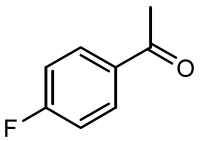
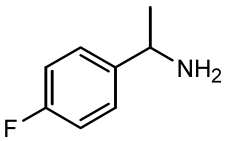
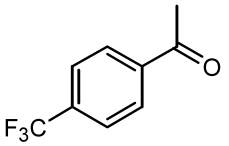
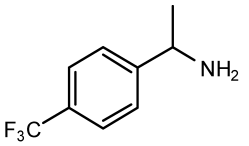
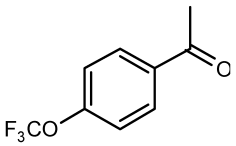
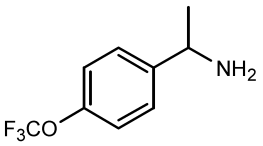
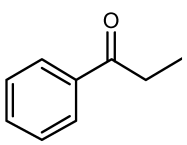
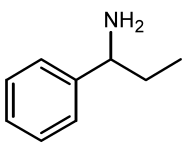
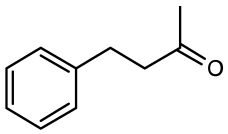
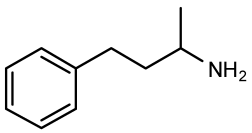
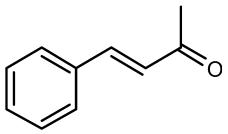
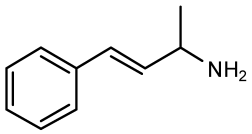
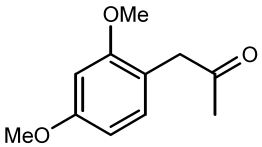
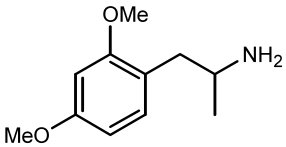
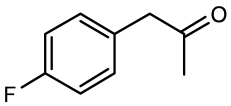
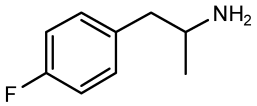
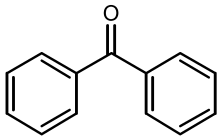
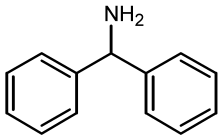
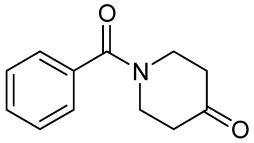
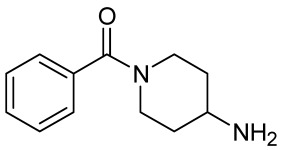
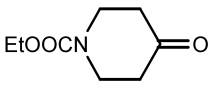
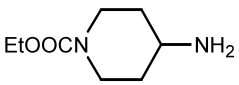
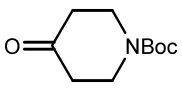
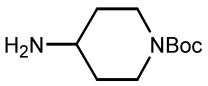
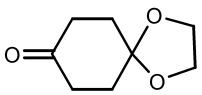
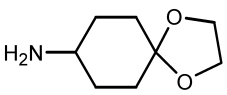
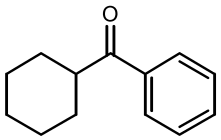
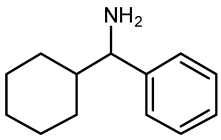
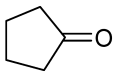
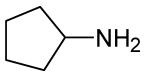
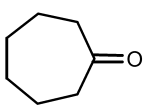
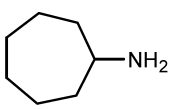
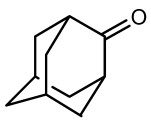
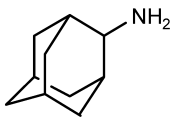
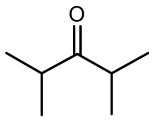
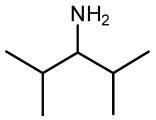
Entry	Starting ketone	Product primary amine	Yield (%)	Purity (%)[a]
1			88	98
2			91	97
3			65	99
4			83	99
5			83	97
6			89	99

Table 1 (*continued*)

Entry	Starting ketone	Product primary amine	Yield (%)	Purity (%)[a]
7			88	98
8			89	98
9			87	97
10			78	99
11			78	98
12			96	100
13			93	100
14			88	98
15			91	99
16			72	98
17			90	99
18			88	98
19			93	100
20			85	100

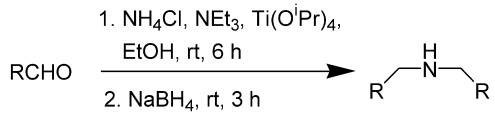
[a] Purity was determined by GC or LC–MS.

ammonia in ethanol, the ketone and titanium(IV) isopropoxide was stirred in a capped flask at ambient temperature to form the intermediate titanium(IV) complex **1**. The progress of the reaction was probed by IR spectral analysis.[5c] In general, the reaction required 6 h for complete formation of the intermediate **1**, as the IR spectrum of the reaction mixture showed no ketone band after 6 h. The reducing agent, sodium borohydride, was then added and the resulting mixture was allowed to stir for a further period of 3 h. Finally, the reaction was quenched with aqueous ammonia. The resulting inorganic precipitate was filtered and the filtrate was extracted with ethyl acetate. The reduction step generally required 3 h for maximum conversion to the primary amine. When reactions were quenched after 1 h, the yields were ca. 40% less. In most of the cases, the product primary amine was isolated in its pure form by simple extraction of the ethyl acetate solution with dilute hydrochloric acid (1 M), basification of the aqueous layer and subsequent extraction with ethyl acetate.

As demonstrated in Table 1, both alkyl and aryl ketones afforded the corresponding primary amines in good yields in most of the cases. In contrast to many acid-mediated reductive amination methods, the present method is equally applicable to substrates containing enolizable carbonyl groups. Aromatic ketones were reported[3,6] to be least reactive in a number of reductive amination protocols. However, under these reaction conditions, acetophenones (Table 1, entries 1–6) afforded the corresponding primary amines in good to excellent yields. Among all the aromatic ketones evaluated, benzophenone and cyclohexyl phenyl ketone were found to be the least reactive (Table 1, entries 11 and 14). In general, aliphatic ketones were more reactive than their aromatic counterparts. Both cyclic and acyclic aliphatic ketones were converted to their primary amines in high to excellent yields. The α,β-unsaturated ketone, 4-phenyl-butenone (Table 1, entry 8) was reductively aminated in high yield with no observable reduction of the C–C double bond. Steric hindrance appeared to play no role in dictating the outcome of the reaction as exemplified by the excellent conversion of 2-adamantanone and diisopropyl ketone to their respective primary amines (Table 1, entries 19 and 20). The reaction conditions were found compatible with acid-labile groups such as ketals, N-Boc and N-COOEt (Table 1, entries 13–15). For example, N-Boc protected 4-piperidone underwent smooth reductive amination under these conditions. Similarly, 1,4-cyclohexanedione monoethylene ketal was successfully converted into the corresponding primary amine in high yield.

2.2. Reductive alkylation of ammonia with aldehydes

Unlike the case of ketones, the reactions with aldehydes could not be controlled at the primary amine stage even by using a 10–20-fold molar excess of ammonia–ethanol solution with respect to the aldehyde substrates. A mixture of primary and symmetrical dialkylamine of varying proportions was obtained with a range of aldehydes. However, the reactions were controlled at the secondary amine stage, formation of any tertiary amine by further alkylation of the secondary amine was not observed. In an effort to survey the reaction conditions for chemoselectivity, we selected benzaldehyde as the test substrate. The initial experiments were performed with 0.5 and 40 equiv. of an ethanol solution of ammonia with respect to benzaldehyde in the presence of $Ti(O^iPr)_4$ and $NaBH_4$, and the crude products analyzed by GC. With 0.5 equiv. of ammonia, the ratio of benzylamine to dibenzylamine was found to be 15:85, while with 40 equiv. of ammonia the ratio was 68:32. The results clearly indicated that even the use of a large excess of ammonia did not favor exclusive formation of the primary amine. However, the high selectivity of dibenzylamine formation was encouraging from the viewpoint of a general synthesis of symmetrical secondary amines. In order to further optimize the reaction conditions, we decided to explore the use of a mixture of ammonium chloride and triethylamine in anhydrous ethanol as the source of ammonia. We surmised that this reagent system would slowly release ammonia due to the low solubility of ammonium chloride in ethanol, and this would allow the initially formed primary amine to react further with the aldehyde present in the reaction mixture to generate symmetrical dialkylamine selectively. Indeed this was the case, as symmetrical secondary amines were isolated in moderate to good yields when aldehydes were reacted with a mixture of ammonium chloride, triethylamine and $Ti(O^iPr)_4$ in ethanol, followed by reduction with $NaBH_4$ (Scheme 2). The scope of dialkylamine synthesis was demonstrated using a variety of aliphatic and aromatic aldehydes. As shown in Table 2, variously substituted aromatic aldehydes containing both electron donating and electron withdrawing groups (Table 2, entries 21–31) were converted to the corresponding dibenzylamines in good yields. The fluorine containing dibenzyl amines (Table 2, entries 26 and 27) were obtained in moderate yields from the corresponding benzaldehydes. An example with a heterocyclic aldehyde included indole-3-aldehyde (Table 2, entry 31). The reductive amination of 3,4-(methylenedioxy)-benzaldehyde afforded the corresponding secondary amine (Table 2, entry 29) in high yield with the acetal group tolerated. The reaction conditions were found equally applicable in the cases of aliphatic aldehydes as exemplified in the entries 32–34 (Table 2).

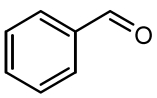
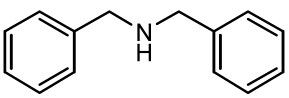
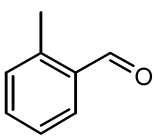
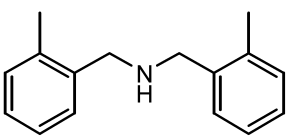
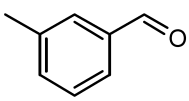
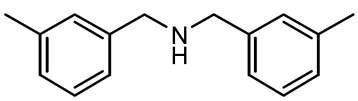
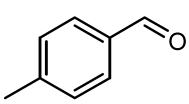
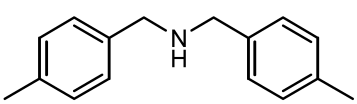
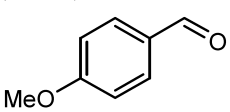
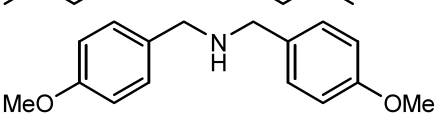
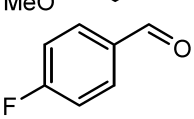
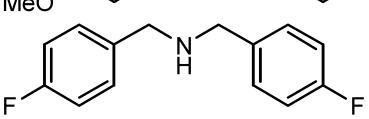
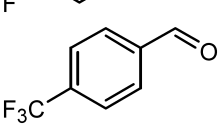
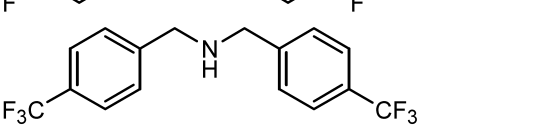
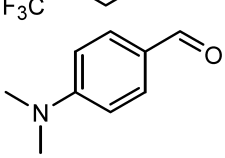
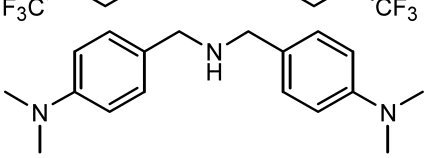
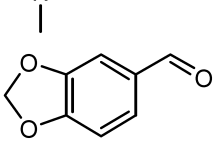
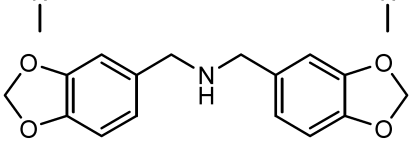
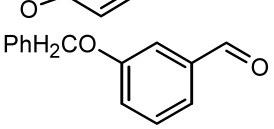
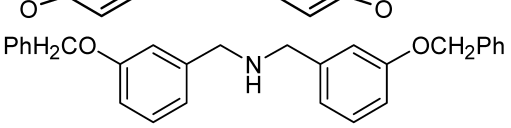
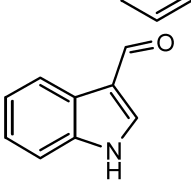
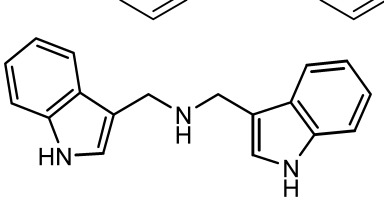
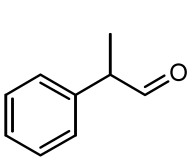
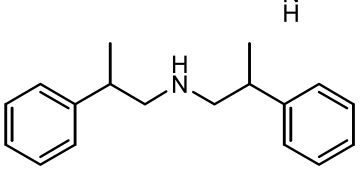
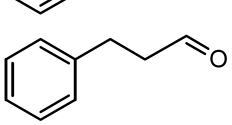
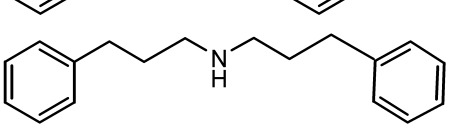
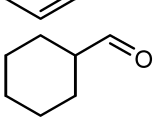
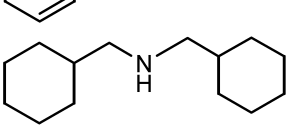


Scheme 2. Symmetrical secondary amines from aldehydes.

3. Conclusion

In summary, we have described an efficient, chemoselective method for the synthesis of primary amines by reductive amination of ketones with ammonia in the presence of titanium(IV) isopropoxide and sodium borohydride. The scope of the reaction has been demonstrated with aliphatic, aromatic, cyclic and acyclic ketones. Because this method allows easy access to structurally diverse primary amines, it should find wide application. Reductive alkylation of ammonia with aldehydes, on the other hand, has afforded symmetrical secondary amines as the only isolated products. Notable advantages of the present method include: mild, neutral reaction conditions that can tolerate a variety of acid-sensitive functional groups such as acetal, ketal, N-Boc and carbamate, and simple workup.

Table 2. Synthesis of symmetrical secondary amines from aldehydes

Entry	Starting aldehyde	Product secondary amine	Yield (%)	Purity (%)[a]
21			76	99
22			70	99
23			71	99
24			78	98
25			50	98
26			75	98
27			70	100
28			62	100
29			77	97
30			67	97
31			65	98
32			58	98
33			75	100
34			68	98

[a] Purity was determined by GC or LC–MS.

4. Experimental

The starting aldehydes and ketones, reagents and solvents were used as obtained from their respective suppliers without further purification. Two molar solutions of ammonia in ethanol are commercially available and were obtained from Aldrich Chemical Company, USA. IR spectra were recorded with $CHCl_3$ as solvent (Bruker Vector 33 FTIR). ^1H NMR spectra were run in $CDCl_3$ at 400 MHz on a Bruker AM 400 spectrometer. Chemical shifts are reported in ppm referenced to TMS. Liquid chromatography and electrospray ionization mass spectrometry (EIMS) were performed with a Waters 2690 Separation Module HPLC system and a Waters/Micromass ZQ 2000 mass spectrometer in the positive ion detection mode. Components were resolved using a Waters Symmetry C18 5 mm HPLC column (2.1×50 mm). Flash chromatography was performed on silica gel (200–400 mesh, Natland). Analytical TLC was performed on pre-coated silica gel plates with fluorescent indicators using purified solvents, followed by iodine visualization, as necessary. All products were characterized by their ^1H NMR, IR and mass spectral data; identities of known compounds were established by comparison of their NMR spectral data with the values reported in the literature. The purities of the product primary and secondary amines were determined by using GC or LC–MS analysis.

4.1. General procedure for the synthesis of primary amines from ketones

A mixture of the ketone (10 mmol), titanium(IV) isopropoxide (6.0 mL, 20 mmol) and ammonia in ethyl alcohol (2 M, 25 mL, 50 mmol) was stirred under argon in a capped flask at ambient temperature for 6 h. Sodium borohydride (0.6 g, 15 mmol) was then added and the resulting mixture was stirred at room temperature for an additional 3 h. The reaction was then quenched by pouring into ammonium hydroxide (2 M, 25 mL), the resulting inorganic precipitate was filtered off, and washed with ethyl acetate (25 mL×2). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (25 mL×2).

The combined organic solution was next extracted with hydrochloric acid (1 M, 30 mL) to separate the neutral materials. The acidic aqueous extracts were washed with ethyl acetate (50 mL), then treated with aqueous sodium hydroxide (2 M) to pH 10–12, and extracted with ethyl acetate (50 mL×3). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the corresponding primary amine.

The data below correspond to the entries in Table 1.

4.1.1. 1-Phenylethylamine[21a] (1). Yield 88%; IR: 3359, 3062, 3028, 2968, 2640, 1640, 1570, 1453, 1359, 1093, 1028, 890, 770, 703, 531 cm^{-1}; ^1H NMR: δ 7.34–7.22 (m, 5H), 4.15–4.08 (q, J=6.6 Hz, 1H), 1.4–1.38 (d, J=6.6 Hz, 3H); EIMS: 122.0 (M+H, calcd for $C_8H_{11}N$, 122.19).

4.1.2. 1-(4′-Methoxyphenyl)ethylamine[21b] (2). Yield 91%; IR: 2998, 2934, 2834, 1611, 1511, 1463, 1246, 1175, 1034, 822, 517 cm^{-1}; ^1H NMR: δ 7.28–7.25 (m, 2H), 6.87–6.85 (m, 2H), 4.10–4.06 (q, J=6.6 Hz, 1H), 3.8 (s, 3H), 1.37–1.36 (d, J=6.5 Hz, 3H).

4.1.3. 1-(4′-Fluorophenyl)ethylamine[21c] (3). Yield 65%; IR: 3370, 2971, 1604, 1510, 1456, 1375, 1224, 1159, 1014, 836, 544 cm^{-1}; ^1H NMR: δ 7.32–7.26 (m, 2H), 7.02–6.97 (m, 2H), 4.13–4.08 (q, J=6.6 Hz, 1H), 1.37–1.35 (d, J=6.6 Hz, 3H); EIMS:140.0 (M+H, calcd for $C_8H_{10}FN$, 140.18).

4.1.4. 1-(4′-Trifluoromethylphenyl)ethylamine[21d] (4). Yield 83%; ^1H NMR: δ 7.59–7.57 (d, J=8.2 Hz, 2H), 7.48–7.46 (d, J=8.2 Hz, 2H), 4.21–4.17 (q, J=6.6 Hz, 1H), 1.40–1.38 (d, J=6.6 Hz, 3H).

4.1.5. 1-(4′-Trifluoromethoxyphenyl)ethylamine[21e] (5). Yield 83%; ^1H NMR: δ 7.38–7.36 (d, J=8.6 Hz, 2H), 7.18–7.16 (d, J=8.4 Hz, 2H), 4.17–4.12 (q, J=6.6 Hz, 1H), 1.38–1.36 (d, J=6.6 Hz, 3H).

4.1.6. 1-Phenylpropylamine[21f] (6). Yield 89%; oil; IR: 3361, 3028, 2964, 1628, 1577, 1454, 1376, 906, 701, 545 cm^{-1}; ^1H NMR: δ 7.35–7.22 (m, 5H), 3.82–3.78 (t, J=6.8 Hz, 1H), 1.74–1.68 (m, 2H), 0.89–0.85 (t, J=7.4 Hz, 3H); EIMS: 136.0 (M+H, calcd for $C_9H_{13}N$, 136.21).

4.1.7. 1-Methyl-3-phenylpropylamine[21g] (7). Yield 88%; IR: 2961, 1647, 1495, 1455, 1378, 1065, 764, 699, 594 cm^{-1}; ^1H NMR: δ 7.3–7.16 (m, 5H), 2.97–2.9 (m, 1H), 2.8–2.5 (m, 2H), 1.7–1.64 (m, 2H), 1.13–1.12 (d, J=6.4 Hz, 3H); EIMS: 150.3 (M+H, calcd for $C_{10}H_{15}N$, 150.24).

4.1.8. 1-Methyl-3-phenylallylamine[21h] (8). Yield 89%; IR: 3026, 2970, 1638, 1559, 1493, 1450, 1374, 1072, 968, 749, 694 cm^{-1}; ^1H NMR: δ 7.38–7.21 (m, 5H), 6.48–6.44 (d, J=16 Hz, 1H), 6.23–6.18 (dd, J=6.6, 16 Hz, 1H), 3.68–3.65 (m, 1H), 1.26–1.25 (d, J=6.5 Hz, 3H).

4.1.9. 2-(2′,4′-Dimethoxyphenyl)-1-methylethylamine[21i] (9). Yield 87%; IR: 3358, 2960, 2837, 1612, 1508, 1464, 1288, 1261, 1157, 1036, 923, 833, 635 cm^{-1}; ^1H NMR: δ 7.02–7.0 (d, J=8 Hz, 1H), 6.45–6.4 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.17–3.08 (m, 1H), 2.68–2.63 (dd, J=5.4, 7.9 Hz, 1H), 2.47–2.42 (dd, J=5.3, 7.8 Hz, 1H), 1.09–1.07 (d, J=6 Hz, 3H); EIMS: 196.2 (M+H, calcd for $C_{11}H_{17}NO_2$, 196.26).

4.1.10. 2-(4′-Fluorophenyl)-1-methylethylamine[21j] (10). Yield 78%; IR: 3359, 2966, 1602, 1509, 1457, 1376, 1222, 1158, 811, 765, 551, 503 cm^{-1}; ^1H NMR: δ 7.14–7.11 (m, 2H), 6.99–6.95 (m, 2H), 3.15–3.1 (m, 1H), 2.68–2.63 (dd, J=5.4, 8 Hz, 1H), 2.51–2.46 (dd, J=8, 5.4 Hz, 1H), 1.1–1.09 (d, J=6.3 Hz, 3H); EIMS: 154.1 (M+H, calcd for $C_9H_{12}NF$, 154.2).

4.1.11. Diphenylmethylamine[21k] (11). Yield 78%; IR: 3369, 3060, 3026, 1600, 1492, 1452, 1277, 1190, 1027, 903, 742, 699, 552 cm^{-1}; ^1H NMR: δ 7.42–7.22 (m, 10H), 5.23 (s, 1H).

4.1.12. *N*-Benzoyl-4-aminopiperidine[21l] (12). Yield 96%; IR: 3349, 2935, 1616, 1448, 1281, 1029, 789, 711,

636 cm^{-1}; ^1H NMR: δ 7.54–7.48 (m, 5H), 4.6 (br s, 1H), 3.74 (br s, 1H), 3.11–3.04 (m, 3H), 2.14–1.92 (m, 4H), 1.62–1.21 (m, 2H); EIMS: 205.5 (M+H, calcd for $C_{12}H_{16}N_2O$, 205.27).

4.1.13. 4-Aminopiperidine-1-carboxylic acid ethyl ester (13). Yield 93%; IR: 3352, 2934, 1689, 1594, 1436, 1385, 1235, 1173, 1100, 1031, 769, 571 cm^{-1}; ^1H NMR: δ 4.12–4.06 (m, 4H), 2.83–2.77 (m, 3H), 1.78–1.75 (m, 2H), 1.24–1.17 (m, 5H); EIMS: 173.1 (M+H, calcd for $C_8H_{16}N_2O_2$, 173.23).

4.1.14. 4-Aminopiperidine-1-carboxylic acid *tert* butyl ester (14). Yield 88%; ^1H NMR: δ 4.05 (br s, 2H), 2.85–2.70 (m, 3H), 1.8–1.7 (m, 4H), 1.43 (s, 9H), 1.3–1.2 (m, 2H); EIMS: 201.4 (M+H, calcd for $C_{10}H_{20}N_2O_2$, 201.15).

4.1.15. 4-Aminocyclohexanone ethylene ketal (15). Yield 91%; ^1H NMR: δ 3.95 (s, 4H), 2.91–2.75 (m, 1H), 2.07 (br s, 2H), 1.89–1.74 (m, 4H), 1.63–1.45 (m, 4H); EIMS: 158.3 (M+H, calcd for $C_8H_{15}NO_2$, 158.11).

4.1.16. Cyclohexylphenylmethylamine[21m] (16). Yield 72%; ^1H NMR: δ 7.35–7.3 (m, 5H), 3.87–3.85 (d, J=8 Hz, 1H), 2.02–1.99 (d, J=12 Hz, 1H), 1.91 (broad, 1H), 1.77–1.73 (d, J=12 Hz, 1H), 1.6–0.85 (m, 10H); EIMS: 190.2 (M+H, calcd for $C_{13}H_{19}N$, 190.3).

4.1.17. Cyclopentylamine[21n] (17). Yield 90%; IR: 3359, 2927, 2853, 2672, 1646, 1595, 1450, 1374, 1106, 1048, 955, 886, 708 cm^{-1}; ^1H NMR: δ 2.59 (m, 1H), 1.81–1.77 (m, 4H), 1.7–1.55 (m, 4H); EIMS: 86.0 (M+H, calcd for $C_5H_{11}N$, 86.21).

4.1.18. Cycloheptylamine[21o] (18). Yield 88%; IR: 2925, 2855, 1560, 1459, 1117, 1023, 961, 812, 653 cm^{-1}; ^1H NMR: δ 2.93–2.88 (m, 1H). 1.6–1.33 (m, 12H); EIMS: 114.0 (M+H, calcd for $C_7H_{15}N$, 114.21.

4.1.19. Adamantan-2-ylamine[21p] (19). Yield 93%; ^1H NMR: δ 2.99 (s, 1H), 1.99–1.96 (d, J=13 Hz, 2H), 1.86–1.79 (m, 4H), 1.74–1.7 (m, 8H), 1.54–1.51 (d, J=7.8 Hz, 2H); EIMS: 152.3 (M+H, calcd for $C_{10}H_{17}N$, 152.25).

4.1.20. 3-Amino-2,4-dimethylpentane[21q] (20). Yield 85%; IR: 2938, 2875, 1647, 1541, 1457, 1061, 617 cm^{-1}; ^1H NMR: δ 2.42 (broad, 1H), 1.7–1.66 (m, 2H), 0.98–0.94 (d, J=6 Hz, 12H); EIMS: 116.0 (M+H, calcd for $C_7H_{17}N$, 116.22).

4.2. General procedure for the synthesis of symmetrical secondary amines from aldehydes

A slurry of the aldehyde (10 mmol), titanium(IV) isopropoxide (6.0 mL, 20 mmol), ammonium chloride (1.1 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol) in absolute ethanol (20 mL) was stirred under argon in a capped flask at ambient temperature for 6 h. Sodium borohydride (0.6 g, 15 mmol) was then added and the resulting mixture was stirred at room temperature for an additional 3 h. The reaction was then quenched by pouring into ammonium hydroxide (2 M, 25 mL), the resulting inorganic precipitate was filtered off, and washed with ethyl acetate (25 mL×2). The organic layer was separated and the remaining aqueous layer was extracted with ethyl acetate (25 mL×2). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and purified over silica gel by flash chromatography using hexanes/ethyl acetate to afford the corresponding symmetrical secondary amines.

The data below correspond to the entries in Table 2.

4.2.1. Dibenzylamine[22a] (21). Yield 76%; IR: 3339, 3062, 2815, 1603, 1495, 1453, 1198, 1027, 734, 697 cm^{-1}; ^1H NMR: δ 7.36–7.26 (m, 10H), 3.83 (s, 4H); EIMS: 198.2 (M+H, calcd for $C_{14}H_{15}N$, 198.2).

4.2.2. Bis-(2-methylbenzyl)amine[22b] (22). Yield 70%; IR: 3328, 3018, 2819, 1604, 1492, 1460, 1377, 1182, 1092, 743 cm^{-1}; ^1H NMR: δ 7.36–7.35 (m, 2H), 7.21–7.18 (m, 6H), 3.85 (s, 4H), 2.36 (s, 6H); EIMS: 226.3 (M+H, calcd for $C_{16}H_{19}N$, 226.34).

4.2.3. Bis-(3-methylbenzyl)amine[22c] (23). Yield 71%; IR: 3324, 3023, 2820, 1608, 1487, 1453, 1357, 1158, 1090, 839, 778, 696 cm^{-1}; ^1H NMR: δ 7.26–7.07 (m, 8H), 3.80 (s, 4H), 2.36 (s, 6H); EIMS: 226.3 (M+H, calcd for $C_{16}H_{19}N$, 226.34).

4.2.4. Bis-(4-methylbenzyl)amine[22d] (24). Yield 78%; IR: 3390, 2919, 2793, 1637, 1456, 1396, 1261, 1092, 1021, 801 cm^{-1}; ^1H NMR: δ 7.26–7.22 (m, 4H), 7.16–7.14 (m, 4H), 3.78 (s, 4H), 2.35 (s, 6H); EIMS: 226.3 (M+H, calcd for $C_{16}H_{19}N$, 226.34).

4.2.5. Bis-(4-methoxybenzyl)amine[22e] (25). Yield 50%; IR: 2999, 2834, 1612, 1511, 1463, 1301, 1246, 1035, 822, 560 cm^{-1}; ^1H NMR: δ 7.26–7.24 (d, J=8.3 Hz, 4H), 6.88–6.86 (d, J=8.6 Hz, 4H), 3.8 (s, 6H), 3.73 (s, 4H); EIMS: 258.3 (M+H, calcd for $C_{16}H_{19}NO_2$, 258.34).

4.2.6. Bis-(4-fluorobenzyl)amine[22f] (26). Yield 75%; IR: 3328, 3041, 2826, 1603, 1509, 1452, 1221, 1155, 1093, 825, 501 cm^{-1}; ^1H NMR: δ 7.32–7.26 (m, 4H), 7.04–6.99 (m, 4H), 3.76 (s, 4H); EIMS: 234.2 (M+H, calcd for $C_{14}H_{13}NF_2$, 234.26).

4.2.7. Bis-(4-trifluoromethylbenzyl)amine[22f] (27). Yield 70%; IR: 2989, 1636, 1325, 1160, 1107, 1068, 664 cm^{-1}; ^1H NMR: δ 7.39–7.35 (m, 4H), 7.2–7.17 (m, 4H), 3.3 (s, 4H); EIMS: 334.1 (M+H, calcd for $C_{16}H_{13}NF_6$, 334.28).

4.2.8. Bis-(4-*N*,*N*-dimethylaminobenzyl)amine (28). Yield 62%; IR: 3328, 2996, 2800, 1615, 1522, 1444, 1345, 1224, 1186, 1163, 947, 806 cm^{-1}; ^1H NMR: δ 7.22–7.20 (d, J=8.5 Hz, 4H), 6.74–6.72 (d, J=8.5 Hz, 4H), 3.71 (s, 4H), 2.94 (s, 12H); EIMS: 284.2 (M+H, calcd for $C_{18}H_{25}N_3$, 284.42).

4.2.9. Bis-(benzo-1,3-dioxol-5-ylmethyl)amine[22g] (29). Yield 77%; ^1H NMR: δ 6.85 (s, 2H), 6.76 (s, 4H), 5.94 (s, 4H), 3.69 (s, 4H); EIMS: 286.4 (M+H, calcd for $C_{16}H_{15}NO_4$, 286.31).

4.2.10. Bis-(3-benzyloxybenzyl)amine (30). Yield 67%; ^1H NMR: δ 7.46–7.24 (m, 12H), 7.01–6.93 (m, 6H), 5.08 (s,

4H), 3.79 (s, 4H); EIMS: 410.6 (M+H, calcd for $C_{28}H_{27}NO_2$, 410.53).

4.2.11. Bis-(indol-3-ylmethyl)amine[22h] (31). Yield 65%; IR: 3409, 3054, 2794, 1556, 1456, 1421, 1338, 125, 1092, 1009, 741 cm^{-1}; ^1H NMR: δ 10.85 (s, 2H), 7.49–7.47 (d, J=8 Hz, 2H), 7.32–7.30 (d, J=8 Hz, 2H), 7.26 (s, 2H), 7.1–6.9 (m, 2H), 6.88–6.85 (m, 2H), 3.67 (s, 4H); EIMS: 276.3 (M+H, calcd for $C_{18}H_{17}N_3$, 276.35).

4.2.12. Bis-(2-phenylpropyl)amine[22i] (32). Yield 58%; IR: 3297, 3027, 2961, 1601, 1493, 1452, 1228, 1129, 761, 700 cm^{-1}; ^1H NMR: δ 7.35–7.09 (m, 10H), 2.9–2.86 (m, 2H), 2.82–2.67 (m, 4H), 1.2–1.18 (2d, J=4 Hz, 6H); EIMS: 254.3 (M+H, calcd for $C_{18}H_{23}N$, 254.39.

4.2.13. Bis-(3-phenylpropyl)amine[22i] (33). Yield 75%; ^1H NMR: δ 7.38–7.06 (m, 10H), 3.5 (t, 1H, J=6.0 Hz), 3.0–2.3 (m, 6H), 2.2–1.5 (m, 6H); EIMS: 254.5 (M+H, calcd for $C_{18}H_{23}N$, 254.39.

4.2.14. Bis-(cyclohexylmethyl)amine (34). Yield 68%; ^1H NMR: δ 2.43 (d, 4H, J=6.0 Hz), 1.85–1.62 (m, 11H), 1.55–1.4 (m, 4H), 1.35–1.1 (m, 8H); EIMS: 211.5 (M+H, calcd for $C_{14}H_{27}N$, 210.37.

References and notes

1. For some leading references, see: (a) Manchand, P. S.; Cerruti, R. L.; Martin, J. A.; Hill, C. H.; Merrett, J. H.; Keech, E.; Belshe, R. B.; Connell, E. V.; Sim, I. S. *J. Med. Chem.* **1990**, *33*, 1992. (b) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771. (c) Main, B. G.; Tucker, H. *Medicinal chemistry*; Genellin, C. R., Roberts, S. M., Eds.; Academic: New York, 1993; 2nd ed., p 187. (d) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (e) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (f) Bergeron, R. J.; Feng, Y.; Weimer, W. R.; McManis, J. S.; Dimova, H.; Porter, C.; Raisler, B.; Phansitiel, O. *J. Med. Chem.* **1997**, *40*, 1475. (g) Kuksa, V.; Buchan, R.; Lin, P. K. T. *Synthesis* **2000**, 1189. (h) Karigiannis, G.; Papaioannou, D. *Eur. J. Org. Chem.* **2000**, 1841. (i) Merla, B.; Risch, N. *Synthesis* **2002**, 1365.
2. (a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55. (b) Henkel, T.; Brunne, R. M.; Mueller, H.; Reichel, F. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 643.
3. For reviews on reductive aminations see: (a) Emerson, W. S. *Organic reactions*; Wiley: New York, 1948; Vol. 4. p 174. (b) Moore, M. L. *Organic reactions*; Wiley: New York, 1949; Vol. 5. p 301. (c) Lane, C. F. *Synthesis* **1975**, 135. (d) Hutchins, R. O.; Natale, N. *Org. Prep. Proced. Int.* **1979**, *11*, 201. (e) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317. (f) Hutchins, R. O.; Hutchins, M. K. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 25. (g) Baxter, E. W.; Reitz, A. B. *Organic reactions*; Wiley: New York, 2002; Vol. 59. p 1.
4. (a) Rylander, P. N. *Catalytic hydrogenation in organic synthesis*; Academic: New York, 1979; p 165. (b) Klyuev, M. V.; Khidekel, M. L. *Russ. Chem. Rev.* **1980**, *49*, 14. (c) Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev.* **1999**, *68*, 55. A modification of Leuckart's synthesis of primary amines from ketones using $HCOONH_4$ and Pd–C has been reported recently: (d) Allegretti, M.; Berdini, V.; Candida Cesra, M.; Curti, R.; Nicolini, L.; Topai, A. *Tetrahedron Lett.* **2001**, *42*, 4257. (e) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055, and references cited therein.
5. (a) Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (c) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.
6. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
7. (a) Pelter, A.; Rosser, R. M.; Mills, S. *J. Chem. Soc. Perkin Trans. 1* **1984**, 717. (b) Bomann, M. D.; Guch, I. C.; Dimare, M. *J. Org. Chem.* **1995**, *60*, 5995.
8. (a) Bhattacharyya, S.; Chatterjee, A.; Duttachowdhury, S. K. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1. (b) Ranu, B. C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 370.
9. See, for example: (a) Saxena, I.; Borah, R.; Sarma, J. C. *J. Chem. Soc. Perkin Trans. 1* **2000**, 503. (b) Bhattacharyya, S. *Synth. Commun.* **1997**, *27*, 4265.
10. (a) Han, Y.; Chorev, M. *J. Org. Chem.* **1999**, *64*, 1972. (b) Chandrasekhar, S.; Reddy, C. R.; Ahmed, M. *Synlett* **2000**, 1655. (c) Chen, B. C.; Sundeen, J. E.; Guo, P.; Bednarz, M. S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245. (d) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745.
11. See, for example: (a) Suwa, T.; Shibata, I.; Nishino, K.; Baba, A. *Org. Lett.* **1999**, *1*, 1579. (b) Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, 789.
12. Itoh, T.; Nagata, K.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, *43*, 3105.
13. (a) Smith, M. B.; March, J. *March's advanced organic chemistry*; Wiley: New York, 2001; p 1187 and references cited therein. (b) Also see, Ref. 3g, pp 28, 31.
14. (a) Soroka, M.; Zygmunt, J. *Synthesis* **1988**, 370. (b) Purchase, C. F.; Goel, O. P. *J. Org. Chem.* **1991**, *56*, 457. (c) Sharma, S. K.; Songster, M. F.; Colpitts, T. L.; Hegyes, P.; Barany, G.; Castellino, F. J. *J. Org. Chem.* **1993**, *58*, 4993. (d) Helion-Garro, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109. (e) Dube, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295. (f) Bernacka, E.; Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2001**, *42*, 5093. (g) Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590, and references therein.
15. For examples, see: (a) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401. (b) Bhattacharyya, S. *Synlett* **1994**, 1029. (c) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928. (d) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, 1079. (e) Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem Soc. Perkin Trans. 1* **1998**, 2527.
16. In addition to our efforts, a few other reductive amination protocols using $Ti(O^iPr)_4$ and borohydride-based reducing agents have been described: See, for example, Refs. 5c,6, and Breitenbucher, J. G.; Hui, H. C. *Tetrahedron Lett.* **1998**, *39*, 8207. Another modification using polymethylhydrosiloxane as the reducing agent (Ref. 10b) has appeared recently, although no references to prior work was cited.
17. A part of this work has been published in a preliminary communication: Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781.

18. There is ample precedence in the literature that the reductive alkylations of ammonia with aldehydes are typically devoid of any chemoselectivity and produce a mixture of amines. See, for example: (a) Abbadi, M.; Holman, G. D.; Morin, C.; Ress, W. D.; Yang, J. *Tetrahedron Lett.* **1999**, *40*, 5861. (b) Hoshino, H.; Sawaki, S.; Shimamura, N.; onodera, A.; Umezawa, B. *Chem. Pharm. Bull.* **1987**, *35*, 2734. (c) Baxter, E. W.; Reitz, A. B. *Organic reactions*; Wiley: New York, 2002; Vol. 59. p 1 and references cited therein.
19. See, for example: (a) Insaf, S. S.; Witiak, D. T. *Synthesis* **1999**, 435, and references therein. (b) Swamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. (c) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497. (d) Hoog, P. D.; Gamez, P.; Driessen, W. L.; Reedijk, J. *Tetrahedron Lett.* **2002**, *43*, 6783. (e) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vagner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441. (f) Bhattacharyya, S.; Fan, L.; Vo, L.; Labadie, *J. Comb. Chem. Highthroughput Screening* **2000**, *3*, 117. (g) Krueger, E. B.; Hopkins, T. P.; Keaney, M. T.; Walters, M. A.; Boldi, A. M. *J. Comb. Chem.* **2002**, *4*, 229.
20. (a) Seebach, D.; Schiess, M. *Helv. Chim. Acta* **1982**, *65*, 2598. (b) Imwinkelried, R.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1496.
21. (a) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1986**, *51*, 5338. (b) Ayres, D. C. *J. Chem. Soc. Perkin Trans. 1* **1978**, 585. (c) Lyle, R. E.; Troscianiec, H. J. *J. Org. Chem.* **1955**, *20*, 1757. (d) Arai, S.; Laponnaz, B. S.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 234. (e) Obata, T.; Fujii, K.; Tsutsumiuchi, K.; Nakamoto, Y. Eur. Pat. Appl. EP 543402 A1 19930526, 1993. (f) Ortiz-Marciales, M.; Tirado, L. M.; Colon, R.; Ufret, M. L.; Figueroa, R.; Lebron, M.; DeJesus, M.; Martinez, J.; Malave, T. *Synth. Commun.* **1998**, *28*, 4067. (g) Seljestokken, B.; Fiksdahl, A. *Acta Chem. Scand.* **1993**, *47*, 1050. (h) Baruah, B.; Dutta, M. P.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Synlett* **1999**, 409. (i) Sy, W. W. *Tetrahedron Lett.* **1993**, *34*, 6223. (j) Plenevaux, A.; Dewey, S. L.; Fowler, J. S.; Guillaume, M.; Wolf, A. P. *J. Med. Chem.* **1990**, *33*, 2015. (k) Smith, H. E.; Willis, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 2282. (l) Obase, H.; Takai, H.; Teranishi, M.; Nakamizo, N. *J. Heterocycl. Chem.* **1983**, *20*, 565. (m) Johansson, A.; Lindstedt, E. L.; Olsson, T. *Acta Chem. Scand.* **1997**, *51*, 351. (n) Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *Synthesis* **1993**, 783. (o) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272. (p) Malik, A. A.; Preston, S. B.; Archibald, T. G.; Cohen, M. P.; Baum, K. *Synthesis* **1989**, 450. (q) Schwoegler, E. J.; Adkins, H. *J. Am. Chem. Soc.* **1939**, *61*, 3499.
22. (a) Bhattacharyya, S. *Synth. Commun.* **1995**, *25*, 2061. (b) Juday, R. E.; Adkins, H. *J. Am. Chem. Soc.* **1955**, *77*, 4559. (c) Rupe, H.; Bernstein, F. *Helv. Chim. Acta* **1930**, *13*, 457. (d) Okamoto, Y.; Kinoshita, T. *Chem. Pharm. Bull.* **1981**, *29*, 1165. (e) Aoyagi, Y.; Asakura, R.; Kondoh, N.; Yamamoto, R.; Kuromatsu, T.; Shimura, A.; Ohta, A. *Synthesis* **1996**, 970. (f) Sakai, T.; Takami, A.; Suzuki, R. PCT Int. Appl. WO 9801417 A1 19980115, 1998. (g) Donetti, A.; Bellora, E. *J. Org. Chem.* **1972**, *37*, 3352. (h) Yamada, F.; Kobayashi, K.; Shimizu, A.; Aoki, N.; Somei, M. *Heterocycles* **1993**, *36*, 2783. (i) Katritzky, A. R.; Zhao, X.; Hitchings, G. J. *Synthesis* **1991**, 703.

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A convenient route to 1-(2-oxiranyl)-1,4-diketones and their application to the synthesis of *endo*-brevicomin, *endo*-isobrevicomin, frontalin and related compounds via alkylated 6,8-dioxabicyclo[3.2.1]octan-2-ones

Vladimir I. Tyvorskii,* Dmitry A. Astashko and Oleg G. Kulinkovich

Department of Organic Chemistry, Belarusian State University, Fr. Scorina Avenue, 4, 220050 Minsk, Belarus

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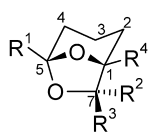
Abstract—1-(2-Oxiranyl)-1,4-alkanediones were prepared from the ethylene acetals of ethyl 4-oxoalkanoates via the oxidation of the intermediate 1,2-dialkylcyclopropanols having a protected carbonyl group in an aliphatic chain. Intramolecular acetalization of these epoxy dicarbonyl compounds gave alkylated 6,8-dioxabicyclo[3.2.1]octan-2-ones in good yields. The latter were found suitable to be precursors for (±)-*endo*-brevicomin and its 2-hydroxy derivative, as well as (±)-*endo*-isobrevicomin and (±)-frontalin.

1. Introduction

Alkylated 6,8-dioxabicyclo[3.2.1]octanes play an important role in systems of chemical communication among many bark beetles, which infect pine trees.[1] Brevicomin is a typical pheromone component of *Dendroctonus* and *Dryocoetes* pine beetles, and it is frequently produced by these insects as a mixture of *exo*- and *endo*-diastereomers at C-7 (**1a** and **1b**, Fig. 1), with a large excess of the (+)-*exo*-brevicomin **1a**.[1,2] In contrast to the latter, the enantiomeric excess in the accompanying *endo*-brevicomin **1b** is rarely greater than 70%.[1,2c–e] Both the *exo*- and *endo*-isomers of isobrevicomin (**1c** and **1d**, respectively) were isolated in 1996 by Francke and co-workers[3] as the minor components of the volatiles, obtained from male mountain pine bark beetles, *Dendroctonus ponderosae*. Frontalin **1e** is the aggregation pheromone of southern pine bark beetle, *Dendroctonus frontalis*.[4]



1a R^1 = Me, R^2 = R^4 = H, R^3 = Et (*exo*-brevicomin);
1b R^1 = Me, R^2 = Et, R^3 = R^4 = H (*endo*-brevicomin);
1c R^1 = Et, R^2 = R^4 = H, R^3 = Me (*exo*-isobrevicomin);
1d R^1 = Et, R^2 = Me, R^3 = R^4 = H (*endo*-isobrevicomin);
1e R^1 = R^4 = Me, R^2 = R^3 = H (frontalin)

Figure 1.

Compounds **1a**–**e** all have been the target of numerous syntheses in both racemic and enantiomerically pure form.[1,5,6] The general strategy of these syntheses is the generation of an appropriate 5,6-epoxyketones or corresponding dihydroxyketone, followed by intramolecular acetalization.[1,3,7] Using the deuterated and ^{18}O-labeled *(Z)*-6-nonen-2-one, Vanderwel and Oehlschlager found that this unsaturated ketone serves as a precursor of (+)-*exo*-brevicomin **1a** in the bark beetles *D. ponderosae* Hopkins and that the pheromone biosynthesis proceeds through a *cis*-epoxyketone intermediate, without its conversion to a diol prior to the cyclization stage.[8] For the formation of *endo*-isomers **1b** and **1d**, the corresponding *trans*-epoxides are required.[1,7a] For example, racemic *endo*-isobrevicomin **1d** has been synthesized from the epoxide of *(E)*-7-nonen-3-one.[3]

Recently, we have reported a flexible and convenient method for the preparation of aliphatic α,β-epoxyketones based on a manganese-catalyzed ring cleavage of 1-substituted and 1,2-disubstituted cyclopropanols with gaseous oxygen followed by transformation of the hydroperoxyketone intermediates into the target products, under the action of potassium hydroxide.[9] The simplicity of this one-pot procedure, coupled with facile availability of the corresponding cyclopropanols,[10,11] makes it attractive for the synthesis of epoxyketones bearing an additional functional group in the aliphatic chain. In the present

Keywords: Cyclopropanols; Oxidation; Oxiranes; 1,4-Dicarbonyl compounds; Pheromones.
* Corresponding author. Tel.: +375-17-2095459; fax: +375-17-2265609; e-mail address: tyvorskii@bsu.by

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work, we wish to describe the application of this methodology to the preparation of 1-(2-oxiranyl)-1,4-diketones **6**, which are then employed in the synthesis of 6,8-dioxabicyclo[3.2.1]octane derivatives, including (±)-*endo*-brevicomin **1b**, (±)-*endo*-isobrevicomin **1d**, (±)-frontalin **1e** and the related hydroxy compounds **8a**, **9a**.

2. Results and discussion

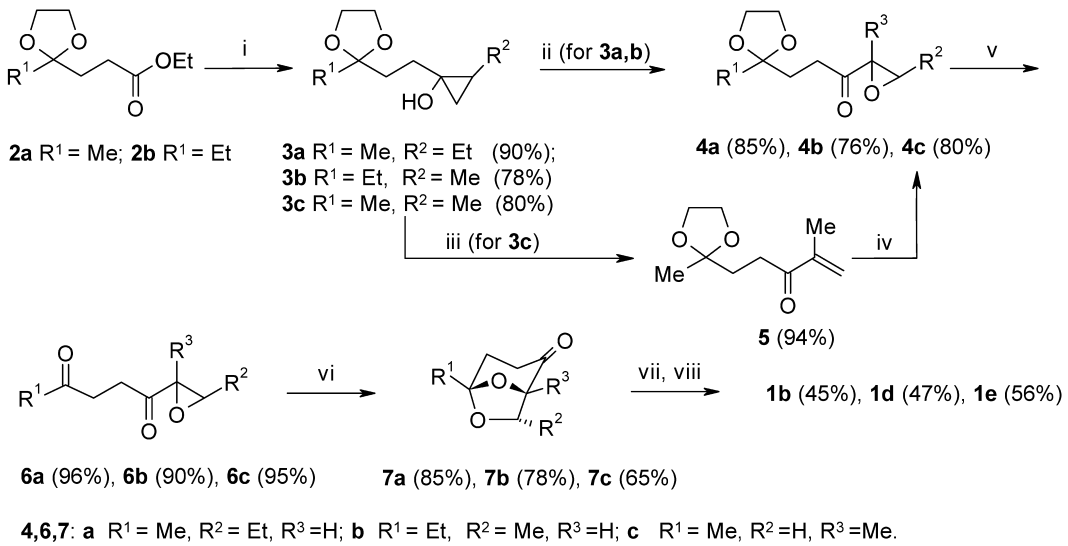
Epoxyketones **4a**,**b**, with an additional protected carbonyl group, have been obtained in two preparative steps in an overall yield of 60–76%, starting from ethylene acetals of ethyl 4-oxoalkanoates **2a**,**b**, via the cyclopropanols **3a**,**b**, as a key intermediates (Scheme 1). The latter were prepared by cyclopropanation of esters **2a**,**b** with butylmagnesium bromide and propylmagnesium bromide, respectively, in the presence of Ti(IV) isopropoxide.[10] This reaction proceeded with high diastereoselectivity (de>94% by ^{1}H NMR spectroscopy). The relative stereochemistry of 1,2-disubstituted cyclopropanols **3a**,**b** was assigned to be *cis* on the basis of literature data.[11] The Mn(II) abietate catalyzed oxidative cleavage of compounds **3a**,**b** with molecular oxygen, followed by treatment of the reaction mixture with aqueous potassium hydroxide, led to the expected products **4a**,**b**, wich exhibit a *trans*-configuration of the oxirane ring.[9]

The synthesis of compound **4c** started with the cyclopropanol **3c**, prepared from the protected ethyl levulinate **2a** and propylmagnesium bromide. Compound **3c** was subjected to the reaction with the bromine–pyridine complex, followed by dehydrobromination of resulting β-bromoketone.[12] The corresponding α,β-unsaturated ketone thus formed was epoxidized without isolation by the action of alkaline hydrogen peroxide[13] to give **4c** in 60% overall yield from **2a** (Scheme 1; steps i, iii, iv).

Attempted transacetalization of compound **4a** into the desired 6,8dioxabicyclo[3.2.1]octan-2-one **7a**, by treatment with 10% aq. H_2SO_4 in diethyl ether, resulted in the formation of a ca. 1:1 mixture of two products, an expected cyclic ketone **7a** and epoxy diketone **6a**. Furthermore, it was proven that no transformation **6a**→**7a** took place during this catalytic process. Therefore, for the preparation of compounds **7a**–**c**, the two-step procedure including deprotection of ketals **4a**–**c** with diluted H_2SO_4 on SiO_2 followed by cyclization of obtained 1-(2-oxiranyl)-1,4-diketones **6a**–**c** under the action of boron trifluoride etherate was found to be more effective (Scheme 1, steps v–vi, 62–82% overall yield of **7a**–**c** from **4a**–**c**). The intramolecular reaction of the *trans*-oxirane moiety with the remote carbonyl group in precursors **6a**,**b** proceeded with high stereoselectivity, the bicyclic *endo*-acetals **7a**,**b** being the single isolated products. The relative configuration of compounds **7a**,**b** was confirmed by comparison of their spectral data with that reported for **7a** and its *exo*-isomer,[14] as well as by subsequent synthetic transformations.

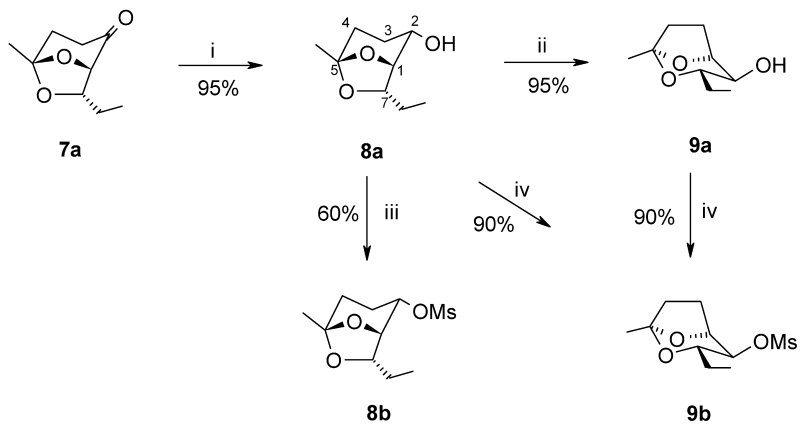
Bicyclic ketones **7a**–**c** have been converted to the racemic *endo*-brevicomin **1b**, *endo*-isobrevicomin **1d**, and frontalin **1e**, respectively, by a conventional deoxygenation method, which was earlier described for the preparation of compounds (±)-**1b**[14] and (+)-**1e**.[15] Each particular ketone **7** was treated with ethanedithiol in the presence of $BF_3{\cdot}OEt_2$ and the resulting cyclic dithioketals were reduced with Raney nickel to furnish the target pheromones. Several other methods known to effect the deoxygenation of ketones or secondary alcohols were tried, but the Wolff–Kishner reaction of ketone **7a**, the reduction of its tosylhydrazone as well as the reduction of mesylate or xanthogenate of alcohol **8a**, failed to give only a trace amount of the desired product.

Compounds **7a**–**c** are potentially suitable starting materials for the synthesis of 2-hydroxylated 6,8-dioxabicyclo[3.2.1]octanes, especially because several isomeric hydroxybrevicomins have been produced by male mountain pine beetles, *D. ponderosae*.[1,3] As anticipated, the reduction of ketone **7a** in an etheral solution, with a slight excess of lithium aluminum hydride, followed by careful addition of



4,6,7: **a** R^1 = Me, R^2 = Et, R^3 =H; **b** R^1 = Et, R^2 = Me, R^3 =H; **c** R^1 = Me, R^2 =H, R^3 =Me.

Scheme 1. *Reagents*: (i) 4 equiv. $R^2CH_2CH_2MgBr$, 20 mol% Ti(O*i*-Pr)$_4$, Et_2O/THF (2:3); (ii) O_2, 1 mol% Mn(II) abietate, PhH, then KOH, H_2O; (iii) Br_2/Py. Et_2O, then Al_2O_3, *n*-C_5H_{12}; (iv) H_2O_2, *i*-PrOH, NaOH; (v) 15% aq. H_2SO_4/SiO_2, CH_2Cl_2; (vi) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (vii) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (viii) Ni(Ra), EtOH.



Scheme 2. *Reagents*: (i) 0.75 equiv. $LiAlH_4$, Et_2O; then 5% HCl; (ii) *p*-TsOH, benzene; (iii) NaH, THF; then MsCl; (iv) MsCl, Et_3N, Et_2O.

diluted hydrochloric acid (to pH=7–8), afforded the new 2-hydroxy-*endo*-brevicomin **8a** in almost quantitative yield and with a de>95% (Scheme 2). Similarly, reduction of **7a** with (*t*-BuO)$_3$LiAlH or with sodium metal in isopropyl alcohol gave the same compound **8a**, containing an equatorial OH group. The formation of **8a** is probably due to steric hindrance imposed by the *endo*-arranged 7-Et group for equatorial attack on the ketone **7a** with the reducing reagent.

Remarkably, the single compound **9a**, containing 2,8-dioxabicyclo[3.2.1]octane sceleton, was isolated in 95% yield by the reduction of ketone **7a** with $LiAlH_4$ followed by quenching with an excess of aqueous HCl. Compound **9a** was earlier identified by Francke's group[3] as a minor volatile component from *D. ponderosae* males. The reduction of ketone **7a** with $NaBH_4$ in methanol resulted in the formation of a mixture of isomers **8a** and **9a** in the ratio of 1:1. We found, that 2-hydroxy-*endo*-brevicomin **8a** is extremely sensitive to acids, including Lewis acids. Thus, compound **8a** rearranges completely after ca. 3 h to its isomer **9a** in a benzene solution, in the presence of a trace amount of *p*-TsOH at room temperature. This is consistent with the observations of Francke,[3] who was first to suggest that the lability of compound **8a** is a possible explanation of its lack among three other natural diastereomeric 2-hydroxylated brevicomins in *D. ponderosae*. The synthesis of compound **8a** involving an acid-catalyzed ring-closing stage was undertaken by Barbas III, Lerner and co-workers,[16] however, the presented spectral data clearly demonstrate that the product **9a** was isolated instead of the desired and mistakenly reported compound **8a**.

The structure of compound **8a** was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectroscopy, however more evident data on the relative stereochemistry of **8a** have been corroborated by spectral characteristics of its mesylate **8b**. Surprisingly, the reaction of **8a** with mesyl chloride in the presence of Et_3N under standard conditions afforded mesylate **9b** of isomeric alcohol **9a**. This may be due to the rearrangement of starting **8a** or its mesylate **8b** under the action of nascent HCl (or $Et_3NH^+Cl^-$). The mesylate **8b** was prepared by standard treatment of **8a** with NaH and reaction of the subsequent sodium alkoxide with MsCl.

The distinctive characteristic of the ^{1}H NMR spectrum of mesylate **8b** is the large coupling constant of 10.9 Hz between the axial protons at C-3 and at C-2, thus indicating the equatorial position of the OH group in precursor compound **8a**. Additionally, the coupling constant of 3.9 Hz between protons at C-1 and C-7 is in a good agreement with the reported data for related *endo*-bicyclic acetals, as this value differs appreciably from $J_{1,7}<1$ Hz observed for known *exo*-isomers of **8a**.[3]

In conclusion, we have developed effective methods for the preparation of 1-(2-oxiranyl)-1,4-diketones which were easily converted into alkylated 6,8-dioxabicyclo[3.2.1]-octan-2-ones. The latter are versatile precusors of various pheromone components, including racemic *endo*-brevicomin, *endo*-isobrevicomin and frontalin, as well as the unknown 2-hydroxylated *endo*-brevicomin.

3. Experimental

IR spectra were measured on a Specord 75 IR or FT-IR Perkin–Elmer 1000 spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz (Bruker Avance 400) with $CDCl_3$ or C_6D_6 as a solvent. ^{13}C NMR spectra were recorded with a Bruker Avance 400 at 100.6 MHz with $CDCl_3$ or C_6D_6 as a solvent. Mass spectra were obtained on a Shimadzu QP-5000 GC/MS spectrometer. Melting points were determined in open capillaries and are uncorrected. Preparative column chromatography was carried out on silica gel (Merck; 70–230 mesh). All chemicals were reagent grade; solvents were dried and distilled prior to use.

Ethyl 3-(2-ethyl-1,3-dioxolan-2-yl)propanoate **2b** was prepared by standard acetalization procedure from ethyl 4-oxohexanoate.[17,18]

3.1. 2-Alkyl-1-[2-(2-alkyl-1,3-dioxolan-2-yl)ethyl]-1-cyclopropanols (3a–c). General procedure

A solution of propyl- or butylmagnesium bromide (35 mmol) in a mixture of THF (8 mL) and diethyl ether (10 mL) was slowly added to a stirred solution of 10 mmol of corresponding ethyl 3-(2-alkyl-1,3-dioxolan-2-yl)-propanoate **2a**,**b** and Ti(O*i*-Pr)$_4$ (0.6 mL, 2 mmol) in THF (12 mL) at room temperature. The mixture was stirred for 2 h, treated with saturated solution of ammonium chloride,

filtered and extracted with ether (3×20 mL). Etheral extracts were washed with brine and dried (Na_2SO_4). The products were isolated by distillation under reduced pressure.

3.1.1. 2-Ethyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-cyclopropanol (3a). Yield: 1.8 g (90%); colourless liquid; bp 93–95 °C/1 Torr. IR (CCl_4): ν 3440, 3066, 2907, 2840, 1440, 1373, 1200, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.03 (t, J=5.2 Hz, 1H); 0.73 (dd, J=9.6, 5.2 Hz, 1H); 0.82–0.92 (m, 1H); 0.93 (t, J=7.2 Hz, 3H); 0.99–1.12 (m, 1H); 1.32 (s, 3H); 1.33–1.45 (m, 1H); 1.52–1.62 (m, 1H); 1.64–1.76 (m, 1H); 1.89 (t, J=7.4 Hz, 2H); 3.45 (br. s, 1H); 3.88–3.96 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.9, 19.1, 22.7, 23.5, 27.6, 28.3, 35.6, 58.6, 64.42, 64.45, 110.1. Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.77; H, 9.87.

3.1.2. 1-[2-(2-Ethyl-1,3-dioxolan-2-yl)ethyl]-2-methyl-1-cyclopropanol (3b). Yield: 1.56 g (78%); colourless liquid; bp 107–109 °C/3 Torr. IR (CCl_4): ν 3451, 3076, 2912, 2853, 1438, 1363, 1219, 1048 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.04–0.02 (m, 1H); 0.75–0.82 (m, 1H); 0.85–0.94 (m, 4H); 1.01 (s, 3H); 1.60–1.70 (m, 4H); 1.85–1.91 (m, 2H); 2.93 (br. s, 1H) 3.9–3.98 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 8.0, 14.1, 19.6, 20.6, 28.0, 29.6, 33.0, 58.5, 64.8, 64.9, 112.1. Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.11; H, 9.89.

3.1.3. 2-Methyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-cyclopropanol (3c). Yield: 1.48 g (80%); colourless liquid; bp 92–93 °C/2 Torr. IR (CCl_4): ν 3467, 3053, 2947, 2893, 1467, 1387, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.05–0 (m, 1H); 0.74–0.8 (m, 1H); 0.88 (dd, J=6.8, 2.0 Hz, 1H); 0.99 (d, J=1.6 Hz, 3H); 1.33 (s, 3H); 1.61–1.67 (m, 2H); 1.87–1.93 (m, 2H); 2.92 (br. s, 1H); 3.93–3.97 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.1, 19.5, 20.5, 23.6, 28.2, 35.6, 58.4, 64.4, 64.5, 110.1. Anal. calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.56; H, 9.57.

3.2. *trans*-3-(2-Alkyl-1,3-dioxolan-2-yl)-1-(3-alkyl-2-oxiranyl)-1-propanones (4a,b). General procedure

A solution of corresponding cyclopropanol **3a**,**c** (10 mmol) and Mn(II) abietate (0.1 g, 1 mol%) in dry benzene (60 mL) was stirred under oxygen atmosphere at room temperature for 3–5 h. Then aq KOH (0.5 M, 5 mL) was added and the mixture was vigorously stirred at room temperature for 1–2 h. After filtration, the organic layer was separated and the aqueous solution was extracted with benzene (3×5 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed and the crude epoxides **3a**–**g** were purified by distillation under reduced pressure.

3.2.1. *trans*-1-(3-Ethyl-2-oxiranyl)-3-(2-methyl-1,3-dioxolan-2-yl)-1-propanone (4a). Yield: 1.82 g (85%); colourless liquid; bp 93–95 °C/1 Torr. IR (film): ν 2977, 2881, 1711, 1436, 1378, 1223, 1131, 1053, 949, 920, 858 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J=7.6 Hz, 3H); 1.28 (s, 3H); 1.57–1.71 (m, 2H); 1.89–2.03 (m, 2H); 2.33 (ddd, J=17.4, 8.2, 6.4 Hz, 1H); 2.50 (ddd, J=17.4, 8.3, 6.4 Hz, 1H); 3.03 (td, J=5.3, 1.6 Hz, 1H); 3.21 (d, J=1.6 Hz, 1H); 3.85–3.94 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.4, 23.8, 24.8, 31.6, 32.3, 59.3, 64.55, 64.61, 109.0, 128.2, 207.1. Anal. calcd for $C_{10}H_{18}O_3$: C, 61.66; H, 8.47. Found: C, 61.84; H, 8.29.

3.2.2. *trans*-3-(2-Ethyl-1,3-dioxolan-2-yl)-1-(3-methyl-2-oxiranyl)-1-propanone (4b). Yield: 1.63 g (76%); colourless liquid; bp 115–117 °C/4 Torr. IR (film): ν 2970, 2883, 1714, 1464, 1422, 1306, 1204, 1141, 1067, 950, 897, 842, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J=7.6 Hz, 3H); 1.36 (d, J=4.8 Hz, 3H); 1.57 (q, J=7.6 Hz, 2H); 1.84–1.98 (m, 2H); 2.28 (ddd, J=17.6, 8.4, 6.4 Hz, 1H); 2.45 (ddd, J=17.6, 8.2, 6.8 Hz, 1H); 3.1 (qd, J=4.8, 1.6 Hz, 1H); 3.15 (d, J=1.6 Hz, 1H); 3.88 (s, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 7.9, 17.4, 29.8, 29.9, 31.6, 54.1, 60.5, 64.8, 64.9, 111.0, 207.1. Anal. calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.68; H, 8.41.

3.2.3. Preparation of 3-(2-methyl-1,3-dioxolan-2-yl)-1-(2-methyl-2-oxiranyl)-1-propanone (4c). Bromine–pyridine complex (2.38 g, 10 mmol) was added slowly to a stirred solution of cyclopropanol **3c** (1.86 g, 10 mmol) in dry Et_2O (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, filtered through a short pad of alumina and the solvent was evaporated. The residue was dissolved in pentane (30 mL) and stirred with Al_2O_3 (10 g) for 12 h. The reaction mixture was filtered, Al_2O_3 was washed with ether and the solvent was evaporated to give 2-methyl-5-(2-methyl-1,3-dioxolan-2-yl)-1-penten-3-one (**5**). This compound **5** was used for further transformations without purification (purity >95%; ^1H NMR spectroscopy). Yield: 1.73 g (94%); colourless liquid. IR (CCl_4): ν 3093, 2933, 2867, 1680, 1440, 1373, 1320, 1053, 933 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H); 1.85 (s, 3H); 1.99 (t, J=7.8 Hz, 2H); 2.76 (t, J=7.8 Hz, 2H); 3.86–3.97 (m, 4H); 5.74 (s, 1H); 5.95 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.7, 23.9, 32.0, 33.34, 64.6, 109.4, 124.2, 128.4. (The signal due to carbonyl group is not observed in the 200 ppm region). Anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.01; H, 8.52.

To a stirred solution of this material (1.73 g, 9.4 mmol) and NaOH (0.5 g) in a mixture of *i*PrOH (12 mL) and H_2O (7 mL) was added 30% H_2O_2 (5 mL, 50 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, diluted with brine (25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed and the crude epoxide **4c** was purified by column chromatography (silica gel, EtOAc–cyclohexane, 1:5). Yield: 1.5 g (80%); colourless liquid. IR (CCl_4): ν 2920, 2853, 1707, 1440, 1373, 1133, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 3H); 1.48 (s, 3H); 1.86–2.02 (m, 2H); 2.25 (ddd, J=17.6, 8.4, 6.4 Hz, 1H); 2.51 (ddd, J=17.6, 8.5, 6.4 Hz, 1H); 2.82 (d, J=5.2 Hz, 1H); 2.96 (d, J=5.2 Hz, 1H); 3.86–3.96 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.6, 23.8, 29.5, 32.5, 51.9, 59.5, 64.46, 64.55, 109.1, 208.9. Anal. calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 60.11; H, 8.19.

3.3. 1-(2-Oxiranyl)-1,4-alkanediones (6a–c). General procedure

To a stirred suspension of silica gel (18 g) in CH_2Cl_2

(50 mL) was added 15% H_2SO_4 (1.7 g) followed by protected compound **4a–c** (10 mmol). The resulting mixture was allowed to stir at room temperature for 5–7 h, filtered and the solvent was evaporated, affording the crude diketones **6a–c** which were purified by column chromatography (silica gel, EtOAc–cyclohexane, 1:5).

3.3.1. *trans*-1-(3-Ethyl-2-oxiranyl)-1,4-pentanedione (6a). Yield: 1.63 g (96%); colourless liquid. IR (film): ν 2972, 2923, 2881, 1712, 1465, 1431, 1403, 1362, 1233, 1163, 1103, 919, 861 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, J=7.6 Hz, 3H); 1.53–1.74 (m, 2H); 2.12 (s, 3H); 2.49 (ddd, J=18.4, 7.0, 5.0 Hz, 1H); 2.54–2.60 (m, 1H); 2.60–2.66 (m, 1H); 2.76 (ddd, J=18.4, 7.8, 5.2 Hz, 1H); 3.13 (td, J=5.3, 2.0 Hz, 1H); 3.20 (d, J=2.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.3, 24.7, 29.6, 30.6, 36.2, 59.2, 59.3, 206.3, 206.4. Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.29; H, 8.15.

3.3.2. *trans*-1-(3-Methyl-2-oxiranyl)-1,4-hexanedione (6b). Yield: 1.53 g (90%); colourless liquid. IR (film): ν 2976, 2939, 1714, 1462, 1421, 1360, 1235, 1115, 1043, 1008, 973, 844 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J=7.2 Hz, 3H); 1.39 (d, J=5.2 Hz, 3H); 2.45 (q, J=7.2 Hz, 2H); 2.48–2.68 (m, 3H); 2.73–2.83 (m, 1H); 3.18 (d, J=1.6 Hz, 1H); 3.27 (qd, J=5.2, 1.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 7.7, 17.5, 30.7, 35.0, 35.7, 54.4, 60.6, 206.4, 209.4. Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.73; H, 8.16.

3.3.3. 1-(2-Methyl-2-oxiranyl)-1,4-pentanedione (6c). Yield: 1.48 g (95%); colourless liquid. IR (CCl_4): ν 2973, 2907, 1707, 1387, 1160, 1067, 960, 920 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 3H); 2.17 (s, 3H); 2.45–2.54 (m, 1H); 2.56–2.67 (m, 2H) 2.77–2.85 (m, 1H); 2.86 (d, J=5.2 Hz, 1H); 3.14 (d, J=5.2 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.4, 29.1, 29.7, 36.5, 52.3, 59.5, 206.7, 208.1. Anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.73; H, 7.55.

3.4. 6,8-Dioxabicyclo[3.2.1]octan-2-ones (7a–c). General procedure

To a stirred solution of 1-(2-oxiranyl)-1,4-alkanedione **6a–c** (10 mmol) in CH_2Cl_2 (240 mL) was added $BF_3{\cdot}OEt_2$ (0.42 g, 3.3 mmol). The reaction mixture was stirred at room temperature for 4–5 h, treated with aqueous 10% NaOH (20 mL) and extracted with CH_2Cl_2 (3×10 mL). The extracts were dried (Na_2SO_4) and the solvent was removed. Compounds **7a–c** were isolated by distillation under reduced pressure or by recristallization.

3.4.1. *endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]-octan-2-one (7a).[14] Yield: 1.45 g (85%); colourless liquid; bp 87–88 °C/10 Torr. IR (film): ν 2970, 2940, 2880, 1729, 1448, 1384, 1225, 1200, 1172, 1084, 1040, 969, 896, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J=7.4 Hz, 3H); 1.38 (dquint, J=14.4, 7.2 Hz, 1H); 1.47–1.61 (m, 1H); 1.54 (s, 3H); 2.01–2.10 (m, 2H); 2.32 (td, J=18.4, 8.4 Hz, 1H); 2.44 (ddd, J=18.4, 7.6, 4.0 Hz, 1H); 3.98 (td, J=7.2, 4.8 Hz, 1H); 4.26 (d, J=4.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.3, 22.5, 24.2, 33.3, 34.2, 80.1, 83.3, 107.4, 205.3. Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.32; H, 8.39.

3.4.2. *endo*-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]-octan-2-one (7b). Yield: 1.33 g (78%); colourless liquid; bp 94–96 °C/14 Torr. IR (CCl_4): ν 2995, 2947, 2880, 1735, 1493, 1467, 1387, 1200, 1120, 1080, 933 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J=7.4 Hz, 3H); 1.14 (d, J=6.4 Hz, 3H); 1.78 (qd, J=7.4, 2.4 Hz, 2H); 1.9–2.07 (m, 2H); 2.30 (td, J=18.4, 8.0 Hz, 1H); 2.46 (ddd, J=18.4, 8.4, 3.2 Hz, 1H); 4.13 (qd, J=6.0, 4.8 Hz, 1H); 4.18 (d, J=4.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 7.2, 14.1, 30.2, 32.6, 33.4, 74.4, 83.9, 109.1, 206.0. MS (70 eV) m/z (%): 170 (0.2), 149 (5), 116 (1), 113 (2), 87 (1), 86 (2), 75 (4), 74 (100), 73 (1), 72 (1), 71 (1), 70 (1), 69 (2), 60 (23), 58 (2), 57 (13), 56 (63), 55 (4), 54 (2), 46 (7), 45 (66), 44 (14), 43 (57), 42 (24), 41 (11), 40 (2), 39 (2). Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.64; H, 8.19.

3.4.3. 1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-2-one (7c).[15] Yield: 1.07 g (69%); mp 53–54 °C (hexane) [Lit.[12] mp 52.7–53.4 °C (hexane/Et_2O)]. IR (CCl_4): ν 2933, 2867, 1734, 1453, 1373, 1200, 1187, 1053, 960 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 1H); 1.53 (s, 1H); 2.13 (dd, J=8.8, 5.6 Hz, 2H); 2.36–2.57 (m, 2H); 3.55 (d, J=8.0 Hz, 1H); 3.91 (d, J=8.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.1, 23.9, 32.6, 36.6, 72.9, 84.6, 108.1, 206.4. Anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.40; H, 7.61.

3.5. Preparation of (±)-*endo*-brevicomin (1b), (±)-*endo*-isobrevicomin (1d) and (±)-frontalin (1e)

3.5.1. (±)-*endo*-Isobrevicomin (1d). To a stirred solution of ketone **7b** (0.34 g, 2 mmol) and 1,2-ethanedithiol (0.2 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) was slowly added a solution of $BF_3{\cdot}Et_2O$ (0.43 g, 3 mmol) in CH_2Cl_2 (5 mL) at −5 °C. The reaction mixture was stirred at −5–0 °C for 12–14 h, treated with aqueous 10% NaOH (10 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined extracts were dried (Na_2SO_4) and concetrated in vacuo. Column chromatography (SiO_2, benzene) of the residue gave the ethylene thioketal of ketone **7b**. Yield: 0.30 g (61%); colourless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J=7.4 Hz, 3H); 1.48 (d, J=6.4 Hz, 3H); 1.67–1.77 (m, 3H); 1.91 (ddd, J=13.6, 11.6, 5.2 Hz 1H); 2.05 (ddt, J=1.6, 5.6, 13.6 Hz, 1H); 2.47 (ddd, J=14.0, 11.6, 6.0 Hz, 1H); 3.04 (ddd, J=11.5, 9.2, 4.7 Hz, 1H); 3.17–3.31 (m, 2H), 3.44 (dt, J=10.9, 4.6 Hz 1H), 4.18–4.26 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 6.9, 15.2, 30.0, 34.3, 36.4, 36.6, 40.9, 67.6, 76.1, 85.3, 108.3.

A solution of ethylene thioketal of ketone **7b** (246 mg, 1 mmol) in EtOH (30 mL) was refluxed for 4 h with W2 Raney nickel (5 g). After cooling the catalyst was removed by filtration. The filtrate was concentrated under atmospheric pressure and (±)-*endo*-isobrevicomin (**1d**) was isolated by column chromatography (pentane–Et_2O, 19:1). Yield: 131 mg (84%); colourless liquid. All spectral data were identical with those reported for **1d**.[3,7e]

3.5.2. (±)-*endo*-Brevicomin (1b). Ethylene thioketal of ketone **7a**[14] was prepared from **7a** (0.34 g, 2 mmol) in the same manner as described above. Yield: 0.26 g (53%);

colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, J=7.4 Hz, 3H); 1.45 (s, 3H); 1.69–2.05 (m, 5H); 2.45 (ddd, J=13.5, 11.6, 6.0 Hz, 1H); 3.03 (ddd, J=11.3, 9.5, 4.8 Hz, 1H); 3.17–3.31 (m, 2H); 3.40 (dt, J=10.9, 4.5 Hz, 1H); 4.01 (ddd, J=8.8, 5.0, 3.9 Hz, 1H); 4.22 (dd, J=3.9, 1.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.9, 22.7, 24.1, 35.9, 36.4, 36.5, 40.7, 67.5, 82.1, 85.0, 106.4.

This material (246 mg, 1 mmol) was converted to (±)-*endo*-brevicomin (**1b**) in 80% yield.[14] All spectral data were identical with those reported for **1b**.[2g,6d,14]

3.5.3. (±)-Frontalin (1e). Ethylene thioketal of ketone **7c**[15] was prepared from **7c** (0.31 g, 2 mmol) in the same manner as described above. Yield: 0.44 g (95%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H); 1.59 (s, 3H); 1.79 (dd, J=13.2, 5.4 Hz, 1H); 1.90 (td, J=12.8, 5.4 Hz, 1H); 2.11 (dd, J=14.2, 5.0 Hz, 1H); 2.33–2.43 (m, 1H); 3.11–3.24 (m, 2H); 3.28–3.4 (m, 2H); 3.62 (d, J=8.0 Hz, 1H); 4.05 (d, J=8.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.1, 23.9, 36.8, 38.1, 39.3, 40.2, 71.8, 74.4, 86.9, 108.3.

This material was converted to (±)-frontalin (**1e**) in 72% yield.[12] All spectral data were identical with those reported for **1e**.[4b,c]

3.6. Preparation of hydroxy compounds 8a, 9a and their derivatives 8b, 9b

3.6.1. (1*R* *,2*S* *,5*S* *,7*S* *)-*endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (8a). To a stirred suspension of $LiAlH_4$ (0.06 g, 1.4 mmol) in Et_2O (3 mL) was slowly added a solution of ketone **7a** (0.34 g, 2 mmol) in Et_2O (2 mL). The reaction mixture was stirred for 2 h, treated with 5% HCl (about 4 mL) until pH=7.5 and extracted with Et_2O (3×5 mL). The organic extracts were dried (Na_2SO_4) and filtered through a short pad of silica gel to provide, after concentration, alcohol **8a** (purity>95%; ^{1}H NMR spectroscopy). Yield: 0.33 g (96%); colourless liquid. IR (CCl_4): ν 3480, 2994, 2947, 2880, 1480, 1401, 1267, 1213, 1186, 1093, 1053, 1020, 920, 893, 867 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ 1.12 (t, J=7.4 Hz, 3H); 1.56 (s, 3H); 1.59–1.78 (m, 4H); 1.91–2.19 (m, 2H); 3.81–3.91 (m, 1H); 4.01 (t, J≈4.4 Hz, 1H); 4.12–4.20 (m, 1H). ^{13}C NMR (100.6 MHz, C_6D_6): δ 11.9, 22.1, 24.4, 27.3, 35.4, 68.7, 78.2, 82.9, 106.6. MS (70 eV) *m*/*z* (%): 172 (0.6), 143 (1), 115 (4), 114 (19), 113 (1), 112 (2), 102 (1), 101 (6), 99 (3), 97 (4), 96 (1), 95 (3), 87 (1), 86 (9), 85 (12), 84 (21), (83 (21), 81 (5), 79 (1), 74 (1), 73 (20), 72 (12), 71 (23), 70 (6), 69 (7), 68 (1), 67 (4), 61 (18), 60 (2), 59 (11), 58 (25), 57 (24), 56 (21), 55 (26), 54 (4), 53 (4), 45 (5), 44 (5), 43 (100), 42 (6), 41 (22), 40 (2), 39 (15). Anal. calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.51; H, 9.23.

3.6.2. (1*R* *,2*S* *,5*S* *,7*S* *)-*endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-2-yl methanesulfonate (8b). To a stirred solution of NaH (50% in oil) (192 mg, 4 mmol) and imidazole (2.5 mg) in THF (5 mL) was added alcohol **8a** (172 mg, 1 mmol). The reaction mixture was stirred at room temperature for 1 h and MsCl (0.4 mL, 5 mmol) was added. The resulting mixture was stirred for 7 h, treated with saturated $NaHCO_3$ (10 mL) and extracted with ether (3×5 mL). The organic extract was dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by recrystallization (hexane–Et_2O, 10:1). Yield: 150 mg (60%); mp 61.5–62.5 °C (hexane–Et_2O). IR (CCl_4): ν 2973, 2933, 2880, 1373, 1347, 1187, 960, 920, 867, 733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J=7.2 Hz, 3H); 1.44 (s, 3H); 1.74–1.95 (m, 4H); 2.00–2.08 (m, 1H); 2.22 (qd, J=10.9, 6.8 Hz, 1H); 3.02 (s, 3H); 4.08 (td, J=7.3, 3.9 Hz, 1H); 4.34 (t, J≈4.0 Hz, 1H); 4.88 (ddd, J=10.9, 6.2, 4.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.3, 21.4, 23.7, 24.6, 35.2, 38.3, 75.8, 75.9, 82.3, 106.8.

3.6.3. (1*R* *,3*S* *,4*S* *,5*S* *)-3-Ethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-4-ol (9a).[3] A solution of alcohol **8a** (172 mg, 1 mmol) and TsOH (8.6 mg, 0.05 mmol) in ether (3 mL) was kept for 3 h at room temperature. The solvent was evaporated and the residue was recrystallized. Yield: 138 mg (80%); mp 64–65 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, J=7.4 Hz, 3H); 1.46 (s, 3H); 1.39–1.51 (m, 1H); 1.69–2.10 (m, 5H); 2.35 (br. s, 1H); 3.30 (td, J=8.4, 2.7 Hz, 1H); 3.47 (dd, J=8.4, 4.2 Hz, 1H); 4.27 (dd, J=6.4, 4.2 Hz, 1H). ^{1}H NMR (400 MHz, C_6D_6): δ 0.92 (br.s, 1H); 1.04 (t, J=7.4 Hz, 3H); 1.52 (s, 3H); 1.45–1.55 (m, 2H); 1.57–1.67 (m, 1H); 1.69–1.80 (m, 2H); 1.88 (ddd, J=12.0, 9.3, 4.0 Hz, 1H); 3.22 (td, J=8.3, 2.3 Hz, 1H); 3.25–3.31 (m, 1H); 4.08 (dd, J=6.8, 3.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.5, 23.4, 23.6, 25.3, 33.8, 68.0, 74.9, 78.1, 105.3. ^{13}C NMR (100.6 MHz, C_6D_6): δ 9.9, 23.91, 23.93, 26.0, 34.3, 68.6, 75.2, 78.3, 105.3.

3.6.4. (1*S* *,2*S* *,3*S* *,5*R* *)-3-Ethyl-5-methyl-4,8-dioxabicyclo[3.2.1]oct-2-yl methanesulfonate (9b). To a stirred solution of alcohol **9a** (0.34 g, 2 mmol) and Et_3N (0.56 mL, 4 mmol) in ether (7 mL) was added MsCl (0.35 g, 3 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, treated with saturated $NaHCO_3$ (10 mL) and extracted with ether (3×5 mL). The organic extract was dried (Na_2SO_4) and solvent was evaporated. The crude product was purified by recristallization (hexane). Yield: 0.45 g (90%); mp 73–74 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J=7.4 Hz, 3H); 1.48 (s, 3H); 1.43–1.56 (m, 1H); 1.67–1.79 (m, 1H); 1.82–1.94 (m, 1H); 1.99–2.10 (m, 3H); 3.02 (s, 3H); 3.51 (td, J=8.9, 2.8 Hz, 1H); 4.39 (dd, J=8.9, 4.3 Hz, 1H); 4.60 (dd, J=6.2, 4.3 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.0, 23.1, 24.0, 24.9, 33.5, 38.3, 71.5, 74.9, 75.9, 105.8.

Methanesulfonate **9b** could also be obtained from alcohol **8a** (0.34 g, 2 mmol) in the same manner as from **9a**. Yield: 0.45 g (90%).

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References and notes

1. For a recent review, see: Francke, W.; Schröder, W. *Curr. Org. Chem.* **1999**, *3*, 407–443.

2. (a) Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889–891. (b) Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896–897. (c) Schurig, V.; Weber, R.; Nicholson, G. J.; Oehlschlager, A. C.; Pierce, H. D., Jr.; Pierce, A. M.; Borden, J. H.; Ryker, L. C. *Naturwissenschaften* **1983**, *70*, 92–93. (d) Kohnle, U.; Vite, J. P. *Naturwissenschaften* **1984**, *71*, 47. (e) Weber, R.; Schurig, V. *Naturwissenschaften* **1984**, *71*, 408–409. (f) Vite, J. P.; Billings, R. F.; Ware, C. W.; Mori, K. *Naturwissenschaften* **1985**, *72*, 99–100. (g) Mori, K.; Sew, Y.-B. *Tetrahedron* **1985**, *41*, 3429–3431.
3. Francke, W.; Schröder, F.; Philipp, P.; Meyer, H.; Sinwell, V.; Gries, G. *Bioorg. Med. Chem.* **1996**, *4*, 363–374.
4. (a) Kinzer, G. W.; Fentiman, A. F., Jr.; Page, F. F., Jr.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature* **1969**, *221*, 477–478. (b) Stewart, T. E.; Plummer, E. L.; McCandless, L. L.; West, J. R.; Silverstain, R. M. *J. Chem. Ecol.* **1977**, *3*, 27. (c) Francke, W.; Bartels, J.; Meyer, H.; Schröder, F.; Kohnle, U.; Baader, E.; Vite, J. P. *J. Chem. Ecol.* **1995**, *21*, 1043.
5. Mori, K. *Chem. Commun.* **1997**, 1153–1158.
6. For recent syntheses, see: (a) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1999**, *64*, 2524–2526. (b) Burke, S. D.; Müller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827–1829. (c) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *19*, 3631–3636. (d) Gallos, J. K.; Kyradjoglou, L. C.; Koftis, T. V. *Heterocycles* **2001**, *55*, 781–784. (e) Chênevert, R.; Caron, D. *Tetrahedron: Asymmetry* **2002**, *13*, 339–342. (f) De Sousa, A. L.; Resck, I. S. *J. Braz. Chem. Soc.* **2002**, *13*, 233–237. (g) Mayer, S. F.; Mang, H.; Steinreiber, A.; Saf, R.; Faber, K. *Can. J. Chem.* **2002**, *80*, 362–369.
7. For selected examples, see: (a) Wassermann, H. H.; Barber, E. H. *J. Am. Chem. Soc.* **1969**, *91*, 3674–3675. (b) Sato, T.; Oikawa, T.; Kobayashi, K. *J. Org. Chem.* **1985**, *50*, 1646–1651. (c) Oehlschlager, A. C.; Johnston, B. D. *J. Org. Chem.* **1987**, *52*, 940–943. (d) Chan, T. H.; Chen, L. M. *Can. J. Chem.* **1993**, *71*, 60–67. (e) Mori, K.; Takikawa, H.; Nishimura, Y.; Horikiri, H. *Liebigs Ann.* **1997**, 327–332. (f) Kroutil, W.; Osprian, I.; Mischitz, M.; Faber, K. *Synthesis* **1997**, 156–158.
8. Vanderwel, D.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 5081–5087.
9. Kulinkovich, O. G.; Astashko, D. A.; Tyvorskii, V. I.; Ilyina, N. A. *Synthesis* **2001**, 1453–1455.
10. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244–2245. (c) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I. *Zh. Org. Khim.* **1991**, *27*, 294–298. (d) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I. *Zh. Org. Khim.* **1991**, *27*, 1428–1430. (e) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Zh. Org. Khim.* **1991**, *27*, 2132–2134.
11. For reviews, see: (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *102*, 2597–2632. (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834.
12. (a) Savchenko, A. I.; Sviridov, S. V.; Kulinkovich, O. G. *Zh. Org. Khim.* **1994**, *30*, 333–335. (b) Kulinkovich, O. G.; Bagutskii, V. V. *Zh. Org. Khim.* **1997**, *33*, 898–901.
13. Weitz, E.; Scheffer, A. *Ber.* **1921**, *54B*, 2327–2344.
14. Padwa, A.; Fryxel, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100–3109.
15. Tanigashi, T.; Nakamura, K.; Ogasawara, K. *Synthesis* **1997**, 509–511.
16. List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **1998**, *4*, 881–885.
17. Tishchenko, I. G.; Kulinkovich, O. G.; Masalov, N. V. *Synthesis* **1982**, 268–270.
18. For other synthetic procedure, see Ref. 7d.

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2,3-Anhydrosugars in glycoside bond synthesis. Application to the preparation of C-2 functionalized α-D-arabinofuranosides

Oana M. Cociorva and Todd L. Lowary*,†

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, OH 43210, USA

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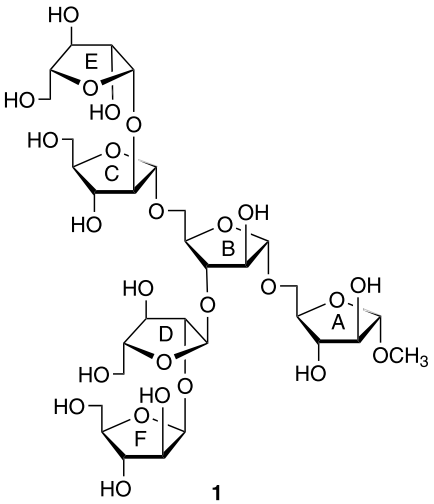
Abstract—A novel two-step route has been developed for the synthesis of a panel of oligosaccharides (**9**–**17**) containing C-2 functionalized α-D-arabinofuranosyl residues. The first step in this route consists of a highly stereocontrolled glycosylation reaction using a 2,3-anhydrosugar thioglycoside (**6**). In the second step, the epoxide ring in the 2,3-anhydrosugar glycoside is regioselectively opened at C-2 with sodium methoxide and sodium azide thus providing products with the α-D-arabinofuranosyl stereochemistry. This approach to these targets circumvents the potential stereocontrol problems inherent in glycosylations with arabinofuranosyl donors possessing non-participating groups at C-2. The route is also highly convergent, allowing the preparation of a range of C-2′ and C-2″ modified oligosaccharides upon reaction of epoxy glycosides **27**–**29** with nucleophiles.

1. Introduction

Over the past few years we have reported[1] syntheses of arabinofuranosyl-containing oligosaccharides that are fragments of two polysaccharides (arabinogalactan and lipoarabinomannan) found in the cell wall of mycobacteria, including the human pathogens *Mycobacterium tuberculosis* and *Mycobacterium leprae*.[2] These synthetic investigations were carried out with the goal of developing routes that would efficiently provide multi-milligram quantities of material for subsequent biochemical studies, including the identification of inhibitors of the enzymes that assemble these cell wall polysaccharides. To date, we have prepared a number of oligosaccharides, the largest of which is hexasaccharide **1** (Chart 1). The glycan portion of **1** is a key structural motif in both mycobacterial arabinogalactan and lipoarabinomannan.[1,2] These synthetic glycans have found application in studies directed towards probing the substrate specificity of mycobacterial arabinosyltransferases (AraT's)[3] as well as in investigations dedicated to mapping the specificities of antibodies that are generated against mycobacterial cell wall polysaccharides.[4]

As part of these investigations, we needed to synthesize di- and trisaccharide analogs in which the C-2 hydroxyl group



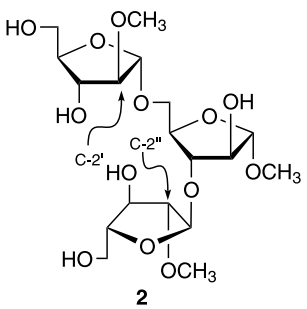


Chart 1.

Keywords: Oligosaccharides; Arabinofuranosides; Anhydrosugars; Glycosylation methodology.
* Corresponding author. Tel.: +1-7804921861; fax: +1-7804927705; e-mail address: tlowary@ualberta.ca
† Present address: Department of Chemistry and Alberta Ingenuity Centre for Carbohydrate Science, Gunning-Lemieux Chemistry Centre, University of Alberta, Edmonton, Alta, Canada T6G 2G2.

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in the non-reducing sugar residues (positions C-2′ and C-2″) was replaced with various other functionalities such as amino or methoxy groups (e.g., **2**, Chart 1). We envisioned that such compounds would be potential inhibitors of the AraT's responsible for the installation of the β-(1→2)-linked residues present in hexasaccharide **1**, due to the absence of the reactive hydroxyl group(s) that would serve as the attachment point of the β-arabinofuranosyl residues (rings E and F). We also envisioned, however, that their stereocontrolled preparation by standard methods used in oligosaccharide synthesis would be problematic. For example, using conventional synthetic methodology, the most straightforward approach to **2** would likely involve the preparation of a 2-methoxy glycosyl donor (e.g., **3**, Fig. 1), which could be coupled with the appropriate acceptor species, **4**. A significant problem with this route is that thioglycoside **2** has a non-participating group at C-2 and thus the glycosylation will not benefit from the formation of an acyloxonium ion intermediate that would ensure good 1,2-*trans* selectivity. The product (**5**) will almost certainly be formed as a mixture of four chromatographically similar diastereomers. Although in pyranose systems it is sometimes possible to obtain good 1,2-*trans* stereoselectivity in the absence of a C-2 participating group in the donor (usually in the preparation of α-mannopyranosides),[5] our experience with arabinofuranosides suggests that these reactions will give α/β mixtures of products, which are generally difficult to separate.[1d,6] While it is not difficult to imagine ways to circumvent this problem using conventional synthetic methods, these approaches would be less efficient. For example, a donor that would allow methylation following the glycosylation could be used, or an α-ribofuranoside could be synthesized and then the stereochemistry at C-2′ and C-2″ inverted.

We have discovered recently that 2,3-anhydrosugars thioglycosides and glycosyl sulfoxides are efficient glycosylating agents, providing glycosides with extremely high stereocontrol.[7] The major product formed from these reactions is the one in which the newly formed glycosidic bond is *cis* to the epoxide ring. Thus, glycosylation of alcohols by thioglycoside **6**[7b] (Fig. 2) affords the α-glycoside **7** as the major product. We have further demonstrated that the products of these glycosylations undergo regioselective nucleophilic ring opening of the epoxide at C-2, affording products with the α-D-arabino stereochemistry (**8**, Fig. 2).[8] Based on these previous results, it appeared to us that this methodology was ideally suited for the synthesis of C-2 modified α-D-arabinofuranosides. In this paper, we describe the synthesis of oligosaccharides **9**–**17** (Chart 2) using our 2,3-anhydrosugar methodology. Oligosaccharide analogs in which specific hydroxyl groups have been modified through substitution with various functional groups (e.g., *O*-methyl, amino, fluoro, or azido) have

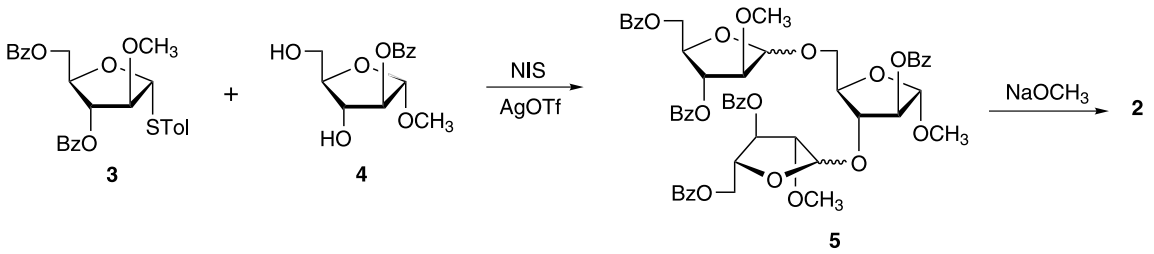


Figure 1. Stereocontrol problem in the synthesis of **5** via the use of a 2-*O*-methylated thioglycoside, **3**.

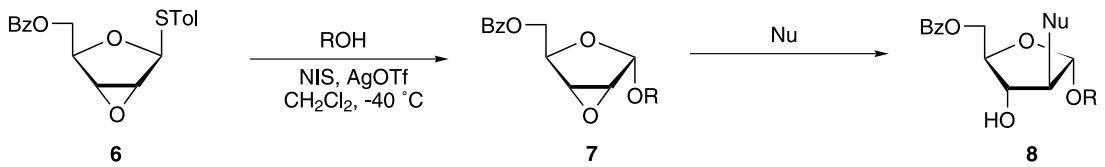


Figure 2. Use of 2,3-anhydrosugar thioglycoside **6** in the synthesis of α-arabinofuranosides (**8**).

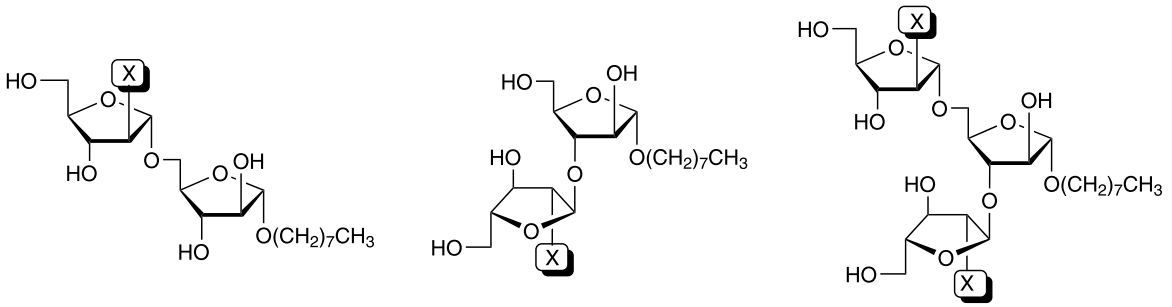


Chart 2.

previously been demonstrated to be inhibitors of glycosyltransferases from mammalian systems[9] as well as those from mycobacteria.[10]

2. Results and discussion

Shown in Figure 3 is the retrosynthetic analysis of the targets. We envisioned that all of the desired compounds could be obtained from one of three anhydrosugar-containing oligosaccharides (**27**–**29**), which in turn could be prepared from four monosaccharide building blocks: **6**, **20**, **22**, and **23**. In addition to circumventing the previously mentioned stereocontrol problems, another advantage of this approach over more conventional ones (e.g., the preparation of a series of C-2 modified monosaccharide donors) is that it is highly convergent. Anhydrosugar glycosides **27**–**29** could be used as precursors to a wide range of C-2′ and C-2″ modified arabinofuranosyl oligosaccharides through reaction with appropriate nucleophiles.

2.1. Synthesis of monosaccharide building blocks

Thioglycoside **6** was synthesized in eight steps from D-xylose as previously described.[7b] The acceptors **20**, **22**, and **23** were prepared without incident from octyl α-D-arabinofuranoside **18**[11] as illustrated in Scheme 1. Treatment of **18** with triphenylmethyl chloride and pyridine in dichloromethane followed by benzoyl chloride gave **19** in 97% yield. Removal of the trityl group with *p*-toluenesulfonic acid in methanol/dichloromethane proceeded in 94% yield to afford **20**. Alternatively, reaction of **18** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine, followed by the addition of benozyl chloride provided the fully protected arabinofuranoside **21** in 89% yield. Subsequent cleavage of the siloxane protecting group with *n*-Bu_4NF was achieved in 92% yield to provide diol **22**. The

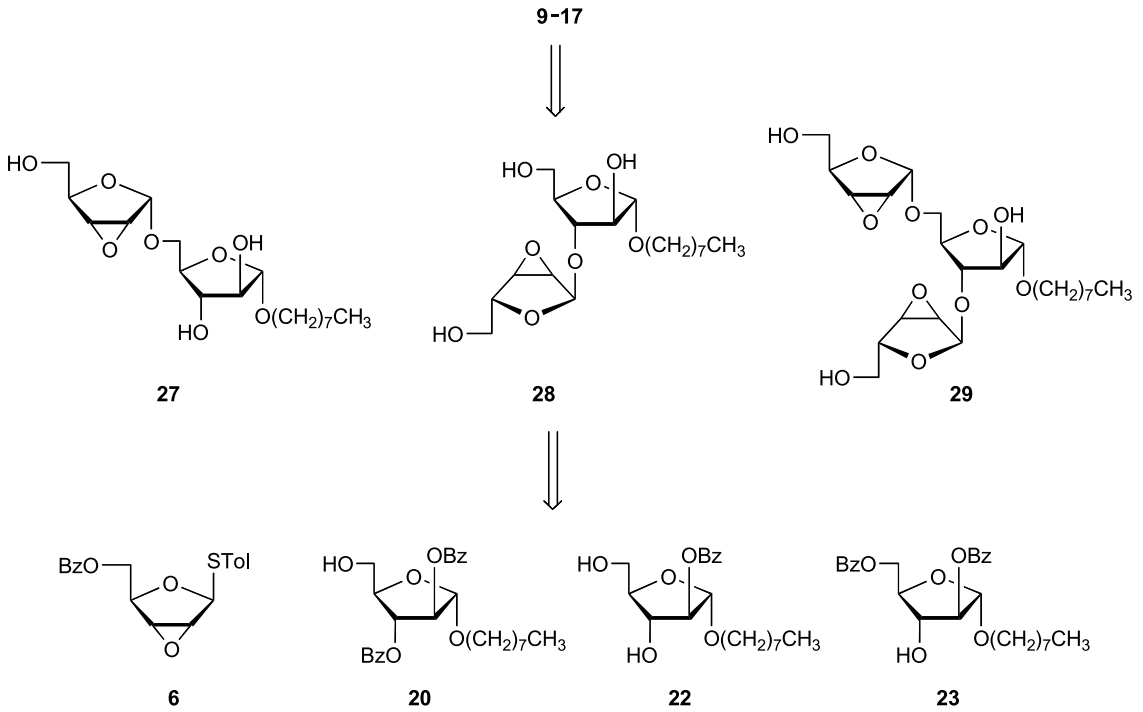
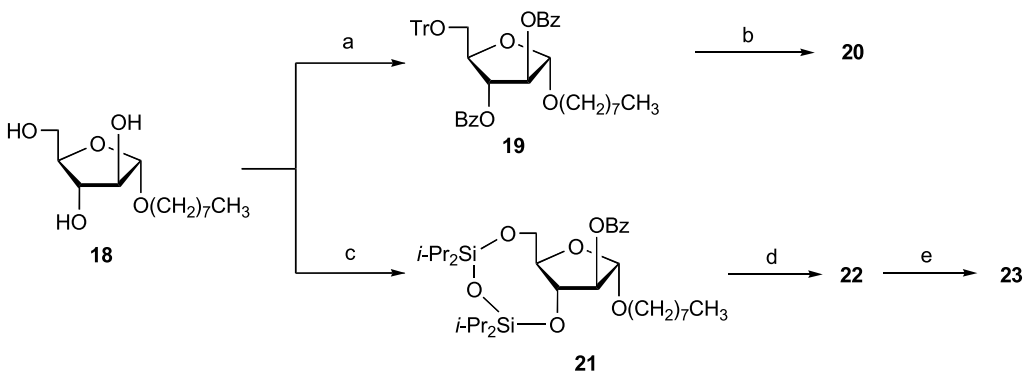
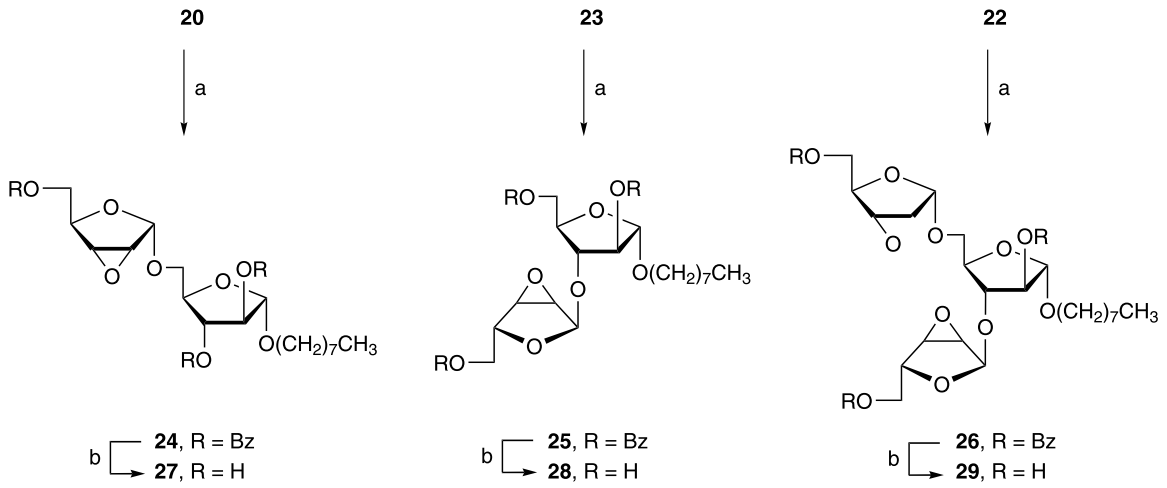


Figure 3. Retrosynthetic analysis of **9**–**17**.



Scheme 1. (a) TrCl, pyridine, CH_2Cl_2, rt, then BzCl, rt 97% (two steps, one pot). (b) *p*-TsOH, CH_2Cl_2, CH_3OH, rt, 94%. (c) 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane, pyridine, rt, then BzCl, rt 89% (two steps, one pot). (d) *n*-Bu_4NF, THF, rt, 92%. (e) BzOH, Ph_3P, DEAD, THF, rt, 93%.



Scheme 2. (a) **6**, *N*-iodosuccinimide, $AgOSO_2CF_3$, CH_2Cl_2, −40 °C, 84% (for **20**), 89% (for **23**) 75% (for **22**). (b) $NaOCH_3$, CH_3OH, rt, 92% (for **24**), 98% (for **25**), 89% (for **26**).

remaining acceptor, **23**, was obtained in one step and 93% yield from **22** upon Mitsunobu reaction with benzoic acid.

2.2. Glycosylation reactions and deprotection

With the four monosaccharides in hand, thioglycoside **6** was used to glycosylate alcohols **20**, **22**, and **23** (Scheme 2). These reactions were carried out using our standard protocol,[7b] which involves the coupling of the thioglycoside and acceptor in dichloromethane at −40 °C using activation by *N*-iodosuccinimide and silver triflate.[12] The products **24**, **25** and **26** were obtained in 84, 89, and 75% yield, respectively. The anomeric stereochemistry in the 2,3-anhydrosugar residues was determined by measuring the magnitude of $^1J_{C\text{-}1,H\text{-}1}$.[13] We have previously demonstrated that this parameter is the only reliable method for establishing anomeric stereochemistry in these 2,3-anhydrosugar derivatives.[13] In none of the glycosylations did we isolate any products with the β-stereochemistry and the substrates required for the ring opening reactions, **27**–**29**, were obtained in 89–98% yield by treatment of **24**–**26** with sodium methoxide.

2.3. Epoxide ring opening reactions

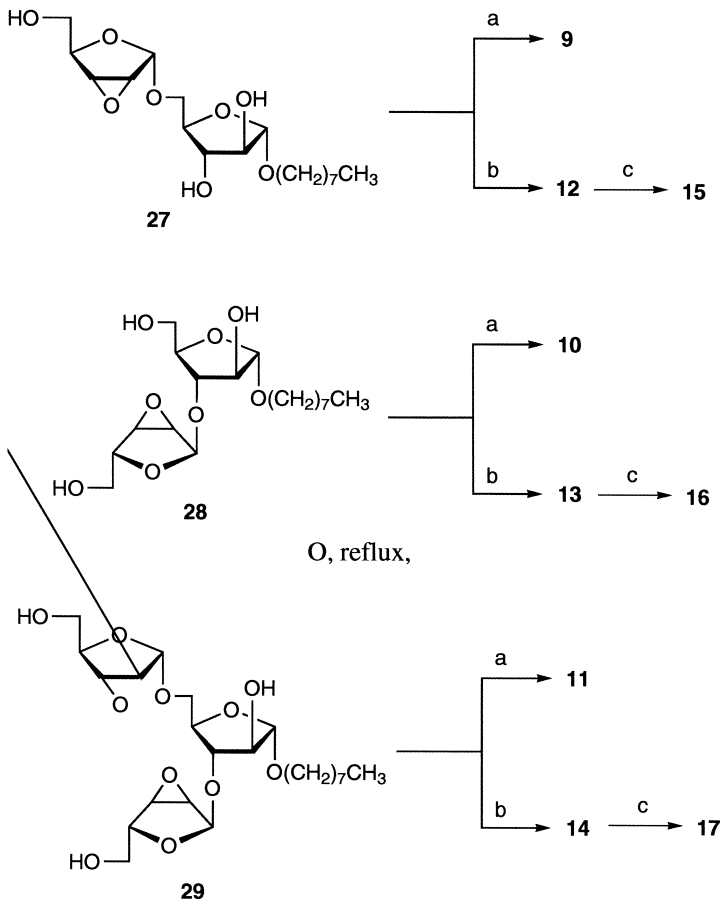
Introduction of the functionality at the C-2′ and C-2″ positions was achieved by heating each of **27**–**29** in the presence of a nucleophile (Scheme 3). Similar to other 2,3-anhydrosugars,[7b,8] the epoxide moiety in these molecules is quite robust and vigorous conditions are required for the reactions to proceed at reasonable rates. Reaction of **27**–**29** with sodium methoxide in methanol at reflux afforded the 2-methoxy derivatives **9**–**11** in yields of 60–82%. Similarly, the azido group was introduced upon heating a solution of the epoxide at reflux in a 3:2 mixture of ethanol and water containing sodium azide and ammonium chloride. Under these conditions, **27**–**29** provided the corresponding C-2′ and C-2″ azidosugar-containing oligosaccharides **12**–**14** in 54–60% yield.

In all cases, the structures of the products could be easily confirmed by ^1H and ^{13}C NMR spectroscopy. For all products the anomeric hydrogen in the ring-opened residues appeared in the ^1H NMR spectrum as a singlet or small doublet ($^3J_{H1,H2}<2.2$ Hz), while the anomeric carbon of these residues appeared in the ^{13}C NMR spectrum between 105 and 109 ppm. These data are consistent with the α-arabino stereochemistry in the products.[14] Attack of the nucleophile at C-3 would have led to products with the α-xylo stereochemistry, in which the anomeric hydrogens would have appeared in the ^1H NMR spectrum as a doublet with $^3J_{H1,H2}>4$ Hz and the anomeric carbon resonance would have appeared in the ^{13}C NMR spectrum between 100 and 104 ppm.[14] We also explored the use of NOE spectroscopy to provide further support for the identity of the ring-opened products. However, as might be expected given the inherent flexibility of five-membered rings, only weak intra-residue NOE's were observed. For example, for **9**, a very weak NOE was observed between H-2′ and H-4′ and somewhat larger NOE was seen between H-3′ and the H-5′s. These NOE's were consistent with the structures determined using other NMR parameters, but their small magnitudes provided little additional insight into the product structures.

In those reactions for which the yields are modest, we saw no evidence of formation of products with the α-xylo stereochemistry. Instead, the remainder of the mass balance was unreacted starting material. We found that at prolonged reaction times that some substrate decomposition began to occur and therefore it was advantageous to stop the reaction before all of the starting material was gone. The final targets, the amino oligosaccharides **15**–**17**, were obtained in 63–81% yield upon reduction of **12**–**14** with triphenylphosphine and water.

3. Conclusions

In conclusion, we describe here efficient syntheses of oligosaccharides containing C-2 modified α-arabinofuranosyl residues (**9**–**17**). The method we have used for the synthesis of these glycans involves a two-step process that combines a highly stereocontrolled glycosylation reaction of a 2,3-anhydrosugar thioglycoside (**6**) with a highly regioselective epoxide ring opening reaction. This



Scheme 3. (a) $NaOCH_3$, CH_3OH, reflux, 82% (for **27**), 71% (for **28**), 60% (for **29**). (b) NaN_3, NH_4CL, EtOH, H_2O, reflux, 60% (for **27**), 54% (for **28**), 56% (for **29**). (c) Ph_3P, H_2O, THF, rt, 70% (for **12**), 63% (for **13**), 81% (for **14**).

approach circumvents the potential stereocontrol problems inherent in glycosylations with arabinofuranose donors with non-participating groups at C-2.[1d,6] Furthermore, this route is highly convergent, allowing the preparation of a range of C-2′ and C-2″ modified oligosaccharides upon reaction of **27**–**29** with any given nucleophile. In its present form, the method is somewhat limited by the vigorous conditions required to open the epoxide moieties and we are currently investigating methods by which these reactions can be made to proceed at lower temperatures. The testing of **27**–**29** as inhibitors of mycobacterial AraT's is in progress and will be reported separately.

4. Experimental

4.1. General methods

Solvents were distilled from appropriate drying agents before use. Unless stated otherwise, all reactions were carried out at room temperature and under a positive pressure of argon and were monitored by TLC on silica gel 60 F_{254}. Spots were detected under UV light or by charring with 10% H_2SO_4, in EtOH. Unless otherwise indicated, all column chromatography was performed on silica gel 60 (40–60 μM). Iatrobeads refers to a beaded silica gel 6RS-8060, which is manufactured by Iatron Laboratories (Tokyo). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 22±2 °C. ^{1}H NMR spectra were recorded at 400 or 500 MHz and chemical shifts are referenced to either TMS (0.0, $CDCl_3$) or HOD (4.78, D_2O). ^{13}C NMR spectra were recorded at 100 or 125 MHz and ^{13}C chemical shifts were referenced to internal $CDCl_3$ (77.23, $CDCl_3$) or external dioxane (67.40, D_2O). Electrospray mass spectra were recorded on samples suspended in mixtures of THF and CH_3OH with added NaCl.

4.1.1. Octyl 5-*O*-(2-*O*-methyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (9). To a solution of **27** (60 mg, 0.15 mmol) in dry CH_3OH (10 mL), was added a 1 M solution of $NaOCH_3$ in CH_3OH (3 mL, 3 mmol). The reaction mixture was heated at reflux for 24 h, then cooled and neutralized with acetic acid (0.2 mL). The solution was concentrated and purified by chromatography (CH_2Cl_2/CH_3OH, 10:1) to give **9** (50 mg, 82%) as a colorless oil: R_f 0.67 (CH_2Cl_2/CH_3OH, 6:1); $[\alpha]_D$ +71.9 (*c* 0.9, CH_3OH); ^{1}H NMR (400 MHz, D_2O, δ_H) 5.12 (s, 1H), 4.96 (s, 1H), 4.26 (s, 1H), 4.13–4.09 (m, 2H), 4.07–4.02 (m, 2H), 3.87–3.83 (m, 2H), 3.79–3.70 (m, 3H), 3.55–3.47 (m, 2H), 3.48 (s, 3H), 1.67–1.65 (m, 2H), 1.35–1.33 (m, 10H), 0.89–0.87 (m, 3H); ^{13}C NMR (100 MHz, D_2O, δ_C) 107.4, 105.5, 87.4, 83.7, 82.2, 81.8, 78.8, 77.2, 68.6, 66.7, 61.1, 57.9, 33.2, 29.8 (2), 29.7, 26.3, 22.9, 14.2; HR-ESI-MS calcd for $[C_{19}H_{36}O_9]Na^+$ 431.2251, found 431.2261.

4.1.2. Octyl 3-*O*-(2-*O*-methyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (10). Epoxide **28** (35 mg, 0.09 mmol)

was dissolved in CH_3OH (10 mL) and treated with a 1 M solution of $NaOCH_3$ in CH_3OH (3 mL, 0.3 mmol) as described for the preparation of **9**. The product was purified by chromatography (CH_2Cl_2/CH_3OH, 10:1) to give **10** (25 mg, 71%) as a colorless oil: R_f 0.81 (CH_2Cl_2/CH_3OH, 6:1); $[\alpha]_D$ +92.5 (*c* 0.8, CH_3OH); ^1H NMR (500 MHz, D_2O, δ_H) 5.17 (d, 1H, *J*=1.4 Hz), 4.94 (s, 1H), 4.15 (s, 1H), 4.06–4.02 (m, 2H), 3.96–3.92 (m, 2H), 3.81–3.77 (m, 2H), 3.74–3.72 (m, 2H), 3.71–3.62 (m, 3H), 3.41 (s, 3H), 1.56–1.52 (m, 2H), 1.27–1.26 (m, 10H), 0.86–0.83 (m, 3H); ^{13}C NMR (125 MHz, D_2O, δ_C) 108.1, 105.0, 91.8, 83.3, 83.2, 83.0, 82.1, 80.1, 74.9, 68.1, 61.2, 57.8, 32.2, 29.7 (2), 29.6, 26.3, 22.9, 14.2; HR-ESI-MS calcd for $[C_{19}H_{36}O_9]Na^+$ 431.2251, found 431.2233.

4.1.3. Octyl 3,5-di-*O*-(2-*O*-methyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (11). Epoxide **29** (32 mg, 0.06 mmol) was dissolved in CH_3OH (10 mL) and treated with a 1 M solution of $NaOCH_3$ in CH_3OH (3 mL, 0.3 mmol) as described for the preparation of **9**. The product was purified by chromatography (CH_2Cl_2/CH_3OH, 10:1) to give **11** (20 mg, 60%) as a colorless oil: R_f 0.65 (CH_2Cl_2/CH_3OH, 6:1); $[\alpha]_D$ +91.4 (*c* 0.7, CH_3OH); ^1H NMR (500 MHz, D_2O, δ_H) 5.16 (d, 1H, *J*=1.0 Hz), 5.08 (s, 1H), 4.96 (s, 1H), 4.19–4.16 (m, 1H), 4.05–4.01 (m, 2H), 3.96–3.92 (m, 3H), 3.89–3.86 (m, 1H), 3.79–3.76 (m, 4H), 3.68–3.63 (m, 3H), 3.47–3.45 (m, 1H), 3.40 (s, 3H), 3.40 (s, 3H), 1.56–1.50 (m, 2H), 1.14–1.11 (m, 10H), 0.86–0.81 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 108.6, 105.5, 105.3, 91.6, 90.5, 86.4, 85.4, 82.9, 81.9, 80.2, 76.2, 75.2, 68.2, 66.3, 65.7, 63.3, 58.2, 58.0, 32.3, 29.9, 29.8, 29.7, 26.1, 23.1, 14.6; HR-ESI-MS calcd for $[C_{25}H_{46}O_{13}]Na^+$ 577.2831, found 577.2814.

4.1.4. Octyl 5-*O*-(2-azido-2-deoxy-α-D-arabinofuranosyl)-α-D-arabinofuranoside (12). A solution of **27** (45 mg, 0.12 mmol), NaN_3 (150 mg, 2.16 mmol) and NH_4Cl (140 mg, 2.45 mmol) in ethanol (15 mL) and water (10 mL) was heated at reflux for 24 h. The reaction mixture was cooled, concentrated, and the residue was purified by chromatography (CH_2Cl_2/CH_3OH, 10:1) to give **12** (30 mg, 60%) as a colorless oil: R_f 0.38 (CH_2Cl_2/CH_3OH, 10:1); $[\alpha]_D$ +84.3 (*c* 0.8, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 5.08 (d, 1H, *J*=2.1 Hz), 4.98 (s, 1H), 4.18–4.16 (m, 2H), 4.10–4.08 (m, 1H), 4.05 (s, 1H), 3.98–3.95 (m, 2H), 3.91–3.86 (m, 2H), 3.77–3.70 (m, 3H), 3.46–3.41 (m, 1H), 1.61–1.59 (m, 2H), 1.25–1.23 (m, 10H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 108.6, 105.0, 85.4, 83.1, 81.8, 79.6, 75.2, 71.1, 68.4, 65.5, 61.9, 32.0, 29.7, 29.5, 29.4, 26.3, 22.8, 14.3; HR-ESI-MS calcd for $[C_{18}H_{33}O_8N_3]Na^+$ 442.2160, found 442.2168.

4.1.5. Octyl 3-*O*-(2-azido-2-deoxy-α-D-arabinofuranosyl)-α-D-arabinofuranoside (13). Epoxide **28** (30 mg, 0.08 mmol) was treated as described for the preparation of **12** with NaN_3 (140 mg, 2.15 mmol) and NH_4Cl (130 mg, 2.43 mmol) in ethanol (15 mL) and water (10 mL). The product was purified by chromatography (CH_2Cl_2/CH_3OH, 10:1) to give **13** (18 mg, 54%) as a colorless oil: R_f 0.42 (CH_2Cl_2/CH_3OH, 10:1); $[\alpha]_D$ +81.3 (*c* 0.8, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 5.17 (d, 1H, *J*=1.9 Hz), 4.94 (s, 1H), 4.16 (s, 1H), 4.11 (m, 1H), 4.05–3.96 (m, 3H), 3.87–3.78 (m, 5H), 3.73–3.64 (m, 1H), 3.44–3.38 (m, 1H), 1.59–1.54 (m, 2H), 1.29–1.27 (m, 10H), 0.90–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 108.0, 104.9, 84.5, 82.7, 82.5, 79.9, 75.2, 71.4, 68.0, 61.6, 61.1, 31.9, 29.5, 29.4, 29.3, 26.1, 22.7, 14.1; HR-ESI-MS calcd for $[C_{18}H_{33}O_8N_3]Na^+$ 442.2160, found 442.2166.

4.1.6. Octyl 3,5-di-*O*-(2-azido-2-deoxy-α-D-arabinofuranosyl)-α-D-arabinofuranoside (14). Epoxide **29** (33 mg, 0.06 mmol) was treated as described for the preparation of **12** with NaN_3 (330 mg, 6.5 mmol) and NH_4Cl (350 mg, 6.5 mmol) in ethanol (15 mL) and water (10 mL). The product was purified by chromatography (CH_2Cl_2/CH_3OH, 10:1) to give **14** (20 mg, 56%) as a colorless oil: R_f 0.35 (CH_2Cl_2/CH_3OH, 10:1); $[\alpha]_D$ +75.6 (*c* 0.8, CH_3OH); ^1H NMR (400 MHz, D_2O, δ_H) 5.13 (d, 1H, *J*=1.9 Hz), 5.07 (d, 1H, *J*=2.1 Hz), 4.97 (s, 1H), 4.23–4.20 (m, 2H), 4.17–4.14 (m, 1H), 4.08–4.04 (m, 4H), 3.91–3.89 (m, 1H), 3.83–3.79 (m, 4H), 3.71–3.63 (m, 4H), 3.34–3.33 (m, 1H), 1.53–1.50 (m, 2H), 1.15–1.11 (m, 10H), 0.83–0.80 (m, 3H); ^{13}C NMR (100 MHz, D_2O, δ_C) 108.5, 105.2, 104.9, 84.0, 83.7, 81.9, 81.6, 81.4, 78.7, 69.3, 67.8, 67.5, 65.5, 61.6, 61.1, 33.3, 31.2, 31.0, 30.9, 30.8, 27.5, 24.1, 15.6; HR-ESI-MS calcd for $[C_{23}H_{40}O_{11}N_6]Na^+$ 599.2647, found 599.2689.

4.1.7. Octyl 5-*O*-(2-amino-2-deoxy-α-D-arabinofuranosyl)-α-D-arabinofuranoside (15). A solution of **12** (25 mg, 0.06 mmol) and triphenylphosphine (24 mg, 0.09 mmol) in THF (5 mL) and few drops of water was stirred for 24 h at rt. The solvent was concentrated and the residue purified by chromatography ($CHCl_3/CH_3OH$, 2:1 with 2% Et_3N) to give **15** (15 mg, 70%) as a white solid: R_f 0.14 ($CHCl_3/CH_3OH$, 2:1); $[\alpha]_D$ +91.2 (*c* 0.8, CH_3OH); ^1H NMR (400 MHz, D_2O, δ) 5.09 (d, 1H, *J*=1.8 Hz), 4.98 (s, 1H), 4.20–4.16 (m, 2H), 4.14–4.09 (m, 1H), 4.04 (dd, 1H, *J*=5.4, 11.6 Hz), 3.98–3.94 (m, 2H), 3.89–3.85 (m, 2H), 3.58–3.48 (m, 3H), 3.37–3.29 (m, 1H), 1.57–1.53 (m, 2H), 1.25–1.21 (m, 10H), 0.82–0.79 (m, 3H); ^{13}C NMR (100 MHz, D_2O, δ) ^{13}C NMR (100 MHz, D_2O, δ_C) 108.2, 105.7, 84.8, 81.2, 80.8, 79.7, 75.5, 72.0, 68.7, 62.0, 60.0, 59.7, 31.5, 29.0, 28.7, 25.6, 22.4, 13.8; HR-ESI-MS calcd for $[C_{18}H_{35}O_8N]Na^+$ 416.2255, found 416.2259.

4.1.8. Octyl 3-*O*-(2-amino-2-deoxy-α-D-arabinofuranosyl)-α-D-arabinofuranoside (16). Azide **13** (20 mg, 0.05 mmol) was converted to **16** as described for the preparation of **15** with triphenylphosphine (24 mg, 0.09 mmol) in THF (5 mL) and few drops of water. Purification of the product by chromatography ($CHCl_3/CH_3OH$, 2:1 with 2% Et_3N) gave **16** (10 mg, 63%) as a white solid: R_f 0.14 ($CHCl_3/CH_3OH$, 2:1); $[\alpha]_D$ +83.2 (*c* 0.7, CH_3OH); ^1H NMR (400 MHz, D_2O, δ_H) 5.07 (d, 1H, *J*=2.1 Hz), 4.84 (s, 1H), 4.06 (m, 1H), 4.05–3.96 (m, 4H), 3.87–3.78 (m, 3H), 3.73–3.64 (m, 2H), 3.44–3.38 (m, 1H), 3.01–2.99 (m, 1H),1.59–1.54 (m, 2H), 1.34–1.29 (m, 10H), 0.90–0.86 (m, 3H); ^{13}C NMR (100 MHz, D_2O, δ_C) 108.2, 105.0, 84.5, 83.7, 82.5, 82.6, 69.2, 68.4, 64.0, 60.6, 59.1, 31.9, 29.6, 29.4, 29.3, 26.1, 22.6, 14.1; HR-ESI-MS calcd for $[C_{18}H_{35}O_8N]Na^+$ 416.2255, found 416.2252.

4.1.9. Octyl 3,5-di-*O*-(2-amino-2-deoxy-α-D-arabinofuranosyl)-α-D-arabinofuranoside (17). Azide **14** (15 mg, 0.03 mmol) was converted to **17** as described for

the preparation of **16** with triphenylphosphine (17 mg, 0.05 mmol) in THF (5 mL) and few drops of water. Purification of the product by chromatography ($CHCl_3$/CH_3OH, 2:1 with 2% Et_3N) gave **17** (11 mg, 81%) as a white solid: R_f 0.12 ($CHCl_3$/CH_3OH, 2:1); $[\alpha]_D$ +106.7 (*c* 0.7, CH_3OH); ^1H NMR (400 MHz, D_2O, δ_H) 5.10 (d, 1H, *J*=1.8 Hz), 5.07 (d, 1H, *J*=2.1 Hz), 4.89 (s, 1H), 4.19–4.16 (m, 1H), 4.17–4.15 (m, 1H), 4.01–3.98 (m, 1H), 3.94–3.93 (m, 3H), 3.89–3.84 (m, 2H), 3.81–3.77 (m, 3H), 3.72–3.67 (m, 3H), 3.55–3.49 (m, 1H), 3.07–3.03 (m, 2H),1.56–1.52 (m, 2H), 1.26–1.17 (m, 10H), 0.82–0.79 (m, 3H); ^{13}C NMR (100 MHz, D_2O, δ_C) 107.9, 107.8, 107.7, 85.7, 85.2, 84.0, 82.2, 81.8, 81.4, 79.4, 68.4, 66.6, 62.1, 62.0, 59.6 (2), 31.5, 29.0, 28.8, 28.6, 25.6, 22.4, 13.8; HR-ESI-MS calcd for $[C_{23}H_{44}O_{11}N_2]Na^+$ 547.2837, found 547.2836.

4.1.10. Octyl 2,3-di-*O*-benzoyl-5-*O*-triphenylmethyl-α-D-arabinofuranoside (19). To a solution of **18**[11] (500 mg, 1.91 mmol) in dry pyridine (10 mL) and dry CH_2Cl_2 (3 mL) was added dropwise triphenylmethyl chloride (837 mg, 3.0 mmol) and DMAP (90 mg, 0.7 mmol). The reaction mixture was stirred at rt overnight before benzoyl chloride (1.5 mL, 11 mmol) was added dropwise. The solution was again stirred at rt overnight, then diluted with CH_2Cl_2 (20 mL) and washed successively with 0.1 M HCl (30 mL), water (15 mL), and brine (15 mL). After drying (Na_2SO_4), the solution was filtered and concentrated to give **19** (1.2 g, 97%) as a light yellow oil: R_f 0.53 (hexanes/EtOAc, 4:1); $[\alpha]_D$ +81.9 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.21–8.19 (m, 7H), 8.12–8.09 (m, 3H), 8.02–8.00 (m, 2H), 7.72–7.44 (m, 7H), 7.37–7.33 (m, 2H), 7.30–7.12 (m, 3H), 5.61 (d, 1H, *J*=1.9 Hz), 5.48 (s, 1H), 5.28 (s, 1H), 4.49 (dd, 1H, *J*=4.9, 9.9 Hz), 3.97 (s, 1H), 3.86–3.77 (m, 1H), 3.61–3.50 (m, 2H), 3.12 (s, 1H), 1.73–1.68 (m, 2H), 1.48–1.32 (m, 10H), 0.94–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 166.0, 165.8, 144.2, 135.0, 134.2, 133.7, 131.0, 130.6, 130.3, 130.0, 129.8, 129.3, 129.2, 128.9 (2), 128.8, 128.2 (2), 127.4, 127.3, 106.2, 87.3, 82.4, 78.4, 68.0, 64.1, 32.3, 30.0, 29.9, 29.7, 26.6, 23.1, 14.5; HR-ESI-MS calcd for $[C_{46}H_{48}O_7]Na^+$ 735.3292, found 735.3303.

4.1.11. Octyl 2,3-di-*O*-benzoyl-α-D-arabinofuranoside (20). To a solution of **19** (2.9 g, 4.07 mmol) in CH_2Cl_2/CH_3OH (20 mL, 3:1) was added *p*-TsOH acid (362 mg, 1.9 mmol) at rt and the mixture was stirred for 12 h, before Et_3N (0.1 mL) was added. The solution concentrated and the residue was purified by chromatography (hexanes/EtOAc, 6:1) to give **20** (1.8 g, 94%) as a colorless oil: R_f 0.51 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +91.5 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.09–8.04 (m, 4H), 7.61–7.56 (m, 2H), 7.47–7.43 (m, 4H), 5.52 (d, 1H, *J*=1.3 Hz), 5.42 (dd, 1H, *J*=0.7, 4.7 Hz), 5.23 (s, 1H), 4.33–4.29 (m, 1H), 4.04–3.95 (m, 2H), 3.78–3.73 (m, 1H), 3.55–3.49 (m, 1H), 1.66–1.59 (m, 2H), 1.41–1.23 (m, 10H), 0.87–0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 166.6, 165.8, 133.9, 130.3 (2), 129.7, 129.6, 128.9 (2), 105.9, 84.0, 82.2, 78.3, 68.0, 62.9, 32.2, 30.0, 29.8, 29.7, 26.6, 23.0, 14.5; HR-ESI-MS calcd for $[C_{27}H_{34}O_7]Na^+$ 493.2197, found 493.2189.

4.1.12. Octyl 2-*O*-benzoyl-3,5-*O*-(1,1,3,3-tetraisopropyl-siloxane-1,3-diyl)-α-D-arabinofuranoside (21). To a solution of **18**[11] (500 mg, 1.90 mmol) in dry pyridine (40 mL), at 0 °C, was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (890 mg, 2.8 mmol) dropwise. The reaction mixture was warmed at rt and stirred for 12 h before benzoyl chloride (0.12 mL, 1.14 mmol) was added dropwise. The reaction mixture was stirred at rt overnight, then diluted with CH_2Cl_2 (25 mL) and washed successively with 0.1 M HCl (50 mL), water (25 mL), and brine (25 mL). After drying (Na_2SO_4), the solution was filtered, concentrated, and the residue was purified by chromatography (hexanes/EtOAc, 6:1) to give **21** (1.07 g, 89%) as a colorless oil: R_f 0.7 (hexanes/EtOAc, 6:1); $[\alpha]_D$ −32.6 (*c* 2.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.06–8.03 (m, 2H), 7.59–7.57 (m, 1H), 7.45–7.43 (m, 2H), 5.43 (dd, 1H, *J*=1.5, 4.7 Hz), 5.00 (d, 1H, *J*=1.5 Hz), 4.50 (dd, 1H, *J*=2.3, 5.1 Hz), 4.11–4.06 (m, 2H), 4.01–3.97 (m, 1H), 3.74–3.68 (m, 1H), 3.58–3.43 (m, 1H), 1.63–1.58 (m, 2H), 1.28–1.26 (m, 10H), 1.15–0.98 (m, 28H), 0.88–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 165.8, 133.4, 129.9, 129.8, 128.6 (2), 105.5, 84.7, 81.5, 76.7, 68.2, 62.3, 32.1, 29.8, 29.6, 29.5, 26.3, 22.9, 17.7, 17.6 (3), 17.2 (3), 14.3, 13.7, 13.5, 13.1, 12.8; HR-ESI-MS calcd for $[C_{32}H_{56}O_7Si_2]Na^+$ 631.3457, found 631.3470.

4.1.13. Octyl 2-*O*-benzoyl-α-D-arabinofuranoside (22). To a solution of **21** (375 mg, 0.62 mmol) in dry THF (15 mL) was added a solution of 1 M *n*-Bu_4NF in THF (1.55 mL, 1.55 mmol). The reaction mixture was stirred at rt for 2 h and then CH_2Cl_2 (50 mL) and a saturated aqueous solution of $NaHCO_3$ (40 mL) were added. The organic layer was dried (Na_2SO_4) then filtered and concentrated. The residue was purified by chromatography (hexanes/EtOAc, 3:1) to give **22** (209 mg, 92%) as colorless oil: R_f 0.42 (hexanes/EtOAc, 1:1); $[\alpha]_D$ 89.7 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.03–8.01 (m, 2H), 7.61–7.58 (m, 1H), 7.47–7.44 (m, 2H), 5.25 (s, 1H), 5.08 (d, 1H, *J*=2.1 Hz), 4.22–4.15 (m, 2H), 3.95–3.92 (m, 1H), 3.80–3.74 (m, 1H), 3.51–3.45 (m, 1H), 3.26 (d, 1H, *J*=5.3 Hz), 1.63–1.61 (m, 2H), 1.34–1.27 (m, 10H), 0.89–0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 167.1, 134.0, 130.2, 129.5, 128.9, 105.7, 86.4, 84.5, 76.8, 68.4, 62.4, 32.2, 29.9, 29.8, 29.6, 26.5, 23.0, 14.5; HR-ESI-MS calcd for $[C_{20}H_{30}O_6]Na^+$ 389.1935, found 389.1935.

4.1.14. Octyl 2,5-di-*O*-benzoyl-α-D-arabinofuranoside (23). To a solution of **22** (143 mg, 0.39 mmol) in dry THF (5 mL), was added Ph_3P (152 mg, 0.58 mmol) and the mixture was stirred at rt for 15 min. Then, DEAD (0.1 mL, 0.58 mmol) and benzoic acid (71 mg, 0.58 mmol) were added. After 1 h, the reaction mixture was concentrated a syrup before ether (25 mL) was added to precipitate the triphenylphosphine oxide. The two-phase mixture was kept at 4 °C overnight then filtered and the precipitate washed with cold ether. The filtrate was concentrated and, after repeating the precipitation, purified by chromatography (hexanes/EtOAc, 8:1) to give **23** (171 mg, 93%) as a white solid: R_f 0.28 (hexanes/EtOAc, 8:1); $[\alpha]_D$ +78.9 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.05–8.01 (m, 4H), 7.61–7.57 (m, 1H), 7.54–7.50 (m, 1H), 7.46–7.42 (m, 2H), 7.37–7.33 (m, 2H), 5.29 (s, 1H), 5.16 (d, 1H, *J*=1.8 Hz), 4.64 (dd, 1H, *J*=4.0, 11.8 Hz), 4.55–4.51 (m, 1H), 4.47–4.44 (m, 1H), 4.25–4.23 (m, 1H), 3.84–3.78 (m, 1H), 3.55–3.49 (m 1H), 3.44 (d, 1H, *J*=5.9 Hz), 1.66–1.61 (m, 2H), 1.39–1.28 (m, 10H), 0.90–0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 166.7, 166.5, 133.8, 133.2, 130.0 (2),

129.9, 129.2, 128.7, 128.5, 105.5, 85.6, 82.1, 77.5, 68.2, 64.1, 32.0, 29.7, 29.5, 29.4, 26.2, 22.8, 14.2; HR-ESI-MS calcd for $[C_{27}H_{34}O_7]Na^+$ 493.2197, found 493.2208.

4.1.15. Octyl 5-*O*-(2,3-anhydro-5-*O*-benzoyl-α-D-ribofuranosyl)-2,3-di-*O*-benzoyl-α-D-arabinofuranoside (24). A solution of acceptor **20** (92 mg, 0.19 mmol), donor **6**[7b] (80 mg, 0.23 mmol) and powdered molecular sieves (4 Å, 150 mg) in dry CH_2Cl_2 (10 mL) was stirred at −40 °C for 10 min. Then, *N*-iodosuccinimide (52 mg, 0.23 mmol) and silver triflate (10 mg, 0.04 mmol) were added. After stirring for 10 min at −40 °C, Et_3N (0.1 mL) was added. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and filtered through Celite. The filtrate was washed successively with a saturated aqueous solution of $Na_2S_2O_3$ (15 mL), water (15 mL), and brine (15 mL). After drying (Na_2SO_4), the organic phase was filtered and concentrated. The residue was purified by chromatography (hexanes/EtOAc, 3:1) to give **24** (110 mg, 84%) as a colorless oil: R_f 0.51 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +89.1 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.11–8.05 (m, 4H), 8.00–7.98 (m, 2H) 7.60–7.53 (m, 3H), 7.46–7.40 (m, 6H), 5.52 (d, 1H, *J*=4.7 Hz), 5.47 (s, 1H), 5.45 (d, 1H, *J*=1.0 Hz), 5.23 (s, 1H), 4.58 (dd, 1H, *J*=3.9, 3.9 Hz), 4.48 (dd, 1H, *J*=3.2, 12.0 Hz), 4.46–4.38 (m, 2H), 4.20 (dd, 1H, *J*=4.9, 11.1 Hz), 4.07 (dd, 1H, *J*=3.7, 11.1 Hz), 3.80–3.73 (m, 3H), 3.54–3.48 (m, 1H), 1.65–1.58 (m, 2H), 1.47–1.24 (m, 10H), 0.88–0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 166.5, 166.1, 165.9, 133.8, 133.7, 130.4, 130.3, 130.0, 129.9, 129.7, 129.0, 128.8, 128.8, 106.1, 102.3, 82.5, 82.2, 78.3, 76.5, 68.4, 67.9, 65.1, 56.3, 56.2, 32.2, 30.0, 29.8, 29.7, 26.6, 23.1, 14.5; $^1J_{C1,H1}$=167.2 Hz; HR-ESI-MS calcd for $[C_{39}H_{44}O_{11}]Na^+$ 711.2776, found 711.2718.

4.1.16. Octyl 3-*O*-(2,3-anhydro-5-*O*-benzoyl-α-D-ribofuranosyl)-2,5-di-*O*-benzoyl-α-D-arabinofuranoside (25). Disaccharide **25** was prepared from **23** (47 mg, 0.1 mmol) and **6**[7b] (40 mg, 0.12 mmol) and powdered molecular sieves (4 Å, 100 mg) in dry CH_2Cl_2 (10 mL) as described for the synthesis of **24** using *N*-iodosuccinimide (27 mg, 0.12 mmol) and silver triflate (10 mg, 0.04 mmol). Purification of the product by chromatography (hexanes/EtOAc, 4:1) gave **25** (130 mg, 89%) as a colorless oil: R_f 0.19 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +97.6 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.05–7.96 (m, 6H), 7.59–7.55 (m, 2H), 7.49–7.37 (m, 5H), 7.27–7.23 (m, 2H), 5.66 (s, 1H), 5.35 (d, 1H, *J*=1.3 Hz), 5.23 (s, 1H), 4.72 (dd, 1H, *J*=2.8, 11.4 Hz), 4.60–4.51 (m, 3H), 4.44 (dd, 1H, *J*=3.2, 11.6 Hz), 4.37 (d, 1H, *J*=5.7 Hz), 4.29 (dd, 1H, *J*=4.2, 12.0 Hz), 3.93 (dd, 1H, *J*=0.4, 2.7 Hz), 3.79–3.73 (m, 2H), 3.53–3.47 (m, 1H), 1.66–1.60 (m, 2H), 1.38–1.27 (m, 10H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 166.7, 166.5, 166.0, 133.9, 133.7, 133.4, 130.3, 130.2, 130.1 (2), 129.9, 129.8, 129.0, 128.9, 128.7, 106.1, 102.0, 83.9, 83.8, 80.8, 76.8, 68.1, 65.0, 63.8, 56.6 (2), 32.3, 29.8 (2), 29.6, 26.5, 23.1, 14.5; $^1J_{C1,H1}$=166.9 Hz; HR-ESI-MS calcd for $[C_{39}H_{44}O_{11}]Na^+$ 711.2776, found 711.2723.

4.1.17. Octyl 3,5-di-*O*-(2,3-anhydro-5-*O*-benzoyl-α-D-ribofuranosyl)-2-*O*-benzoyl-α-D-arabinofuranoside (26). Trisaccharide **26** was prepared from **22** (100 mg, 0.27 mmol) and **6**[7b] (233 mg, 0.68 mmol) and powdered molecular sieves (4 Å, 100 mg) in dry CH_2Cl_2 (15 mL) as described for the synthesis of **24** using *N*-iodosuccinimide (153 mg, 0.68 mmol) and silver triflate (44 mg, 0.17 mmol). Purification of the product by chromatography (hexanes/EtOAc, 4:1) gave **26** (165 mg, 75%) as a colorless oil: R_f 0.14 (hexanes/EtOAc, 2:1); $[\alpha]_D$ +91.2 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.00–7.90 (m, 6H), 7.60–7.52 (m, 3H), 7.46–7.38 (m, 6H), 5.58 (s, 1H), 5.45 (s, 1H), 5.33 (s, 1H), 5.15 (s, 1H), 4.53–4.52 (m, 2H), 4.46 (dd, 2H, *J*=2.9, 12.1 Hz), 4.39–4.28 (m, 4H), 4.12 (dd, 1H, *J*=4.1, 11.7 Hz), 4.02–3.99 (m, 1H), 3.91 (d, 1H, *J*=2.3 Hz), 3.75–3.69 (m, 4H), 3.47–3.42 (m, 1H), 1.62–1.58 (m, 2H), 1.33–1.27 (m, 10H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 166.5, 166.4, 166.0, 133.8, 133.7, 130.2, 130.1, 130.0, 129.9, 129.8, 129.0, 128.4, 106.1, 102.4, 102.2, 83.7, 83.5, 82.1, 76.6, 76.4, 68.0, 67.7, 65.1, 65.0, 56.5 (2), 56.2 (2), 32.2, 29.8, 29.8, 29.6, 26.4, 23.1, 14.5; $^1J_{C1,H1}$=168.4, 167.9; HR-ESI-MS calcd for $[C_{44}H_{50}O_{14}]Na^+$ 825.3093, found 825.3161.

4.1.18. Octyl 5-*O*-(2,3-anhydro-α-D-ribofuranosyl)-α-D-arabinofuranoside (27). To a solution of **24** (90 mg, 0.13 mmol) in dry CH_3OH (10 mL), was added a 0.1 M solution of $NaOCH_3$ in CH_3OH until the pH of the solution was 11. The reaction mixture was stirred at rt overnight and then neutralized with few drops of acetic acid. The solution was concentrated and the residue was purified by chromatography (CH_2Cl_2/CH_3OH, 8:1) to give **27** (45 mg, 92%) as a colorless oil: R_f 0.65 (CH_2Cl_2/CH_3OH, 6:1); $[\alpha]_D$ +97.6 (*c* 0.7, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 5.34 (s, 1H), 5.01 (s, 1H), 4.35 (dd, 1H, *J*=3.8, 3.8 Hz), 4.19 (d, 1H, *J*=2.1 Hz), 4.05 (d, 1H, *J*=10.5 Hz), 4.00–3.96 (m, 1H), 3.89 (dd, 1H, *J*=2.5, 10.7 Hz), 3.85–3.83 (m, 2H), 3.75–3.64 (m, 3H), 3.46–3.40 (m, 1H), 3.11 (d, 1H, *J*=10.8 Hz), 1.58–1.55 (m, 2H), 1.28–1.27 (m, 10H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 108.7, 101.7, 86.3, 79.9, 79.7, 78.7, 68.4, 68.1, 63.3, 58.0, 57.1, 32.2, 29.9, 29.7, 29.6, 26.5, 23.0, 14.5; HR-ESI-MS calcd for $[C_{18}H_{32}O_8]Na^+$ 399.1989, found 399.2004.

4.1.19. Octyl 3-*O*-(2,3-anhydro-α-D-ribofuranosyl)-α-D-arabinofuranoside (28). Disaccharide **25** (130 mg, 0.19 mmol) dissolved in dry CH_3OH (20 mL) was debenzoylated with a 0.1 M solution of $NaOCH_3$ in CH_3OH as described for the synthesis of **27**. The product was purified by chromatography (CH_2Cl_2/CH_3OH, 10:1) to give **28** (70 mg, 98%) as a colorless oil: R_f 0.67 (CH_2Cl_2/CH_3OH, 6:1); $[\alpha]_D$ +100.2 (*c* 0.6, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 5.51 (s, 1H), 4.92 (s, 1H), 4.32 (m, 1H), 4.20–4.10 (m, 3H), 3.86–3.85 (m, 3H), 3.75 (m, 1H), 3.68 (d, 1H, *J*=2.7 Hz), 3.67–3.63 (m, 2H), 3.41–3.38 (m, 1H), 1.59–1.55 (m, 2H), 1.28–1.27 (m, 10H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 108.1, 101.9, 84.0, 82.3, 81.1, 79.8, 68.2, 63.1, 61.0, 56.8 (2), 32.2, 29.9, 29.8, 29.7, 26.5, 23.0, 14.5; HR-ESI-MS calcd for $C_{18}H_{32}O_8]Na^+$ 399.1989, found 399.1980.

4.1.20. Octyl 3,5-di-*O*-(2,3-anhydro-α-D-ribofuranosyl)-α-D-arabinofuranoside (29). Trisaccharide **26** (70 mg, 0.08 mmol) dissolved in dry CH_3OH (10 mL) was debenzoylated with a 0.1 M solution of $NaOCH_3$ in CH_3OH as described for the synthesis of **27**. The product was purified by chromatography (CH_2Cl_2/CH_3OH, 6:1) to give **29** (35 mg, 89%) as a colorless oil: R_f 0.60 (CH_2Cl_2/

CH_3OH, 6:1); $[\alpha]_D$ +68.9 (*c* 1.0, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 5.46 (s, 1H), 5.37 (s, 1H), 4.95 (s, 1H), 4.34–4.31 (m, 2H), 4.22–4.17 (m, 3H), 4.11–4.08 (m, 1H), 3.91–3.85 (m, 3H), 3.75–3.62 (m, 6H), 3.43–3.37 (m, 1H), 1.58–1.55 (m, 2H), 1.28–1.26 (m, 10H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 108.4, 102.4, 102.0, 84.7, 81.8, 80.8, 79.8, 79.6, 68.3 (2), 63.2 (2), 57.5, 57.1, 56.7 (2), 32.2, 29.9, 29.8, 29.7, 26.4, 23.1, 14.5; HR-ESI-MS calcd for $[C_{23}H_{38}O_{11}]Na^+$ 513.2306, found 513.2289.

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References and notes

1. (a) D'Souza, F. W.; Cheshev, P. E.; Ayers, J. D.; Lowary, T. L. *J. Org. Chem.* **1998**, *63*, 9037. (b) D'Souza, F. W.; Ayers, J. D.; McCarren, P. R.; Lowary, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 1251. (c) D'Souza, F. W.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 1493. (d) Yin, H.; D'Souza, F. W.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 892.
2. Lowary, T. L. Mycobacterial cell wall components. In *Glycoscience: chemistry and chemical biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; pp 2005–2080.
3. (a) Ayers, J. D.; Lowary, T. L.; Morehouse, C. B.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 437. (b) Cociorva, O. M.; Gurcha, S. S.; Besra, G. S.; Lowary, T. L. *Bioorg. Med. Chem.* Manuscript in preparation.
4. Kaur, D.; Lowary, T. L.; Vissa, V. D.; Crick, D. C.; Brennan, P. J. *Microbiology UK* **2002**, *148*, 3059.
5. (a) Boons, G.-J. Glycosides as donors. In *Glycoscience: chemistry and chemical biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; pp 551–581. (b) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137. (c) Ley, S. V.; Priepke, H. W. M. *Angew. Chem. Intl. Ed. Engl.* **1994**, *33*, 2292. (d) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1434.
6. Yin, H. F.; Lowary, T. L. *Tetrahedron Lett.* **2001**, *42*, 5829.
7. (a) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *Org. Lett.* **2001**, *3*, 607. (b) Gadikota, R. R.; Callam, C. S.; Wagner, T.; DelFraino, B.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155–4165.
8. The propensity of furanose rings with the 2,3-anhydro-ribo stereochemistry (e.g., **7**) to undergo regioselective nucleophilic opening at C-2 has long been appreciated: Williams, N. R. *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 109.
9. (a) Lowary, T. L.; Hindsgaul, O. *Carbohydr. Res.* **1993**, *249*, 163. (b) Lowary, T. L.; Hindsgaul, O. *Carbohydr. Res.* **1994**, *251*, 33–67.
10. (a) Wen, X. H.; Crick, D. C.; Brennan, P. J.; Hultin, P. G. *Bioorg. Med. Chem.* **2003**, *11*, 3579. (b) Pathak, A. K.; Pathak, V.; Kulshrestha, M.; Kinnaird, D.; Suling, W. J.; Gurcha, S. S.; Besra, G. S.; Reynolds, R. C. *Tetrahedron* **2003**, *59*, 10239.
11. Pathak, A. K.; Pathak, V.; Maddry, J. A.; Suling, W. J.; Gurcha, S. S.; Besra, G. S.; Reynolds, R. C. *Bioorg. Med. Chem.* **2001**, *9*, 3145.
12. Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.
13. The $^1J_{C\text{-}1,H\text{-}1}$ magnitudes for the anhydrosugar residues in **27**–**29** are between 166.9 and 168.4 Hz, which are consistent with the 2,3-anhydro-α-D-ribofuranosyl stererochemistry: Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 4549.
14. Mizutani, K.; Kasai, R.; Nakamura, M.; Tanaka, O.; Matsuura, H. *Carbohydr. Res.* **1989**, *185*, 27.

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Partial synthesis of C-ring derivatives from oleanolic and maslinic acids. Formation of several triene systems by chemical and photochemical isomerization processes

Andrés García-Granados, Pilar E. López, Enrique Melguizo, Andrés Parra* and Yolanda Simeó

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, 18071 Granada, Spain

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Abstract—Some triterpenic compounds modified in C-ring were semi-synthesised from oleanolic acid contained in the solid waste of olive-oil pressing. The corresponding esters of oleanolic and maslinic acids rendered products with a diene system, which led to oleantrienes resembling previtamin D_2 by an electrocyclic reaction. Chemical and photochemical isomerization of these compounds yielded two different trienes with similar structure to tachysterol and vitamin D_2.

1. Introduction

Oleanolic acid (3β-hydroxy-12-oleanen-28-oic acid, **1**) and maslinic acid (2α,3β-dihydroxy-12-oleanen-28-oic acid, **2**) are widespread in plants in the form of free acids or derivatives such as methyl esters, acetyl-, oxo-, glycosyl- and other compounds.[1]These triterpenic acids also appear, in large amounts, in olive-oil pressing residues, and our group has developed a procedure for their isolation from these solid waste that renders a 0.4% in weight of oleanolic acid and 0.8% of maslinic acid.[2] The large amounts of both products available allow their use as suitable starting material for the semi-synthesis of other biologically or chemically remarkable compounds.[3] Moreover, these natural oleanene acids and several closely related derivatives exhibit biological and pharmacological properties, such as anti-HIV, hepatoprotective, anti-inflammatory, cytotoxic or antimicrobial activities, which have been summarised in some reviews.[4]

In previous papers, we have described the semi-synthesis of several triterpenic derivatives with the A-ring functionalized from oleanolic and maslinic acids.[5] In this way, contracted A-ring, deoxygenated and halohydrins derivatives, aside from a synthon of A, B-rings of Finasteride® [5α,17β-*N*-(1,1-dimethylethyl)-3-oxo-4-azaandrostan-1-ene-17-carboxamide],[6] were obtained.[7] Finasteride® belongs to the 4-azasteroid structural class of compounds and is being used in the treatment of disorders caused by an excessive production of dihydrotestosterone by the enzyme 5α-reductase, such as prostate disorders, hair growth and pubertal changes. Likewise, we reported recent preliminary results about the formation of several trienes in C-ring from oleanolic and maslinic acids.[8]

In the present paper, above-mentioned trienes and some other derivatives in C-ring of this starting material are semi-synthesised and characterised. Thus, ozonolysis of oleanolic acid (**1**) yielded lactone **7**, the reactivity of which was studied with the aim of forming a homodiene (product **18**), which was finally semi-synthesised by reduction of oleanolic acid (**1**) with $LiAlH_4$ to obtain erythrodiol[9] and subsequent treatment with NBS. On the other hand, the reaction of methyl oleanate, methyl maslinate and their acetyl derivatives with NBS led to dienes **20**–**23** and some brominated and rearranged products. We also described the method of obtaining trienes **30**–**33** with similar structure to preergocalciferol (previtamin D_2) by a photochemical reaction starting from the aforementioned dienes. A chemical isomerization of these compounds with iodine gave trienes **34**–**37** (similar in structure to tachysterol) and a photochemical reaction rendered exocyclic trienes **38**–**41**, resembling ergocalciferol (vitamin D_2). These processes were based on photochemical interconversions of pro-vitamin D_2, lumisterol, previtamin D_2, tachysterol and some derivatives,[10] in addition to photochemical and thermal transformations of some pentacyclic triterpenoids such as methyl dehidroursolate.[11]

2. Results and discussion

Oleanolic (**1**) and maslinic (**2**) acids were obtained from olive-pressing residues by successive extractions with

Keywords: Oleanolic; Maslinic; Triterpene; Diene; Triene; Isomerization.
* Corresponding author. Tel.: +34-58-240480; fax: +34-58-243364; e-mail address: aparra@ugr.es

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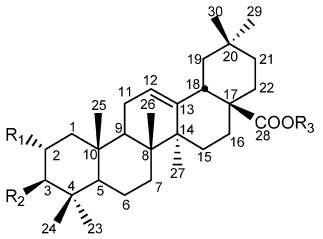


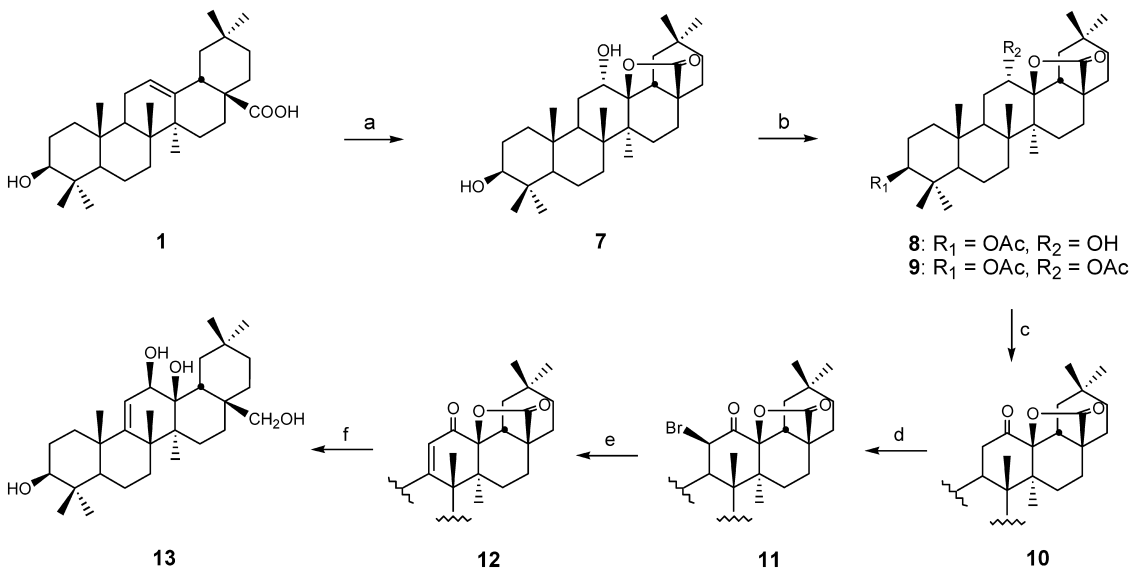
Figure 1. Structures of products **1**–**6**.

hexane and ethyl acetate in soxhlet.[2] The hexane extract contained mostly oleanolic acid (**1**) (80–85%), whereas the EtOAc extract contained mostly maslinic acid (**2**) (80–85%). After flash chromatography on a silica gel column, large amounts of these starting materials were obtained. The structures of the two oleanene acids (**1** and **2**) were established from their spectroscopic data, which were compared with those in earlier reports.[1] Subsequently, we carried out the esterification of both acids with an ethereal solution of diazomethane or NaOH–MeI, yielding the corresponding methyl alcohol esters, compounds **3** and **4**. Acetylation of these esters with Ac_2O/Py at reflux provided acetylated derivatives **5** and **6** (Fig. 1).

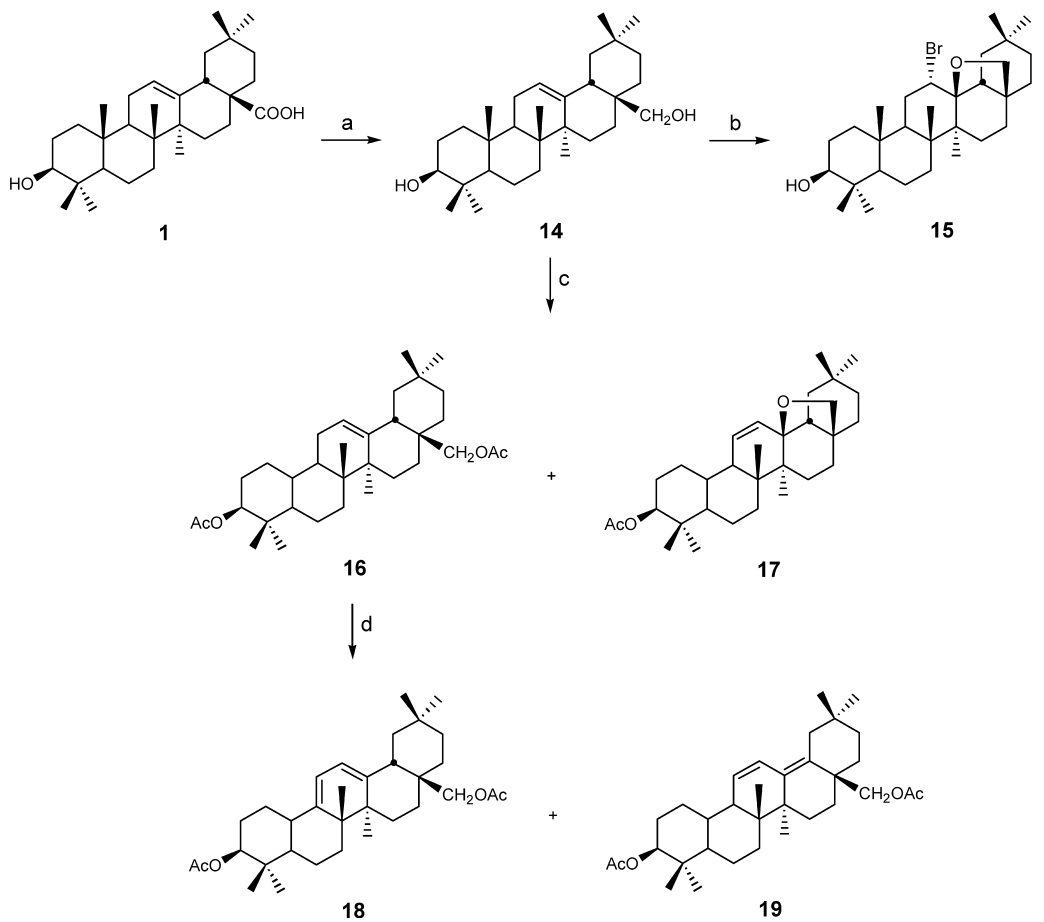
Ozonolysis of oleanolic acid (**1**) in $CHCl_3$:MeOH (1:1) at −78 °C gave lactone **7** (Scheme 1), which was formed by attack of the carboxylic group at C-28 on C-13 and opening of the α-epoxide previously formed by the ozonolysis process between C-12 and C-13. This reaction was similar to the photochemical lactonization of oleanolic acid reported by Misra and Laatsch.[12] Controlled acetylation of product **7** at 0 °C provided compounds **8** and **9**, acetylated in different positions of the molecule. The main product of this reaction, **8** was oxidized with Jones' reagent to obtain the keto lactone **10**. To produce a bromination in α-position to the carbonyl group, we treated product **10** with a solution of Br_2 in CCl_4, rendering compound **11**. The stereochemistry of the halogen atom was established by comparison of the experimental coupling constant between H-9 and H-11 and the theoretical values for the two possible dispositions for H-11. To form a double bond in C-9/C-11, we treated product **11** with Li_2CO_3 and LiBr, obtaining the α,β-unsaturated ketone **12**. Searching to form a diene system in C-ring of triterpene, we opened the lactonic group between C-13 and C-17 by reduction with $LiAlH_4$, yielding tetrol **13** (Scheme 1). In this product, the stereochemistry of the hydroxyl group at C-12 was β, since the hydride ion should enter from the less hindered face, the α face, giving rise to an hydroxyl group in β.

On the other hand, to avoid lactonization, we reduced oleanolic acid (**1**) with $LiAlH_4$ to give product **14**, which was identified as erythrodiol from their NMR data (Scheme 2).[9] Bromination of this compound at C-11 and subsequent dehydrohalogenation could lead to the diene sought. However, treatment of this product with NBS gave compound **15**, resulting from the cyclation of the hydroxyl group at C-28 on C-13 and reaction of negatively charged C-12 with NBS. To avoid the formation of this cyclic ether, we protected the hydroxyl group at C-28. Thus, product **14** was acetylated with Ac_2O/Py, yielding compounds **16** and **17**. The major product of this process, **16**, was the corresponding diacetylated derivative and the minor product had a cyclic ether between C-28 and C-13 and a double bond in C-11/C-12 as a consequence of the cyclation of the hydroxyl group at C-28 before acetylation. Finally, treatment of product **16** with NBS gave diene **18** in one step by bromination in allylic position and subsequent spontaneous dehydrohalogenation, and a minor product, **19**, which is another diene with different positions for the double bonds.

According to the above-described results, in order to avoid the reduction of oleanolic acid and the formation of cyclic ethers or lactones, and to improve the yield of diene, we

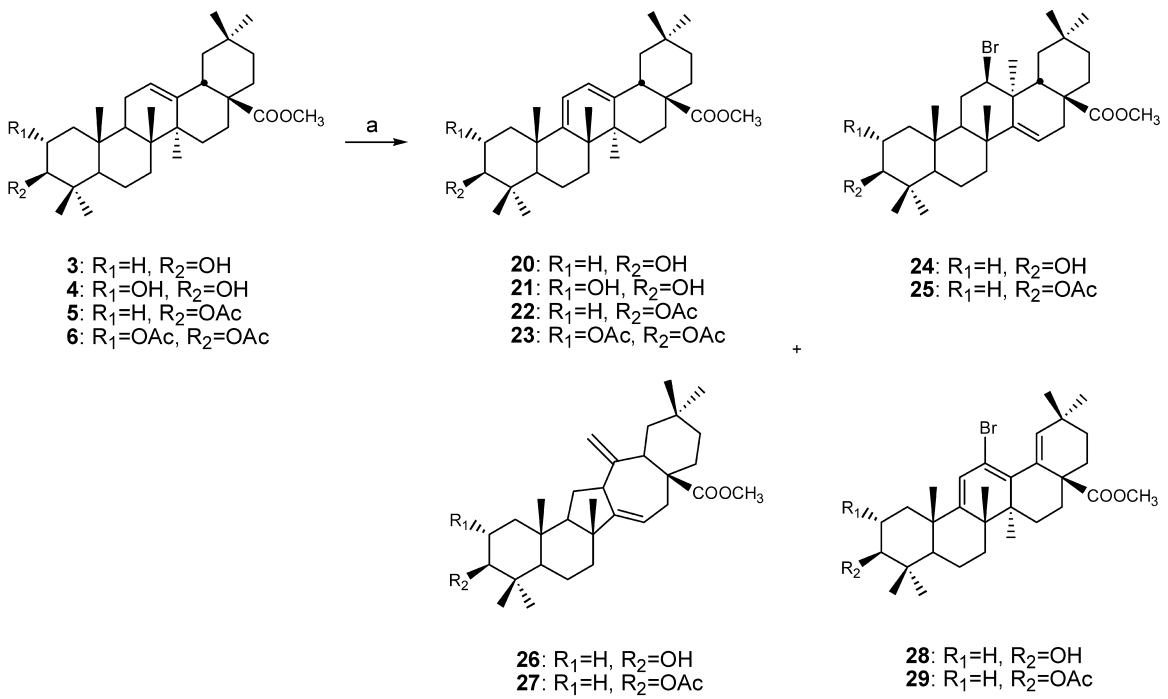


Scheme 1. *Reagents and conditions*: (a) O_3/$CHCl_3$:MeOH/−78 °C/30 min **7** (70%); (b) Ac_2O/Py/0 °C/3 h **8** (70%) and **9** (20%); (c) Jones' reagent/0 °C/1 h **10** (95%); (d) Br_2/CCl_4/rt/5 h **11** (80%); (e) Li_2CO_3/LiBr/reflux/3 h **12** (60%); (f) $LiAlH_4$/THF/reflux/1.5 h **13** (95%).



1 **14** **15** **16** **17** **18** **19**

Scheme 2. *Reagents and conditions*: (a) $LiAlH_4$/THF/reflux/3.5 h **14** (95%); (b) NBS/AIBN/CCl_4/rt/1 h **15** (50%); (c) Ac_2O/Py/reflux/1.5 h **16** (70%) and **17** (20%); (d) NBS/AIBN/CCl_4/rt/1 h **18** (40%) and **19** (5%).



3: R_1=H, R_2=OH
4: R_1=OH, R_2=OH
5: R_1=H, R_2=OAc
6: R_1=OAc, R_2=OAc

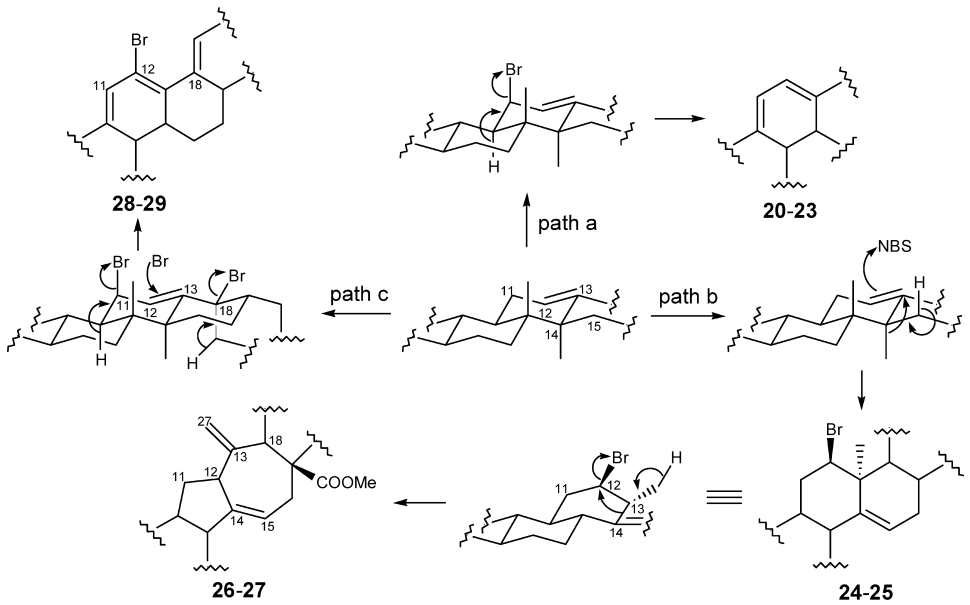
20: R_1=H, R_2=OH
21: R_1=OH, R_2=OH
22: R_1=H, R_2=OAc
23: R_1=OAc, R_2=OAc

24: R_1=H, R_2=OH
25: R_1=H, R_2=OAc

26: R_1=H, R_2=OH
27: R_1=H, R_2=OAc

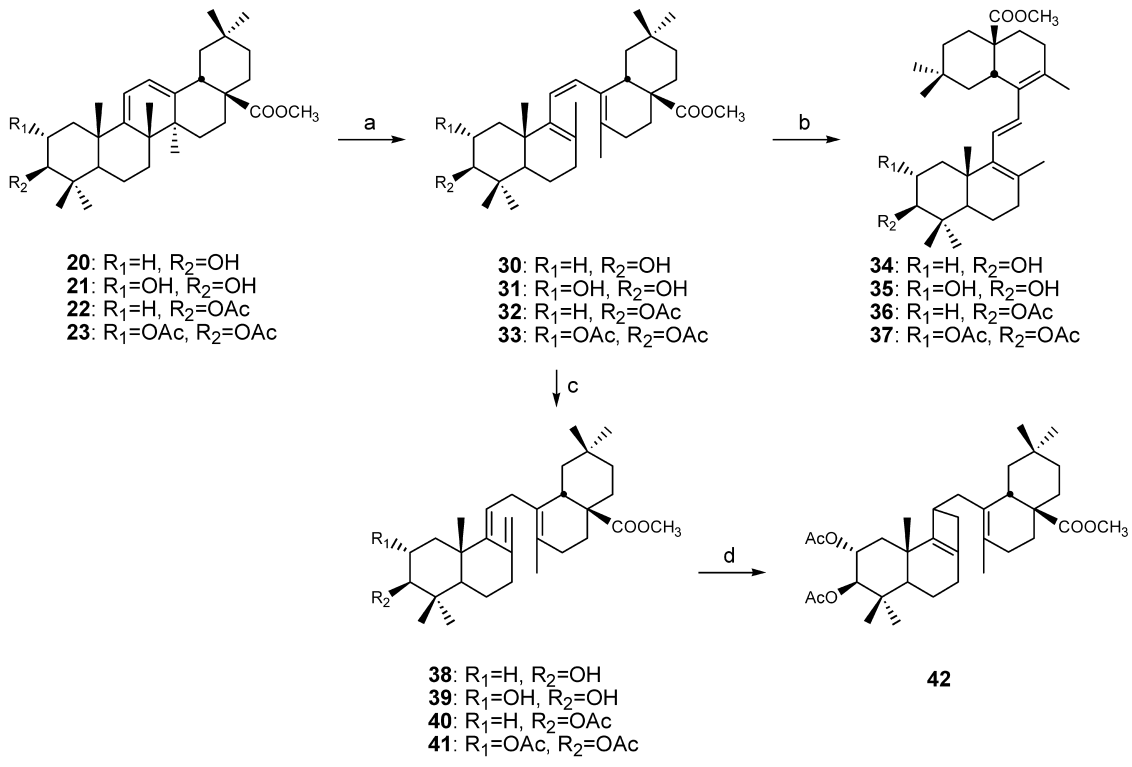
28: R_1=H, R_2=OH
29: R_1=H, R_2=OAc

Scheme 3. *Reagents and conditions*: (a) starting from **3**, NBS/AIBN/CCl_4/rt/2 h **20** (70%), **24** (10%), **26** (5%) and **28** (10%); starting from **4**, NBS/AIBN/CCl_4/reflux/1 h **21** (90%); starting from **5**, NBS/AIBN/CCl_4/rt/2 h **22** (60%), **25** (15%), **27** (5%) and **29** (15%); starting from **6**, NBS/AIBN/CCl_4/reflux/1 h **23** (90%).



Scheme 4. Proposed mechanisms for the obtention of products **20**–**29**.

used methyl oleanate (**3**), methyl maslinate (**4**) and their acetylated derivatives **5** and **6** as starting material for the diene system formation. Thus, treatment of maslinic esters **4** and **6** with NBS at reflux for 1 h rendered an excellent yield of dienes **21** and **23** (90%; Scheme 3). Again, a bromination/dehydrobromination process between C-9 and C-11 had occurred, giving rise to a conjugated double bond in the C-ring of the triterpenic compounds (Scheme 4, path a). However, the reaction of oleanolic esters **3** and **5** with this reagent at rt for 2 h gave dienes **20** and **22**[13], and compounds **24** and **25**, **26** and **27**, and **28** and **29** (Scheme 3), which were characterized by their spectroscopic properties. Products **24** and **25** presented a taraxerene structure and were formed by the loss of a hydrogen of C-15, migration of the methyl group at C-14 to C-13 with the same configuration, and the entry of a halogen atom in C-12 (Scheme 4, path b). This change of skeleton was studied by Corey et al. from a mixture of α-amiryn and β-amiryn.[14] The taraxerene skeleton is more unstable than the olean-12-ene (methyl oleanate) system, and the halogenation in C-12 must provide the required energy to change the skeleton.

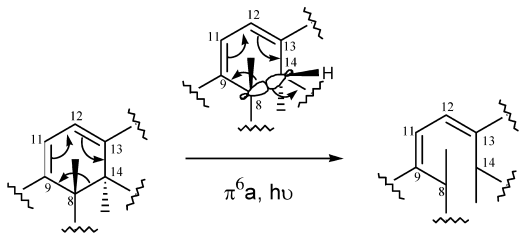


Scheme 5. *Reagents and conditions*: (a) *hν*/EtOH/borosilicate flask/20 min **30**, **31**, **32** and **33** (95%); (b) I_2/hexane/reflux/5 h **34**, **35**, **36** and **37** (60%); (c) *hν*/EtOH/quartz flask/30 min **38**, **39**, **40** and **41** (95%); (d) starting from **41**, *hν*/EtOH/quartz flask/30 min **42** (50%).

Moreover, starting from compounds **24** and **25**, a rearrangement process took place. This transformation could occur due to the transperiplanar disposition of bonds C-12/Br and C-13/C-14, leading to products **26** and **27**, which presented a five-membered ring C and a seven-membered ring D (Scheme 4). The structure of these compounds was established by their spectroscopic characteristics. The appearance of two ethylenic protons each coupled in ^{1}H NMR spectrum, which correlated with the signals of C-12 and C-18 in HMBC spectrum, supports the proposed structure.

Finally, by a double bromination/dehydrobromination process in allylic position and the addition of a halogen atom in C-12, products **28**–**29** were formed (Scheme 4, path c). The presence of four ethylenic quaternary carbon atoms in ^{13}C NMR spectrum confirmed this structure and the low shift for C-12 indicated that the halogen atom was situated in this position.

On the other hand, irradiation of homodienes **20**–**23** with a high pressure Hg street lamp in a borosilicate flask yielded trienes **30**–**33** (95%), respectively (Scheme 5). This C-ring opening occurred by a conrotatory photochemical electrocyclic reaction similar to the transformation of ergosterol in previtamin D. This process could take place due to the *trans*-disposition between Me on C-8 (C-26) and Me on C-14 (C-27), that allowed an antarafacial reaction of the 6π electron system, giving rise to the cleavage of C-8/C-14 bond and thus rendered trienes **30**–**33** (Scheme 6). The structure of compound **33** was established by their mono- and bidimensional spectra and an X-ray experience, that showed an helicolidal disposition of D, E-rings over A, B-rings.

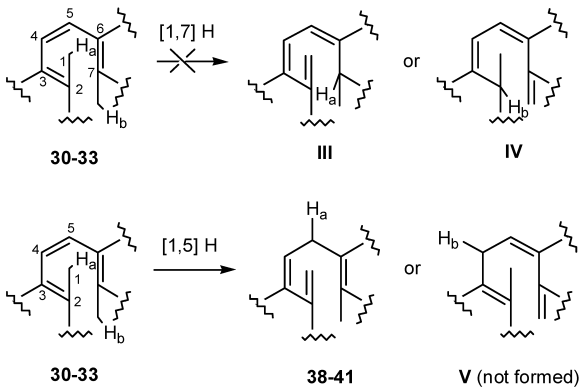


Scheme 6. Electrocyclic reaction of products **20**–**23**.

After separation by column chromatography, purification and characterization, products **30**–**33** were independently treated with different oxidative reagents (ozone, OsO_4/$NaIO_4$, $RuCl_3$/$NaIO_4$), rendering a mixture of various epoxy or methylketone compounds resulting from oxidation in the most substituted double bonds while the central double bond (C-11/C-12 double bond) remained unaltered. Subsequently, we carried out the chemical isomerization of *cis*-trienes **30**–**33** to *trans*-trienes **34**–**37** by treatment with iodine in hexane in acceptable yield (60%) (Scheme 5). The *trans*-disposition of the double bond between C-11 and C-12 was verified mainly by comparison of ^{1}H NMR and ^{13}C NMR data. Thus, compounds **30**–**33** (*cis*-trienes) had moderately high coupling constants (Table 1). However, compounds **34**–**37** (*trans*-trienes) presented similar shifts for H-11 and H-12, but had higher coupling constants between these two protons. Furthermore, products **34**–**37** had lower ^{13}C NMR shifts for C-11 and C-12 than compounds **30**–**33**.

Table 1. Comparison of some remarkable shifts of products **30**–**37**

	30	**31**	**32**	**33**	**34**	**35**	**36**	**37**
$J_{11/12}$ (Hz)	12.9	12.8	12.9	12.6	16.2	16.2	16.2	16.0
C-11 (ppm)	127.3	126.8	127.3	127.2	123.2	122.7	123.0	122.4
C-12 (ppm)	132.9	133.1	132.9	133.3	131.3	131.8	131.4	131.7



Scheme 7. Possible [1,5]H and [1,7]H displacements for products **30**–**33**.

Hypothetically, although the *trans* disposition of the central double bond was fixed, there were four possible stereochemical dispositions for the double bonds between C-9 and C-11 or C-12 and C-13 due to the possible rotation around these bonds. However, it was verified experimentally that mainly one product was obtained. Data from NOE experiments confirmed that one of the ethylenic protons (H-11 or H-12) was located between the two allylic methyl groups (Fig. 2). Therefore, we discarded *cis*–*cis* and *trans*–*trans* dispositions, since in these structures each ethylenic proton correlated with only one allylic methyl group. Finally, to distinguish between the *cis*–*trans* (I) or *trans*–*cis* (II) disposition, we examined the results of HMBC and HMQC experiments. These spectra showed that the ethylenic proton located between the two allylic methyls in NOE spectrum correlated in the HMBC spectrum with C-18, leading us to deduce that this ethylenic hydrogen was H-12 and products **34**–**37** presented a *cis*–*trans* structure. Therefore, *trans* trienes had a $S_{9,11}Z$ $S_{12,13}E$ disposition (Fig. 3).

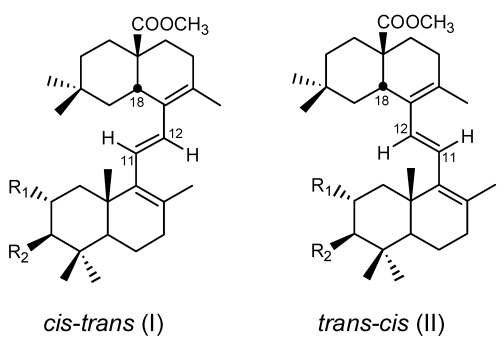
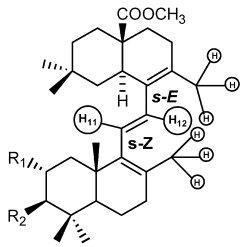


Figure 2. Two possible dispositions for products **34**–**37**.



34: R_1=H, R_2=OH
35: R_1=OH, R_2=OH
36: R_1=H, R_2=OAc
37: R_1=OAc, R_2=OAc

Figure 3. Structures of products **34**–**37**.

Moreover, irradiation of products **30**–**33** (*cis*-trienes) independently in a quartz flask for 30 min yielded exocyclic trienes **38**–**41** in very high yield (95%) (Scheme 5). The appearance of an exocyclic double bond was confirmed by the spectroscopic characteristic of the methylene group. This product was formed by a [1,5]H displacement, since a suprafacial migration of one hydrogen from C-26 methyl group to C-12 took place (Scheme 7). However, a spontaneous or photochemical [1,7]H sigmatropic rearrangement did not occur as in the transformation of provitamin D_2 to vitamin D_2,[10,15] because C-26 and C-27 methyls in trienes **30**–**33** distorted the molecular conformation, impeding any antarafacial or suprafacial migration between 1 and 7 positions of the H sigmatropic shift.

Thus, the molecular disposition allowed only one of the two possible [1,5]H displacements, since experimentally only trienes **38**–**41**, which presented two conjugated double bonds between C-8/C-26 and C-9/C-11 and another isolated double bond between C-13 and C-14 atoms, were formed.

Finally, when exocyclic triene **41** was isolated and irradiated again under the same conditions for an extra time of 30 min, product **42** was obtained (Scheme 5). Analogous compounds to diene **42** were described as over-irradiation products by Barton et al. in the photochemical reaction of a triene obtained from methyl dehydroursolate acetate.[11] This compound **42** could be formed by an electrocyclic reaction of a 4π electron system, giving rise to a C-26/C-11 bond and a double bond between C-8 and C-9. The structure was deduced from spectroscopic data, which showed four ethylenic quaternary carbon atoms and no methylene group.

3. Conclusion

Oleanolic and maslinic acids were suitable starting material for the semi-synthesis of several remarkable derivatives modified in C and/or D rings of the oleanene skeleton. Treatment of the esters of aforementioned acids with NBS gave rise to a promising diene system in C-ring by a spontaneous bromination/dehydrobromination process.

The cleveage of the C-8/C-14 bond of the diene by an electrocyclic reaction was achieved, yielding a triene with the C-ring opened. Starting from this compound, an exocyclic triene was obtained by a photochemical reaction, while a chemical isomerization led to a *trans*-triene, whose stereochemical disposition was determined accurately. These triene products will be used in future research as starting material for the semi-synthesis of significant sesquiterpene chiral synthons by cleavage of the central double bonds.

4. Experimental

4.1. General

Measurements of NMR spectra (300.13 MHz ^{1}H and 75.47 MHz ^{13}C) were made in $CDCl_3$ (which also provided the lock signal) using BRUKER AM-300 or ARX-400 spectrometers. The assignments of ^{13}C chemical shifts were made with the aid of distortionless enhancement by polarization transfer (DEPT) using a flip angle of 135°. Bruker's programs were used for COSY (45°) and C/H and C/C correlation. IR spectra were recorded on a MATTSON SATELLITE FTIR spectrometer. High-resolution mass spectra were made in a MICROMASS AUTOSPEC-Q spectrometer (EBE geometry). Mps were determined using a Kofler (Reichter) apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 25 °C. All reaction solvents were dried and distilled immediately prior to use; chromatography solvents were distilled prior to use. Commercially available reagents were used without further purification. Silica gel Scharlau 60 (40–60 μm) was used for flash chromatography. CH_2Cl_2 or $CHCl_3$ containing increasing amounts of Me_2CO were used as eluents. Analytical plates (silica gel, Merck 60 G) were rendered visible by spraying with H_2SO_4–AcOH, followed by heating to 120 °C.

4.2. Isolation of starting materials

Oleanolic acid (**1**)[1,2] and maslinic acid (**2**)[1,2] were isolated from solid wastes resulting from olive-oil production, which were extracted in a Soxhlet with hexane and EtOAc successively. Hexane extracts were a mixture of oleanolic acid and maslinic acid (80:20) whereas this relationship was (20:80) for the EtOAc extracts. Both products were purified from these mixtures by column chromatography over silica gel, eluting with a $CHCl_3$–MeOH or CH_2Cl_2–Acetone mixtures of increasing polarity. Oleanolic acid (**1**) and maslinic acid (**2**) were transformed into the corresponding methyl esters with ethereal CH_2N_2 or NaOH–MeI and thus, methyl 3β-hydroxy-12-oleanen-28-oate (**3**)[5] and methyl 2α,3β-dihydroxy-12-oleanen-28-oate (**4**)[5] were obtained. Acetylation of these esters with Ac_2O/Py at reflux provided acetylated derivatives **5**[5] and **6**[5].

4.2.1. Ozonolysis of 1. Product **1** (1.5 g, 3.3 mmol), after being dissolved in 15 mL of $CHCl_3$ and 15 mL of MeOH, was stirred at −78 °C and passed through an O_3 flow of 0.1 L/min (10% O_2–90% O_3). After 30 min, excess ozone was removed with argon. The mixture was maintained with stirring while being cooled down for 4 h. Then it was evaporated and purified over silica gel, yielding 1.08 g (70%) of **7**: white solid; mp 247–249 °C; $[\alpha]_D^{25}$=26 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3472, 2949, 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.87 (1H, dd, J_1=J_2=2.9 Hz, H-12), 3.21 (1H,

dd, J_1=5.4 Hz, J_2=10.9 Hz, H-3), 1.29 (3H, s, 3H-27), 1.13 (3H, s, 3H-26), 0.98 (3H, s, 3H-23), 0.97 (3H, s, 3H-29), 0.88 (3H, s, 3H-30), 0.86 (3H, s, 3H-25), 0.76 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.4 (C-24), 16.4 (C-25), 17.8 (C-6), 18.6 and 18.7 (C-26 and C-27), 21.3 (C-16), 24.0 (C-30), 27.3, 27.5, 28.1 and 28.8 (C-2, C-11, C-15 and C-22), 28.1 (C-23), 31.6 (C-20), 33.3 (C-29), 34.0 and 34.2 (C-7 and C-21), 36.5 (C-10), 38.9 (C-1), 39.0 (C-4), 39.5 (C-19), 42.1 (C-14), 42.4 (C-8), 44.6 (C-9), 44.8 (C-17), 51.2 (C-18), 55.2 (C-5), 76.4 (C-12), 78.9 (C-3), 90.7 (C-13), 180.0 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 495.3454 ($C_{30}H_{48}O_4Na$, calcd 495.3450).

4.2.2. Acetylation of 7. Product **7** (650 mg, 1.4 mmol) was dissolved in 20 mL of pyridine and 10 mL of Ac_2O and stirred for 3 h at 0 °C. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aqueous $KHSO_4$ solution and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 65 mg (10%) of **7**, 495 mg (70%) of product **8**: white solid; mp 261–263 °C; $[\alpha]_D^{25}$=37 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3487, 2928, 2360, 1739, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.48 (1H, dd, J_1=5.7 Hz, J_2=9.7 Hz, H-3), 3.87 (1H, dd, J_1=J_2=2.5 Hz, H-12), 2.04 (3H, s, CO*CH*$_3$), 1.29 (3H, s, Me), 1.13 (3H, s, Me), 0.97 (3H, s, Me), 0.89 (3H, s, Me), 0.89 (3H, s, Me), 0.86 (3H, s, Me), 0.84 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.5 (C-24), 16.5 (C-25), 17.7 (C-6), 18.6 and 18.7 (C-26 and C-27), 21.3 (C-16), 21.4 (CO*CH*$_3$), 23.6 (C-2), 24.0 (C-30), 27.6, 28.1 and 28.9 (C-11, C-15 and C-22), 28.0 (C-23), 31.6 (C-20), 33.3 (C-29), 34.0 and 34.2 (C-7 and C-21), 36.4 (C-10), 37.9 (C-4), 38.6 and 39.4 (C-1 and C-19), 42.1 (C-14), 42.4 (C-8), 44.6 (C-9), 44.8 (C-17), 51.2 (C-18), 55.4 (C-5), 76.3 (C-12), 80.9 (C-3), 90.7 (C-13), 171.2 (*COCH*$_3$), 180.1 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 537.3557 ($C_{32}H_{50}O_5Na$, calcd 537.3556); and 150 mg (20%) of **9**: white solid; mp 241–243 °C; $[\alpha]_D^{25}$=57 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2928, 2360, 1776, 1743, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.01 (1H, dd, J_1=J_2= 2.9 Hz, H-12), 4.47 (1H, dd, J_1=6.2 Hz, J_2=10.0 Hz, H-3), 2.09 (3H, s, CO*CH*$_3$), 2.04 (3H, s, CO*CH*$_3$), 1.26 (3H, s, Me), 1.15 (3H, s, Me), 0.96 (3H, s, Me), 0.87 (3H, s, Me), 0.86 (3H, s, Me), 0.84 (3H, s, Me), 0.81 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.3 and 16.5 (C-24 and C-25), 17.7 (C-6), 18.4 and 18.6 (C-26 and C-27), 21.1 (C-16), 21.4 (CO*CH*$_3$), 21.5 (CO*CH*$_3$), 23.6 (C-2), 23.9 (C-30), 25.2 (C-15), 27.4 and 27.9 (C-11 and C-22), 28.0 (C-23), 31.6 (C-20), 33.4 (C-29), 33.9 (C-7), 33.9 (C-21), 36.4 (C-10), 37.9 (C-4), 38.5 (C-1), 39.5 (C-19), 42.2 (C-14), 42.3 (C-8), 44.6 (C-17), 45.4 (C-9), 50.3 (C-18), 55.4 (C-5), 76.8 (C-12), 80.7 (C-3), 89.5 (C-13), 169.4 (*CO*CH_3), 171.2 (*CO*CH_3), 179.1 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 579.3664 ($C_{34}H_{52}O_6Na$, calcd 579.3662).

4.2.3. Oxidation of 8. Jones' reagent was added dropwise to a stirred solution of product **8** (450 mg, 0.9 mmol) in acetone at 0 °C until an orange-brown colour persisted. Methanol was added and the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 425 mg (95%) of **10**: white solid; mp 287–289 °C; $[\alpha]_D^{25}$=8 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2951, 1780, 1727, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.46 (1H, dd, J_1=5.0 Hz, J_2=10.8 Hz, H-3), 2.69 (1H, dd, J_1=J_2=13.9 Hz, H-11a), 2.52 (1H, dd, J_1=J_2=8.2 Hz, H-18), 2.35 (1H, dd, J_1=3.0 Hz, J_2= 13.9 Hz, H-11b), 2.03 (3H, s, CO*CH*$_3$), 1.30 (3H, s, 3H-25), 0.96 (3H, s, 3H-29), 0.94 (3H, s, 3H-26), 0.94 (3H, s, 3H-27), 0.92 (3H, s, 3H-23), 0.85 (3H, s, 3H-30), 0.85 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.9 and 18.2 (C-26 and C-27), 16.4 (C-24), 17.5 (C-6), 18.6 (C-25), 20.7 (C-16), 21.3 (CO*CH*$_3$), 23.4 (C-2), 23.8 (C-30), 25.9 (C-15), 27.3 (C-22), 27.9 (C-23), 31.6 (C-20), 32.9 (C-1), 33.2 (C-29), 34.2 (C-7), 37.2 and 37.9 (C-4 and C-10), 37.3 and 37.4 (C-11 and C-21), 38.1 (C-19), 42.5 (C-8), 43.7 (C-14), 44.0 (C-18), 44.0 (C-17), 51.0 (C-9), 55.0 (C-5), 80.3 (C-3), 91.0 (C-13), 171.0 (*CO*CH_3), 178.5 (C-28), 206.0 (C-12); HRLSIMS, *m/z*: $[M+Na]^+$ 535.3391 ($C_{32}H_{48}O_5Na$, calcd 535.3399).

4.2.4. Treatment of 10 with bromine. Product **10** (405 mg, 0.8 mmol) was dissolved in 10 mL of CH_2Cl_2 and 4 mL of a 0.1 M solution of Br_2 in CCl_4 were added.The reaction mixture was maintained at room temperature for 5 h, and then diluted with CH_2Cl_2, neutralized with a $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and evaporated to dryness. Chromatography over silica gel yielded 374 mg (80%) of **11**: white solid; mp 252–254 °C; $[\alpha]_D^{25}$=4 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1780, 1719, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.47 (1H, dd, J_1=4.5 Hz, J_2=11.1 Hz, H-3), 4.32 (1H, d, J=6.6 Hz, H-11), 2.67 (1H, dd, J_1= 2.7 Hz, J_2=13.7 Hz, H-18), 2.03 (3H, s, CO*CH*$_3$), 1.46 (3H, s, Me), 0.98 (3H, s, Me), 0.97 (3H, s, Me), 0.90 (3H, s, Me), 0.87 (3H, s, Me), 0.85 (3H, s, Me), 0.84 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.3 (Me), 16.7 (Me), 17.3 (C-6), 19.4 (Me), 20.3 (Me), 21.3 (CO*CH*$_3$), 21.5 (C-16), 23.4 (C-2), 23.5 (C-30), 26.5 and 26.8 (C-15 and C-22), 27.8 (C-23), 31.5 (C-1), 31.7 (C-20), 33.3 (C-29), 34.3 (C-7), 37.1 (C-21), 38.0 (C-4), 39.0 (C-19), 39.1 (C-10), 41.7 and 42.2 (C-8 and C-14), 44.6 (C-17), 46.1 and 48.4 (C-9 and C-18), 55.1 (C-5), 57.4 (C-11), 80.1 (C-3), 90.6 (C-13), 171.0 (*CO*CH_3), 177.7 (C-28), 200.3 (C-12); HRLSIMS, *m/z*: $[M+Na]^+$ 613.2510 ($C_{32}H_{47}O_5BrNa$, calcd 613.2505).

4.2.5. Dehydrohalogenation of 11. Product **11** (318 mg, 0.5 mmol) was dissolved in 10 mL of anhydrous DMF, and LiBr (116 mg, 1.3 mmol) and Li_2CO_3 (155 mg, 2.1 mmol) were added. After 3 h at reflux, the reaction mixture was extracted with an acetic acid solution and CH_2Cl_2, neutralized with $NaHCO_3$, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 95 mg (30%) of **11** and 166 mg (60%) of **12**: white solid; mp 274–276 °C; $[\alpha]_D^{25}$=74 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2951, 1778, 1735, 1667, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.97 (1H, s, H-11), 4.47 (1H, dd, J_1=5.0 Hz, J_2=11.3 Hz, H-3), 2.94 (1H, dd, J_1=2.7 Hz, J_2=13.5 Hz, H-18), 2.06 (3H, s, CO*CH*$_3$), 1.44 (3H, s, Me), 1.27 (3H, s, Me), 0.98 (3H, s, Me), 0.95 (3H, s, Me), 0.95 (3H, s, Me), 0.92 (3H, s, Me), 0.90 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.7 (Me), 17.2 (C-6), 20.3 (C-16), 21.3 (CO*CH*$_3$), 23.1 (Me), 23.9 (C-2), 23.9 (Me), 24.5 (Me), 25.9 (C-15), 27.2 (C-22), 28.1 (Me), 30.1 (Me), 31.7 (C-20), 33.2 (C-29), 34.0 and 34.1 (C-1 and C-7), 36.1 and 36.7 (C-19 and C-21), 38.3 (C-4), 40.3 (C-10), 41.7 (C-8), 43.6 (C-14), 44.0 (C-18), 46.0 (C-17), 50.4 (C-5), 79.6 (C-3), 87.9 (C-13), 121.8 (C-11), 171.0 (*CO*CH_3), 178.8 (C-28), 183.6 (C-9), 192.4

(C-12); HRLSIMS, *m/z*: $[M+Na]^+$ 533.3249 ($C_{32}H_{46}O_5Na$, calcd 533.3243).

4.2.6. Reduction of 12. 140 mg (0.3 mmol) of product **12** were dissolved in 2 mL of dry THF and 1 mL of a solution of $LiAlH_4$ in THF (1 M) was added. The reaction mixture was maintained at reflux for 1.5 h, and then diluted with aqueous ether, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated to dryness. Chromatography over silica gel yielded 124 mg (95%) of **13**: white solid; mp 233–235 °C; $[\alpha]_D^{25}$=23 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3371, 2938 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.25 (1H, d, *J*=2.3 Hz, H-11), 4.24 (1H, d, *J*=2.3 Hz, H-12), 3.93 (1H, d, *J*=10.9 Hz, H-28a), 3.42 (1H, d, *J*=10.9 Hz, H-28b), 3.17 (1H, dd, J_1=4.8 Hz, J_2=11.3 Hz, H-3), 1.42 (3H, s, Me), 1.17 (3H, s, Me), 1.02 (3H, s, Me), 0.97 (3H, s, Me), 0.89 (3H, s, Me), 0.89 (3H, s, Me), 0.80 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.5 (Me), 18.0 (C-6), 22.3 (Me), 24.1 (Me), 24.4 (Me), 25.5 (Me), 26.1 (C-15), 26.1 (C-16), 27.9 (C-2), 28.1 (Me), 31.2 (C-20), 32.7 (C-29), 33.2, 34.0 and 34.3 (C-7, C-21 and C-22), 36.7 and 39.4 (C-4 and C-10), 38.2 (C-1), 39.8 (C-18), 39.9 (C-8), 40.1 (C-19), 44.1 (C-14), 44.5 (C-17), 53.2 (C-5), 68.5 (C-12), 70.6 (C-28), 77.8 (C-13), 78.5 (C-3), 119.2 (C-11), 154.8 (C-9); HRLSIMS, *m/z*: $[M+Na]^+$ 497.3600 ($C_{30}H_{50}O_4Na$, calcd 497.3607).

4.2.7. Reduction of 1. Product **1** (500 mg, 1.1 mmol) was dissolved in 20 mL of dry THF and 8 mL of a 1 M solution of $LiAlH_4$ in THF were added. After 3.5 h at reflux, the reaction mixture was diluted with aqueous ether, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed over silica gel to obtain 478 mg (95%) of product **14**.[9]

4.2.8. Bromination of 14. Product **14** (228 mg, 0.5 mmol) was dissolved in 15 mL of CCl_4, and 90 mg (0.5 mmol) of NBS and a catalytic amount of AIBN were added. The reaction mixture was maintained at room temperature for 1 h and then extracted with a solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to dryness. Chromatography over silica gel yielded 113 mg (50%) of **14** and 130 mg (50%) of **15**: white solid; mp 124–126 °C; $[\alpha]_D^{25}$=78 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3422, 2927 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.24 (1H, dd, J_1=2.5 Hz, J_2=3.5 Hz, H-12), 3.73 (1H, d, *J*=7.0 Hz, H-28a), 3.28 (1H, d, *J*=7.0 Hz, H-28b), 3.24 (1H, dd, J_1=4.9 Hz, J_2=11.2 Hz, H-3), 1.30 (3H, s, Me), 1.25 (3H, s, Me), 0.98 (3H, s, Me), 0.97 (3H, s, Me), 0.89 (3H, s, Me), 0.87 (3H, s, Me), 0.76 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.5 (Me), 17.1 (Me), 17.8 (C-6), 19.3 (Me), 21.8 (Me), 23.7 (Me), 25.0 (C-16), 27.3 (C-2), 28.1 (C-23), 29.2 (C-15), 31.1 (C-7), 31.1 (C-11), 32.0 (C-20), 33.7 (C-29), 34.3 (C-21), 35.0 (C-22), 36.7 (C-4), 38.4 (C-1), 39.0 (C-10), 40.2 (C-19), 42.7 and 43.0 (C-8 and C-17), 45.7 (C-14), 46.0 (C-9), 53.2 (C-18), 55.3 (C-5), 60.6 (C-12), 77.5 (C-28), 78.9 (C-3), 87.5 (C-13); HRLSIMS, *m/z*: $[M+Na]^+$ 543.2812 ($C_{30}H_{49}O_2BrNa$, calcd 543.2814).

4.2.9. Acetylation of 14. Product **14** (138 mg, 0.3 mmol) was dissolved in 6 mL of pyridine and 3 mL of Ac_2O and stirred for 1.5 h at reflux. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aqueous $KHSO_4$ solution and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 111 mg (70%) of **16**: white solid; mp 168–170 °C; $[\alpha]_D^{25}$=56 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1737, 1245 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.18 (1H, dd, J_1=J_2=3.6 Hz, H-12), 4.48 (1H, dd, J_1=7.3 Hz, J_2=9.1 Hz, H-3), 4.01 (1H, d, *J*=11.0 Hz, H-28a), 3.68 (1H, d, *J*=11.0 Hz, H-28b), 2.03 (3H, s, COO*CH*$_3$), 2.03 (3H, s, COO*CH*$_3$), 1.14 (3H, s, Me), 0.93 (3H, s, Me), 0.93 (3H, s, Me), 0.87 (3H, s, Me), 0.85 (3H, s, Me), 0.85 (3H, s, Me), 0.84 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.6 (C-26), 16.7 (C-24), 16.7 (C-25), 18.3 (C-6), 21.0 (CO*CH*$_3$), 21.4 (CO*CH*$_3$), 21.4 (C-30), 22.3 (C-16), 23.6 (C-2), 23.6 (C-11), 25.6 (C-15), 26.0 (C-27), 28.1 (C-23), 30.9 (C-20), 31.4 (C-22), 32.5 (C-7), 33.2 (C-29), 34.0 (C-21), 35.8, 36.9, 37.8 and 39.8 (C-4, C-8, C-10 and C-17), 38.3 (C-1), 41.7 (C-14), 42.6 (C-18), 46.3 (C-19), 47.6 (C-9), 55.3 (C-5), 70.8 (C-28), 80.9 (C-3), 122.9 (C-12), 143.7 (C-13), 171.1 (*CO*CH_3), 171.4 (*CO*CH_3); HRLSIMS, *m/z*: $[M+Na]^+$ 549.3913 ($C_{34}H_{54}O_4Na$, calcd 549.3920); and 29 mg (20%) of **17**: white solid; mp 205–207 °C; $[\alpha]_D^{25}$=74 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2925, 1737, 1244 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.83 (1H, d, *J*=10.3 Hz, H-12), 5.36 (1H, dd, J_1=3.2 Hz, J_2=10.2 Hz, H-11), 4.47 (1H, dd, J_1=8.3 Hz, J_2=9.2 Hz, H-3), 3.69 (1H, d, *J*=6.7 Hz, H-28a), 3.25 (1H, d, *J*=6.7 Hz, H-28b), 2.04 (3H, s, CO*CH*$_3$), 1.07 (3H, s, Me), 0.95 (3H, s, Me), 0.92 (3H, s, Me), 0.91 (3H, s, Me), 0.85 (3H, s, Me), 0.84 (3H, s, Me), 0.84 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.1 (Me), 17.6 (C-6), 18.0 (Me), 19.4 (Me), 19.5 (Me), 21.4 (CO*CH*$_3$), 23.5 (C-16), 23.6 (Me), 25.3 and 25.7 (C-2 and C-15), 27.8 (C-27), 30.9 (C-7), 31.3 (C-21), 31.7 (C-20), 33.7 (C-29), 34.9 (C-22), 36.4, 37.9, 41.6, 41.6 and 43.8 (C-4, C-8, C-10, C-14 and C-17), 37.1 and 38.0 (C-1 and C-19), 51.1 (C-9), 53.2 (C-18), 54.9 (C-5), 77.0 (C-28), 80.9 (C-3), 84.8 (C-13), 131.0 and 132.1 (C-11 and C-12), 171.1 (*CO*CH_3); HRLSIMS, *m/z*: $[M+Na]^+$ 505.3669 ($C_{32}H_{50}O_3Na$, calcd 505.3658).

4.2.10. Treatment of 16 with NBS. Product **16** (81 mg, 0.15 mmol) was dissolved in 8 mL of CCl_4, and 27 mg (0.15 mmol) of NBS and a catalytic amount of AIBN were added. The reaction mixture was maintained at room temperature for 1 h and then extracted with a solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to dryness. Chromatography over silica gel yielded 32 mg (40%) of **18**: syrup; $[\alpha]_D^{25}$=210 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1738, 1244 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.55 (1H, d, *J*=5.8 Hz, H-11), 5.49 (1H, d, *J*=5.8 Hz, H-12), 4.50 (1H, dd, J_1=5.8 Hz, J_2=10.6 Hz, H-3), 4.06 (1H, d, *J*=11.0 Hz, H-28a), 3.76 (1H, d, *J*=11.1 Hz, H-28b), 2.04 (3H, s, CO*CH*$_3$), 2.04 (3H, s, CO*CH*$_3$), 1.19 (3H, s, 3H-25), 1.11 (3H, s, 3H-26), 0.99 (3H, s, 3H-27), 0.89 (3H, s, 3H-23), 0.89 (3H, s, 3H-30), 0.88 (3H, s, 3H-24), 0.86 (3H, s, 3H-29); ^{13}C NMR ($CDCl_3$): δ 16.8 (C-24), 18.2 (C-6), 20.0 (C-27), 20.9 (CO*CH*$_3$), 21.1 (CO*CH*$_3$), 21.4 (C-26), 22.7 (C-16), 23.6 (C-30), 24.3 (C-2), 25.1 (C-15), 25.3 (C-25), 28.2 (C-23), 31.0 (C-20), 31.4 (C-22), 32.0 (C-7), 33.1 (C-29), 33.9 (C-21), 35.6 (C-17), 36.9 (C-1), 37.9 (C-4), 38.7 (C-10), 40.7 (C-14), 40.9 (C-18), 42.7 (C-8), 46.4 (C-19), 51.2 (C-5), 71.1 (C-28), 80.6 (C-3), 115.9 (C-11), 121.5 (C-12), 145.2 (C-13), 154.5 (C-9), 171.1 (*CO*CH_3), 171.4 (*CO*CH_3); HRLSIMS, *m/z*: $[M+Na]^+$ 547.3762 ($C_{34}H_{52}O_4Na$, calcd 547.3763); and 4 mg (5%) of **19**: white solid; mp 139–141 °C; $[\alpha]_D^{25}$=−6 (*c* 0.4, $CHCl_3$); IR

($CHCl_3$): ν 2929, 1737, 1242 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.39 (1H, dd, J_1=3.1 Hz, J_2=10.6 Hz, H-11), 5.57 (1H, d, J=10.6 Hz, H-12), 4.50 (1H, dd, J_1=6.2 Hz, J_2=10.0 Hz, H-3), 4.16 (1H, d, J=11.2 Hz, H-28a), 3.98 (1H, d, J=11.2 Hz, H-28b), 2.05 (3H, s, COCH_3), 2.04 (3H, s, COCH_3), 0.95 (3H, s, Me), 0.94 (3H, s, Me), 0.91 (3H, s, Me), 0.85 (3H, s, Me), 0.84 (3H, s, Me), 0.77 (3H, s, Me), 0.71 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.2 (Me), 16.7 (Me), 18.1 (Me), 18.3 (C-6), 20.4 (Me), 21.2 (COCH_3), 21.4 (COCH_3), 23.5 and 24.3 (C-2 and C-15), 24.4 (Me), 27.9 (C-23), 30.0 (C-16), 32.3 (C-29), 32.4, 33.0 and 35.0 (C-7, C-21 and C-22), 33.0 (C-20), 36.7, 37.9 and 38.0 (C-4, C-8 and C-10), 37.8 and 38.2 (C-1 and C-19), 40.4 and 42.3 (C-14 and C-17), 54.2 (C-9), 55.0 (C-5), 65.8 (C-28), 80.9 (C-3), 125.5 and 126.6 (C-11 and C-12), 133.2 and 137.1 (C-13 and C-18), 171.1 (*CO*CH_3), 171.4 (*CO*CH_3); HRLSIMS, *m/z*: $[M+Na]^+$ 547.3764 ($C_{34}H_{52}O_4Na$, calcd 547.3763).

4.2.11. Treatment of 3 with NBS. Product **3** (1.4 g, 3 mmol) was dissolved in 30 mL of CCl_4, and 535 mg (3 mmol) of NBS and a catalytic amount of AIBN were added. After 2 h at room temperature, the reaction mixture was extracted with a solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 989 mg (70%) of **20**: white solid; mp 133–135 °C; $[\alpha]_D^{25}$=258 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3457, 2947, 1723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.57 (1H, d, J=5.9 Hz, H-11), 5.54 (1H, d, J=5.9 Hz, H-12), 3.62 (3H, s, COOCH_3), 3.21 (1H, dd, J_1=4.9 Hz, J_2=11.2 Hz, H-3), 2.99 (1H, dd, J_1=3.7 Hz, J_2=13.2 Hz, H-18), 1.14 (3H, s, 3H-25), 1.00 (3H, s, 3H-23), 0.99 (3H, s, 3H-27), 0.92 (3H, s, 3H-30), 0.92 (3H, s, 3H-26), 0.88 (3H, s, 3H-29), 0.78 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.7 (C-24), 18.3 (C-6), 20.2 (C-26), 20.2 (C-27), 23.7 (C-30), 23.8 (C-16), 25.1 (C-25), 27.00 (C-15), 27.9 (C-2), 28.3 (C-23), 30.7 (C-20), 32.2 (C-7), 32.2 (C-22), 33.0 (C-29), 33.8 (C-21), 37.1 (C-1), 38.9 (C-10), 39.0 (C-4), 39.7 (C-18), 40.7 (C-14), 42.4 (C-8), 45.9 (C-19), 46.1 (C-17), 51.2 (C-5), 51.8 (COOCH_3), 78.7 (C-3), 115.7 (C-11), 120.6 (C-12), 145.2 (C-13), 154.6 (C-9), 178.4 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 491.3500 ($C_{31}H_{48}O_3Na$, calc. 491.3501); 165 mg (10%) of **24**: white solid; mp 173–175 °C; $[\alpha]_D^{25}$=31 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3330, 2945, 1723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.66 (1H, dd, J_1=3.3 Hz, J_2=8.1 Hz, H-15), 4.84 (1H, dd, J_1=J_2=9.4 Hz, H-12), 3.55 (3H, s, COOCH_3), 3.17 (1H, dd, J_1=5.2 Hz, J_2=10.8 Hz, H-3), 2.71 (1H, dd, J_1=6.0 Hz, J_2=13.5 Hz, H-18), 1.07 (3H, s, 3H-27), 0.96 (3H, s, 3H-30), 0.94 (3H, s, 3H-23), 0.91 (3H, s, 3H-29), 0.87 (3H, s, 3H-25), 0.83 (3H, s, 3H-26), 0.75 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.4 (C-24), 15.7 (C-25), 18.8 (C-6), 20.7 (C-27), 25.7 (C-30), 27.1 (C-2), 27.6 (C-26), 27.9 (C-23), 29.2 (C-11), 30.9 (C-20), 31.9, 32.4 and 33.9 (C-7, C-21 and C-22), 32.3 (C-29), 37.1 (C-1), 37.8 (C-10), 37.8 (C-16), 38.8 (C-4), 39.6 (C-8), 41.1 (C-19), 41.4 (C-18), 43.7 (C-13), 51.2 (C-17), 51.4 (C-9), 51.7 (COOCH_3), 55.4 (C-5), 66.2 (C-12), 78.8 (C-3), 121.5 (C-15), 157.5 (C-14), 178.2 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 571.2761 ($C_{31}H_{49}O_3BrNa$, calcd 571.2763); 75 mg (5%) of **26**: white solid; mp 143–145 °C; $[\alpha]_D^{25}$=5 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3356, 2930, 1728, 1451, 1196 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.96 (1H, dd, J_1=4.7 Hz, J_2=7.6 Hz, H-15), 4.79 (1H, d, J=1.8 Hz, H-27a), 4.73 (1H, d, J=1.8 Hz, H-27b), 3.63 (3H, s, COOCH_3), 3.40 (1H, dd, J_1=0.0 Hz, J_2=9.0 Hz, H-12), 3.30 (1H, dd, J_1=2.4 Hz, J_2=12.5 Hz, H-18), 3.17 (1H, dd, J_1=6.5 Hz, J_2=9.2 Hz, H-3), 2.17 (1H, dd, J_1=2.2 Hz, J_2=4.7 Hz, H-16), 0.95 (3H, s, 3H-23), 0.95 (3H, s, 3H-29), 0.93 (3H, s, 3H-26), 0.86 (3H, s, 3H-30), 0.83 (3H, s, 3H-25), 0.78 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.3 and 15.4 (C-24 and C-25), 19.1 (C-6), 22.3 (C-30), 27.1 and 27.2 (C-2 and C-7), 27.5 and 28.2 (C-23 and C-29), 29.7 (C-20), 31.9 (C-26), 31.9 (C-16), 33.6 and 34.7 (C-21 and C-22), 36.9 (C-10), 38.1, 38.2 and 38.6 (C-1, C-11 and C-19), 38.9 (C-4), 41.0 (C-18), 42.0 (C-12), 46.2 (C-8), 50.4 (C-17), 51.9 (COOCH_3), 56.3 (C-5), 59.7 (C-9), 79.3 (C-3), 105.2 (C-27), 113.0 (C-15), 155.7 (C-13), 157.3 (C-14), 179.9 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 491.3492 ($C_{31}H_{48}O_3Na$, calcd 491.3501); and 167 mg (10%) of **28**: white solid; mp 148–150 °C; $[\alpha]_D^{25}$=83 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3469, 2949, 1724, 1458, 1217, 1033 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.93 (1H, s, H-19), 5.81 (1H, s, H-11), 3.64 (3H, s, COOCH_3), 3.22 (1H, dd, J_1=4.9 Hz, J_2=11.3 Hz, H-3), 1.24 (3H, s, Me), 1.09 (3H, s, Me), 1.06 (3H, s, Me), 1.00 (3H, s, Me), 0.97 (3H, s, Me), 0.88 (3H, s, Me), 0.79 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.8 (C-24), 16.8 (C-27), 18.2 (C-6), 21.9 (C-26), 25.5 (C-25), 27.0 (C-15), 27.8 (C-2), 28.3 (C-23), 28.3 (C-30), 29.4 (C-29), 32.5 (C-22), 33.3 (C-7), 33.3 (C-20), 33.5 (C-21), 34.3 (C-16), 37.1 (C-1), 39.0 (C-10), 39.0 (C-4), 42.3 (C-8), 46.0 (C-14), 47.6 (C-17), 51.3 (C-5), 52.1 (COOCH_3), 78.5 (C-3), 113.2 (C-12), 123.0 (C-11), 131.6 (C-18), 139.3 (C-13), 141.4 (C-19), 156.5 (C-9), 177.1 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 567.2447 ($C_{31}H_{45}O_3BrNa$, calcd 567.2450).

4.2.12. Treatment of 4 with NBS. Product **4** (1.2 g, 2.5 mmol) was dissolved in 30 mL of CCl_4, and 446 mg (2.5 mmol) of NBS and a catalytic amount of AIBN were added. The reaction mixture was maintained at reflux for 1 h, and then extracted with a solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 1.1 g (90%) of **21**: white solid; mp 221–223 °C; $[\alpha]_D^{25}$=107 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3433, 2946, 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.59 (1H, d, J=5.8 Hz, H-11), 5.53 (1H, d, J=5.8 Hz, H-12), 3.71 (1H, ddd, J_1=4.3 Hz, J_2=9.6 Hz, J_3=11.6 Hz, H-2), 3.61 (3H, s, COOCH_3), 2.98 (1H, d, J=9.6 Hz, H-3), 2.29 (1H, dd, J_1=4.4 Hz, J_2=12.5 Hz, H-18), 1.18 (3H, s, Me), 1.02 (3H, s, Me), 0.97 (3H, s, Me), 0.91 (3H, s, Me), 0.90 (3H, s, Me), 0.86 (3H, s, Me), 0.80 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.9 (Me), 18.3 (C-6), 20.3 (Me), 20.4 (Me), 23.7 (Me), 23.8 (C-16), 26.1 (Me), 26.9 (C-15), 28.8 (Me), 30.7 (C-20), 32.1 (C-7), 32.2 (C-22), 33.0 (Me), 33.8 (C-21), 39.1 (C-4), 39.7 (C-18), 40.0 (C-8), 40.8 (C-10), 42.3 (C-14), 45.1 (C-1), 45.9 (C-19), 46.1 (C-17), 51.3 (C-5), 51.8 (COOCH_3), 69.5 (C-2), 83.6 (C-3), 116.0 (C-11), 120.5 (C-12), 145.5 (C-13), 153.4 (C-9), 178.4 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 507.3446 ($C_{31}H_{48}O_4Na$, calcd 507.3450).

4.2.13. Treatment of 5 with NBS. Product **5** (1 g, 2 mmol) was dissolved in 30 mL of CCl_4, and 357 mg (2 mmol) of NBS and a catalytic amount of AIBN were added. After 2 h at room temperature, the reaction mixture was extracted with a solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 668 mg (60%) of product **22**,[13] 195 mg (15%) of product **25**: white solid; mp 178–180 °C;

$[\alpha]_D^{25}$=40 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): ν 2947, 1729, 1245 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.66 (1H, dd, J_1=3.3 Hz, J_2=8.1 Hz, H-15), 4.84 (1H, dd, J_1=J_2=9.3 Hz, H-12), 4.44 (1H, dd, J_1=5.8 Hz, J_2=10.4 Hz, H-3), 3.55 (3H, s, COO*CH*$_3$), 2.71 (1H, dd, J_1=6.0 Hz, J_2=13.5 Hz, H-18), 2.02 (3H, s, CO*CH*$_3$), 1.57 (3H, s, Me), 1.07 (3H, s, Me), 0.96 (3H, s, Me), 0.92 (3H, s, Me), 0.90 (3H, s, Me), 0.83 (3H, s, Me), 0.82 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.8 (C-25), 16.5 (C-24), 18.6 (C-6), 20.6 (C-27), 21.4 (CO*CH*$_3$), 23.4 (C-2), 25.7 (C-30), 27.6 (C-26), 27.9 (C-23), 29.2 (C-11), 30.9 (C-20), 31.9, 32.3 and 33.9 (C-7, C-21 and C-22), 32.3 (C-29), 37.1 (C-1), 37.5 (C-16), 37.7 (C-4), 37.7 (C-10), 39.6 (C-8), 41.0 (C-19), 41.4 (C-18), 43.7 (C-13), 51.2 (C-17), 51.3 (C-9), 51.7 (COO*CH*$_3$), 55.6 (C-5), 66.0 (C-12), 80.7 (C-3), 121.6 (C-15), 157.4 (C-14), 171.0 (*CO*CH$_3$), 178.3 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 613.2874 ($C_{33}H_{51}O_4BrNa$, calcd 613.2868); 53 mg (5%) of **27**: white solid; mp 168–170 °C; $[\alpha]_D^{25}$=15 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): ν 2928, 1728, 1244 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.97 (1H, dd, J_1=4.9 Hz, J_2=7.7 Hz, H-15), 4.78 (1H, d, *J*=1.7 Hz, H-27a), 4.74 (1H, d, *J*=1.7 Hz, H-27b), 4.44 (1H, dd, J_1=6.0 Hz, J_2=9.5 Hz, H-3), 3.64 (3H, s, COO*CH*$_3$), 3.40 (1H, dd, J_1=0.0 Hz, J_2=9.4 Hz, H-12), 3.30 (1H, dd, J_1=2.4 Hz, J_2=12.5 Hz, H-18), 2.18 (1H, dd, J_1=2.1 Hz, J_2=4.9 Hz, H-16), 0.96 (3H, s, Me), 0.93 (3H, s, Me), 0.86 (3H, s, Me), 0.86 (3H, s, Me), 0.86 (3H, s, Me), 0.83 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.5 (C-25), 16.4 (C-24), 19.0 (C-6), 21.4 (CO*CH*$_3$), 22.3 (C-30), 23.5 (C-2), 27.1 (C-7), 27.5 and 28.2 (C-23 and C-29), 29.7 (C-20), 31.9 (C-26), 31.9 (C-16), 33.7 and 34.7 (C-21 and C-22), 36.8 (C-10), 37.8 (C-4), 37.9, 38.0 and 38.6 (C-1, C-11 and C-19), 41.1 (C-18), 42.0 (C-12), 46.2 (C-8), 50.4 (C-17), 51.9 (COO*CH*$_3$), 56.4 (C-5), 59.6 (C-9), 81.2 (C-3), 105.4 (C-27), 113.1 (C-15), 155.5 (C-13), 157.1 (C-14), 171.0 (*CO*CH$_3$), 179.9 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 533.3612 ($C_{33}H_{50}O_4Na$, calcd 533.3607); and 191 mg (15%) of **29**: white solid; mp 185–187 °C; $[\alpha]_D^{25}$=96 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2951, 1729, 1461, 1369, 1246, 1031 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.89 (1H, s, H-19), 5.76 (1H, s, H-11), 4.44 (1H, dd, J_1=5.2 Hz, J_2=11.0 Hz, H-3), 3.58 (3H, s, COO*CH*$_3$), 1.99 (3H, s, CO*CH*$_3$), 1.21 (3H, s, 3H-25), 1.04 (3H, s, 3H-29), 1.01 (3H, s, 3H-26), 0.92 (3H, s, 3H-30), 0.83 (3H, s, 3H-23), 0.82 (3H, s, 3H-27), 0.82 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 16.5 (C-27), 16.7 (C-24), 17.9 (C-6), 21.2 (CO*CH*$_3$), 21.8 (C-26), 24.0 (C-2), 25.4 (C-25), 26.8 (C-15), 28.0 (C-23), 28.1 (C-30), 29.3 (C-29), 32.3 (C-22), 33.1 (C-7), 33.1 (C-20), 33.4 (C-21), 34.1 (C-16), 36.7 (C-1), 37.8 (C-4), 38.7 (C-10), 42.1 (C-8), 45.8 (C-14), 47.4 (C-17), 51.2 (C-5), 51.9 (COO*CH*$_3$), 80.0 (C-3), 113.0 (C-12), 123.0 (C-11), 131.4 (C-18), 139.3 (C-13), 141.2 (C-19), 155.9 (C-9), 170.8 (*COCH*$_3$), 176.8 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 609.2548 ($C_{33}H_{47}O_4BrNa$, calcd 609.2555).

4.2.14. Treatment of 6 with NBS. Product **6** (1.2 g, 2.1 mmol) was dissolved in 30 mL of CCl_4, and 374 mg (2.1 mmol) of NBS and a catalytic amount of AIBN were added. The reaction mixture was maintained at reflux for 1 h, and then extracted with a solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 1.1 g (90%) of **23**: white solid; mp 191–193 °C; $[\alpha]_D^{25}$=152 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1741, 1369, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.53 (1H, d, J_1=5.9 Hz, H-11), 5.51 (1H, d, J_1=5.9 Hz, H-12), 5.11 (1H, ddd, J_1=4.5 Hz, J_2=10.4 Hz, J_3=11.7 Hz, H-2), 4.72 (1H, d, *J*=10.4 Hz, H-3), 3.60 (3H, s, COO*CH*$_3$), 2.97 (1H, dd, J_1=4.3 Hz, J_2=14.2 Hz, H-18), 2.02 (3H, s, CO*CH*$_3$), 1.96 (3H, s, CO*CH*$_3$), 1.25 (3H, s, Me), 0.95 (3H, s, Me), 0.90 (3H, s, Me), 0.89 (3H, s, Me), 0.88 (3H, s, Me), 0.87 (3H, s, Me), 0.86 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.7 (Me), 18.2 (C-6), 20.3 (Me), 20.3 (Me), 21.0 (CO*CH*$_3$), 21.2 (CO*CH*$_3$), 23.7 (Me), 23.7 (C-16), 25.9 (Me), 26.9 (C-15), 28.6 (Me), 30.7 (C-20), 32.0 (C-7), 32.2 (C-22), 33.0 (Me), 33.8 (C-21), 39.2 (C-4), 39.7 (C-18), 39.8 (C-8), 40.7 (C-10), 42.3 (C-14), 42.5 (C-1), 45.8 (C-19), 46.1 (C-17), 51.0 (C-5), 51.7 (COO*CH*$_3$), 70.4 (C-2), 80.4 (C-3), 116.3 (C-11), 120.5 (C-12), 145.8 (C-13), 152.8 (C-9), 170.6 (*CO*CH$_3$), 170.9 (*CO*CH$_3$), 178.3 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 591.3664 ($C_{35}H_{52}O_6Na$, calcd 591.3661).

4.2.15. Photolysis of 20. Product **20** (325 mg, 0.7 mmol) was dissolved in 65 mL of ethanol and irradiated in a borosilicate flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. After 20 min, the solvent was evaporated and the residue chromatographed on a silica gel column to obtain 308 mg (95%) of **30**: white solid; mp 196–198 °C; $[\alpha]_D^{25}$=145 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): ν 3442, 2945, 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.98 (1H, d, *J*=12.8 Hz, H-12), 5.80 (1H, d, *J*=12.8 Hz, H-11), 3.60 (3H, s, COO*CH*$_3$), 3.24 (1H, dd, J_1=4.9 Hz, J_2=11.3 Hz, H-3), 2.77 (1H, dd, J_1=3.6 Hz, J_2=12.7 Hz, H-18), 1.47 (3H, s, 3H-27), 1.25 (3H, s, 3H-26), 1.08 (3H, s, 3H-25), 1.00 (3H, s, 3H-23), 0.86 (3H, s, 3H-30), 0.85 (3H, s, 3H-29), 0.81 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.6 (C-24), 18.8 (C-6), 20.8 (C-27), 21.5 (C-26), 21.9 (C-25), 22.7 (C-16), 25.0 (C-30), 28.0 (C-2), 28.3 (C-23), 29.8 (C-7), 30.7 (C-20), 32.8 (C-22), 33.0 (C-29), 34.1 (C-21), 34.3 (C-15), 36.0 (C-1), 37.1 (C-18), 38.6 and 39.0 (C-4 and C-10), 43.0 (C-19), 45.4 (C-17), 50.7 (C-5), 51.7 (COO*CH*$_3$), 79.0 (C-3), 127.3 (C-11), 127.8 (C-14), 129.8 (C-8), 132.9 (C-12), 134.5 (C-13), 138.0 (C-9), 178.4 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 491.3511 ($C_{31}H_{48}O_3Na$, calcd 491.3501).

4.2.16. Photolysis of 21. A solution of 325 mg (0.7 mmol) of product **21** in 65 mL of ethanol was irradiated for 20 min in a borosilicate flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. The reaction mixture was evaporated. Chromatography over silica gel yielded 310 mg (95%) of **31**: syrup; $[\alpha]_D^{25}$=48 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3423, 2946, 1729, 1459, 1255, 1170, 1046 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.03 (1H, d, *J*=12.8 Hz, H-12), 5.80 (1H, d, *J*=12.8 Hz, H-11), 3.72 (1H, ddd, J_1=4.6 Hz, J_2=10.6 Hz, J_3=10.6 Hz, H-2), 3.61 (3H, s, COO*CH*$_3$), 3.05 (1H, d, *J*=10.6 Hz, H-3), 2.79 (1H, dd, J_1=4.0 Hz, J_2=12.5 Hz, H-18), 1.50 (3H, s, Me), 1.41 (3H, s, Me), 1.29 (3H, s, Me), 1.14 (3H, s, Me), 1.05 (3H, s, Me), 0.86 (3H, s, Me), 0.86 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.7 (Me), 18.8 (C-6), 20.9 (Me), 21.5 (Me), 22.7 (C-16), 23.2 (Me), 25.0 (Me), 28.8 (Me), 29.7 and 29.9 (C-7 and C-22), 30.8 (C-20), 32.9 (C-15), 33.0 (Me), 34.1 (C-21), 37.1 (C-18), 39.1 and 39.7 (C-4 and C-10), 43.0 (C-1), 43.9 (C-19), 45.5 (C-17), 50.5 (C-5), 51.7 (COO*CH*$_3$), 69.7 (C-2), 83.8 (C-3), 126.8 (C-11), 128.3 (C-14), 129.5 (C-13), 133.1 (C-12), 134.4 (C-8), 137.6 (C-9), 178.5 (C-28);

HRLSIMS, *m/z*: $[M+Na]^+$ 507.3444 ($C_{31}H_{48}O_4Na$, calcd 507.3450).

4.2.17. Photolysis of 22. A solution of 350 mg (0.7 mmol) of product **22** in 65 mL of ethanol was irradiated for 20 min in a borosilicate flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. The reaction mixture was evaporated. Chromatography over silica gel yielded 332 mg (95%) of **32**: syrup; $[\alpha]_D^{25}=157$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2946, 1731, 1247 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.90 (1H, d, $J=12.8$ Hz, H-12), 5.80 (1H, d, $J=12.8$ Hz, H-11), 4.52 (1H, dd, $J_1=5.0$ Hz, $J_2=11.3$ Hz, H-3), 3.62 (3H, s, COO*CH*$_3$), 2.79 (1H, dd, $J_1=3.9$ Hz, $J_2=12.7$ Hz, H-18), 2.04 (3H, s, CO*CH*$_3$), 1.48 (3H, s, 3H-27), 1.27 (3H, s, 3H-26), 1.10 (3H, s, 3H-25), 0.89, 0.88 and 0.88 (3H each, s, 3H-23, 3H-24 and 3H-30), 0.85 (3H, s, 3H-29); ^{13}C NMR ($CDCl_3$): δ 16.7 (C-24), 18.8 (C-6), 20.8 (C-27), 21.4 and 21.5 (C-26 and CO*CH*$_3$), 22.0 (C-25), 22.7 (C-16), 24.4 (C-2), 25.0 (C-30), 28.3 (C-23), 29.8 (C-7), 30.8 (C-20), 32.9 (C-22), 33.0 (C-29), 34.1 (C-15), 34.1 (C-21), 35.5 (C-1), 37.1 (C-18), 37.9 and 38.6 (C-4 and C-10), 43.1 (C-19), 45.4 (C-17), 50.6 (C-5), 51.7 (COO*CH*$_3$), 81.0 (C-3), 127.3 (C-11), 128.0 (C-14), 129.7 (C-8), 132.9 (C-12), 134.5 (C-13), 137.8 (C-9), 171.1 (*CO*CH$_3$), 178.4 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 533.3600 ($C_{33}H_{50}O_4Na$, calcd 533.3607).

4.2.18. Photolysis of 23. Product **23** (400 mg, 0.7 mmol) was dissolved in 65 mL of ethanol and irradiated in a borosilicate flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. After 20 min, the solvent was evaporated and the residue chromatographed on a silica gel column to obtain 381 mg (95%) of **33**: white solid; mp 169–171 °C; $[\alpha]_D^{25}=29$ (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1740, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.02 (1H, d, $J=12.6$ Hz, H-12), 5.78 (1H, d, $J=12.6$ Hz, H-11), 5.09 (1H, ddd, $J_1=4.5$ Hz, $J_2=10.5$ Hz, $J_3=15.0$ Hz, H-2), 4.82 (1H, d, $J=10.5$ Hz, H-3), 3.66 (3H, s, COO*CH*$_3$), 2.81 (1H, dd, $J_1=3.4$ Hz, $J_2=12.3$ Hz, H-18), 2.03 (3H, s, CO*CH*$_3$), 1.96 (3H, s, CO*CH*$_3$), 1.44 (3H, s, Me), 1.23 (3H, s, Me), 1.16 (3H, s, Me), 0.92 (3H, s, Me), 0.91 (3H, s, Me), 0.87 (3H, s, Me), 0.85 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.6 (C-24), 18.6 (C-6), 20.7 (C-27), 21.0 (C-26), 21.2 (CO*CH*$_3$), 21.7 (CO*CH*$_3$), 22.7 (C-16), 22.7 (C-25), 24.9 (C-30), 28.5 (C-23), 29.8 (C-7), 30.7 (C-20), 32.9 (C-22), 33.0 (C-29), 34.2 (C-15), 34.2 (C-21), 37.0 (C-18), 39.3 (C-4), 39.6 (C-10), 40.7 (C-1), 43.0 (C-19), 45.4 (C-17), 51.8 (C-5), 51.8 (COO*CH*$_3$), 70.9 (C-2), 80.7 (C-3), 127.2 (C-11), 128.1 (C-14), 133.3 (C-12), 133.5 (C-8), 134.4 (C-13), 136.9 (C-9), 170.6 (*CO*CH$_3$), 170.9 (*CO*CH$_3$), 178.3 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 591.3668 ($C_{35}H_{52}O_6Na$, calcd 591.3662).

4.2.19. Isomerization of 30 with I_2. Product **30** (45 mg, 0.1 mmol) was dissolved in 50 mL of hexane and 5 mg (0.02 mmol) of I_2 were added. After 5 h at light reflux, 0.5 mL of sodium bisulfite were added. The reaction mixture was washed with water, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 9 mg (20%) of **30** and 27 mg (60%) of **34**: syrup; $[\alpha]_D^{25}=52$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): ν 3349, 1639 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.16 (1H, d, $J=16.3$ Hz, H-12), 5.97 (1H, d, $J=16.3$ Hz, H-11), 3.61 (3H, s, COO*CH*$_3$), 3.24 (1H, dd, $J_1=4.7$ Hz, $J_2=11.3$ Hz, H-3), 3.13 (1H, dd, $J_1=3.1$ Hz, $J_2=12.7$ Hz, H-18), 1.66 (3H, s, 3H-26), 1.64 (3H, s, 3H-27), 1.01 (3H, s, Me), 1.01 (3H, s, Me), 1.00 (3H, s, Me), 0.88 (3H, s, Me), 0.81 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.5 (C-24), 18.7 (C-6), 19.1 (C-27), 20.4 (C-25), 21.4 (C-26), 22.5 (C-16), 24.1 (C-30), 28.0 (C-2), 28.1 (C-23), 30.7 (C-7), 30.9 (C-20), 32.1 (C-22), 32.9 (C-18), 33.3 (C-29), 33.8 and 34.2 (C-15 and C-21), 36.6 (C-1), 38.1 (C-10), 39.0 (C-4), 42.2 (C-19), 45.7 (C-17), 50.6 (C-5), 51.7 (COO*CH*$_3$), 79.0 (C-3), 123.2 (C-11), 126.8 (C-8), 129.5 (C-14), 131.3 (C-12), 132.5 (C-13), 141.6 (C-9), 178.2 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 491.3509 ($C_{31}H_{48}O_3Na$, calcd 491.3501).

4.2.20. Isomerization of 31 with I_2. 5 mg (0.02 mmol) of iodine were added to a solution of 50 mg (0.1 mmol) of product **31** in 50 mL of hexane. After 5 h at light reflux, 0.5 mL of sodium bisulfite were added. The reaction mixture was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. Chromatography over silica gel yielded 10 mg (20%) of starting material and 31 mg (60%) of product **35**: syrup; $[\alpha]_D^{25}=69$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3422, 2946, 1727, 1456, 1257, 1171 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.17 (1H, d, $J=16.2$ Hz, H-12), 5.96 (1H, d, $J=16.2$ Hz, H-11), 3.71 (1H, ddd, $J_1=4.2$ Hz, $J_2=9.5$ Hz, $J_3=11.5$ Hz, H-2), 3.62 (3H, s, COO*CH*$_3$), 3.13 (1H, dd, $J_1=3.0$ Hz, $J_2=12.7$ Hz, H-18), 3.03 (1H, d, $J=9.5$ Hz, H-3), 1.66 and 1.64 (3H each, s, 3H-26 and 3H-27), 1.08 (3H, s, Me), 1.05 (3H, s, Me), 1.02 (3H, s, Me), 0.89 (3H, s, Me), 0.85 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.6 (Me), 18.7 (C-6), 19.1 (Me), 21.4 (Me), 21.6 (Me), 22.5 (C-16), 24.2 (Me), 28.6 (Me), 30.7 (C-7), 30.9 (C-20), 32.1 (C-22), 33.0 (Me), 33.4 (C-18), 33.6 and 34.2 (C-15 and C-21), 39.1 and 39.2 (C-4 and C-10), 42.3 and 44.6 (C-1 and C-19), 45.7 (C-17), 50.6 (C-5), 51.7 (COO*CH*$_3$), 69.6 (C-2), 83.8 (C-3), 122.7 (C-11), 127.0 (C-8), 129.8 (C-14), 131.8 (C-12), 132.4 (C-13), 141.1 (C-9), 178.2 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 507.3450 ($C_{31}H_{48}O_4Na$, calcd 507.3450).

4.2.21. Isomerization of 32 with I_2. Product **32** (50 mg, 0.1 mmol) was dissolved in 50 mL of hexane and 5 mg (0.02 mmol) of I_2 were added. After 5 h at light reflux, 0.5 mL of sodium bisulfite were added. The reaction mixture was washed with water, dried over anhydrous Na_2SO_4, evaporated to dryness and chromatographed on a silica gel column to obtain 10 mg (20%) of **32** and 30 mg (60%) of **36**: syrup; $[\alpha]_D^{25}=80$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1729, 1247, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.15 (1H, d, $J=16.3$ Hz, H-12), 5.94 (1H, d, $J=16.3$ Hz, H-11), 4.48 (1H, dd, $J_1=4.5$ Hz, $J_2=11.4$ Hz, H-3), 3.59 (3H, s, COO*CH*$_3$), 3.11 (1H, dd, $J_1=3.3$ Hz, $J_2=13.1$ Hz, H-18), 2.03 (3H, s, CO*CH*$_3$), 1.65 (3H, s, 3H-26), 1.62 (3H, s, 3H-27), 1.02 (3H, s, 3H-25), 0.98 (3H, s, 3H-30), 0.87, 0.87 and 0.86 (3H each, s, 3H-23, 3H-24 and 3H-29); ^{13}C NMR ($CDCl_3$): δ 16.6 (C-24), 18.6 (C-6), 19.0 (C-27), 20.5 (C-25), 21.4 (C-26), 21.4 (CO*CH*$_3$), 22.4 (C-16), 24.1 (C-30), 24.2 (C-2), 28.1 (C-23), 30.6 (C-7), 30.9 (C-20), 32.1 (C-22), 32.9 (C-18), 33.3 (C-29), 33.6 and 34.1 (C-15 and C-21), 36.2 (C-1), 37.9 (C-4), 37.9 (C-10), 42.2 (C-19), 45.7 (C-17), 50.7 (C-5), 51.7 (COO*CH*$_3$), 81.0 (C-3), 123.0 (C-11), 126.8 (C-8), 129.5 (C-14), 131.4 (C-12), 132.4 (C-13), 141.3 (C-9), 171.0 (*CO*CH$_3$), 178.2 (C-28);

HRLSIMS, *m/z*: $[M+Na]^+$ 533.3602 ($C_{33}H_{50}O_4Na$, calcd 533.3607).

4.2.22. Isomerization of 33 with I_2. 5 mg (0.02 mmol) of iodine were added to a solution of 55 mg (0.1 mmol) of product **33** in 50 mL of hexane. After 5 h at light reflux, 0.5 mL of sodium bisulfite were added. The reaction mixture was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. Chromatography over silica gel yielded 11 mg (20%) of starting material and 34 mg (60%) of **37**: syrup; $[\alpha]_D^{25}=1$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1739, 1369, 1249 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.19 (1H, d, J=16.0 Hz, H-12), 5.91 (1H, d, J=16.0 Hz, H-11), 5.14 (1H, ddd, J_1=4.0 Hz, J_2=11.3 Hz, J_3=11.3 Hz, H-2), 4.75 (1H, d, J=11.3 Hz, H-3), 3.60 (3H, s, COO*CH*$_3$), 3.10 (1H, dd, J_1=2.8 Hz, J_2=13.0 Hz, H-18), 2.04 (3H, s, CO*CH*$_3$), 1.96 (3H, s, CO*CH*$_3$), 1.69 (3H, s, Me), 1.63 (3H, s, Me), 1.17 (3H, s, Me), 0.98 (3H, s, Me), 0.93 (3H, s, Me), 0.91 (3H, s, Me), 0.86 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.5 (Me), 18.6 (C-6), 19.1 (Me), 21.0 (CO*CH*$_3$), 21.2 (CO*CH*$_3$), 21.5 (Me), 21.5 (Me), 22.4 (C-16), 24.0 (Me), 28.4 (Me), 29.8 (C-7), 30.6 and 33.4 (C-21 and C-22), 30.9 (C-20), 33.0 (Me), 33.3 (C-18), 34.1 (C-15), 38.9 and 39.4 (C-4 and C-10), 42.2 (C-19), 42.3 (C-1), 45.7 (C-17), 50.1 (C-5), 51.7 (COO*CH*$_3$), 70.4 (C-2), 80.6 (C-3), 122.4 (C-11), 127.1 (C-8), 130.0 (C-14), 131.7 (C-12), 132.3 (C-13), 140.3 (C-9), 170.3 (*CO*CH$_3$), 170.9 (*CO*CH$_3$), 178.1 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 591.3664 ($C_{35}H_{52}O_6Na$, calcd 591.3662).

4.2.23. Photolysis of 30. Product **30** (325 mg, 0.7 mmol) was dissolved in 65 mL of ethanol and irradiated in a quartz flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. After 30 min, the solvent was evaporated and the residue chromatographed on a silica gel column to obtain 309 mg (95%) of **38**: syrup; $[\alpha]_D^{25}=20$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3445, 2945, 1726 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.99 (1H, d, J=2.3 Hz, H-26a), 4.93 (1H, dd, J_1=4.5 Hz, J_2=9.4 Hz, H-11), 4.53 (1H, d, J=2.3 Hz, H-26b), 3.60 (3H, s, COO*CH*$_3$), 3.23 (1H, dd, J_1=4.9 Hz, J_2=10.0 Hz, H-3), 1.51 (3H, s, 3H-27), 0.97 (3H, s, 3H-25), 0.94 (3H, s, 3H-23), 0.89 (3H, s, 3H-30), 0.87 (3H, s, 3H-29), 0.81 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.5 (C-24), 19.0 (C-27), 20.8 (C-25), 23.0 and 23.2 (C-6 and C-16), 24.3 (C-30), 27.9 (C-2), 28.4 (C-23), 29.9 and 30.5 (C-12 and C-15), 30.7 (C-20), 32.2 (C-22), 33.0 (C-29), 34.1 (C-21), 35.2 (C-1), 36.0 (C-18), 37.3 (C-7), 39.5 (C-4), 40.6 (C-10), 41.5 (C-19), 45.8 (C-17), 51.7 (COO*CH*$_3$), 52.7 (C-5), 79.1 (C-3), 112.1 (C-26), 117.2 (C-11), 125.0 (C-14), 133.5 (C-13), 145.4 (C-8), 151.0 (C-9), 178.3 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 491.3502 ($C_{31}H_{48}O_3Na$, calcd 491.3501).

4.2.24. Photolysis of 31. A solution of 325 mg (0.7 mmol) of product **31** in 65 mL of ethanol was irradiated for 30 min in a quartz flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. The reaction mixture was evaporated. Chromatography over silica gel yielded 311 mg (95%) of **39**: syrup; $[\alpha]_D^{25}=32$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3412, 2945, 1727, 1462, 1255, 1170 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.02 (1H, d, J=2.3 Hz, H-26a), 4.95 (1H, dd, J_1=4.3 Hz, J_2=9.6 Hz, H-11), 4.56 (1H, d, J=2.3 Hz, H-26b), 3.78 (1H, ddd, J_1=4.0 Hz, J_2=9.5 Hz, J_3=11.6 Hz, H-2), 3.62 (3H, s, COO*CH*$_3$), 3.03 (1H, d, J=9.5 Hz, H-3), 2.90 (1H, dd, J_1=9.6 Hz, J_2=15.4 Hz, H-12a), 2.75 (1H, dd, J_1=4.3 Hz, J_2=15.4 Hz, H-12b), 1.51 (3H, s, Me), 1.02 (3H, s, Me), 1.00 (3H, s, Me), 0.89 (3H, s, Me), 0.87 (3H, s, Me), 0.84 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.7 (Me), 19.0 (Me), 20.8 (Me), 22.9 and 23.1 (C-6 and C-16), 24.4 (Me), 28.9 (Me), 30.0 (C-15), 30.7 and 32.2 (C-12 and C-22), 30.7 (C-20), 33.0 (Me), 34.1 (C-21), 36.2 (C-18), 37.1 (C-7), 39.7 and 41.6 (C-4 and C-10), 41.5 (C-1), 43.3 (C-19), 45.8 (C-17), 51.8 and 52.7 (C-5 and COO*CH*$_3$), 69.5 (C-2), 83.9 (C-3), 112.7 (C-26), 117.8 (C-11), 125.2 (C-14), 133.4 (C-13), 144.9 (C-9), 150.1 (C-8), 178.4 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 507.3444 ($C_{31}H_{48}O_4Na$, calcd 507.3450).

4.2.25. Acetylation of 38. Product **38** (100 mg, 0.2 mmol) was dissolved in 4 mL of pyridine and 2 mL of Ac_2O and stirred for 1 h at reflux. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aqueous $KHSO_4$ solution and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 104 mg (95%) of **40**: syrup; $[\alpha]_D^{25}=38$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): ν 2946, 1730, 1242 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.00 (1H, d, J=2.4 Hz, H-26a), 4.96 (1H, dd, J_1=4.5 Hz, J_2=9.5 Hz, H-11), 4.55 (1H, d, J=2.4 Hz, H-26b), 4.50 (1H, dd, H-3), 3.63 (3H, s, COO*CH*$_3$), 2.05 (3H, s, CO*CH*$_3$), 1.51 (3H, s, 3H-27), 0.97 (3H, s, 3H-25), 0.90 (3H, s, 3H-23), 0.89 (3H, s, 3H-30), 0.88 (3H, s, 3H-29), 0.86 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 16.7 (C-24), 19.0 (C-27), 20.9 (C-25), 21.4 (CO*CH*$_3$), 23.1 (C-6), 23.1 (C-16), 24.4 (C-30), 24.4 (C-2), 28.3 (C-23), 30.0 and 30.8 (C-12 and C-15), 30.7 (C-20), 32.2 (C-22), 33.0 (C-29), 34.1 (C-21), 34.9 (C-1), 36.4 (C-18), 37.1 (C-7), 38.4 (C-4), 40.4 (C-10), 41.6 (C-19), 45.8 (C-17), 51.8 (COO*CH*$_3$), 52.8 (C-5), 81.1 (C-3), 112.2 (C-26), 117.6 (C-11), 125.2 (C-14), 133.5 (C-13), 145.3 (C-8), 150.6 (C-9), 171.0 (*COCH*$_3$), 178.2 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 533.3601 ($C_{33}H_{50}O_4Na$, calcd 533.3607).

4.2.26. Photolysis of 33. Product **33** (390 mg, 0.7 mmol) was dissolved in 65 mL of ethanol and irradiated in a quartz flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. After 30 min, the solvent was evaporated and the residue chromatographed on a silica gel column to obtain 370 mg (95%) of **41**: white solid; mp 71–73 °C; $[\alpha]_D^{25}=28$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2946, 2356, 1743, 1251 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.19 (1H, ddd, J_1=3.9 Hz, J_2=11.2 Hz, J_3=11.2 Hz, H-2), 5.04 (1H, d, J=2.1 Hz, H-26a), 4.88 (1H, dd, J_1=4.3 Hz, J_2=9.5 Hz, H-11), 4.76 (1H, d, J=11.2 Hz, H-3), 4.58 (1H, d, J=2.1 Hz, H-26), 3.64 (3H, s, COO*CH*$_3$), 2.89 (1H, dd, J_1=9.5 Hz, J_2=15.5 Hz, H-12a), 2.73 (1H, dd, J_1=4.3 Hz, J_2=15.5 Hz, H-12b), 2.05 (3H, s, CO*CH*$_3$), 2.00 (3H, s, CO*CH*$_3$), 1.51 (3H, s, Me), 1.08 (3H, s, Me), 0.93 (3H, s, Me), 0.90 (3H, s, Me), 0.89 (3H, s, Me), 0.88 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.6 (Me), 19.0 (Me), 21.0 (Me), 21.2 (CO*CH*$_3$), 21.6 (CO*CH*$_3$), 22.9 (C-6), 23.0 (C-16), 24.3 (Me), 28.6 (Me), 29.8 (C-15), 29.9 (C-20), 30.6 (C-12), 30.7 (C-22), 33.0 (Me), 34.1 (C-21), 36.2 (C-18), 36.8 (C-7), 39.7 (C-4), 40.8 (C-1), 41.4 (C-10), 41.6 (C-19), 45.8 (C-17), 51.8 (COO*CH*$_3$), 52.3 (C-5), 70.6 (C-2), 80.6 (C-3), 113.0 (C-26), 117.9 (C-11), 125.3 (C-14), 133.2 (C-13),

144.4 (C-9), 149.5 (C-8), 170.5 (COCH$_3$), 170.8 (COCH$_3$), 178.2 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 591.3670 ($C_{35}H_{52}O_6Na$, calcd 591.3662).

4.2.27. Photolysis of 41. A solution of 340 mg (0.6 mmol) of product **41** in 55 mL of ethanol was irradiated for 30 min in a quartz flask using a 125 W high-pressure Hg street lamp with the outermost glass shell removed. The reaction mixture was evaporated. Chromatography over silica gel yielded 175 mg (50%) of starting material and 154 mg (45%) of **42**: white solid; mp 100–102 °C; $[\alpha]_D^{25}=-5$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2947, 1733, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.15 (1H, ddd, J_1=4.6 Hz, J_2=10.7 Hz, J_3=11.3 Hz, H-2), 4.78 (1H, d, J=10.7 Hz, H-3), 3.59 (3H, s, COOCH_3), 3.05 (1H, m, H-11), 2.65 (1H, dd, J_1=3.7 Hz, J_2=10.3 Hz, H-18), 2.27 (1H, dd, J_1=4.2 Hz, J_2=13.0 Hz, H-26), 2.05 (3H, s, COCH_3), 2.00 (3H, s, COCH_3), 1.52 (3H, s, Me), 1.12 (3H, s, Me), 0.97 (3H, s, Me), 0.90 (3H, s, Me), 0.90 (3H, s, Me), 0.90 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.3 (C-24), 19.3 (C-6), 19.6 (C-27), 21.0 (C-25), 21.0 (COCH_3), 21.3 (COCH_3), 22.6 (C-16), 24.3 (C-30), 26.6 (C-15), 28.3 (C-23), 29.9 (C-21), 30.8 (C-20), 32.2 (C-22), 32.9 (C-29), 34.0 (C-12), 34.5 (C-7), 35.2 (C-18), 35.3 (C-26), 37.7 (C-4), 38.9 (C-11), 39.5 (C-10), 40.0 (C-1), 41.9 (C-19), 45.8 (C-17), 51.1 (C-5), 51.6 (COOCH_3), 70.1 (C-2), 80.9 (C-3), 125.4 (C-14), 132.8 (C-13), 136.8 (C-8), 152.8 (C-9), 170.7 (COCH$_3$), 170.8 (COCH$_3$), 178.4 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 591.3669 ($C_{35}H_{52}O_6Na$, calcd 591.3662).

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References and notes

1. Dictionary of Natural Products on CD-ROM, Chapman and Hall, ISSN 0966-2146 ver. 5.1 (1996), oleanolic acid CAS (508-02-01), maslinic acid CAS (4373-41-5).
2. Garcia-Granados, A.; Martinez, A.; Parra, A.; Rivas, F. P.C.T. Int. Appl. W0 043331, 1998; (*Chem. Abstr.* **1998**, *128*, 179706).
3. Manna, S.; Yadagiri, P.; Falck, *J. Chem. Soc., Chem. Commun.* **1987**, 1324–1325.
4. Liu, *J. Ethnopharmacol.* **1995**, *49*, 57–68.
5. Garcia-Granados, A.; Dueñas, J.; Moliz, J. N.; Parra, A.; Perez, F. L.; Dobado, J. A.; Molina, J. *J. Chem. Res. (S)* **2000**, 56–57. Garcia-Granados, A.; Dueñas, J.; Moliz, J. N.; Parra, A.; Perez, F. L.; Dobado, J. A.; Molina, J. *J. Chem. Res. (M)* **2000**, *2*, 0326–0339. Garcia-Granados, A.; Dueñas, J.; Melguizo, E.; Moliz, J. N.; Parra, A.; Perez, F. L.; Dobado, J. A.; Molina, J. *J. Chem. Res. (S)* **2000**, 212–213. Garcia-Granados, A.; Dueñas, J.; Melguizo, E.; Moliz, J. N.; Parra, A.; Perez, F. L.; Dobado, J. A.; Molina, J. *J. Chem. Res. (M)* **2000**, *2*, 0653–0670.
6. Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298. Spera, G.; Lubrano, C. *Int. J. Immunopathol. Pharmacol.* **1996**, *91*, 33. Ling, Y. Z.; Li, J. S.; Kato, K.; Liu, Y.; Wang, X.; Klus, G. T.; Marat, K.; Nnane, I. P.; Brodie, A. M. H. *Bioorg. Med. Chem.* **1998**, *6*, 1683.
7. Garcia-Granados, A.; Lopez, P. E.; Melguizo, E.; Moliz, J. N.; Parra, A.; Simeo, Y. *J. Org. Chem.* **2003**, *68*, 4833–4844.
8. Garcia-Granados, A.; Lopez, P. E.; Melguizo, E.; Parra, A.; Simeo, Y. *Tetrahedron Lett.* **2003**, *44*, 6673–6677.
9. Monaco, P.; Caputo, R.; Palumbo, G.; Mangoni, L. *Phytochemistry* **1973**, *12*, 939.
10. Havinga, E.; de Kock, R. J.; Rappoldt, M. P. *Tetrahedron* **1960**, *11*, 276–284. Lugtenburg, J.; Havinga, E. *Tetrahedron Lett.* **1969**, *28*, 2391–2394. Gottfried, N.; Kaiser, W.; Braun, M.; Fuss, W.; Kompa, K. L. *Chem. Phys. Lett.* **1984**, *110*, 335–339. Schönecker, B.; Reichenbächer, M.; Gliesing, S.; Gonschior, M.; Griebenow, S.; Scheddin, D.; Mayer, H. *Steroids* **1998**, *63*, 28–36.
11. Autrey, R. L.; Barton, D. H. R.; Ganguly, A. K.; Reusch, W. H. *J. Chem. Soc.* **1961**, *3*, 3313–3319.
12. Misra, L.; Laatsch, H. *Phytochemistry* **2000**, *54*, 969–974.
13. Lampasona, M. E. P.; Catalan, C. A. N.; Gedris, T. E.; Herz, W. *Phytochemistry* **1998**, *49*, 2061–2064.
14. Agata, I.; Corey, E. J.; Hortmann, A. G.; Klein, J.; Proskow, S.; Ursprung, J. J. *J. Org. Chem.* **1965**, *30*, 1698–1710.
15. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. Organic Chemistry. *Pericyclic reactions 2: sigmatropic and electrocyclic reactions*; Oxford University Press: Oxford, 2001; Chapter 36.

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Rhodium(II) catalyzed intramolecular insertion of carbenoids derived from 2-pyrrolyl and 3-indolyl α-diazo-β-ketoesters and α-diazoketones

Erick Cuevas-Yañez,[a,*] Joseph M. Muchowski[b] and Raymundo Cruz-Almanza[a,†]

[a]*Instituto de Química, UNAM. Circuito Exterior, Ciudad Universitaria, Coyoacán, 04510 México, DF, Mexico*
[b]*Department of Chemistry, Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, CA 94304-1320, USA*

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Abstract—α-Diazo-β-ketoesters and α-diazoketones derived from 2-pyrrolylacetic, 2-pyrrolylpropionic, 3-indolylacetic and 3-indolylpropionic acids afforded carbenoid derived cyclization products on treatment with catalytic rhodium(II) acetate.

1. Introduction

The first intramolecular carbenoid insertions at C-2 of pyrroles were described by Muchowski, et al.[1] and shortly thereafter by Jefford and coworkers.[2] The Jefford group extensively studied the Rh(II) catalyzed process using α-diazoketones as the carbenoid precursors, demonstrated that it was high yielding process and utilized it to synthesize several naturally occurring indolizine derivatives.[3]

In connection with other projects, we some time ago initiated studies on the insertion of α-keto carbenoids into the C-3H of pyrroles, no examples of which were then known, as well as into the C-2H of indoles. A recent publication of Capretta and Salim,[4] which describes examples of both processes, causes us to disclose our results in this area.

The pyrrolyl α-diazo-β-ketoesters **6** and **7** were generated (ca. 65%) by a diazo transfer reaction on the β-ketoesterers **4** and **5** with *p*-toluenesulfonylazide.[5] These β-ketoesters were obtained when the nitriles **2**[6] and **3** were reacted with excess ethyl bromoacetate and zinc.[7] The pyrrolepropionitrile **3** was obtained by catalytic hydrogenation of the acrylonitrile **1**, which in turn was prepared from 1-methylpyrrole-2-aldehyde and triphenylphosphanylidene acetonitrile.[8]

The α-diazo-β-ketoesters **6** and **7** were unaffected by catalytic rhodium(II) acetate in dichloromethane, even at reflux temperature. Conversion of these compounds into the expected bicyclic ketones **8** and **9** did occur, however (ca. 50% yields), in 1,2-dichloroethane at reflux temperature (bp 72 °C in Mexico City). It is not clear what factors control the rate of these reactions given that related β-ketoester carbenoid insertions into aromatic CH bonds are reported to require 1,2-dichloroethane at reflux temperature,[9] whereas others take place at room temperature.[10] It is noteworthy that the cyclization of the carbenoids derived from indoles **10** and **11** also require 1,2-dichloroethane at reflux temperature (see below) (Scheme 1).

The indolyl α-diazo-β-ketoesters **10** and **11** were obtained (ca. 50%) from the acid chlorides of indole-3-acetic and indole-3-propionic acids (oxalyl chloride/−65 °C) and ethyl diazoacetate containing an equivalent of triethylamine using a modification of a procedure described by Bestmann and Kolm.[11] Rhodium(II) catalyzed decomposition of the diazo compounds **10** and **11** ($ClCH_2CH_2Cl$/reflux) generated the anticipated tricyclic ketones **12** (55%) and **13** (52%) as the major products in each case (Scheme 2).

Additionally, some α-diazoketones derived from 2-pyrrolylacetic, 2-pyrrolylpropionic, 3-indolylacetic and 3-indolylpropionic acids were explored. The pyrrole-2-alkanoic acids **17**, **18** and **20** used in this study were prepared by adaptations of literature methodology. Thus, the pyrrole-2-acetic acids **17** and **18** were obtained by alkaline hydrolysis[12] of the nitriles **2** and **16**, which in turn were derived from the ammonium salts of the Mannich bases **14** and **15** and sodium cyanide.[6] Pyrrole-2-propionic acid **20** was obtained by catalytic reduction and subsequent hydrolysis of the acrylate derivative **19**, which was prepared

Keywords: Rhodium carbenoids; α-diazo-β-ketoesters; α-diazoketones; Insertion pyrrol,indol.
* Corresponding author. Tel.: +52-56-224408; fax: +52-56-162217; e-mail address: erick.cuevas@correo.unam.mx
† Deceased on October, 2003.

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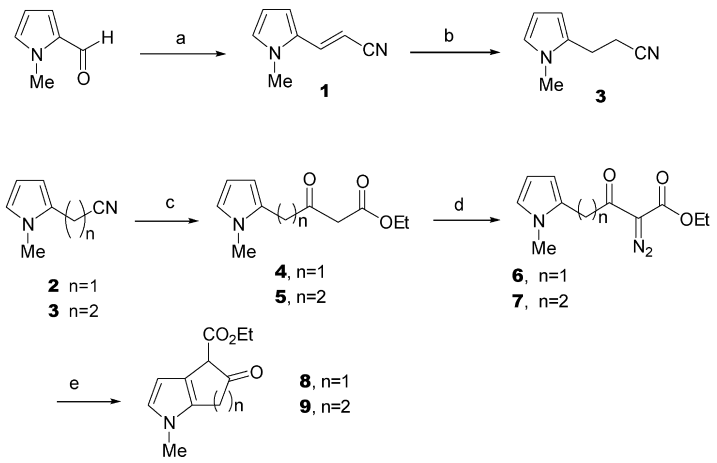
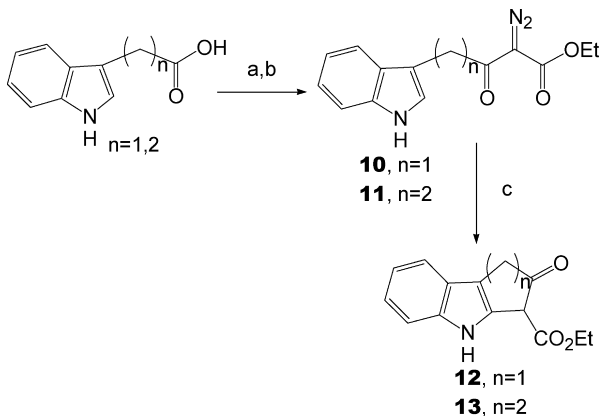


Scheme 1. *Reagents and conditions*: (a) Ph_3PCHCN, toluene/CH_2Cl_2, reflux, 36 h; (b) H_2, Pd/C, MeOH, RT, 6 h; (c) $BrCH_2CO_2Et$, Zn, THF, reflux, 8 h; (d) TsN_3, Et_3N, CH_2Cl_2, RT, 12 h; (e) $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, reflux, 3 h.



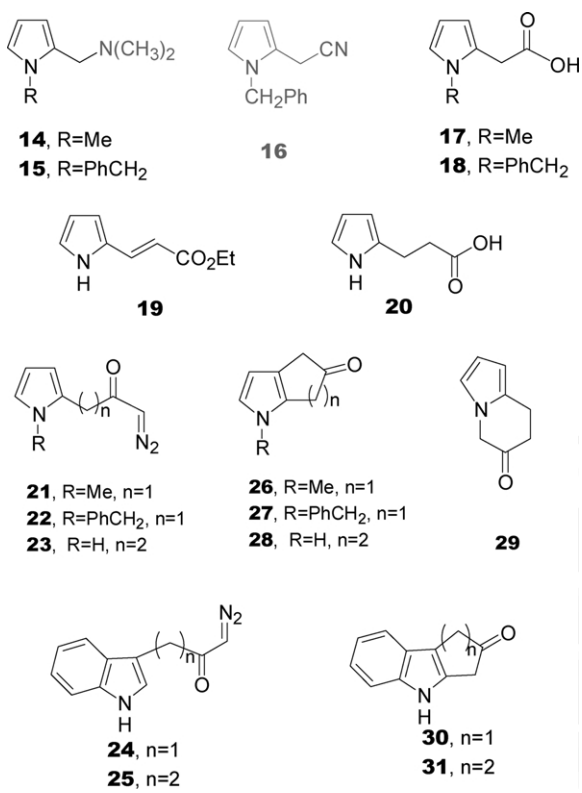
Scheme 2. *Reagents and conditions*: (a) oxalyl chloride, DMAP, THF, −65 °C. 30 min; (b) ethyl diazoacetate, Et_3N, −65 °C for 30 min and 12 h at RT; (c) $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, reflux, 3 h.

from pyrrole-2-aldehyde and the mono ethyl ester of malonic acid.[13]

The pyrrolyl diazoketones **21**–**23** were prepared (60–85%) by addition of excess ethereal diazomethane at 0 °C to an ethereal solution of the mixed ethyl carbonic–carboxylic anhydrides generated in situ at 0 °C. Exposure of the diazo compounds **21** and **22** to catalytic amounts of rhodium(II) acetate in dichloromethane solution at room temperature afforded the expected bicyclic ketones **26** and **27** respectively, as the only isolable products in 55–60% yields.

However, the α-diazobutanone **23** gave a mixture of ketones **28** (30% yield) and **29** (15% yield) derived from intramolecular insertion into the C-3H and N–H bonds of the pyrrole ring. This product ratio was independent of both the reaction temperature and the catalyst concentration. On the other hand, Capretta and Salim[4] report a 2.7:1 ratio of N–H to C-3H insertion for both the α-diazopropanone **23** (n=1) and the corresponding indole analog. Although the formation of both **28** and **29** was expected, the preferential formation of the CH insertion product **28**, was not. We are currently carrying out mechanistic studies on these seemingly counterintuitive results.

The indolyl diazoketones **24**[14] and **25** were prepared (70–



85%) from the commercially available carboxylic acids in a manner identical to that used for the synthesis of the 2-pyrrolyl analogs **21**–**23**. Rhodium(II) catalyzed decomposition of the diazo compound **24** (CH_2Cl_2/RT) and **25** ($ClCH_2CH_2Cl$/reflux) generated the anticipated tricyclic ketones **30** (70%) and **31** (82%) as the major products in each case.

In summary, this report shows that appropriately constituted 2-pyrrolyl and 3-indolyl-α-diazo-β-ketoesters and α-diazo alkanones are efficiently converted into bicyclic and tricyclic 5- and 6-membered ketones. These last results display alternative synthesis methodologies to obtain diverse pyrrolyl and indolyl diazo compounds, which complement and extend the results of Capretta and Salim.[4] In addition, all the cyclic ketones described herein

are useful points of departure enroute to certain natural products, and the cyclic β-ketoesters are particularly interesting in this regard because of the facility which further regiospecific chemical elaborations can be effected.

2. Experimental

2.1. General

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. The N-alkylated pyrroles were prepared according to the literature.[15] Solvents were distilled before use; ether and tetrahydrofuran (THF) were dried over sodium using benzophenone as indicator. Diazomethane was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) using a minimum amount of water and ethanol as cosolvent, and dried over KOH pellets before use. Silica gel (230–400 mesh) and neutral alumina were purchased from Merck. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher–Johns melting point apparatus and they are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini 200, the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (*m*/*z*) are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

2.1.1. Preparation of 3-(1-methylpyrrol-2-yl)propionitrile (3). A solution of triphenylphosphanylidene acetonitrile[8] (7.78 g, 25.8 mmol) in CH_2Cl_2 (20 mL) was added to a solution of 1-methylpyrrole-2-aldehyde[16] (0.76 g, 6.98 mmol) in toluene (50 mL). The resulting mixture was refluxed under a nitrogen atmosphere for 36 h. The mixture was cooled to room temperature and the solvent was removed in vacuo. Purification by column chromatography (SiO_2, hexane/AcOEt 8:2) afforded the pyrrole acrylonitrile **1** (0.74 g, 80%) as a colorless oil. IR ($CHCl_3$, cm^{-1}) 2949, 2210, 1615; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.67 (s, 3H), 5.46 (d, 1H), 5.52 (d, 1H), 6.18 (m, 2H), 6.78 (t, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.9, 101.6, 107.1, 108.0, 116.5, 117.4, 117.7, 131.3. MS [EI+] *m*/*z* (RI%): 132 $[M]^+$ (100), 131 $[M-H]^+$ (40). HRMS (EI^+): for $C_8H_8N_2$ calcd 132.0687, found 132.0690.

The pyrrole acrylonitrile **1** was dissolved in anhydrous MeOH (50 mL) and hydrogenated (760 mm) over Pd/C (0.08 g) for 6 h. The catalyst was removed by filtration and the solvent was evaporated to give the crude pyrrole propionitrile **3** (0.68 g, 90%) as a colorless oil which was used without purification. IR ($CHCl_3$, cm^{-1}) 2924, 2246, 1494; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.64 (t, 2H), 2.96 (t, 2H), 3.56 (s, 3H), 5.98m, 1H), 6.07 (m, 1H), 6.59 (t, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.6, 24.8, 37.6, 106.1, 108.0, 116.5, 117.7, 131.3. MS [EI+] *m*/*z* (RI%): 134 $[M]^+$ (50), 94 $[M-CH_2CN]^+$ (100). HRMS (FAB^+): for $C_8H_{11}N_2$ calcd 135.0922, found 135.0919.

2.2. Preparation of pyrrolyl-β-ketoesters

Typical procedure. To a suspension of zinc dust (0.32 g, 5 mmol) in refluxing anhydrous THF (3 mL) under a nitrogen atmosphere was added 4 drops of ethyl bromoacetate (0.055 mL, 0.08 g, 0.5 mmol). After the appearance of the green color, the pyrrolyl nitrile (1 mmol) was added in 1 portion, and ethyl bromoacetate (0.43 mL, 0.66 g, 4 mmol) was injected by syringe pump over 1 h and the mixture was refluxed for additional 8 h. The dark solution was cooled to 0 °C and it was treated with 10% aqueous HCl (1 mL) for 30 min. The mixture was concentrated in vacuo, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.2.1. 4-(1-Methylpyrrol-2-yl)-3-oxo-butyric acid ethyl ester (4). Colorless oil (63%). IR ($CHCl_3$, cm^{-1}) 2985, 1732, 1316; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3H), 2.61 (s, 2H), 3.44 (s, 3H), 3.79 (s, 2H), 4.18 (q, 2H), 6.02 (m, 1H), 6.08 (m, 1H), 6.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 40.5, 49.2, 59.0, 106.5, 107.1, 122.1, 131.2, 171.1, 194.8; MS [EI+] *m*/*z* (RI%): 209 $[M]^+$ (20), 94 $[M-COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{11}H_{15}NO_3$ calcd 209.1052, found 209.1056.

2.2.2. 5-(1-Methylpyrrol-2-yl)-3-oxo-pentanoic acid ethyl ester (5). Colorless oil (58%). IR ($CHCl_3$, cm^{-1}) 2940, 1728; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H), 2.85 (t, 2H), 3.19 (t, 2H), 3.42 (s, 2H), 3.56 (s, 3H), 4.21 (q, 2H), 5.93 (m, 1H), 6.06 (m, 1H), 6.52 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 15.3, 33.8, 37.6, 49.4, 59.4, 106.2, 107.0, 121.9, 131.0, 171.0, 194.0; MS [EI+] *m*/*z* (RI%): 223 $[M]^+$ (5), 180 $[M-C_2H_3O]^+$ (50), 94 $[M-COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{12}H_{17}NO_3$ calcd 223.1208, found 223.1210.

2.3. Preparation of pyrrolyl-α-diazo-β-ketoesters by diazo transfer reaction

Typical procedure. An ice-cold solution of pyrrolyl-β-ketoester (1 mmol) in CH_2Cl_2 (5 mL) was treated with triethylamine (0.27 mL, 0.20 g, 2 mmol) and *p*-toluenesulfonyl azide (0.197 g, 1 mmol) and the mixture was stirred under a nitrogen atmosphere at room temperature overnight. The solvent was removed in vacuo, the solid residue was triturated with ether (20 mL) and the mixture including the insoluble residue was washed successively with a 20% aqueous NaOH (3×20 mL). The red ethereal phase was dried over Na_2SO_4, and the solvent was removed in vacuo. The final product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.3.1. 2-Diazo-4-(1-methylpyrrol-2-yl)-3-oxo-butyric acid ethyl ester (6). Red oil (52%). IR ($CHCl_3$, cm^{-1}) 2987, 2139, 1725; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, 3H), 2.42 (s, 2H), 3.64 (s, 3H), 4.24 (q, 2H), 5.79 (m, 1H), 5.98 (m, 1H), 6.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 40.5, 59.6, 72.0, 106.4, 107.0, 122.0, 131.1, 171.2, 205.0. MS [EI+] *m*/*z* (RI%): 235 $[M]^+$ (5), 94 $[M-COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{11}H_{13}N_3O_3$ calcd 235.0957, found 235.0954.

2.3.2. 2-Diazo-5-(1-methylpyrrol-2-yl)-3-oxo-pentanoic acid ethyl ester (7). Red oil (65%). IR ($CHCl_3$, cm^{-1}) 2939, 2138, 1715; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H), 2.85 (t, 2H), 2.92 (t, 2H), 3.61 (s, 3H), 4.20 (q, 2H), 5.82 (m, 1H), 6.00 (m, 1H), 6.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 19.5, 33.7, 59.4, 71.1, 106.2, 107.0, 121.9, 131.0, 171.0, 204.0; MS [EI+] *m/z* (RI%): 249 $[M]^+$ (10), 94 $[M-CH_2COCH_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{12}H_{15}N_3O_3$ calcd 249.1113, found 249.1119.

2.4. Cyclization of pyrrolyl-α-diazo-β-ketoesters

Typical procedure. A solution of pyrrolyl-α-diazo-β-ketoester (1 mmol) in dry 1,2-dichloroethane (10 mL) was treated with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere and the resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The final product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.4.1. 1-Methyl-5-oxo-1,4,5,6-tetrahydrocyclopenta[*b*]-pyrrole-4-carboxylic acid ethyl ester (8). Colorless oil (54%). IR ($CHCl_3$, cm^{-1}) 2986, 1731; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, 3H), 3.40 (s, 2H), 3.63 (s, 3H), 4.12 (q, 2H), 4.16 (s, 1H) 5.92 (d, 1H), 6.70 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 40.8, 40.9, 60.1, 60.6, 108.4, 119.0, 122.9, 133.3, 171.0, 215.0; MS [EI+] *m/z* (RI%): 207 $[M]^+$ (5), 134 $[M-CO_2Et]^+$ (40), 29 $[CH_2CH_3]^+$ (100). HRMS (EI^+): for $C_{11}H_{13}NO_3$ calcd 207.0895, found 207.0897.

2.4.2. 1-Methyl-5-oxo-4,5,6,7-tetrahydroindole-4-carboxylic acid ethyl ester (9). Colorless oil (57%). IR ($CHCl_3$, cm^{-1}) 2929, 1726; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H), 2.85 (t, 2H), 2.92 (t, 2H), 3.61 (s, 3H), 4.11 (q, 2H), 4.16 (s, 1H) 6.05 (d, 1H), 6.55 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.1, 38.2, 40.8, 60.1, 60.5, 108.3, 118.9, 122.8, 133.1, 171.0, 210.2; MS [EI+] *m/z* (RI%): 221 $[M]^+$ (10), 149 $[M-C_3H_4O_2]^+$ (65), 148 $[M-CO_2Et]^+$ (100). HRMS (EI^+): for $C_{12}H_{15}NO_3$ calcd 221.1052, found 221.1057.

2.5. Preparation of indolyl-α-diazo-β-ketoesters

Typical procedure. A dry ice-cold solution of the acid (1 mmol) in freshly distilled THF (10 mL) was treated successively with oxalyl chloride (0.087 mL, 0.127 g, 1 mmol) and 4-(dimethylamino)pyridine (0.012 g, 0.1 mmol), the mixture was stirred under a nitrogen atmosphere for 30 min at −65 °C. The mixture was treated with ethyl diazoacetate (0.105 mL, 0.114 g, 1 mmol) and triethylamine (0.139 mL, 0.101 g, 1 mmol) at −65 °C. The stirring was continuing for additional 2 h under nitrogen atmosphere at −65 °C and the reaction was allowed to warm to room temperature overnight. The solvent was removed in vacuo and the product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.5.1. 2-Diazo-4-(indol-3-yl)-3-oxobutyric acid ethyl ester (10). Red oil (50%). IR ($CHCl_3$, cm^{-1}) 3479, 2987, 2154, 1725, 1716; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, 3H), 3.80 (s, 2H), 4.31 (q, 2H), 7.09–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 30.9, 61.5, 71.0, 107.4, 111.2, 118.6, 119.7, 122.2, 123.3, 127.0, 136.0, 177.7, 213.6; MS [EI+] *m/z* (RI%): 271 $[M]^+$ (5), 243 $[M-N_2]^+$ (5), 175 $[M-COCN_2CO]^+$ (65), 130 $[M-COCN_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{14}H_{13}N_3O_3$ calcd 271.0957, found 271.0963.

2.5.2. 2-Diazo-4-(indol-3-yl)-3-oxopentanoic acid ethyl ester (11). Red oil (50%). IR ($CHCl_3$, cm^{-1}) 3480, 2927, 2145, 1720, 1712; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H), 2.70 (t, 2H), 3.07 (t, 2H), 4.26 (q, 2H), 6.97–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 20.3, 34.5, 61.9, 71.0, 111.1, 114.1, 118.2, 118.7, 121.4, 121.6, 126.9, 136.0, 177.7, 213.6; MS [EI+] *m/z* (RI%): 285 $[M]^+$ (2), 284 $[M-H]^+$ (5), 130 $[M-CH_2COCN_2CO_2Et]^+$ (100). HRMS (EI^+): for $C_{15}H_{15}N_3O_3$ calcd 285.1113, found 285.1117.

2.6. Cyclization of indolyl α-diazo-β-ketoesters

Typical procedure. A solution of indolyl diazo compound (1 mmol) in dry 1,2-dichloroethane (10 mL) was treated with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere and the resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The final product was purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.6.1. 2-Oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole-3-carboxylic acid ethyl ester (12). White solid (55%). Mp 145–147 °C (ether–hexane). IR ($CHCl_3$, cm^{-1}) 3479, 2987, 1725, 1716; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, 3H), 3.80 (s, 2H), 4.31 (q, 2H), 4.73 (s, 1H), 7.09–7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 30.9, 61.5, 63.6, 107.4, 111.2, 118.6, 119.7, 122.2, 123.3, 127.0, 136.0, 177.7, 213.6; MS [EI+] *m/z* (RI%): 243 $[M]^+$ (2), 242 $[M-H]^+$ (5), 130 $[M-COCCO_2Et]^+$ (100). HRMS (EI^+): for $C_{14}H_{13}NO_3$ calcd 243.0895, found 243.0896.

2.6.2. 2-Oxo-2,3,4,9-tetrahydrocarbazole carboxylic acid ethyl ester (13). White solid (52%). Mp 156 °C (ether–hexane). IR ($CHCl_3$, cm^{-1}) 3480, 2929, 1721, 1711; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3H), 2.75 (t, 2H), 3.10 (t, 2H), 4.22 (q, 2H), 4.67 (s, 1H), 6.99–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 20.3, 34.5, 61.9, 68.0, 111.1, 114.5, 118.5, 119.3, 121.4, 122.0, 127.0, 136.2, 178.9, 213.0; MS [EI+] *m/z* (RI%): 257 $[M]^+$ (5), 130 $[M-CH_2COCCO_2Et]^+$ (100). HRMS (EI^+): for $C_{15}H_{15}NO_3$ calcd 257.1052, found 257.1057.

2.7. Preparation of dimethylaminomethylpyrroles

Typical procedure. A mixture of 37% aqueous formaldehyde (9 mL, 3.6 g, 0.12 mol) and dimethylamine hydrochloride (9.78 g, 0.12 mol) was added with stirring to the pyrrole (0.10 mol) at a rate such that the reaction temperature did not exceed 60 °C. The stirring was continued a further 2 h. At the end of this time, 20% NaOH (15 mL) and H_2O (40 mL) were added and the product was extracted with ether (3×20 mL). The organic layers were combined, they were washed with saturated NaCl solution (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by distillation under a reduced pressure.

2.7.1. 1-Methyl-2-(dimethylaminomethyl)pyrrole (14). Colorless oil (71%). Bp 58 °C/5 mm. IR (film, cm^{-1}) 3404, 2971, 2941, 2812; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 6H), 3.32 (s, 2H), 3.62 (s, 3H), 6.00 (m, 2H), 6.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.7, 41.7, 41.7, 58.2, 108.6, 108.7, 121.1, 121.2; MS [EI+] *m/z* (RI%): 138 $[M]^+$ (40), 94 $[M-(CH_3)_2N]^+$ (100). HRMS (EI^+): for $C_8H_{14}N_2$ calcd 138.1157, found 138.1159.

2.7.2. 1-Benzyl-2-(dimethylaminomethyl)pyrrole (15). Colorless oil (52%). Bp 110 °C/5 mm. IR (film, cm^{-1}) 3400, 2970, 2938, 2824; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (s, 6H), 3.30 (s, 2H), 3.59 (s, 3H), 5.09 (s, 2H), 6.13 (m, 2H), 6.67 (m, 1H). ^{13}C NMR (CDCl3, 50 MHz) δ 41.4, 41.4, 51.5, 58.0, 107.6, 109.8, 122.7, 126.3, 126.4, 127.2, 127.4, 128.4, 128.5, 137.5. MS [EI+] *m/z* (RI%): 208 $[M]^+$ (35), 164 $[M-(CH_3)_2N]^+$ (25), 91 $[PhCH_2]^+$ (100). HRMS (EI^+): for $C_{14}H_{18}N_2$ calcd 214.1470, found 214.1475.

2.8. Preparation of pyrrole acetic acids

Typical procedure. Iodomethane (7.47 mL, 17.04 g, 0.12 mol) was added slowly to a stirred and cooled (0 °C) solution of 2-(dimethylaminomethyl)pyrrole (0.1 mol) in acetone (5 mL/g pyrrole) maintained in a nitrogen atmosphere, at a rate such that the reaction temperature did not exceed 4 °C. When the addition was completed, the solution was stirred at room temperature for 1 h, then the solvent was removed and a solution of NaCN (14.7 g, 0.3 mol) in H_2O (150 mL) and EtOH (50 mL) was added and the resulting solution was heated at reflux overnight. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo, then, H_2O was added and the product was extracted with ether. The extract was washed with saturated NaCl solution and after drying the solvent was removed in vacuo and the product was purified by distillation under a reduced pressure (100 °C/5 mm). The pyrroleacetonitriles (**2** and **16**) were mixed with a solution of KOH (6 equiv.) H_2O (1.5 mL/mmol pyrroleacetonitrile) and EtOH (3.0 mL/mmol pyrroleacetonitrile) and the mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo, then H_2O was added and the resulting solution was acidified with 10% HCl solution to pH=1. The product was extracted with ethyl acetate (3×50 mL), the extract was washed and dried over Na_2SO_4, the solvent was removed in vacuo and the product was purified by crystallization.

2.8.1. 1-Methylpyrrol-2-yl acetic acid (17). White solid (70%). Mp 135 °C (ether–hexane). IR (KBr, cm^{-1}) 3465, 3339, 1660, 1624; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.57 (s, 2H), 3.65 (s, 3H), 6.07 (m, 2H), 6.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.4, 41.8, 108.6, 108.7, 121.1, 121.2, 178.0. MS [EI+] *m/z* (RI%): 139 $[M]^+$ (50), 94 $[M-COOH]^+$ (100). HRMS (FAB^+): for $C_7H_{10}NO_2$ calcd 140.0712, found 140.0719.

2.8.2. 1-Benzylpyrrol-2-yl acetic acid (18). White solid (40%). Mp 122 °C (ether–hexane). IR (film, cm^{-1}) 3201, 3032, 2929, 1645; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.52 (s, 2H), 5.09 (s, 2H), 6.14 (m, 2H), 6.67 (m, 1H), 7.00–7.31 (m, 5H); ^{13}C NMR (CDCl3, 50 MHz) δ 39.0, 50.9, 107.7, 109.8, 122.6, 126.2, 126.2, 127.2, 127.3, 128.2, 128.3, 137.5, 179.1; MS [EI+] *m/z* (RI%): 215 $[M]^+$ (30), 170 $[M-COOH]^+$ (20), 91 $[PhCH_2]^+$ (100). HRMS (EI^+): for $C_{13}H_{13}NO_2$ calcd 215.0946, found 215.0947.

2.8.3. Preparation of 3-(pyrrol-2-yl)propionic acid (20). Pyrrole-2-aldehyde (1 g, 10.3 mmol) was mixed with hydrogen ethyl malonate (2.78 g, 21 mmol) in pyridine (10 mL) and piperidine (0.5 mL) and the mixture was warmed at 50 °C with stirring for 48 h and 80 °C for 24 h. 10% HCl (150 mL) was added, the product was extracted with ether, the organic phase was washed with aqueous Na_2CO_3 and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification by distillation under reduced pressure afforded the 3-(pyrrol-2-yl)acrylic acid ethyl ester **19** as colorless oil. Bp 120 °C/5 mm. IR ($CHCl_3$, cm^{-1}) 3463, 1695; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (t, 3H), 4.20 (q, 2H), 5.94 (d, 3H), 5.99 (d, 1H), 6.18 (m, 1H), 6.28 (m, 1H), 6.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.6, 105.9, 107.9, 116.1, 123.4, 131.1, 142.8, 165.9; MS [EI+] *m/z* (RI%): 165 $[M]^+$ (100). HRMS (EI^+): for $C_9H_{11}NO_2$ calcd 165.0790, found 165.0792. Compound **19** may be used without purification.

The crude acrylic ester **19** was dissolved in anhydrous MeOH (75 mL) and hydrogenated (760 mm) over 10% Pd/C (0.1 g) for 6 h. The catalyst was removed by filtration and the solvent was evaporated. Distillation of the product afforded the ethyl propionic ester, as a colorless oil. Bp 100 °C/5 mm. IR ($CHCl_3$, cm^{-1}) 3462, 1732; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, 3H), 2.74 (t, 2H), 3.09 (t, 2H), 4.13 (q, 2H), 6.08 (m, 1H), 6.13 (m, 1H), 6.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.6, 41.0, 59.1, 105.9, 107.9, 116.1, 131.1, 171.5; MS [EI+] *m/z* (RI%): 167 $[M]^+$ (10), 94 $[M-CO_2Et]^+$ (100). HRMS (EI^+): for $C_9H_{13}NO_2$ calcd 167.0946, found 165.0745.

The ethyl propionic ester was added to a solution of K_2CO_3 (2 equiv.) in H_2O (6 mL) and EtOH (24 mL) and the mixture was heated at reflux overnight. The mixture was cooled at room temperature, the solvent was removed and H_2O (50 mL) was added, the solution was acidified with 10% HCl solution to pH=1, the product was extracted with ethyl acetate, the organic phase was washed, dried and the solvent was evaporated in vacuo. Crystallization afforded the pyrrolepropionic acid **20** in 40% global yield. Mp 138 °C (ether). IR ($CHCl_3$, cm^{-1}) 3479, 3060, 1712; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.78 (t, 2H), 3.12 (t, 2H), 6.01 (m, 2H), 6.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 40.9, 105.9, 107.9, 116.1, 131.1, 176.3; MS [EI+] *m/z* (RI%): 139 $[M]^+$ (50), 94 $[M-COOH]^+$ (100). HRMS (EI^+): for $C_7H_9NO_2$ calcd 139.0633, found 139.0639.

2.9. Preparation of pyrrolyldiazoketones

Typical procedure. An ice-cold solution of the acid (1 mmol) in freshly distilled ether was treated successively with ethyl chloroformate (0.10 mL, 0.11 g, 1.1 mmol) and *N*-methylmorpholine (0.10 mL, 0.10 g, 1 mmol), the mixture was stirred under nitrogen atmosphere for 15 min at 0 °C, then an ether solution of diazomethane (10 mmol) from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (3.06 g, 14.3 mmol) was added at 0 °C. A vigorous evolution of

nitrogen occurred, and the mixture was allowed to warm to room temperature overnight. The solvent was removed in vacuo and the product was purified by column chromatography (alumina activity III, hexane/AcOEt 95:5).

2.9.1. 1-Diazo-3-(1-methylpyrrol-2-yl)propanone (21). Orange oil (80%). IR (film, cm^{-1}) 2105, 1738, 1637; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.53 (s, 3H), 3.59 (s, 2H), 5.13 (s, 1H), 6.02 (m 1H), 6.07 (t, 1H, J_{3-4}=3.5 Hz), 6.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.4, 41.8, 52.4, 108.6, 108.7, 121.1, 121.2, 195.2; MS [EI+] *m/z* (RI%): 163 $[M]^+$ (77), 135 $([M-N_2]^+$ (10), 94 $[M-COCHN_2]^+$ (100).HRMS (FAB^+): for $C_8H_{10}N_3O$ calcd 164.0824, found 164.0834.

2.9.2. 1-Diazo-3-(1-benzylpyrrol-2-yl)propanone (22). Orange oil (63%). IR ($CHCl_3$, cm^{-1}) 2104, 1745, 1638; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.49 (s, 2H), 5.02 (s, 2H), 5.06 (s, 1H), 6.09 (m, 1H), 6.15 (t, 1H, J_{3-4}=3.46 Hz), 6.71 (m, 1H)7.0–7.3 (m, 5H); ^{13}C NMR (CDCl3, 50 MHz) δ 39.0, 50.5, 53.9, 107.6, 109.8, 122.7, 126.3, 126.4, 127.2, 127.4, 128.4, 128.5, 137.5, 192.0; MS [EI+] *m/z* (RI%): 239 $[M]^+$ (15), 211 $[M-N2]^+$ (10), 170 $[M-COCHN2]^+$ (55), 91 $[PhCH_2]^+$ (100). HRMS (FAB^+): for $C_{14}H_{14}N_3O$ calcd 240.1139, found 240.1137.

2.9.3. 1-Diazo-4-(pyrrol-2-yl)-butan-2-one (23). Orange oil (70%). IR ($CHCl_3$, cm^{-1}) 3478, 2976, 2109, 1730; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.73 (t, 2H), 2.95 (t, 2H), 6.10 (m, 2H), 6.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.5, 40.9, 55.1, 105.9, 107.9, 116.1, 131.1, 195.5; MS [EI+] *m/z* (RI%): 163 $[M]^+$ (10), 94 $[M-COCHN_2]^+$ (100).HRMS (FAB^+): for $C_8H_{10}N_3O$ calcd 164.0824, found 164.0833.

2.10. Cyclization of pyrrolyldiazopropanones

Typical procedure. A solution of the diazopropanone (1 mmol) in dry CH_2Cl_2 (5 mL) was stirred with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere at room temperature. After 2 h, the mixture was evaporated in vacuo and purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

2.10.1. 1-Methyl-4,6-dihydrocyclopenta[*b*]pyrrol-5-one (26). Colorless oil (60%). IR (film, cm^{-1}) 2925, 2854, 1738; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.56 (s, 2H), 3.58 (s, 3H), 3.69 (s, 2H), 6.04 (d, 1H, J_{4-5}=2.7 Hz), 6.56 (d, 1H, J_{5-4}=2.76 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.9, 40.8, 40.9, 108.6, 119.3, 122.9, 131.2, 215.2; MS [EI+] *m/z* (RI%): 135 $[M]^+$ (40), 134 $[M-H]^+$ (100). HRMS (EI^+): for C_8H_9NO calcd 135.0684, found 135.0686.

2.10.2. 1-Benzyl-4,6-dihydrocyclopenta[*b*]pyrrol-5-one (27). Colorless oil (55%). IR ($CHCl_3$, cm^{-1}) 2956, 2927, 1724; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.50 (s, 2H), 4.56 (s, 2H), 5.01 (s, 2H), 6.10 (d, 1H, J_{4-5}=2.74 Hz), 6.65 (d, 1H, J_{5-4}=2.72 Hz), 7.0–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.5, 40.7, 52.2, 109.5, 119.5, 122.8, 126.4, 127.1, 127.8, 128.6, 128.8, 131.0, 137.3, 215.4; MS [EI+] *m/z* (RI%): 211 $[M]^+$ (5), 210 $[M-H]^+$ (100). HRMS (EI^+): for $C_{14}H_{13}NO$ calcd 211.0997, found 211.0999.

2.11. Reaction of 1-diazo-4-(2-pyrrolyl)-2-butanone (23) with rhodium(II) acetate

The procedure was similar to that used in the cyclization of pyrrolyldiazopropanones. Column chromatography (SiO_2, hexane/AcOEt 9:1) afforded the compounds **28** and **29**.

2.11.1. 1,4,6,7-Tetrahydroindol-5-one (28). White solid (30%). Mp 137 °C. IR (film, cm^{-1}) 3476, 2920, 1711; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.68 (t, 2H), 2.97 (t, 2H), 3.40 (s, 2H), 5.98 (d, 1H, J_{4-5}=2.7 Hz), 6.68 (d, 1H, J_{5-4}=2.76 Hz), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.2, 38.3, 39.0, 107.4, 114.2, 117.7, 124.7, 210.7; MS [EI+] *m/z* (RI%): 135 $[M]^+$ (100), 134 $[M-H]^+$ (10).HRMS (FAB^+): for $C_8H_{10}NO$ calcd 136.0762, found 136.0751.

2.11.2. 7,8-Dihydroindolizin-6-one (29). Colorless oil (15%). IR (film, cm^{-1}) 2958, 1724; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.70 (t, 2H), 3.06 (t, 2H), 4.52 (s, 2H), 5.98 (dd, 1H), 6.17 (d, 1H), 6.58 (d, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 38.1, 54.8, 104.7, 108.9, 118.8, 128.0, 205.9; MS [EI+] *m/z* (RI%): 135 $[M]^+$ (40), 134 $[M-H]^+$ (75), 80 $[M-CH_2COCH]^+$ (100).HRMS (FAB^+): for $C_8H_{10}N_3O$ calcd 136.0762, found 136.0774.

2.12. Preparation of indolyl diazoalkanones 24 and 25

The procedure was similar to that used in the preparation of pyrrolyldiazoketones.

2.12.1. 1-Diazo-3-(indol-3-yl)propanone (24). Orange oil (84%). IR ($CHCl_3$, cm^{-1}) 3477, 2108, 1735, 1633; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 2H), 5.17 (s, 1H), 7.1–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.9, 54.3, 108.5, 111.3, 118.8, 119.9, 122.4, 123.4, 127.2, 136.2, 194.2; MS [EI+] *m/z* (RI%): 199 $[M]^+$ (10), 171 $[M-N_2]^+$ (11), 130 $[M-COCHN_2]^+$ (100). HRMS (EI^+): for $C_{11}H_9N_3O$ calcd 199.0746, found 199.0743.

2.12.2. 1-Diazo-4-(indol-3-yl)butan-2-one (25). Orange oil (87%). IR ($CHCl_3$, cm^{-1}) 3481, 2110, 1732; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.72 (t, 2H), 3.11 (t, 2H), 5.15 (s, 1H), 6.99–7.45 (m, 5H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 41.1, 54.6, 111.2, 114.3, 118.6, 119.4, 121.6, 121.6, 127.2, 136.4, 195.0; MS [EI+] *m/z* (RI%): 213 $[M]^+$ (10), 185 $[M-N_2]^+$ (15), 130 $[M-CH_2COCHN_2]^+$ (100). HRMS (EI^+): for $C_{12}H_{11}N_3O$ calcd 213.0902, found 213.0907.

2.12.3. Cyclization of 1-diazo-3-(indol-3-yl)propanone (24) with rhodium(II) acetate. The procedure was similar to that used in the cyclization of pyrrolyldiazopropanones. Purification by column chromatography (SiO_2, hexane/AcOEt 8:2) afforded 3,4-dihydrocyclopenta[*b*]indol-2-one **30** as white solid (70%). Mp 145 °C. IR ($CHCl_3$, cm^{-1}) 3477, 2916, 1753; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.49 (s, 2H), 3.78 (s, 2H), 7.1–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.2, 39.3, 111.1, 111.6, 118.8, 120.2, 121.9, 136.0, 136.0, 138.8, 214.2; MS [EI+] *m/z* (RI%): 171 $[M]^+$ (20), 143 $[M-CO]^+$ (30), 130 $[M-CHCO]^+$ (100).). HRMS (EI^+): for $C_{11}H_9NO$ calcd 171.0684, found 171.0697.

2.12.4. Cyclization of indolyl diazoketone 25. A solution of indolyl diazoketone **25** (1 mmol) in dry 1,2-dichloroethane (10 mL) was treated with $Rh_2(OAc)_4$ (2 mg) under a nitrogen atmosphere and the resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. Purification by column chromatography (SiO_2, hexane/AcOEt 8:2) afforded 1,3,4,9-tetrahydrocarbazol-2-one **31** as a white solid (82%). Mp 150 °C. IR ($CHCl_3$, cm^{-1}) 3481, 2957, 1732; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.74 (t, 2H), 3.12 (t, 2H), 3.68 (s, 2H), 7.0–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 29.7, 34.7, 111.1, 114.9, 118.6, 119.2, 121.3, 122.0, 130.8, 136.2, 218.0; MS [EI+] *m/z* (RI%): 185 $[M]^+$ (5), 130 $[M-CHCH_2CO]^+$ (100). HRMS (EI^+): for $C_{12}H_{11}NO$ calcd 185.0841, found 185.0845.

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References and notes

1. (a) Galeazzi, E.; Guzman, A.; Piñedo, A.; Saldaña, A.; Torre, D.; Muchowski, J. M. *Can. J. Chem.* **1983**, *61*, 454. (b) Müller, P.; Polleux, P. *Helv. Chim. Acta* **1998**, *81*, 317.
2. Jefford, C. W.; Johncock, W. *Helv. Chim. Acta* **1983**, *66*, 2666.
3. (a) Jefford, C. W.; Kubota, T.; Zaslona, A. *Helv. Chim. Acta* **1986**, *69*, 2048. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *Helv. Chim. Acta* **1989**, *72*, 1749. (c) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (d) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119.
4. Capretta, A.; Salim, M. *Tetrahedron* **2000**, *56*, 8063.
5. Doyle, M. P.; McKervey, M. A.; Ye, T. Modern catalytic methods for organic synthesis with diazo compounds: from cyclopropanes to ylides; Wiley: New York, 1998; p 10.
6. (a) Herz, W.; Rogers;, J. *J. Am. Chem. Soc.* **1951**, *73*, 4921. (b) Herz, W.; Ditter, K.; Cristol, S. J. *J. Am. Chem. Soc.* **1947**, *69*, 1698.
7. Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.
8. Tamiaki, H.; Kouraba, M. *Tetrahedron* **1997**, *53*, 10677.
9. Hashimoto, S.; Watanabe, N.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1992**, 1508.
10. Zaragoza, F. *Tetrahedron* **1995**, *51*, 8829.
11. Bestmann, H. J.; Kolm, H. *Chem. Ber.* **1963**, *96*, 1948.
12. Carpio, H.; Cho, D.; Gallegra, P.; Halpern, O.; Koehler, R.; Maddox, M. L.; Muchowski, J. M.; Prince, A.; Tegg, D.; Thurber, T. C.; Van Horn, A. R.; Wren, D. *Can. J. Chem.* **1982**, *60*, 2295.
13. (a) Bates;, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. (b) Volz, H.; Draese, R. *Tetrahedron Lett.* **1970**, *11*, 4917.
14. Franceschetti, L.; Garzon-Aburbeh, A.; Mahmoud, M. R.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1993**, *34*, 3185.
15. Heany, H.; Ley, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499.
16. 1-Methylpyrrole-2-aldehyde was prepared using the procedure described by Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203.

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Synthesis of carbazomycin B by radical arylation of benzene

David Crich* and Sochanchingwung Rumthao

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607-7061, USA

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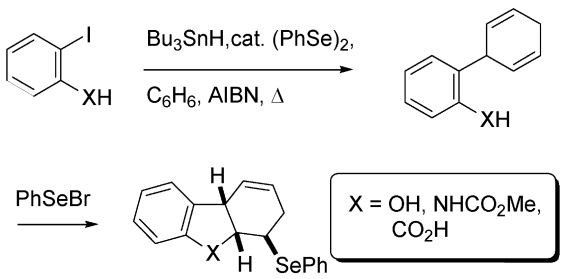
Abstract—Iodination of 2-methoxy-3,4-dimethyl-5-nitrophenol followed by acetylation yields (6-iodo-2-methoxy-3,4-dimethyl-5-nitrophenyl) acetate. Reduction with iron and acetic acid followed by reaction with methyl chloroformate then provides *N*-methoxycarbonyl-3-acetoxy-2-iodo-4-methoxy-5,6-dimethylaniline. Treatment of this substance in benzene at reflux with tributyltin hydride and a catalytic quantity of diphenyl diselenide leads to the formation of *N*-methoxycarbonyl-3-acetoxy-2-(2,5-cyclohexadienyl)-4-methoxy-5,6-dimethylaniline which on exposure to phenylselenenyl bromide affords a phenylselenenyl tetrahydrocarbazole. Oxidation deselenation and rearomatization are achieved by heating with *tert*-butylhydroperoxide finally affording carbazomycin B after saponification.

1. Introduction

Benzeneselenol catalyzes the stannane-mediated addition of aryl radicals to benzene with the predominant formation of 3-aryl-1,4-cyclohexadienes.[1] When the aryl radical is functionalized in the *ortho*-position, subsequent cyclization reactions lead to tetrahydrocarbazoles and/or tetrahydrodibenzofurans depending on the nature of the functionality employed (Scheme 1).[2]



Scheme 1. Formation of tetrahydrocarbazoles and dibenzofurans from benzene.

We considered that, when coupled to a suitable rearomatization step, this sequence would provide a ready and direct entry into a number of carbazole alkaloids,[3] especially those heavily functionalized in one benzenoid ring yet devoid of substitution in the other. An extreme example of the kind is carbazomycin B (**1**), an inhibitor of 5-lipoxygenase[4] and of the growth of some phytopathogenic fungi,[5] with weak antibacterial activity.[5] Accordingly, we selected this target as a test bed for the intended chemistry. Previous syntheses of carbazomycin B have involved (i) the formation of a simpler carbazole skeleton followed by introduction of the remaining functionality; (ii) Friedel–Crafts alkylation of a functionalized aniline with the η^5-cyclohexadienylirontricarbonyl cation, followed by an aromatizing cyclization with 'highly active' manganese dioxide,[6] and (iii) a radical cyclization approach employing an *N*-cyclohexadien-3-yl-*o*-bromoaniline.[7] The synthesis that we describe here differs significantly from the precedent in so far as one ring is derived directly from benzene with no prior functionalization, adjustment of oxidation state, or complexation to a metal required.

2. Results and discussion

Nitrophenol **3** was readily derived from the acetate **2**, whose synthesis was previously described by Clive and co-workers.[7] Iodination of **3** with sodium iodide, iodine, and butylamine in water afforded the iodide **4**, which was acetylated to provide **5**. This was then cleanly reduced, with iron and ferric chloride in acetic acid,[8] to the aniline **6**, derivatization of which afforded the iodocarbamate **7** (Scheme 2) ready for the key radical reaction.

In the key radical dearomatization step, an 0.05 M solution of iodide (**7**) and diphenyl diselenide (20 mol%) in benzene was treated at reflux dropwise with tributyltin hydride and AIBN.[9] After partitioning of the reaction mixture between hexanes and acetonitrile,[10] the adduct **8** was obtained by chromatography of the acetonitrile phase in 40% yield, together with 8% of the recovered substrate and 12% of the

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* Corresponding author. Tel.: +1-312-996-5189; fax: +1-312-996-2183; e-mail address: dcrich@uic.edu

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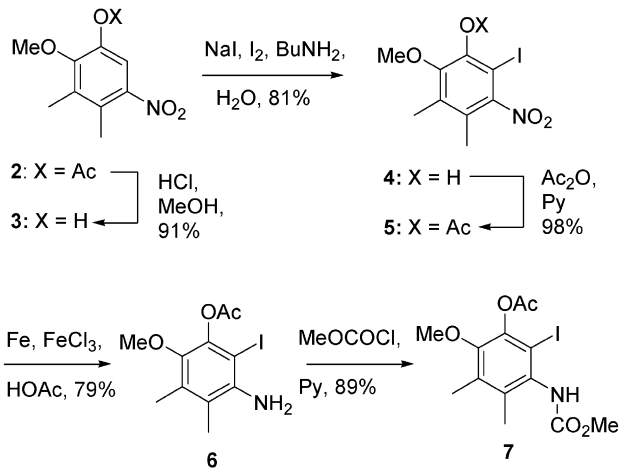


Scheme 2. Formation of the iodocarbamate **7**.

deiodinated product **9** (Scheme 3). Treatment of **8** with phenylselenenyl bromide in dichloromethane then afforded the tetrahydrocarbazole **10** in 74% yield. Mindful of the earlier work of Barton and co-workers in which benzeneseleninic anhydride was demonstrated to be an efficient reagent for the oxidation of indolines to indoles,[11,12] **10** was heated to reflux in benzene with an excess of *tert*-butyl hydroperoxide resulting in the formation of the fully aromatic species **11** in 53% isolated yield. Finally, exposure of **11** to hot methanolic sodium hydroxide afforded carbazomycin B (**1**) in 75% yield (Scheme 3) with spectral data consistent with the literature values.[7]

3. Experimental

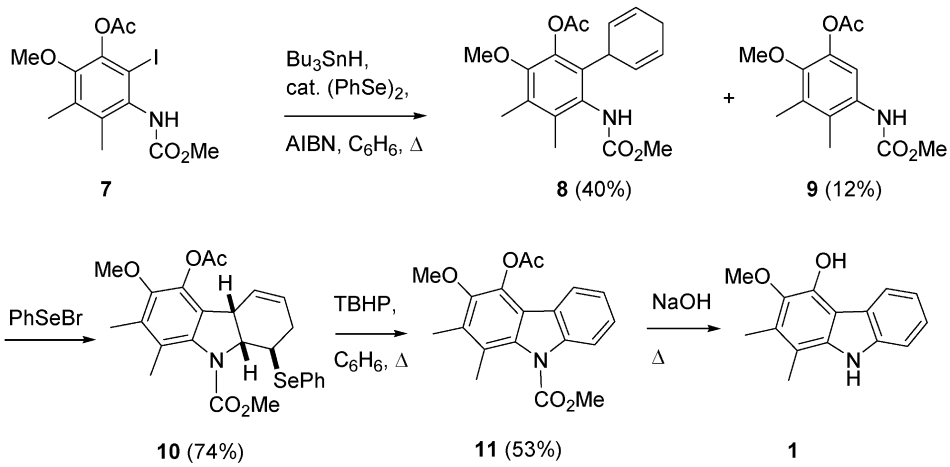
3.1. General

3.1.1. 2-Methoxy-3,4-dimethyl-5-nitrophenol (3). Anhydrous HCl in MeOH (20 mL of 7 M) was added under Ar to acetate **2**[7] (5.76 g, 24.0 mmol), after which the reaction mixture was heated to 70 °C with stirring for 4 h. The reaction mixture was cooled to room temperature, concentrated and the residue was diluted with EtOAc and washed with water. The organic layer was dried, concentrated and purified by silica gel column chromatography eluting with ethyl acetate–hexane (1:4) to afford the title phenol as viscous yellow oil (4.28 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.23 (s, 1H), 6.43 (br s, 1H), 3.76 (s, 3H), 2.48 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 149.1, 146.9, 146.7, 132.4, 124.4, 109.5, 61.1, 15.3, 13.1; ESIHRMS Calcd for $C_9H_{10}NO_4$ $[M-H]^-$ 196.0610, found 196.0609.

3.1.2. 2-Iodo-6-methoxy-4,5-dimethyl-3-nitrophenol (4). A solution of NaI (5.03 g, 34 mmol) and iodine (4.77 g, 19 mmol) in water (17 mL) was added dropwise to a 20% aqueous solution of $BuNH_2$ (24 mL) and **3** (2.24 g, 11 mmol) at room temperature. The resulting brown solution was stirred for 30 min at ambient temperature then diluted with dichloromethane. The organic layer was washed with water, 10% aqueous sodium thiosulphate solution, dried, and concentrated. The residue was filtered through a short silica gel pad and recrystallized from EtOAc–Hex to afford the crystalline iodophenol **4** (3.00 g, 81%). Mp 178–180 °C; ^{1}H NMR ($CDCl_3$): δ 6.26 (br s, 1H), 3.79 (s, 3H), 2.22 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.0, 148.4, 145.8, 132.0, 122.0, 71.3, 61.3, 15.0, 13.2; ESIHRMS Calcd for $C_9H_9NO_4I$ $[M-H]^-$ 321.9576, found 321.9576.

3.1.3. 2-Iodo-3-acetoxy-4-methoxy-5,6-dimethyl nitrobenzene (5). To a solution of iodophenol **4** (3.0 g, 10.6 mmol) in Ac_2O (3.3 g, 32 mmol) was added pyridine (0.042 g, 0.53 mmol) and DMAP (0.195 g, 1.6 mmol) at room temperature. The reaction mixture was stirred for 10 h at room temperature then quenched with ice/water. The precipitate formed was filtered off and washed with water, then was taken up in dichloromethane and filtered through a short silica gel pad to afford acetate **5** (3.34 g, 98%). Mp 150–151 °C; ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 3H), 2.38 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.7, 152.5, 151.4, 144.2, 133.9, 128.6, 81.0, 61.3, 21.0, 15.6, 13.2; ESIHRMS Calcd for $C_{11}H_{12}NO_5I[M]^+$ 364.9760, found 364.9776.

3.1.4. 2-Iodo-3-acetoxy-4-methoxy-5,6-dimethylaniline (6). A solution of nitrobenzene **5** (2.58 g, 8.0 mmol) and AcOH (1.55 mL) in EtOH (13 mL) was heated to reflux with stirring for 10 min before iron powder (3.23 g,



Scheme 3. Completion of the synthesis.

58 mmol) and $FeCl_3{\cdot}6H_2O$ (0.13 g, 0.48 mmol) were added. The resulting mixture was heated to reflux with stirring for 4 h before it was cooled to room temperature and concentrated. The residue was extracted with EtOAc and the organic layer was washed with water, brine, and dried. Purification of the extracts by silica gel column chromatography eluting with EtOAc–Hex (3:7) afforded aniline **6** (1.85 g, 79%). Mp 85–87 °C; IR ($CHCl_3$): 3404, 1797 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.02 (br s, 2H), 3.65 (s, 3H), 2.38 (s, 3H), 2.19 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.5, 142.9, 142.6, 142.2, 131.5, 119.4, 79.1, 61.1, 21.2, 14.9, 13.1; ESIHRMS Calcd for $C_{11}H_{15}NO_3I$ $[M+H]^+$ 336.0097, found 336.0097.

3.1.5. *N*-Methoxycarbonyl-2-iodo-3-acetoxy-4-methoxy-5,6-dimethylaniline (7). To a solution of aniline **6** (0.78 g, 2.6 mmol) in pyridine (4.2 g, 53.2 mmol) was added dropwise methyl chloroformate (0.38 g, 4.0 mmol) at 0 °C under Ar. The reaction mixture was stirred for 4 h at room temperature then diluted with water and extracted with EtOAc. The organic layer was washed with water, 20% $CuSO_4$ solution, dilute HCl, brine, and dried. Concentration of the extracts and purification by silica gel column chromatography eluting with EtOAc–Hex (2:3) afforded carbamate **7** (0.93 g, 89%). Mp 119–121 °C; IR ($CHCl_3$): 3450, 1783 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.29 (br s, 1H), 3.77 (br s, 3H), 3.71 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.2, 154.9, 149.7, 143.3, 135.6, 133.1, 132.5, 77.4, 61.0, 53.0, 21.1, 16.6, 13.3; ESIHRMS Calcd for $C_{13}H_{15}NO_5I$ $[M-H]^-$ 391.9995, found 391.9995.

3.1.6. *N*-Methoxycarbonyl-2-(2,5-cyclohexadienyl)-3-acetoxy-4-methoxy-5,6-dimethylaniline (8) and *N*-Methoxycarbonyl-5-acetoxy-4-methoxy-2,3-dimethylaniline (9). To a stirred solution of iodide **7** (0.120 g, 0.31 mmol) and diphenyl diselenide (0.019 g, 0.06 mmol) at reflux in benzene (6.0 mL) under Ar was added a solution of Bu_3SnH (0.106 g, 0.37 mmol) and AIBN (0.005 g, 0.02 mmol) in benzene (2.5 mL) over 10 h. After the addition was complete, the reaction mixture was further stirred for an additional 1 h at 85 °C, then cooled to room temperature and concentrated. The residue was partitioned between acetonitrile and hexane and the acetonitrile layer was concentrated and purified by silica gel column chromatography eluting with EtOAc–Hex to give the adduct **8** (0.042 g, 40%), recovered **7** (0.025 g, 8%), and the desiodo compound **9** (0.012 g, 12%). **8**: IR (film): 3387, 1767, 1716, 1505, 1457, 1185 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.50 (s, 1H), 5.95–5.85 (m, 2H), 5.55 (br d, J=8.1 Hz, 2H), 4.29–4.22 (m, 1H), 3.71 (s, 3H), 3.68 (br s, 3H), 2.80 (m, 2H), 2.31 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.8, 155.8, 135.6, 131.3, 130.9, 129.6, 127.3, 126.5, 61.3, 61.1, 52.8, 52.6, 34.4, 25.9, 21.7, 20.9, 15.1, 13.7, 13.4; ESIHRMS Calcd for $C_{19}H_{23}NO_5Na$ $[M+Na]^+$ 368.1474, found 368.1467. **9** Mp 117–119 °C; IR (film): 3320, 1768, 1727, 1199 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26 (s, 1H), 6.30 (br s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.32 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.6, 147.4, 141.9, 132.0, 131.7, 61.2, 54.6, 20.9, 14.3, 13.9; ESIHRMS Calcd for $C_{13}H_{17}NO_5Na$ $[M+Na]^+$ 290.1004, found 290.0995.

3.1.7. Methyl 5-acetoxy-6-methoxy-7,8-dimethyl-1-phenylselenenyl-1,2,4a,9a-tetrahydrocarbazole-9-carboxylate (10). To a stirred solution of cyclohexadiene **8** (0.036 g, 0.10 mmol) in dichloromethane (2 mL) was added phenylselenenyl bromide (0.027 g, 0.11 mmol) at −78 °C under Ar. The reaction mixture was allowed to come to room temperature, then was stirred for 10 h, before it was diluted with dichloromethane, washed with water and dried. Concentration and purification of the crude reaction mixture by silica gel column chromatography eluting with EtOAc–Hex afforded the tetrahydrocarbazole **10** carbazole (0.038 g, 74%); IR (film): 1770, 1715, 1457, 1194 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.58 (d, J=6.8 Hz, 2H), 7.26–7.19 (m, 3H), 5.88–5.86 (m, 1H), 5.73–5.69 (m, 1H), 4.80 (dd, J=7.0, 11.6 Hz, 1H), 4.06 (br s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.31 (dt, J=5.4, 11.2 Hz, 1H), 2.31 (s, 3H), 2.35–2.25 (m, 2H), 2.18 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4, 155.8, 148.0, 138.6, 136.9, 136.0, 133.8, 131.1, 129.3, 128.9, 128.6, 128.1, 127.9, 127.0, 123.5, 66.9, 61.2, 53.3, 43.9, 40.8, 32.2, 23.0, 17.3, 13.1; ESIHRMS Calcd for $C_{25}H_{27}NO_5SeNa$ $[M+Na]^+$ 524.0952, found 524.0970.

3.1.8. Methyl 4-acetoxy-3-methoxy-1,2-dimethyl-carbazole-9-carboxylate (11). To a solution of selenide **10** (0.047 g, 0.093 mmol) in benzene (2 mL) was added 70% aqueous ^{t}BuOOH (0.047 mL, 0.5 mmol) at room temperature. The reaction mixture was heated to reflux with stirring for 2.5 h, then was cooled and concentrated. The crude reaction mixture was purified by silica gel column chromatography eluting with EtOAc–Hex (3:7) to afford carbazole **11** (0.017 g, 53%); IR (film): 1770, 1738, 1194 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.08 (d, J=7.2 Hz, 1H), 7.83 (d, J=7.6 Hz, 1H), 7.43 (t, J=7.6 Hz, 1H), 7.32 (t, J=7.6 Hz, 1H), 4.03 (s, 3H), 3.81 (s, 3H), 2.52 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.6, 153.1, 146.9, 140.4, 135.9, 135.7, 130.9, 126.9, 124.6, 124.1, 123.6, 121.2, 118.8, 115.4, 61.1, 53.8, 20.8, 18.0, 13.2; ESIHRMS Calcd for $C_{19}H_{19}NO_5Na$ $[M+Na]^+$ 364.1161, found 364.1165.

3.1.9. Carbazomycin B (1). A solution of carbamate (**11**) (2 mg, 0.006 mmol) and NaOH (0.006 g, 0.15 mmol) in MeOH–H_2O (1:1, 1 mL) was heated with stirring in an oil bath at 92 °C for 3 h. The methanol was then removed under vacuum and the remaining solution was neutralized (~pH 7) with dil. HCl (1 mL) and extracted with EtOAc. Concentration of the extracts and purification by silica gel column chromatography eluting with EtOAc–Hex (3:7) afforded carbazomycin B (**1**) (1 mg, 75%) with spectra data comparable to the literature values;[7] ^1H NMR ($CDCl_3$): δ 8.23 (d, J=7.5 Hz, 1H), 7.77 (br s, 1H), 7.38–7.35 (m, 2H), 7.25–7.18 (t, J=7.5 Hz, 1H), 6.01 (s, 1H), 3.82 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.4, 139.6, 138.8, 137.1, 127.3, 125.1, 123.6, 123.0, 119.8, 110.3, 109.6, 63.4, 13.6, 13.2; ESIMS Calcd for $C_{15}H_{15}NO_2Na$ $[M+Na]^+$ 241.29, found 241.29.

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References and notes

1. Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765–2770.
2. Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319–3322.
3. Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427.
4. Hook, D. J.; Yacobucci, J. J.; O'Connor, S.; Lee, M.; Kerns, E.; Krishnan, B.; Matson, J.; Hesler, G. *J. Antibiot.* **1990**, *53*, 1347–1348.
5. Sakano, K.-I.; Ishimaru, K.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 683–689.
6. Knölker, H.-J.; Bauermeister, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1468–1470.
7. Clive, D. L. J.; Etkin, N.; Joseph, T.; Lown, J. W. *J. Org. Chem.* **1993**, *58*, 2442–2445.
8. Gabrielle, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607–4613.
9. In this chemistry benzeneselenol, the active catalyst, is conveniently introduced as the diselenide, which is reduced in situ by the stannane: Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood, J. S. *J. Org. Chem.* **1996**, *61*, 2368–2373.
10. Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471–473.
11. Barton, D. H. R.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1985**, *41*, 4727–4738.
12. Ninomia, I.; Hashimoto, C.; Kiguchi, T.; Naito, T.; Barton, D. H. R.; Lusinchi, X.; Milliet, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 529–532.

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Cytotoxic and anti-HIV-1 constituents from leaves and twigs of *Gardenia tubifera*

Vichai Reutrakul,[a,*] Chongkon Krachangchaeng,[a] Patoomratana Tuchinda,[a,*] Manat Pohmakotr,[a] Thaworn Jaipetch,[b] Chalobon Yoosook,[c] Jittra Kasisit,[c] Samaisukh Sophasan,[d] Kulawee Sujarit[d] and Thawatchai Santisuk[e]

[a]*Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand*
[b]*Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand*
[c]*Department of Microbiology, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand*
[d]*Department of Physiology, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand*
[e]*The Forest Herbarium, Department of Royal Forest, Phaholyothin Road, Bangkok 10900, Thailand*

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Abstract—Two new natural cycloartanes, tubiferolide methyl ester (**1**) and tubiferaoctanolide (**2**), together with the known coronalolide (**3**) and coronalolide methyl ester (**4**) have been isolated from leaves and twigs of *Gardenia tubifera*. In addition, a new flavone 5,3′,5′-trihydroxy-7,4′-dimethoxyflavone (**5**), five known flavones **6**–**10** and hexacosyl 4′-hydroxy-*trans*-cinnamate (**11**) were also obtained from the same source. The structures were assigned on the basis of spectroscopic methods. Compounds **3**, **7**, **9**, and **10** showed significant cytotoxic activities only in P-388 cell line. Compound **1** was cytotoxic against P-388, KB, Col-2 and Lu-1, while **4** was active in P-388 and BCA-1. Compounds **3** and **4** displayed significant anti-HIV activities in the HIV-1RT assay; compound **7** showed moderate activity in this assay. Compounds **5**–**10** were also found to be active in the $^{\Delta Tat/Rev}$MC 99 syncytium assay.

1. Introduction

Several species of plants in *Gardenia* genus (Rubiaceae) have been used ethnomedically in various countries, primarily for abortifacient[1] and contraceptive[1–3] purposes. Some species are used as a febrifuge[4] and a larvicide,[5] as well as for the treatment of headaches,[6] asthma[7] and malaria.[8] Extracts of various species exhibiting anti-implantation and abortifacient effects,[9] anti-ulcer,[10] anti-bacterial,[11] diuretic,[12] analgesic,[12] hypertensive,[12] and larvicidal activity[13] have been previously reported. Our investigations of *G. coronaria* and *G. sootepensis*[14] led to the isolation of four ring-A *seco*-cycloartanes, and the work on *G. obtusifolia*[15] yielded one ring-A *seco*-cycloartane, two cycloartanes and five flavones. Herein we describe the investigation of hexane and chloroform extracts of *G. tubifera* which led to the isolation of tubiferolide methyl ester (**1**), tubiferaoctanolide (**2**), coronalolide (**3**), coronalolide methyl ester (**4**), 5,3′,5′-trihydroxy-7,4′-dimethoxyflavone (**5**), 5,3′,5′-trihydroxy-3,6,7,4′-tetramethoxyflavone (**6**), 5,7,4′-trihydroxy-6-methoxyflavone (**7**), 5,7,3′-trihydroxy-6,4′,5′-trimethoxyflavone (**8**), 5,3′-dihydroxy-7,4′,5′-trimethoxyflavone (**9**), 5,3′-dihydroxy-6,7,4′,5′-tetramethoxyflavone (**10**), and hexacosyl 4′-hydroxy-*trans*-cinnamate (**11**) (see Fig. 1). Compounds **1**, **2** and **5** have not been isolated previously. The structures of all isolated compounds were elucidated on the basis of spectroscopic methods. The results from cytotoxic and anti-HIV-1 activity evaluations are also included.

2. Results and discussion

Tubiferolide methyl ester (**1**) was shown to possess a molecular formula $C_{31}H_{46}O_4$ by HR-FABMS ($[M+H]^+$= 483.3458). Its IR ($CHCl_3$) spectrum displayed two carbonyl absorptions at 1755 and 1734 cm^{-1}, corresponding to the C=O stretching of α,β-unsaturated lactone and C=O stretching of ester, respectively. The ^1H NMR spectral data of **1** (Table 1) were similar to those of coronalolide methyl ester (**4**) obtained from the same species and previously isolated from *G. coronaria* and *G. sootepensis*.[14] Compound **1** exhibited a characteristic pair of doublets at δ 0.17 and 0.43 (J=5.3 Hz each), assignable to C-19 methylene protons of the cyclopropane ring of a cycloartane triterpene.[16–23] Two doublets at δ 6.34 (J=2.5 Hz) and 5.74 (J=2.1 Hz) were ascribed to H-28a and H-28b in exocyclic methylene γ-lactone ring, while the signals of the β and γ-methine protons of the lactone ring appeared at δ 3.24 (br d,

Keywords: Ring-A *seco*-cycloartane; Octanolide; Flavones; Cytotoxic activity; Anti-HIV activity.
* Corresponding authors. Tel.: +66-02-2015152; fax: +66-02-6445126; e-mail addresses: scvrt@mahidol.ac.th; scptc@mahidol.ac.th

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Table 1. ^{1}H and ^{13}C NMR data of compounds **1** and **2**

Position	δ_H[a]		δ_C[b]	
	1[c]	**2**[d]	**1**[e]	**2**[f]
1	(a) 2.23 (m) (b) 1.59 (obsc.)	(a) 2.10 (obsc.) (b) 1.30 (obsc.)	30.95	29.07
2	(a) 2.53 (m) (b) 2.44 (m)	(a) 2.61 (m) (b) 2.15 (obsc.)	31.25	32.00
3	—	—	173.42	173.66
4	—	—	139.27	147.33
5	3.24 (br d, 8.3)	2.35 (m)	39.14	38.61
6	4.75 (td, 8.3, 6.5)	(a) 1.75 (obsc.) (b) 0. 67 (obsc.)	74.46	29.47
7	(a) 1.78 (obsc.) (b) 1.53 (obsc.)	(a) 1.25 (obsc.) (b) 0.94 (obsc.)	27.26	25.30
8	2.14 (br t, 5.7)	1.52 (obsc.)	38.37	47.89
9	—	—	25.18	21.00
10	—	—	28.26	27.42
11	(a) 1.75 (obsc.) (b) 1.64 (obsc.)	(a) 2.13 (obsc.) (b) 1.21 (obsc.)	26.61	26.74
12	(a) 1.70 (obsc.) (b) 1.60 (obsc.)	(a) 1.65 (obsc.) (b) 0.88 (obsc.)	33.01	32.94
13	—	—	45.70	45.11
14	—	—	48.66	48.87
15	1.30 (obsc.)	(a) 1.23 (obsc.) (b) 0.89 (obsc.)	34.84	35.70
16	(a) 1.93 (obsc.) (b) 1.32 (obsc.)	(a) 1.84 (obsc.) (b) 1.24 (obsc.)	27.72	28.05
17	1.62 (obsc.)	1.55 (obsc.)	51.48	52.23
18	0.93 (s)	0.91 (s)	15.91	18.13
19	(a) 0.43 (d, 5.3) (b) 0.17 (d, 5.3)	(a) 0.76 (d, 4.0) (b) 0.46 (d, 4.0)	23.18	30.23
20	1.47 (obsc.)	1.35 (obsc.)	35.87	35.86
21	0.89 (d, 6.4)	0.83 (d, 6.3)	18.40	18.19
22	(a) 1.42 (obsc.) (b) 1.06 (obsc.)	1.37 (obsc.)	36.33	36.29
23	(a) 2.08 (obsc.) (b) 1.86 (obsc.)	(a) 1.98 (obsc.) (b) 1.77 (obsc.)	24.88	24.92
24	5.10 (br t, 7.0)	5.04 (br t, 6.9)	125.05	125.20
25	—	—	131.02	130.90
26	1.69 (br s)	1.62 (br s)	25.66	25.71
27	1.61 (br s)	1.54 (br s)	17.60	17.62
28	(a) 6.34 (d, 2.5) (b) 5.74 (d, 2.1)	(a) 5.22 (br s) (b) 5.11 (br s)	122.95	116.13
29	—	(a) 4.56 (d, 11.3) (b) 4.30 (d, 11.3)	170.64	68.23
30	0.91 (s)	0.86 (s)	20.07	19.35
OMe	3.70 (s)	—	51.75	—

[a] Chemical shift given in ppm using TMS as internal reference; multiplicities and coupling constants (Hz) are given in parentheses; obsc.=obscured signal.
[b] Chemical shift given in ppm; $CDCl_3$ signal at δ_C 77.00 as reference.
[c] Recorded at 500 MHz.
[d] Recorded at 300 MHz.
[e] Recorded at 125 MHz.
[f] Recorded at 75 MHz.

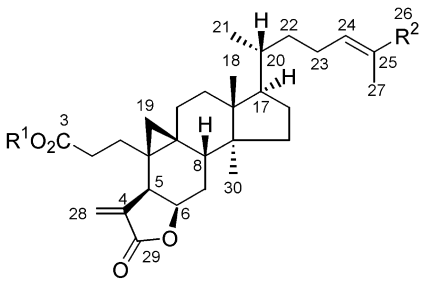
Table 2. Observed HMBC correlations in compounds **1** and **2**

HMBC		
C	**1** correlated H	**2** correlated H
1	5, 2a, 2b, 8 (w), 11b, 19a, 19b	19a, 19b
2	1a, 1b	1b
3	1a, 1b, 2a, 2b, 31	2a, 2b, 29a, 29b
4	5, 6, 28a	5, 28a, 28b, 29a, 29b
5	1a, 1b, 6 (w), 7a, 28a, 28b	1b, 19a, 19b, 28a, 28b
6	5, 7a, 7b, 8	5, 7a, 8, 28a, 28b
7	5, 8	8, 11b
8	1a, 6, 7a, 7b, 19a, 19b, 30	7a, 19a, 19b
9	1a, 8, 7a, 7b, 11a, 11b, 12b, 19a, 19b	1a, 7a, 8, 11a, 12a, 19a, 19b
10	1a, 1b, 2a, 2b, 5, 6, 7a, 8b, 11b, 19a, 19b, 28a	5, 1b, 19a, 19b
11	7a, 7b, 19a, 19b	12a, 19a, 19b
12	11a, 11b, 17, 18	18, 11a
13	8, 11a, 12a, 12b, 15b, 16a, 16b, 30	12a, 18, 20, 30
14	8, 7a, 7b, 12b, 15, 16b, 18	8, 12a, 17, 18, 30
15	8, 16a, 16b, 30	30
16	15, 17, 20	15a, 20
17	16a, 16b, 18, 20, 21	18, 30
18	12b, 17	12a, 17, 20
19	5, 7a, 8, 11a, 11b, 12b	1b, 11a, 8
20	17, 21, 22a, 22b	21
21	20, 22a	17, 20, 22
22	21, 23a, 23b, 24	21
23	22a, 22b	17, 22
24	20, 22a, 22b, 23a, 23b, 26, 27	26, 27
25	23a, 23b, 26, 27	26, 27
26	24, 27	24, 27
27	22a, 24, 26	26
28	5	5, 29a, 29b
29	5, 6, 28a, 28b	5, 28a, 28b
30	8, 15	8, 15a
31	31	—

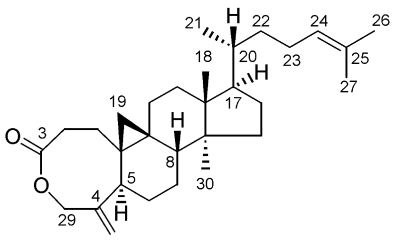
w=weak correlation.

J=8.3 Hz, H-5) and 4.75 (td, J=8.3, 6.5 Hz, H-6), respectively. When compared to the data of the known compound **4**, differences were found only for the side-chain signals. A broad triplet of an olefinic proton (H-24) at δ 5.10 (J=7 Hz), together with two broad singlets of two methyl groups at δ 1.69 (26-Me) and 1.61 (27-Me) indicated the presence of a terminal dimethylvinyl group in the side-chain of **1**. The structural feature of the side-chain as shown in **1** was confirmed by the EI-MS fragment ions at *m/z* 371 $(M-C_8H_{15})^+$ and 111 $(C_8H_{15})^+$ which were consistent with a cleavage of the bond between C-17 and C-20. Apart from the singlets of 18-Me and 30-Me at δ 0.93 and 0.91, a doublet of a secondary methyl group (21-Me) was observed at δ 0.89 (J=6.4 Hz). The ^{13}C NMR spectrum of **1** (Table 1) was analyzed and found to consist of two carbonyl carbons, five methyl carbons, eleven methylene carbons, six methine carbons and six quarternary carbons. Assignments of the ^{1}H and ^{13}C signals as shown in Table 1 were carried out on the basis of 2D-NMR spectral data (see Section 5 and Table 2) and by direct comparison of the chemical shifts with those of similar compounds reported in the literature.[14] The HMBC correlations of 18-Me signal to C-12, C-14 and C-17 signals confirmed the assignment of 18-Me signal, while the correlations of 30-Me signals to C-8, C-13 and C-15 supported the identification of 30-Me. The relative stereochemistry of **1** was determined on the basis of NOE difference data (see Fig. 2).

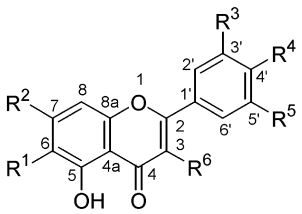
Tubiferaoctanolide **2** ($C_{30}H_{46}O_2$) showed an $[M+H]^+$ peak at 439.3546 in the HRMS. The IR absorptions at 1724 and 1647 cm^{-1} indicated the presence of C=O and C=C units in the structure. The ^{1}H NMR spectral data (Table 1) of **2** displayed a characteristic pair of doublets (δ 0.46 and 0.76, J=4.0 Hz each) of the methylene protons in cyclopropane ring of a cycloartane triterpene. Compound **2** was found to possess the same side-chain as **1**, as a broad triplet of



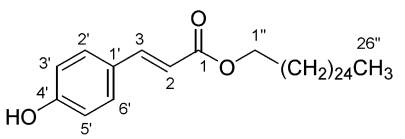
1 $R^1 = R^2 = Me$
3 $R^1 = H$, $R^2 = CHO$
4 $R^1 = Me$, $R^2 = CHO$



2



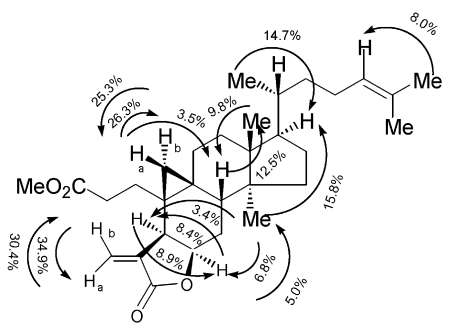
5 $R^1 = R^6 = H$, $R^2 = R^4 = OMe$, $R^3 = R^5 = OH$
6 $R^1 = R^2 = R^4 = R^6 = OMe$, $R^3 = R^5 = OH$
7 $R^1 = OMe$, $R^2 = R^4 = OH$, $R^3 = R^5 = R^6 = H$
8 $R^1 = R^4 = R^5 = OMe$, $R^2 = R^3 = OH$, $R^6 = H$
9 $R^1 = R^6 = H$, $R^2 = R^4 = R^5 = OMe$, $R^3 = OH$
10 $R^1 = R^2 = R^4 = R^5 = OMe$, $R^3 = OH$, $R^6 = H$



11

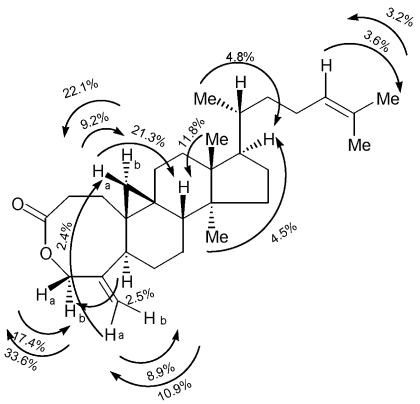
Figure 1.

olefinic H-24 (δ 5.04, J=6.9 Hz), together with two broad singlets of two methyls (δ 1.62 for 26-Me and 1.54 for 27-Me) in dimethylvinyl moiety were observed. The signal of 21-Me in the side-chain appeared as a doublet at δ 0.83 (J=6.3 Hz). The fragment ions due to the loss of side-chain at m/z 327 for $(M-C_8H_{15})^+$ and 111 $(C_8H_{15})^+$ in the EI-MS confirmed the skeleton of the side-chain. In addition, the two singlets at δ 0.91 (3H) and 0.86 (3H) were assigned to the signals of 18-Me and 30-Me, respectively. The HMBC correlations of 18-Me to C-12, C-13 and C-14; C-18 to H-12a, H-17 and H-20; 30-Me to C-13, C-14, C-15 and C-17; C-30 to H-8 and H-15a confirmed the assignments of these two angular methyls. Information from the ^{13}C NMR and DEPT spectra indicated the presence of carbonyl carbon of an ester or a lactone at δ 173.66 which was confirmed to be at C-3 by the observed HMBC correlations of H-2a and H-2b to C-3. Instead of having the signals corresponding to gem-dimethyl groups at C-4 as in typical cycloartanes, two broad singlets of sp^2 methylene signals of H-28a and H-28b (δ 5.22 and 5.11) and a pair of low-field doublets (δ 4.56 and 4.30, J=11.3 Hz each) of *gem*-methylene (H-29a and H-29b) on a carbon bearing an oxygen atom were observed. The observed HMBC correlations of H-28a and H-28b signals to C-4 signal, as well as H-29a and H-29b signals to C-4 signal confirmed the connection of C-28 and C-29 to C-4. The oxygen atom on C-29 was found to be attached to C-3, as HMBC correlations of H-29a and H-29b to C-3 were observed. Other connectivities which established the structure of **2** were obtained from HMBC correlation data (Table 2). The NOE difference data which support the assignments of the relative stereochemistry are shown in Figure 3.



1

Figure 2. NOE enhancements observed in compound **1**.



2

Figure 3. NOE enhancements observed in compound **2**.

Table 3. Cytotoxic and antimitotic activities (ASK assay) of the isolated compounds **1**–**11**

Compound	Cytotoxicity (ED_{50}, μg/mL)					ASK assay
	Cell line					
	P-388	KB	Col-2	BCA-1	Lu-1	
1	0.89	1.48	2.28	8.39	1.89	−
2	>20	>20	>20	>20	>20	−
3	1.73	9.11	12.06	>20	10.83	−
4	1.50	15.10	10.70	3.59	18.22	−
5	9.07	13.32	>20	>20	>20	−
6	6.82	10.97	>20	>20	18.83	−
7	2.38	6.53	18.33	>20	19.95	−
8	7.03	16.11	17.27	18.65	>20	−
9	3.00	7.17	>20	>20	>20	−
10	2.82	6.31	14.78	10.08	8.18	−
11	>20	>20	>20	>20	>20	−
Ellipticine	0.58	0.56	0.58	0.77	0.47	

Cytotoxic assay: $ED_{50} \leq 5$ μg/mL is considered active; P-388: murine lymphocytic leukemia, KB: human nasopharyngeal carcinoma, Col-2: human colon cancer, BCA-1: human breast cancer, Lu-1: human lung cancer, Ellipticine, an anticancer drug, was used as a positive control in the cytotoxicity test; ASK: rat glioma, ASK assay: +=active; −=inactive.

The new flavone **5** exhibited an $[M]^+$ peak at *m*/*z* 330 in the EI-MS, corresponding to a molecular formula $C_{17}H_{14}O_7$. The UV maxima at 269 and 330 nm were consistent with those observed in flavone derivatives. The presence of phenolic and the conjugated carbonyl groups in flavone **5** were indicated in its IR spectrum at 3466 (phenolic O–H), 1667 (conj. C=O), 1614 (C=C) and 1199 (C–O of phenol) cm^{-1}. The presence of a chelated 5-OH signal at δ 12.83 (1H) and a free OH signal at δ 9.59 (2H) in the ^1H NMR spectrum (see Section 5) confirmed that **5** was triphenolic. In addition, **5** was found to possess two methoxyl groups; the two methoxyl signals resonated at δ 3.83 (3H) and 3.75 (3H). A characteristic singlet signal of H-3 in flavone was observed at δ 6.66. The *J* value of 2.1 Hz observed at the aromatic signals [δ 6.67 (H-6) and 6.33 (H-8)] indicated the *meta*-oxygenation pattern in ring A. The remaining aromatic signal at δ 6.97 (s, 2H) was assigned to H-2′and H-6′of ring B. A series of NOE enhancement experiments was performed to prove the oxy-genation pattern in **5**. The signals of H-6 and H-8 were enhanced by 15.2 and 14%, respectively, when the signal of 7-OMe was irradiated. The locations of the two free hydroxyl groups were proved to be at C-3′and C-5′, as en- hancements of 2.0 and 7.1% were observed at the free OH and H-3 signals, respectively, when H-2′ and H-6′ signals were irradiated. Thus, the remaining methoxyl group was assigned to C-4′. Interpretation of 15 signals for 17 carbons was facilitated by analyses of the HETCOR and COLOCspectra (see Section 5). The assignments of ^1H and ^{13}C signals accomplished by the 2D-NMR spectal analyses established the structure of **5** as 5,3′,5′-trihydroxy-7,4′-dimethoxyflavone.

Compounds **3** and **4** are ring-A *seco*-cycloartane triterpenes which have been reported previously from leaves and/or stems of *G. coronaria* and *G. sootepensis*.[14] Compound **6** is the only 3-methoxyflavone found in this plant, while compounds **7**–**10** are flavone derivatives. The structures were identified by direct comparison of their melting points and spectral data to the values reported in the literature.[24–28] Compound **11** is a phenolic ester which has been isolated from *Dikamali* gum, the exudation of the leaf-bud of *Gardenia lucida*.[29]

3. Biological evaluations

Pure isolated compounds **1**–**11** were tested for cytotoxic effects against a panel of cultured mammalian cell lines,[30] antimitotic[31] and anti-HIV-1 activities. The results are given in Tables 3 and 4. It was found that compounds **1**, **3**, **4**, **7**, **9**, and **10** exhibited cytotoxic acitivity against P-388 cell line and **1** also showed cytotoxic activity against KB, Col-2 and Lu-1; while compound **4** was also active in BCA-1 cell line. Compounds **2**, **5**, **6**, **8**, and **11** were found inactive in all tested cell lines. In the ASK assay, the tested compounds did not exhibit antimitotic effects. All isolated compounds were also tested, employing HIV-1 reverse transcriptase (RT),[32] and a syncytium assay[33] using $^{\Delta Tat/Rev}$MC99 virus and 1A2 cell line system[33,34] (see Table 4). The results indicated that compounds **5**–**10** were active in the $^{\Delta Tat/Rev}$MC99 syncytium assay, while compounds **1** and **3** were toxic. However, compounds **3** and **4** were very active (99.9% and 71.1% inhibition at 200 μg/mL; with IC_{50} values of 17.0

Table 4. Anti-HIV-1 activities of the isolated compounds **1**–**11** by syncytium and HIV-1 RT assays

Compound	Syncytium ($^{\Delta Tat/Rev}$MC99+1A2) assay				HIV-1 RT assay	
	IC_{50} (μg/mL)	EC_{50} (μg/mL)	TI (IC_{50}/EC_{50})	Activity	Inhibition (%)	Activity
1	<3.9	—	—	T	9.9	I
2	27	—	—	I	2.6	I
3	4.4	—	—	T	99.9	VA
4	12.5	—	—	I	71.1	VA
5	>125	8.8	>14.1	A	12.1	I
6	21.1	9.8	2.1	A	16.2	I
7	8.8	<3.9	>2.3	A	57.9	M
8	16.7	9.5	1.8	A	25.5	I
9	72.5	6.8	10.7	A	5.9	I
10	>125	48.7	>2.6	A	18.6	I
11	>125	—	—	I	23.4	I

Syncytium assay: IC_{50}=dose of compound that inhibited 50% metabolic activity of uninfected cells. EC_{50}=dose of compound that reduced 50% syncytium formation by $^{\Delta Tat/Rev}$MC99 virus. A=active; I=inactive, <50% reduction at the IC_{50} indicated, T=Toxic; EC_{50} AZT, averaged from 2 experiments, 4×10^{-9} M. RT assay: inhibition (%) at 200 μg/mL; VA=very active (>70% inhibition), M=moderately active (>50–70% inhibition), W=weakly active (30–50% inhibition), I=inactive (<30% inhibition); positive control, fagaronine chloride, IC_{50} 9.8 μg/mL and non-nucleoside reverse transcriptase inhibitor, nevirapine, IC_{50} 1.8 μg/mL.

and 49.7 μg/mL, respectively) and compound **7** was moderately active in the HIV-1 RT assay.

4. Conclusion

Although cycloartane triterpenes and flavones are commonly found in plants, 3,4-*seco*-cycloartanes with α-methylene-γ-butyrolactone fused at C-5 and C-6 as in compound **1** are particularly rare. The extraordinary cycloartane **2** with oxygen insertion between C-29 and C-3 to form an eight membered ring-A lactone represents a novel skeleton which has not been previously reported. The highly significant anti-HIV-1 activity of compounds **3** and **4** is reported for the first time.

5. Experimental

5.1. General procedure

Mps: uncorr.; UV: EtOH or MeOH; IR: $CHCl_3$ or KBr. NMR spectra were recorded on either Bruker DPX 300 or Bruker Avance 500 spectrometer, using TMS as an internal standard, unless otherwise stated; CC and prep. TLC were carried out on silica gel 60 (63–200 μm) and silica gel 60 PF_{254} (5–40 μm), respectively.

5.2. Plant material

The leaves and twigs of *Gardenia tubifera* were collected from Kalasin province of Thailand in January 1998 and identified by one of the authors (T. S.). The voucher specimen (BKF 25199) has been deposited at the Forest Herbarium, Royal Forest Department, Bangkok, Thailand.

5.3. Extraction and isolation

The air-dried and finely powdered leaves and twigs of *G. tubifera* (1.85 kg) were successively percolated with hexane (4×3 L), $CHCl_3$ (8×3.5 L) and MeOH (3×4 L), respectively. Removal of solvents gave a crude hexane fraction (110 g), a $CHCl_3$ fraction (190 g) and a MeOH fraction (190 g), respectively.

The hexane fraction (69 g) was separated by CC (silica gel, 1.5 kg), eluting with 0–100% acetone–hexane, followed by 0–100% MeOH–acetone to afford fractions A1–A10. Fr. A6 (eluted with 10% acetone–hexane, 2.60 g) gave **11** (179.6 mg) upon recrystallization from CH_2Cl_2–hexane. Fr. A7 (eluted with 10% acetone–hexane, 8.98 g) was further separated by CC over silica gel (acetone–hexane and MeOH–acetone gradients, respectively) to give fractions B1–B5. Fr. B2 (eluted with 5–8% acetone–hexane, 1.26 g) yielded **1** (115.5 mg) and **11** (229.1 mg) after prep. TLC (silica gel, 90% CH_2Cl_2–hexane, 2 elutions). Fr. A8 (eluted with 15% acetone–hexane, 8.99 g) was separated by CC over silica gel ($CHCl_3$–hexane and MeOH–$CHCl_3$ gradients, respectively) to give fractions C1–C4. Fr. C1 (eluted with 1% MeOH–$CHCl_3$, 1.14 g) provided **4** (45.2 mg) after prep. TLC (silica gel, 90% CH_2Cl_2–hexane, 2 elutions).

The $CHCl_3$ fraction (188 g) was subjected to a coarse separation by CC (silica gel, 1.3 kg), eluting with 0–100% CH_2Cl_2–hexane, followed by 0–100% MeOH–CH_2Cl_2, to yield fractions C1–C7. Further separation of Fr. C3 (eluted with 1.5–2% MeOH–CH_2Cl_2, 68.9 g) by CC over silica gel (acetone–hexane and MeOH–acetone gradients) gave fractions D1–D8. Fr. D4 (eluted with 14–20% acetone–hexane, 14.3 g) was separated by CC over silica gel ($CHCl_3$–hexane and MeOH–$CHCl_3$ gradients) to give fractions E1–E5. Fr. E2 (eluted with 0.5% MeOH–$CHCl_3$, 2.71 g) afforded **4** (107.7 mg) after prep. TLC (silica gel, 30% acetone–hexane) and recrystallization from CH_2Cl_2–hexane. Fr. D5 (eluted with 22–25% acetone–hexane, 12.1 g) was further separated by CC (CH_2Cl_2–hexane and MeOH–CH_2Cl_2 gradients, respectively) to provide **9** (eluted with 60–70% CH_2Cl_2–hexane, 2.01 g). Fr. D6 (eluted with 40–80% acetone–hexane, 13.7 g) yielded fractions F1–F4 after separation by CC over silica gel (CH_2Cl_2–hexane and MeOH–CH_2Cl_2 gradients, respectively). Fr. F2 (eluted with 1% MeOH–CH_2Cl_2, 2.62 g) afforded **10** (1.48 g) after prep. TLC (silica gel, 40% acetone–hexane) and recrystallization from MeOH. Fr. D7 (eluted with 5–20% MeOH–acetone, 16.9 g) gave fractions G1–G4 after CC (silica gel, $CHCl_3$–hexane and MeOH–$CHCl_3$ gradients). Fr. G3 (eluted with 2–5% MeOH–$CHCl_3$, 2.62 g) yielded **3** (247.8 mg) after prep. TLC (silica gel, 30% acetone–hexane). Fr. C4 (eluted with 2–3% MeOH–CH_2Cl_2, 6.49 g) was separated by CC (silica gel, EtOAc–hexane and MeOH–EtOAc gradients, respectively) to give fractions H1–H7. Fr. H3 (eluted with 25% EtOAc–hexane, 659.1 mg) gave **5** (56.1 mg) upon recrystallization in MeOH. Fr. H5 (eluted with 25–30% EtOAc–hexane, 2.28 g) afforded **6** (1.06 g) after recrystallization from EtOH. Fr. C5 (eluted with 3–3.5% MeOH–CH_2Cl_2, 35.05 g) was purified by CC over silica gel (CH_2Cl_2–hexane and MeOH–CH_2Cl_2 gradients, respectively) to give fractions I1–I7. Fr. I1 (eluted with 3–5% acetone–hexane, 612.2 mg) yielded **2** (36.0 mg) upon recrystallization from CH_2Cl_2–hexane. Fr. I5 (eluted with 15% acetone–hexane, 8.39 g) was separated by CC (silica gel, acetone–hexane and MeOH–acetone gradients, respectively) to provide fractions J1–J7. Fr. J5 (eluted with 20% acetone–hexane, 1.03 g) afforded **7** (327.5 mg) upon recrystallization from MeOH. Fr. J6 (eluted with 25–35% acetone–hexane, 9.41 g) was further separated by CC (silica gel, acetone–hexane and MeOH–acetone gradients, respectively) to give **8** (eluted with 30–40% acetone–hexane, 792.9 mg).

5.3.1. Tubiferolide methyl ester (1). White solid from CH_2Cl_2–hexane, mp 125.7–126.3 °C. $[\alpha]_D^{30}$=+142.0 (*c* 0.26, $CHCl_3$). UV (EtOH) λ_{max} nm (log ε): 206 (3.96). IR ($CHCl_3$) ν_{max}: 3027, 2952, 2875, 1755 (C=O stretching of α,β-unsaturated lactone), 1734 (C=O stretching of ester), 1654 (C=C stretching), 1457, 1438, 1377, 1297, 1270, 1171, 1149, 1017, 982, 945, 823 cm^{-1}. ^1H and ^{13}C NMR: see Table 1. COSY correlations: H/H; 1a/1b, 2a, 2b; 1b/1a, 2a, 2b; 2a/1a, 1b, 2b; 2b/1a, 1b, 2a; 5/6, 28a, 28b; 6/5, 7a, 7b; 7a/6, 8, 7b; 7b/6, 7a, 8; 8/7a, 7b, 30; 11a/11b, 12a, 12b; 11b/11a, 12a, 12b; 12a/11a, 12b, 18; 12b/11b, 12a; 15/16a, 16b; 16a/16b, 17; 16b/16a, 17; 17/16a, 16b, 18, 20, 22a; 18/12a, 17; 19a/19b; 19b/5, 19a; 20/17, 21, 22a, 22b; 21/20; 22a/21, 22b, 23a; 22b/20, 22a, 23a; 23a/22a, 22b, 23b, 24; 23b/22a, 22b, 23a; 24/23a, 26, 27; 26/24; 27/24; 28a/5;

28b/5; 30/8. HMBC correlations: see Table 2. EIMS (70 eV) *m/z* (%): 482 ([M]$^+$, 30), 398 (25), 371 (32), 286 (2), 111 (8), 69 (100). HRFABMS calcd for $C_{31}H_{47}O_4$ [M+H]$^+$483.3474, found 483.3458.

5.3.2. Tubiferaoctanolide (2). White solid from CH_2Cl_2–hexane, mp 139.5–140.3 °C. $[\alpha]_D^{28}$=+32.0 (*c* 0.25, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3029, 2936, 2875, 1724 (C=O stretching of lactone), 1647 (C=C stretching), 1457, 1379,1361, 1235, 1161, 997, 921, 839 cm^{-1}. ^{1}H and ^{13}C NMR: see Table 1. COSY correlations: H/H; 1a/1b, 2a, 2b; 1b/1a, 2a, 2b; 2a/1a, 1b, 2b; 2b/1a, 2a; 5/6a, 6b; 6a/5, 6b, 7a; 6b/5, 6a, 7b; 7b/6a, 7a, 8; 8/7a, 7b; 11a/11b, 12a; 11b/11a, 12a, 12b; 12a/11a, 11b; 15a/15b, 16a; 15b/15a, 16a; 16a/16b, 17; 17/20; 19a/19b; 19b/19a; 20/21; 21/20; 22/23a; 23a/22; 23b/22, 23a; 24/23a, 23b, 26, 27; 26/24; 27/24; 28a/28b; 28b/29a, 29b; 29a/28b, 29b; 29b/28a, 29a. HMBC correlations see Table 2. EIMS (70 eV) *m/z* (%): 438 ([M$^+$], 4), 410 (4), 340 (4), 327 (15), 111 (14), 69 (77), 55 (100). HRFABMS calcd for $C_{30}H_{47}O_2$ [M+H]$^+$439.3576, found 439.3546.

5.3.3. Coronalolide (3). White powder from CH_2Cl_2–hexane, mp 82.2–83.1 °C (lit.[14] 82.5–83.0 °C). $[\alpha]_D^{30}$=+126.9 (*c* 0.26, $CHCl_3$) [lit.[14] $[\alpha]_D^{25}$=+119.1 (*c* 0.69, $CHCl_3$)]. UV (EtOH) λ_{max} nm (log ε): 225 (4.05). IR ($CHCl_3$) ν_{max}: 3688, 3508 (OH-stretching of carboxylic acid), 3026, 2950, 2876 (C–H stretching of aldehyde), 1755 (C=O stretching of α,β-unsaturated lactone), 1711 (C=O stretching of carboxylic acid), 1681 (C=O stretching of α,β-unsaturated aldehyde), 1644 (C=C stretching), 1459, 1379, 1349, 1270 cm^{-1}. EIMS (70 eV) *m/z* (%): 482 ([M]$^+$, 7), 454 (11), 384 (24), 357 (70), 125 (7), 69 (31).

5.3.4. Coronaloride methyl ester (4). White solid from CH_2Cl_2–hexane, mp 91.5–93.2 °C (lit.[14] mp 91.0–92.5 °C). $[\alpha]_D^{28}$=+113.9 (*c* 0.26, $CHCl_3$). [lit.[14] $[\alpha]_D^{25}$=+121.6 (*c* 0.86, $CHCl_3$). UV (EtOH) λ_{max} nm (log ε): 215 (4.92). IR ($CHCl_3$) ν_{max}: 3026, 2987, 2952, 2875 (C–H stretching of aldehyde), 1755 (C=O stretching of α,β-unsaturated lactone), 1735 (C=O stretching of ester), 1681 (C=O stretching of α,β-unsaturated aldehyde), 1644 (C=C stretching), 1459, 1377, 1358, 1270 cm^{-1}. EIMS (70 eV) *m/z* (%): 496 ([M]$^+$, 1), 478 (2), 468 (2), 398 (4), 371 (22), 125 (15), 69 (27), 59 (11).

5.3.5. 5,3′,5′-Trihydroxy-7,4′-dimethoxyflavone (5). Yellow needle from MeOH, mp 281.5–282.2 °C dec. UV (MeOH) λ_{max} nm (log ε): 330 (4.22), 269 (4.19), 210 (4.58). IR (KBr) ν_{max}: 3466 (O–H stretching), 1667 (C=O stretching of conjugated ketone), 1614, 1595, 1560, 1467, 1369, 1216, 1199, 1072 cm^{-1}. 300 MHz ^{1}H NMR (DMSO-d_6): δ 12.83 (1H, s, 5-OH), 9.59 (1H each, s, 3′-OH, 5′-OH), 6.97 (2H, s, H-2′, H-6′), 6.67 (1H, d, *J*=2.1 Hz, H-6), 6.66 (1H, s, H-3), 6.33 (1H, d, *J*=2.1 Hz, H-8), 3.83 (3H, s, 7-OMe), 3.75 (3H, s, 4′-OMe). 75 MHz ^{13}C NMR (DMSO-d_6): δ 181.86 (C-4), 165.26 (C-7), 163.83 (C-2), 161.25 (C-8a), 157.26 (C-5), 151.25 (C-3′, C-5′), 139.08 (C-4′), 125.64 (C-1′), 105.91 (C-2′, C-6′), 104.77 (C-4a), 104.45 (C-3), 98.06 (C-8), 92.53 (C-6), 59.93 (4′-OMe), 56.04 (7-OMe). COLOC correlations: C/H; 2/3, 2′,6′; 4/3; 5/6; 6/3,8; 7/6, 8, 7-OMe; 4a/6, 8, 5-OH; 8a/8, 5-OH; 1′/3; 3′/2′; 4′/2′, 6′, 4′-OMe; 5′/6′. EIMS (70 eV) *m/z* (%): 330 ([M$^+$], 100), 287 (29), 259 (25), 167 (7), 138 (2), 95 (4). HRFABMS calcd for $C_{17}H_{15}O_7$ [M+H]$^+$331.0817, found 331.0819.

5.3.6. 5,3′,5′-Trihydroxy-3,6,7,4′-tetramethoxyflavone (6). Yellow needle from MeOH, mp 175.5–176.3 °C (lit.[24] mp 175–176 °C). UV (MeOH) λ_{max} nm (log ε): 336 (4.47), 272 (4.43), 212 (5.83). IR (KBr) ν_{max}: 3392 (O–H stretching), 1655 (C=O stretching of conjugated ketone), 1592, 1556, 1460, 1431, 1358, 1268, 1220, 1180, 1118, 1096, 1018, 859 and 818 cm^{-1}. EIMS (70 eV) *m/z* (%): 390 ([M]$^+$, 100), 375 (46), 373 (9), 347 (14), 153 (28), 125 (8). HRFABMS calcd for $C_{19}H_{19}O_9$ [M+H]$^+$391.1029, found 391.1023.

5.3.7. 5,7,4′-Trihydroxy-6-methoxyflavone (hispidulin) (7). Yellow needle from MeOH, mp 293–294 °C (lit.[25] mp 291–292 °C). UV (MeOH) λ_{max} nm (log ε): 336 (2.03), 275 (1.96), 216 (2.19). IR (KBr) ν_{max}: 3332 (O–H stretching), 1652 (C=O stretching of conjugated ketone), 1611, 1558, 1492,1439, 1368, 1250, 1155, 1110, 827, 882 cm^{-1}. EIMS (70 eV) *m/z* (%): 300 ([M]$^+$, 100), 285 (47), 257 (59), 121(11), 119 (26), 118 (20), 93 (6). HRFABMS calcd for $C_{16}H_{13}O_6$ [M+H]$^+$301.0712, found 301.0709.

5.3.8. 5,7,3′-Trihydroxy-6,4′,5′-trimethoxyflavone (8). Yellow needles from acetone, mp 243–244 °C (lit.[26] mp 243–245 °C). UV (MeOH) λ_{max} nm (log ε): 332 (4.26), 277 (4.20), 215 (4.59). IR (KBr) ν_{max}: 3470 (OH-stretching), 1656 (C=O stretching of conjugated ketone), 1619, 1588, 1496, 1204 cm^{-1}. EIMS (70 eV) *m/z* (%): 360 (M$^+$, 100), 345 (62), 342 (30), 331 (7), 317 (46), 167 (5), 139 (9), 111 (2), 178 (2), 181 (2). HRFABMS calcd for $C_{18}H_{17}O_8$ [M+H]$^+$361.0923, found 361.0907.

5.3.9. 5,3′-Dihydroxy-7,4′,5′-trimethoxyflavone (9). Yellow needle from EtOH, mp 194–195 °C (lit.[27] mp 194–195 °C). UV (EtOH) λ_{max} nm (log ε): 332 (3.99), 270 (3.94), 210 (4.39). IR (KBr) ν_{max}: 3432 (O–H stretching), 1651 (C=O stretching of conjugated ketone), 1623, 1587, 1557, 1448, 1430, 1355, 1195, 1110, 1049, 836, 746. EIMS (70 eV) *m/z* (%): 334 ([M]$^+$, 100), 329 (7), 315 (7), 301 (17), 283 (3), 273 (12), 258 (8), 227 (14), 178 (1), 167 (10), 158 (10), 135 (6), 95 (7). Anal. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.45; H, 5.01.

5.3.10. 5,3′-Dihydroxy-6,7,4′,5′-tetramethoxyflavone (10). Pale yellow powder from MeOH, mp 217.4–218.3 °C dec. (lit.[28] m.p 216 °C dec.). UV (MeOH) λ_{max} nm (log ε): 330 (3.16), 277 (3.05), 214 (3.45). IR (KBr) ν_{max}: 3384 (OH-stretching), 1665 (C=O stretching of conjugated ketone), 1591, 1523, 1496, 1450, 1366, 1210, 1129. EIMS (70 eV) *m/z* (%): 374 ([M]$^+$, 100), 359 (88), 331 (24), 181 (23), 153 (47). HRFABMS calcd for $C_{19}H_{19}O_8$ [M+H]$^+$375.1079, found 375.1082.

5.3.11. Hexacosyl 4′-hydroxy-*trans*-cinnamate (11). White powder from CH_2Cl_2–hexane, mp 95–96 °C (lit.[29] mp 95–96 °C). UV (MeOH) λ_{max} nm (log ε): 312 (4.15), 227 (3.87), 211 (3.84). IR ($CHCl_3$) ν_{max}: 3589, 3310 (O–H stretching), 1698 (C=O stretching of α,β-unsaturated ester), 1635 (C=C stretching), 1607, 1588, 1514, 1436, 1322, 1169, 1102, 983, 832, 760, 720 cm^{-1}. EIMS (70 eV)

m/z (%): 528 ([M^+], 28), 164 (100), 147 (67). HRFABMS calcd for $C_{35}H_{61}O_3$ [M+H]$^+$529.4620, found 529.4613.

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References and notes

1. Woo, W. S.; Lee, E. B.; Shin, K. H.; Kang, S. S.; Chi, H. J. *Korean J. Pharmacogn.* **1981**, *12*, 153–170.
2. Mbela, T. K. M.; Shabani, M.; Dieyi, S.; Cimanga, K.; Moswa, L. *Fitoterapia* **1992**, *63*, 179–181.
3. Jain, S. P. *Int. J. Crude Drug Res.* **1989**, *27*, 29–32.
4. El-Hamidi, A. *Planta Med.* **1970**, *18*, 278–280.
5. Nayar, S. L. *Bull. Natl Inst. Sci. India* **1955**, *4*, 137–145.
6. Croft, K. D.; Tu'Ipulotu, P. S. *Pac. J. Nat. Sci.* **1980**, *1*, 45–47.
7. Chhabra, S. C.; Mahunnah, R. L. A.; Mshiu, E. N. *J. Ethnopharmacol.* **1991**, *33*, 143–157.
8. Gessler, M. C.; Msuya, D. E.; Nkunya, M. H. H.; Mwasumbi, L. B.; Schar, A.; Heinrich, M.; Tanner, M. *J. Ethnopharmacol.* **1995**, *48*, 131–144.
9. Lu, R. F.; Aeng, Y. R.; Wang, W. C. *Sheng Chih Yu Bi Yun* **1981**, *12*, 16–18.
10. Takase, H.; Imanishi, K.; Miura, O.; Yumioka, E.; Watanabe, H. *Jpn. J. Pharmacol.* **1989**, *49*, 301–308.
11. Laurens, A.; Mboup, S.; Tignokpa, M.; Sylla, O.; Masquelier, J. *Pharmazie* **1985**, *40*, 482–484.
12. Hussain, M. M.; Sokomba, E. N.; Shok, M. *Int. J. Pharmacognosy* **1991**, *29*, 94–100.
13. Manson, D. *J. Malaria Inst. India* **1939**, *2*, 85–93.
14. Silva, G. L.; Gil, R. R.; Cui, B.; Chai, H.; Santisuk, T.; Srisook, E.; Reutrakul, V.; Tuchinda, P.; Sophasan, S.; Sujarit, S.; Upathum, S.; Lynn, S. M.; Farthing, J. E.; Yang, S.-L.; Lewis, J. A.; O'Neill, M. J.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *Tetrahedron* **1997**, *53*, 529–538.
15. Tuchinda, P.; Pompimon, W.; Reutrakul, V.; Pohmakotr, M.; Yoosook, C.; Kongyai, N.; Sophasan, S.; Sujarit, K.; Upathum, S. E.; Santisuk, T. *Tetrahedron* **2002**, *58*, 8073–8086.
16. Kikuchi, M.; Yoshikoshi, A. *Chem. Lett.* **1972**, 725–728.
17. Sun, H.-D.; Qui, S.-X.; Lin, L.-Z.; Wang, Z.-Y.; Lin, Z.-W.; Pengsuparp, T.; Pezzuto, J. M.; Fong, H. H. S.; Cordell, G. A.; Farnsworth, N. R. *J. Nat. Prod.* **1996**, *59*, 525–527.
18. Liu, J.-S.; Huang, M.-F.; Ayer, W. A.; Bigam, G. *Tetrahedron Lett.* **1983**, *24*, 2355–2358.
19. Raldugin, V. A.; Kukina, T. P.; Yaroshenko, N. I.; Pentegora, V. A. *Khim. Prir. Soedin.* **1987**, *2*, 306–307.
20. Chen, Y.; Lin, Z.; Zhang, H.; Sun, H. *Phytochemistry* **1990**, *29*, 3358–3359.
21. Tan, R.; Xue, H.; Li, L.-N. *Planta Med.* **1991**, *57*, 87–88.
22. Vijaya, S. B.; Vimal, S. J.; Dwipin, D. N. *Tetrahedron Lett.* **1982**, *23*, 5207–5210.
23. Cabrera, G. M.; Gallo, M.; Seldes, A. M. *J. Nat. Prod.* **1996**, *59*, 343–347.
24. Leslie Gunatilaka, A. A.; Sirimanne, S. R.; Sotheeswaran, S.; Nakanishi, T. *J. Chem. Res. (S)* **1979**, 216–217.
25. Herz, W.; Sumi, Y. *J. Org. Chem* **1964**, *29*, 3438–3439.
26. Liu, Y. L.; Mabry, T. J. *Phytochemistry* **1981**, *20*, 309–311.
27. Zahir, A.; Jossang, A.; Bodo, B. *J. Nat. Prod.* **1996**, *59*, 701–703.
28. Iinuma, M.; Tanaka, T.; Matsuura, S. *Chem. Pharm. Bull.* **1984**, *32*, 2296–2300.
29. Chatterjee, A.; Saha, S. K.; Bhattacharya, S. *Indian J. Chem.* **1980**, *19B*, 421–422.
30. Likhitwitayawuid, K.; Angerhofer, C. K.; Cordell, G. A.; Pezzuto, J. M.; Ruangrungsi, N. *J. Nat. Prod.* **1993**, *56*, 30–38.
31. Swanson, S. M.; Jiang, J. X.; Chang, Y. S.; De Souza, N. J.; Pezzuto, J. M. *J. Nat. Prod.* **1988**, *51*, 929–936.
32. Tan, G. T.; Pezzuto, J. M.; Kinghorn, A. D.; Hughes, S. H. *J. Nat. Prod.* **1991**, *54*, 143–154.
33. Nara, P. L.; Hatch, W. C.; Dunlop, N. M.; Robey, W. G.; Arthur, L. O.; Gonda, M. A.; Fischinger, P. J. *AIDS Res. Hum. Retrovir.* **1987**, *3*, 283–302.
34. Kiser, R.; Makovsky, S.; Terpening, S. J.; Laing, N.; Clanton, *J. Virol. Meth.* **1996**, *58*, 99–109.

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Dynamic ^{1}H NMR study of 4-methylphenoxyimidoyl azides: conformational or configurational isomerisation?

Ali Reza Modarresi-Alam,[a,*] Hossein Keykha,[a] Ferydoon Khamooshi[a] and Hossein A. Dabbagh[b]

[a]*Department of Chemistry, Sistan and Baluchestan University, Zahedan 98135, Iran*
[b]*College of Chemistry, Isfahan University of Technology, Isfahan 84156, IR, Iran*

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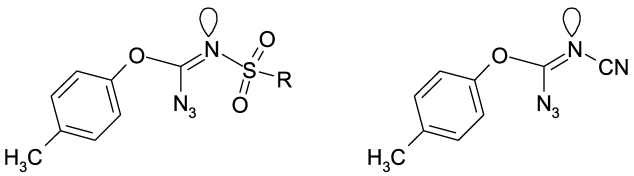
Abstract—Dynamic ^{1}H NMR (500 MHz) investigation of 4-methylphenoxyimidoyl azides (4-CH_3–C_6H_4–O–C═N–Y)–N_3, Y=4-CH_3–C_6H_4–SO_2–, 4-Br–C_6H_4–SO_2–, $C_6H_5SO_2$–, CH_3–SO_2–, –CN in acetone-d_6 at temperature range of 195–280 K is reported. The observed free energy barrier (almost 12 kcal mol^{-1}) is attributed to conformational isomerisation about the N–S bond for Y=4-CH_3–C_6H_4–SO_2–, 4-Br–C_6H_4–SO_2–, $C_6H_5SO_2$–, CH_3–SO_2– and (almost 14 kcal mol^{-1}) to configurational isomerisation (*E*/*Z*) about C═N bond for Y=–CN.

1. Introduction

Nitrogen-containing compounds are very important precursors to a wide range of biologically active molecules such as amino acids, antibiotics, alkaloids, imines and many others.[1–7] The two most important aspects of this class of compounds have been the stereo-regio-selectivity of their synthesis[1–7] and the energy barrier to nitrogen interconversion.[7–17] Both aspects have made very important contributions to the physical and/or chemical properties. Thus, the interconversion about nitrogen bonds of nitrogen-containing organic molecules has been a cornerstone of research interests for the last half century.[7–16]

Organoazides are one of the most important synthetic intermediates for the preparation of nitrogen-containing organic compounds. The azido functionality not only reacts with nucleophiles and electrophiles but also serves as a nitrene precursor for thermolysis or photolysis. In recent years, imidoyl azides have been used as a convenient reagent to generate nitrenes.[16–22] Recently, we reported a dynamic ^{1}H NMR study of 2-(*tert*-butoxymethyl)-1-[*N*′-(4-methylbenzenesulfonyl) (4-methylphenoxy) imidoyl] aziridine **8** (Scheme 4).[17]

We wish to describe herein the dynamic NMR studies of imidoyl azides **1**–**5** and factors that influence the interconversion energy barrier of the isomers (Scheme 1).



1 : R = 4-$CH_3C_6H_4$
2 : R = C_6H_5
3 : R = 4-BrC_6H_4
4 : R = CH_3

5

Scheme 1.

The question raised here, is whether the free energies observed correspond to conformational isomerisation (rotation) about the N–S bond or configurational isomerisation (*E*/*Z*) about the C═N bond?

2. Results and discussion

The imidoyl azides **1**–**5** were prepared from 5-(4-methylphenoxy) tetrazole **6** and electron-withdrawing reagents such as TsCl, $PhSO_2Cl$, BsCl, MsCl, and Br–CN, respectively, using a previously described method,[18] (Scheme 2).

The results of the temperature dependence study of the ^{1}H NMR (500 MHz) spectra of imidoyl azides **1**–**5** are shown in Table 1. Gradual cooling of the samples broadens the ^{1}H NMR signals of azides **1**–**5**, which coalesce and then, at lower temperatures split into two set of signals. For example, variable temperature ^{1}H NMR (500 MHz) spectra

Keywords: Dynamic ^{1}H NMR; Imidoyl azides; Tetrazoles; *E*/*Z* isomerisation; Rotation about the N–S bond.
* Corresponding author. Tel.: +98-0541-2431146; fax: +98-0541-2446565; e-mail address: modaresi@hamoon.usb.ac.ir

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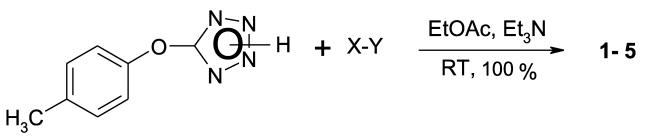


6

Y = 4-$CH_3C_6H_4SO_2$, $C_6H_5SO_2$, 4-$BrC_6H_4SO_2$, CH_3SO_2, CN

X = Cl, Br

Scheme 2.

and the expanded peaks corresponding to the methyl groups in the 2.0–2.5 ppm region (2.400, 2.363, 2.283 and 2.260) have showed for imidoylazide **1** at the lowest temperature reached (195 K) in Figures 1 and 2, respectively. A mixture of two diastereomers with almost equal populations is displayed at low temperatures. The peaks corresponding to the methyl group of 4-methylphenoxy groups were utilized in our calculations.

The rate constants, k, for the interconversion of the imidoyl azides **1**–**5** at the coalescence temperature (T_c) were calculated from Gutowsky–Holm equation ($k_c=\pi\Delta\nu/2^{-1/2}$). Assuming the transmission coefficient, κ, to be unity the free energy of activation ($\Delta G^{\ddagger}$), was calculated from Eyring equation ($\Delta G^{\ddagger}=RT_c[\ln T_c-\ln k_c+23.76]$).[12–14,17] The Gutowsky–Holm equation is strictly valid for two states having equal populations, but the errors introduced by these deviations are small.[13,14,17] The imidoyl azides **1**–**4**, all showed similar energies of activation (see Table 1) with small variations in peak height for the two isomers. However, the free energy of activation for compound **5** is higher by about 2 kcal mol^{-1}.

The energy barrier for **5** (14.2 kcal mol^{-1}) corresponds to configurational isomerisation (*E*/*Z*) which is the interconversion of nitrogen about the C=N bonds. Similar results are reported for *N*-cyano-*O*-phenylisoureas **7** [14.4 kcal mol^{-1}, T_c=6 °C (279 K)] by Garratt and co-workers[13] and related compounds have energy barriers higher than 15 kcal mol^{-1}[13] (Scheme 3). Other examples of nitrogen interconversion (*E*/*Z* isomerisation) of

Table 1. Dynamic ^{1}H NMR data for imidoyl azides **1**–**5** in acetone-d_6

Compound	δ (ppm)	Isomers ratio	The lowest temperature reached (K)	$\Delta\nu$ (Hz)	T_c, °C (K)	k (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
1	2.283, 2.260[a]	1.0:2.0	195	11.50	−41 (232)	26	12.4
1	2.400, 2.363[b]	—	—	18.50	−30 (243)	41	12.7
2	2.292, 2.279[a]	1.0:1.3	223	6.50	−38 (235)	14	12.4
3	2.288, 2.269[a]	1.0:1.2	213	9.50	−38 (235)	21	12.2
4	2.304, 2.289[a]	1.0:2.1	203	7.50	−38 (235)	17	12.3
4	3.181, 2.945[c]	—	—	118.03	−25 (258)	262	12.2
5	2.341, 2.298[a]	2.0:1.0	233	21.51	+8 (280)	48	14.2

[a] The chemical shift corresponding to protons of methyl of 4-methylphenoxy group.
[b] The chemical shift corresponding to protons of methyl of Ts group.
[c] The chemical shift corresponding to protons of methyl of Ms group.

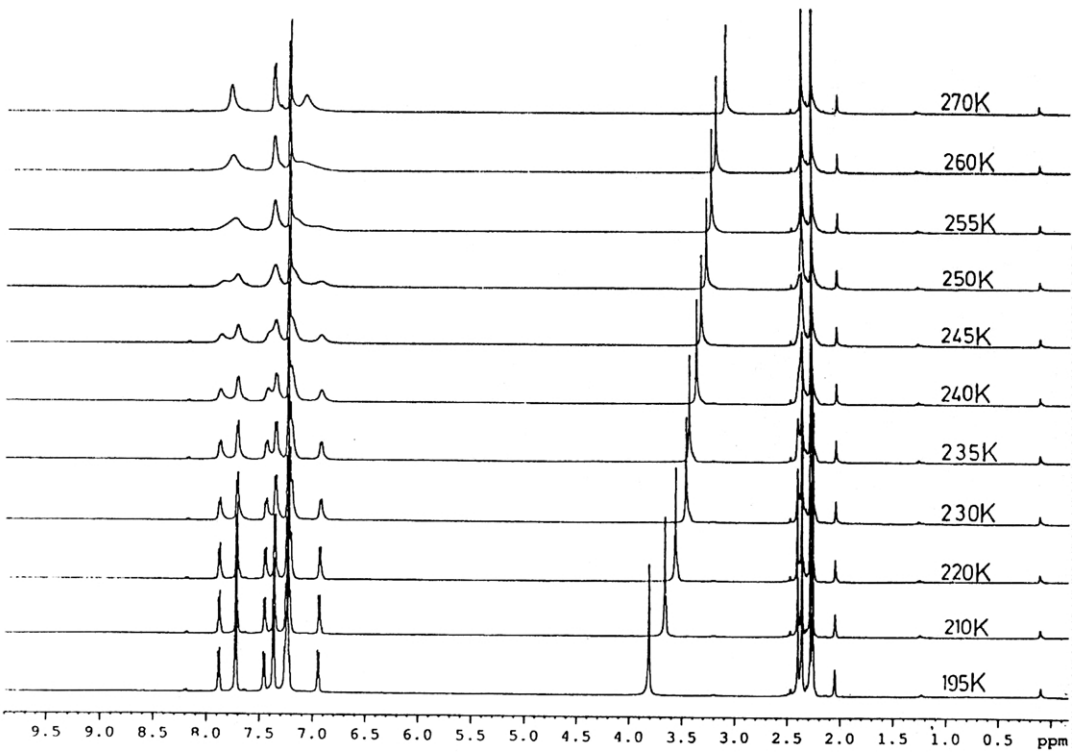


Figure 1. Variable temperature ^{1}H NMR (500 MHz) spectra for imidoylazide **1**.

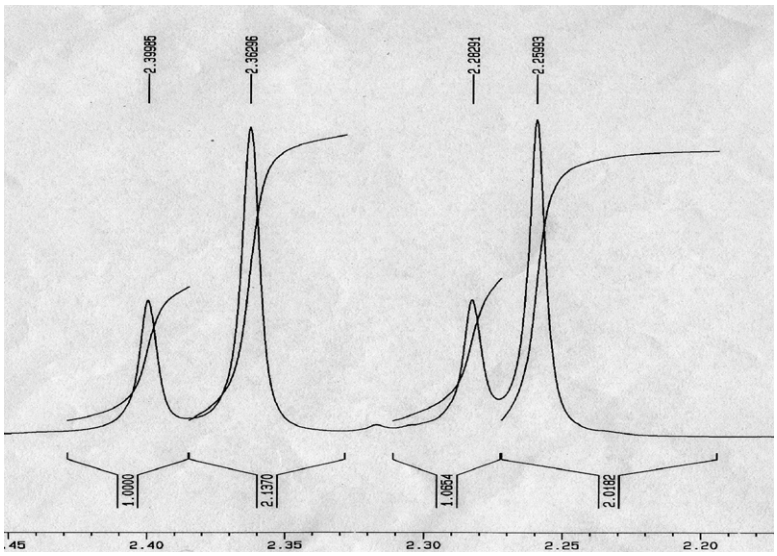
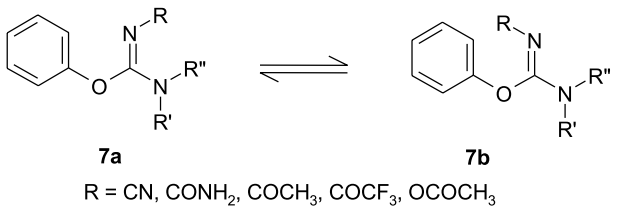


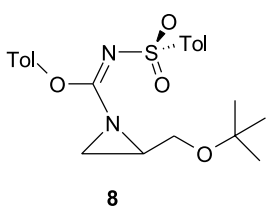
Figure 2. ^{1}H NMR (500 MHz) the expanded spectrum of methyl groups in the 2.0–2.5 ppm region (2.400, 2.363, 2.283 and 2.260) for imidoylazide **1** in CD_3CO at 195 K.



Scheme 3.

N-substituted imines are reported to have energy barriers higher than 15 kcal mol^{-1}.[12–17]

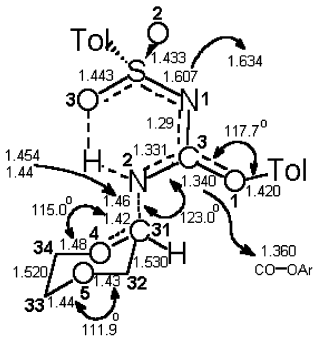
We also found a very high energy barrier (more than 24 kcal mol^{-1}) for the interconversion of nitrogen about the C=N bond in 2-(*tert*-butoxymethyl)-1-[*N*′-(4-methylbenzenesulfonyl)(4-methylphenoxy) imidoyl] aziridine **8** (Scheme 4).[16,17] Above 403 K, in nitrobenzene, there is competition between the imine interconversion and the aziridine rearrangement.[16,17] The detailed investigations of the imine interconversion and the characterization of the new compound **1X** are now underway.



Scheme 4.

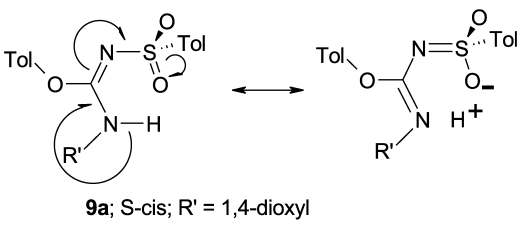
Azides **1**–**4** show an energy barrier which is lower by nearly 2 kcal mol^{-1}. These barriers represent the lower energy conformational isomerisation about the N–S bond (Table 1).

Recently, we reported X-ray conformational and configurational analysis of *N*-2-(1,4-dioxane)-*N*′-(*p*-methylbenzenesulfonyl)-*O*-(*p*-methylphenoxy) isourea **9** (Scheme 5).[19] The X-ray crystallographic analysis showed that the S=O3



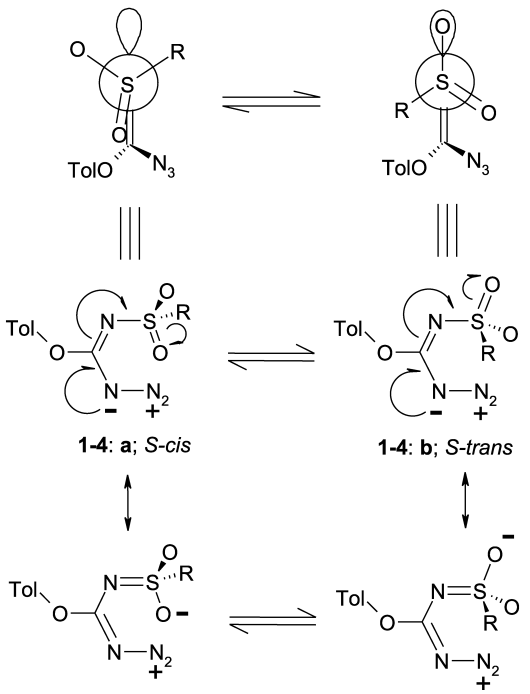
Scheme 5.

bond retains *s-cis* conformation with the C3=N1 bond (the torsion angle is almost equal to zero). In addition, there is a relatively strong intramolecular hydrogen bond between the N–H and the oxygen of S=O3 (Scheme 5). The *s-cis* conformation of S=O3, C3=N1 bonds and the S=O3···H–N hydrogen bonding helps the formation of a stable six-membered ring. This indicates the S=N1 bond has double bond character. This double bond character may be a result of hyperconjugation (Scheme 6).



Scheme 6.

The imidoyl azides **1**–**4** should form similar conformations (Scheme 7). The two main conformers, *s-cis* and *s-trans*, are the favored geometries. The *s-cis* in compounds **9** and **1**–**4** should be more stable than *s-trans*, because, the negative

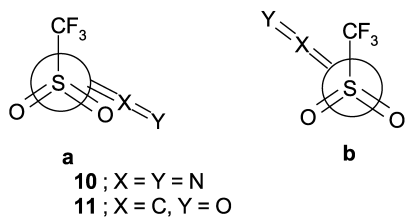


Scheme 7.

charge density on oxygen atom of S═O bond is neutralized by the positive charge on the hydrogen and nitrogen atoms, respectively.

However, the stability of the *s-cis* form of compound **9** is much more than imidoyl azides **1**–**4**. In the former case, the intramolecular hydrogen bond is stronger than electrostatic attraction. In other words, the energy barrier for the rotation about the N–S bond in **9** is much higher than that of imidoyl azides **1**–**4**.[16] Other similar examples have previously been conclusively demonstrated for diazoketones.[23,24] The diazoketones exist as an equilibrium mixture of *s-cis* and *s-trans* conformations, see the resonance structure in Scheme 7.

Haist and co-workers recently studied the structure and conformational properties of trifluoromethanesulfonyl azide **10** ($F_3CSO_2N_3$) and trifluoromethanesulfonyl isocyanate **11** (F_3CSO_2NCO) by electron diffraction and theoretical methods.[25] They concluded that both compounds posses a single conformation with eclipsed (*s-cis*) or nearly eclipsed orientation of the NCO or N_3 group relative to one S═O double bond (Scheme 8). Furthermore, they reported a rotation energy barrier of 10.3 kcal mol^{-1} about the N–S bond for compound **10**. The same orientation has been also observed for FSO_2NCO and $ClSO_2NCO$.[25]



Scheme 8.

Indeed, there are several investigations on the energy barriers of the rotation about the N–S bond (in sulfenamides and sulfinamides) indicating energies greater than 12 kcal mol^{-1}.[26–32]

3. Conclusion

The imidoyl azides **1**–**4** show quite similar energies of activation indicating that the substitute R has no influence on the observed energy barrier, while the nature of the substituent attached to the imine nitrogen has a significant effect on the energy barrier of *E*/*Z* isomerisation.[12–17] The proton chemical shifts of the R group are affected more than the protons of methyl or phenyl of the phenoxy group (see compounds **1** and **4** in Table 1, Figs. 1 and 2 and Scheme 1). Both effects are induced by rotation about the N–S bond. We attribute the observed dynamic ^{1}H NMR effect for **1**–**4** to rotation about the N–S bond.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded by BRUKER AVANCE DRX500 (500 MHz) and Varian EM 390 (90 MHz). The IR spectra were obtained on a SHIMADZU-470 and SHIMADZU ZU-435. Mass spectra were analyzed by Finnigan-Matt 8430 instruments (70 eV). Elemental analysis was performed using Heraeus CHN-O-Rapid analyser. Melting points were taken by the Electrothermal 9100 and the GallenKamp melting point apparatus and were uncorrected.

Variable temperature ^{1}H NMR spectra were obtained on BRUKER AVANCE DRX500 (500 MHz) and calibrated with a standard methanol sample.[33] The temperature was measured at the probe (±0.1 °C). Samples were allowed to equilibrate for 10 min at each temperature before recording the spectrum.

4.2. Chemicals

All starting materials and solvents were purified with appropriate purification techniques before use.[34] Tetrazoles were prepared according to literature.[16–22]

4.3. The general procedure for preparation of the imidoyl azides 1–5

Method A.[16–22] To a solution of tetrazole **6** (10 mmol) in 30 mL of peroxide-free anhydrous THF was added **X**–**Y** (10 mmol) in 10 mL THF, with cooling in an ice-salt bath under nitrogen (or argon). Triethylamine (10 mmol) in 10 mL THF was added over a period of 30 min. The mixture was stirred and allowed to come to room temperature, over several hours. Filtration, washing with THF, evaporation of the THF solutions, and chromatography on silica gel, gives imidoyl azides. All imidoyl azides recrystallize from chloroform (or dichloromethane) and petroleum ether (40–60 °C).

Method B.[18] To a stirred solution of tetrazole **6** (10 mmol) and **X**–**Y** (10 mmol) in 20 mL ethyl acetate, in a 50 mL flask equipped with a stopper, triethylamine (13 mmol) was added dropwise over 5 min at room temperature. The mixture was stirred over 2–5 h. Reaction progress was monitored by TLC. The filtrate was washed with ethyl acetate. Evaporation of the ethyl acetate solution (under vacuum and at room temperature), gave pure imidoyl azides in a quantitative yield. All imidoyl azides recrystallize from chloroform (or dichloromethane) and petroleum ether (40–60 °C).

N′-(4-Methylbenzenesulfonyl) (4-methylphenoxy) imidoyl azide **1**, *N*′-(benzenesulfonyl) (4-methylphenoxy) imidoyl azide **2** and *N*′-(cyano) (4-methylphenoxy) imidoyl azide **5** were prepared using the methods described above, as reported earlier[18] (Scheme 2).

4.3.1. *N*′-(4-Bromobenzenesulfonyl) (4-methylphenoxy) imidoyl azide 3. According to the general procedure (Method B) using 5-(4-methylphenoxy) tetrazole **6** and BsCl afforded white crystals which soften on handling; [found: C, 43.61; H, 2.63; N, 13.89. $C_{14}H_{11}BrN_4O_3S$ requires C, 42.54; H, 2.81; N, 14.18%]; IR (KBr); 3060 (w), 2900 (w), 2720 (w), 2650 (w), 2170 (w), 2110 (w), 1610–1560 (vs), 1490 (s), 1330 (s), 1270 (s), 1180 (s), 1140 (s), 1070 (m), 1000 (m), 810 (s), 750 (s), 620 (s), 590 (s), 540 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 300 K), δ ppm; 2.37 (s, 3H, CH_3–C_6H_4–O), 7.09 (d, J=8.2 Hz, 2H, CH_3–C_6H_4–O), 7.24 (d, J=8.2 Hz, 2H, CH_3–C_6H_4–O), 7.77 (d, J=8.5 Hz, 2H, Br–C_6H_4–SO_2), 7.83 (d, J=8.5 Hz, 2H, Br–C_6H_4–SO_2). Mass spectrum: *m*/*z* (%)=396 [2, M+2 (^{81}Br)], 394 [2, M (^{79}Br)], 326 (15, $^{81}BrC_6H_4NTol$ from Chapman rearrangement[17]), 324 (15, $^{79}BrC_6H_4NTol$ from Chapman rearrangement[17]), 221 (47, $^{81}BrC_6H_4SO_2$), 219 (47, $^{79}BrC_6H_4SO_2$), 157 (50, $^{81}BrC_6H_4$), 155 (50, $^{79}BrC_6H_4$), 119 (20, Tol-N_2), 107 (100, TolO), 91 (50, Tol).

4.3.2. *N*′-(Methylsulfonyl) (4-methylphenoxy) imidoyl azide 4. According to the general procedure (Method B) using 5-(4-methylphenoxy) tetrazole **6** and MsCl afforded a white crystals, mp 88–90 °C; [found: C, 42.70; H, 4.11; N, 21.46. $C_9H_{10}N_4O_3S$ requires C, 42.51; H, 3.96; N, 22.04%]; IR (KBr); 3000 (w), 2800 (w), 2700 (w), 2175 (s), 2120 (s), 1620–1560 (vs), 1485 (s), 1310 (vs), 1195 (s), 1140 (vs), 1040 (s), 1000 (s), 820 (s), 770 (s), 600 (s), 530 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 300 K), δ ppm; 2.35 (s, 3H, CH_3–C_6H_4–O), 3.01 (s, 3H, CH_3–SO_2), 7.20 (d, J=8.5 Hz, 2H, CH_3–C_6H_4–O), 7.27 (d, J=8.5 Hz, 2H, CH_3–C_6H_4–O). Mass spectrum: *m*/*z* (%)=254 (1, M), 184 (5, $TolNSO_2$ from Chapman rearrangement[17]), 175 (20, $TolOCN_4$), 119 (9, Tol-N_2), 108 (27, TolOH), 91 (100, Tol), 79 (10, CH_3SO_2).

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References and notes

1. (a) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599–619. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365.
2. Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872.
3. Jorgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3558–3588.
4. Boeckman, R. K., Jr.; Walters, M. A. *Adv Heterocycl. Nat. Prod. Synth.* **1990**, *1*, 1–41.
5. Bravo, P.; Crucianelli, M.; Ono, T.; Zanda, M. *J. Fluorine Chem.* **1999**, *97*, 27–49.
6. Patani, G. A.; Lavoie, E. J. *Chem. Rev.* **1996**, *96*, 3147–3176.
7. Valters, R. E.; Fulop, F.; Korbonits, D. *Adv. Heterocycl. Chem.* **1996**, *66*, 1–71.
8. Smith, W. B.; Amezcua, C. A. *Chem. Magn. Reson.* **1999**, *37*, 110–118.
9. Brown, J. H.; Bushweller, C. H. *J. Phys. Chem. A* **1997**, *101*, 5700–5706.
10. Buckingham, D. A.; Clark, C. R.; et al. *J. Am. Chem. Soc.* **1997**, *119*, 4050–4058.
11. Ali Sk, A.; Hassan, A.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1479–1483.
12. (a) Günnter, H. *NMR spectroscopy*; 2nd ed. Wiley: New York, 1995; Chapter 9. (b) Öki, M. *Application of dynamic NMR spectroscopy to organic chemistry*; VCH: New York, 1985.
13. Garratt, P. J.; Thom, S. N.; Wrigglesworth, R. *Tetrahedron* **1994**, *50*, 12219–12234.
14. (a) Carlson, E.; Jones, F. B.; Raban, M. *Chem. Commun.* **1969**, 1235–1237. (b) Raban, M.; Jones, F. B. *J. Am. Chem. Soc.* **1971**, *93*, 2692–2699.
15. (a) Kalinowski, H.-O.; Kessler, H. *Top. Stereochem.* **1973**, *7*, 295–383. (b) In *The chemistry of the carbon–nitrogen double bond*; Patai, S., Ed.; Wiley: New York, 1970. (c) In *The chemistry of amidines and imidates*; Patai, S., Ed.; Wiley: New York, 1975.
16. Modarresi-Alam, A. R. Ph.D. Thesis, Isfahan University of Technology, Isfahan, Iran, 2000.
17. Dabbagh, H. A.; Modarresi-Alam, A. R. *J. Chem. Res. (S.)* **2000**, 190–192.
18. Dabbagh, H. A.; Modarresi-Alam, A. R. *J. Chem. Res. (S.)* **2000**, 44–45.
19. Dabbagh, H. A.; Modarresi-Alam, A. R.; Tadjarodi, A.; Taeb, A. *Tetrahedron* **2002**, *58*, 2621–2625.
20. Dabbagh, H. A.; Karimzadeh, R. *Moleculares* **2002**, *7*, 189–199.
21. Dabbagh, H. A.; Ghaelee, S. *J. Org. Chem.,* **1996**, *62*, 3439–3445.
22. Dabbagh, H. A.; Lwowski, W. *J. Org. Chem.* **2000**, *65*, 7284–7290.
23. Dickert, F. L.; Soliman, F. M.; Bestman, H. J. *Tetrahedron Lett.* **1982**, *23*, 2639–2640.
24. Kaplan, F.; Meloy, G. K. *J. Am. Chem. Soc.* **1966**, *88*, 950–956.
25. Haist, R.; Mack, H. G.; Vedova, C. O. D.; Cutin, E. H.; Oberhammer, H. *J. Mol. Struct. (Theochem)* **1997**, *445*, 197–205, and references therein.
26. Raban, M.; Kost, D. In *Acyclic organonitrogen stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992.
27. Öki, M. *Application of dynamic NMR spectroscopy to organic chemistry*; VCH: New York, 1985; Chapter 8, pp 349–352.
28. Jennings, W. B. *J. Chem. Soc. Chem. Commun.* **1970**, 1418–1420.
29. Jackson, W. R.; Kee, T. G.; Jennings, W. B. *J. Chem. Soc. Chem. Commun.* **1972**, 1154–1155.

30. Kost, D.; Zeichner, A.; Sprecher, M. S. *J. Chem. Soc. Perkin Trans. 2* **1980**, 317–325.
31. Kost, D.; Raban, M. *J. Am. Chem. Soc.* **1976**, *98*, 8333–8338.
32. Lehn, J. M.; Wagner, J. *J. Chem. Soc. Chem. Commun.* **1968**, 1298–1299.
33. Günnter, H. *NMR spectroscopy*; 2nd ed. Wiley: New York, 1995; Chapter 3, p 66.
34. (a) Casey, M.; Leonard, J.; Lygo, B.; Procter, G. *Advanced practical organic chemistry*; Chapman and Hall: New York, 1990. (b) Armarego, W. L. F.; Perrin, D. D. *Purification of laboratory chemicals*; Butter worth-Heinmam: Oxford, 1996.

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Group 3 metal (Sc, La) triflates as catalysts for the carbomethoxylation of aliphatic amines with dimethylcarbonate under mild conditions

Monica Distaso[a] and Eugenio Quaranta[a,b,*]

[a]*Dipartimento di Chimica, Campus Universitario, Università di Bari, 70126 Bari, Italy*
[b]*ICCOM-CNR, Dipartimento di Chimica, Campus Universitario, 70126 Bari, Italy*

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Abstract—The activity of $Sc(OTf)_3$ and $La(OTf)_3$ ($OTf=SO_3CF_3$) as catalysts for the phosgene-free synthesis of carbamate esters via carbomethoxylation of aliphatic amines with dimethylcarbonate (DMC) has been investigated. In the presence of $M(OTf)_3$ (M=Sc, La), primary and secondary aliphatic amines easily react with dimethylcarbonate, under very mild conditions (20 °C), to afford carbamate esters with good yield and excellent selectivity (≅ 100%). $Sc(OTf)_3$ is a more effective catalyst than the homologue La salt. The carbomethoxylation reaction requires as strict anhydrous conditions, as, at 20 °C, the presence of water inhibits markedly the catalytic activity of both triflate salts. Temperature influences carbamate selectivity, which is lower at higher temperature because of deleterious formation of N-methylation side-products.

1. Introduction

The search for new synthetic methods that minimize energy requirements and reduce or eliminate the utilization of hazardous reagents is a major target for 'Green Chemistry'.[1] Much effort is currently being focussed on replacing phosgene,[2] which, because of its toxicity, is being less and less employed in chemical industry as a starting material for the synthesis of a number of chemicals, such as carbamates, ureas, isocyanates and organic carbonates.[3]

We have shown that carbon dioxide can be an effective substitute for phosgene in the synthesis of carbamate esters $RR'NHC(O)OR''$ (R=alkyl, aryl; R′=H, alkyl; R″=alkyl).[2] These compounds are largely used as pharmaceuticals and agrochemicals and also play a key role as intermediates in chemical industry for the production of fine and commodity chemicals.[4] The development of phosgene-free routes to carbamates is an important synthetic task and several other approaches, based, for example, on the use of either CO[5] or carbonic acid diesters,[6] are currently under study.

Aminolysis of organic carbonates has gained growing attention as an alternative clean route to carbamate esters in the last few years.[2] This is favoured by the fact that innovative phosgene-free methodologies for the industrial synthesis of organic carbonates have been implemented.[7] Aliphatic amines easily react with diphenylcarbonate,[8] or other organic carbonates having fairly good leaving groups.[6,9] However, carboalkoxylation of aliphatic amines by unactivated organic carbonates, such as dialkylcarbonates (Eq. 1; R=alkyl; R′=H, alkyl; R″=alkyl), usually needs a suitable catalyst in order to observe satisfactory conversion rate and selectivity.[10–13] We have demonstrated that CO_2 itself is an effective catalyst for the synthesis

$$RR'NH + (R''O)_2CO \xrightarrow{Cat.} RR'NC(O)OR'' + R''OH \qquad (1)$$

of *N*-alkyl methylcarbamates from aliphatic primary amines and dimethylcarbonate (DMC).[2,12] However, Lewis acid metal catalysts have been more usually used to this end.[10,13] A few of them have been studied as catalysts for the carbamation of aromatic amines.[10,13,14] Such processes (Eq. 1; R=aryl; R′=H, alkyl, aryl; R″=alkyl or aryl) can be catalysed both by organo-phosphorous Brönsted acids[2,8,15] and organic or inorganic bases.[16] In most cases, quite severe experimental conditions, such as high temperatures (>90 °C), are required, which often promote the formation of undesired by-products, such as ureas and/or N-alkylation products, lowering the selectivity to give the carbamate.

Despite the number of metal systems investigated, so far the behaviour of early transition metal derivatives and, more specifically, d^0 transition metal systems as catalysts in the aminolysis reaction of unactivated carbonic acid diesters still remains very poorly documented.[13] To date, no report has ever described the activity of Group 3 metal salts as

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* Tel./fax: +39-080-544-20-83;
e-mail address: quaranta@chimica.uniba.it

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catalysts for this particular purpose. As a continuation to our previous studies,[2,15] we have therefore focused our attention on the use of Group 3 metal triflates $M(OTf)_3$ (M=Sc, La; OTf=SO_3CF_3) as potential catalysts for amine carbomethoxylation. We have investigated the catalytic activity of these salts at ambient temperature (20 °C), because of the current widespread interest for new synthetic protocols requiring mild experimental conditions,[1] scarcely investigated so far. In the last few years, Group 3 metal triflates and, more generally, rare-earth metal (Ln) triflates have been receiving great attention for their ability to promote a wide variety of organic reactions selectively, under not severe conditions.[17] Interestingly, they have been shown to exhibit excellent catalytic properties even in the presence of Lewis bases containing N, O, P, S donor atoms.

Herein, we describe, for the first time, the activity of both $Sc(OTf)_3$ and $La(OTf)_3$ as catalysts for carbomethoxylation of primary and secondary aliphatic amines with DMC and document a few examples of utilization of these salts as effective catalysts for the selective synthesis of carbamate esters via aminolysis of DMC at ambient temperature.

2. Results and discussion

2.1. Carbomethoxylation of aliphatic primary amines with DMC promoted by $M(OTf)_3$ (M=Sc, La) salts

Table 1 compares the behaviour of a few Group 3 metal (Sc, La) salts as catalysts for the carbomethoxylation of benzylamine with anhydrous DMC, at 20 °C. Anhydrous $LaCl_3$, or hydrated La salts, such as $LaCl_3{\cdot}7H_2O$ and $La(NO_3)_3{\cdot}7H_2O$, show no or poor catalytic activity (entries 2–4, Table 1).[18] Conversely, under otherwise comparable reaction conditions, both $La(OTf)_3$ and $Sc(OTf)_3$ effectively promote the carbomethoxylation of the amine (entries 6 and 8, Table 1).[19]

Whatever $M(OTf)_3$ (M=Sc or La) catalyst salt is used, the carbomethoxylation reaction requires strict anhydrous conditions. We have ascertained that addition of water to the reaction markedly inhibits the catalytic activity of both $M(OTf)_3$ salts (M=Sc, La; Table 2).

In principle, water is expected to effectively compete with other donor species (amine, OTf anion, DMC itself, etc.) for the coordination sites on the metal centre and, therefore, can inhibit the activation of the substrate (DMC). Anhydrous conditions are required also to prevent the precipitation of poorly soluble metal-carbamato-species (see Section 4.2), which can easily form as a result of DMC hydrolysis in the presence of the amine.

Table 1. Carbomethoxylation of $PhCH_2NH_2$ with DMC in the presence of a Group 3 metal (La, Sc) salt at ambient temperature (20 °C)[a]

Entry	Metal salt	*M* (La, Sc) (mmol)	Time (h)	Carbamate yield (%)[b]
1	None	—	17	2
2	$LaCl_3$	0.067	23.5	2
3	$LaCl_3{\cdot}7H_2O$	0.067	6	1
4	$La(NO_3)_3{\cdot}7H_2O$	0.067	4	10
5	$La(OTf)_3$	0.067	0.5	27
6	$La(OTf)_3$	0.067	24.0	71
7	$Sc(OTf)_3$	0.072	0.7	34
8	$Sc(OTf)_3$	0.072	20.9	75

[a] To the used Sc or La salt in DMC, the amine was added. $PhCH_2NH_2$: 0.100 mL, 0.916 mmol; DMC: 1.0 mL, 11.87 mmol (in all the runs).
[b] GC-yield versus the amine (internal standard: *n*-undecane (30 μL)).

Table 2. Carbomethoxylation of $PhCH_2NH_2$ with DMC in the presence of $M(OTf)_3$ (M=La, Sc) at ambient temperature (20 °C): influence of H_2O on the catalytic activity of the triflate salts[a]

Entry	Metal salt	*M* (La, Sc) (mmol)	Time (h)	Carbamate yield (%)[b]
1	$La(OTf)_3$	0.067	24.0	71
2	$La(OTf)_3/H_2O$[c]	0.065	9.5	7
3	$Sc(OTf)_3$	0.072	20.9	75
4	$Sc(OTf)_3/H_2O$[d]	0.079	24	10

[a] $PhCH_2NH_2$: 0.100 mL, 0.916 mmol; DMC: 1.0 mL, 11.87 mmol (in all the runs).
[b] GC-yield versus the amine (internal standard: *n*-undecane (30 μL)).
[c] H_2O (8 μL; mol H_2O/mol La=7:1) was added to the suspension of the salt in DMC before adding the amine.
[d] H_2O (8.5 μL; mol H_2O/mol Sc=6:1) was added to the DMC solution of the salt before adding the amine.

Table 3 summarizes the results obtained when linear or branched aliphatic primary amines RNH_2 (R=benzyl, *n*-butyl, allyl, *iso*-butyl) were reacted with DMC at 20 °C, at a DMC/amine molar ratio close to 13:1, in the absence of any catalyst (entries 3, 6, 9, and 12, Table 3) or in the presence of catalytic amounts of $M(OTf)_3$ (7–8% (mol/mol) vs RNH_2; M=Sc or La). The triflate salts $M(OTf)_3$ smoothly promote the carbomethoxylation of the investigated amines which are converted into the corresponding carbamate esters in good yield (Table 3).

An analogous catalytic effect is clearly evident also when an amine/DMC molar ratio higher than unity (RNH_2/DMC=2.5–3 (mol/mol), Table 4) is used together with catalytic amounts of $M(OTf)_3$ (3–4% (mol/mol) vs DMC; M=Sc or La).

The carbomethoxylation reaction is very selective. In all cases (Tables 3 and 4), the metal triflate promotes the carbamation of the amine in a selective way (≅ 100%).

2.2. Kinetic and mechanistic considerations

After addition of amine to the $M(OTf)_3$ salt in DMC, the separation of poorly soluble metal species from the reaction medium may occur. In only a few cases (entries 2 and 8, Table 3; entries 3 and 9, Table 4), the reaction mixture remains homogeneous throughout the catalytic run. These features make it difficult to compare, for each amine, the catalytic efficiency of the $M(OTf)_3$ (M=Sc, La) salts quantitatively (as measured, for instance, by turnover-numbers (TONs)). A better insight into this issue is provided by the inspection of Figure 1 which shows the profile of formation of RNHC(O)OMe (R=benzyl, *n*-butyl, allyl, *iso*-butyl) carbamates in the presence of the $M(OTf)_3$ (M=Sc, La) salts, under the experimental conditions reported in Table 3. Curves (c) and (d) for (*n*-butyl)NHC(O)OMe and (g) and (h) for (*iso*-butyl)NHC(O)OMe show that carbamate

Table 3. Carbomethoxylation of aliphatic amines RNH_2 with DMC at ambient temperature (20 °C): catalytic effect of $M(OTf)_3$ (M=Sc, La) salts[a]

Entry	R	RNH_2 (mmol)	DMC (mmol)	$Sc(OTf)_3$ (mmol)	$La(OTf)_3$ (mmol)	Time (h)	RNHC(O)OMe yield (%)[b]
1	Benzyl	0.916	11.87	0.0723	—	20.9	75
2	Benzyl	0.916	11.87	—	0.0669	24.0	71
3	Benzyl	0.916	11.87	—	—	17	2
4	*n*-Butyl	0.908	11.87	0.0680	—	24.8	79
5	*n*-Butyl	0.908	11.87	—	0.0699	24.8	69
6	*n*-Butyl	0.908	11.87	—	—	20	15
7	Allyl	0.868	11.87	0.0642	—	22.5	76
8	Allyl	0.868	11.87	—	0.0678	25.4	77
9	Allyl	0.868	11.87	—	—	26	3
10	*i*-Butyl	0.897	11.87	0.0670	—	25.0	70
11	*i*-Butyl	0.897	11.87	—	0.0695	78.3	58[c]
12	*i*-Butyl	0.897	11.87	—	—	25	7

[a] To the $M(OTf)_3$ salt in DMC, the amine and *n*-undecane (internal standard) were in sequence added.
[b] GC-yield versus amine.
[c] Carbamate yield was equal to 49% after a reaction time of 22.5 h.

Table 4. Aminolysis of DMC by aliphatic amines RNH_2 (excess), at ambient temperature (20 °C), in the presence of $M(OTf)_3$ (M=Sc, La) salts

Entry	R	RNH_2 (mmol)	DMC (mmol)	$Sc(OTf)_3$ (mmol)	$La(OTf)_3$ (mmol)	Time (h)	RNHC(O)OMe yield (%)[a]
1	Benzyl	4.58	1.78	—	—	24	23
2	Benzyl	4.58	1.78	0.0657	—	21.2	82
3	Benzyl	4.58	1.78	—	0.0698	48	83
4	Allyl	5.04	1.78	—	—	24	43
5	Allyl	5.35	1.78	0.070	—	4	83
6	Allyl	5.35	1.66	—	0.0665	4	69
7	*i*-Butyl	6.85	1.78	—	—	24	59
8	*i*-Butyl	4.68	1.78	0.0657	—	24.3	86
9	*i*-Butyl	4.88	1.78	—	0.0693	23.5	76

[a] GC-yield versus DMC (internal standard: *n*-undecane).

formation is more efficient under $Sc(OTf)_3$ catalysis. For (benzyl)NHC(O)OMe (curves (a) and (b)) and (allyl)NHC(O)OMe (curves (e) and (f)) the curves of formation in the presence of $La(OTf)_3$ or $Sc(OTf)_3$ almost overlap, although the reaction mixture remains homogeneous throughout the reaction time in the former case (M=La), while is heterogeneous in the latter (M=Sc), because of the precipitation of poorly soluble Sc-derivatives. These features suggest that $Sc(OTf)_3$ is a more effective catalyst than $La(OTf)_3$ in this reaction.[20]

The higher catalytic activity of the Sc salt can be related with the higher Lewis acidity of Sc(III) with respect to La (III),[21] as a result of their different ionic radii (0.89 Å for $Sc^{3+}$and 1.17 Å for La^{3+}).[22] The higher the acidity of the metal centre, the higher the reactivity of the substrate (DMC), which is more strongly activated towards the nucleophilic attack by amine.

The curves reported in Figure 1 indicate that, with the exception of the system $La(OTf)_3$/*iso*-butylamine/DMC

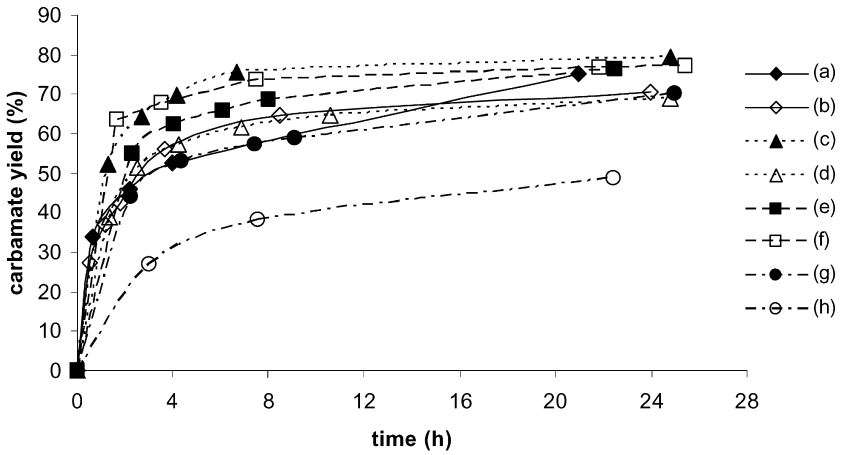

Figure 1. Curves of formation (20 °C) of RNHC(O)OMe carbamate esters by carbomethoxylation of aliphatic primary amines RNH_2 with DMC (1.0 mL, 11.87 mmol) in the presence of $M(OTf)_3$ (M=Sc, La). Experimental conditions: (a) $PhCH_2NH_2$: 0.916 mmol; $Sc(OTf)_3$: 0.0723 mmol. (b) $PhCH_2NH_2$: 0.916 mmol; $La(OTf)_3$: 0.0669 mmol. (c) $CH_3(CH_2)_3NH_2$: 0.908 mmol; $Sc(OTf)_3$: 0.0680 mmol. (d) $CH_3(CH_2)_3NH_2$: 0.908 mmol; $La(OTf)_3$: 0.0699 mmol. (e) CH_2=$CHCH_2NH_2$: 0.868 mmol; $Sc(OTf)_3$: 0.0642 mmol. (f) CH_2=$CHCH_2NH_2$: 0.868 mmol; $La(OTf)_3$: 0.0678 mmol. (g) $(CH_3)_2CHCH_2NH_2$: 0.897 mmol; $Sc(OTf)_3$: 0.0670 mmol. (h) $(CH_3)_2CHCH_2NH_2$: 0.897 mmol; $La(OTf)_3$: 0.0695 mmol. Carbamate yield was equal to 58.3% after a reaction time of 78.3 h.

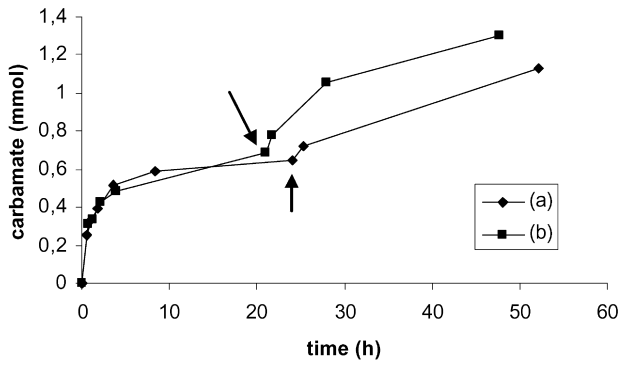

Figure 2. Carbomethoxylation of $PhCH_2NH_2$ with DMC in the presence of $M(OTf)_3$ (M=Sc, La) at ambient temperature (20 °C): effect of further addition of amine at the plateau. Experimental conditions: (a) $La(OTf)_3$: 0.0669 mmol, $PhCH_2NH_2$: 0.916 mmol, DMC: 11.87 mmol. After 24 h, 0.100 mL (0.916 mmol) of benzylamine were added. (b) $Sc(OTf)_3$: 0.0723 mmol, $PhCH_2NH_2$: 0.916 mmol, DMC: 11.87 mmol. After 21 h, 0.100 mL (0.916 mmol) of benzylamine were added.

(curve (h), Fig. 1), a quite interesting initial conversion is observed as the carbamate yield ranges between 50 and 65%, at ambient temperature, within a reaction time of 3 h. Figure 2 shows that, for the system $M(OTf)_3/PhCH_2NH_2$/DMC (M=Sc, La) at 20 °C, if amine is added to the reaction mixture at the plateau, the reaction restarts with an appreciable production of more carbamate ester. This demonstrates that the catalyst is still active, although not so effective as at the beginning. The restart of the reaction upon addition of fresh amine indicates that the residual unreacted amine may be in a form that is not prone to react with DMC: the nucleophilicity of the amine must be reduced in some way. Also, the diminished catalytic activity is indicative of a modification of the catalyst which may progressively deactivate by converting into a catalytically less active species.

In order to shed light on these issues, we have carried out a complete analysis of the reaction solution. We have found that the amine can undergo protonation and convert into the corresponding alkylammonium cation RNH_3^+, that is not reactive towards DMC and can be recovered at the end of the reaction as alkylammonium triflate salt, $(RNH_3)OTf$. This particular issue has been investigated in detail for the system $Sc(OTf)_3/PhCH_2NH_2$/DMC (Sc/amine/DMC≅ 1:13:172 (mol/mol)). IR monitoring of the reaction solution revealed the formation of $(PhCH_2NH_3)OTf$ (characteristic absorptions at 3258, 3166, 643 cm^{-1}) soon after (about 30–45 min) the reactants were mixed. The work-up of the reaction mixture, at the end of the catalytic run, allowed to isolate the salt $(PhCH_2NH_3)OTf$ (1.80 mol of salt per mol of Sc), that was characterized by IR and NMR spectroscopy.[23]

Most likely, the proton source is the coproduced methanol,[24] as suggested in Eq. 2.

$$L_nM(OTf)_3 + xMeOH + xRR'NH \rightarrow L_nM(OMe)(OTf)_{3-x} + x(RR'NH_2)OTf \quad (2)$$

M=Sc, La and L=ligand, R′=H, alkyl.

The reactivity described by Eq. 2 is not completely new, as it has been documented in the literature and used for the synthesis of rare-earth alkoxides, $Ln(OR)_3$, by reaction of the corresponding chlorides, $LnCl_3$, with alcohols in the presence of bases (Eq. 3).[25]

$$LnCl_3 + 3ROH + 3NH_3 \rightarrow Ln(OR)_3 + 3(NH_4)Cl \quad (3)$$

Ln=rare-earth metal

Ad hoc experiments allowed us to exclude that $(RR'NH_2)$OTf salts may play a significant role as carbomethoxylation catalysts. In fact, as shown in Table 5 for the carbamation of $PhCH_2NH_2$ with DMC at 20 °C, $(PhCH_2NH_3)OTf$ (0.06585 g, 0.257 mmol; completely soluble in DMC (1 mL)) exhibits only a modest catalytic activity,[26] which is, however, somewhat lower than that of the $M(OTf)_3$ (M=Sc, La) salts.

2.3. Influence of temperature

Benzylamine has been used for studying the influence of temperature on the carbomethoxylation reaction. Table 6 summarizes the results obtained with $Sc(OTf)_3$ as catalyst.[28]

At 90 °C, the carbamation of the amine, albeit faster, takes place less selectively than at room temperature (see entries 1 and 2, Table 6).

Entries 3 and 4 (Table 6) illustrate the results obtained at 90 °C under conditions different from those used in entry 2. In entry 3, the use of a higher (vs entry 2) amount of the amine ($Sc(OTf)_3$/amine=3.1% vs 8.04% (mol/mol) in entry 2), without appreciably changing the analytical concentration of the catalyst ($[Sc(OTf)_3]$=0.06 mol/L vs 0.07 mol/L in entry 2) results in a better carbamate yield, but the selectivity is lower (95%), albeit still good. A marked reduction of selectivity and yield is observed in entry 4, where a significantly lower (vs entry 2) catalyst loading is used with respect to both the amine ($Sc(OTf)_3$/amine= 0.62% (mol/mol)) and DMC ($[Sc(OTf)_3]$=0.005 mol/L).

Analogous trends are found when $La(OTf)_3$ is used as catalyst in place of $Sc(OTf)_3$ (90 °C). Figure 3 shows the curve of formation of $PhCH_2NHC(O)OMe$ by carbomethoxylation of $PhCH_2NH_2$ with DMC in the presence of $La(OTf)_3$, under conditions otherwise comparable with

Table 5. Carbomethoxylation of $PhCH_2NH_2$ with DMC at ambient temperature (20 °C): $(PhCH_2NH_3)OTf$ vs $M(OTf)_3$ (M=Sc, La) catalytic activity

Catalyst	$PhCH_2NH_2$ (mmol)	DMC (mmol)	Catalyst/amine (mol/mol)%	Time (h)	$PhCH_2NHC(O)OMe$ yield (%)[a]
None	0.916	11.87	0	17	2
$(PhCH_2NH_3)OTf$	0.916	11.87	28	19	10
$Sc(OTf)_3$	0.916	11.87	7.9	20.9	75
$La(OTf)_3$	0.916	11.87	7.3	24.0	71

[a] GC-yield versus the amine (internal standard: *n*-undecane).

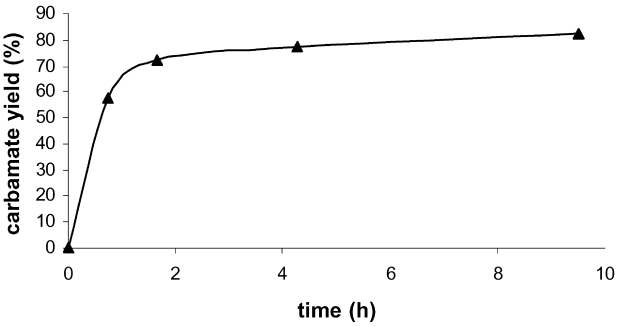

Figure 3. Carbomethoxylation of $PhCH_2NH_2$ with DMC in the presence of $La(OTf)_3$ at 90 °C. Experimental conditions: $La(OTf)_3$: 0.0681 mmol, $PhCH_2NH_2$: 2.29 mmol, DMC: 11.87 mmol.

those used in entry 3, Table 6. After 9.5 h at 90 °C, a carbamate yield close to 83% is obtained, with a selectivity to the carbamate ester around 95%.

2.4. Synthetic applications

The carbomethoxylation of a few amines was carried out at ambient temperature (20 °C) under conditions more appealing from the synthetic point of view than those employed in Table 3, by using a lower catalyst/amine molar ratio (≦ 3% vs ≦ 8% (mol/mol)). In order to realize a higher concentration of both nucleophile and catalyst in the reaction mixture, a markedly lower DMC/triflate salt molar ratio (75–95 vs 160–185 (mol/mol)) was also used. We focused our attention on the use of $Sc(OTf)_3$ as the catalyst, because of its higher catalytic activity with respect to the homologue La salt.

Table 6. Carbomethoxylation of $PhCH_2NH_2$ with DMC in the presence of $Sc(OTf)_3$ under different experimental conditions

Entry	RNH_2 (mmol)	DMC (mmol)	$Sc(OTf)_3$ (mmol)	T (°C)	Time (h)	Yield[a] (%)	Selectivity[b] (%)
1	0.916	11.87	0.0723	20	20.9	75	> 99.5
2[c]	0.916	11.87	0.0737	90	9.1	75	98
3	2.29	11.87	0.0701	90	8.7	84	95
4	9.16	118.7	0.0569	90	27.4	57[d]	89

[a] Carbamate GC-yield vs the amine (internal standard: *n*-undecane).
[b] Selectivity to carbamate ester. The observed side-products were $(PhCH_2)N(Me)H$ and $(PhCH_2)N(Me)_2$.
[c] The reaction mixture was heated at 90 °C for 9.1 h and analyzed by GC. Then, 0.100 mL (0.916 mmol) of $PhCH_2NH_2$ were further added and the reaction mixture heated at 90 °C for 6 h longer. After this time, the overall carbamate yield (vs the total amount of amine used) was 70% (95% selectivity).
[d] After the first 2 h, the carbamate yield was equal to 16% and selectivity >99%. However, the selectivity decreased with time and, after 27.4 h, the overall yield of N-alkylation products was close to 7%.

Under the described conditions, aliphatic primary amines, such as benzylamine, *n*-butylamine and allylamine, are selectively (≦ 100%) converted into the corresponding methylcarbamate esters in good yields (Table 7).

This study has been extended to secondary aliphatic amines, such as morpholine and piperidine. At 20 °C, under the conditions reported in Table 7, also these amines are very selectively (≦ 100%) carbomethoxylated, but at a lower rate than the primary ones. After ~24 h, in both cases, the amount of unreacted amine was still close to 20%. The carbamation of morpholine was carried out also at higher temperature. At 65 °C (Sc/amine=3.0% (mol/mol); DMC/Sc=76.0 (mol/mol)), as expected, a marked decrease in selectivity is observed due to the appreciable side-formation of *N*-methylmorpholine.[29]

As for the fate of the catalyst, we have emphasized above that, to some extent, Sc(III) precipitates during the reaction in the form of unsoluble species that have been recovered at the end of the catalytic run by filtration.[30] Unfortunately, their poor solubility in common organic solvents precluded any re-crystallization and in no case have we been able to isolate well defined compounds.[31] When reused at 20 °C, the crude precipitate still exhibits a catalytic activity. However, this results in lower activity as compared to the starting catalyst.

3. Conclusions

For the first time Group 3 metal salts have been employed as catalysts for the carbamation of amines with dimethylcarbonate. Both $Sc(OTf)_3$ and $La(OTf)_3$ effectively promote the carbomethoxylation of aliphatic amines with DMC at 20 °C to afford the corresponding carbamate esters with good yields and excellent selectivity (≦ 100%). $Sc(OTf)_3$ exhibits a higher catalytic activity than $La(OTf)_3$. The presence of water in the reaction medium inhibits the catalytic activity of both triflate salts at ambient temperature. Temperature affects the selectivity of the carbomethoxylation reaction, being less selective at higher temperature, because of the increased incidence of the N-methylation processes.

4. Experimental

4.1. General

Unless otherwise stated, all reactions and manipulations were conducted under a dinitrogen atmosphere, by using vacuum line techniques. All solvents were dried according

Table 7. Synthesis of methyl carbamates from amines and DMC in the presence of $Sc(OTf)_3$, at ambient temperature (20 °C)

Amine	Sc/amine (mol/mol)%	DMC/Sc (mol/mol)	Time (h)	RNHC(O)OMe isolated yield (%)
$PhCH_2NH_2$	3.0	97.0	24	83
$CH_2{=}CHCH_2NH_2$	3.0	94.7	24	77
$CH_3(CH_2)_3NH_2$	3.0	90.1	24	82
Piperidine	3.1	78.9	48	81
Morpholine	3.0	75.2	48	80

to literature methods[32] and stored under N_2. DMC (Fluka) was dried over 5 Å molecular sieves for 24 h, filtered, distilled, and stored under N_2. The amines (Fluka or Aldrich products) were dried over KOH, distilled, and stored under N_2. $M(OTf)_3$ (M=Sc, La) salts (Fluka, Aldrich) were used as received and manipulated under an inert gas atmosphere.

IR spectra were obtained with a Perkin Elmer 883 spectrophotometer or with a Perkin Elmer FTIR 1710 instrument. NMR spectra were run on a Varian XL-200 or a Bruker AM 500 instrument, as specified in the text. ^1H and ^{13}C chemical shifts are in ppm versus TMS and referenced to the solvent peak. GC–MS analyses were carried out with a Shimadzu GC-17A linked to a Shimadzu GCMS-QP5050 selective mass detector (capillary column: Supelco MDN-5S, 30 m×0.25 mm, 0.25 μm film thickness). GC analyses were performed with a HP 5890 Series II gas-chromatograph (capillary column: Heliflex AT-5, 30 m×0.25 mm, 0.25 μm film thickness).

4.2. Carbomethoxylation of $PhCH_2NH_2$ with DMC: influence of H_2O on the catalytic activity of the $M(OTf)_3$ (M=Sc, La) salts

To the solution of $Sc(OTf)_3$ in DMC, or to the suspension of $La(OTf)_3$ in the same solvent,[19] H_2O was added (see Table 2). Upon addition of $PhCH_2NH_2$ to the resulting homogeneous solutions, the fast separation of a poorly soluble colorless solid was observed. The resulting mixture was allowed to react at 20 °C and then analyzed by GC (Table 2).

The separated solids, isolated by centrifugation after their precipitation (30 min) or at the end of the catalytic run (Table 2), were found to contain Sc(III) or La(III)[33] (according to the used $M(OTf)_3$ salt) and evolved CO_2 upon acidolysis with diluted HCl. Moreover, their IR spectra showed strong absorptions at 3350–3340, 1570–1500, 1345–1340 cm^{-1}, consistent with the presence of a carbamate group.[34] The low solubility of these species in D_2O, where decomposition is also observed, and other common organic solvents has precluded their purification and full characterization.

4.3. Synthesis of carbamate methyl esters by aminolysis of DMC in the presence of $Sc(OTf)_3$ at ambient temperature (20 °C)

Product yields were not optimized. The MS, IR, ^1H and ^{13}C NMR of $PhCH_2NHC(O)OMe$ and $CH_2{=}CHCH_2NHC(O)OMe$ were identical with those of authentic samples.[12a]

4.3.1. Synthesis of $PhCH_2NHC(O)OMe$ by reaction of $PhCH_2NH_2$ with DMC in the presence of $Sc(OTf)_3$. Benzylamine (1.30 mL, 11.91 mmol) was added to the solution of $Sc(OTf)_3$ (0.18055 g, 0.367 mmol) in DMC (3.0 mL, 35.60 mmol) and the reaction mixture was allowed to react for 24 h at ambient temperature. After filtration, the mother solution and washing (DMC) liquors, collected together, were concentrated in vacuo. Upon addition of CH_2Cl_2 (15 mL) and cooling to 0 °C, pure $(PhCH_2NH_3)OTf$ separated and was isolated by filtration, washed with CH_2Cl_2 and dried in vacuo (0.13670 g, 0.531 mmol) [IR (Nujol, cm^{-1}): 3181, 3093 (s, br), 1617 (m), 1499, 1385, 1245 (vs), 1165 (s), 1115, 1056, 1032 (s), 967, 918, 865, 788, 749, 723, 699, 635, 585, 574, 515, 487. ^1H NMR (THF-d_8, 500.138 MHz): δ 4.22 (s, 2H, CH_2), 7.34–7.42 (m, 3H, $H_{aromatic}$), 7.52 (m, 2H, $H_{aromatic}$), 7.82 (br, 3H, NH_3). ^{13}C NMR (THF-d_8, 125.760 MHz): δ 44.39 (CH_2), 121.76 (q, CF_3, J_{CF}=320.5 Hz), 129.67, 129.85, 134.52 ($C_{aromatic}$)].

The resulting solution was washed with H_2O, which extracted more $(PhCH_2NH_3)OTf$ together with minor amounts of carbamate ester. The organic solution was dried (Na_2SO_4) and concentrated in vacuo to give the pure carbamate $PhCH_2NHC(O)OMe$ (83%, mp: 65–67 °C). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.67; N, 8.47. Found: C, 65.55; H, 6.73; N, 8.40.

4.3.2. Synthesis of $CH_2{=}CHCH_2NHC(O)OMe$ by reaction of $CH_2{=}CHCH_2NH_2$ with DMC in the presence of $Sc(OTf)_3$. Allylamine (0.930 mL, 12.43 mmol) was added to the solution of $Sc(OTf)_3$ (0.18505 g, 0.376 mmol) in DMC (3.0 mL, 35.60 mmol). The reaction mixture was stirred at 20 °C for 24 h, diluted with diethylether (30 mL) and filtered.

The resulting solution was treated with H_2O, which extracted allylammonium triflate [IR (Nujol, cm^{-1}): 3171 (vs, br), 1651 (m, sh), 1614 (m, br), 1505 (m), 1430, 1250 (vs), 1198, 1168 (s), 1130, 1032 (s), 991, 951, 876, 763, 645, 582, 517. ^1H (CD_3CN, 500.138 MHz): δ 3.58 (dt, 2H, CH_2, $^3J_{H-H}$=6.29 Hz, $^4J_{H-H}$=1.3 Hz), 5.38 (dm, 1H, H_{cis}), 5.43 (dm, 1H, H_{trans}), 5.91 (ddt, 1H, $CH_2{=}CH$, J_{cis}=10.34 Hz, J_{trans}=17.30 Hz, $^3J_{H-H}$=6.3 Hz), 6.51 (br, 3H, NH_3). ^{13}C (CD_3CN, 125.760 MHz): δ 43.05 ($C_{allylic}$), 119.08 (q, CF_3, $^1J_{CF}$=320 Hz), 122.00 ($H_2C{=}CH$), 129.76 ($CH_2{=}CH$)] together with minor amounts of carbamate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the pure carbamate $CH_2{=}CHCH_2NHC(O)OMe$ (77%). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.16. Found: C, 52.10; H, 7.93; N, 12.10.

4.3.3. Synthesis of $CH_3(CH_2)_3NHC(O)OMe$ by reaction of $CH_3(CH_2)_3NH_2$ with DMC in the presence of $Sc(OTf)_3$. *n*-Butylamine (1.30 mL, 13.18 mmol) was added to the solution of $Sc(OTf)_3$ (0.19445 g, 0.395 mmol) in DMC (3.0 mL, 35.60 mmol). The reaction mixture was reacted at room temperature for 24 h, diluted with diethylether (10 mL), and filtered. To the resulting solution *n*-pentane (70 mL) was added. Upon cooling to −20 °C overnight, colorless needles of pure $[(CH_3(CH_2)_3NH_3]OTf$ separated from the solution and were isolated by filtration (0.07395 g, 0.331 mmol) [IR (Nujol, cm^{-1}): 3178 (vs, br), 1613 (m-s), 1514, 1248 (vs, br), 1170 (vs), 1037 (s), 914, 794, 762, 738, 641, 581, 517. ^1H (CD_3CN, 200 MHz): δ 0.91 (t, 3H, CH_3, $^3J_{H-H}$=7.23 Hz), 1.37 (m, 2H, CH_2CH_3), 1.59 (m, 2H, $CH_2CH_2CH_3$), 2.93 (m, 2H, NCH_2), 6.27 (br, 3H). ^{13}C (CD_3CN, 125.760 MHz): δ 13.65 (CH_3), 20.07 (CH_2CH_3), 29.53 ($CH_2CH_2CH_3$), 40.93 (NCH_2), 122.58 (q, CF_3, $^1J_{CF}$=320.7 Hz)].

The solution was extracted with H_2O (15 mL) from which residual amounts of $[(CH_3(CH_2)_3NH_3]OTf$ were recovered (as established by IR), but not further purified. From the

organic solution, dried over Na_2SO_4 and concentrated in vacuo, pure carbamate $CH_3(CH_2)_3NHC(O)OMe$ was isolated (82%). Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.67. Found: C, 54.87; H, 10.07; N, 10.50. IR (neat, cm^{-1}): 3338 (m-s, br), 2961, 2874, 1707 (vs), 1535 (vs), 1458, 1381, 1260 (vs), 1193, 1142, 1113, 1057, 1025, 781. ^1H NMR ($CDCl_3$, 500.138 MHz): δ 0.82 (t, 3H, CH_3, $^3J_{H-H}$=7.35 Hz), 1.24 (m, 2H, CH_2CH_3), 1.38 (quintuplet, 2H, $CH_2CH_2CH_3$, J=7.3 Hz), 3.07 (quartet, 2H, NCH_2, J=6.6 Hz), 3.55 (s, 3H, OCH_3), 5.2 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 125.760 MHz): δ 13.76 (CH_3), 19.91 (CH_2CH_3), 32.14 ($CH_2CH_2CH_3$), 40.80 (NCH_2), 51.91 (OCH_3), 157.23 (C(O)O). MS (m/z): 131 ($M^{+\cdot}$), 116, 102, 88, 76, 59, 44.

4.3.4. Synthesis of 1-carbomethoxypiperidine by reaction of piperidine with DMC in the presence of $Sc(OTf)_3$. To the solution of $Sc(OTf)_3$ (0.17785 g, 0.361 mmol) in DMC (2.4 mL, 28.51 mmol) piperidine (1.15 mL, 11.62 mmol) was added. The reaction mixture was stirred for 48 h at ambient temperature, treated with diethylether (35 mL) and cooled to −20 °C. After filtration, the mother liquor and washing ethereal solutions (2×10 mL), collected together, were extracted with H_2O. The organic layer, dried over Na_2SO_4, was concentrated in vacuo to give pure carbamate with 81% yield. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.65; H, 9.20; N, 9.70. IR (neat, cm^{-1}): 1702 (s), 1535, 1474, 1446, 1410, 1372, 1352, 1282, 1265, 1238, 1190, 1152, 1090, 1029, 947, 900, 854, 839, 791, 719. ^1H NMR ($CDCl_3$, 200 MHz): δ1.41 (m, 6H, $CH_2CH_2CH_2$), 3.26 (m, 4H, CH_2-N-CH_2), 3.53 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 125.760 MHz): δ 24.44 and 25.33 ($CH_2-CH_2-CH_2$), 44.45 (CH_2-N-CH_2), 52.03 (OCH_3), 155.60 (C(O)O). MS (m/z): 143 ($M^{+\cdot}$), 128, 102, 84, 70, 56, 42.

Formed piperidinium triflate could be isolated in a pure form according to the following experimental procedure. The reaction mixture ($Sc(OTf)_3$: 0.18450 g, 0.375 mmol; DMC: 2.40 mL, 28.51 mmol; $C_5H_{11}N$: 1.15 mL, 11.62 mmol), prepared as previously described and stirred for 48 h at 20 °C, was filtered. The solution, after addition of diethylether (60 mL), was cooled to −20 °C overnight. The separated colorless solid was isolated by filtration, washed with diethylether, dried in vacuo and identified as pure piperidinium triflate (0.10170 g, 0.432 mmol) [IR (Nujol, cm^{-1}): 3163 (br, vs), 1592 (s), 1480, 1435, 1318, 1239 (vs), 1158 (s), 1082, 1029, 953, 922, 872, 866, 816, 761, 722, 633, 576, 547. ^1H NMR (CD_3CN, 200 MHz): δ 1.74 (m, 2H, $CH_2CH_2CH_2$), 1.92 (m, 4H, $CH_2CH_2CH_2$), 3.10 (t, 4H, CH_2-N-CH_2, J_{H-H}=5.7 Hz), 6.6 (br). ^{13}C NMR (CD_3CN, 125.760 MHz): δ 22.31 and 22.98 ($CH_2CH_2CH_2$), 45.87 (CH_2-N-CH_2), 121.79 (q, CF_3, $^1J_{CF}$=320 Hz)].

Upon treating the filtered solution with H_2O and concentrating in vacuo the aqueous layer, a solid residue (0.075 g; not further purified) was obtained, that resulted to contain more piperidinium triflate (as established by IR).

4.3.5. Synthesis of 1-carbomethoxymorpholine by reaction of morpholine with DMC in the presence of $Sc(OTf)_3$. To the solution of $Sc(OTf)_3$ (0.18655 g, 0.379 mmol) in DMC (2.4 mL, 28.51 mmol) morpholine (1.10 mL, 12.61 mmol) was added. The reaction mixture was reacted for 48 h at 20 °C, then diluted with diethylether (30 mL) and cooled to −20 °C overnight. After filtration, the solution was evaporated in vacuo, and the residue chromatographed on silica gel with diethylether/*n*-hexane (2:1, v/v) as eluent to give pure carbamate with 80% yield. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.64. Found: C, 49.57; H, 7.72; N, 9.57. IR (neat, cm^{-1}): 2960, 2900, 2859, 1702 (vs), 1466, 1445, 1407, 1363, 1301, 1280, 1245, 1222 (vs), 1191, 1117, 1073, 1025, 958, 917, 851, 800, 769, 656, 568, 524, 475. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.36 (m, 4H, CH_2-N-CH_2), 3.56 (m, 4H, CH_2-O-CH_2), 3.62 (s, 3H, CH_3). ^{13}C NMR (125.760 MHz, $CDCl_3$): δ 43.61 (CH_2-N-CH_2), 52.34 (CH_3), 66.07 (CH_2-O-CH_2), 155.32 (C(O)O). MS(m/z): 145 ($M^{+\cdot}$), 130, 114, 100, 86, 70, 56, 42.

Formed morpholinium triflate could be isolated in a pure form according to the experimental procedure reported below. The reaction mixture ($Sc(OTf)_3$: 0.18570 g, 0.377 mmol; DMC: 2.40 mL, 28.51 mmol; C_4H_9NO: 1.10 mL, 12.61 mmol), prepared as previously described and stirred for 48 h at 20 °C, was filtered. The solution, after addition of diethylether (60 mL), was cooled to −20 °C overnight. The solid precipitated was isolated by filtration, washed with diethylether, dried in vacuo and identified as pure morpholinium triflate (0.15255 g, 0.643 mmol) [IR (Nujol, cm^{-1}): 3066, 1604, 1276 (br), 1197, 1165, 1107, 1031, 903, 876, 763, 723, 638, 591, 575, 518, 476, 440, 420. ^1H NMR (CD_3CN, 200 MHz): δ 3.18 ppm (m, 4H, CH_2-N-CH_2), 3.83 (m, 4H, CH_2-O-CH_2), 6.8 (br, NH_2). ^{13}C NMR (CD_3CN, 125.760 MHz): 44.81 ppm (CH_2-N-CH_2), 64.19 (CH_2-O-CH_2), 121.78 (q, CF_3, $^1J_{CF}$=320.4 Hz)]. The IR and NMR spectra reported above were carried out on the aged product (stored under dinitrogen, for 1 month, at ambient temperature) and were identical to those shown by a sample of morpholinium triflate prepared from morpholine and triflic acid in ether at 20 °C. The IR spectrum (Nujol) of the fresh product, registered soon after the isolation (see above), shows absorptions at 3022, 1554, 1417, 1262 (vs), 1233, 1221, 1161, 1098, 1043, 884, 867, 760, 645, 587, 515, 431, 410 cm^{-1}.

4.4. Isolation of $(PhCH_2NH_3)(OTf)$ from the reaction of MeOH with $PhCH_2NH_2$ in the presence of $Sc(OTf)_3$

To a CH_2Cl_2 (9 mL) solution of $Sc(OTf)_3$ (0.22870 g, 0.465 mmol) and MeOH (0.270 mL, 6.657 mmol) benzylamine (0.155 mL, 1.420 mmol) was added and the resulting suspension stirred at ambient temperature (20 °C) for 3 h. After filtration, the mother solution and washing (THF) liquors, collected together, were concentrated in vacuo. Upon addition of *n*-pentane and cooling to −20 °C, colorless crystals of $(PhCH_2NH_3)(OTf)$ separated and were isolated by filtration (0.22580 g; 0.88 mmol; $mol_{(RNH_3)OTf}/mol_{Sc} = 1.89$).

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References and notes

1. Anastas, P. T.; Kirchoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.
2. Aresta, M.; Quaranta, E. *ChemTech* **1997**, *27*(3), 32 and references therein.
3. Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75.
4. (a) Barthelemy, J. *Lyon Pharm.* **1986**, *37*(6), 297. (b) Wu, T.-T.; Huang, J.; Arrington, N. D.; Dill, J. M. *J. Agric. Food Chem.* **1987**, *35*, 817. (c) Kato, T.; Suzuki, K.; Takahashi, J.; Kamashita, K. *J. Pestic. Sci.* **1984**, *9*, 489. (d) Rivetti, F.; Romano, U.; Sasselli, M. G. U.S. Patent 4514339, 1985. (e) Green, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*; 3rd ed. Wiley: New York, 1999; pp 503–550.
5. Cenini, S.; Pizzetti, M.; Crotti, C. *Aspects of homogeneous catalysis*; Ugo, R., Ed.; Riedel: Dordrecht, The Netherlands, 1998; Vol. 6, pp 97–108.
6. Hagemann, C. Kolhensaure derivate. In *Methoden der organishen chemie*; 4th ed., Houben-Weil, Ed.; Georg Thieme: Stuttgart, 1983; p 159 Band E4.
7. (a) Massi Mauri, M.; Romano, U.; Rivetti, F. *Ing. Chim. Ital.* **1985**, *21*(6), 6 and references cited therein. (b) Rivetti, F. *Comptes Rendus Acad. Sci., Series II: Chimie* **2000**, *3*(6), 497 and references therein.
8. Aresta, M.; Berloco, C.; Quaranta, E. *Tetrahedron* **1995**, *51*, 8073.
9. Kita, Y.; Haruta, J.; Yasuda, H.; Fukunaga, K.; Shirouchi, Y.; Tamura, Y. *J. Org. Chem.* **1982**, *47*, 2697.
10. (a) Porta, F.; Cenini, S.; Pizzotti, M.; Crotti, C. *Gazz. Chim. Ital.* **1985**, *115*, 275. (b) Garcia Deleon, R.; Kobayashi, A.; Yamauchi, T.; Ooishi, J.; Baba, T.; Masaki, S.; Hiarata, F. *Appl. Catal. A: Gen.* **2002**, *225*, 43. (c) Baba, T.; Fujiwara, M.; Oosaku, A.; Kobayashi, A.; Deleon, R. G.; Ono, Y. *Appl. Catal. A: Gen.* **2002**, *227*, 1. (d) Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Tetrahedron Lett.* **2002**, *43*, 4895. (e) Baba, T.; Ono, Y. JP 089435, 2001. (f) Smith, R. C.; Hunns, J. C. B. WO 9856758, 1998. (g) Shimazaki, Y.; Kambe, N.; Sotozono, M. JP 07328435, 1995. (h) Shimazaki, Y.; Kambe, N.; Sotozono, M. JP 07330708, 1995. (i) Calderoni, C.; Mizia, F.; Rivetti, F.; Romano, U. EP 391473, 1990. (j) Bosetti, A.; Cesti, P.; Calderazzo, F. EP 752413, 1997. (k) Gurgiolo, A. E. US 4268684, 1981. (l) Onoda, T.; Tano, K.; Hara, Y. JP 55004316, 1980. (m) Romano, U.; Tesei, R. DE 2714540, 1977.
11. (a) Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 6347. (b) Gupte, S. P.; Shivarcar, A. B.; Chaudari, R. V. *J. Chem. Soc., Chem. Commun.* **2001**, 2620. (c) Carloni, S.; De Vos, D. E.; Jacobs, P. A.; Maggi, R.; Sartori, G. *J. Catal.* **2002**, *205*, 199. (d) Sima, T.; Guo, S.; Shi, F.; Deng, Y. *Tetrahedron Lett.* **2002**, *43*, 8145. (e) Orsat, B.; Alper, P. B.; Moree, W.; Mak, C.-P.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 712. (f) Hacking, M. A. P. J.; van Rantwijk, F.; Sheldon, R. A. *J. Mol. Catal. B: Enzym.* **2000**, *9*, 201.
12. (a) Aresta, M.; Quaranta, E. *Tetrahedron* **1991**, *47*, 9489. (b) Aresta, M.; Dibenedetto, A.; Quaranta, E.; Boscolo, M.; Larsson, R. *J. Mol. Catal.* **2001**, *174*, 7. (c) See also Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* **2002**, *43*, 1217.
13. (a) Brill, W. F. DE 2160111, 1972. (b) Cong, J.-S.; Xue, W.; Zhao, X.-Q.; Wang, Y.-J. *Hebei Gongye Daxue Xuebao* **2001**, *30*, 32. *Chem. Abstr. 135*, 228449. (c) Baba, T.; Kobayashi, A.; Yamauchi, T.; Tanaka, H.; Aso, S.; Inomata, M.; Kawanami, Y. *Catal. Lett.* **2002**, *82*, 193.
14. (a) Fu, Z.-H.; Ono, Y. *J. Mol. Catal.* **1994**, *91*, 399. (b) Fu, Y.; Baba, T.; Ono, Y. *J. Catal.* **2001**, *197*, 91.
15. (a) Aresta, M.; Dibenedetto, A.; Quaranta, E. *Green Chem.* **1999**, 237. (b) Aresta, M.; Dibenedetto, A.; Quaranta, E. *Tetrahedron* **1998**, *54*, 14145.
16. (a) Onoda, T.; Tano, K.; Hara, Y. JP 54163527, 1979. (b) Romano, U.; Fornasari, G.; Di Gioacchino, S. DE 3202690, 1982. (c) Lissel, M.; Rohani-Dezfuli, A. R.; Vogt, G. *J. Chem. Res. (S)* **1989**, 312.
17. For a recent comprehensive review, see: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.
18. $LaCl_3$, $LaCl_3{\cdot}7H_2O$, and $La(NO_3)_3{\cdot}7H_2O$ resulted to be poorly soluble in DMC (Table 1). No solubilization of the used salt was observed upon subsequent addition of the amine.
19. Lanthanum triflate was not completely soluble in anhydrous DMC. Addition of benzylamine (Table 1) to the DMC suspension of $La(OTf)_3$ caused the complete solubilization of the salt. $Sc(OTf)_3$ easily dissolved in anhydrous DMC (Table 1), but a heterogeneous reaction mixture was obtained upon subsequent addition of $PhCH_2NH_2$ to the DMC solution of the Sc salt (see later in the text).
20. Analogous conclusions can be drawn also when an amine/DMC molar ratio higher than 1 is used (Table 4).
21. Tsuruta, H.; Yamaguchi, K.; Imamoto, T. *J. Chem. Soc., Chem. Commun.* **1999**, 1703.
22. Cotton, F. A.; Wilkinson, G. *Advanced inorganic chemistry*: 5th ed., Wiley: New York, 1988; p 973.
23. The formation of amine triflate salts has been documented also for amines other than benzylamine (see Section 4). The spectroscopic features of the isolated salts fully agree with those exhibited by authentic samples obtained by reacting the amine (1 equiv.) with CF_3SO_3H (1 equiv.) in diethylether.
24. In support of this, we note that, at 20 °C, a CH_2Cl_2 solution of $Sc(OTf)_3$ and MeOH (added in excess vs Sc to dissolve the metal triflate salt in the solvent used) immediately reacted with benzylamine to afford $(PhCH_2NH_3)(OTf)$ (see Section 4). In good agreement with what reported above, only two of the three used equivalents of benzylamine were protonated, as demonstrated by the fact that the moles of isolated $(PhCH_2NH_3)(OTf)$ salt per mole of Sc were close to 2 ($mol_{(RNH_3)}OTf/mol_{Sc}=1.89$). Work is in progress to purify and full characterize the very hygroscopic scandium derivative that co-precipitated with $(PhCH_2NH_3)(OTf)$ upon addition of the amine. IR (Nujol, cm^{-1}): 1331 (vs, OTf) and 1310 (s, shoulder, OTf), 1238 (s, shoulder, OTf), 1212 (vs, OTf) and 1195 (s, shoulder), 1044 (vs, C–O) and 1030 (s, shoulder, OTf), 639 (s, OTf). The IR spectrum in hexachlorobutadiene showed medium–weak absorptions at 2942, 2833 and 1463 cm^{-1} consistent with the presence of methoxo-groups.[25]
25. (a) Turevskaya, E. P.; Belokon, A. I.; Starikova, Z. A.; Yanovsky, A. I.; Kirushenkov, E. N.; Turova, N. Ya. *Polyhedron* **2000**, *19*, 705. (b) Mehrotra, R. C.; Batwara, J. M. *Inorg. Chem.* **1970**, *9*, 2505. (c) Funk, H.; Kohler, B. Z. *Anorg. Allg. Chem.* **1963**, *325*, 67.
26. This result is reminiscent of the modest catalytic effect played by pirrolidinium ion, when added as perchlorate salt, in the aminolysis of phenyl or *p*-chlorophenyl *p*-nitrobenzoate by pirrolidine.[27]
27. Menger, F. A.; Smith, J. N. *J. Am. Chem. Soc.* **1972**, *94*, 3824.
28. At 90 °C, in the presence of $Sc(OTf)_3$, the reaction mixture, initially heterogeneous, became homogeneous within 1.5 h.
29. The formation of *N*-methylmorpholine was confirmed by GC

and GC–MS (*m*/*z*: 101 ($M^{+\cdot}$), 87, 57, 42) analyses. After 8 h at 65 °C, the selectivity (determined by GC) of the carbomethoxylation process was equal to 92% and decreased to 87% after 23 h.

30. Minor amounts of Scandium (III) remain in solution and can be recovered, together with residual amounts of alkylammonium triflate, by means of extractions with water (see Section 4).
31. The IR spectra of the crude precipitates shows some common features, independently from the used amine. In all cases, an intense absorption is found between 1069 and 1056 cm^{-1}, that may be suggestive of metal-bonded-methoxo-groups. Strong bands, due to triflate anion, are located at 1300–1200, 1180–1170, 1031 and 639 cm^{-1}. A medium–strong band is also observed between 1665 and 1675 cm^{-1}, which we tentatively assign to the carbonyl stretching of carbamate ester molecules, most probably weakly coordinated to Scandium (as the low-frequency shift suggests). Accordingly, the intensity of the latter band markedly reduces upon washing the crude precipitate with DMC. Moreover, the GC–MS analysis of the DMC washing solution shows the presence of carbamate ester, that is further confirmed, by IR spectroscopy, on the residue of the DMC solution after evaporation of solvent (band at approximately 1700 cm^{-1} (see Section 4) due to $\nu_{C=O}$ in free carbamate esters).
32. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of laboratory chemicals*; Pergamon: Oxford, 1986.
33. Feigl, F.; Anger, V. *Spot texts in inorganic analysis*; 6th ed., Elsevier: Amsterdam, 1972; pp 125 and 407.
34. (a) Chisolm, M. H.; Extine, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 782. (b) Aresta, M.; Dibenedetto, A.; Quaranta, E. *J. Chem. Soc., Dalton Trans.* **1995**, 3359.

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Synthesis of novel lariat azathia crown macrocycles containing two triazole rings and bis crown macrocycles containing four triazole rings

Ashraf A. Abbas*

Department of Chemistry, Faculty of Science, Cairo University, 12613 Giza, Egypt

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Abstract—The 13-hydroxy macrocycles **7a-d** were prepared in 40–50% yields by the condensation of 1,ω-bis(4-amino-1,2,4-triazol-3-ylsulfany)alkanes **2a-d** with 1,3-bis(2-formyphenoxy)-2-propanol (**9**). Acylation of **7a-d** with 2-chloroacetylchloride gave the corresponding esters **11a**,**b**. Amination of **11a**,**b** with different amines in acetone furnished exclusively the target lariat macrocycles **12a**,**b** and **13** in 60–70% yields. Reaction of 2 equiv. of the macrocycles **11a**,**b** with 1 equiv. of piperazine afforded the novel bis macrocyles **14a**,**b** in 50–60% yields. Reduction of **7a-d** with $NaBH_4$ afforded the corresponding 13-hydroxyazathia crown ethers **15a-d** in 65–70% yields.

1. Introduction

A progressive interest was directed in the last few years to the chemistry of the crown ethers containing heterocyclic rings in the system. These macrocycles were found to exhibit interesting host-guest complexation characteristic.[1,2] Incorporation of heterocyclic moiety within the cavity of the crown ligands were also provides rigidity and are able to participate in complexation through their soft donor atoms, for example, macrocyclic ethers with pyridine and other nitrogen containing heterocyclic subunits were reported to form strong and selective interactions with various charged and neutral guest molecules.[3–7] Moreover, lariat crown ethers which bear side-chain containing donor atoms possess unique cation binding properties compared with the parent crown ether containing no extra donor sites.[8,9] Also, as efficient organic ligands lariat crown ethers meet the requirement of rapid, strong and three-dimensional cation binding and can mimic the properties of natural ionophores.[10] Furthermore, during the last decades considerable attention has been devoted to the chemistry of bis crown ethers for their applications in various area especially in ion-selective electrodes.[11–15] Moreover, bis crown ethers show extra binding properties than the monocrown ethers, where by the cooperatives action of two adjacent crown units, bis(crown ethers) tend to form stronger complexes with particular metal ion than the corresponding monocrown ethers, where it forms complexes with two crown moieties per cation: 'sandwich complexes' that improve the stability of the complex especially when the cation is too large to fit the cavity of the crown ethers.[16,17]

In connection with these findings and in continuation of our interest in synthesizing macrocyclic crown compounds containing heterocycles moieties,[18–20] and bis macrocyles.[21] We report here the synthesis of a series of 22–23 membered macrocycles fused with two triazole rings containing N, O and S inside the macrocyclic ring as donor atoms and possess pendant hydroxy group as precursor for the synthesis of lariat macrocycles. In an attempt to enhance the selectivity of these ligands and the stability of the complexes formed with both metals and organic cations. This project also describes the synthesis of the novel lariat macrocycles containing *N*,*N*-diethyamino, piperidino and morpholinoacetoxy moieties as side arm containing O and N as donor atoms and the corresponding bis macrocycles.

2. Results and discussion

Several methods have been described for the reaction of epichlorohydrin with bisphenols as precursor for the synthesis of crown ethers with pendant hydroxy group attached to the crown ether ring.[22,23] Heo et al[22] reported the synthesis of hydroxy crown ethers in a good yield 39–60% by the reaction of epichlorohydrin with the appropriate

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* Tel.: +20-23252831; fax: +20-25685799;
e-mail addresses: ashraf@chem-sci.cairo.eun.eg; ashrafaa50@hotmail.com

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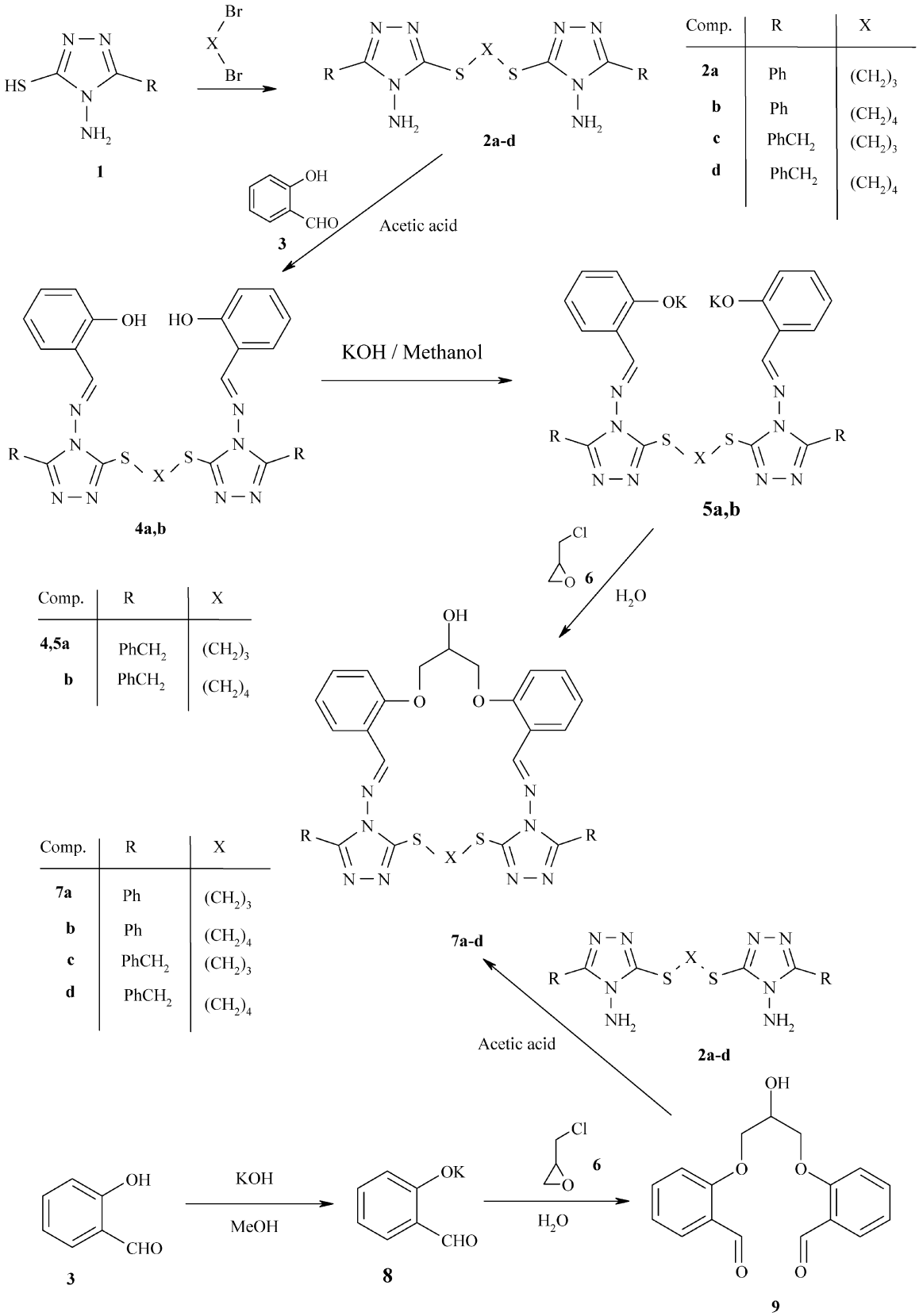
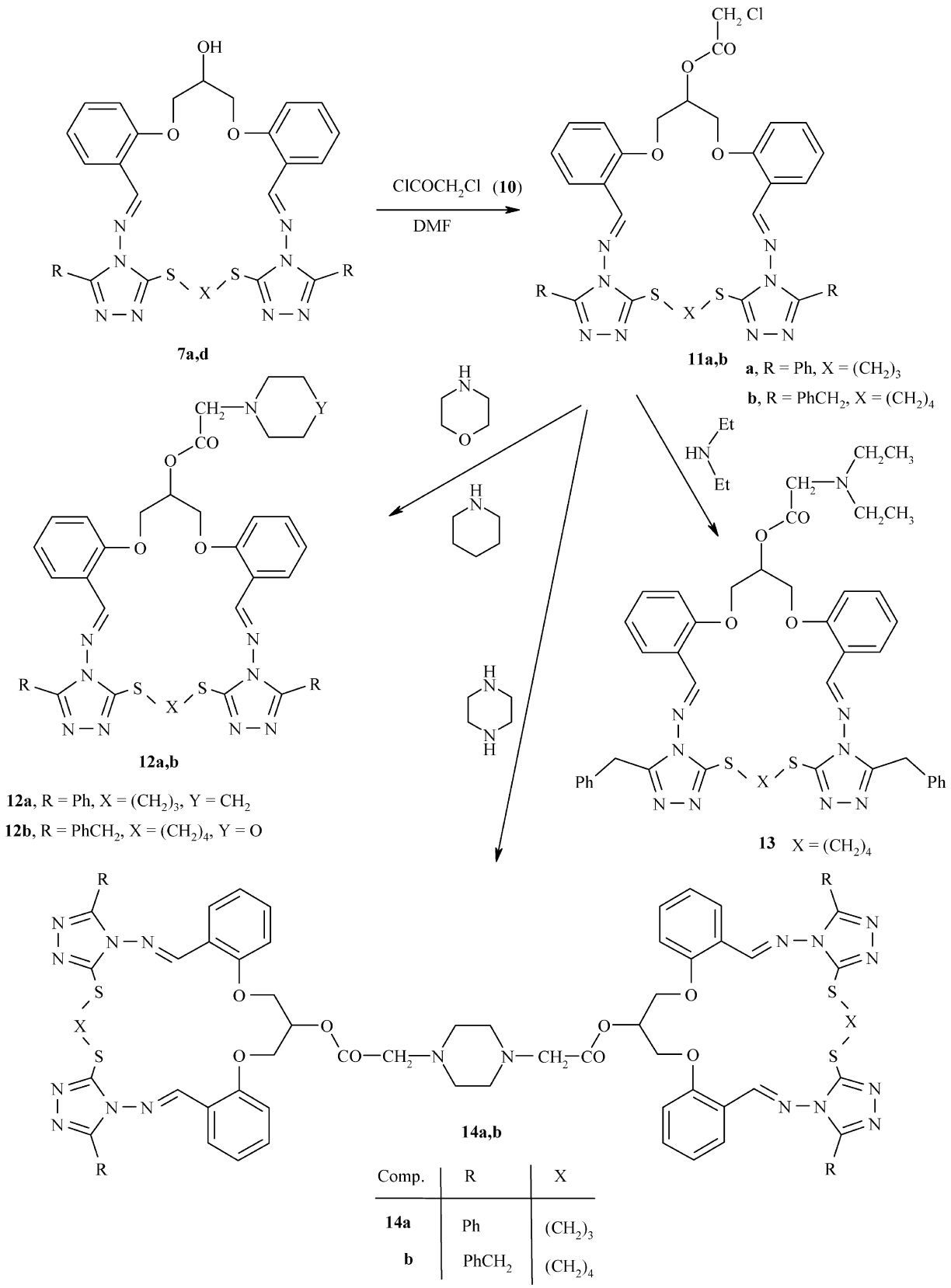
diphenols in basic aqueous media. This project describes the synthesis of novel 13-hydroxy aza-thia crown ethers containing two triazole rings as subcyclic unit as shown in Schemes 1–3.

Two strategies were attempted for the synthesis of the 13-hydroxy macrocycles **7a-d**. In the first one (Scheme 1), we applied a similar approach to that described by Heo et al.[22] Thus, condensation of 1,ω-bis(4-amino-1,2,4-triazol-3-

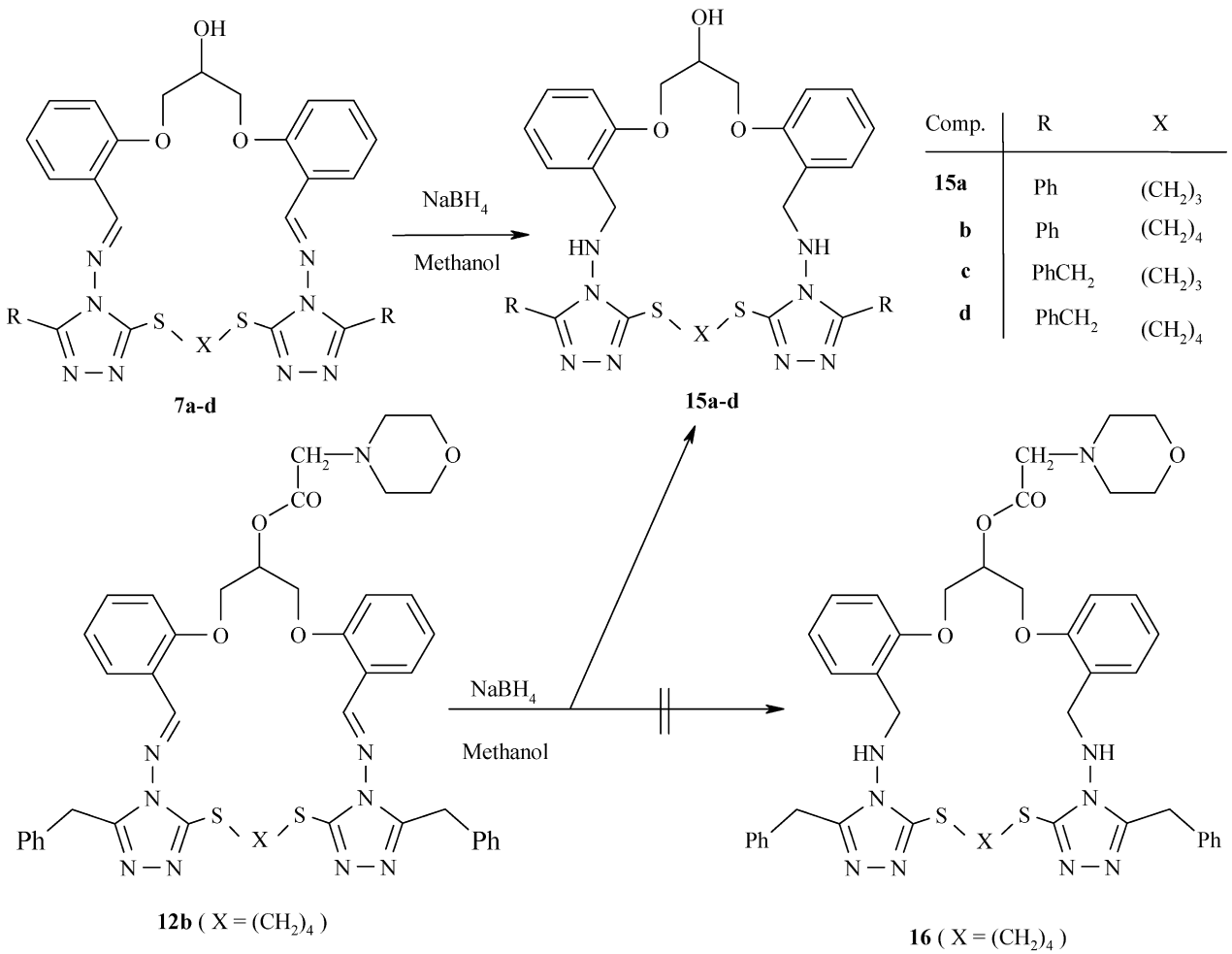


Scheme 1.



Scheme 2.

ylsulfany)alkanes **2a**-**d** with salicylaldehyde (**3**) in acetic acid gave the corresponding 1,ω-bis(4-*o*-hydroxybenzyl-ideneamino-5-aryl-1,2,4-triazol-3-ylsulfany)alkanes **4a**,**b** in 70–75% yield. Reaction of the latter compounds with methanolic potassiun hydroxide gave the corresponding bis potassium salt **5a**,**b**. Unfortunately, reaction of the bis potassium salts **5a**,**b** with epichlorohydrin (**6**) following the method described by Heo et al.[22] gave only 2% of the target



Scheme 3.

macrocycles **7c**,**d**. This may be attributed for the extent of the spacing between the terminal bis hydroxy groups. In anticipation of the low yield of the macrocycles **7c**,**d** we then applied the second strategy as outlined in Scheme 1. Thus, reactions of the potassium salt **8** [obtained upon treatment of salicyaldehyde (**3**) with methanolic potassium hydroxide solution] with epichlorohydrin (**6**) in aqueous media furnished the corresponding 1,3-bis(2-formyphenoxy)-2-propanol (**9**) in a good yield (65%). Condensation of **9** with the appropriate bis(aminotriazoles) **2a**-**d** in acetic acid under the high dilution condition which often used as the most versatile procedure used for the synthesis of the macrocycles[24] gave 50–60% of the target 13-hydroxy macrocycles Schiff bases **7a**-**d**. Having now available the 13-hydroxy macrocycles Schiff bases **7a**-**d** which stimulated the author to study their transformation into the first lariat aza-thia crown ethers containing two triazole rings as sub-cyclic units and their bis macrocycles containing two macrocyclic units connected by flexible bridge having piperazine moiety as shown in Schemes 2 and 3.

Thus, acylation the hydroxy group of compounds **7a**,**d** with 2-chloroacetylchloride (**10**) in DMF afforded the corresponding 13-chloroacetoxy macrocycles **11a**,**b** in 65–70% yields. The latter compound could be used as a key intermediate for the synthesis of lariat macrocycles **12a**,**b** and **13** containing different donor atoms in the side-arm. So, reaction of compounds **11a**,**b** with a series of secondary amines namely, *N*,*N*-diethylamine, piperidine and morpholine in refluxing acetone for 2 h furnished 50–60% yields of the corresponding lariat macrocycles **12a**,**b** and **13**. Similarly, the synthesis of the novel bis macrocycles **14a**,**b** was performed efficiently through the amination of esters **11a**,**b** with piperazine as shown in Scheme 2. Thus, reaction of 2 equiv. of chloroacetoxy macrocycles **11a**,**b** with 1 equiv. of piperazine in acetone gave the corresponding 1,4-bis[13-acetoxy macrocycles] piperazine derivatives **14a**,**b** in 50–55% yield. In order to increase the donor characters of the *N*-benzalimino and subsequently the cation binding ability of the macrocycle Schiff bases **7a**-**d** we successfully prepare the 13-hydroxy azathia crown ethers **15a**-**d** through the reduction of **7a**-**d** as shown in Scheme 3. Reduction of the macrocycles **7a**-**d** with $NaBH_4$ in methanol afforded the corresponding macrocycles **15a**-**d** in 65–72% yield. It is important to mention that all attempts for reduction of **12b** did not afford the corresponding lariat macrocyclic **16** but gave instead the 13-hydroxy macrocyclic **15d** in 65% yield which may be attributed to the basic hydrolysis of the ester group of compound **13b** in the reaction medium.

In conclusion of this project we successfully prepared macrocycles having pendant hydroxy group as a key intermediate for the synthesis of novel lariat macrocycles

containing a strong donor group as a supporting ligand at the end of the side-arm and bis macrocycles possess two crown units connected by flexible bridge. We believe that by development of the foregoing synthetic methodology lariat macrocyles and bis macrocycles with a wide variety of side-chains with different lengths and donor atoms aiming to improve the cation binding ability and the stability of the ligands metal complexes could be easily prepared.

3. Experimental

3.1. General

All melting points are uncorrected. Compounds prepared by different procedures were characterized by mixed melting points and IR. IR spectra (KBr) were recorded on Bruker Vector 22 spectrophotometer. NMR spectra were measured with a Varian Gemini 200 spectrometer (200 MHz, ^{1}H NMR) and chemical shift are given in ppm from TMS. ^{13}C NMR spectra were recorded using APT pulse sequence. with a Varian Mercury 300 (300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR). Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. 1,3-Dibromopropane, 1,4-dibromobutane, epichlorohydrin, diethylamine, piperidine, morpholine and piperazine were used as purchased from Aldrich. The starting bis(4-amino-1,2,4-triazol-3-ylsulfanyl)alkanes **2a**-**d** were prepared as reported.[18,19]

3.1.1. Bis(4-arylmethylideneamino-1,2,4-triazol-3-ylsulfanyl)alkanes 4a,b. *General procedure*. To a solution of each of **3c**,**d** (5 mmol) in glacial acetic acid (30 ml) was added salicylaldehyde (**3**) (10 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was then removed in vacuo and the remaining residue washed with water. The solid obtained was collected and crystallized from the appropriate solvent to give crystals of **4a**,**b**.

3.1.2. 1,3-Bis(4-*o*-hydroxybenzylideneamino-5-benzyl-1,2,4-triazol-3-ylsulfanyl)propane (4a). With the use of the general procedure **2c** gave crude **4a** which was crystallized from ethanol as colorless crystals (75%), mp 164 °C; ^{1}H NMR ($CDCl_3$) δ 2.19 (quintet, 2H, J=6.8 Hz, SCH_2CH_2), 3.27 (t, 4H, J=7 Hz, SCH_2), 4.13 (s, 4H, PhCH_2), 6.85–7.42 (m, 18H, ArH's), 8.39 (s, 2H, OH), 9.95 (s, 2H, CH=N) ppm. (Calcd for $C_{35}H_{32}N_8O_2S_2$ (660.82): C, 63.62; H, 4.88; N, 16.96; S, 9.70. Found: C, 63.41; H, 4.90; N, 16.80; S, 9.60%).

3.1.3. 1,4-Bis(4-*o*-hydroxybenzylideneamino-5-benzyl-1,2,4-triazol-3-ylsulfanyl)butane (4b). With the use of the general procedure **2d** gave crude **4b** which was crystallized from DMF as colorless crystals (70%), mp 252–254 °C; IR (cm^{-1}) 3400 (CO),1607 (NH); ^{1}H NMR (DMSO) δ 1.74 (br s, 4H, SCH_2CH_2), 3.14 (br s, 4H, SCH_2), 4.19 (s, 4H, PhCH_2), 6.95–7.81 (m, 18H, ArH's), 8.88 (s, 2H, CH=N), 10.49 (br s, 2H, OH) ppm. (Calcd for $C_{36}H_{34}N_8O_2S_2$ (674.85): C, 64.07; H, 5.08; N, 16.60; S, 9.50. Found: C, 63.91; H, 4.90; N, 16.40; S, 9.31%.

3.1.4. Preparation of the potassium salts 5a,b and 8. To a solution of KOH (1.14 g, 10 mmol) in methanol (10 ml) was added each of salicylaldehyde (**3**) (10 mmol) or bis(phenols) **4a**,**b** (5 mmol). The mixture was stirred at room temperature for 10 min. The solvent was then removed in vacuo. The remaining solid was triturated with dry ether, collected, dried, and used in the next step without further purification.

3.1.5. Reaction of epichlorohydrin with phenolic compounds for preparation of compounds 9 and 7c,d. *General procedure* (*A*). Potassium salts **8** (20 mmol) or **5a**,**b** (10 mmol) were dissolved in boiling water (20 ml). The solution is cool to 50 °C, epichlorohydrin (10 mmol) was added drop by drop with stirring over a period of 3 h. The reaction mixture is stirred at 50 °C for an additional 4 h and then cooled to room temperature to give **9** and **7c**,**d**.

3.2. Synthesis of compound 9

3.2.1. 1,3-Bis(2-formayphenoxy)-2-propanol (9). With the use of the general procedure (A) potassium salt **8** gave oily product which was extracted with chloroform. The organic layer washed with 1 N NaOH solution, dried with anhydrous $MgSO_4$. The solvent was then removed in vacuo. The solid obtained was collected and crystallized from benzene as yellow crystals, to give (65%) of **9**, mp 105 °C [lit.[25] 109.5–110.5 °C]; IR (cm^{-1}) 3467 (OH), 1679 (CO); ^{1}H NMR ($CDCl_3$) δ 3.65 (br s, 1H, OH), 4.32 (d, 4H, J=5 Hz, OCH2), 4.53 (quintet, 1H, J=5.4 Hz, CHOH), 7.02–7.83 (m, 8H, ArH's), 10.4 (s, 2H, CHO) ppm. (Calcd for $C_{16}H_{16}O_5$ (288.29): C, 66.66; H, 5.59. Found: C, 66.80; H, 5.70).

3.3. Synthesis of the macrocycles 7a-d

General procedure (*B*). To a solution of bis(carbonyl) ether **9** (5 mmol) in glacial acetic acid (50 ml) was added a solution of the appropriate bis(4-amino-1,2,4-triazol-3-ylsulfanyl)alkanes **3a**-**d** (5 mmol) in glacial acetic acid (30 ml). The reaction mixture was then heated under reflux for 3 h. The solvent was then removed in vacuo and the remaining residue washed with water and the solid obtained was collected and crystallized from the proper solvent to give colorless crystals of **7a**-**d**.

3.3.1. 3,23-Diphenyl-13-hydroxy-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (7a). With the use of the general procedure (B) **9** and **2a** gave crude **7a** which was crystallized from acetic acid as colorless crystals (50%), mp 264–6 °C; IR (cm^{-1}) 3380 (OH), 1599 (C=N); MS: m/z 688 (M$^+$, 80%); ^{1}H NMR (DMSO) δ 2.31 (quintet, 2H, J=7 Hz, SCH_2CH_2), 3.34 (m, 4H, SCH_2), 4.15–4.41 (m, 5H, OCH_2, CH–OH), 5.51 (d, 1H, J=4.2 Hz, OH), 7.1–8.15 (m, 18H, ArH's), 9.38 (s, 2H, CH=N) ppm. (Calcd for $C_{36}H_{32}N_8O_3S_2$ (688.83): C, 62.77; H, 4.68; N, 16.27; S, 9.31. Found: C, 62.90; H, 4.57; N, 16.40; S, 9.20).

3.3.2. 3,23-Diphenyl-13-hydroxy-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (7b). With the use of the general procedure (B) **9** and **2b** gave crude **7b** which was crystallized from dioxan as

colorless crystals (45%), mp 240–42 °C; IR (cm^{-1}) 3197 (OH), 1595 (C═N); MS: *m/z* 703 (M^++1, 50%); ^1H NMR (DMSO) δ 1.9 (br s, 4H, SCH_2CH_2), 3.23 (m, 4H, SCH_2), 4.15–4.54 (m, 5H, OCH_2, *CH*–OH), 5.53 (d, 1H, *J*=3.6 Hz, OH), 7.11–8.03 (m, 18H, ArH's), 9.40 (s, 2H, CH═N) ppm. (Calcd for $C_{37}H_{34}N_8O_3S_2$ (702.86): C, 63.23; H, 4.88; N, 15.94; S, 9.12. Found: C, 62.99; H, 4.77; N, 16.01; S, 9.31).

3.3.3. 3,23-Dibenzyl-13-hydroxy-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*]-[1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (7c). (a) With the use of the general procedure (B) **9** and **2c** gave crude **7c** which was crystallized from ethanol as colorless crystals (40%), mp 182–84 °C; IR (cm^{-1}) 3197 (OH), 1596 (C═N); MS: *m/z* 716 (M^+, 53%); ^1H NMR (DMSO) δ 2.23 (quintet, 2H, *J*=5.6 Hz, SCH_2CH_2), 3.28 (t, 4H, *J*=6.6 Hz, SCH_2), 4.1–4.35 (m, 5H, OCH_2, *CH*–OH), 4.22 (s, 4H, CH_2Ph), 5.5 (d, 1H, *J*=4.4 Hz, OH), 7.10–7.97 (m, 18H, ArH's), 9.28 (s, 2H, CH═N) ppm. (Calcd for $C_{38}H_{36}N_8O_3S_2$ (716.89): C, 63.67; H, 5.06; N, 15.63; S, 8.95. Found: C, 62.92; H, 5.22; N, 15.80; S, 9.21).

(b) With the use of the general procedure (A) **4a** gave 2% of **7c**

3.3.4. 3,23-Dibenzyl-13-hydroxy-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*]-[1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (7d). (a) With the use of the general procedure (B) **9** and **2d** gave crude **7d** which was crystallized from dioxan as colorless crystals (50%), mp 170–72 °C; IR (cm^{-1}) 3199 (OH), 1599 (C═N); MS: *m/z* 730 (M^+, 62%); ^1H NMR (DMSO) δ 1.8 (br s, 4H, SCH_2CH_2), 3.15 (m, 4H, SCH_2), 4.19 (s, 4H, CH_2Ph), 4.05–4.32 (m, 5H, OCH_2, *CH*–OH), 5.51 (d, 1H, *J*=4 Hz, OH), 7.10–7.99 (m, 18H, ArH's), 9.29 (s, 2H, CH═N) ppm. (Calcd for $C_{39}H_{38}N_8O_3S_2$ (730.91): C, 64.09; H, 5.24; N, 15.33; S, 8.77. Found: C, 63.99; H, 4.97; N, 15.11; S, 8.59).

(b) With the use of the general procedure (A) **4b** 2% of **7d**

3.4. Synthesis of chloroacetoxy macrocycles 11a,b

General procedure. A solution of each of macrocycles **7a**,**d** (5 mmol) in DMF (10 ml) was added 2-chloroacetyl chloride (5 mmol). The reaction mixture was stirred at room temperature for 3 h. then poured on cursed ice. The solid obtained was collected by filtration and crystallized from benzene to afforded colorless crystals of **11a**,**b**.

3.4.1. 13-Chloroacetoxy-3,23-diphenyl-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (11a). With the use of the general procedure **7a** gave **11a** (65%), mp 182–84 °C; IR (cm^{-1}) 1749 (CO), 1599 (C═N); ^1H NMR ($CDCl_3$) δ 2.43 (m, 2H, SCH_2CH_2), 3.48 (m, 4H, SCH_2), 4.02 (s, 2H, CH_2Cl), 4.42 (d, 4H, *J*=5 Hz, OCH_2), 5.74 (quintet, 1H, *J*=5.4 Hz, *CH*–OCO), 7.0–8.06 (m, 18H, ArH's), 9.15 (s, 2H, CH═N) ppm; ^{13}C ($CDCl_3$) δ 27.18, 32.77, 40.50, 66.90, 120.90, 126.65, 145.71, 152.80, 157.87, 166.44 (CH_2's and C's); 72.36, 112.61, 122.28, 127.62, 128.29, 128.45, 129.75, 134.38, 159.30 (CH's) ppm. (Calcd for $C_{38}H_{33}N_8O_4S_2Cl$ (765.31): C, 56.64; H, 4.35; N, 14.64; S, 8.38, Cl, 4.63. Found: C, 59.88; H, 4.44; N, 14.80; S, 8.20; Cl, 4.50).

3.4.2. 13-Chloroacetoxy-3,23-dibenzyl-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (11b). With the use of the general procedure **7d** gave **11b** (70%), mp 170–72 °C; IR (cm^{-1}) 1766 (CO), 1600 (C═N); ^1H NMR ($CDCl_3$) δ 1.93 (br s, 4H, SCH_2CH_2), 3.27 (br s, 4H, SCH_2), 3.96 (s, 2H, CH_2Cl), 4.25 (s, 4H, CH_2Ph), 4.36 (d, 4H, *J*=5.6 Hz, OCH_2), 5.79 (quintet, 1H, *J*=5.4 Hz, *CH*–OCO), 6.93–7.99 (m, 18H, ArH's), 9.16 (s, 2H, CH═N) ppm. (Calcd for $C_{41}H_{39}N_8O_4S_2Cl$ (807.40): C, 60.99; H, 4.87; N, 13.88; S, 7.94, Cl, 4.39. Found: C, 60.70; H, 4.74; N, 13.95; S, 8.10; Cl, 4.52).

3.5. Reaction of esters 11a,b with secondary amines (synthesis of compounds 12a,b, 13 and 14a,b)

General procedure. A mixture of each of **11a**,**b** (5 mmol) and excess of the appropriate secondary amines (*N*,*N*-diethylamine, morpholine, piperidine and piperazine) [6 mmol for compounds **13a**,**b**, **14** and 2.5 mmol of piperazine for compounds **11a**,**b**] in acetone (30 ml) was heated under reflux for 2 h. The solvent was then removed in vacuo. The solid obtained was crystallized from the proper solvent to give compounds **12a**,**b**, **13** and **14a**,**b**, respectively.

3.5.1. 3,23-Diphenyl-13-[2-(*N*-piperidino)acetoxy]-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclodocosine (12a). With the use of the general procedure **11a** and morpholine gave crude **12b** which was crystallized from ethanol as colorless crystals (70%), mp 216–18 °C; ^1H NMR ($CDCl_3$) δ 1.32 (quintet, 2H, *J*=4.6 Hz, N–$CH_2CH_2CH_2$), 1.49 (quintet, 4H, *J*=4.8 Hz, N–$CH_2CH_2CH_2$), 2.4 (m, 6H, SCH_2CH_2, N–CH_2CH_2-CH_2), 3.17 (s, 2H, CH_2CO), 3.48 (br s, 4H, SCH_2), 4.41 (d, 4H, *J*=5.4 Hz, OCH_2), 5.68 (quintet, 1H, *J*=5.2 Hz, *CH*–OCO), 7.02–8.08 (m, 18H, ArH's), 9.16 (s, 2H, CH═N) ppm. (Calcd for $C_{43}H_{43}N_9O_4S_2$ (814.00): C, 63.45; H, 5.32; N, 15.49; S, 7.88. Found: C, 63.30; H, 5.50; N, 15.52; S, 7.80).

3.5.2. 3,23-Dibenzyl-13-[2-(*N*-morpholino)acetoxy]-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (12b). (a) With the use of the general procedure **11b** and morpholine gave crude **12b** which was crystallized from benzene as colorless crystals (65%), mp 204–6 °C; IR (cm^{-1}) 1749 (CO), 1599 (C═N), ^1H NMR ($CDCl_3$) δ 1.89 (br s, 4H, SCH_2CH_2), 2.43 (t, 4H, *J*=4.4 Hz, N–CH_2CH_2–O), 3.17 (s, 2H, CH_2CO), 3.23 (br s, 4H, SCH_2), 3.58 (t, 4H, *J*=4.4 Hz, N–CH_2CH_2–O), 4.25 (s, 4H, CH_2Ph), 4.35 (d, 4H, *J*=4.8 Hz, OCH_2), 5.73 (quintet, 1H, *J*=5 Hz, *CH*–OCO), 6.94–8.03 (m, 18H, ArH's), 9.18 (s, 2H, CH═N) ppm; ^{13}C ($CDCl_3$) δ 27.72, 31.58, 33.21, 52.88, 59.15, 66.58, 66.93, 120.82, 135.83, 144.82, 154.02, 157.62, 168.99 (CH_2's and C's); 70.16, 112.04, 121.96, 126.65, 127.02, 128.37, 128.79, 134.10, 156.35 (CH's) ppm. (Calcd for $C_{45}H_{47}N_9O_5S_2$ (858.06): C,

62.99; H, 5.52; N, 14.69; S, 7.47. Found: C, 63.10; H, 5.37; N, 14.80; S, 7.36).

3.5.3. 3,23-Dibenzyl-13-[2-(*N*,*N*-diethylamino)acetoxy]-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo-[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (13). With the use of the general procedure **11b** and diethylamine gave crude **13** which was crystallized from ethanol as colorless crystals (60%), mp 162–4 °C; IR (cm^{-1}) 1599 (C═N), 1746 (CO); ^1H NMR ((CDCl$_3$) δ 0.84 (t, 6H, J=7.2 Hz, CH_3), 1.81 (br s, 4H, SCH_2CH_2), 2.47 (q, 4H, J=7.2 Hz, CH_2CH_3), 3.13 (br s, 4H, SCH_2), 3.28 (s, 2H, CH_2CO), 4.18 (s, 4H, CH_2Ph), 4.34 (d, 4H, J=5.8 Hz, OCH_2), 5.75 (quintet, 1H, J=5.4 Hz, *CH*–OCO), 6.97–8.15 (m, 18H, ArH's), 9.25 (s, 2H, CH═N) ppm. (Calcd for $C_{45}H_{49}N_9O_4S_2$ (844.07): C, 64.03; H, 5.85; N, 14.93; S, 7.60. Found: C, 63.91; H, 5.75; N, 14.79; S, 7.40).

3.5.4. 1,4-Bis{(3,23-diphenyl-12,13,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*q*]-[1,19,5,6,14,15,8,12]dioxatetraazadithiacyclododocosine)-13-yloxycarbonylmethyl}piperazine (14a). With the use of the general procedure **11a** and piperazine gave crude **14a** which was crystallized from acetic acid as colorless crystals (50%), mp 204–205 °C; IR (cm^{-1}) 1747 (CO), 1600 (C═N); ^1H NMR (CDCl$_3$) δ 2.42 (quintet, 4H, J=6.4 Hz, SCH_2CH_2), 2.77 (br s, 8H, NCH_2), 3.38 (s, 4H, CH_2CO), 3.48 (m, 8H, SCH_2), 4.41 (m, 8H, OCH_2),5.79 (br s, 2H, CH–OCO), 7.02–8.04 (m, 36H, ArH's), 9.15 (s, 4H, CH═N) ppm. (Calcd for $C_{80}H_{74}N_{18}O_8S_4$ (1543.84): C, 62.24; H, 4.83; N, 16.33; S, 8.31. Found: C, 62.33; H, 4.92; N, 16.45; S, 8.51).

3.5.5. 1,4-Bis{(3,23-dibenzyl-12,13,27,28,29,30-hexahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]dibenzo[*b*,*r*]-[1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine)-13-yloxycarbonylmethyl}piperazine (14b). With the use of the general procedure **11b** and piperazine gave crude **14b** which was crystallized from acetic acid as colorless crystals (60%), mp 236–38 °C; IR (cm^{-1}) 1759 (CO), 1600 (C═N); ^1H NMR (CDCl$_3$) δ 1.8 (br s, 8H, SCH_2CH_2), 2.26 (s, 8H, NCH_2), 3.02 (s, 4H, CH_2CO), 3.14 (br s, 8H, SCH_2), 4.14 (s, 8H, CH_2Ph), 4.27 (d, 8H, J=5.2 Hz, OCH_2), 5.66 (quintet, 2H, J=5 Hz, CH–OCO), 6.89–7.93 (m, 36H, ArH's), 9.10 (s, 4H, CH═N) ppm; ^{13}C NMR (DMSO) δ 26.65, 29.98, 31.91, 50.63, 57.35, 66.55, 119.28, 135.36, 143.48, 152.32, 157.15, 168.26 (CH_2's and C's), 69.43, 112.31, 120.75, 125.81, 125.91, 127.61, 127.89, 133.90, 157.87 (CH's). (Calcd for $C_{86}H_{86}N_{18}O_8S_4$ (1628.01): C, 63.45; H, 5.32; N, 15.49; S, 7.88. Found: C, 63.52; H, 5.42; N, 15.60; S, 7.72).

3.6. Action of sodium borohydride on 7a-d and 12b. Synthesis of 15a-d

General procedure. To a stirred boiling solution of each of **7a-d** and **12b** (0.7 mmol) in methanol (30 ml) was added sodium borohydride (0.4 g) over a period of 15 min. The reaction mixture was heated under reflux for 1 h. The solvent was then removed in vacuo and the remaining residue washed with water. The solid obtained was collected and crystallized from the proper solvent to give colorless crystals of **15a-d**.

3.6.1. 3,23-Diphenyl-13-hydroxy-5,6,12,13,20,21,27,28-octahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*q*][1,19,5,6,14,15,8,12]dioxatetraazadithiacyclododocosine (15a). With the use of the general procedure **7a** gave crude **15a** which was crystallized from dil. ethanol as colorless crystals (70%), mp 270–72 °C; IR (cm^{-1}) 3347 (NH), 3181 (OH); ^1H NMR (DMSO) δ 2.15 (quintet, 2H, J=6.8 Hz, SCH_2CH_2), 3.23 (t, 4H, J=6.8 Hz, SCH_2), 3.91–4.25 (m, 9H, OCH_2, Ar–CH_2, *CH*–OH), 4.39 (t, 2H, J=5 Hz, NH), 5.26 (d, 1H, J=4.6 Hz, OH), 6.83–8.06 (m, 18H, ArH's) ppm. (Calcd for $C_{36}H_{36}N_8O_3S_2$ (692.86): C, 62.41; H, 5.24; N, 16.17; S, 9.26. Found: C, 62.60; H, 5.33; N, 16.23; S, 9.10).

3.6.2. 3,23-Diphenyl-13-hydroxy-5,6,12,13,20,21,27,28,29,30-decahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (15b). With the use of the general procedure **7b** gave crude **15b** which was crystallized from acetic/ethanol mixture as colorless crystals (70%), mp 262–64 °C; IR (cm^{-1}) 3537 (NH), 3276 (OH); ^1H NMR (DMSO) δ 1.79 (br s, 4H, SCH_2CH_2), 3.2 (br s, 4H, SCH_2), 3.9–4.35 (m, 9H, OCH_2, Ar–CH_2, *CH*–OH), 5.3 (br s, 1H, OH), 6.81–8.05 (m, 20H, ArH's, NH) ppm. (Calcd for $C_{37}H_{38}N_8O_3S_2$ (706.89): C, 62.87; H, 5.42; N, 15.85; S, 9.07. Found: C, 62.59; H, 5.60; N, 15.70; S, 8.90).

3.6.3. 3,23-Dibenzyl-13-hydroxy-5,6,12,13,20,21,27,28-tetrahydro-14*H*,29*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo][*b*,*q*[1,19,5,6,14,15,8,12]dioxatetraazadithiacyclododocosine (15c). With the use of the general procedure **7c** gave crude **15c** which was crystallized from ethanol as colorless crystals (65%), mp 268–70 °C; IR (cm^{-1}) 3347 (NH), 3181 (OH); ^1H NMR (DMSO) δ 2.09 (br s, 2H, SCH_2CH_2), 3.22 (br s, 4H, SCH_2), 3.98–4.35 (m, 13H, PhCH_2, OCH_2, Ar–CH_2, *CH*–OH), 5.21 (s, 1H, OH), 6.72 (t, 2H, J=5.2 Hz, NH), 6.92–7.33 (m, 18H, ArH's) ppm. (Calcd for $C_{38}H_{40}N_8O_3S_2$ (720.92): C, 63.31; H, 5.59; N, 15.54; S, 8.90. Found: C, 63.20; H, 5.65; N, 15.31; S, 8.74).

3.6.4. 3,23-Dibenzyl-13-hydroxy-5,6,12,13,20,21,27,28,29,30-decahydro-14*H*-bis[1,2,4]triazolo[4,3-*f*:3,4-*m*]-dibenzo[*b*,*r*][1,20,5,6,15,16,8,13]dioxatetraazadithiacyclotricosine (15d). (a) With the use of the general procedure **7d** gave crude **15d** which was crystallized from acetic / ethanol mixture as colorless crystals (68%), mp 138–40 °C; IR (cm^{-1}) 3300 (NH), 3230 (OH); ^1H NMR (CDCl$_3$) δ 1.82 (br s, 4H, SCH_2CH_2), 3.2 (m, 4H, SCH_2), 3.71–4.13 (m, 9H, OCH_2, Ar–CH_2, *CH*–OH), 4.01 (s, 4H, CH_2Ph), 4.54 (br s, 1H, OH), 5.35 (t, 2H, J=6.4 Hz, NH), 6.85–7.35 (m, 18H, ArH's) ppm. (Calcd for $C_{39}H_{42}N_8O_3S_2$ (734.94): C, 63.74; H, 5.76; N, 15.25; S, 8.73. Found: C, 63.59; H, 5.63; N, 15.45; S, 8.70).

(b) Compound **12b** gave 65% of **15d**.

References and notes

1. Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M. *J. Org. Chem.* **1990**, *55*, 3129.

2. Bradshaw, J. S.; Thompson;, P. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1984**, *21*, 897.
3. Izatt, R. M.; Bordunov, A. V.; Zhu, C. Y.; Hathaway, J. K. *Comprehensive supramolecular chemistry*; Gokel, G. W., Ed.; Pergamon: New York, 1996; Vol. 1, p 3595.
4. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
5. Gokel, G. W. *Crown ethers and cryptands (monographs in supramolecular chemistry)*; The Royal Society of Chemistry: Cambridge, 1991; Vol. 3. Cram, D. J.; Cram, J. M. *Container molecules and their guests (monographs in supramolecular chemistry)*; The Royal Society of Chemistry: Cambridge, 1994; Vol. 4. Bell, T. W.; Salmi, S. K. *Inclusion compounds*; Atwood, J. L., Davies, J. E. D., Macnicol, D. D., Eds.; Oxford University Press: Oxford, 1991; Vol. 4, p 325.
6. Weber, E.; Kohler, H. J.; Reuter, H. *J. Org. Chem.* **1991**, *56*, 1236.
7. Weber, E.; Kohler, H. J. *J. Prakt. Chem.* **1995**, *337*, 451.
8. Chung, K. B.; Tomoi, M. *J. Polym. Sci. Part A: Polym. Chem.* **1992**, *30*, 1089.
9. Weber, E.; Vogtle, F. In *Crown-type compounds: an introductory overview*. *Host guest complex chemistry, part 1/topics in current organic chemistry series*; Vogtle, F., Ed.; Springer: New York, 1981; pp 14–15.
10. Gokel, G. W.; Trafton, J. E. Cation binding by lariat ethers. In *Cation binding by macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990; pp 253–257, see also pp 279–294.
11. Kimura, K.; Shono, T. In *Cation binding by macrocycles*; Inoue, Y., Gokel, G. W., Eds.; Marcel Dekker: New York, 1990; pp 429–463, Chapter 10.
12. Oggenfuss, P.; Morf, W. E.; Oesch, U.; Ammann, D.; Pretsch, E.; Simon, W. *Anal. Chim. Acta* **1986**, *180*, 299.
13. Kimura, K.; Shono, T. *Anal. Chem. Symp. Ser.* **1984**, 22. (*Ion-selective Electrodes*, 4), 155; *Chem. Abstr* **1986**, *104*, 44989.
14. Oesch, U.; Anker, P.; Ammann, D.; Simon, W. *Anal. Chem. Symp. Ser.* **1985**, 22. (*Ion-selective Electrodes*, 4), 81; *Chem. Abstr*. **1986**, *104*, 65242.
15. Ammann, D.; Morf, W. E.; Anker, P.; Meier, P. C.; Pretsch, E.; Simon, W. *Ion-Sel. Electrode Rev.* **1983**, *5*, 3.
16. Wong, K. H.; Bourgoin, M.; Smid, J. *J. Chem. Soc., Chem. Commun.* **1974**, 715.
17. Bourgoin, M.; Wong, K. H.; Hui, J. Y.; Smid, J. *J. Am. Chem. Soc.* **1975**, *97*, 3462.
18. Ibrahim, Y. A.; Elwahy, A. H. M.; Abbas, A. A. *J. Chem. Res. (S)* **1996**, 182. *J. Chem. Res*. (*M*), **1996**, 1066.
19. Elwahy, A. H. M.; Abbas, A. A. *Tetrahedron* **2000**, *56*, 885.
20. Elwahy, A. H. M.; Abbas, A. A. *Synthesis* **2002**, 260.
21. Abbas, A. A. *Tetrahedron* **1998**, *54*, 12421.
22. Heo, G. S.; Bartsch, R. A.; Schlobohm, L. L.; Lee, J. G. *J. Org. Chem.* **1981**, *46*, 3575.
23. Bartsch, R. A.; Liu, Y.; Kang, S. I.; Son, B.; Heo, G. S.; Hipes, P. G.; Bills, L. J. *J. Org. Chem.* **1983**, *48*, 4864.
24. Krakowiak, K. E.; Bradshaw, J. S.; Zamecka-Krakowiak, D. *Chem. Rev.* **1989**, *89*, 929.
25. Zhao, B.; Wu, Y. J.; Tao, J. C. *Polyhedron* **1996**, *15*, 1197.

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About diastereoselective oxidations of ferrocenyl amino alcohols

Olivier Delacroix,[a] Bakolinirina Andriamihaja,[b] Sophie Picart-Goetgheluck[a,*] and Jacques Brocard[a,*]

[a]*Laboratoire de Catalyse de Lille, Equipe de Catalyse Homogène, UMR CNRS 8010, ENSCL, Cité Scientifique, BP 108, F-59652 Villeneuve d'Ascq Cedex, France*
[b]*Laboratoire de Chimie Organométallique, Faculté des Sciences, Université d'Antananarivo BP 906, 101 Antananarivo, Madagascar*

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Abstract—Oxidation of some 2-(*N*,*N*-dimethylaminomethyl)ferrocenylalkylcarbinols by MnO_2 is totally diastereoselective: only one diastereomer is oxidized. A study was performed to highlight the influential factors of this phenomenon. Several ferrocenyl alcohols have been studied. First, two diastereomers of the ferrocenyl amino alcohol bearing a deuterium as an R group have been synthesized and oxidized. The good reactivity of both diastereomers displayed the importance of the size of the alkyl group, which needs to be bulkier than a deuterium. The synthesis and the oxidation of *endo*- and *exo*-α-hydroxy [4](1,2)ferrocenophane enabled the elimination of the hypothesis involving the spatial position of the hydroxy group, while the two diastereomers were oxidized. The replacement of the dimethylamino group by a methoxy or a methyl, the oxidation of these compounds, and the study of the preferential conformation of each diastereomer showed clearly the influence of an intramolecular hydrogen bond. So,the diastereoselectivity was shown to depend on the steric bulk of the alkyl group and on the presence of a strong intramolecular hydrogen bond between the hydroxy group and the nitrogen.

1. Introduction

Chiral ferrocenyl ligands have been used with success in a large number of asymmetric catalytic reactions.[1–3] These compounds can be synthesized by various methods. However, pathways using a totally diastereoselective oxidation have not been frequently used to produce diastereopure alcohols.[4,5] In the most representative examples of stereoselective oxidation, a chiral agent[6] or a biocatalyst[7–9] have been employed. In our laboratory, we synthesized chiral ferrocenyl amino alcohols with the purpose of using them as chiral ligands in asymmetric catalysis.[10,11] Interestingly, during the synthesis of one of these ligands, a rare totally diastereoselective oxidation has been observed. Indeed, only one isomer of a diastereomeric mixture of 2-(*N*,*N*-dimethylaminomethyl)ferrocenylethanol **1** was converted by MnO_2 into the corresponding ketone without any external chiral inducing agent (Fig. 1).[11,12] In this paper, we report on the study of this particular phenomenon by considering the different factors possibly responsible for this total diastereoselectivity.

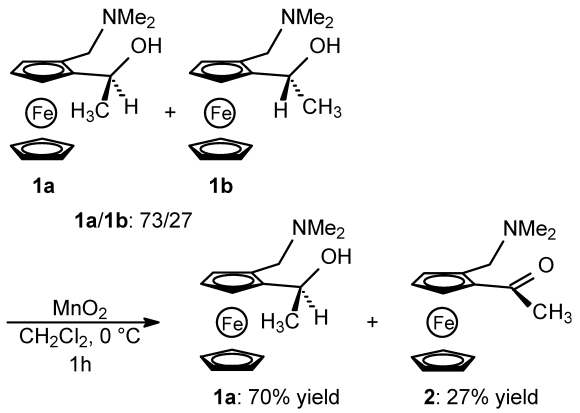

Figure 1. Diastereospecific oxidation of **1**.

2. Results

During our research on chiral ferrocenyl amino alcohols, the oxidation of a **1a/1b**[13] mixture had to be performed (Fig. 1).[11,12] Very surprisingly, the reaction was totally diastereoselective since diastereomer **1b** was completely oxidized whereas **1a** stayed unchanged.[14]

Different factors could be considered responsible for the observed stereospecificity: substitution on the carbon bearing the OH function to be oxidized, interaction of the OH moiety with iron, participation of a hydrogen bond between OH moiety and the nitrogen atom. We sought to perform experiments that might help to determine which factor controls the diastereospecificity of the process.

Keywords: Ferrocene; Alcohol; Diastereoselectivity; Oxidation.
* Corresponding authors. Tel.: +33-320434893; fax: +33-320436585 (S.P.-G.); tel.: +33-320436501; fax: +33-320436585 (J.B.); e-mail addresses: sophie.goetgheluck@ensc-lille.fr; jacques.brocard@univ-lille1.fr

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2.1. Influence of the substitution

The synthesis of a new ferrocenyl amino alcohol and of two previously described[11] ones has been carried out.

In these three selected derivatives, the methyl group of **1** has been replaced, respectively, by deuterium (**4**, Fig. 2), *n*-butyl, and phenyl (**5** and **6**, Fig. 3).

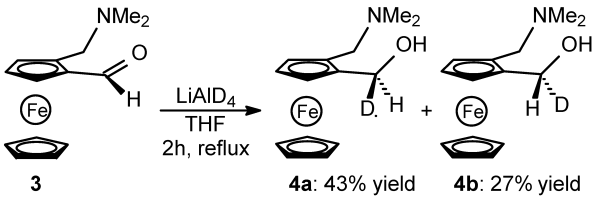

Figure 2. Synthesis of **4**.

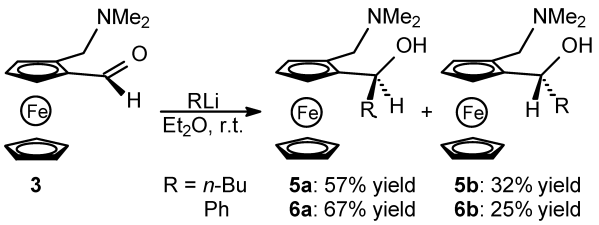

Figure 3. Synthesis of **5** and **6**.

The required diastereomeric mixture of derivatives **4** has been obtained by reduction of aldehyde **3**[15] by $LiAlD_4$. The resulting diastereomeric ratio **4a/4b** could be determined by comparison of the ^1H NMR spectrum recorded on the mixture of **4a/4b** with the ^1H NMR data obtained from non-deuterated **4**. As a matter of fact, the CH_2–O protons of **4** are diastereotopic. They are observed as two doublets located at 4.12 and 4.75 ppm (J_{H-H}=12.2 Hz). In the case of the deuterated mixture **4a/4b**, the spectrum presents two singlets at 4.11 ppm (**4a**) and 4.74 ppm (**4b**) in the ratio **4a/4b**: 62:38.

The mixtures of diastereomers **5a/5b** and **6a/6b** were prepared as depicted in Figure 3 following earlier reported procedures.[11]

Then, in separate experiments, the three mixtures of diastereomers were stirred in the presence of MnO_2 in dichloromethane at 0 °C. The structures of the products obtained are presented in Figure 4.

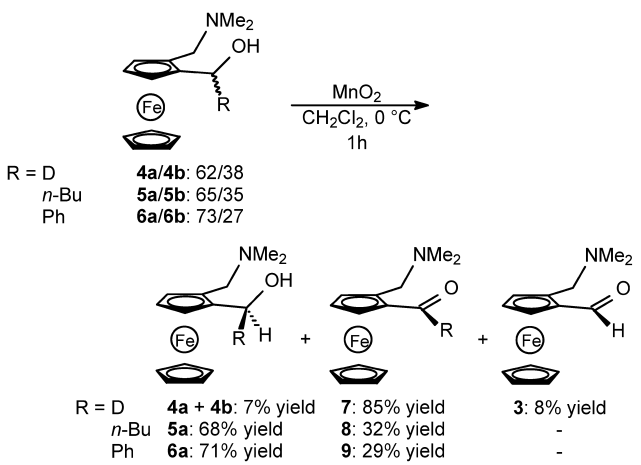

Figure 4. Oxidation of **4**, **5** and **6**.

The oxidation of **5a/5b** and **6a/6b** led to results identical to those obtained during oxidation of **1** via diastereoselective transformation. As such, **5b** and **6b** were converted quantitatively into ketones **8** and **9**, whereas **5a** and **6a** remained unchanged and could be completely recovered.[11]

Interestingly, the oxidation of the mixture **4a/4b** provided four products: deuterated aldehyde **7** (85%), non-deuterated aldehyde **3** (8%), and recovered **4a/4b** (7%). For the latter, the diastereomeric ratio is identical to that of the starting mixture. In this particular case, the reaction was not stereoselective. The increased amount of **7** as compared to **8** and **9** can be attributed to the isotopic effect rather than to a selective oxidation. In fact, it is well known that hydrogen reacts more readily than deuterium in such reactions.[16]

2.2. Influence of the relative position of the OH group versus iron

In order to get information about the influence of the location of the OH moiety onto the selectivity of the oxidation, two substrates have been synthesized (Fig. 5).

Thus, ferrocene **10** and succinic anhydride were reacted providing the Friedel–Craft's ketoacide **11**.[17] A Clemmensen's reduction furnished acid **12**, which was further cyclized in the presence of trifluoroacetic anhydride providing a racemic mixture of **13**.[18,19] Finally, the targeted mixture of the two diastereomeric alcohols **14a/14b** was obtained by reduction of the ketone by $LiAlH_4$.[20] The two diastereomers were produced in a 86:14 ratio in favour of the *endo* isomer **14a**. **14a** and **14b** could be easily separated through column chromatography.

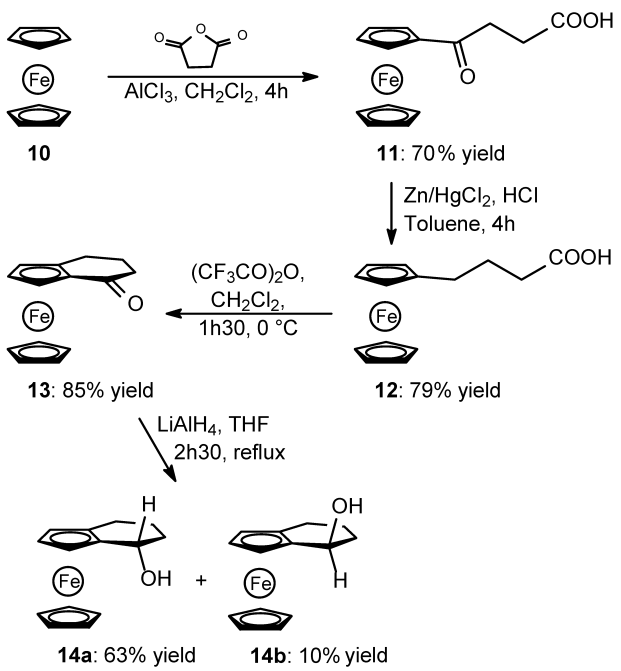

Figure 5. Synthesis of **14**.

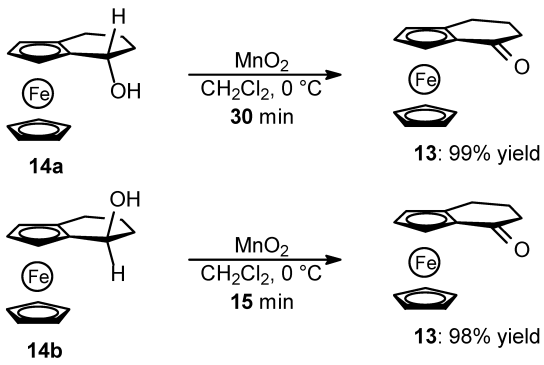

Figure 6. Oxidation of **14**.

In separated experiments, **14a** and **14b** were oxidized in a way similar to the one used above (Fig. 6).[21]

Both derivatives were converted into ketone **13**. Nevertheless, the oxidation of **14b** was twice as fast as that of **14a**. It has to be noticed that a hydrogen bond may exist between the OH moiety and iron[19] which can slow the oxidation process. In order to assess the influence of such a hydrogen bond, additional compounds were synthesized.

2.3. Influence of hydrogen bonds

Next, two new compounds bearing a chain possessing different 'electronic properties' were thought, this chain being *ortho* to the hydroxyethyl residue. Thus, the two derivatives **18** and **23** were prepared. In these compounds, the initial amine residue was replaced by respectively a methoxymethyl moiety and an ethyl group.

The syntheses of these compounds are depicted in Figures 7 and 8.

First, the ferrocenylcarbinol **15** was methylated by methanol in the presence of acetic acid providing ether **16**. The latter was converted into the corresponding aldehyde by a deprotonation (*n*-BuLi)/addition (DMF) sequence. The *ortho* selectivity of the process is attributed to the oxygen assistance via coordination to the intermediate metalated Fc–Li species.[22–24] The addition of CH_3Li onto the aldehyde **17** produced the diastereomeric mixture of alcohols **18a/18b**. The relative ratio (**18a/18b**: 64:36) was

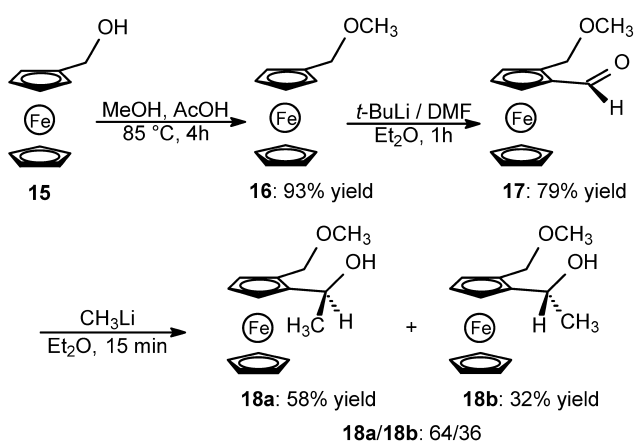

Figure 7. Synthesis of **18**.

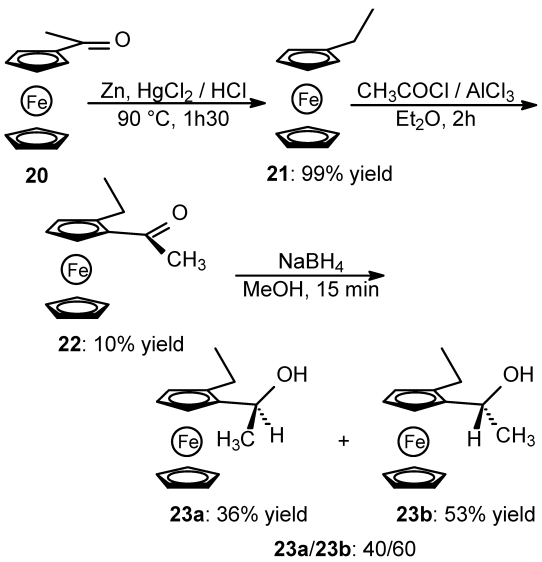

Figure 8. Synthesis of **23**.

determined by ^{1}H NMR. Indeed, **18a** exhibited a quadruplet at 4.91 ppm attributed to Fc–C*H*(OH), whereas the corresponding quadruplet is located at 4.60 ppm for **18b**.

Secondly, acetyl ferrocene **20** was reduced according to Clemmensen's method. Ethyl ferrocene **21** was obtained in 99% yield and was then acylated by a Friedel–Craft's reaction in the presence of CH_3COCl and $AlCl_3$. However, only 10% of the 1,2-disubstituted product **22** were formed due to the competitive formation of two other isomers (1,3- and 1,1′-disubstituted ferrocenes).[25] Nevertheless, the reduction of **22** by $NaBH_4$ was carried out and afforded a mixture of **23a** and **23b**. The relative ratio was again determined by ^{1}H NMR: diastereomer **23a** exhibits a deshielded doublet located at 1.56 ppm (vs. 1.33 ppm for **23b**) corresponding to the methyl group near the alcohol function and a deshielded quadruplet located at 4.78 ppm (vs. 4.61 ppm for **23b**) corresponding to the Fc–C*H*(OH). The proximity of the methyl residue and iron can explain the deshielding observed (see below). A 40:60 ratio of **23a/23b** could be determined by integration.

Then, in separate experiments, the oxidation was performed on both mixtures (Figs. 9 and 10). Thus, the **18a/18b**

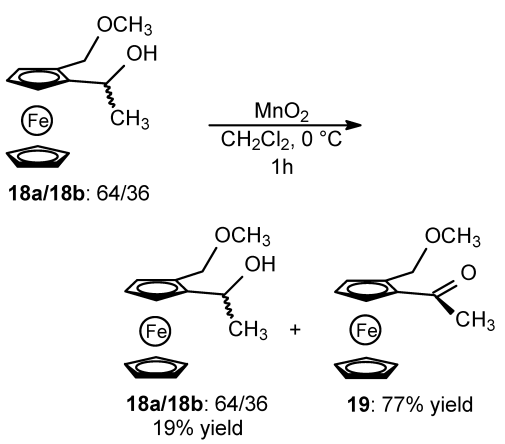

Figure 9. Oxidation of **18**.

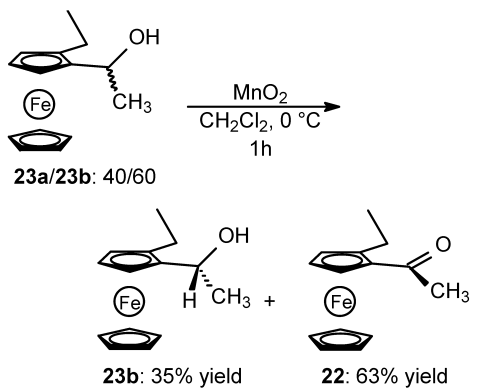

Figure 10. Oxidation of **23**.

mixture was oxidized in the presence of MnO_2 and the reaction was followed by ^1H NMR. It could be observed that both isomers were transformed with approximately the same rate.

The oxidation of the mixture constituted by **23a** and **23b** behaved differently. Indeed, **23a** was completely oxidized whereas **23b** reacted slower during the same time.

3. Discussion

The first factor examined was the effect of the substitution on the carbon atom bearing the OH moiety to be oxidized (Fig. 4). When R is a deuterium, the only effect, as expected, is an isotopic effect, as the deutero aldehyde was mainly produced. When R was an alkyl group (CH_3, *n*-Bu, Ph) a total diastereoselectivity was clearly observed, regardless of the size of the alkyl group (Figs. 1 and 4). Indeed, one diastereomer was totally oxidized while the other remained unchanged. In our compounds (**1**, **4**, **5** and **6**), two types of hydrogen bonds can exist: one between the OH moiety and

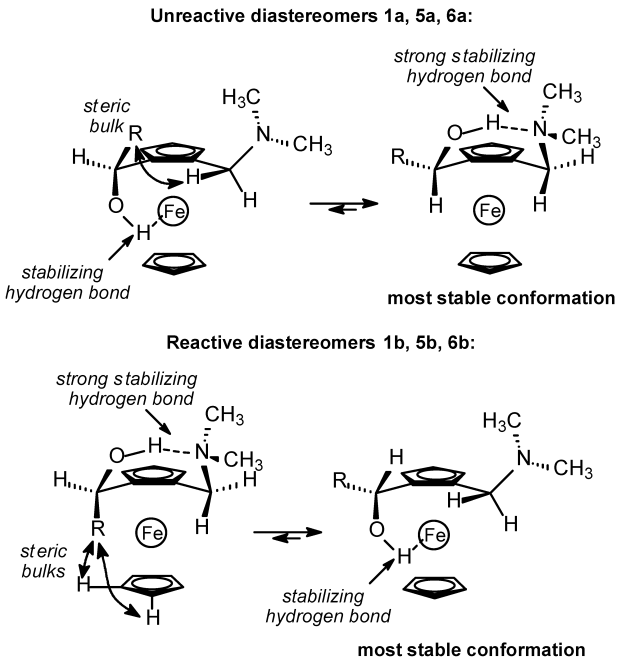

Figure 11. Different conformations of diastereomers of **1**, **5** and **6** (R=CH_3, *n*-Bu, Ph).

NMe_2, the other one between the OH moiety and iron (via d orbitals).[26] On the basis of molecular models and literature, we can propose the most stable conformation for each derivative. The structure of four conformers are given in Figure 11.[27,28]

When considering the most stable structures possessing the less hindered and most accessible (reactive) OH moiety, that is, presenting the weakest hydrogen bond (OH–Fe),[27,28] only diastereomer **b** can be sorted out. The latter is selectively oxidized providing the results observed experimentally.

For carbon skeleton rigidity reasons, such an hydrogen bond can exist but in a lesser extent in compound **14b** (Fig. 12).[19]

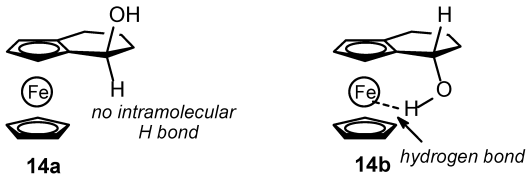

Figure 12. Possibility of an H bond in diastereomers **14a** and **14b**.

Accordingly both isomers **14a** and **14b** are oxidized but with lower rate for the species presenting the hydrogen bond OH–Fe (**14b**, Fig. 6).

For diastereomers **18a** and **18b**, in which the NMe_2 residue has been replaced by an ether function (OCH_3), two hydrogen bonds can still exist (with iron and with OCH_3). Nevertheless, the interaction between OH and OCH_3 is certainly weaker as compared to OH–NMe_2 inducing an identical reactivity for the two most stable diastereomers (Fig. 13).

For the two diastereomers of **23a** and **23b** where only a weak hydrogen bond can exist with the iron atom (Fig. 14),[19] both isomers are oxidized with nevertheless a greater rate

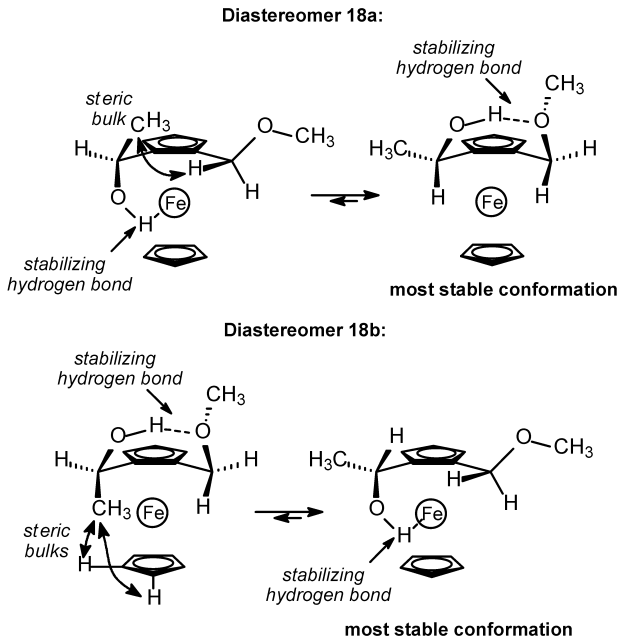

Figure 13. Different conformations of diastereomers **18a** and **18b**.

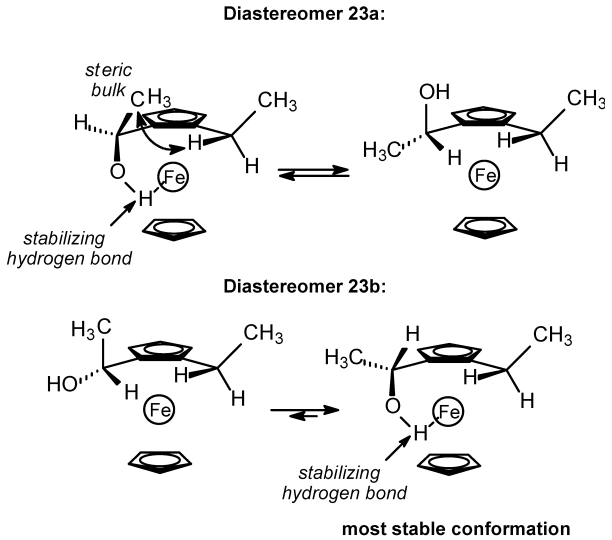

Figure 14. Different conformations of diastereomers **23a** and **23b**.

difference if compared to the closely related situation encountered during the oxidation of **14a/14b**.

Finally, an infrared study has been carried out in order to correlate the strength of the hydrogen bonds and the reactivity of several isomers. Table 1 presents the vibration frequencies of the OH groups in compounds **1**, **18** and **23** along with the oxidation results.

When comparing isomers **1a** with **18a** and **23a**, their relative reactivity increased in the order **1a**<**18a**<**23a** as compared to the order **1b**>**18b**>**23b**. Indeed, diastereomer **1a** is less reactive than **1b** (less than 1% of **1a** reacted while oxidation of **1b** was complete, entries 1 and 2). Compounds **18a** and **18b** presented the same reactivity (respectively, 80 and 81% reacted during the same period of time, entries 4 and 5). Finally, alcohol **23a** is more reactive than **23b** (100% of **23a** reacted while **23b** was oxidized only in 44% yield, entries 7 and 8).

The only isomer that was totally inert towards oxidation is **1a**. As a matter of fact, in **1a** a strong hydrogen bond exists between OH and NMe_2 (ν_{OH}: 3220 cm^{-1}, entry 1). That bond is weaker in the other compounds (ν_{OH}>3220 cm^{-1}).[29] That could be oxidized even with different rates.

Even if the mechanism of the oxidation of alcohols with MnO_2 is unknown, we have clear evidence that the main factor governing the selectivity of the oxidation process is the strength of the hydrogen bonds that might exist for the OH moiety to be oxidized.

4. Conclusion

The total diastereoselectivity of the oxidation process observed for compounds **1**, **5** and **6** has been related to the hydrogen bonds that might involve the OH group to be oxidized. The important role of a strong intramolecular H bond has been highlighted. Indeed, the strength of the hydrogen bond plays a significant role in the selectivity of the oxidation process. When several similar types of hydrogen bonds can coexist (OH–OR, OH–Fe), the selectivity is less important. The variable bond strengths will provide essentially different rates of oxidation.

5. Experimental

5.1. General

The reactions were performed in glassware under an atmosphere of nitrogen. Diethyl ether was freshly distilled from sodium. Manganese dioxide was obtained from Acros and alkyllithium reagents from Aldrich. Column chromatography were performed on SiO_2 (Merck, 70–230 mesh, Kieselgel 60). ^1H NMR, and ^{13}C NMR spectra were measured at room temperature with a Bruker AC 300 spectrometer for samples in $CDCl_3$ with tetramethylsilane as an internal reference. Mass spectra were obtained with a RIBER 10-10 (EI) or Kratos Concept II H–H (FAB) mass spectrometers. The infrared spectra were performed with a PERKIN–ELMER 1420 and a Nicolet Impact 400D. Elemental analyses were performed at the Laboratoire de Chimie Marine in Lille.

Table 1. Comparison reactivity/nature of the hydrogen bond of both diastereomers of **1**, **18** and **23**

Entry	Compound	Percentage of compound before oxidation	Percentage of compound after oxidation	Percentage of disappeared compound	Reactivity[a]	Nature of the intramol. H bond[b]	Frequencies of O–H (cm^{-1})[c]
1	**1a**	73	72	<1	0	OH–N	3220
2	**1b**	27	<1	100	+++	OH–Fe	3392
3	**2**	—	28	—	—	—	—
4	**18a**	64	13	80	++	OH–O	3431
5	**18b**	36	7	81	++	OH–Fe	3432
6	**19**	—	80	—	—	—	—
7	**23a**	40	<1	100	+++	OH–Fe	3356
8	**23b**	60	36	44	+	OH–Fe	3384
9	**22**	—	64	—	—	—	—

[a] Depending on the conversion in ketone and on the reaction time.
[b] In the most stable comformation.
[c] The IR analyses were performed without any solvent.

5.2. General procedure for oxidation

Manganese dioxide (18.4 mmol, 1.6 g) was added to a solution containing the mixture of alcohols (1.9 mmol) in dichloromethane (30 ml) at 0 °C. The reaction was then allowed to warm to room temperature. After 1 h, the mixture was filtered on celite and the solvent evaporated under reduced pressure. The remaining alcohols and the ketone were separated through silica gel chromatography.

5.3. Preparation of new compounds

5.3.1. [2-(*N*,*N*-Dimethylaminomethyl)ferrocenyl]deuteriomethanol (4a and 4b). A solution of 2-(*N*,*N*-dimethylaminomethyl)ferrocenecarboxaldehyde (900 mg, 3.3 mmol) in dry THF (10 ml) was added drop wise to $LiAlD_4$ (694 mg, 18.3 mmol) in dry THF (10 ml) at room temperature. The solution turned from grey to green. The mixture was refluxed for 2.5 h. To the cooled solution 40 ml of water saturated diethyl ether was slowly added followed by 20 ml of water. The organic compounds were extracted with several portions of diethyl ether, the extracts were combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. A purification through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine) yielded 70% (630 mg) of a 62:38 mixture of alcohols **4a** and **4b** as a yellow oil: ^{1}H NMR δ 4.74 (0.62H, m, CHD **4a**), 4.18 (1H, m, C_5H_3), 4.11 (0.38H, m, CHD **4b**), 4.08 (1H, m, C_5H_3), 4.06 (5H, m, C_5H_5), 4.00 (1H, m, C_5H_3), 3.88 (1H, d, J=4.2 Hz, CH_2N), 2.75 (1H, d, J=4.2 Hz, CH_2N), 2.15 (6H, s, $N(CH_3)_2$).

5.3.2. Deuterio[2-(*N*,*N*-dimethylaminomethyl)ferrocenyl]carboxaldehyde (7). The general procedure described above was applied to the mixture of diastereomers **4a** and **4b** (430 mg, 1.6 mmol) using 1.369 g (15.7 mmol) of MnO_2. A purification through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine) afforded 30 mg (7% yield) of a mixture of alcohols **4a** and **4b** and 383 mg (88% yield) of a 91:9 mixture of aldehydes **7** and **3** as a red oil: ^{1}H NMR δ 10.10 (0.09H, s, CHO **3**), 4.81 (1H, m, C_5H_3), 4.61 (1H, m, C_5H_3), 4.56 (1H, m, C_5H_3), 4.21 (5H, m, C_5H_5), 3.85 (1H, d, J=13.1 Hz, CH_2N), 3.35 (1H, d, J=13.1 Hz, CH_2N), 2.23 (6H, s, $N(CH_3)_2$).

5.3.3. Oxidation of *endo*-α-hydroxy [4](1,2)ferro-cenophane (14a). The general procedure described above was applied to **14a** (130 mg, 0.5 mmol) using 421 mg (4.8 mmol) of MnO_2. The reaction lasted 30 min. A purification through column chromatography (50% diethyl ether and 50% petroleum ether) afforded 128 mg (99% yield) of α-oxo [4](1,2)ferrocenophane **13**.

5.3.4. Oxidation of *exo*-α-hydroxy [4](1,2)ferro-cenophane (14b). The general procedure described above was applied to **14b** (130 mg, 0.5 mmol) using 421 mg (4.8 mmol) of MnO_2. The reaction lasted 15 min. A purification through column chromatography (50% diethyl ether and 50% petroleum ether) afforded 127 mg (98% yield) of α-oxo [4](1,2)ferrocenophane **13**.

5.3.5. 2-(Methoxymethyl)ferrocenecarboxaldehyde (17). Methoxymethylferrocene **16** (1.7 g, 7.4 mmol) was placed at room temperature under an inert atmosphere in a round-bottomed flask and then dissolved in dry diethyl ether (30 ml). After 5 min stirring, *t*-BuLi (7.4 ml, 11.1 mmol, 1.5 M in pentane) was added slowly and the solution was stirred for another 1 h. Then, 1.15 ml of DMF (14.8 mmol) was added. The solution was stirred for 15 min, quenched with water saturated diethyl ether (20 ml) and with brine (20 ml). The organic compounds were extracted with diethyl ether (2×20 ml), the extracts were combined, washed with brine (2×60 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (50% diethyl ether and 50% petroleum ether) yielded 79% (1.5 g) of **17** as a red oil: ^{1}H NMR δ 10.08 (1H, s, CHO), 4.78 (1H, m, C_5H_3), 4.68 (1H, m, C_5H_3), 4.64 (1H, d, J=11.6 Hz, CH_2O), 4.56 (1H, m, C_5H_3), 4.41 (1H, d, J=11.6 Hz, CH_2O), 4.25 (5H, m, C_5H_5), 3.39 (3H, s, OCH_3); ^{13}C NMR δ 193.6 (CHO), 86.3 (CIV C_5H_3), 77.4 (CIV C_5H_3), 74.8 (CIII C_5H_3), 72.0 (CIII C_5H_3), 71.1 (CIII C_5H_3), 70.4 (C_5H_5), 68.7 (CH_2), 58.3 (CH_3); MS *m*/*e* 258 [M^+] (100), 152 (26), 122 (491), 56, (42). Anal. Calcd for $C_{13}H_{14}FeO_2$: C, 60.50; H, 5.47. Found: C, 60.35; H, 5.37.

5.3.6. [2-(Methoxymethyl)ferrocenyl]ethanol (18a and 18b). A solution of **17** (1 g, 3.9 mmol) in dry diethyl ether (40 ml) was stirred at room temperature under nitrogen. After 5 min 3.6 ml (5.8 mmol) of methyllithium (1.6 M) were slowly added. After 15 min, the solution was hydrolysed with 20 ml of water saturated diethyl ether and then with 20 ml of water. Products were extracted with several portions of diethyl ether, the extracts were combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (50% diethyl ether and 50% petroleum ether) yielded 90% (959 mg) of the 64:36 mixture **18a/18b** as an orange oil: **18a**: ^{1}H NMR δ 4.91 (0.64H, q, J=6.5 Hz, CH−O), 4.69 (0.64H, d, J=11.0 Hz, CH_2O), 4.3–4.0 (4H, m, C_5H_3 and CH_2O), 3.34 (1.92H, s, CH_3O), 1.53 (1.92H, d, J=6.5 Hz, CH_3); ^{13}C NMR δ 92.2 (CIV C_5H_3), 81.6 (CIV C_5H_3), 70.6 (CIII C_5H_3), 70.0 (CH_2), 68.9 (C_5H_5), 66.7 (CIII C_5H_3), 66.4 (CIII C_5H_3), 58.5 (OCH_3), 20.1 (CH_3); **18b**: ^{1}H NMR δ 4.60 (0.36H, q, J=6.5 Hz, CH−O), 4.41 (0.36H, d, J=11.0 Hz, CH_2O), 4.3–4.0 (4H, m, C_5H_3 and CH_2O), 4.21 (5H, s, C_5H_5), 3.33 (1.08H, s, CH_3O), 1.53 (1.08H, d, J=6.5 Hz, CH_3); ^{13}C NMR δ 95.1 (CIV C_5H_3), 81.3 (CIV C_5H_3), 69.5 (CH_2), 68.7 (C_5H_5), 66.5 (CIII C_5H_3), 66.1 (CIII C_5H_3), 64.6 (C−OH), 64.2 (C−OH), 57.8 (OCH_3), 24.3 (CH_3); MS *m*/*e* (MALDI-TOF, matrix: thap) 313 [(M+K)$^+$], 297 [(M+Na)$^+$], 275 [MH^+], 274 [M^+].

5.3.7. 1-Acetyl-2-(methoxymethyl)ferrocene (19). The general procedure described above was applied to the mixture of the two diastereomers **18a** and **18b** (130 mg, 0.47 mmol) using 400 mg (4.6 mmol) of MnO_2. A purification through column chromatography (50% diethyl ether and 50% petroleum ether) afforded 25 mg (19% yield) of a 64:36 mixture of alcohols **18a** and **18b** and 99 mg (77% yield) of aldehyde **19** as a red oil: ^{1}H NMR δ 4.74 (1H, d, J=12.0 Hz, CH_2), 4.65 (2H, m, C_5H_3), 4.45 (1H, d,

J=12.0 Hz, CH_2), 4.42 (1H, m, C_5H_3), 4.17 (5H, s, C_5H_5), 3.43 (3H, s, CH_3O), 2.41 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR δ 203.2 (CO), 86.4 (CIV C_5H_3), 76.7 (CIV C_5H_3), 73.9 (CIII C_5H_3), 73.2 (CIII C_5H_3), 72.1 (CIII C_5H_3), 70.4 (C_5H_5), 69.8 (CH_2), 58.5 (OCH_3), 28.3 (CH_3); MS *m/e* (MALDI TOF, matrix: thap) 311 $[M+K]^+$, 295 $[M+Na]^+$, 273 $[MH^+]$, 272 $[M^+]$. Anal. Calcd for $C_{14}H_{16}FeO_2$: C, 61.79; H, 5.93. Found: C, 61.62; H, 5.88.

5.3.8. (2-Ethylferrocenyl)methylketone (22). To ferrocenylethane **21** (2.85 g, 13.3 mmol) diluted in dry dichloromethane (30 ml), a solution of acetyl chloride (1.3 ml, 18.8 mmol) and aluminium chloride (2.4 g, 17.7 mmol) in dichloromethane (30 ml) was added drop wise over 1 h. The mixture was then stirred for 1 h. Hydrolysis was performed by adding water saturated dichloromethane drop wise followed by water. The organic compounds were extracted with dichloromethane (2×20 ml), the extracts were combined, washed with water (2×100 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (30% diethyl ether and 70% petroleum ether) yielded 10% (341 mg) of **22** as a red oil: ^1H NMR δ 4.61 (1H, m, C_5H_3), 4.45 (1H, m, C_5H_3), 4.33 (1H, m, C_5H_3), 4.15 (5H, s, C_5H_5), 2.80 (1H, m, CH_2), 2.66 (1H, m, CH_2), 2.41 (3H, s, CH_3CO), 1.17 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR δ 203.5 (CO), 93.5 (CIV C_5H_3), 76.1 (CIV C_5H_3), 72.5 (CIII C_5H_3), 71.5 (CIII C_5H_3), 70.2 (C_5H_5), 69.6 (CIII C_5H_3), 28.6 ($COCH_3$), 21.3 (CH_2), 14.9 (CH_3); MS *m/e* 256 $[M^+]$ (84), 213 (84), 121 (147). Anal. Calcd for $C_{14}H_{16}FeO$: C, 65.65; H, 6.30. Found: C, 65.52; H, 6.21.

5.3.9. (2-Ethylferrocenyl)ethanol (23a and 23b). To a solution of (2-ethylferrocenyl)methylketone **22** (154 mg, 0.6 mmol) in methanol (20 ml) was added $NaBH_4$ (228 mg, 6 mmol). The solution was stirred until discolouration. A hydrolysis was performed by adding water saturated dichloromethane and water. The organic compounds were extracted with dichloromethane (2×20 ml), the extracts were combined, washed with water (2×60 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (50% diethyl ether and 50% petroleum ether) yielded 89% (138 mg) of a 40:60 mixture of alcohols **23a** and **23b** as a yellow oil: **23a**: ^1H NMR 4.78 (1H, q, J=6.5 Hz, CH–O), 4.16 (1H, m, C_5H_3), 4.12 (1H, m, C_5H_3), 4.07 (5H, s, C_5H_5), 4.05 (1H, m, C_5H_3), 2.55–2.40 (2H, m, CH_2), 1.56 (3H, d, J=6.5 Hz, CH_3), 1.19 (3H, t, J=7.5 Hz, CH_3); **23b**: ^1H NMR 4.61 (1H, q, J=6.4 Hz, CH–O), 4.21 (1H, m, C_5H_3), 4.14 (5H, s, C_5H_5), 4.13 (1H, m, C_5H_3), 4.04 (1H, m, C_5H_3), 2.45–2.25 (2H, m, CH_2), 1.33 (3H, d, J=6.4 Hz, CH_3), 1.14 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR δ 94.0 (CIV C_5H_3), 89.2 (CIV C_5H_3), 68.9 (C_5H_5), 67.8 (CIII C_5H_3), 65.6 (CIII C_5H_3), 64.1 (CIII C_5H_3), 64.0 (CH–O), 24.3 (CH_3), 20.7 (CH_2), 14.9 (CH_3); MS *m/e* (MALDI-TOF, matrix: thap) 297 $[M+K]^+$, 281 $[M+Na]^+$, 259 $[MH^+]$, 258 $[M^+]$, 241 $[M-OH]^+$.

5.3.10. Oxidation of (2-ethylferrocenyl)ethanol (23a and 23b). The general procedure described above was applied to the mixture of diastereomers **23a** and **23b** (100 mg, 0.4 mmol) using 339 mg (3.9 mmol) of MnO_2. A purification through column chromatography (40% diethyl ether and 60% petroleum ether) afforded 36 mg (35% yield) of alcohol **23b** and 65 mg (63% yield) of ketone **22**.

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References and notes

1. Togni, A.; Hayashi, T. Ferrocenes. VCH: Weinheim, 1995.
2. See for example: Shu-Li, Y.; Xue-Long, X.; Li-Xin, D.; Yi-Hua, Y.; Wei, X. *J. Org. Chem.* **2002**, *67*, 4684–4695.
3. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
4. Mijs, W. J.; De Jonge, C. R. H. I. Organic syntheses by oxidation with metal compounds. Plenum: New York, 1986; pp 132–134.
5. Parish, E. J.; Schroepfer, G. J., Jr. *Chem. Phys. Lipids* **1980**, *27*, 281–288.
6. Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202–8203.
7. See for example: Boyd, R. B.; Sharma, N. D.; Ljubez, V.; Byrne, B. E.; Shepherd, A. D.; Allen, C. C. R.; Kulakov, L. A.; Larkin, J. M.; Dalton, H. *Chem. Commun.* **2002**, 1914–1915.
8. Simpson, H. D.; Alphand, V.; Furstoss, R. *J. Mol. Catal. B: Enzym.* **2001**, *16*, 101–108.
9. Molinari, F.; Villa, R.; Aragozzini, F.; Leon, R.; Prazeres, D. M. F. *Tetrahedron: Asymmetry* **1999**, *10*, 3003–3009.
10. Brunin, T.; Cabou, J.; Bastin, S.; Pelinski, L. *Tetrahedron: Asymmetry* **2002**, *13*, 1241–1243.
11. Delacroix, O.; Picart-Goetgheluck, S.; Maciejewski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4417–4425.
12. Delacroix, O.; Picart-Goetgheluck, S.; Maciejewski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1999**, *10*, 1835–1837.
13. All diastereomers named **a** in this article are those which have a 1*RS*,*SR*$_p$ configuration and all diastereomers named **b** a 1*RS*,*RS*$_p$ configuration. The denomination 1*RS* refers to the central chirality and the denominations *RS*$_p$ and *SR*$_p$ refer to the planar chirality. All the metallocene chiralities were determined according to the nomenclature of Cahn, Ingold and Prelog extended to planar chiralities by Schlögl: Schlögl, K. *Top. Stereochem.* **1967**, *1*, 39–91.
14. Oxidation of the compound was not achieved on increasing reaction time to 6 h or adding 21 equiv. of MnO_2. We could not heat the solution or the amine chain would be oxidized into a carboxaldehyde group: Malfait, S.; Pelinski, L.; Maciejewski, L.; Brocard, J. *Synlett* **1997**, *7*, 830–832.
15. For the synthesis of **3**, see: Picart-Goetgheluck, S.; Delacroix, O.; Maciejewski, L.; Brocard, J. *Synthesis* **2000**, *10*, 1421–1426.
16. March, J. *Advanced organic chemistry, reactions, mechanisms, and structure*; 4th ed. Wiley-Interscience: New York, 1992; p 1170.

17. Rinehart, K. L.; Curby, R. J. *J. Am. Chem. Soc.* **1957**, *79*, 3420–3423.
18. Rinehart, K. L.; Curby, R. J. *J. Am. Chem. Soc.* **1957**, *79*, 3290–3291.
19. Hill, E. A.; Richards, J. H. *J. Am. Chem. Soc.* **1961**, *83*, 4211–4216.
20. Trifan, D. S.; Bacskai, R. *Tetrahedron Lett.* **1960**, *13*, 1–8.
21. The ^{1}H NMR spectrum of the mixture of these alcohols was complex, so it did not allow us to determine the proportion of each diastereomer. For this reason the oxidation needed to be performed separately on each compound.
22. Valkovich, P. B.; Gokel, G. W.; Ugi, I. K. *Tetrahedron Lett.* **1973**, *31*, 2947–2950.
23. Slocum, D. W.; Koonsvitsky, B. P.; Ernst, C. R. *J. Organomet. Chem.* **1972**, *38*, 125–132.
24. Slocum, D. W.; Engelmann, T. R.; Ernst, C.; Jennings, C. A.; Jones, W.; Koonsvitsky, B.; Lewis, J.; Shenkin, P. *J. Chem. Educ.* **1969**, *46*, 144–150.
25. Rinehart, K. L.; Motz, K. L.; Moon, S. *J. Am. Chem. Soc.* **1957**, *79*, 2749–2753.
26. Trifan, D. S.; Hoglen, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 5010–5011.
27. A study on a similar ferrocenic amino alcohol was made and highlighted the preferential conformation of each diastereomer and the nature of the intramolecular hydrogen bond: Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakawa, R. T.; Ugi, I. K. *J. Am. Chem. Soc.* **1973**, *95*, 482–486.
28. Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakawa, R. T.; Ugi, I. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 138–140.
29. Hesse, M.; Meier, H.; Zeeh, B. Méthodes spectroscopiques pour la chimie organique. Masson: Paris, 1997.

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1,3-Dipolar cycloaddition reaction of bipyridinium ylides with the propynamido-β-cyclodextrin. A regiospecific synthesis of a new class of fluorescent β-cyclodextrins

François Delattre,[a] Patrice Woisel,[a,*] Gheorghe Surpateanu,[a] Marc Bria,[b] Francine Cazier[a] and Patrick Decock[a]

[a]*Laboratoire de Synthèse Organique et Environnement, EA: 2599, MREID 145, Avenue Maurice Schumann, 59140 Dunkerque, France*
[b]*Service Commun de RMN, Université des Sciences et Technologies de Lille, rue Paul Langevin, 59655 Villeneuve d'Ascq cedex, France*

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Abstract—The 1,3-dipolar cycloaddition reaction of bipyridinium ylides with the electron deficient propynamido-β-cyclodextrin was studied. This reaction resulted in the regiospecific formation of a new class of fluorescent β-cyclodextrins. The new fluorophore systems were characterized spectroscopically by their absorption and emission maxima and their quantum yields.

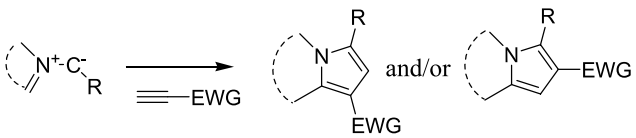
1. Introduction

The 1,3-dipolar [3+2] cycloaddition constitutes undoubtedly the most efficient, versatile and widely used method for the synthesis of nitrogen pentaatomic heterocycles.[1] In particular, cycloimmonium ylides undergo [3+2] dipolar cycloaddition reactions with various activated carbon–carbon multiple bonds and have proved to be the most attractive precursors for the preparation of indolizines derivatives (Scheme 1).[2] Indolizine ring systems are a common structural motif found in natural products which have received particular attention due to their wide range of biological and medicinal activity.[3] In addition to exhibiting a spectrum of pharmacological effects, synthetic indolizine derivatives and more specially those including a pyridine subunit, have also been recently studied extensively for their fluorescent properties and some of them already have practical applications as markers.[4]

During the last few years, the design and the construction of supramolecular based materials exhibiting fluorescent properties have and continue to pose a great challenge to synthetic chemists and materials scientists.[5] A survey of the literature shows that the most commonly employed supramolecular architecture is one in which a fluorophore and a receptor are covalently linked.[6] In particular, in recent years fluorescent cyclodextrins have generated considerable interest from the synthetic community as witnessed by recent articles dealing with their synthesis and emphasizing their sensory,[7] biochemical[8] and photoelectronic[9] properties. Consequently, the design and the synthesis of new fluorescent appended β-cyclodextrins are still the object of considerable attention.

As a part of our ongoing research program in the reactivity of cycloimmonium ylides[10] and with a view to synthesizing a new class of fluorescent β-cyclodextrins, we herein report the synthesis of pyridinoindolizine-βCD conjugates **9a–f** via 1,3-dipolar cycloaddition of the 6-propynamido-β-cyclodextrin **4** with various bipyridinium ylides **7a–f** (Scheme 2).

To the best of our knowledge, there is no report dealing with the 1,3-dipolar [3+2] cycloaddition reactions between cycloimmonium ylide and β-CD bearing an activated triple bond. The emission and fluorescence maxima as well the quantum yield of each new synthesized compounds **9a–f** are also reported.



Scheme 1.

Keywords: Cycloaddition; Ylides; β-Cyclodextrin; Fluorescence.
* Corresponding author. Tel.: +33-328658246; fax: +33-328658254; e-mail address: woisel@univ-littoral.fr

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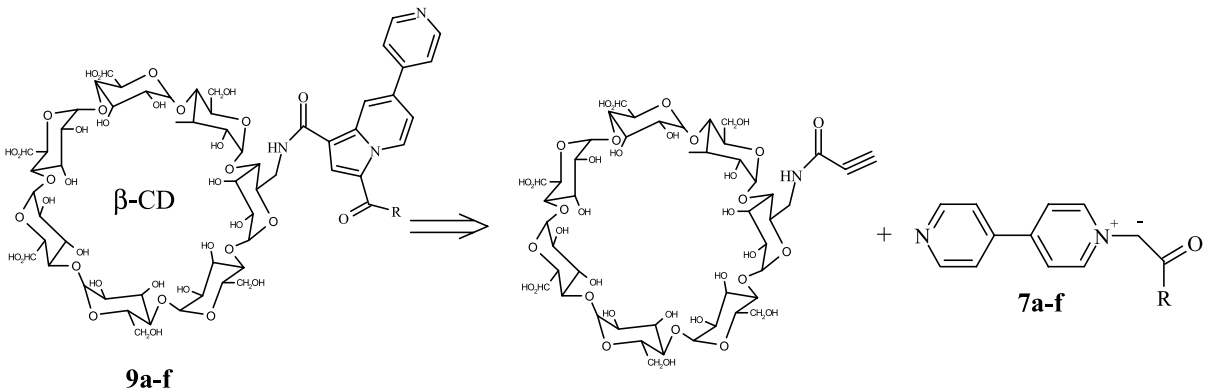


9a : R = OC_2H_5
9b : R= Ph
9c : R = 4-CH_3-C_6H_4
9d : R = 4-MeO-C_6H_4
9e: R = 4-Cl -C_6H_4
9f: R= 4-NO_2-C_6H_4

Scheme 2.

2. Results and discussion

2.1. Synthesis

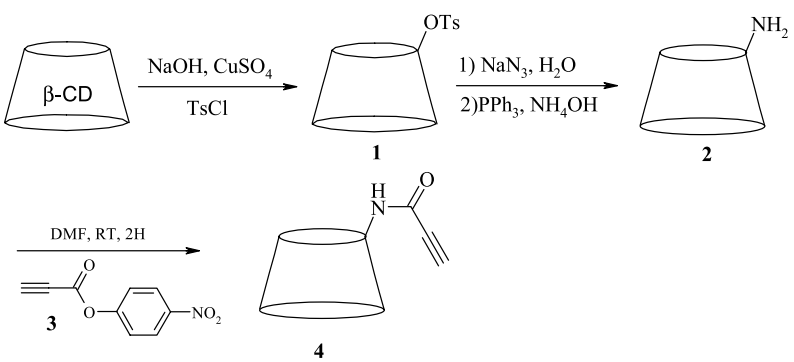
The starting material mono-6-deoxy-6-(*p*-tolylsulfonyl)-β-cyclodextrin **1** was synthesized as reported previously (Scheme 3).[11] The 6-amino-6-desoxy-β-cyclodextrin **2** was prepared in two step according to the method of Hamasaki.[12]

An early report for the preparation of the propynamido-β-cyclodextrin **4**[13] involved the reaction of **2** with the propyonic chloride under basic (NaOH) aqueous conditions (yield=71%). In the present work, the propynamido-β-cyclodextrin **4** was readily prepared in 80% yield by the condensation of **2** with the 4-nitrophenyl propynoate **3**,[14] which is easier to prepare and handle than propionic chloride, in DMF at room temperature. The crude product could be used for the subsequent preparation of the pyridinoindolizine core without further purification.

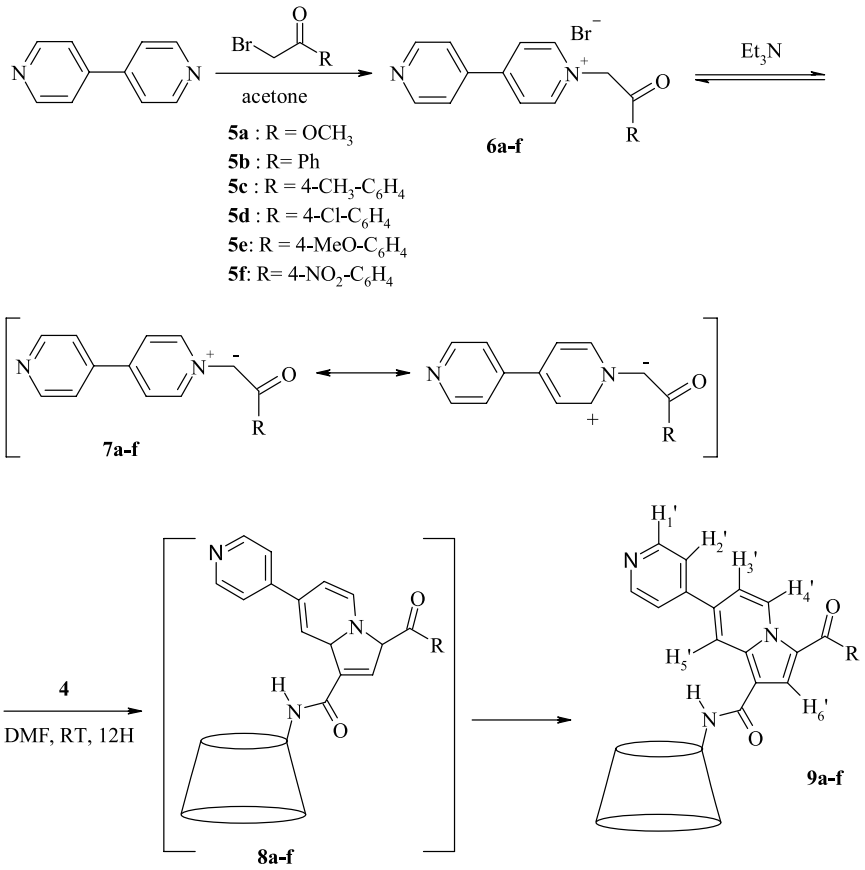
The 'salt method'[15] has been applied in order to obtain the bipyridinium ylides (Scheme 4). Thus, the commercially available 1,4-bipyridine quaternized with ω-brominated derivatives in boiling dry acetone furnished, after recrystallization (ethanol), the corresponding salts **6a**–**f**, in good yield.[16] Next, these salts, in the presence of the mild base triethylamine, form in situ, at room temperature in DMF, the red monosubstituted carbanions ylides **7a**–**f**. The ylides were then reacted with **4** to generate the primary cycloadducts **8a**–**f** which subsequently eliminate hydrogen to give the crude indolizine-βCD derivatives **9a**–**f**. It should be noted that this reaction must be carried out without light in order to prevent cleavage of the C^-–N^+bond. After 2 h, fluorescent β-CD were precipitated by addition of acetone (in all cases, the ^1H NMR spectra of the crude products reveal the presence of only one fluorescence derivative) and then successively purified by ion exchange chromatography on a CM-25 column and by gel filtration using Sephadex G-15.

2.2. Characterization

Evidence for the structures of new compounds was obtained from their elemental analysis and their spectroscopic data (MS, IR, ^1H and ^{13}C spectrometries). Complete spectral characterization of new compounds is provided in the experimental section. In all cases, the mass spectra



Scheme 3.



Scheme 4.

(ESMS+, H_2O/CH_3OH: 1:1, cone voltage: 110 V) showed a peak at m/z +23 due to the $[M+Na]^+$ ion. ^1H NMR spectra of **9a–f** exhibited broad resonance signals in the regions expected for the glycon moiety. The ^{13}C data clearly indicated the presence of two C=O bonds (δ_{CONH} 160–165 ppm, δ_{COAr} 178–186 ppm and δ_{COOEt} 164.4) which were confirmed by the presence of two overlapping absorption bands (1592–1676 cm^{-1}) in the IR spectrum. These data are in good agreement with typical literature values.[2b,c] DEPT, ^1H–^1H COSY and ^1H–^{13}C experiments allowed the assignment of all the proton and carbon resonances of the glycon moiety. The relative position of the amido fragment of the pyridinoisoindole backbone was established through TOCSY[17] and NOESY experiments. Correlations between H_5'/H_3' and H_5'/H_4' were observed, while no correlations were detected between H_5' and H_6' on TOCSY spectra. NOESY spectra confirmed the position of H_6' since in all cases no correlation was observed between H_5' and H_6'.

Table 1 summarizes data collected to assess the optical properties of compounds **9a–f**. All new modified β-cyclodextrins **9**, except **9f**, fluoresce. Compound **9g** does not exhibit recordable fluorescence probably due to a well known quenching effect of the NO_2 group linked to the phenylic ring. While **9b–c** (R=aromatic) result in only a weak fluorescence (ϕ_f<0.019), the fluorescence of compound **9a** (R=COOEt) displays a markedly improved quantum yield (ϕ_f=0.51). This particularity observed for **9a** in respect to the other similar compounds **9b–e** could be only explained by a deep modification of its polarity (perhaps due to the partial inclusion of the fluorophore arm in the apolar β-CD cavity).

3. Conclusion

In conclusion, the present work provides the first insight into the [3+2] cycloaddition reactions between cycloimmonium ylides and β-cyclodextrin bearing a dipolarophile moiety. This procedure, starting from 4,4′-bipyridinium salts, has allowed the synthesis of six new fluorescent β-cyclodextrins. The fluorescent properties of each compound has also been proved. It is likely that this new class of fluorescent β-cyclodextrin will find application as chemical sensors, furthermore, we are also trying to extend this reaction in order to synthesize new fluorescent β-cyclodextrins dimers. In addition, in order to explain the regiospecificity observed, further theoretical investigation of the reaction pathway is currently underway.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded with a Brüker AMX 400 spectrometer with tetramethylsilane as internal standard. Chemical shift values δ are reported in ppm and coupling constants (J) are in Hz. Mass spectra were measured using a Platform II Micromass Apparatus. FT-IR spectra were recorded using a Perkin–Elmer 2000

Table 1. Yields and optical properties of compounds **9a–f**

Compound	Yield (%)	$\lambda_{max.abs}$ (nm)	$\lambda_{max.emis}$ (nm)	Stokes shift (cm^{-1})	ε (M^{-1} cm^{-1})	ϕ_f
9a	35	257[a]	442	4476	19,578[a]	0.51[b]
		269[c]	446	4901	17,459[c]	
9b	27	274[c]	454	3337	45,418[c]	0.013[d]
9c	21	273[c]	450	3777	18,370[c]	0.019[d]
9d	18	275[c]	456	3759	14,108[c]	0.017[d]
9e	28	276[c]	468	4150	18,958[c]	0.013[d]
9f	21	269[c]	—[e]	—[e]	21,350[c]	—[e]

[a] In ethanol.
[b] Anthracene as reference (ϕ_f=0.27).[15]
[c] In water, PH=7.2, 25 °C.
[d] Tryptophan as reference (ϕ_f=0.14).[16]
[e] Too low to be measured accurately.

instrument. Absorbance and fluorescence spectra were recorded on a Perkin–Elmer LS50B, respectively. Melting points were obtained with a Reichert Thermopan apparatus and are uncorrected. All reagents were used as purchased unless otherwise stated. Cyclodextrin derivatives were dried under vacuum at 120 °C for 12 h. 6^A-Amino-6^A-desoxy-β-cyclodextrin **2**,[9,10] 4-nitrophenyl-propynoate **3**[12] and 4-(4′-pyridyl)pyridinium salts **6a–f**16 were prepared as reported previously.

4.1.1. 6^A-Deoxy-6^A-propynamido-β-cyclodextrin 4. The 4-nitrophenylpropynoate **3** (0.007 g, 0.35 mmol) was added at room temperature under argon to a solution of 6^A-amino-6^A-desoxy-β-cyclodextrin **2** (0.4 g, 0.35 mmol) in dry DMF (10 mL). The mixture was stirred for 2 h before it was poured into acetone (80 mL) dropwise. The resultant precipitate was collected and washed with acetone (20 mL) and diethyl ether (20 mL). ^1H and ^{13}C NMR spectra of this compound were consistent with literature data.[11]

4.1.2. General procedure for reactions of the 6^A-deoxy-6^A-propynamido-β-cyclodextrin 4 with 4-(4′-pyridyl)-pyridinium salts 6a–f. A solution of freshly distilled Et_3N (0.012 mmol) in DMF (0.5 mL) was added to a stirred solution of **6a–f** (0.085 mmol) and **4** (0.1 g, 0.085 mmol) in DMF (1 mL) at room temperature at O °C under Ar. The mixture was allowed to warm to room temperature, in the absence of light, over 12 h. The reaction was poured in acetone (50 mL) and the resultant precipitate was passed through a CM-25 column by eluting with water. The fractions containing the fluorescent β-cyclodextrin were combined, concentrated in vacuo. Finally, the mixture was applied to gel filtration using Sephadex G-15 to give **9a–f** as fine yellow powder.

4.1.3. *N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-(ethoxycarbonyl)-7-pyridin-4-ylindolizine 9a. ^1H NMR (DMSO-d_6, δ, *J*, Hz): 1.38 (3H, t, $-CH_3$), 3.18–3.98 (42H, m, *H*-2, *H*-4, *H*-3, *H*-5, *H*-$6^{A,B}$), 4.38–4.62 (8H, m, $-CH_2-$, $-OH_6$), 4.81–5.05 (7H, m, *H*-1), 5.59–6.92 (14H, m, $-OH_2$, $-OH_3$), 7.61 (1H, dd, *J*=2.0, 7.7 Hz, H_3'), 7.80 (2H, d, *J*=5.9 Hz, H_2'), 8.12 (1H, m, N*H*), 8.27 (1H, s, H_6'), 8.71 (2H, d, *J*=6.0 Hz, H_1'), 8.87 (1H, s, H_5'), 9.48 (1H, d, *J*=7.8 Hz, H_4'); ^{13}C NMR (DMSO-d_6, δ): 15.27 ($-CH_3$), 60.44, 60.77, 60.99 (C_6), 60.79 ($-CH_2$), 70.72, 73.07, 73.27, 73.90 (C_2, C_3, C_5), 81.96, 82.28, 82.51, 84.70 (C_4), 102.78, 103.04 (C_1), 113.59 (C_3'), 117.97 (C_5'), 121.61 (C_2'), 122.59 (C_6'), 128.34 (C_4'), 151.42 (C_1'), 161.35 (NH–*C*O), 164.38 (*C*O–OEt); IR (KBr, cm^{-1}): 3398 (OH free, NH), 2918 (C–H strech), 1676 (CO); *m*/*z* (%): 1449 (M+Na, 100), 1427 (M+1, 25). Anal. calcd for $C_{59}H_{83}N_3O_{37}\cdot 6H_2O$: C, 46.18; H, 6.24; N, 2.74. Found: C, 46.31; H, 6.54; N, 2.95.

4.1.4. *N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-benzoyl-7-pyridin-4-ylindolizine 9b. ^1H NMR (DMSO-d_6, δ, *J*, Hz): 3.25–3.90 (42H, m, *H*-2, *H*-4, *H*-3, *H*-5, *H*-$6^{A,B}$), 4.28–4.58 (6H, m, $-OH_6$), 4.84–5.01 (7H, m, *H*-1), 5.63–6.08 (14H, m, $-OH_2$, $-OH_3$), 7.52–7.76 (4H, m, H_3', *H meta*/*CO*, *H para*/*CO*), 7.92 (2H, d, *J*=8.3 Hz, *H ortho*/*CO*), 7.94 (2H, d, *J*=5.9 Hz, H_2'), 8.21 (1H, s, H_6'), 8.39 (1H, m, N*H*), 8.73 (2H, d, *J*=5.9 Hz, H_1'), 9.02 (1H, s, H_5'), 9.92 (1H, d, *J*=7.3 Hz, H_4'); ^{13}C NMR (DMSO-d_6, δ): 60.82, 60.84 (C_6), 70.97, 72.77, 73.17, 73.99 (C_2, C_3, C_5), 81.95, 82.27, 82.50, 82.73, 85.13 (C_4), 102.72, 103.11 (C_1), 113.82 (C_3'), 117.35 (C_5'), 121.24 (C_2'), 126.43 (C_6'), 128.66 (C_4'), 128.80 (C_8'), 129.31 (C_7'), 131.83 (C_9'), 150.84 (C_1'), 164.24 (NH–*C*O), 185.41 (*C*O-φ); IR (KBr, cm^{-1}) 3399 (OH free, NH), 2919 (C–H strech), 1602 (CO); *m*/*z* (%): 1481 (M+Na,100), 1459 (M+1, 22). Anal. calcd for $C_{63}H_{83}N_3O_{36}\cdot 5H_2O$: C,48.87; H, 6.05; N, 2.71. Found: C, 49.21; H, 6.23; N, 3.02.

4.1.5. *N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-(4-methylbenzoyl)-7-pyridin-4-ylindolizine 9c. ^1H NMR (DMSO-d_6, δ, *J*, Hz): 2.44 (3H, s, $-CH_3$), 3.13–3.84 (42H, m, *H*-2, *H*-3, *H*-4, *H*-5, *H*-$6^{A,B}$), 4.38–4.58 (6H, m, $-OH_6$), 4.78–4.97 (7H, m, *H*-1), 5.58–6.01 (14H, m, $-OH_2$, OH_3), 7.14 (2H, d, *J*=8.8 Hz, *H meta*/*CO*), 7.76 (1H, dd, *J*=1.9, 7.4 Hz, H_3'), 7.85 (2H, d, *J*=5.8 Hz, H_2'), 7.89 (2H, d, *J*=8.8 Hz, *H ortho*/CO), 8.15 (1H, s, H_6'), 8.34 (1H, m, N*H*), 8.73 (2H, d, *J*=5.7 Hz, H_1'), 8.95 (1H, s, H_5'), 9.84 (1H, d, *J*=7.4 Hz, H_4'); ^{13}C NMR (DMSO-d_6, δ): 21.90 ($-CH_3$), 60.57, 60.86 (C_6), 71.23, 73.19, 73.32, 73.92, 74.03 (C_2, C_3, C_5), 82.10, 82.47, 82.54, 85.05 (C_4), 102.71, 102.86, 103.10 (C_1), 114.60 (C_3'), 117.85 (C_5'), 121.65 (C_2'), 126.68 (C_6'), 129.32 (C_4'), 130.07 (C_7'), 151.48 (C_1'), 164.30 (NH–*C*O), 185.23 (*C*O-φ); IR (KBr, cm^{-1}): 3402 (OH free, NH), 2918 (C–H strech), 1624 (CO); *m*/*z* (%): 1495 (M+Na, 100); 1473 (M+1, 20). Anal. calcd for $C_{64}H_{85}N_3O_{36}\cdot 5H_2O$: C, 49.20; H, 6.13; N, 2.69. Found: C, 49.46; H, 6.20; N, 2.72.

4.1.6. *N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-(aminocarbonyl)-3-(4-methoxybenzoyl)-7-pyridin-4-ylindolizine 9d. ^1H NMR (DMSO-d_6, δ, *J*, Hz): 3.03–3.88 (42H, m, *H*-2,

H-3, *H*-4, *H*-5, *H*-6^{A,B}), 3.95 (3H, s, –OC*H*$_3$), 4.33–4.59 (6H, m, –O*H*$_6$), 4.78–4.97 (7H, m, *H*-1), 5.54–6.07 (14H, m, –O*H*$_2$, *OH*$_3$), 7.14 (2H, d, *J*=8.7 Hz, *H meta*/*CO*), 7.73 (1H, d, *J*=7.4 Hz, *H*$_3'$), 7.89 (2H,d, *J*=8.66 Hz, *H ortho*/*CO*), 8.21 (1H, s, *H*$_6'$), 8.23 (2H, d, *J*=6.1 Hz, *H*$_2'$), 8.40 (m, 1H, N*H*), 8.88 (2H, d, *J*=6.1 Hz, *H*$_1'$), 9.03 (1H, s, *H*$_5'$), 9.82 (1H, d, *J*=7.38 Hz, *H*$_4'$); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ ppm: 56.39 (–O*C*H$_3$), 60.54, 60.75, 60.93 (*C*$_6$), 71.05, 72.23–74.34 (*C*$_2$, *C*$_3$, *C*$_5$), 82.02–82.70, 84.96 (*C*$_4$), 102.62, 102.79, 103.05 (*C*$_1$), 113.76 (*C*$_3'$), 114.77 (*C*$_8'$), 119.36 (*C*$_5$), 123.45 (*C*$_2'$), 126.22 (*C*$_6'$), 129.32 (*C*$_4'$), 132.30 (*C*$_7'$), 146.52 (*C*$_1'$), 163.19 (NH–*C*O), 184.52 (*C*O-φ); IR(KBr, cm^{-1}) 3399 (OH free, NH), 2916 (C–H strech), 1618 (CO); *m*/*z* (%): 1511 (M+Na, 100), 1489 (M+H, 20). Anal. calcd for $C_{64}H_{85}N_3O_{37}\cdot 6H_2O$: C, 48.15; H, 6.12; N, 2.63. Found: C, 48.41; H, 6.25; N, 2.72.

4.1.7. *N*-(6^{A}-Deoxy-β-cyclodextrin-6^{A}-yl)-1-(aminocarbonyl)-3-(4-chlorobenzoyl)-7-pyridin-4-ylindolizine 9e. ^{1}H NMR (DMSO-*d*$_6$, δ, *J*, Hz): 3.23–3.90 (42H, m, *H*-2, *H*-4 *H*-3, *H*-5, *H*-6^{A,B}), 4.20–4.57 (6H, m, –O*H*$_6$), 4.76–4.94 (7H, m, *H*-1), 5.51–5.99 (14H, m, –O*H*$_2$, *OH*$_3$), 7.64 (2H, d, *J*=8.5 Hz, *H meta*/*CO*), 7.70 (1H, dd, *J*=7.4 Hz, *H*$_3'$), 7.81 (2H, d, *J*=8.5 Hz, *H ortho*/CO), 7.83 (2H, d, *J*=6.1 Hz, *H*$_2'$), 8.15 (1H, s, *H*$_6'$), 8.26 (1H, m, N*H*), 8.7 (2H, d, *J*=6.1 Hz, *H*$_1'$), 8.94 (1H, s, *H*$_5'$), 9.87 (1H, d, *J*=7.5 Hz, *H*$_4'$); ^{13}C NMR (DMSO-*d*$_6$, δ): 60.42, 60.53, 60.82 (*C*$_6$), 71.11, 72.76–74.04 (*C*$_2$, *C*$_3$, *C*$_5$), 81.92, 82.05, 82.10, 82.48, 82.61, 82.87, 85.07 (*C*$_4$), 102.71, 102.86, 103.12 (*C*$_1$), 114.43 (*C*$_3'$), 117.86 (*C*$_5'$), 121.69 (*C*$_2'$), 127.06 (*C*$_6'$), 129.41 (*C*$_4'$), 129.46 (*C*$_8'$), 131.75 (*C*$_7'$), 151.49 (*C*$_1'$), 164.22 (NH–*C*O), 184.21 (*C*O-φ); IR (KBr, cm^{-1}): 3397 (OH free, NH), 2918 (C–H strech), 1601 (CO); *m*/*z* (%): 1516 (M+Na, 32), 1514 (M+Na−2). Anal. calcd for $C_{63}H_{82}ClN_3O_{36}\cdot 5H_2O$: C, 47.81; H, 5.86; N, 2.65. Found: C, 48.02; H, 5.99; N, 2.84.

4.1.8. *N*-(6^{A}-Deoxy-β-cyclodextrin-6^{A}-yl)-1-(aminocarbonyl)-3-(4-nitrobenzoyl)-7-pyridin-4-ylindolizine 9f. ^{1}H NMR (DMSO-*d*$_6$, δ, *J*, Hz): 3.21–4.04 (42H, m, *H*-2, *H*-3, *H*-4, *H*-5, *H*-6^{A,B}), 4.42–4.71 (6H, m, –O*H*$_6$), 4.80–5.06 (7H, m, *H*-1), 5.72–6.01 (14H, m, –*OH*$_2$, –*OH*$_3$), 7.83 (1H, d, *J*=7.5 Hz, *H*$_3'$), 7.92 (2H, d, *J*=5.8 Hz, *H*$_2'$), 8.14 (2H, d, *J*=8.5 Hz, *H meta*/*CO*), 8.22 (1H, s, *H*$_6'$), 8.47 (2H, d, *J*=8.5 Hz, *H ortho*/*CO*), 8.40 (1H, m, N*H*), 8.80 (2H, d, *J*=5.8 Hz, *H*$_1'$), 9.02 (1H, s, *H*$_5'$), 9.98 (1H, d, *J*=7.5 Hz, *H*$_4'$); ^{13}C NMR (DMSO-*d*$_6$, δ): 59.88, 60.42 (*C*$_6$), 73.02, 73.56, 74.34 (*C*$_2$, *C*$_3$, *C*$_5$), 80.53, 80.98, 81.37, 82.42 (*C*$_4$), 102.09, 102.38, 103.01 (*C*$_1$), 115.39 (*C*$_3'$), 119.02 (*C*$_5'$), 123.73 (*C*$_2'$), 124.51 (*C*$_6'$), 129.17 (*C*$_8'$), 130.82 (*C*$_4'$), 131.33 (*C*$_7'$), 151.53 (*C*$_1'$), 160.48 (NH–*C*O), 178.57 (*C*O-φ); IR (KBr, cm^{-1}): 3402 (OH free, NH), 2915 (C–H strech), 1649 (CO); *m*/*z* (%): 1526 (M+Na, 100), 1504 (M+1, 30). Anal. calcd for $C_{63}H_{82}N_4O_{38}\cdot 5H_2O$: C, 47.49; H, 5.82; N, 3.52. Found: C, 47.76; H, 5.96; N, 3.61.

References and notes

1. Huisgen, R. *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1–176.
2. (a) Houben, J.; Weyl, T. R. *Organische Stickstoff-Verbindungen mit einer C,N-Doppelbindungen*; Thieme: Stuttgart, 1991. (b) Mangalagiu, I.; Druta, I.; Constantinescu, M.; Humelnicu, I.; Petrovanu, M. *Tetrahedron* **1996**, *52*, 8853. (c) Druta, I.; Dinica, R.; Bacu, E.; Humelnicu, I. *Tetrahedron* **1998**, *54*, 1081. (d) Caprosu, M.; Olariu, I.; Mangalagiu, I.; Constantinescu, M.; Petrovanu, M. *Eur. J. Org. Chem.* **1999**, 3501. (e) De Bue, G.; Nasielski, J. *Bull. Soc. Chim. Belg.* **1997**, *106*, 97. (f) Padwa, A.; Austin, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144. (g) Miki, Y.; Hachiken, H.; Takemura, S. *Heterocycles* **1984**, *22*, 701. (h) Tsuge, O.; Kanemasa, S.; Kuraoko, S.; Takenaka, S. *Chem. Lett.* **1984**, 279. (i) Katritzky, A. R.; Guofang, Q.; Baozhen, Y.; Hai-Ying, H. *J. Org. Chem.* **1999**, *64*, 7614. (j) Georgescu, F.; Georgescu, E. I.; Chiraleu, F.; Zugravescu, I. *Rev. Roum. Chim.* **1981**, *26*(6), 879. (k) Georgescu, F.; Georgescu, E. I.; Draghici, C.; Caproiu, M. T. *Rev. Roum. Chim.* **1997**, *42*(3), 205. (l) Marchalin, S.; Cvopova, K.; Pham-Huu, D. P.; Chudik, M.; Kozisek, J.; Svoboda, I.; Daïch, A. *Tetrahedron Lett.* **2001**, *42*, 5663.
3. (a) Harell, N. B.; Doerge, R. F. *J. Pharm. Sci.* **1967**, *56*, 225. (b) Grubin, J.; Vogalaer, H.; Inion, H.; Houben, C.; Lucchetti, J.; Mahaux, J.; Rossels, G.; Peiren, M.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1993**, *36*, 1425. (c) Grubin, J.; Descamp, H.; Chatelain, P. Eur. Pat. Appl. EP235111, **1987**; *Chem. Abstr.* **1988**, *109*, 6405b.
4. (a) Vlahovici, A.; Andrei, M.; Druta, I. *J. Lumin.* **2002**, *96*, 279. (b) Sonnenschein, H.; Hennrich, G.; Resch-Genger, U.; Schulz, B. *Dyes Pigments* **2000**, *46*, 23. (c) Vlahovici, A.; Druta, I.; Andrei, M.; Cotlet, M.; Dinica, R. *J. Lumin.* **1999**, *82*, 155.
5. (a) Lehn, J. M. *Supramolecular chemistry*; VCH: Vergagsgesellshaft, 1995. (b) Czarnik, A. W. *Fluorescent chemosensors for ion and molecule recognition*. *ACS Symposium Series 538*; American Chemical Society: Washington, DC, 1992. (c) Grynkiewicz, G.; Poenie, M.; Tsien, R. *J. Biol. Chem.* **1985**, *260*, 3440. (d) Fabrizzi, L.; Poggi, A. *Chem. Soc. Rev.* **1995**, *24*, 197. (e) Czarnik, A. W. *Acc. Chem. Res.* **1994**, *27*, 302. (f) De Silva, A. P.; Gunaratne, H. Q. N.; McVeigh, C.; Maguire, G. E. M.; Maxwell, P. R. S.; O'Hanlon, E. *Chem. Commun.* **1996**, 2191. (g) Chen, C. T.; Wagner, H.; Still, W. C. *Science* **1998**, 279.
6. (a) De Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515. (b) Prodi, L.; Bolleta, F.; Monalti, M.; Zaccheroni, N. *Coord. Chem. Rev.* **2000**, *205*, 59. (c) De Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Chem. Rev.* **2000**, *205*, 41. (d) Granda Valdés, M.; Badia, R.; Pina Luis, G.; Diaz-Garcia, M. E. *Quim. Anal.* **2000**, *19*, 1910. (e) James, T. D.; Samankuramara Sandanayake, K. R. A.; Shinkaï, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1910. (f) Tong, A. J.; Yanauchi, A.; Hayashita, T.; Zang, A. Y.; Smith, B. D.; Teramae, N. *Anal. Chem.* **2001**, *73*, 1530.
7. (a) Nakashima, H.; Takenka, Y.; Higashi, M.; Yoshida, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2096. (b) Wagner, M.; Engrand, P.; Regnouf-de-Vains, J. B.; Marsura, A. *Tetrahedron Lett.* **2001**, *42*, 5207. (c) Corradini, R.; Dossena, A.; Galaverna, G.; Marchelly, R.; Paragia, A.; Sartor, G. *J. Org. Chem.* **1997**, *62*, 6283. (d) Ueno, A.; Minato, I.; Suzuki, M.; Osa, T. *Anal. Chem.* **1990**, *62*, 2461. (e) Ueno, A.; Suzuki, M.; Fukushima, M.; Ohkubo, M.; Osa, T.; Hamada, F.; Murai, K. *Chem. Lett.* **1990**, 605. (f) McAlpine, S. R.; Garibay, M. A. G. *J. Am. Chem. Soc.* **1996**, *118*, 2750. (g) Hubbard, B. K.; Beisltein, L. A.; Heath, C. E.; Abelt, C. J. *J. Chem. Soc.*,

Perkin Trans. 2 **1996**, 1005. (h) Ito, N.; Yoshida, N.; Ichikawa, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 965. (i) Bibeau, C. T.; Hubbard, B. K.; Abelt, C. *J. Chem. Commun.* **1997**, 437. (j) Narita, A.; Hamada, F.; Suzuki, I.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2751. (k) Pagliari, S.; Corradini, R.; Galaverna, G.; Sforza, S.; Dossena, A.; Marchelly, R. *Tetrahedron Lett.* **2000**, *41*, 3691. (l) Narita, M.; Koshizaka, S.; Hamada, F. *J. Inclusion Phenom.* **1999**, *35*, 605. (m) Sato, M.; Narita, M.; Ogawa, N.; Hamada, F. *Anal. Sci.* **1999**, *15*, 1199.

8. (a) Eddaoudi, M.; Lopez, H.-P.; De Lamotte, S. F.; Ficheux, D.; Prognon, P.; Coleman, A. W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1771. (b) Matsumura, S.; Sakamoto, S.; Ueno, A.; Mihara, H. *Chem. Eur. J.* **2000**, *6*, 1781.
9. (a) Bissel, R. A.; De Silva, A. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1148. (b) Mortellaro, M. A.; Hartmann, W. K.; Nocera, D. G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1945. (c) Nelissen, H. F. M.; Schut, A. F. J.; Venema, F.; Feiters, M. C.; Nolte, R. J. M. *Chem. Commun.* **2000**, 577.
10. (a) Woisel, P.; Lehaire, M. L.; Surpateanu, G. *Tetrahedron* **2000**, *56*, 377. (b) Woisel, P.; Surpateanu, G.; Delattre, F.; Bria, M. *Eur. J. Org. Chem.* **2001**, 1407. (c) Woisel, P.; Surpateanu, G. G.; Surpateanu, G. *Targets Heterocycl. Chem.* **2001**, *5*, 261. (d) Badea, I.; Surpateanu, G. G.; Woisel, P.; Vergoten, G.; Surpateanu, G. G. *New J. Chem.* **2002**, *26*, 1658.
11. Defaye, J.; Crouzy, S.; Evrard, N.; Law, H. PCT Int. WO 99-FR1217, **1999**; *Chem. Abstr.* **1999**, *130*, 764078.
12. Hamasaki, A.; Ikeda, H.; Nakamura, A.; Ueno, A.; Toda, F.; Susuki, I.; Osa, T. *J. Am. Chem. Soc.* **1993**, *115*, 5035.
13. Meyer, A. G.; Easton, C. J.; Lincoln, S. F.; Simpson, G. W. *J. Org. Chem.* **1998**, *63*, 9069.
14. Bialecka-Florjanczyk, E. *Synth. Commun.* **2000**, *30*, 4417.
15. Krönke, F. *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 1177.
16. (a) Depature, L. PhD Thesis, University of Littoral Côte d'Opale, 2002. (b) Druta, I.; Avram, E.; Cozan, V. *Eur. Polym. J.* **2000**, *36*, 221.
17. Schneider, H.-J.; Hacket, F.; Rüdiger, V.; Ikeda, I. *Chem. Rev.* **1998**, *98*, 1755.

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Synthesis of periphery-functionalized dendritic polyethers

Enrique Díez-Barra,* Raquel González, Prado Sánchez-Verdú and Juan Tolosa

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Campus Universitario, Universidad de Castilla-La Mancha, 13071 Ciudad Real, Spain

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Abstract—New dendritic polyethers with bromo-, hydroxy- and vinyl-end groups have been synthesized by a convergent strategy. Planar, 1,3,5-trischlorocarbonylbenzene and 1,3,5-trihydroxybenzene, and tetrahedral, tetrakis(*p*-hydroxyphenyl)methane, cores have been used.

1. Introduction

The synthesis and applications of new dendrimeric structures have been the focus of several research teams. Synthetic methodologies, involving convergent[1] and divergent[2] routes have been reviewed.[3] Other strategies involving 'hypermonomers',[4] exponential[5] and orthogonal[6] growth, and 'activated' monomers[7] have also been reported.

Polyether backbones have been widely used for preparing dendritic architectures by Fréchet's convergent strategies.[8] 3,5-Dihydroxybenzyl alcohol has been used as keystone for preparing a large number of dendrons and dendrimers via the iterative use of the Williamson reaction.

Modification of functional groups on the periphery of a dendritic structure offers a convenient route to new dendrimers with a structure of the external generation different from that of the first generations. This approach has been mainly used for preparing dendrimers with catalytically active centers on the periphery.[9]

This work aims at the synthesis of new periphery-functionalized dendritic polyethers having planar and tetrahedral cores.

The versatile hydroxy-, bromo- and vinyl groups have been chosen as peripheral groups and 1,3,5-trischlorocarbonyl benzene, **1**, 1,3,5-trihydroxybenzene, **2**, and tetrakis-(*p*-hydroxyphenyl) methane, **3** have been selected as cores. Core **1** has been widely used in dendrimer synthesis. Core **2** has been used only in few occasions. Chow[10] reported in 1996 the reaction of **2** with 1,3-dibromopropane to prepare polyether dendrons with a hydroxy group as focal point. In 1997, he also reported the use of 5-benzyloxy-resorcinol to built dendrimers derived from core **2**.[11] In 2002, the transformation of **2** in a extended core by reaction with 1,5-dibromopentane was described.[12] In all these papers, the dendritic growth was effected by a Williamson reaction. Also in 1996 was reported the use of **2** as core and a focal-pointed carboxyl dendron.[13] In 2002, dendrons having chlorocarbonyl as focal point have been connected to **2**.[14] The tetrahedral core **3** was used for the first time in this work.

2. Results

Figure 1 shows the hydroxy-(**A**) and bromo-(**B**) dendrons used in this work. **A**-type dendrons were prepared by reacting the appropriate benzyl halides with 3,5-dihydroxybenzyl alcohol. **B**-type dendrons were prepared by reacting **A**-type dendrons with Br_4C/Ph_3P. In the case of **7B**, these reaction conditions provoked the deprotection of phenolic hydroxy groups. Dendron **7B** was conveniently prepared by mesylation of **7A** followed by reaction with sodium bromide.

Benzyl halides were reacted with 3,5-dihydroxybenzyl alcohol in acetone/K_2CO_3 to give the corresponding **A**-dendrons. Commercial benzyl bromide, *p*-bromobenzyl bromide and *p*-vinylbenzyl chloride were used without further purification. Although the synthesis of **7A** by reduction of methyl 3,5-bis(*tert*-butyldimethylsilyloxy)-benzoate with HLA had been reported,[15] we prepared **7A** by a two-step sequence involving the protection of the three hydroxy groups of 3,5-dihydroxybenzyl alcohol with *tert*-butyldimethylsilyl chloride followed by selective deprotection of the benzylic hydroxy group with Oxone®. This procedure followed a recent communication[16] describing a similar cleavage on less functionalized *tert*-butyldimethylsilyl ethers. Dendron **8A** was prepared as described in Scheme 1. Hydroquinone was sequentially

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* Corresponding author. Tel.: +34-926295337; fax: +34-926295318; e-mail address: enrique.diez@uclm.es

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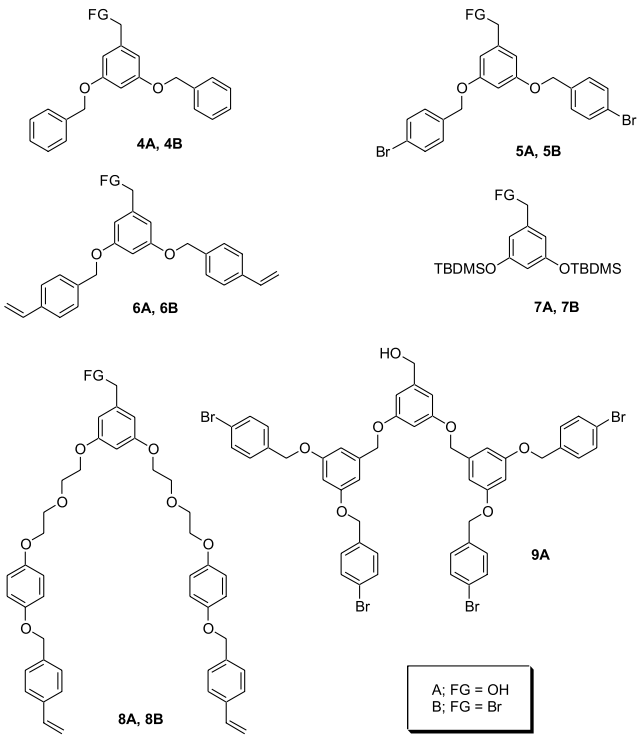
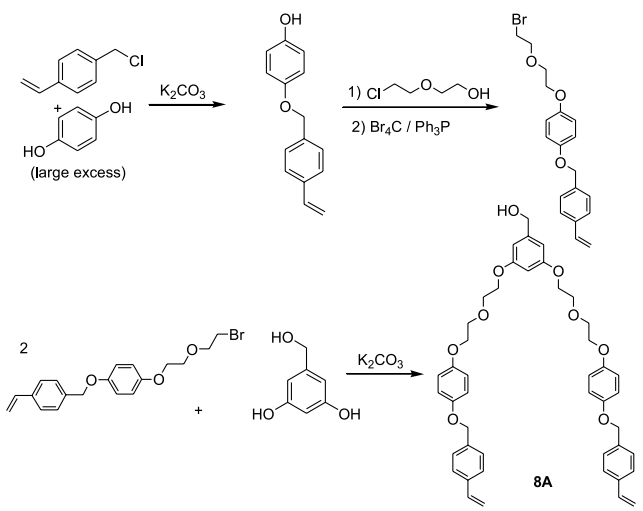


Figure 1. Hydroxy-(**A**) and bromo-(**B**) dendrons used in this work.

O,*O*-disubstituted by reactions with *p*-vinylbenzyl chloride and 2-chloroethyloxyethanol. Reaction with Br_4C/Ph_3P yielded the corresponding bromide, which was reacted with 3,5-dihydroxybenzyl alcohol giving **8A**.

Reactions of type-**A** dendrons with core **1** yielded dendrimers with ester connectivity. Esterification was performed in the presence of 4-dimethylaminopyridine following a standard procedure.[17] Dendrimer **10** was deprotected by hydrogenation yielding a new hypercore bearing six hydroxy groups **11**. Dendrimer **12** having peripheral *p*-bromophenyl groups could be useful to prepare differently substituted dendrimers.[18] Dendrimers **13** and **14** having peripheral vinyl groups are useful cross-linker in polymerization.[19] Attempts to deprotect dendrimer **15** failed probably as a result of competitive oxidation processes.



Scheme 1. Preparation of dendron **8A**.

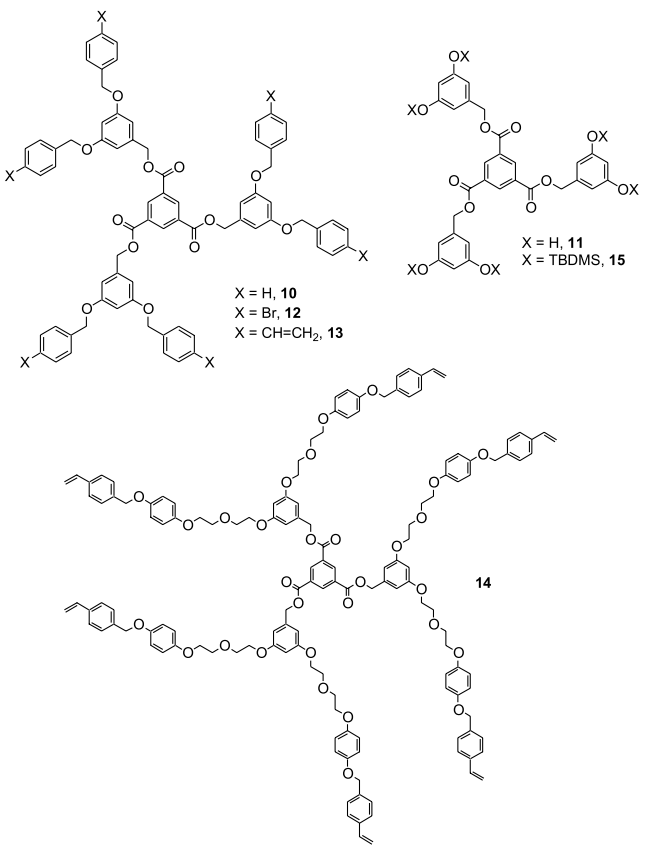


Chart 1. Periphery-functionalized dendrimers with 1,3,5-tris(oxycarbonyl) benzene **1** as core.

However, this dendrimer could be considered as a latent form of the hydroxylic hypercore **11**. Deprotection with KF followed by reaction with benzyl bromides in a one-pot procedures has been reported for related compounds.[20]

Connections to core **2** have been usually achieved by Williamson's reactions. We have also tested the Mitsunobu reaction. Results were satisfactory for small dendrons (**5A** and **7A**) but the reaction failed with a larger dendron **8A** or a second generation dendron **9A**. Dendrimers **16** and **17** were also prepared by Mitsunobu reactions (Chart 1).

It is known that peripheral *p*-bromo substituted dendrimers can be used for preparing new dendrimers.[18] Thus, dendrimer **16** was reacted with *n*-butyllithium to give the

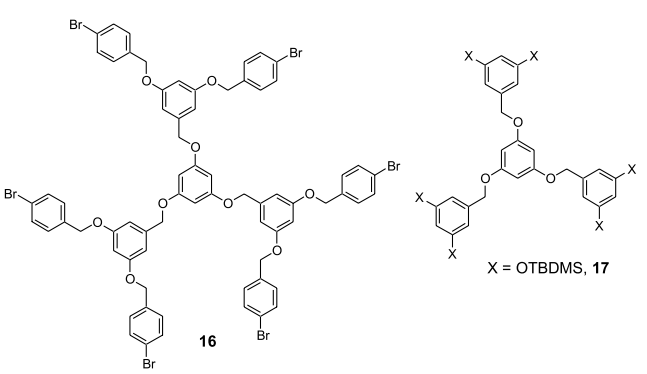


Chart 2. Pheriphery-functionalized dendrimers with phoroglucinol (1,3,5-trihydroxybenzene) **2** as core.

Table 1. Chemical shifts (δ, ppm) for benzylic methylenes

Compound	**6A**	**7A**	**8A**	**9A**	**6B**	**8B**
GF-CH_2[a]	4.62	4.56	4.60	4.61	4.41	4.38
End-CH_2[b]	5.02	–	4.99	4.96	5.02	4.99
Compound	**10**	**11**	**12**	**13**	**14**	**15**
GF-CH_2[a]	5.34	5.30	5.35	5.33	5.28	5.28
End-CH_2[b]	5.01	–	4.97	5.00	4.97	–
Compound	**16**	**17**	**18**	**19**		
GF-CH_2[a]	4.93	4.88	4.95	4.91		
End-CH_2[b]	4.97	—	5.02	4.96		

[a] Methylene close to the focal point or the core.
[b] Methylene close to the periphery.

dendritic hexa-anion as shown by a reaction with chlorotrimethylsilane. ^{1}H NMR spectra showed the complete substitution on the peripheral six phenyl rings. Dendrimer **17** can be considered as a latent hydroxylic core (Chart 2).

Core **3** was prepared from the corresponding tetraamino derivative[21] by reaction with $NaNO_2/H_2SO_4$ followed by hydrolysis of the tetradiazonium salt. Attempts to apply the Mitsunobu conditions to dendron **6A** failed. Dendrons **6B** and **8B** were reacted with core **3** following the standard procedure (K_2CO_3/acetone). Dendrimers **18** and **19** are also useful molecules for preparing polymeric support.

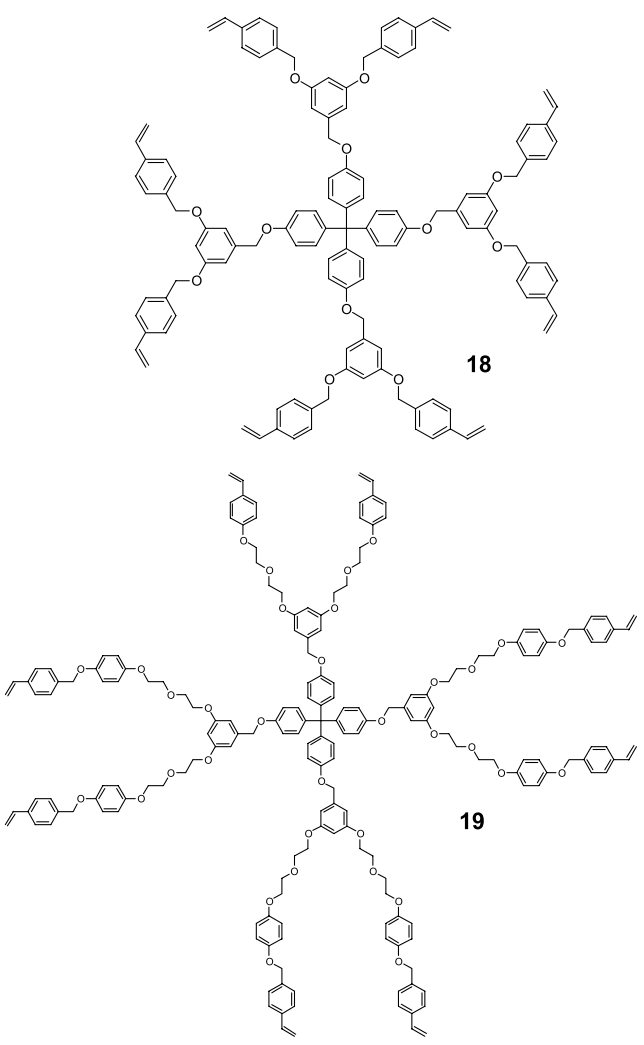


Chart 3. Peryphery-functionalized dendrimers with tetrakis(*p*-hydroxyphenyl)methane **3** as core.

The characterization of all new compounds have been performed by HRMS (except dendrimers) and ^{1}H and ^{13}C NMR and their chemical shifts are indicated in Section 3. The signals of the different benzylic methylene groups (Table 1) are significant and have been used for verify both the completion of the reactions and, the purity (>95%) of the dendrimers (Chart 3).

In conclusion, new hydroxy-, bromo- and vinyl end-capped dendritic polyethers have been prepared. Both ester and ether connectivities have been employed. Ether connectivity of small dendrons has been successfully performed under Mitsunobu reaction conditions. The tetrahedral core tetrakis(*p*-hydroxyphenyl) methane have been used for the first time.

3. Experimental

3.1. General considerations

All starting materials were purchased from Aldrich chemical Co. and Acros and were used without further purification. The following chemicals were prepared according to literature procedures: 3,5-bis(benzyloxy)-benzyl alcohol (**4A**),[1] 3,5-bis(benzyloxy)benzyl bromide (**4B**),[1] 3,5-bis(*p*-bromophenylmethyloxy)benzyl alcohol (**5A**),[22] 3,5-bis(*p*-bromophenylmethyloxy)benzyl bromide (**5B**)[22] and 3,5-bis[3,5-bis(*p*-bromophenylmethyloxy)phenyl-methyloxy] benzyl alcohol (**9A**).[22] All solvents used for extractions or reactions were dried according to standard procedures and kept over molecular sieves. Flash chromatography was run on 230–400 mesh silica-gel (Merck). NMR spectra were recorded in $CDCl_3$ using a VARIAN UNITY 300 spectrometer operating at 299.980 MHz for proton and 75.423 MHz for carbon-13 at a temperature of 293 K. Mass spectrometry was performed at the SIDI (Universidad Autónoma of Madrid).

3.1.1. Tetrakis(*p*-hydroxyphenyl)methane (3). Tetrakis-(*p*-aminophenyl)methane[21] (760 mg, 2 mmol) was placed in 20 mL of water and sulfuric acid (98%) was added dropwise until complete dissolution of the reactive. The reaction was then cooled to 0 °C and a solution of sodium nitrite (610 mg, 8.8 mmol) in 10 mL of water was added dropwise. The reaction mixture was stirred for 15 min. A solution of concentrated sulfuric acid (0.5 mL) in water (10 mL) was added and the reaction heated at 50 °C for 2 h. The solution was extracted with ethyl acetate (20 mL×3) and the combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography (ethyl acetate). The desired compound was obtained as a brown solid after crystallization from methanol/chloroform. Mp: >270 °C. Yield 32%. ^{1}H NMR, δ (d_6-DMSO): 9.26 (s, 4H); 6.84 and 6.80 (d, 8H, A_2 of A_2B_2 system, J=8 Hz); 6.60 and 6.40 (d, 8H, B_2 of A_2B_2 system, J=8 Hz). ^{13}C NMR, δ (d_6-DMSO): 154.6, 137.8, 131.2, 114.0 and 61.4. MS (EI), *m*/*z*: 384 (M^+). HRMS, calcd for $C_{25}H_{20}O_4$ 384.1362, found 384.1382.

3.2. Preparation of dendrons

3.2.1. 3,5-Bis(*p*-vinylphenylmethyloxy)benzyl alcohol (6A). A mixture of 3,5-dihydroxybenzyl alcohol (1.4 g, 10 mmol), 4-vinylbenzyl chloride (3.2 g, 21 mmol), potassium carbonate (3.0 g, 22 mmol) and Aliquat 336 (5 mol%) in 35 mL of acetone was placed in a 100 mL round-bottom flask fitted with a condenser reflux. The reaction was heated for 12 h at 80 °C. Inorganic salts and Aliquat 336 were carried out by filtration over Florisil®, the solvent was evaporated and the crude product was crystallized in ethyl acetate/hexane as a white solid. Mp: 63–5 °C. Yield 90%. ^{1}H NMR, δ: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, J=8 Hz); 7.38 and 7.34 (d, 4H, B_2 of A_2B_2 system, J=8 Hz); 6.72 (dd, 2H, J_{trans}=18 Hz, J_{cis}=11 Hz); 6.61 (d, 2H, J=2 Hz); 6.53 (t, 1H, J=2 Hz); 5.76 (dd, 2H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.26 (dd, 2H, J_{gem}=1 Hz, J_{cis}=11 Hz); 5.02 (s, 4H); 4.62 (s, 2H). ^{13}C NMR, δ: 160.6, 143.9, 137.9, 136.9, 128.2, 126.9, 114.6, 112.8, 106.3, 101.9, 70.4 and 65.8. MS (EI), *m*/*z*: 372 $(M)^+$HRMS, calcd for $C_{25}H_{24}O_3$ 372.1725, found 372.1712.

3.2.2. 3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl alcohol (7A).[15] In a 250 mL round-bottomed flask, *O,O,O*-tris-(*tert*-butyldimethylsilyloxy)benzyl alcohol (490 mg, 1 mmol) was dissolved in ethanol (80 mL) and a solution of Oxone® (614 mg, 1 mmol) in the minimum amount of water was added dropwise. The reaction was stirred at room temperature. The reaction was monitored by GC to fix the reaction time (4 h) avoiding higher level of deprotection. Inorganic salts were filtered off and the ethanol was evaporated. Water (25 mL) was added and the reaction was extracted with ethyl acetate (25 mL×3). The organic layer was dried over $MgSO_4$, and the solvent was evaporated after filtration. The crude product was purified by column chromatography (hexane/ethyl acetate 5:1). Mp: 45–6 °C. Yield 52%. ^{1}H NMR, δ: 6.46 (d, 2H, J=2 Hz); 6.26 (t, 1H, J=2 Hz); 4.56 (s, 2H); 0.97 (s, 9H); 0.19 (s, 6H). ^{13}C NMR, δ: 156.5, 111.7, 111.1, 94.4, 65.2, 25.8, 18.3 and −4.2. MS (EI), *m*/*z*: 368 (M^+).

3.2.3. 3,5-Bis(*p*-vinylphenylmethyloxy-*p*-phenyloxyethyleneoxyethylenoxy)benzyl alcohol (8A). A mixture of 1,4-(bromoethyleneoxyethyleneoxy), (*p*-vinylphenyloxymethyloxy)benzene (1.0 g, 2.65 mmol), KOH (154 mg, 2.70 mmol), 3,5-dihydroxybenzyl alcohol (180 mg, 1.07 mmol) and tetrabutyl ammonium bromide (TBAB) (9 mol%) was heated without solvent for 24 h at 80 °C. Ethyl acetate (20 mL) was added, the inorganic salts were filtered off and the solvent was evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate 1:1). The desired compound was obtained as a white solid after crystallization from ethanol. Mp: 105–7 °C. Yield 68%. ^{1}H NMR, δ: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, J=8 Hz); 7.39 and 7.35 (d, 4H, B_2 of A_2B_2 system, J=8 Hz); 6.91–6.81 (m, 8H); 6.72 (dd, 2H, J_{trans}=18 Hz, J_{cis}=11 Hz); 6.53 (d, 2H, J=2 Hz); 6.43 (t, 1H, J=2 Hz); 5.75 (dd, 2H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.25 (dd, 2H, J_{gem}=1 Hz, J_{cis}=11 Hz); 4.99 (s, 4H); 4.60 (s, 2H); 4.07–4.15 (m, 8H); 3.92–3.86 (m, 8H). ^{13}C NMR, δ: 160.1, 153.1, 143.3, 137.3, 136.8, 136.5, 127.7, 126.4, 115.8, 115.7, 114.0, 105.6, 100.9, 99.4, 70.4, 70.0, 69.9, 68.2, 67.6 and 65.3. MS (EI), *m*/*z*: 732 $(M)^+$HRMS, calcd for $C_{45}H_{48}O_9$ 732.3298, found 732.3329.

3.2.4. 4-(*p*-Vinylphenylmethyloxy)phenol. A mixture of 1,4-hydroquinone (8.8 g, 80 mmol), 4-vinylbenzyl chloride (3.0 g, 20 mmol), potassium carbonate (2.8 g, 20 mmol) and Aliquat 336 (2 mmol) in acetone (75 mL) was placed in a 250 mL round-bottomed flask fitted with a condenser reflux. The reaction mixture was heated for 24 h at 80 °C. The inorganic salts were filtered off and the solvent was evaporated. Chloroform (75 mL) was added to precipitate the excess of 1,4-hydroquinone, which was removed together with the Aliquat 336 by filtration over Florisil. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate, 9:1). Mp: 143–4 °C (ethyl acetate/hexane). Yield 62%. ^{1}H NMR, δ: 7.44 and 7.41 (d, 2H, A_2 of A_2B_2 system, J=8 Hz); 7.39 and 7.36 (d, 2H, B_2 of A_2B_2 system, J=8 Hz); 6.87–6.67 (m, 5H); 5.75 (dd, 1H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.25 (dd, 2H, J_{gem}=1 Hz, J_{cis}=11 Hz); 4.99 (s, 2H). ^{13}C NMR, δ: 153.0, 149.7, 137.3, 136.8, 136.5, 127.7, 126.4, 116.1, 114.0 and 70.5. MS (EI), *m*/*z*: 226 $(M)^+$HRMS, calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.1009.

3.2.5. 1-(Hydroxyethyleneoxyethyleneoxy)-4-(*p*-vinylphenyloxymethyloxy)benzene. A mixture of 4-(*p*-vinylphenylmethyloxy)phenol (2.3 g, 10 mmol), KOH (840 mg, 15 mmol), 2-(2-chloroethoxy)ethanol (1.5 g, 12 mmol) and TBAB (9 mol%) was heated without solvent for 32 h at 80 °C. Acetone was added and the inorganic salts were filtered off. The crude product was purified by column chromatography (hexane/ethyl acetate, 3:1); when the undesired products were carried out, ethyl acetate was used as eluent. The product was obtained as a white solid. Mp: 100–1 °C. Yield 60%. ^{1}H NMR, δ: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, J=8 Hz); 7.39 and 7.35 (d, 4H, B_2 of A_2B_2 system, J=8 Hz); 6.91–6.81 (m, 4H); 6.72 (dd, 2H, J_{trans}=18 Hz, J_{cis}=11 Hz); 5.75 (dd, 2H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.25 (dd, 2H, J_{gem}=1 Hz, J_{cis}=11 Hz); 5.00 (s, 2H); 4.09 (t, 2H, J=4 Hz); 3.83 (t, 2H, J=4 Hz); 3.74 (t, 2H, J=4 Hz); 3.68 (t, 2H, J=4 Hz). ^{13}C NMR, δ: 153.2, 153.0, 137.3, 136.8, 136.5, 127.7, 126.4, 115.9, 115.7, 114.0, 72.5, 70.4, 69.8, 68.1 and 61.8. MS (EI), *m*/*z*: 314 $(M)^+$HRMS, calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1541.

3.2.6. 1,4-(Bromoethyleneoxyethyleneoxy)(*p*-vinylphenyloxymethyloxy)benzene. In a previously flamed Schlenk tube was placed carbon tetrabromide (5.1 g, 15 mmol), 1,4-(hydroxyethyleneoxyethyleneoxy),(*p*-vinylphenyloxymethyloxy)benzene (1.3 g, 4 mmol) and triphenylphosphine (4.0 g, 15 mmol); dry THF was added (20 mL) and the mixture was stirred at room temperature under Ar atmosphere for 4 h. Triphenylphosphonium oxide formed was filtered off and the solvent was evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate, 8:1). For further purification the product was crystallized from ethanol. Mp: 72–4 °C. Yield 87%. ^{1}H NMR, δ: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, J=8 Hz); 7.39 and 7.35 (d, 4H, B_2 of A_2B_2 system, J=8 Hz); 6.91–6.81 (m, 4H); 6.72 (dd, 2H, J_{trans}=18 Hz, J_{cis}=11 Hz); 5.75 (dd, 2H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.25 (dd, 2H, J_{gem}=1 Hz, J_{cis}=11 Hz); 5.00 (s, 2H); 4.09 (t, 2H, J=4 Hz); 3.91–2.82 (m, 4H); 3.49 (t, 2H, J=6 Hz). ^{13}C NMR, δ:

153.2, 153.0, 137.3, 136.8, 136.5, 127.7, 126.4, 115.9, 115.7, 114.0, 71.4, 70.4, 69.8, 68.2 and 30.2. MS (EI), *m/z*: 376 $(M)^+$, 378 $(M+2)^+$HRMS, calcd for $C_{19}H_{21}BrO_2$ 376.0674, found 376.0651and 378.0670.

3.2.7. 3,5-Bis(*p*-vinylphenylmethyloxy)benzyl bromide (6B). To a solution of **6A** (1.0 g, 2.7 mmol) in the minimum amount of dry THF (10 mL), carbon tetrabromide (1.2 g, 3.38 mmol) and triphenylphosphine (880 mg, 3.38 mmol) were added. The mixture was stirred at room temperature for 20 min. Water (20 mL) was added and the aqueous layer was extracted with methylene chloride (20 mL×3). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (hexane/ethyl acetate, 3:1) to give the pure product as a white solid. Mp: 78–9 °C. Yield 65%. ^{1}H NMR, δ: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, J=8 Hz); 7.38 and 7.34 (d, 4H, B_2 of A_2B_2 system, J=8 Hz); 6.72 (dd, 2H, J_{trans}=18 Hz, J_{cis}=11 Hz); 6.61 (d, 2H, J=2 Hz); 6.53 (t, 1H, J=2 Hz); 5.76 (dd, 2H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.26 (dd, 2H, J_{gem}=1 Hz, J_{cis}= 11 Hz); 5.02 (s, 4H); 4.41 (s, 2H). ^{13}C NMR, δ: 159.8, 139.6, 137.3, 136.3, 136.0, 127.6, 126.3, 114.1, 108.2, 102.2, 70.0 and 33.6. MS (EI), *m/z*: 434 $(M)^+$, 436 $(M+2)^+$HRMS, calcd for $C_{25}H_{23}BrO_2$ 434.0881, found 434.0894 and 436.0861 (M+2).

3.2.8. 3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl bromide (7B). In a previously flamed Schlenk tube a solution of **7A** (1.104 g, 3 mmol) in dry dichloromethane (15 mL) and dry triethylamine (455 mg, 4.5 mmol) was placed, the mixture was cooled to 0 °C under argon atmosphere. Methanesulfonyl chloride (412 mg, 3.6 mmol) was added dropwise and the reaction was stirred for 30 min. Then, a solution of LiBr (2.60 g, 30 mmol) in dry acetone (17 mL) was added and the reaction was stirred at RT for 3 h. Inorganic salts were filtered off over Celite® 545 and the solvent was evaporated. 15 mL of diethyl ether was added to precipitate the excess of LiBr which was filtered off. The solvent was evaporated and the pure product was isolated as a white solid. Mp: 40–1 °C. Yield 73%. ^{1}H NMR, δ: 6.44 (d, 2H, J=2 Hz); 6.21 (t, 1H, J=2 Hz); 4.30 (s, 2H); 0.93 (s, 18H); 0.15 (s, 12H). ^{13}C NMR, δ: 156.3, 111.5, 111.0, 94.6, 34.0, 25.8, 18.3, −4.2. MS (EI), *m/z*: 430 $(M)^+$, 432 $(M+2)^+$. HRMS, calcd for $C_{13}H_{23}Si_2O_2$ 346.0420, found 346.0448 and 348.0457 (M+2).

3.2.9. 3,5-Bis(*p*-vinylphenylmethyloxy-*p*-phenyloxyethyleneoxyethyleneoxy)benzyl bromide (8B). To a solution of **8A** (2.9 g, 4 mmol) in the minimum amount of dry THF, carbon tetrabromide (1.7 g, 5 mmol) and triphenylphosphine (1.3 g, 5 mmol) were added. The mixture was stirred at room temperature for 20 min. Water (20 mL) was added and the aqueous layer was extracted with methylene chloride (20 mL×3). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (chloroform) to give the pure product as a white solid. Mp: 66–8 °C. Yield 63%. ^{1}H NMR, δ: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, J=8 Hz); 7.38 and 7.34 (d, 4H, B_2 of A_2B_2 system, J=8 Hz); 6.91–6.81 (m, 8H); 6.72 (dd, 2H, J_{trans}=18 Hz, J_{cis}=11 Hz); 6.53 (d, 2H, J=2 Hz); 6.43 (t, 1H, J=2 Hz); 5.75 (dd, 2H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.25 (dd, 2H, J_{gem}=1 Hz, J_{cis}=11 Hz); 4.99 (s, 4H); 4.38 (s, 2H); 4.15–4.07 (m, 8H); 3.92–3.86 (m, 8H). ^{13}C NMR, δ: 160.1, 153.3, 139.9, 137.5, 137.1, 136.7, 127.9, 126.7, 116.2, 116.0, 114.3, 108.4, 105.9, 102.2, 70.9, 70.5, 70.2, 68.6, 68.1 and 34.0. HRMS (L-SIMS), *m/z* calcd for $C_{45}H_{47}BrO_8$ 794.2454, found 794.2441 $(M+H)^+$and 796.2456 $(M+H+2)^+$.

3.3. Preparation of dendrimers

General procedure for dendrimers with ester connectivity. In a previously flamed Schlenk tube, equimolar amounts of the corresponding dendron and 4-dimethylaminopyridine under Ar atmosphere were dissolved in dry dichloromethane (3 mL/mmol). 1,3,-benzenetricarboxylic acid chloride (33 mol%) was added dropwise. The reaction was stirred at room temperature for 4 h. The 4-dimethylaminipyridium chloride formed was filtered off and the solvent was evaporated. Pure products were purified as indicated below.

3.3.1. 3,5-Bis(phenylmethyloxy)phenylmethyl 1,3,5-benzenetricarboxylate (10). The pure product was obtained as a with solid after crystallization from ethyl acetate/hexane. Mp: 112–4 °C. Yield 1.83 g, 94%. ^{1}H NMR, δ: 8.90 (s, 3H); 7.41–7.28 (m, 30H); 6.68 (t, 3H, J=2 Hz); 6.58 (t, 3H, J=2 Hz); 5.34 (s, 6H); 5.01 (s, 12H). ^{13}C NMR, δ: 164.7, 160.1, 137.7, 136.6, 134.9, 131.2, 128.6, 128.0, 127.5, 107.3, 102.0, 70.1 and 67.2. MS (MALDI-TOF), *m/z*: 1139.3 $(M+Na)^+$.

3.3.2. 3,5-Bis(*p*-bromophenylmethyloxy)phenylmethyl 1,3,5-benzenetricarboxylate (12). The pure product was obtained as a white solid after crystallization from ethyl acetate/hexane. Mp: 149–51 °C. Yield 842 mg, 95%. ^{1}H NMR, δ: 8.90 (s, 3H); 7.47 and 7.45 (d, 12H, A_2 of A_2B_2 system, J=8 Hz); 7.26 and 7.24 (d, 12H, B_2 of A_2B_2 system, J=8 Hz); 6.65 (d, 6H, J=2 Hz); 6.51 (t, 3H, J=2 Hz); 5.35 (s, 6H); 4.97 (s, 12H). ^{13}C NMR, δ: 164.4, 159.6, 137.7, 135.5, 134.7, 131.5, 131.0, 128.9, 121.8, 107.3, 102.0, 69.3 and 67.1. MS (MALDI-TOF)), *m/z*: 1612.9 $(M+Na+6)^+$(100), 1614.9 $(M+H+8)^+$(86).

3.3.3. 3,5-Bis(*p*-vinylphenylmethyloxy)phenylmethyl 1,3,5-benzenetricarboxylate (13). The pure product was obtained as a white solid after crystallization from ethyl acetate/hexane. Mp: 113–5 °C. Yield 1.36 g, 90%. ^{1}H NMR, δ: 8.90 (s, 3H); 7.39 and 7.36 (d, 12H, A_2 of A_2B_2 system, J=8 Hz); 7.35 and 7.32 (d, 12H, B_2 of A_2B_2 system, J=8 Hz); 6.73–6.63 (m, 12H); 6.56 (t, 3H, J=2 Hz); 5.72 (dd, 6H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.33 (s, 6H); 5.23 (dd, 6H, J_{gem}=1 Hz, J_{cis}=11 Hz); 5.00 (s, 12H). ^{13}C NMR, δ: 167.6, 160.1, 137.7, 136.4, 136.1, 134.9, 131.2, 127.7, 126.4, 114.1, 107.3, 102.1, 69.9 and 67.2. MS (MALDI-TOF), *m/z*: 1295.5 $(M+Na)^+$.

3.3.4. 3,5-Bis(*tert*-butyldimethylsilyloxy)benzyl 1,3,5-benzene tricarboxylate (15). The crude of the reaction was dissolved in CH_2Cl_2 (20 mL) and washed with water (15 mL x 3). The organic layer was dried over $MgSO_4$ and filtered over silica to remove the excess of DMAP. After evaporation of the solvent the pure product was isolated as a white solid. Mp: 91–3 °C. Yield 73%. ^{1}H NMR, δ: 8.89 (s, 3H) 6.53 (d, 6H, J=2 Hz); 6.29 (t, 3H, J=2 Hz); 5.28 (s, 6H); 0.96 (s, 54H); 0.18 (s, 36H). ^{13}C NMR, δ: 164.7,

156.7, 137.4, 134.8, 131.4, 113.3, 112.1, 67.2, 26.0, 18.5 and −4.0. MS (MALDI-TOF), *m/z*: 1283.3 $(M+Na)^+$.

3.3.5. 3,5-Bis(*p*-vinylphenylmethyloxy-*p*-phenyloxyethylene-oxyethyleneoxy)phenylmethyl 1,3,5-benzenetricarboxylate (14). The pure product was obtained after crystallization from dichloromethane/ethanol. Mp: 52–5 °C. Yield 413 mg, 63%. ^{1}H NMR, δ: 8.87 (s, 3H); 7.43 and 7.39 (d, 12H, A_2 of A_2B_2 system, J=8 Hz); 7.37 and 7.33 (d, 12H, B_2 of A_2B_2 system, J=8 Hz); 6.73 (dd, 6H, J_{cis}=11 Hz, J_{trans}=18 Hz); 6.59 (d, 6H, J=2 Hz); 6.48 (t, 3H, J=2H); 5.74 (dd, 6H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.28 (s, 6H); 5.25 (dd, 6H, J_{gem}=1 Hz, J_{cis}=11 Hz); 4.97 (s, 12H); 4.09 (m, 24H); 3.87 (m, 24H). ^{13}C NMR, δ: 164.6, 160.1, 153.1, 137.6, 137.2, 136.8, 136.4, 134.9, 131.2, 127.6, 126.3, 115.8, 115.6, 114.0, 107.1, 101.6, 99.4, 70.4, 70.0, 69.8, 68.1, 67.6 and 67.2. MS (MALDI-TOF), *m/z*: 2375.7 $(M+Na)^+$.

3.3.6. (3,5-Dihydroxyphenyl)methyl 1,3,5-benzenetricarboxylate (11). 3,5-Bis(phenylmethyloxy)phenylmethyl 1,3,5-benzenetricarboxylate (1.1 g, 1 mmol) and palladium over carbon (6 mol%) was suspended in dimethoxyethane (20 mL) and the reaction mixture was stirred at room temperature under H_2 atmosphere until the expected volume of H_2 was consumed. Palladium over carbon was filtered off over Celite 545® and the solvent was evaporated. The pure product was obtained as a pale brown solid. Mp: 226–8 °C. Yield 100%. ^{1}H NMR, δ (d_6-DMSO): 8.85 (s, 3H); 6.48 (d, 6H, J=2 Hz); 6.33 (t, 3H, J=2H); 5.30 (s, 6H); 3.17 (s, 6H). ^{13}C NMR, δ (d_6-DMSO): 165.1, 159.6, 138.8, 134.7, 132.4, 107.2, 103.3 and 67.8. MS (FAB^+), *m/z*: 576 (M^+).

3.3.7. General procedure for dendrimers with ether connectivity (Williamson conditions). 3B or **5B** (4.2 mmol), **3** (384 mg, 1 mmol), 18-crown-6 (10% mol), potassium carbonate (580 mg, 4.2 mmol) and acetone (20 mL) were placed in a round-bottomed flask, and the reaction mixture was heated at 70 °C for 24 h. The solvent was evaporated and 20 mL of water were added. The reaction was extracted with chloroform (20 mL×3).

3.3.8. Tetrakis[(3,5-bis(*p*-vinylphenylmethyloxy)phenylmethyloxyphenyl]methane (18). After column chromatography (chloroform) the pure product was obtained as a pale brown solid. Mp: 78–80 °C. Yield 954 mg, 53%. ^{1}H NMR, δ: 7.43 and 7.40 (d, 16H, A_2 of A_2B_2 system, J= 8 Hz); 7.38 and 7.35 (d, 16H, B_2 of A_2B_2 system J=8 Hz); 6.84 and 6.80 (d, 8H, A_2 of A_2B_2 system, J=8 Hz), from 6.72–6.60 (m, 24H); 6.53 (t, 4H, J=2 Hz); 5.76 (dd, 8H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.26 (dd, 8H, J_{gem}=1 Hz, J_{cis}=11 Hz); 5.02 (s, 16H); 4.95 (s, 8H). ^{13}C NMR, δ: 159.8, 156.5, 139.9, 139.6, 137.3, 136.3, 136.0, 131.7, 127.6, 126.3, 114.1, 113.8, 108.2, 102.2, 70.6, 70.0 and 61.6. MS (MALDI-TOF), *m/z*: 1823.8 $(M+Na)^+$.

3.3.9. Tetrakis[(3,5-bis(*p*-vinylphenylmethyloxy-*p*-phenyloxyethyleneoxyethyleneoxy)phenylmethyloxyphenyl] methane (19). After column chromatography (chloroform) the pure product was obtained as a pale yellow solid. Mp: 62–4 °C. Yield 1.4 g, 43%. ^{1}H NMR, δ: 7.44 and 7.40 (d, 16H, A_2 of A_2B_2 system, J=8 Hz); 7.38 and 7.34 (d, 16H, B_2 of A_2B_2 system, J=8 Hz), 7.05 (d, 8H, A_2 of A_2B_2 system (core), J=8 Hz); 6.86–6.63 (m, 48H); 6.58 (d, 8H, J=2 Hz); 6.44 (t, 4H, J=2 Hz); 5.75 (dd, 8H, J_{gem}=1 Hz, J_{trans}=18 Hz); 5.25 (dd, 8H, J_{gem}=1 Hz, J_{cis}=11 Hz); 4.96 (s, 16H); 4.91 (s, 8H); 4.08 (m, 32H); 3.87 (m, 32H). ^{13}C NMR, δ: 159.9, 156.5, 153.0, 139.8, 139.4, 137.1, 136.7, 136.3, 131.9, 131.7, 127.5, 126.2, 115.8, 115.6, 113.9, 113.5, 106.2, 101.2, 99.5, 70.5, 70.1, 69.9, 68.2, 67.6 and 64.8. MS (MALDI-TOF), *m/z*: 3264.1 $(M+Na)^+$.

3.4. Dendrimers with ether connectivity (Mitsunobu conditions)

3.4.1. 1,3,5-Tris[3,5-bis(*p*-bromophenylmethyloxy)phenylmethyloxy]benzene (16). In a previously flamed Schlenk a mixture of phloroglucinol (126 mg, 1 mmol), **5A** (2.4 g, 5 mmol) and triphenylphosphine (1.1 g, 4 mmol) was dissolved in dry THF (15 mL) under argon atmosphere. A solution of DEAD (695 mg, 4 mmol) in dry THF (5 mL) was added dropwise and the reaction was stirred at room temperature overnight. The solvent was evaporated and diethyl ether was added to precipitate the desired compound with a little amount of triphenylphosphine, the crude product was purified by crystallization from ethyl acetate/carbon tetrachloride. Mp: 152–3 °C. Yield 70%. ^{1}H NMR, δ: 7.49 and 7.47 (d, 12H, A_2 of A_2B_2 system, J=8 Hz); 7.27 and 7.25 (d, 12H, B_2 of A_2B_2 system, J=8 Hz); 6.63 (d, 6H, J=2 Hz); 6.49 (t, 3H, J=2 Hz); 6.20 (s, 3H); 4.97 (s, 12H); 4.93 (s, 6H). ^{13}C NMR, δ: 160.4, 159.8, 139.3, 135.6, 131.7, 129.1, 122.0, 106.4, 101.5, 94.8, 69.8 and 69.3. MS (L-SIMS), *m/z*: 1506.89 $(M+H+6)^+$(100), 1508.89 $(M+H+8)^+$(85).

3.4.2. 1,3,5-Tris[3,5bis(*tert*-butyldimethylsilyloxy)benzyloxy]benzene (17). In a previously flamed Schlenk a mixture of phloroglucinol (88 mg, 0.7 mmol), **7A** (1.0 g, 2.8 mmol) and triphenylphosphine (642 mg, 2.45 mmol) was dissolved in dry THF (20 mL) under argon atmosphere. A solution of DEAD (427 mg, 2.45 mmol) in dry THF (5 mL) was added drop wise and the reaction was stirred at room temperature overnight. The solvent was evaporated and the crude product was purified by column chromatography (hexane). The product was isolated as a white solid. Mp: 74–6 °C. Yield 35%. ^{1}H NMR, δ: 6.52 (d, 6H, J=2 Hz); 6.28 (t, 3H, J=2 Hz); 6.22 (s, 3H); 4.88 (s, 6H); 4.93 (s, 6H); 0.98 (s, 54H); 0.19 (s, 36H). ^{13}C NMR, δ: 160.5, 156.6, 138.8, 112.3, 101.4, 95.1, 69.8, 25.7, 18.2 and −4.4. MS (MALDI-TOF), *m/z*: 1215.7 $(M+Na)^+$.

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References and notes

1. Ling, R.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

2. (a) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **2004**, *1985*, 50. (b) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117.
3. (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and dendrons*; Wiley-VCH: Weinheim, 2001. (b) In *Dendrimers and other dendritic polymers*; Fréchet, J. M. J., Tomalia, D. A., Eds.; Wiley: Chichester, 2001. (c) In *Top. Curr. Chem.* Vögtle, F., Ed.;, 1998; p 197. (d) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665. (e) Majoral, J. P.; Caminade, A. M. *Chem. Rev.* **1999**, *99*, 845. (f) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681. (g) Smith, D. K.; Diederich, F. *Chem. Eur. J.* **1998**, *4*, 1353.
4. (a) L'abbé, G.; Forier, B.; Dehaen, W. *J. Chem. Soc., Chem. Commun.* **1996**, 1262. (b) Gilat, S. L.; Adronov, A.; Fréchet, J. M. J. *J. Org. Chem.* **1999**, *64*, 7474.
5. Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159.
6. Zeng, F.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326.
7. Freeman, A. W.; Fréchet, J. M. J. *Org. Lett.* **1999**, *1*, 685.
8. (a) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819. (b) Grayson, S. M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2000**, *122*, 10335.
9. For recent reviews see: (a) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991. (b) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1828.
10. Chow, H.-F.; Chan, I.; Mak, C. C.; Ng, M.-K. *Tetrahedron* **1996**, *52*, 4277.
11. Chow, H.-F.; Mak, C. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 91.
12. Nithyanandahan, J.; Jayaraman, N. *J. Org. Chem.* **2002**, *67*, 6282.
13. Haddleton, D. M.; Sahota, H. S.; Taylor, P. C.; Yeates, S. G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 649.
14. Nakanozo, M.; Ma, L.; Zaitsu, K. *Tetrahedron Lett.* **2002**, *43*, 8185.
15. Sun, W. Y.; Zong, Q.; Gu, R. L.; Pan, B. C. *Synthesis* **1998**, 1619.
16. Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *1*, 1701.
17. Davies, P. J.; Grove, D. M.; van Koten, G. *Organometallics* **1997**, *16*, 800.
18. (a) Wijkens, P.; Jastrzebski, J. T. B. H.; van der Schaff, P. A.; Kolly, R.; Hafner, A.; van Koten, G. *Org. Lett.* **2000**, *2*, 1621. (b) Groenendaal, L.; Fréchet, J. M. J. *J. Org. Chem.* **1998**, *63*, 5675.
19. Burguete, M. I.; Díez-Barra, E.; Fraile, J. M.; García, J. I.; García-Verdugo, E.; González, R.; Herrerías, C. I.; Luis, S. V.; Mayoral, J. A.; Sánchez-Verdú, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1821.
20. Bo, Z.; Schlüter, A. D. *Chem. Eur. J.* **2000**, *6*, 3235.
21. Neugebauer, F. A.; Fischer, H.; Bernhardt, R. *Chem. Ber.* **1976**, *109*, 2389.
22. Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1059.

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^{7}Li- and ^{31}P NMR spectra of cyclopentanone lithium enolate in ethereal solvents: identification of the HMPA-coordinated aggregate structures

Masaaki Suzuki,[a,*] Hiroko Koyama[a] and Ryoji Noyori[b,*]

[a]*Division of Regeneration and Advanced Medical Science, Graduate School of Medicine, Gifu University, Yanagido, Gifu 501-1193, Japan*
[b]*Department of Chemistry and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*

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This paper is dedicated to Professor K. C. Nicolau (Scripps Research Institute) and Professor D. Seebach (ETH) on their honor of the Tetrahedron Prize.

Abstract—The structures of cyclopentanone lithium enolate under HMPA titration in 0.04–0.8 M diethyl ether and dimethyl ether solvents have been investigated using the low-temperature ^{7}Li, ^{31}P, and ^{13}C NMR. The progressive solvation by HMPA occurs for the tetra- and dimeric enolates, and upon addition of >2 equiv. of HMPA, the lithium enolate has been converged on a mixture of tetra-HMPA coordinated tetramer and bis-HMPA coordinated dimer with the ratio of 5:95 and <1:99 in diethyl ether and dimethyl ether, respectively. Neither monomeric nor trimeric enolate is detectable under such HMPA titration.

1. Introduction

Organolithium compounds generally exist as aggregates in both solid state[1–3] and solution.[4–8] The aggregation states play crucial roles to determine the reactivity and selectivity in organic reactions.[9–12] NMR is a particularly powerful tool for elucidating the aggregation structure in solution. Actually, the $^{6/7}$Li–^{15}N or $^{6/7}$Li–^{13}C coupling patterns provide direct evidence of monomeric, dimeric, tetrameric, and higher oligomeric structures of lithium amide[4] and alkyllithium species.[5] On the other hand, there have been few NMR studies of lithium enolates because of the lack of the $^{6/7}$Li–^{17}O vicinal coupling.[9] Therefore, Jackman conducted to determine the tetrameric aggregation state of isobutyrophenone lithium enolate in ethereal solvents by combination of vapor pressure osmometry, $^{6/7}$Li and ^{13}C chemical shifts, and ^{7}Li quadrupole splitting constants.[6]

HMPA addend modulates the reactivity of the lithium enolate in a way to realize the high selectivity in alkylation.[11,12] This effect has well been utilized in the three-component coupling prostaglandin (PG) synthesis.[13] In this regard, we have analyzed the structure of cyclopentanone lithium enolate in the presence of HMPA in THF using ^{7}Li and ^{31}P NMR.[14] Further, kinetic studies, coupled with the structural analyses, elucidated the origin of the HMPA effects on the enhancement of the reactivity and selectivity.[14] There, the ^{31}P chemical shift and ^{31}P–^{7}Li long-range coupling obtained at low-temperature served to determine HMPA-coordinated dimeric structures in solution. We here describe the study on the enolate structure in diethyl ether and dimethyl ether solvents.[15] In such open-chain ethereal solvents, both the ^{7}Li and ^{31}P signals were sharper than in THF at low temperature (−100 to −110 °C) and well discriminated enough to complement particularly the assignment of the ^{7}Li signals for the HMPA-coordinated structures in THF. Thus, a mixture of the HMPA-involved tetrameric and dimeric enolates observed in such ethereal solvents eventually converged on the corresponding tetra-HMPA coordinated tetramer and bis-HMPA coordinated dimer in the presence of HMPA more than 2 equiv.

2. Results and discussion

2.1. NMR analysis of the enolate in the presence of HMPA

The structures of cyclopentanone lithium enolate (**1**) in diethyl ether or dimethyl ether were studied using low-temperature ^{7}Li, ^{31}P, and ^{13}C NMR with their chemical shifts and coupling constants, $^{2}J(^{7}\text{Li}-^{31}\text{P})$, observed in HMPA–Li solvates.[16] The solution of lithium enolate **1** was prepared by reaction of 1-(trimethylsiloxy)cyclopentene

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* Corresponding authors. Tel./fax: +81-58-293-2635 (M.S.); tel.: +81-52-789-2956; fax: +81-52-783-4177 (R.N.);
e-mail address: suzukims@biomol.gifu-u.ac.jp; noyori@chem3.chem.nagoya-u.ac.jp

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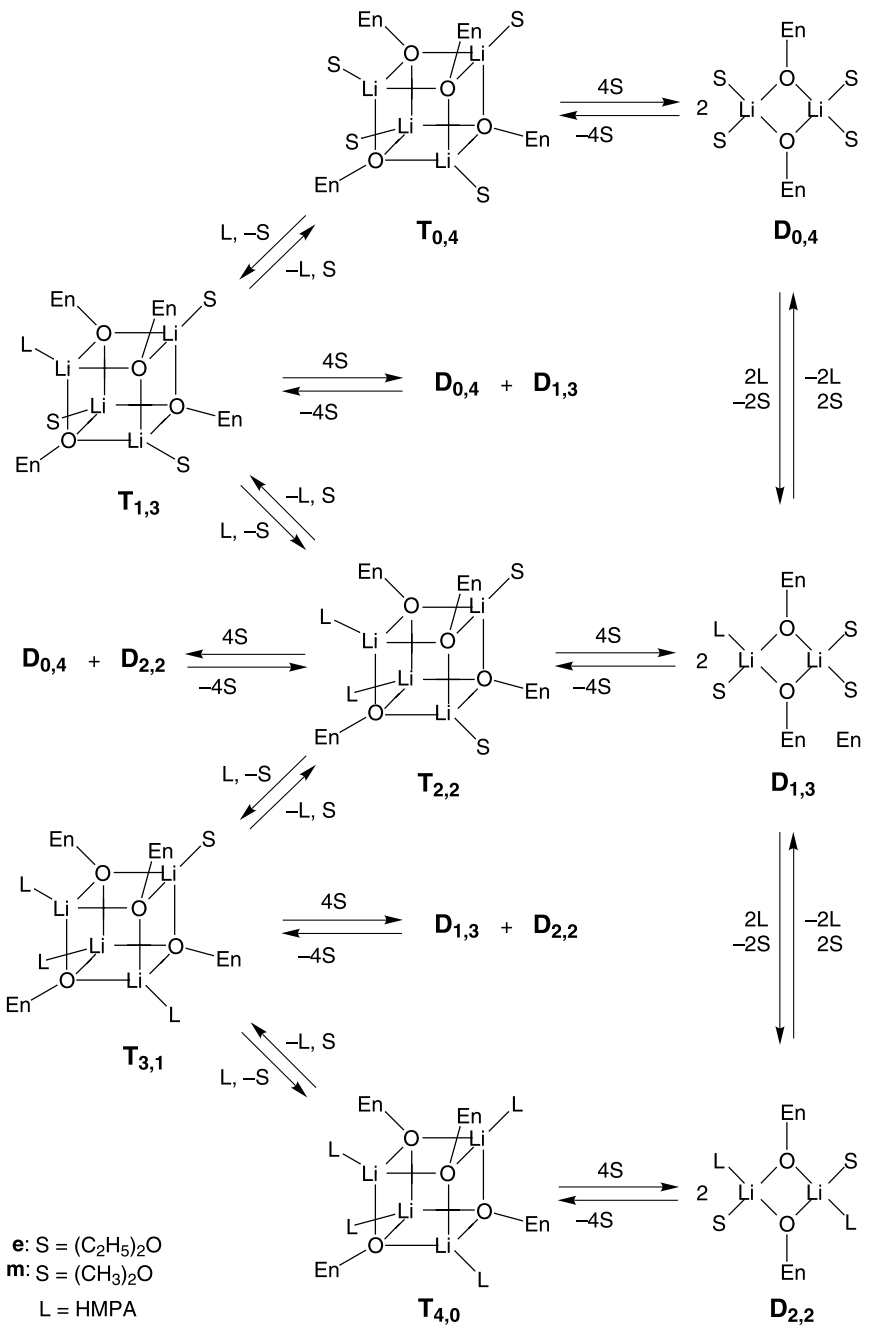
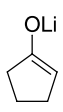


Scheme 1. Equilibrium of cyclopentanone lithium enolate in the presence of HMPA.

and *n*-butyllithium in an ethereal solvent. In the presence of HMPA, the enolate **1** was found to establish the dynamic equilibrium illustrated in Scheme 1 in such a solvent. In this Scheme, for both the tetramer **T** and the dimer **D**, the first subfix represents the number of attached HMPAs and the second subfix denotes the number of coordinated ethereal ligands.[17] The latter is associated with **e** or **m**, representing diethyl ether and dimethyl ether, respectively. The equilibrium point is thermodynamically determined by the enolate concentration, the quantity of HMPA, and the properties of the ethereal solvent S.[18,19] In the presence of excess HMPA the enolate largely exists as an bis-HMPA coordinated dimer $\mathbf{D_{2,2}}$ which equilibrates with some tetra-HMPA coordinated tetramer $\mathbf{T_{4,0}}$. This $\mathbf{T_{4,0}}/\mathbf{D_{2,2}}$ ratio depends on the basicity of S.[18,19] Monomers[16] and trimers,[20] however, were not observed.



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2.1.1. ^{7}Li and ^{31}P NMR in diethyl ether. Figure 1, A and B shows the ^{7}Li- and ^{31}P NMR spectra of 0.16 M diethyl ether solutions of **1** at −100 °C.[21] The signals in such an ethereal solvent were much more sharper than in THF presumably due to the slower S/L ligand exchange on the NMR time scale at this temperature.[14] Although lithium enolate **1** was

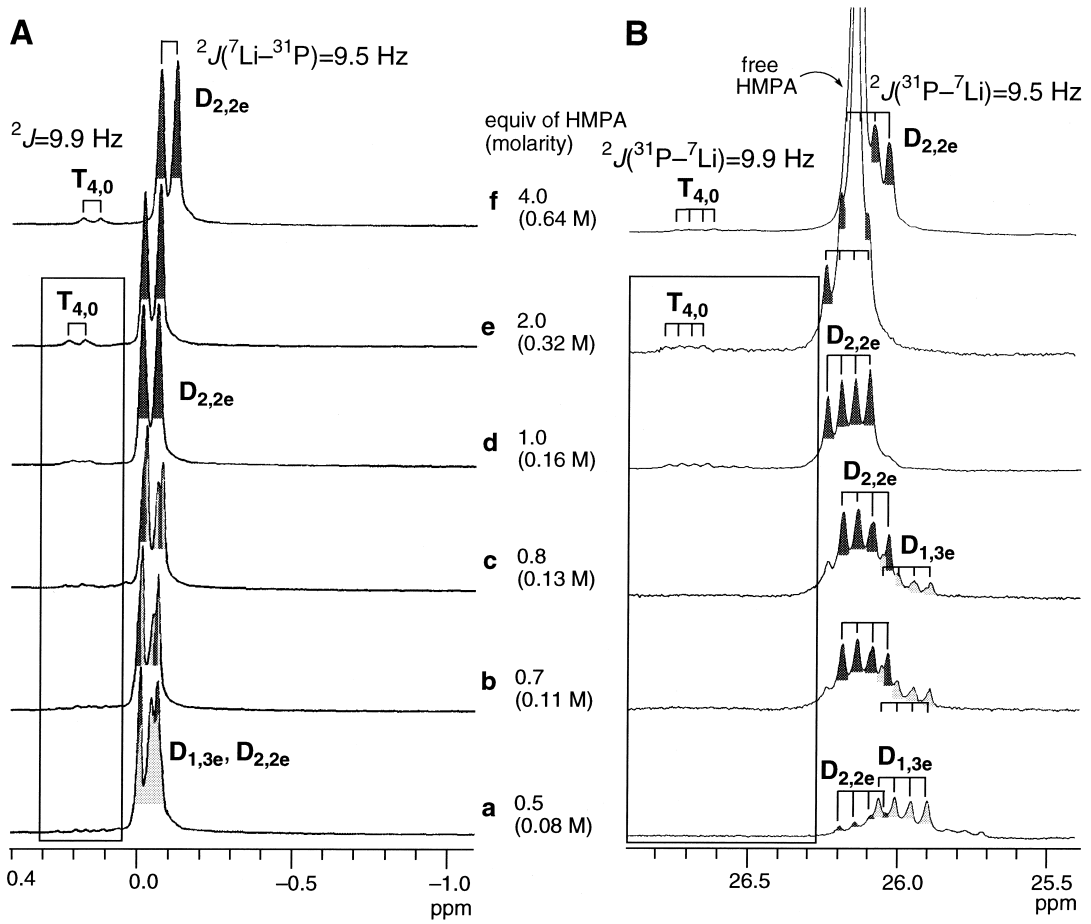

Figure 1. HMPA titration of a 0.16 M diethyl ether solution of cyclopentanone lithium enolate **1** at −100 °C. A: ^{7}Li NMR spectra. B: ^{31}P NMR spectra. The enclosed spectra are enlarged and shown in Figure 2.

insoluble in this solvent in the absence of HMPA, it dissolved upon the addition of >0.5 equiv. of HMPA in 0.16 M solution. The addition of 2 equiv. of HMPA yielded two doublets, at 0.21 and −0.03 ppm, with $^2J(^7\text{Li}-^{31}\text{P})$=9.9 and 9.5 Hz (Fig. 1, Ae). Further increase in HMPA (4 equiv.) had no effect on the signal pattern with the same ratio of two doublets (Fig. 1, Af), although there was a significant upfield shift;[22] these doublets were assignable to $\mathbf{T_{4,0}}$ (minor) and $\mathbf{D_{2,2e}}$ (major), respectively, in a 5:95 ratio. In the presence of <1 equiv. of HMPA, three additional peaks were observed in a 0.1 to −0.1 ppm region in ^{7}Li NMR (Fig. 1, Aa–c). The inside singlet peak at −0.03 ppm (Fig. 1, Aa) disappeared at higher HMPA concentrations, resulting in a doublet due to $\mathbf{D_{2,2e}}$, as judged by the $^2J(^7\text{Li}-^{31}\text{P})$ value of 9.5 Hz (Fig. 1, Ad).[14,16] The transient singlet was therefore assigned to the HMPA-free ^{7}Li atom in $\mathbf{D_{1,3e}}$, and the outside doublet to the HMPA-coordinated ^{7}Li atoms in $\mathbf{D_{1,3e}}$ and $\mathbf{D_{2,2e}}$. In a similar manner, the profile of the successive conversion to $\mathbf{D_{1,3e}}$ and then to $\mathbf{D_{2,2e}}$ during HMPA titration was also clearly monitored by ^{31}P NMR signals (Fig. 1, B). A signal due to $\mathbf{D_{1,3e}}$ appeared at 26.0 ppm with the $^2J(^{31}\text{P}-^7\text{Li})$ value of 10.3 Hz upon the addition of 0.5 equiv. of HMPA (Fig. 1, Ba); with the increase in HMPA, this signal decreased, and a signal due to $\mathbf{D_{2,2e}}$ appeared at 26.1 ppm with ^2J=9.5 Hz, predominating at 1 equiv. of HMPA (Fig. 1, Bd). After the addition of 2 equiv. of HMPA, the coordinated and free HMPAs were partially overlapped, but the side signals around a huge free HMPA signal can be assigned to $\mathbf{D_{2,2e}}$. Minor tetramer $\mathbf{T_{4,0}}$ was observed at 26.7 ppm as a quartet in the presence of 2 equiv. of HMPA (Fig. 1, Be) with the same $\mathbf{T_{4,0}/D_{2,2e}}$ integral ratio (ca. 5:95) as in the ^{7}Li NMR.

Enlarging the 0.1–0.3 ppm region in the ^{7}Li spectra (Fig. 1, A) showed four types of 1:1 doublets at 0.13, 0.16–0.17, 0.20–0.21, 0.22 ppm (Fig. 2, A). The intensities of these doublets changed with the increase in HMPA and the precedent three kinds of doublets disappeared at the addition of 2 equiv. of HMPA to give sole doublet at 0.21 ppm (Fig. 2, Ae). These precedent three doublets could, therefore, be assigned to the ^{7}Li atoms in the HMPA-coordinated complexes, $\mathbf{T_{1,3e}}$, $\mathbf{T_{2,2e}}$, and $\mathbf{T_{3,1e}}$ formed by the progressive HMPA solvation of the tetramer with the increase in added HMPA.[23] Here, the HMPA-free ^{7}Li signals in the tetramers are superimposed on the most intense low-field peak at 0.01 ppm (Fig. 1, Aa–d). In a similar manner, as shown in the enlarged ^{31}P spectra in the 26.3–27.0 ppm region (Fig. 2, B), the four tetramers, $\mathbf{T_{1,3e}}$, $\mathbf{T_{2,2e}}$, $\mathbf{T_{3,1e}}$, and $\mathbf{T_{4,0}}$, yielded four kinds of a 1:1:1:1 quartet with ^2J values of 9.9–11.2 Hz at 26.7, 26.5, 26.6, and 26.7 ppm, respectively, well correlating with the structural assignment in the ^{7}Li NMR. Thus, the profile of four kinds of ^{7}Li doublets and ^{31}P quartets and the change in their relative intensities during HMPA titration indicated that the successive coordination of four HMPA to Li cations in the tetrameric structure to converge on $\mathbf{T_{4,0}}$ with HMPA addend more than 2 equiv.

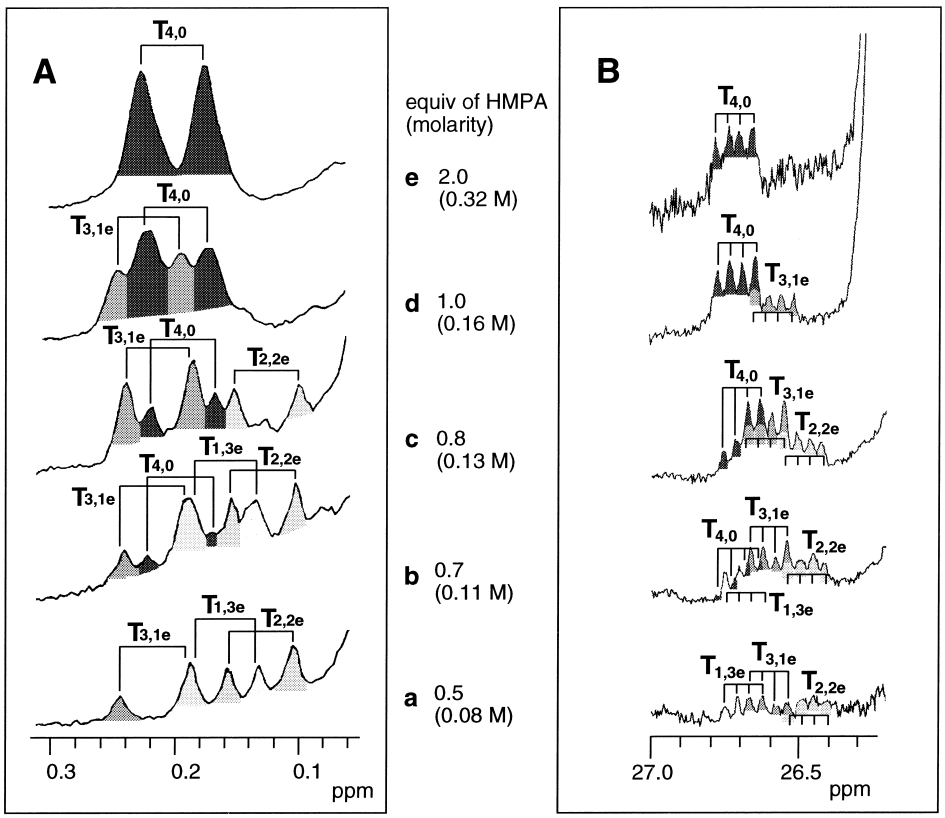

Figure 2. Enclosed spectra in Figure 1. A: ^{7}Li NMR spectra. B: ^{31}P NMR spectra.

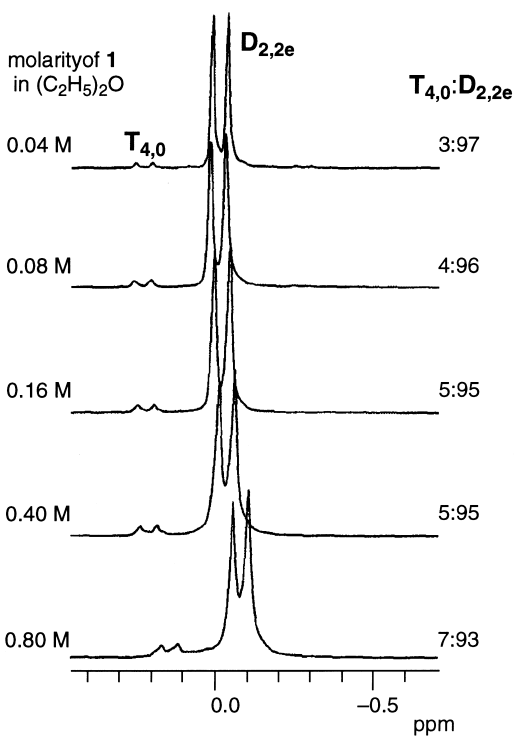

Figure 3. Concentration dependence of ^{7}Li NMR spectra of cyclopentanone lithium enolate **1** (−100 °C) in diethyl ether in the presence of 2 equiv. of HMPA.

In addition, the $\mathbf{T_{4,0}/D_{2,2e}}$ ratio was independent of the quantity of added HMPA in a range of more than 2 equiv. (Fig. 1, Ae and f), but was influenced by the enolate concentration (Fig. 3). Thus, the relative ratio varied from 7:93 to 3:97 upon the dilution of **1** from 0.80 to 0.04 M, confirming the above structural assignment and the presence of a dynamic equilibrium between $\mathbf{T_{4,0}}$ and $\mathbf{D_{2,2e}}$ shown in Scheme 1.

2.1.2. ^{7}Li and ^{31}P NMR in dimethyl ether. The lithium enolate **1** is soluble in this solvent even without HMPA. Figure 4A and B, shows the ^{7}Li- and ^{31}P NMR spectra of 0.32 M dimethyl ether solutions of **1** at −110 °C. Without HMPA, the lithium enolate gave a ^{7}Li broad singlet at 0.16 ppm (Fig. 4, Aa).[24] Upon the addition of 2 equiv. of HMPA, **1** mostly exists as a bis-HMPA coordinated dimer, giving a 1:1 doublet at 0.21 ppm in the ^{7}Li spectrum and 1:1:1:1 quartet at 26.3 ppm in the ^{31}P spectrum, with the same coupling constants, $^{2}J(^{7}\text{Li}-^{31}\text{P})=^{2}J(^{31}\text{P}-^{7}\text{Li})=9.5$ Hz (Fig. 4, Ai and Bi, respectively). The formation of dimers was monitored by the characteristic signal patterns of ^{7}Li NMR and the change in their signal intensities due to three different Li atoms in $\mathbf{D_{1,3m}}$ and $\mathbf{D_{2,2m}}$ during the HMPA titration. Thus, the addition of 0.2 equiv. of HMPA (Fig. 4, Ac) yielded a doublet with a coupling constant of 10.1 Hz at 0.28 ppm and a singlet at 0.22 ppm. Both signals are assignable to the ^{7}Li atoms in $\mathbf{D_{1,3m}}$. When 0.5 equiv. of HMPA was added (Fig. 4, Ad), the latter doublet appeared at 0.24 ppm, assignable to $\mathbf{D_{2,2m}}$. This doublet signal was intensified at the expense of the initially observed doublet

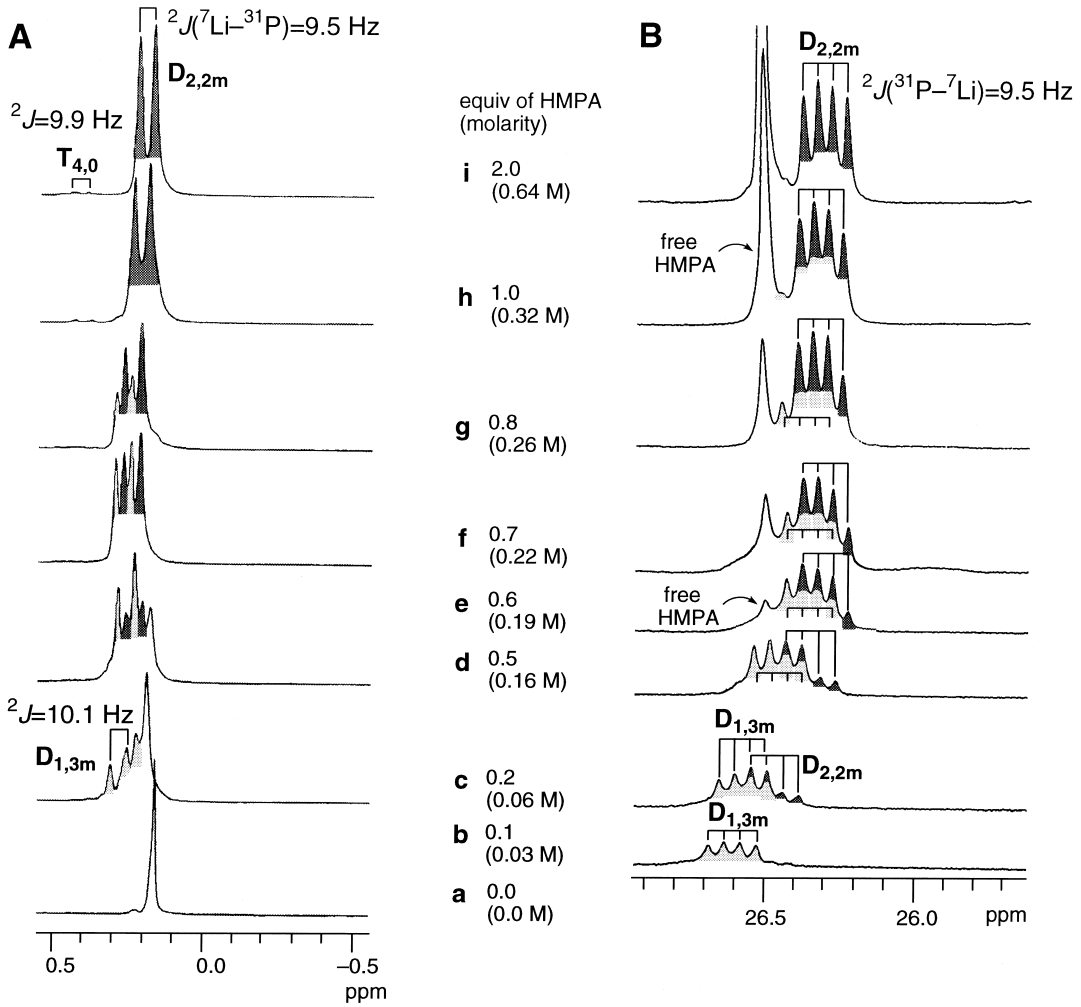

Figure 4. HMPA titration of a 0.32 M dimethyl ether solution of cyclopentanone lithium enolate **1** at −110 °C. A: ^{7}Li NMR spectra. B: ^{31}P NMR spectra.

Table 1. ^{7}Li and ^{31}P chemical shifts and coupling constants of the HMPA-solvated dimers and tetramers formed from cyclopentanone lithium enolate (**1**) in diethyl ether[a]

HMPA (equiv.)	^{7}Li (s[b]) δ[c]	^{7}Li (d[b]) δ[c] ($^2J(^7Li–^{31}P)$[d])		^{7}Li (d[b]) δ[c] ($^2J(^7Li–^{31}P)$[d])			
	$D_{1,3e}$	**$D_{1,3e}$**	**$D_{2,2e}$**	**$T_{1,3e}$**	**$T_{2,2e}$**	**$T_{1,3e}$**	**$T_{4,0}$**
0.5	−0.03	−0.02 (10.1)		0.16 (11.2)	0.13 (10.7)	0.22 (11.2)	
0.7	−0.03	−0.01[e] (10.1)	−0.01[e] (9.5)	0.17 (11.1)	0.13 (10.7)	0.22 (11.2)	0.20 (9.9)
0.8	−0.03	−0.01[e] (10.1)	−0.01[e] (9.5)		0.13 (10.7)	0.22 (11.2)	0.20 (9.9)
1.0			−0.02 (9.5)			0.22 (11.2)	0.20 (9.9)
2.0			−0.03 (9.5)				0.21 (9.9)
4.0			−0.06 (9.5)				0.18 (9.9)

HMPA (equiv.)	^{31}P (q[b]) δ[c] ($^2J(^{31}P–^7Li)$[d])		^{31}P (q[b]) δ[c] ($^2J(^{31}P–^7Li)$[d])			
	$D_{1,3e}$	**$D_{2,2e}$**	**$T_{1,3e}$**	**$T_{2,2e}$**	**$T_{1,3e}$**	**$T_{4,0}$**
0.5	26.0 (10.3)	26.1 (9.5)	26.7 (11.1)	26.5 (10.2)	26.6 (11.1)	
0.7	26.0 (10.3)	26.1 (9.5)	26.7 (11.1)	26.5 (10.2)	26.6 (11.1)	26.7 (10.0)
0.8	26.0 (10.3)	26.1 (9.5)		26.5 (10.2)	26.6 (11.1)	26.7 (9.9)
1.0		26.1 (9.5)			26.6 (11.1)	26.7 (10.0)
2.0		26.1 (9.5)				26.7 (9.9)
4.0		26.1 (9.5)				26.7 (9.9)

[a] Spectra were recorded at −100 °C.
[b] s, singlet; d, doublet, and q, quartet.
[c] The chemical shifts are reported relative to external standard as described in Section 4.
[d] All coupling constants *J* are reported in Hertz.
[e] Two doublets due to **$D_{1,3e}$** and **$D_{2,2e}$** are overlapped.

Table 2. ^{7}Li and ^{31}P chemical shifts and coupling constants of the HMPA-solvated dimers and tetramers formed from cyclopentanone lithium enolate (**1**) in dimethyl ether[a]

HMPA (equiv.)	^{7}Li (s[b]) δ[c]	^{7}Li (d[b]) δ[c] ($^{2}J(^{7}\mathrm{Li}-^{31}\mathrm{P})$[d])	^{7}Li (d[b]) δ[c] ($^{2}J(^{7}\mathrm{Li}-^{31}\mathrm{P})$[d])		^{31}P (d[b]) δ[c] ($^{2}J(^{31}\mathrm{P}-^{7}\mathrm{Li})$[d])	
	$D_{1,3m}$	**$D_{1,3m}$**	**$D_{2,2m}$**	**$T_{4,0}$**	**$D_{1,3m}$**	**$D_{2,2m}$**
0.1					26.6 (10.3)	
0.2	0.22	0.28 (10.1)			26.6 (10.3)	26.5 (9.5)
0.5		0.27 (10.1)	0.24 (10.1)		26.4 (10.3)	26.3 (9.5)
0.6					26.3 (10.3)	26.3 (9.5)
0.7		0.27 (10.1)	0.24 (9.5)		26.3 (10.3)	26.3 (9.5)
0.8		0.29 (10.1)	0.25 (9.5)		26.3 (10.3)	26.3 (9.5)
1.0			0.23 (9.5)	0.42 (9.9)		26.3 (9.5)
2.0			0.21 (9.5)	0.43 (9.9)		26.3 (9.5)

[a] Spectra were recorded at −110 °C.
[b] s, singlet; d, doublet, and q, quartet.
[c] The chemical shifts are reported relative to external standard as described in Section 4.
[d] All coupling constants J are reported in Hertz.

(Fig. 4, Af–h), and became the sole signal upon the addition of 2 equiv. of HMPA (Fig. 4, Ai).[25] In addition, a very small doublet of 9.9 Hz was detected at 0.43 ppm (at low field), indicating the formation of the tetramer **$T_{4,0}$** (<1%) (Fig. 4, Ai) (see also the structural convergence in diethyl ether shown in Fig. 2). The same structural conclusion was provided by ^{31}P NMR analysis (Fig. 4B). Thus, the two quartets due to **$D_{1,3m}$** and **$D_{2,2m}$** appeared at 26.3–26.6 ppm with $^{2}J(^{31}\mathrm{P}-^{7}\mathrm{Li})$=10.3 Hz and 26.3–26.5 ppm with ^{2}J=9.5 Hz, respectively. The intensity of the quartet belonging to **$D_{1,3m}$** became maximal at the addition of 0.6 equiv. of HMPA (Fig. 4, Be). The second quartet due to **$D_{2,2m}$** overwhelmed **$D_{1,3m}$** at the addition of 0.8 equiv. of HMPA (Fig. 4, Bg) and became exclusive after the addition of 2 equiv. of HMPA. In addition, a tiny broad singlet due to free HMPA appeared at 26.5 ppm at the addition of 0.6 equiv. of HMPA and grew up with the increase in HMPA addend (Fig. 4, Be–i), revealing the existence of the dynamic equilibria among the enolate aggregates **$D_{0,4m}$**, **$D_{1,3m}$**, **$D_{2,2m}$**, and free HMPA as shown in Scheme 1. Unfortunately, a quartet for **$T_{4,0}$** was not observed in the ^{31}P NMR spectra because of the low resolution due to the miniscule amount of tetramer, and the ^{31}P–^{7}Li multi-coupling.

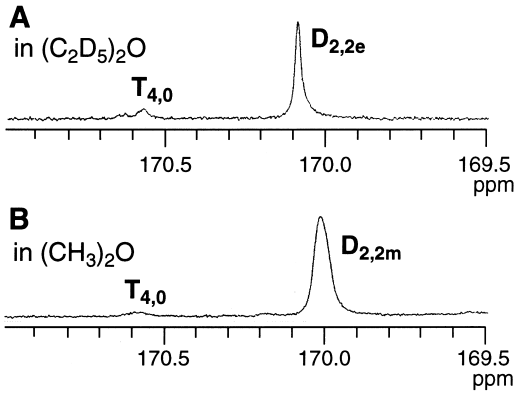

Figure 5. ^{13}C signals of the oxygen-bearing carbon atoms. A: Tetramer **$T_{4,0}$** (170.6 ppm) and dimer **$D_{2,2e}$** (170.1 ppm) formed from **1** (0.16 M) in diethyl-d_{10} ether with 0.32 M HMPA. B: Tetramer **$T_{4,0}$** (170.6 ppm) and dimer **$D_{2,2m}$** (170.0 ppm) for med from **1** (0.32 M) in dimethyl ether with 0.64 M HMPA.

Full spectral data for the HMPA-coordinated aggregates of cyclopentanone lithium enolate are summarized in Tables 1 and 2.

2.2. ^{13}C NMR

The predominance of the dimeric structures in the presence of HMPA was also reflected in the ^{13}C NMR signals of their oxygen-bearing carbons of the lithium enolate (Fig. 5). In diethyl-d_{10} ether, a 0.16 M solution of **1** in the presence of 2 equiv. of HMPA resulted in broad signals appearing at 170.6 and 170.1 ppm, which were assigned to **$T_{4,0}$** and **$D_{2,2e}$**, respectively, with a **$T_{4,0}$/$D_{2,2e}$** ratio of 5:95 (Fig. 5A). The corresponding signals in dimethyl ether containing 2 equiv. of HMPA were seen at 170.6 (<1%) and 170.0 ppm, (Fig. 5B). These signal ratios were the same as those observed in the ^{7}Li NMR (Figs. 1, A and 4A).

2.3. Quadrupole splitting constant (QSC)

The QSC values are considered to correlate with the degree of aggregation and the solvation of lithium.[14] In this context, the QSC values[26,27] were calculated from the observed dipole–dipole relaxation times for the hydrogen-bearing vinylic carbon and ^{7}Li spin–lattice relaxation times, (i.e., for $T_1(^{13}\mathrm{C})$ and $T_1(^{7}\mathrm{Li})$), in 0.32 M diethyl- and dimethyl ether solutions of **1** in the presence of 4 equiv. of HMPA[28] at 30 °C, $T_1(^{13}\mathrm{C})$: 2.50 and 3.27 s, respectively; $T_1(^{7}\mathrm{Li})$: 1.11 and 1.35 s, respectively; to give values of 113 and 117 kHz, respectively, whose values are similar as that obtained in

Table 3. Spin–lattice relaxation times (T_1) and quadrupole splitting constants (QSC) for lithium enolate **1** at 30 °C

Solvent	Viscosity (mPa s)[a]	Concentration (M)	HMPA (equiv.)	Compound	$T_1(^{13}\mathrm{C})$ (s)	$T_1(^{7}\mathrm{Li})$ (s)	QSC (kHz)
$(C_2H_5)_2O$	0.23	0.32	4	**$D_{2,2e}$**	2.50	1.11	113
$(CH_3)_2O$	1.3×10^{-4}	0.32	4	**$D_{2,2m}$**	3.27	1.35	117
THF-*d*s	0.49	0.2	5		1.56	0.66	116[b]

[a] Viscosities at 25 °C for $(C_2H_5)_2O$ and THF are taken from Ref. 30 and for $(CH_3)_2O$ from Ref. 29.
[b] Ref. 14.

THF (116 kHz) (Table 3).[14] Thus, when the lithium enolate almost exists as the $\mathbf{D_{2,2}}$ type complex, the coordinated ethereal ligands do not influence the QSC values significantly. On the other hand, longer relaxation times were observed in diethyl- and dimethyl ether than in THF as shown in Table 3, reflecting on their solvent viscosities in the order of dimethyl ether (1.3×10^{-4} mPa s at 25 °C[29])< diethyl ether (0.23 mPa s at 25 °C[30])<THF (0.49 mPa s at 25 °C[30]).[6,26a]

3. Conclusion

The lithium enolate **1**, which presumably exists as a mixture of tetramer $\mathbf{T_{0,4}}$ and dimer $\mathbf{D_{0,4}}$ in diethyl ether and dimethyl ether, undergoes the successive S/L ligand exchange by the increase in added HMPA to converge on tetra-HMPA coordinated tetramer, $\mathbf{T_{4,0}}$ (minor product) and bis-HMPA coordinated dimers, $\mathbf{D_{2,2e}}$ and $\mathbf{D_{2,2m}}$ (major products), respectively, with 2 equiv. of HMPA per Li. Here, the ratio of the tetra-HMPA coordinated tetramer and bis-HMPA coordinated dimer was independent of the quantity of added HMPA, but was influenced by the enolate concentration. Thus, the ratio of such tetramer and dimer changes in order of 5:95, <1:99, and 0:100 in diethyl ether, dimethyl ether, and THF,[14] respectively, depending on the basicity of S. The clear-cut signal assignment and the profile of the convergence to $\mathbf{T_{4,0}}$ and $\mathbf{D_{2,2}}$ under HMPA titration gave no indication of any monomers[16] and trimers.[20] In addition, no monomers were detected even at an enolate concentration as low as 0.04 M or at the concentration of >2 equiv. of HMPA.

These substantial structural studies in combination with those and kinetic studies in THF,[14] will provide basic information for considering the roles of triorganotin(IV) halides, dialkylzinc compounds, and other additives in the HMPA-involved enolate systems[31] to modulate the reactivity and selectivity for the enolate alkylation reaction particularly useful for the three component coupling PG synthesis.[13]

4. Experimental

4.1. General

All apparatus used in the reactions were dried in an oven (100 °C) overnight and baked out with a heat gun under reduced pressure to remove air and moisture, and then filled with argon (Ar) after they had cooled to room temperature. The air and moisture sensitive materials were manipulated under Ar using a glove box, vacuum line, and syringe techniques.

4.1.1. Solvent and materials. Diethyl ether was distilled over sodium benzophenone ketyl. Diethyl-d_{10} ether were distilled over sodium benzophenone ketyl under vacuum, and then transferred into a receiver containing a sodium–potassium alloy and distilled under vacuum. These solvents were degassed prior to use. Hexamethylphosphoric triamide (HMPA) was obtained from Tokyo Kasei and distilled over CaH_2 under reduced pressure. 1-(Trimethylsiloxy)cyclopentene was purchased as commercial grade (97%). NMR studies were done using the enol silyl ether of 99.8% purity after distillation (bp 156 °C, 101 kPa) equipped with a Hempel-type distilling column. HMPA and the enol silyl ether were stored in ampoules under Ar. *n*-Butyllithium in hexane was purchased from Nacalai Tesque, Inc., and stored in a Schlenk tube equipped with a Young's tap under Ar at 4 °C. Diphenylacetic acid used as an indicator was recrystallized from methanol and dried at 60 °C under high vacuum.

4.1.2. NMR spectroscopy. All the NMR experiments were recorded on a JEOL JNM Λ-500 spectrometer operated at 194.25 MHz (^{7}Li), 202.35 MHz (^{31}P), or 125.65 MHz (^{13}C). The ^{7}Li and ^{31}P chemical shifts were referenced to external standards, 0.41 M LiCl/THF-d_8 (δ 0.0) and 1.0 M $P(C_6H_5)_3$/THF-d_8 (δ −6.0), respectively, at −100 °C. Shiming was performed on the external reference at −100 °C, and ^{7}Li and ^{31}P NMR spectra were then taken without locking. The ^{13}C chemical shifts were referenced to tetramethylsilane/THF-d_8 (δ 0.0) as an external standard at −100 °C. Digital resolutions were 0.59, 0.79 and 0.46 Hz for ^{7}Li, ^{31}P and ^{13}C, respectively. The ^{7}Li and ^{13}C relaxation times were measured with the inversion-recovery method, and data were processed by nonlinear least-squares programs.

4.2. Preparation of cyclopentanone lithium enolate for ^{7}Li- and ^{31}P NMR spectroscopic analysis

4.2.1. Enolate samples in diethyl ether (Figs. 1 and 2). 1-(Trimethylsiloxy)cyclopentene (78.2 mg, 0.500 mmol) was placed into a 10-mL test tube capped by a septum with positive Ar pressure. Diethyl ether (1.5 mL) was added, and then the solution was transferred through a stainless cannula into a 20-mL Schlenk tube. To the solution was added *n*-butyllithium (1.43 M hexane solution, 0.344 mL, 0.500 mmol) at 0 °C via a syringe under Ar purge. The mixture was vigorously stirred at room temperature for 2.0 h. Resulted solution was cooled to 0 °C with an ice bath, and 0.5 equiv. of HMPA (44.8 mg, 0.25 mmol) was added, followed by an additional diethyl ether to give a total volume of 3.1 mL. The suspension including precipitate caused by undissolved lithium enolate was treated with HMPA, and the mixture was stirred for 10 min at 10 °C to become a clear solution. A 5-mm NMR tube was charged with this solution (750 μL), and was cooled to 77 K, and then sealed with a flame under vacuum. Samples added by 0.7, 0.8, 1, 2 and 4 equiv. of HMPA were prepared according to this procedure. Spectral confidence was confirmed by repeating the same preparation procedure. NMR samples in diethyl ether were stable at −80 °C for at least 1 year.

4.2.2. 0.80 M Solution of 1 in diethyl ether (Fig. 3). A diethyl ether solution of the lithium enolate (59.4 mg, 0.600 mmol) prepared as described above was transferred through a stainless cannula in a 5-mm NMR tube, and solvents were removed under reduced pressure. After the tube was filled with Ar, HMPA (104 μL, 0.600 mmol) and diethyl ether were added at 0 °C to the residue to give a total volume of 750 μL.

4.2.3. 0.04–0.40 M Solutions of 1 in diethyl ether (Fig. 3). A diethyl ether solution of the lithium enolate was prepared

as described above. Here, the use of diethyl ether distilled from sodium benzophenone ketyl was not suitable in the preparation of highly diluted solution of the lithium enolate (<0.08 M) because of the contamination of undesirable peaks in the upfield. Therefore, the solvent must be distilled further over sodium–potassium alloy under vacuum using apparatus with Young's taps.

4.2.4. Enolate samples in dimethyl ether (Fig. 4). 1-(Trimethylsiloxy)cyclopentene (42.7 μL, 0.240 mmol) was placed into a 5-mm NMR tube via a micro-syringe. To this tube cooled to −78 °C was filled with dimethyl ether (0.600 μL), followed by the addition of *n*-butyllithium (1.43 M hexane solution, 0.168 mL, 0.240 mmol) at the same temperature under Ar atmosphere. The mixture was left to stand at −40 °C for 2.0 h. To the resulting solution was added HMPA (4.00 μL, 0.024 mmol). A 5-mm NMR tube was charged with this solution (750 μL), cooled to 77 K, then sealed with a flame under vacuum. Samples added by 0.1, 0.2, 0.5, 0.6, 0.7, 0.8, 1 and 2 equiv. of HMPA were prepared according to this procedure.

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References and notes

1. Review: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.
2. (a) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617–2621. (b) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403–5409. (c) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462–468.
3. Williard, P. G.; Salvino, J. M. *J. Org. Chem.* **1993**, *58*, 1–3.
4. Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227–234.
5. (a) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371–2379. (b) Reich, H. J.; Holladay, J. E.; Walker, T. G.; Thompson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 9769–9780.
6. Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954–4962.
7. (Freezing-point depression measurements in THF) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972–1988.
8. (Structural analysis of a lithium enolate based on UV–vis spectroscopy) Abbotto, A.; Streitwieser, A. *J. Am. Chem. Soc.* **1995**, *117*, 6358–6359.
9. Instead, Streitwieser has utilized UV–vis spectroscopy to study on the aggregation and reactivity of the lithium enolate of *p*-phenylisobutyrophenone and related compounds at low concentrations in THF: (a) Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 4688–4689. (b) Abbotto, A.; Leung, S. S.-W.; Streitwieser, A.; Kilway, K. V. *J. Am. Chem. Soc.* **1998**, *120*, 10807–10813. (c) Streitwieser, A.; Wang, D. Z.-R. *J. Am. Chem. Soc.* **1999**, *121*, 6213–6219. (d) Wang, D. Z.; Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2000**, *122*, 10754–10760.
10. Ikuta, Y.; Tomoda, S. *Tetrahedron Lett.* **2003**, *44*, 5931–5934.
11. (a) Leung, S. S.-W.; Streitwieser, A. *J. Org. Chem.* **1999**, *64*, 3390–3391. (b) Streitwieser, A.; Husemann, M.; Kim, Y.-J. *J. Org. Chem.* **2003**, *68*, 7937–7942, and references cited therein.
12. For the role of HMPA in other reactions, see: (a) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B.Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201–7210. (b) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14–15. (c) Sikorski, W. H.; Reich, J. *J. Am. Chem. Soc.* **2001**, *123*, 6527–6535.
13. (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348–3349. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718–4726. (c) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785–1787. (d) Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809–4822.
14. Effects of HMPA on the structure and reactivity of the lithium enolate of cyclopentanone in THF: the dimer is responsible for alkylation and proton exchange reactions Suzuki, M.; Koyama, H.; Noyori, R. *Bull. Chem. Soc. Jpn* **2004**, in press.
15. Some of the results were reported in Abstracts (detailed in English); Suzuki, M.; Koyama, H.; Noyori, R. In *48th Symposium on Organometallic Chemistry*, Japan; Kinki Chemical Society: Yokohama National University, Kanagawa, Japan, 2001; pp 114–115. Suzuki, M.; Koyama, H.; Noyori, R. In *50th Symposium on Organometallic Chemistry*, Japan; Kinki Chemical Society: Osaka University, Osaka, Japan, 2003; pp 44–45.
16. (a) Reich, H. J.; Green, D. P. *J. Am. Chem. Soc.* **1989**, *111*, 8729–8731. (b) Reich, H. J.; Borst, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1835–1837. (c) Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728–8741. (d) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403–411. (e) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751–5757.
17. The coordination number of lithium cation was represented as four according to the general empirical formula. This description simplifies the following structural analyses and discussion.
18. *Organic solvents: for physical properties and methods of purification*. Riddick, J. A., Bunger, W. B., Sakano, T. K., Eds.; Wiley: New York, 1986.
19. For solvation energy to lithium cation, see: (a) Kaufmann, E.; Gose, J.; Schleyer, P. v. R. *Organometallics* **1989**, *8*, 2577–2584. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863–9874. (c) Reich, H. J.; Kulicke, K. *J. Am. Chem. Soc.* **1996**, *118*, 273–274. (d) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217–2225. (e) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567–5572. (f) Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J. K. *Org. Lett.* **2000**, *2*, 3739–3741.
20. Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 10198–10202. Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 199–202.
21. The ^{7}Li and ^{31}P spectra were similar at −110 °C.
22. Similar upfield shift phenomena were observed in a previous NMR study[16d].
23. The irregular movement of chemical shifts with the increase of

the coordination number of HMPA is characteristic of this cyclopentanone lithium enolate and contrasted with the down- and upfield shifts for the methyllithium[16c] and lithium 3,5-dimethylphenolate,[16d] respectively.
24. The structures without HMPA are not specified.[7]
25. The spectral pattern no longer changed with increase of HMPA (4 equiv.).
26. (a) Jackman, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105*, 4177–4184. (b) Jackman, L. M.; Scarmoutzos, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1987**, *109*, 5355–5361. (c) Jackman, L. M.; Çizmeciyan, D. *Magn. Reson. Chem.* **1996**, *34*, 14–17.
27. Wen, J. Q.; Grutzner, J. B. *J. Org. Chem.* **1986**, *51*, 4220–4224.
28. The dimers $\mathbf{D_{2,2e}}$ and $\mathbf{D_{2,2m}}$ are exclusively formed under these conditions as judged by low-temperature ^{31}P NMR analysis.
29. Wu, J.; Liu, Z.; Bi, S.; Meng, X. *J. Chem. Engng Data* **2003**, *48*, 426–429.
30. *CRC handbook of chemistry and physics*. 81th ed. Lide, D. R., Ed.; CRC: Boca Raton, 2000; pp 6–181 see also pp 6–182.
31. Lithium enolates can exist in various forms dependent on their steric and electronic properties, used solvents, concentrations, temperatures, and the presence/absence of the additives, etc.[14]

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Formal synthesis of (±)-udoteatrial hydrate

Meng-Yang Chang,[a,*] Ching-Han Lin[b] and Nein-Chen Chang[b,*]

[a]*Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan, ROC*
[b]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, ROC*

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Abstract—The formal synthesis of antimicrobial diterpene udoteatrial hydrate (**1**) is described in nine steps. Diol **6** used as starting material. The key intermediate **4** was obtained from bicyclic ketone **5** via the key Norrish type I reaction.

1. Introduction

The synthetic studies for highly oxygenated polycyclic acetals and lactones have provided various approaches toward molecules, such as udoteatrial hydrate,[1] bilobalide,[2] ginkgolide A and B,[3] gracilin B and C,[4] and specionin.[5] In this report, we describe the formal synthesis of udoteatrial hydrate (**1**), which has an 'udoteane' carbon skeleton with all *cis* substituents relationship on the cyclopentane ring and a geranyl side chain. This unusual monocyclic diterpenoid trialdehyde udoteatrial is isolated from the calcareous marine green algae *Udotea flabellum* has existed in a mono-hydrate form and showed antimicrobial activities against *Staphylococcus aureus* and *Candida albicans* (Fig. 1).[1e]

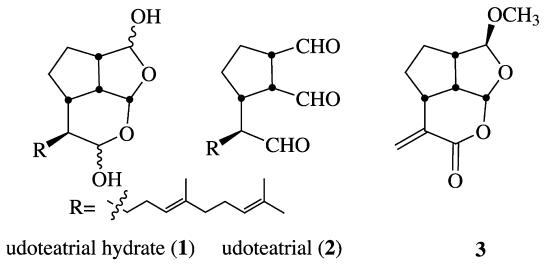


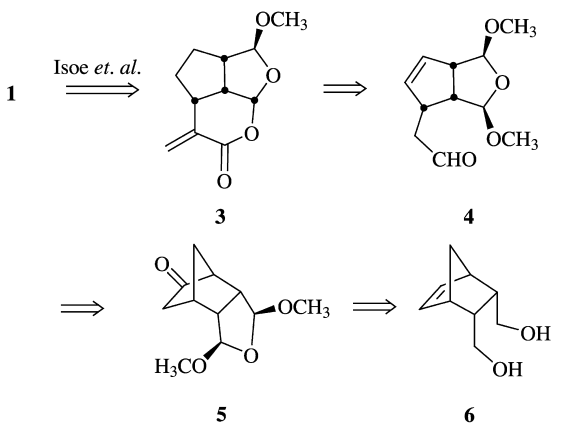
Figure 1. Structure of udoteatrial hydrate (**1**), udoteatrial (**2**) and **3**.

To date, there are only two reports for the total synthesis of udoteatrial hydrate citations. In 1983, Whitesell and his co-workers reported the racemic synthesis of udoteatrial hydrate using the Claisen rearrangement and zirconium-catalyzed carboalumination as key steps. In 1993, Isoe and his co-workers[1b,c] described an asymmetrical synthesis of the antipode of udoteatrial hydrate using genipin as a building block. The tricyclic *exo*-methylene lactone with *cis*-fused ring junction and contiguous stereogenic centers were designated to be a key intermediate. The geranyl side chain was introduced into the iridoid carbon framework thermodynamically.

2. Results and discussion

Recently, we found that bicyclo[2.2.1]heptanone can undergo the Norrish type I reaction[6] to afford the corresponding *cis*-trisubstituted cyclopentenoid compound. We applied this approach in the synthesis of natural products, such as pedicularis-lactone,[7a] ningpogenin,[7a] boschnialactone,[7b] and iridolactone.[7c]

The methodological studies we have carried out to date have left addressed a pertinent issue, which impacts the general applicability of the method to give access to a wide range of



Scheme 1. Retrosynthetic study of udoteatrial hydrate (**1**).

Keywords: Udoteatrial hydrate; Bicyclo[2.2.1]heptanone; Norrish type I reaction.
* Corresponding authors. Tel.: +886-7-5919464; fax: +886-7-5919348 (M.-Y.C.); tel.: +886-7-5252000x3913; fax: +886-7-5253913 (N.-C.C.); e-mail addresses: mychang@nuk.edu.tw; ncchang@mail.nsysu.edu.tw

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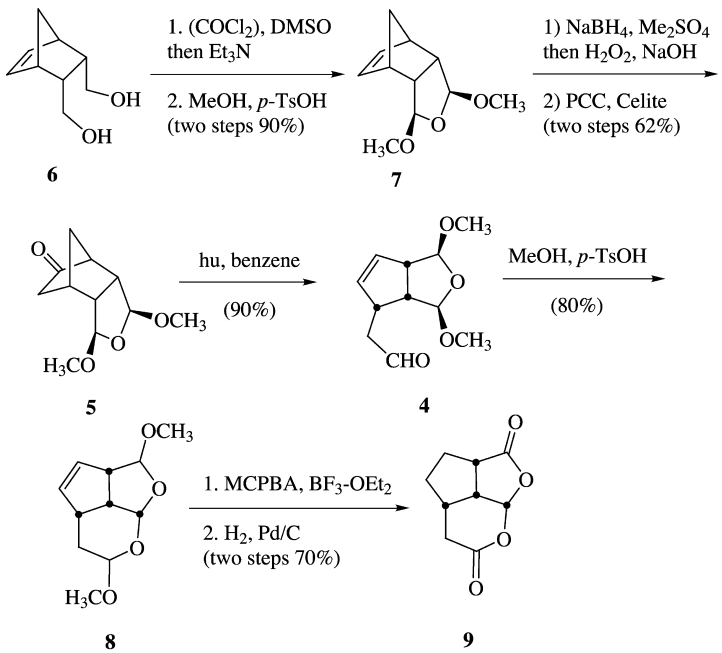


Scheme 2. Synthesis of tricyclic lactone **9**.

related targets. With respect to the previous results, we describe the application of this Norrish type I reaction to the formal synthesis of **1**. The retrosynthetic strategy is illustrated in Scheme 1. The target, Isoe's key intermediate **3**, was synthesized from aldehyde **4**, which in turn was derived from the Norrish type I reaction of ketone **5**. The functional group transformation of diol **6** was performed in a straightforward reaction involving oxidation, protection and hydroboration reactions.

The formal synthesis of udoteatrial hydrate (**1**), as shown in Scheme 2, uses a facile strategy from diol **6**. Diol **6** was readily obtained from cyclopentadiene in two-step reactions of the Diels–Alder cycloaddition with maleic anhydride and reduction with lithium aluminum hydride. Swern oxidation of diol **6** produced the resulting dialdehyde. Without further purification, treatment of the dialdehyde with methanol containing a catalytic amount of *p*-toluenesulfonic acid caused cyclization to give the sole compound **7**. Treatment

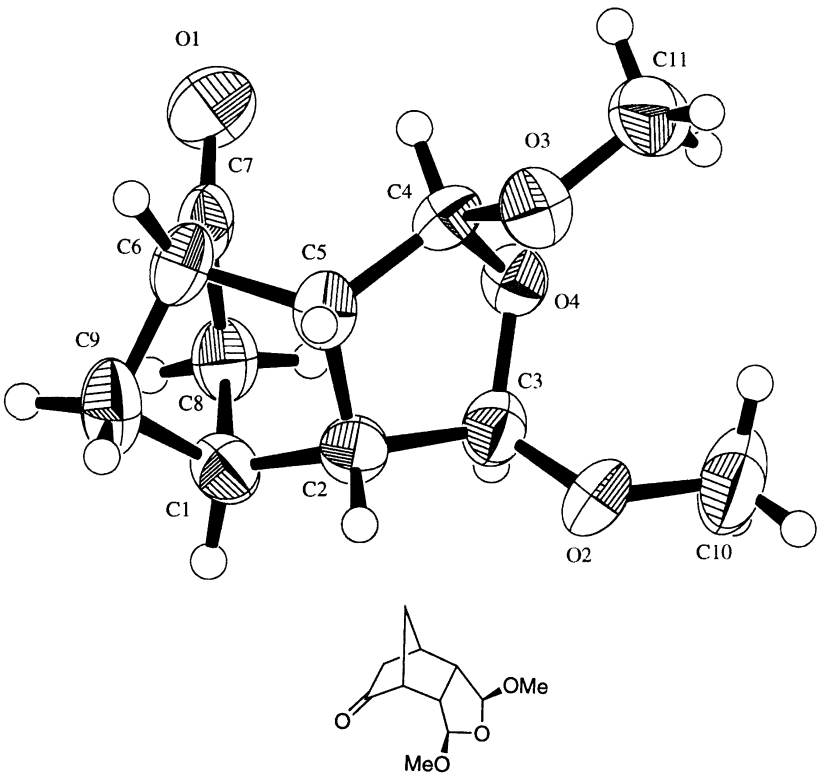


Diagram 1. X-ray crystallography of **5**.

of **7** with a mixture of sodium borohydride and dimethyl sulfate, followed by oxidative work-up led to the alcohol as a single stereoisomer.[7a] The alcohol then reacted with pyridinium chlorochromate to give the corresponding bicyclo[2.2.1]heptanone **5**. The structure of **5** was determined by single-crystal X-ray analysis (Diagram 1).

The key intermediate, trisubstituted cyclopentenoid **4**, was obtained in high yield via photolytic cleavage (λ>310 nm) of the bicyclo[2.2.1]heptanone **5** in methanol for 15 h. The sole tricyclic product **8** was generated in one efficient cyclization by the treatment of **4** with methanol under mild acidic condition.

With compound **8** in hand, we focused on the alkylation at the α-position of the six-membered ring on the tricyclic skeleton. Tricyclic compound **8** was oxidized with *m*-chloroperoxybenzoic acid to yield the unstable bis-lactone catalyzed with boron trifluoride etherate.[2a] Without further purification, the unsaturated bis-lactone was hydrogenated to yield saturated bis-lactone **9** in ethyl acetate. Unfortunately, when **9** was treated with base, such as sodium hydride, lithium diisopropylamide, or potassium *t*-butoxide, to generate the anion for the alkylation, the complex products produced. Since bis-lactone **9** did not survive at basic condition, an alternative approach forward Isoe's intermediate **3** was investigated (Scheme 3). Hydrogenation of the unsaturated **4** catalyzed with palladium on activated carbon in methanol gave the corresponding saturated product, which was followed by the reaction with a mixture of dibromomethane and diethylamine yielded α-methylene product **10**.[8] Next, we examined the oxidation of **10** using variety oxidants, such as ruthenium tetraoxide, silver oxide and Jones reagent, but the desired acid was not obtained. Finally, oxidation of **10** with sodium chlorite successfully yielded the corresponding acid which was further reacted with a catalytic amount of boron trifluoride etherate to produce the tricyclic lactone **3**.

3. Conclusion

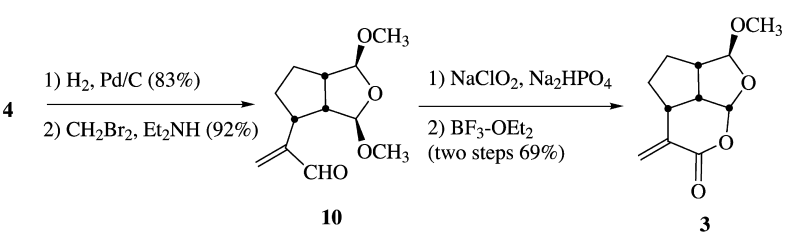
In conclusion, the successful synthesis of tricyclic lactone **3** demonstrates the utility of the Norrish type I reaction on a bicyclo[2.2.1]heptanone skeleton for the formal synthesis of udoteatrial hydrate (**1**). Efforts directed toward the synthesis of other naturally occurring iridoids are currently under way in our laboratory.

4. Experimental

4.1. General

THF and benzene were distilled before use from a deep blue solution resulting from sodium and benzophenone under nitrogen All reagents and solvents were obtained from commercial sources and used without further purification. Thin layer chromatography (TLC) analysis was performed with precoated silica gel (60 f_{254} plates) and column chromatography was carried out on silica (70–230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those in aqueous solutions) spherical flasks and stirred with magnetic bars. Organic layers were dried with anhydrous magnesium sulfate before concentration in vacuo. ^{1}H NMR spectra were determined at 300 or 500 MHz, and ^{13}C NMR spectra were determined at 75 or 125 MHz, respectively. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) in the solvents specified. The multiplicities of ^{13}C signals were determined by DEPT techniques.

4.1.1. *cis-endo*-3,5-Dimethoxy-4-oxa-tricyclo[5.2.1.0^{2,6}]-dec-8-ene (7). A solution of oxalyl chloride (17.74 g, 12.0 mL, 139.8 mmol) in dichloromethane (80 mL) at −78 °C, and dimethyl sulfoxide (20.35 g, 18.5 mL, 260.5 mmol) were added carefully. The solution was warmed to −40 °C for 5 min and recooled to −78 °C, and then a solution of alcohol (5.1 g, 32.5 mmol) in dichloromethane (15 mL) was added dropwise for 20 min followed by excess triethylamine (45 mL) for 30 min. The reaction mixture was warmed to room temperature and poured into saturated aqueous ammonium chloride solution (2 mL), and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce the crude compound. Without further purification, a mixture of crude dialdehyde and *p*-toluenesufonic acid (10 mg) in methanol (40 mL) was stirred for 3 h at room temperature. After removing the solvents, the residue was extracted with ethyl acetate (3×40 mL) and water (10 mL) and the combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate, 4:1) produced compound **7** (7.0 g, 90%) as a colorless oil. IR ($CHCl_3$) 1642 cm^{-1}. EI-MS $C_{11}H_{16}O_3$ *m/z* (%)=196 (M^+, 1), 164 (54), 130 (96), 99 (100); HRMS (EI, M^+) calcd for $C_{11}H_{16}O_3$ 196.1100, found 196.1108; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (t, *J*=1.9 Hz, 2H), 4.50 (s, 2H), 3.32 (s, 6H), 2.99–2.97 (m, 2H), 2.92–2.90 (m, 2H), 1.42 (AB, *J*=8.4 Hz, 1H), 1.30 (AB, *J*=8.4 Hz, 1H); ^{13}C



Scheme 3. Synthesis of Isoe's intermediate (**3**).

NMR (75 MHz, $CDCl_3$) δ 134.46, 108.80, 54.80, 53.45, 51.36, 44.68.

4.1.2. *cis-endo*-3,5-Dimethoxy-4-oxa-tricyclo[5.2.1.0^{2,6}]-decan-8-one (5). To a mixture of olefin **7** (4.33 g, 22.1 mmol) and sodium borohydride (1.05 g, 26.5 mmol) in THF (60 mL) was added carefully dimethyl sulfate (2.3 mL, 3.06 g, 24.3 mmol) in THF (40 mL) in an ice bath. The mixture was stirred at room temperature for 2 h. Oxidation was carried out by dropwise addition of hydrogen peroxide solution (35%, 20 mL)/3 N sodium hydroxide (10 mL)/water (10 mL) (vol.=2/2/1). The mixture was held an additional 1 h at reflux temperature, cooled and extracted with ethyl acetate (3×30 mL). After separation, the organic layers were dried, filtrated and evaporated to yield the crude alcohol. The crude alcohol in dichloromethane (40 mL) was added to a mixture of pyridinium chlorochromate (7.2 g, 34.9 mmol) and Celite (10 g) in dichloromethane (60 mL). After being stirred at room temperature for 4 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel column. The filtrate was dried, filtered and concentrated to produce crude ketone. Purification on silica gel (hexane/ethyl acetate, 2:1) afforded **5** (2.9 g, 62%) as a solid. Mp 76–78 °C; IR ($CHCl_3$) 1745, 1641 cm^{-1}; EI-MS $C_{11}H_{16}O_4$ *m/z* (%)=212 (M^+, 1), 181 (41), 152 (78), 110 (93), 79 (100); HRMS (EI, M^+) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (s, 1H), 4.62 (s, 1H), 3.32 (s, 6H), 2.77–2.73 (m, 2H), 2.62 (br s, 1H), 2.55–2.53 (m, 1H), 1.87–1.83 (m, 2H), 1.59–1.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.91, 107.19, 107.13, 55.41, 55.17, 53.38, 51.77, 49.60, 40.21, 39.55, 36.46. Crystal of **5** was grown by slow diffusion of ethyl acetate into a solution of **5** in dichloromethane to yield the prism: primitive orthorhombic, a=19.096(4) Å, b=10.829(3) Å, c=10.430(4) Å, V=2157.0(9) Å^3, Z=8, d_{calcd}=1.307 g/cm^3, F(000)=912.00, 2θ range 25 (16.8–23.0°).

4.1.3. (1,3-Dimethoxy-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-4-yl)acetaldehyde (4). Ketone (0.2 g, 0.94 mmol) dissolved in benzene (200 mL) free of oxygen was irradiated under a nitrogen atmosphere with a UV lamp (λ>310 nm), using a pyrex glass filter at room temperature for 15 h. The solvent was evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate, 4:1) afforded **4** (0.18 g, 90%) as a solid: IR ($CHCl_3$) 1707, 1639 cm^{-1}; EI-MS $C_{11}H_{16}O_4$ *m/z* (%)=212 (M^+, 1), 181 (20), 149 (43), 108 (100); HRMS (EI, M^+) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (t, J=1.4 Hz, 1H), 5.77–5.63 (m, 2H), 4.88 (d, J=2.1 Hz, 1H), 4.87 (s, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.05 (td, J=1.8, 8.1 Hz, 1H), 2.72 (ddd, J=1.5, 6.9, 15.6 Hz, 1H), 2.58 (ddd, J=1.5, 6.9, 15.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.71, 134.98, 130.17, 109.59, 108.49, 57.85, 55.48, 55.19, 49.82, 45.47, 40.56.

4.1.4. 2,6-Dimethoxy-2a,4a,5,6,7a,7b-hexahhydro-2*H*-1,7-dioxacyclopenta[*cd*]indene (8). A mixture of aldehyde **4** and *p*-toluenesufonic acid (10 mg) in methanol (40 mL) was stirred for 8 h at room temperature. After removing the solvents, the residue was extracted with ethyl acetate (3×10 mL) and water (5 mL) and the combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate, 5:1) produced compound **8** (80 mg, 80%) as a colorless oil: IR ($CHCl_3$) 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70–5.63 (m, 2H), 4.77 (s, 1H), 4.64 (dd, J=2.7, 8.7 Hz, 1H), 3.47 (s, 3H), 3.39 (s, 3H), 3.50–3.34 (m, 2H), 3.22–3.18 (m, 1H), 2.87–2.80 (m, 1H), 1.90–1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.98, 129.98, 104.96, 101.83, 95.64, 58.28, 55.90, 54.74, 41.29, 36.92, 30.95.

4.1.5. Perhydro-1,7-dioxafuro[1,2,3-*cd*]isobenzofuran-2,6-dione (9). To a solution of *m*-chloroperoxybenzoic acid (860 mg, 5.0 mmol) in dichloromethane (10 mL) and diethyl ether (1 mL) at rt was added boron trifluoride etherate (1 M, 2.1 mL, 2.1 mmol). The solution was heated to 60 °C for 10 min, and then a solution of **8** (150 mg, 0.7 mmol) in dichloromethane (5 mL) was added dropwise for 5 min. The reaction mixture was reacted at reflux temperature for 2 h. And the mixture was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate solution (3 mL). The organic layers were washed with aqueous sodium bicarbonate solution (10 mL) and then dried, filtered and evaporated. Without further purification, the unstable product (100 mg) in ethyl acetate (10 mL) was stirred under 1 atm of hydrogen at room temperature with 10% palladium on activated carbon as catalyst (10 mg) for 2 h. Filtration through a short plug of Celite and washing with ethyl acetate (3×10 mL) resulted in the desired crude compound. Purification on silica gel (hexane/ethyl acetate, 1:1) produced tricyclic bislactone **9** (92 mg, 72%) as a colorless solid: mp 99–100 °C; IR ($CHCl_3$) 1770, 1130 cm^{-1}; HRMS (EI, M^++1) calcd for $C_9H_{11}O_4$ 183.0657, found 183.0657; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (d, J=6.6 Hz, 1H), 3.40–3.20 (m, 2H), 2.75–2.56 (m, 2H), 2.35–2.21 (m, 3H), 2.10–1.95 (m, 1H), 1.70–1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.39, 167.84, 99.46, 45.34, 42.27, 36.16, 32.70, 32.35, 28.06. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.30; H, 5.74.

4.1.6. (1,3-Dimethoxy-hexahydro-cyclopenta[*c*]furan-4-yl)-acetaldehyde (10). Olefin **4** (0.38 g, 1.79 mmol) was dissolved in ethyl acetate (10 mL) and 10% palladium on activated carbon as catalyst was added. Then hydrogen was bubbled into the mixture for 10 min, and stirred at room temperature for 3 h. Filtration through a short plug of Celite and washing with ethyl acetate (3×10 mL) resulted in the desired saturated compound (0.31 g, 83%): IR ($CHCl_3$) 1739 cm^{-1}; FAB-MS $C_{11}H_{18}O_4$ *m/z* (%)=213 (M^++1, 10), 199 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.78 (s, 1H), 4.72 (s, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.75–2.63 (m, 3H), 2.51–2.35 (m, 2H), 1.76–1.74 (m, 2H), 1.64–1.60 (m, 1H), 1.11–1.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.09, 113.07, 107.83, 55.31, 54.95, 52.34, 49.09, 45.51, 36.15, 30.93, 29.40. A solution of resulting aldehyde (200 mg, 0.93 mmol) was added to a mixture of diethylamine (200 mg, 2.8 mmol) and dibromomethane (10 mL) and the reaction mixture was heated to 55 °C for 2 h and cooled to room temperature. The reaction mixture was evaporated and purified on silica gel (hexane/ethyl acetate, 4:1) to produce olefin **10** (194 mg, 92%) as a colorless oil: IR ($CHCl_3$) 1648 cm^{-1}; EI-MS $C_{12}H_{18}O_4$ *m/z* (%)=225 (M^++1, 1), 195 (93), 134 (100); HRMS (EI, M^+) calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1212; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 6.30 (s, 1H), 6.17 (s, 1H), 4.78 (s,

1H), 4.48 (s, 1H), 3.38 (s, 3H), 3.28 (s, 3H), 3.07 (t, J=7.5 Hz, 1H), 2.94 (m, 1H), 2.84 (t, J=8.0 Hz, 1H), 1.84–1.70 (m, 3H), 1.55–1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.09, 150.17, 134.17, 113.65, 108.88, 55.17, 54.99, 50.56, 49.10, 41.08, 29.13, 27.55.

4.1.7. 2-(1,3-Dimethoxy-hexahydro-cyclopenta[*c*]furan-4-yl)-propenal (3) (Isoe's intermediate). A solution of aldehyde **10** (100 mg, 0.44 mmol) and 2-methyl-2-butene (chlorine scavenger) (1 mL) in *t*-butanol (10 mL) was treated with a solution of sodium chlorite (80%, 550 mg, 5.0 mmol) and potassium dihydrogen phosphate (KH_2PO_4, 600 mg) in water (5 mL) at room temperature. The mixture was stirred for an additional 30 min, then the organic solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3×10 mL) and water (5 mL) and the combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated to yield the crude product. Without further purification, boron trifluoride etherate (1 M, 0.1 mL) was added to a solution of the resulting product (90 mg) for 4 h at room temperature. After removing the solvents, the residue was extracted with ethyl acetate (3×10 mL) and water (5 mL). The organic layers were washed with aqueous sodium bicarbonate solution (10 mL) and then dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate, 5:1) produced compound **3** (64 mg, 69%) as a colorless oil: IR ($CHCl_3$) 2950, 1735, 1630 cm^{-1}; HRMS (EI, M^+ +1) calcd for $C_{11}H_{15}O_4$ 211.0970, found 211.0965; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (t, J=1.0 Hz, 1H), 5.84 (d, J=6.5 Hz, 1H), 5.57 (t, J=1.0 Hz, 1H), 4.87 (d, J=2.5 Hz, 1H), 3.43 (s, 3H), 3.16–3.00 (m, 2H), 2.77–2.69 (m, 1H), 1.91–1.82 (m, 2H), 1.80–1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.18, 136.44, 125.38, 110.52, 102.83, 56.16, 50.65, 45.68, 42.00, 33.65, 29.15.

5. Supplementary material

Additional spectroscopic data for compounds **3**–**5**, **7**–**10** (^{1}H NMR in $CDCl_3$).

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References and notes

1. (a) Tai, H. M.; Yang, C. C.; Chang, N. C. *J. Chin. Chem. Soc.* **1995**, *42*, 821–823. (b) Ge, Y.; Kondo, S.; Katsumura, S.; Nakatani, K.; Isoe, S. *Tetrahedron* **1993**, *49*, 10555–10576. (c) Ge, Y.; Kondo, S.; Odagaki, Y.; Katsumura, S.; Nakatani, K.; Isoe, S. *Tetrahedron Lett.* **1993**, *34*, 2621–2624. (d) Whitesell, J. K.; Fisher, M.; Jardine, P. D. S. *J. Org. Chem.* **1983**, *48*, 1556–1557. (e) Nakatsu, T.; Ravi, B. N.; Faulkner, D. J. *J. Org. Chem.* **1981**, *46*, 2435–2438.
2. (a) Corey, E. J.; Su, W.-g. *J. Am. Chem. Soc.* **1987**, *109*, 7534–7535. (b) Nakanishi, K.; Habaguchi, K.; Nakadaira, Y.; Woods, M. C.; Maruyama, M.; Major, R. T.; Alauddin, M.; Patel, A. R.; Weings, K.; Bahr, W. *J. Am. Chem. Soc.* **1971**, *93*, 3544–3546.
3. (a) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201–3204. (b) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205–3206. (c) Corey, E. J.; Kang, M.-c.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651.
4. Corey, E. J.; Letavic, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617, and references cited therein.
5. Chang, M. Y.; Chang, C. P.; Chang, N. C. *J. Chin. Chem. Soc.* **1996**, *43*, 459–461, and references cited therein.
6. (a) Turro, N. J. *Modern molecular photochemistry*; Benjamin/Cummings: Menlo Park, CA, 1978; Chapter 13. (b) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820–836. (c) Gallant, P.; Storme, P.; van der Eycken, E.; Vandewalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797. (d) Van der Eycken, E.; Gallant, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 367. (e) De Keukeleire, D.; He, S.-L. *J. Chem. Soc., Chem. Commun.* **1992**, 419–420.
7. (a) Lee, A. Y.; Chang, M. Y.; Chang, N. C. *Heterocycles* **1999**, *51*, 295–302. (b) Chang, M. Y.; Lin, C. H.; Lee, A. Y.; Tai, H. M.; Chang, N. C. *J. Chin. Chem. Soc.* **1999**, *46*, 205–210. (c) Lee, A. Y.; Chang, M. Y.; Tai, H. M.; Chang, N. C. *J. Chin. Chem. Soc.* **1999**, *46*, 937–940.
8. (a) Hon, Y. S.; Chang, F. J.; Lu, L. *J. Chem. Soc., Chem. Commun.* **1994**, 2041–2042. (b) Hon, Y. S.; Chang, F. J.; Lu, L.; Lin, S. W. *Tetrahedron* **1998**, *54*, 5233–5246. (c) Hon, Y. C.; Lin, W. C. *Tetrahedron Lett.* **1995**, *36*, 7693–7696.

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An effective method for the synthesis of carboxylic esters and lactones using substituted benzoic anhydrides with Lewis acid catalysts

Isamu Shiina*

Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

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Abstract—An efficient mixed-anhydride method for the synthesis of carboxylic esters and lactones using benzoic anhydride having electron withdrawing substituent(s) is developed by the promotion of Lewis acid catalysts. In the presence of a catalytic amount of $TiCl_2(ClO_4)_2$, various carboxylic esters are prepared in high yields through the formation of the corresponding mixed-anhydrides from 3,5-bis(trifluoromethyl)benzoic anhydride and carboxylic acids. The combined catalyst consisting of $TiCl_2(ClO_4)_2$ together with chlorotrimethylsilane functions as an effective catalyst for the synthesis of carboxylic esters from free carboxylic acids and alcohols with 4-(trifluoromethyl)benzoic anhydride. Various macrolactones are prepared from the free ω-hydroxycarboxylic acids by the combined use of 4-(trifluoromethyl)benzoic anhydride and titanium(IV) catalysts together with chlorotrimethylsilane under mild reaction conditions. The lactonization of trimethylsilyl ω-(trimethylsiloxy)carboxylates using 4-(trifluoromethyl)benzoic anhydride is also promoted at room temperature in the presence of a catalytic amount of $TiCl_2(ClO_4)_2$. An 8-membered ring lactone, a synthetic intermediate of cephalosporolide D, is successfully synthesized according to this mixed-anhydride method using 4-(trifluoromethyl)benzoic anhydride by the promotion of a catalytic amount of $Hf(OTf)_4$.

1. Introduction

While numerous esterifications using Brønsted and Lewis acid catalysts have been reported, a few methods have actually been utilized for the effective preparation of carboxylic esters from equimolar amounts of carboxylic acids and alcohols under mild conditions.[1] On the other hand, some acylation reactions of alkyl silyl ethers, alcohols or thiols with an excess amount of acetic or benzoic anhydrides were presented since acid anhydrides could be efficiently activated by acidic species.[2] Furthermore, it is also well known that a mixed-anhydride method using trifluoroacetic anhydride is sometimes very convenient for the generation of bulky carboxylic esters.[3]

During the course of our studies on the exploration of new catalytic synthetic reactions using Lewis acids,[4] a unique method for the preparation of carboxylic esters was developed in 1992 starting from silyl carboxylates and alkyl silyl ethers via the active intermediary mixed-anhydrides prepared in situ from silyl carboxylates with 4-(trifluoromethyl)benzoic anhydride (TFBA) using a catalytic amount of a Lewis acid such as $Sn(OTf)_2$, $TiCl_2(ClO_4)_2$, $TiCl_2(OTf)_2$, $ZrCl_2(OTf)_2$, $HfCl_2(OTf)_2$, $AlCl(OTf)_2$, $InCl(OTf)_2$, etc.[5] In 1994, we extended this method to the reaction between nearly equimolar amounts free carboxylic acids and alcohols by varying the combination of Lewis acids.[6] The corresponding carboxylic esters or lactones are obtained in high yields by treating nearly equimolar amounts of free carboxylic acids and alcohols or ω-hydroxycarboxylic acids with substituted benzoic anhydrides possessing electron withdrawing group(s) in the presence of catalytic amounts of $TiCl_2(ClO_4)_2$ or $TiCl_2(OTf)_2$ together with chlorotrimethylsilane. Yamamoto et al. also found that $Sc(OTf)_3$ or $Sc(NTf_2)_3$ is an effective Lewis acid for the promotion of this reaction in 1995 and the desired carboxylic esters including medium-sized lactones were produced in high yields.[2e–g]

In this paper, we describe in detail the results of our investigations on the effective method for the preparation of carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols using an active Lewis acid catalyst initially reported in a previous communication,[6a] and also further developments of the above reactions applied to the preparations of lactones including synthetic intermediates of natural compounds.[5c,6b,7]

Keywords: Carboxylic esters; Macrolactones; Medium-sized lactones; Cephalosporolide D; 4-(Trifluoromethyl)benzoic anhydride; 3,5-Bis-(trifluoromethyl)benzoic anhydride; Mixed-anhydrides; Lewis acid catalysts.
* Tel.: +81-3-3260-4271; fax: +81-3-3260-5609;
e-mail address: shiina@ch.kagu.sut.ac.jp

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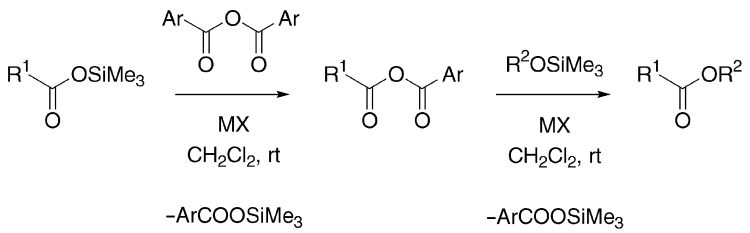


Scheme 1. Synthesis of carboxylic esters from silyl carboxylates with alkyl silyl ethers using benzoic anhydrides.

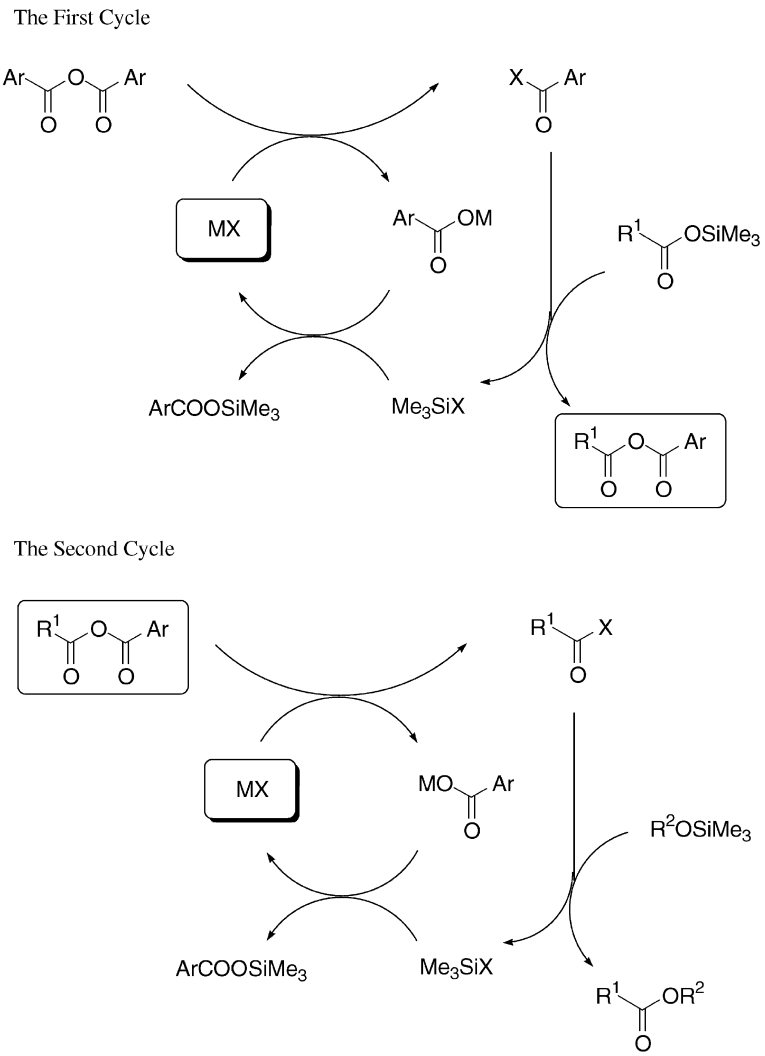
2. Results and discussion

2.1. Esterification reaction via mixed-anhydrides using benzoic anhydrides

Recently, an effective method for the synthesis of carboxylic esters from nearly equimolar amounts of silyl carboxylates and alkyl silyl ethers via mixed-anhydrides was developed by employing a substituted benzoic anhydride and a Lewis acid catalyst (Scheme 1).[5a,b] In the report, it was indicated that the following successive reactions would lead to the formation of carboxylic esters; that is, (1) the initial formation of the mixed-anhydride from benzoic anhydride and silyl carboxylates by the promotion of Lewis acid, and (2) the alcoholysis of the mixed-anhydrides by alkyl silyl ethers with the assistance of a Lewis acid.

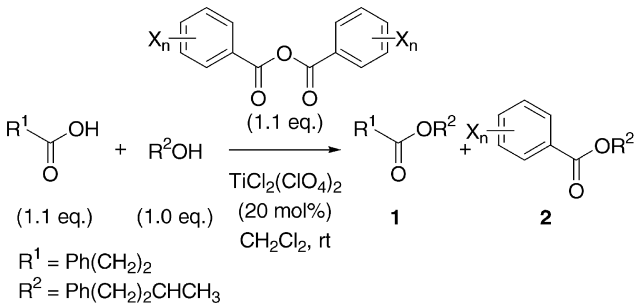
The mixed-anhydride consisting of aromatic and aliphatic acyl parts is generated in the first cycle and it will be successively consumed in the second cycle to afford the desired carboxylic ester (Scheme 2). Therefore, the mixed-anhydride formed in situ is assumed to be the most important intermediate in the catalytic process.

It was also found in previous research that the use of silyl derivatives of carboxylic acids and of alcohols was essential for the completion of the esterification reaction at room



Scheme 2. Catalytic cycle for the production of carboxylic esters using benzoic anhydrides as coupling reagents.

Table 1. Effect of substituted benzoic anhydrides



Entry	X_n	Yield[a] (%)	**1/2**[b]
1	H	50	17/1
2	2-F	82	70/1
3	3-NO_2	72	60/1
4	4-NO_2	57	40/1
5	2-CF_3	88	80/1
6	3-CF_3	87	180/1
7	4-CF_3	88	180/1
8	3,5-$(CF_3)_2$	89	>200/1

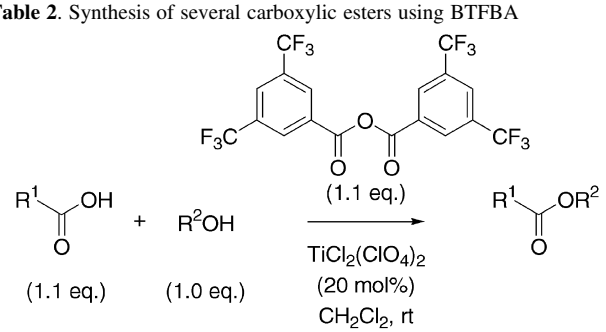
[a] Isolated yield of **1**.
[b] Determined by ^{1}H NMR using a crude mixture.

temperature. Therefore, the development of further useful and convenient methods for the preparation of carboxylic esters from free carboxylic acids and alcohols was next required. However, when the condensation of 3-phenylpropanoic acid and 4-phenyl-2-butanol was carried out in the presence of TFBA and 20 mol% of $TiCl_2(ClO_4)_2$, the alcohol was not completely consumed and the desired ester was obtained in 88% yield along with a small amount of an undesirable ester, 1-methyl-3-phenylpropyl (4-trifluoromethyl)benzoate (product selectivity=180:1). Several substituted benzoic anhydrides were then examined for the reaction of free carboxylic acids and alcohols to improve the yield and chemoselectivity (Table 1). The reaction smoothly took place to afford the desired carboxylic ester in good yields using mono-substituted benzoic anhydrides having an electron withdrawing group such as fluoride, nitro and trifluoromethyl, however, the chemoselectivity was not perfect (entries 2–7). Although the formation of a small amount of 1-methyl-3-phenylpropyl (3-trifluoromethyl)-benzoate, a by-product, was observed when using (3-trifluoromethyl)benzoic anhydride as the condensation reagent, the product selectivity is nearly equal to that of the reaction using TFBA (see entries 6 and 7). It was finally determined that the desired ester was exclusively obtained when 3,5-bis(trifluoromethyl)benzoic anhydride (BTFBA) was employed as shown in entry 8.

Some examples for the synthesis of carboxylic esters from the corresponding carboxylic acids and alcohols using BTFBA and $TiCl_2(ClO_4)_2$ are shown in Table 2. In every case, the reactions smoothly proceed at room temperature in dichloromethane to give the corresponding carboxylic esters in good to high yields from nearly equimolar amounts of carboxylic acids and alcohols. It is noteworthy that pivalic acid esters, derived from a bulky carboxylic acid, were also obtained in high yields by the present reaction (entries 5 and 6).

Although the yields of the esterification using BTFBA were relatively higher compared to those obtained by TFBA, the reaction did not completely proceed under these conditions probably due to the deactivation of the catalyst. Next, several combinations of reactants were examined using the present mixed-anhydride method for the preparation of carboxylic esters in higher yields (Table 3). When trimethylsilyl 3-phenylpropanoate and 4-phenyl-2-butanol were employed in the presence of 20 mol% of $TiCl_2(ClO_4)_2$ with BTFBA, nearly the same yield of the desired ester was obtained as that for the reaction between silyl carboxylate and alkyl silyl ether (see entries 1 and 2). However, the yield slightly decreased when using 3-phenylpropanoic acid and 1-methyl-3-phenylpropyl trimethylsilyl ether as the substrates under the identical reaction conditions (entry 3). Therefore, it was assumed that the free carboxylic acid particularly deactivated the Lewis acid catalyst by ligand exchange on the catalyst. The esterification yield of the free carboxylic acid with the free alcohol was apparently lower compared to those of the other combinations (entry 4).

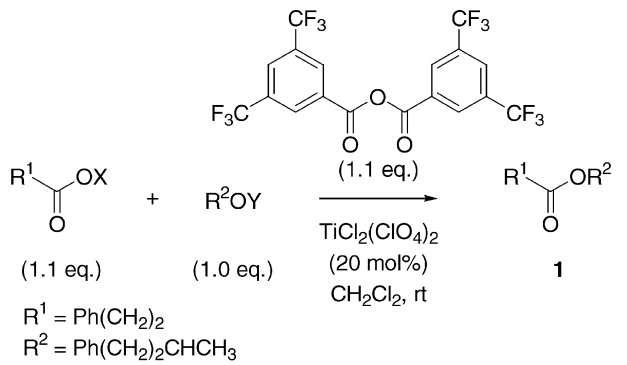
Table 2. Synthesis of several carboxylic esters using BTFBA



Entry	R^1	R^2	R^1COOR^2	Yield[a] (%)
1	$Ph(CH_2)_2$	$Ph(CH_2)_3$	**3**	91
2	$Ph(CH_2)_2$	$Ph(CH_2)_2CHCH_3$	**1**	89
3	*c*-C_6H_{11}	$Ph(CH_2)_3$	**4**	88
4	*c*-C_6H_{11}	$Ph(CH_2)_2CHCH_3$	**5**	86
5	^{t}Bu	$Ph(CH_2)_3$	**6**	91
6	^{t}Bu	$Ph(CH_2)_2CHCH_3$	**7**	88

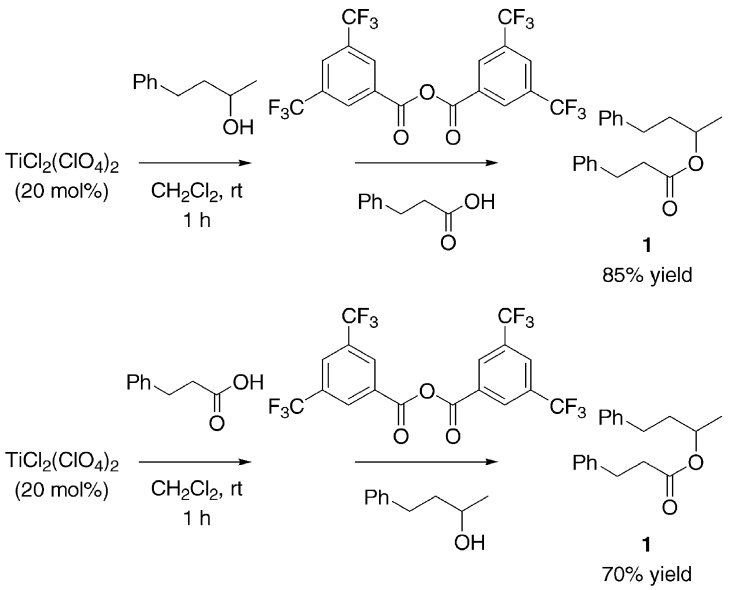
[a] Isolated yield.

Table 3. Synthesis of carboxylic esters using silylated or free substrates



Entry	X	Y	Yield[a] (%)
1	$SiMe_3$	$SiMe_3$	98
2	$SiMe_3$	H	96
3	H	$SiMe_3$	93
4	H	H	89

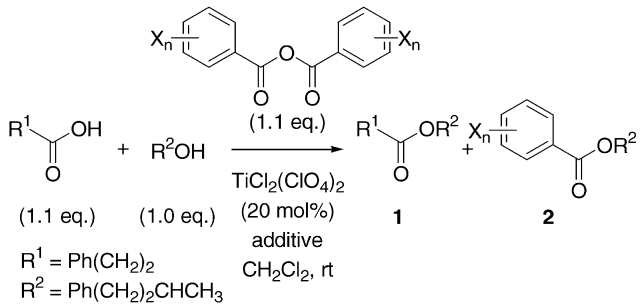
[a] Isolated yield.



Scheme 3. Yield of **1** using pre-treated titanium(IV) catalysts.

Furthermore, the order of addition of the free carboxylic acids and alcohols was examined to clarify the deactivation process (Scheme 3). When 4-phenyl-2-butanol was mixed with 20 mol% of $TiCl_2(ClO_4)_2$ in dichloromethane for 1 h prior to the addition of 3-phenylpropanoic acid and BTFBA, the desired ester was obtained in relatively good yield (85%). However, the titanium(IV) catalyst, which was treated with 3-phenylpropanoic acid before the esterification, gave the desired ester in 70% yield. The activity of the $TiCl_2(ClO_4)_2$ was considerably decreased in the latter case. Therefore, we next tried to employ a suitable additive which functions as a co-reagent to maintain the activity of the titanium(IV) catalyst under the influence of the free carboxylic acids.

Table 4. Effect of additives

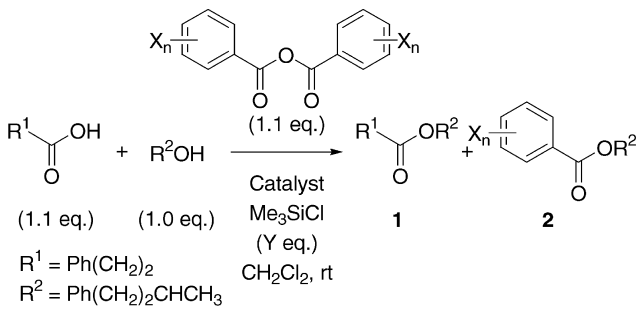


Entry	X_n	Additive	Yield[a] (%)	**1/2**[b]
1	3-CF_3	—	87	180/1
2	3-CF_3	MS 5 Å	89	90/1
3	4-CF_3	—	88	180/1
4	4-CF_3	MS 5 Å	90	70/1
5	3,5-$(CF_3)_2$	—	89	>200/1
6	3,5-$(CF_3)_2$	MS 3 Å	90	>200/1
7	3,5-$(CF_3)_2$	MS 4 Å	78	>200/1
8	3,5-$(CF_3)_2$	MS 5 Å	85	120/1
9	3,5-$(CF_3)_2$	Me_3SiCl (2 equiv.)	94	>200/1
10	3,5-$(CF_3)_2$	$(Me_3Si)_2O$ (2 equiv.)	88	>200/1

[a] Isolated yield of **1**.
[b] Determined by ^1H NMR using a crude mixture.

First, molecular sieves (MS 5 Å) were added to the reaction mixture consisting of 3-phenylpropanoic acid and 4-phenyl-2-butanol in the presence of (3-trifluoromethyl)benzoic anhydride, TFBA or BTFBA since MS 5 Å are known to have a weak acidity. However, the reactions did not go to completion and the formation of sufficient quantities of the by-products was observed in each case (Table 4, entries 2, 4 or 8). Further screening was carried out using several ingredients such as other molecular sieves and hexamethyldisiloxane for the model reaction with BTFBA; it was found that chlorotrimethylsilane was a very effective co-reagent for keeping the activity of the titanium(IV) catalyst. In the presence of 2 mol of chlorotrimethylsilane and 1.1 mol of BTFBA, 10 mol% of $TiCl_2(ClO_4)_2$ was not deactivated during the reaction, and the desired ester was exclusively obtained in 94% yield (entry 9).

Table 5. Effect of catalysts and reaction conditions



Entry	Catalyst (amount/mol%)	X_n	Y	Yield[a] (%)
1	$TiCl_2(ClO_4)_2$ (10)	3,5-$(CF_3)_2$	2	94
2	$TiCl_2(ClO_4)_2$ (10)	4-CF_3	2	95
3	$TiCl_2(ClO_4)_2$ (10)	4-CF_3	1	96
4	$TiCl_2(ClO_4)_2$ (10)	4-CF_3	0.5	97
5	$TiCl_2(ClO_4)_2$ (10)	4-CF_3	0.2	94
6	$TiCl_2(OTf)_2$ (10)	4-CF_3	0.2	78
7	$Sn(OTf)_2$ (20)	4-CF_3	0.2	78 (5)[b]

[a] Isolated yield of **1**.
[b] Yield of 1-methyl-3-phenylpropyl 4-(trifluoromethyl)benzoate.

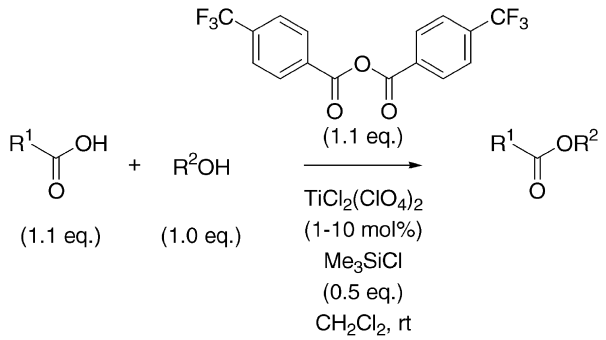
The reaction conditions were optimized using several catalysts (see Table 5). The existence of chlorotrimethylsilane was so effective that the corresponding ester was obtained in high yield without the accompanying undesired ester even though TFBA was used as the condensation reagent instead of BTFBA (entries 2–6). For example, the desired ester was exclusively produced in nearly quantitative yield when the reaction was carried out in the presence of TFBA, 10 mol% of $TiCl_2(ClO_4)_2$ and 0.5 mol of chlorotrimethylsilane (entry 4).

Various examples of the present condensation reaction are listed in Table 6. In every case, the reaction smoothly proceeded at room temperature in dichloromethane to give the corresponding esters in excellent yields from nearly equimolar amounts of free carboxylic acids and alcohols. It was also revealed that the use of 1 mol% of the catalyst was enough to produce 1-methyl-3-phenylpropyl 3-phenylpropanoate in 99% yield from the corresponding carboxylic acid and alcohol (entry 4). When using branched alcohols such as menthol and chorestanol or a hindered carboxylic acid such as pivalic acid, the corresponding carboxylic esters were also produced in high yields at room temperature (entries 6, 7, 10 or 11). The reaction of benzoic acid with primary and secondary alcohols afforded the desired alkyl benzoates with good chemoselectivities using BTFBA as the condensation reagent as shown in entries 12 and 13.

It is noted that the procedure for this synthesis is quite simple and almost pure carboxylic esters are obtained just by washing the reaction mixture with saturated aqueous $NaHCO_3$.

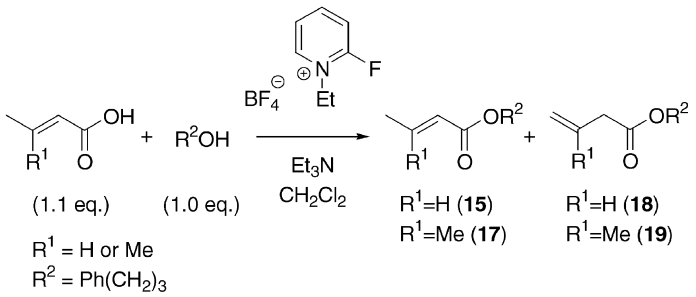
The esterification reaction of crotonic acid or 3-methyl-2-butenoic acid is a base sensitive reaction leading to the rearrangement of a double bond to form an α,β-unsaturated ester **18** or **19** even under weakly basic conditions (Scheme 4).[5b,8] For example, the esterification reaction of crotonic acid with 3-phenylpropanol using 1-ethyl-2-fluoropyridinium tetrafluoroborate and triethylamine produced a mixture of the desired ester and rearrangement product (76%, **15/18**=4:1). A similar result was also observed in the case of 3-methyl-2-butenoic acid (50%, **17/19**=1:2). Therefore, the esterification reaction between equimolar amounts of crotonic acid and alcohol has been generally carried out using DCC or thionyl chloride. It is also noted that the present method was successfully applied to the synthesis of alkyl crotonate and alkyl 3-methyl-2-butenoate from nearly equimolar amounts of carboxylic acids and alcohols under mild conditions. When 10 mol% of $TiCl_2(ClO_4)_2$ was used in the present experiment, no

Table 6. Synthesis of various carboxylic esters using TFBA or BTFBA



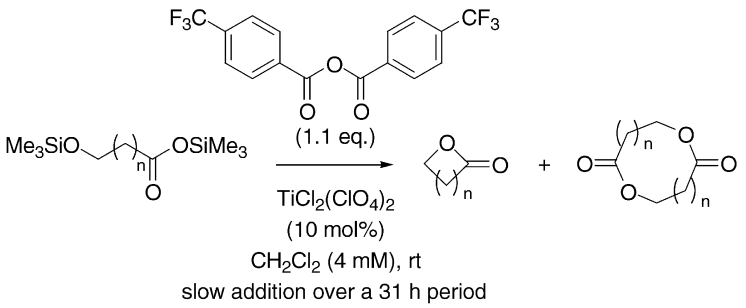
Entry	R^1	R^2	R^1COOR^2	Time (h)	Yield[a] (%)
1	$Ph(CH_2)_2$	Bn	**8**	12	93
2	$Ph(CH_2)_2$	CH_2═$CHCH_2$	**9**	0.5	92
3	$Ph(CH_2)_2$	$Ph(CH_2)_3$	**3**	0.5	96
4	$Ph(CH_2)_2$	$Ph(CH_2)_2CHCH_3$	**1**	13	97 (99)[b]
5	$Ph(CH_2)_2$	*c*-C_6H_{11}	**10**	12	93
6	$Ph(CH_2)_2$	Menthyl	**11**	13	93
7	$Ph(CH_2)_2$	5α-Chorestan-3β-yl	**12**	17	90
8	*c*-C_6H_{11}	$Ph(CH_2)_3$	**4**	0.5	96
9	*c*-C_6H_{11}	$Ph(CH_2)_2CHCH_3$	**5**	3	95
10	^{t}Bu	$Ph(CH_2)_3$	**6**	0.5	95
11	^{t}Bu	$Ph(CH_2)_2CHCH_3$	**7**	16	95
12[c]	Ph	$Ph(CH_2)_3$	**13**	12	90 (1.1)[d]
13[c]	Ph	$Ph(CH_2)_2CHCH_3$	**14**	12	93 (1.5)[e]
14	(*E*)-CH_3CH═CH	$Ph(CH_2)_3$	**15**	12	93
15	(*E*)-CH_3CH═CH	$Ph(CH_2)_2CHCH_3$	**16**	12	93
16	$(CH_3)_2CH$═CH	$Ph(CH_2)_3$	**17**	12	95

[a] Isolated yield. 10 mol% of catalyst was used.
[b] 1 mol% of catalyst was used.
[c] BTFBA was used instead of TFBA.
[d] Yield of 3-phenylpropyl 3,5-bis(trifluoromethyl)benzoate.
[e] Yield of 1-methyl-3-phenylpropyl 3,5-bis(trifluoromethyl)benzoate.



Scheme 4. Base-induced rearrangement in the synthesis of alkyl crotonate and 3-methyl-2-butenoate.

Table 7. Synthesis of lactones from silyl ω-siloxycarboxylates using TFBA



Entry	*n*	Yield[a] (%) (ring number)	
		Monomer	Dimer
1	10	75 (13)	4 (26)
2	13	89 (16)	2 (32)

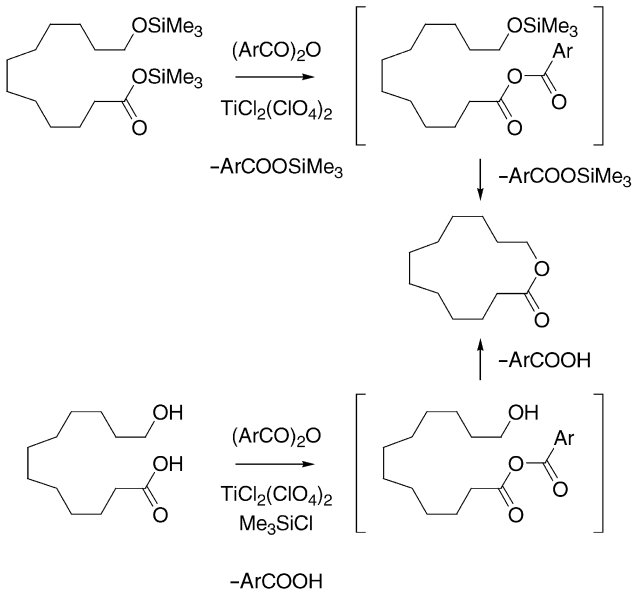
[a] Isolated yield.

rearranged product was isolated at all and the desired esters were obtained in high yields (Table 6, entries 14–16). These examples show the mildness of the conditions in the present esterification reaction.

2.2. Lactonization via mixed-anhydrides using benzoic anhydrides

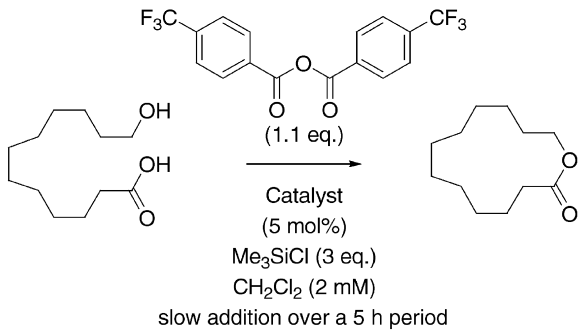
Several macrolide antibiotics have become important therapeutic agents in clinical medicine. As a result, numerous derivatives of various macrolactones have been synthesized and the discovery of new macrolide antibiotics has attracted our attention over the past two decades.[9] The chemical synthesis of macrolactones has made great progress due to the development of efficient methods for the ring closure from ω-hydroxycarboxylic acids (*seco*-acids) or their activated derivatives. Though a variety of methods have been reported for the synthesis of macrolactones,[1a] there are a few reactions which efficiently proceed under acidic conditions.[10] Recently, we developed an effective method for the preparation of macrolactones starting from the silyl derivatives of *seco*-acids via formation of the corresponding mixed-anhydrides.[5c] Namely, in the presence of TFBA and 10 mol% of $TiCl_2(ClO_4)_2$, the cyclization of trimethylsilyl ω-(trimethylsiloxy)carboxylates smoothly takes place at room temperature to afford the corresponding lactones in good to high yields as shown in Table 7.

To avoid deactivation of the titanium(IV) catalyst during the addition of the substrates to the reaction mixture, silyl derivatives of *seco*-acids were employed as precursors for the present cyclization instead of using free ω-hydroxycarboxylic acids. On the other hand, the equimolar condensation reaction between free carboxylic acids and



Scheme 5. Synthesis of macroactones starting from silyl ω-siloxycarboxylates or ω-hydroxycarboxylic acids using benzoic anhydrides as the condensation reagents.

Table 8. Effect of catalysts and reaction temperature

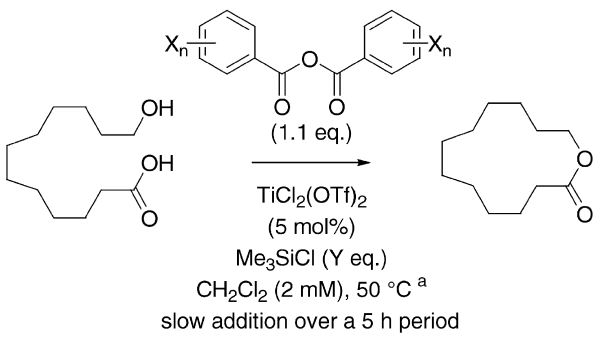


Entry	Catalyst	Temp.[a] (°C)	Yield[b] (%)	
			Monomer	Dimer
1	$TiCl_2(ClO_4)_2$	rt	68	2
2	$TiCl_2(OTf)_2$	rt	29	1
3	$TiCl_2(OTf)_2$	40	81	4
4	$TiCl_2(OTf)_2$	50	83	5
5	$TiCl(OTf)_3$	50	77	3
6	$TiCl_2(OTf)_2$	60	55	8

[a] Bath temperature.
[b] Isolated yield.

alcohols had been established in the former section by the combined use of TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ together with chlorotrimethylsilane, therefore, it was then anticipated that the direct lactonization of free ω-hydroxycarboxylic acids would function more efficiently by the promotion of Lewis acids under the influence of a co-catalyst (Scheme 5). In this section, a useful method for the preparation of macrolactones directly from ω-hydroxycarboxylic acids will be described by the combined use of TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ or $TiCl_2(OTf)_2$ together with chlorotrimethylsilane.

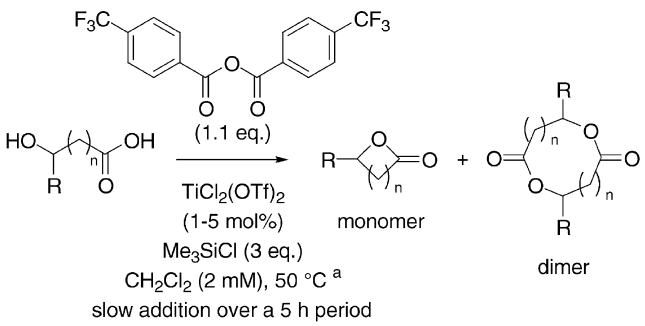
Table 9. Effect of benzoic anhydrides and amounts of chlorotrimethylsilane



Entry	X	Y	Yield[b] (%)	
			Monomer	Dimer
1	4-CF_3	0	31	3
2	4-CF_3	2	60	4
3	4-CF_3	3	83	5
4	4-CF_3	10	80	6
5	3,5-$(CF_3)_2$	3	51	7
6	4-F	3	44	7

[a] Bath temperature.
[b] Isolated yield.

Table 10. Synthesis of lactones from ω-hydroxycarboxylic acids using TFBA



Entry	R	*n*	Yield[b] (%) (ring number)	
			Monomer	Dimer
1	H	10	83 (13)	5 (26)
2	C_6H_{13}	10	91 (13)	3 (26)
3[c]	C_6H_{13}	10	83 (13)	8 (26)
4	H	11	80 (14)	3 (28)
5	H	12	89 (15)	2 (30)
6	H	13	88 (16)	5 (32)
7[c]	H	13	63 (16)	5 (32)
8	H	14	88 (17)	1 (34)

[a] Bath temperature.
[b] Isolated yield. 5 mol% of catalyst was used.
[c] 1 mol% of catalyst was used.

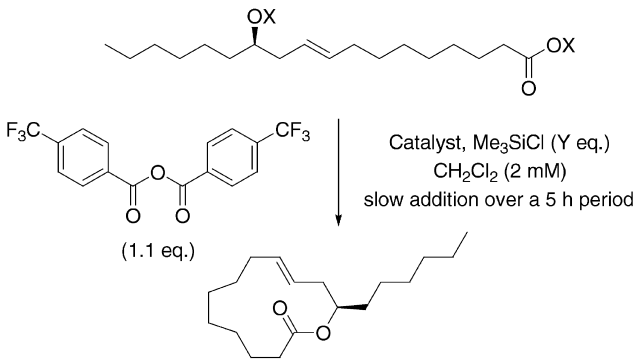
When the mixture of 12-hydroxydodecanoic acids and TFBA in dichloromethane was added over a 5 h period to the suspension of 5 mol% of $TiCl_2(ClO_4)_2$ and 3 mol of chlorotrimethylsilane in dichloromethane at room temperature, the desired macrolactone was obtained in 68% yield. In order to improve the yield of the monomeric lactone, several catalysts and reaction temperatures were examined (Table 8). As shown in entry 4, the best result was attained when using $TiCl_2(OTf)_2$ as the catalyst in gently refluxing dichloromethane.

Next, the effect of the amount of chlorotrimethylsilane and the kind of substituent(s) in benzoic anhydrides was screened under the optimized reaction conditions. It was found that the existence of chlorotrimethylsilane was essential to this reaction in order to maintain the activity of the titanium(IV) catalyst, and the use of 3 mol of chlorotrimethylsilane was enough to provide a good result for the production of the monomeric 13-membered ring lactone (see Table 9, entry 3).

Several examples of the present cyclization reaction are listed in Table 10. In entries 4–6 and 8, macrolactones including over 13-membered rings were obtained in higher yields compared with those of the previously reported methods. A 13-membered ring lactone derived from a branched *seco*-acid was also isolated in 91% yield (entry 2), and the reaction was effectively accelerated using only 1 mol% of $TiCl_2(OTf)_2$ together with chlorotrimethylsilane as shown in entry 3.

Even for the labile *seco*-acids, the reactions smoothly proceeded to afford the corresponding lactones in high yields. (+)-(*E*)-9-Octadecen-12-olide ((*R*)-ricinelaidic acid lactone)[11] and (+)-(*Z*)-9-octadecen-12-olide ((*R*)-ricinoleic

Table 11. Synthesis of (*R*)-ricinelaidic acid lactone using TFBA



(*R*)-ricinelaidic acid lactone

Entry	X	Catalyst (amount/mol%)	Y	Temp.[a] (°C)	Yield[b] (%)
1	H	$TiCl_2(OTf)$ (5)	3	50	89
2	H	$TiCl_2(ClO_4)_2$ (5)	3	rt	92
3	Me_3Si	$TiCl_2(ClO_4)_2$ (10)	0	rt	73

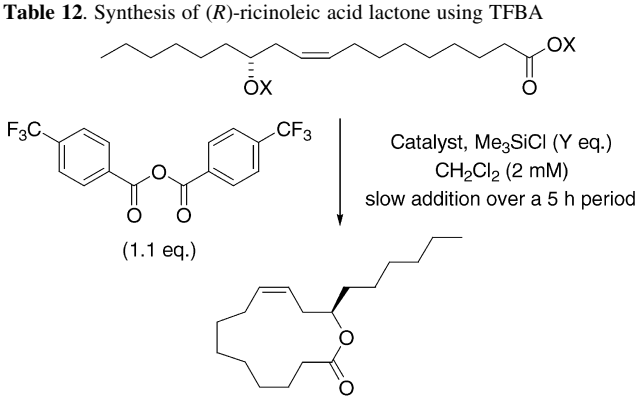
[a] Bath temperature.
[b] Isolated yield.

acid lactone)[11b,12] were respectively obtained in high yields employing 5 mol% of $TiCl_2(OTf)_2$ without any accompanying isomerization of the double bond and also racemization (Tables 11 and 12, entry 1). $TiCl_2(ClO_4)_2$ is an equally effective catalyst in these cases to produce the desired macrolactones in high yields at room temperature (entry 2). Furthermore, these unsaturated macrolides were also produced from the corresponding trimethylsilyl ω-(trimethylsiloxy)carboxylates in the presence of TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ at room temperature without using chlorotrimethylsilane as an additive (entry 3).

2.3. Synthesis of the 8-membered ring lactone moiety of cephalospoloride D

Cephalosporolide D (**22**), a fungus metabolite, was isolated

Table 12. Synthesis of (*R*)-ricinoleic acid lactone using TFBA

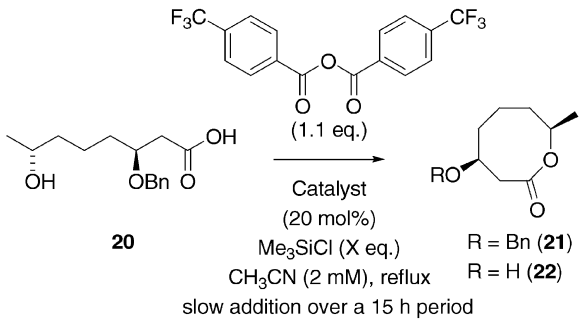


(*R*)-ricinoleic acid lactone

Entry	X	Catalyst (amount/mol%)	Y	Temp.[a] (°C)	Yield[b] (%)
1	H	$TiCl_2(OTf)_2$ (5)	3	50	83
2	H	$TiCl_2(ClO_4)_2$ (5)	3	rt	83
3	Me_3Si	$TiCl_2(ClO_4)_2$ (10)	0	rt	72

[a] Bath temperature.
[b] Isolated yield.

Table 13. Synthesis of an 8-membered ring lactone using TFBA



Entry	Catalyst	X	Yield[a] (%)	Recovery (%)
1	$TiCl_2(OTf)_2$	3	2	0
2	$Sc(OTf)_3$	0	44	31
3	$Zr(OTf)_4$	0	20	48
4	$Hf(OTf)_4$	0	67	17

[a] Isolated yield.

in 1985 from *Cephalosporium aphidicola* together with related compounds by Hanson et al.[13] The structure contained two chiral centers and an unusual saturated 8-membered ring lactone moiety. A similar characteristic structure possessing a medium-sized lactone moiety was also found in octalactin A which exhibited a potent cytotoxic activity against some tumor cell lines.[14]

Next, lactonization of a *seco*-acid **20**, a synthetic intermediate of cephalosporolide D, was tried using the present mixed-anhydride method with a catalytic amount of a Lewis acid in the presence of TFBA.[7] First, the reaction was carried out by the promotion of a catalytic amount of $TiCl_2(OTf)_2$ together with chlorotrimethylsilane, however, several unidentifiable products were obtained and the 8-membered ring lactone **21** was obtained in only 2% yield. Since Yamamoto et al. reported that $Sc(OTf)_3$ effectively functions with this mixed-anhydride method producing medium sized lactones,[2f] we then utilized $Sc(OTf)_3$ as a catalyst combined with TFBA. The cyclization reaction of **20** was actually catalyzed to afford the desired lactone **21** in 44% yield, and 31% of **20** was recovered. To improve the yield of the desired 8-membered ring lactone, we re-investigated other Lewis acids consisting of metals in group IV as shown in Table 13. Although the reaction was not facilitated using $Zr(OTf)_4$, it was found that $Hf(OTf)_4$ is very effective for the promotion of the cyclization to produce the desired 8-membered ring lactone **21** in 67% yield.[15] Since 17% of the starting *seco*-acid **20** was recovered after the reaction, conversion yield of **21** reached 81% based on the consumed **20**. It is noted that this cyclization exclusively gave the monomeric lactone and the corresponding diolide was not formed at all.[16] Thus, an efficient method for the preparation of the synthetic precursor of cephalosporolide D was established via the effective construction of the 8-membered ring lactone moiety.

3. Conclusion

In summary, it is determined that the mixed-anhydride

method using a substituted benzoic anhydride provided an efficient method for the preparation of various derivatives of carboxylic acids.[17] As an example of this synthetic methodology, we demonstrated the combined use of BTFBA or TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ together with chlorotrimethylsilane for the preparation of carboxylic esters from free carboxylic acids and alcohols. An efficient and convenient method for the preparation of lactones from ω-hydroxycarboxylic acids or trimethylsilyl ω-(trimethylsiloxy)carboxylates was also established using the substituted benzoic anhydride and a catalytic amount of a Lewis acid such as $TiCl_2(ClO_4)_2$, $TiCl_2(OTf)_2$ or $Hf(OTf)_4$ under mild conditions.

4. Experimental

4.1. General methods

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Optical rotations were recorded on a Jasco DIP-360 or a Jasco P-1020 digital polarimeter. IR spectra were recorded on a Horiba FT-300 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270L, a JEOL JNM-AL300 or a JEOL JNM-LA500 spectrometer with tetramethylsilane (TMS), chloroform (in chloroform-*d*) or benzene (in benzene-d_6) as internal standard. HPLC was carried out using a Hitachi LC-Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. High-resolution mass spectra were recorded on a JEOL JMS-SX102A instrument using 4-nitrobenzyl alcohol as a matrix. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F.

All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å, benzene and toluene were distilled from diphosphorus pentoxide, and dried over MS 4 Å, and THF and diethyl ether were distilled from sodium/benzophenone immediately prior to use.

4.2. Starting materials

All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc. or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted. Titanium dichlorobis(trifluoromethanesulfonate) was prepared by the literature method.[18]

4.2.1. 4-(Trifluoromethyl)benzoic anhydride (TFBA). 4-(Trifluoromethyl)benzoic anhydride was purchased from Tokyo Kasei Kogyo Co., Ltd. (TCI) or synthesized from 4-(trifluoromethyl)benzoic acid and 4-(trifluoromethyl)benzoyl chloride. To a mixture of 4-(trifluoromethyl)benzoic acid (13.7 g, 72.0 mmol) and 4-(trifluoromethyl)benzoyl chloride (15.0 g, 72.0 mmol) in dichloromethane (144 mL) at 0 °C was added pyridine (6.11 mL, 75.6 mmol). The reaction mixture was stirred for 21 h at room temperature and then cold water (50 mL) was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by recrystallization from dichloromethane to afford 23.2 g (89%) of TFBA as a white solid: mp 132–133 °C; IR (KBr) 1732, 1795 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (4H, d, J=8.1 Hz), 8.26 (4H, d, J=8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 123.2 (q, J=272.2 Hz), 125.9 (q, J=3.9 Hz), 130.8, 131.5, 135.9 (q, J=33.0 Hz), 160.6.

4.2.2. 3,5-Bis(trifluoromethyl)benzoic anhydride (BTFBA). A mixture of 3,5-bis(trifluoromethyl)benzoic acid (5.2 g, 20 mmol) and thionyl chloride (9.5 g, 80 mmol) was stirred for 4 h at 80 °C. The solvent and thionyl chloride were distillated under reduced pressure at 50 °C and then dichloromethane (80 mL), 3,5-bis(trifluoromethyl)benzoic acid (5.2 g, 20.0 mmol) and a solution of pyridine (1.7 mL, 21 mmol) in dichloromethane (40 mL) were successively added at 0 °C. After the reaction mixture had been stirred for 21 h at room temperature, cooled water (100 mL) was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by recrystallization from dichloromethane to afford 7.0 g (70%) of BTFBA as a white solid: mp 104.5–105 °C; IR (KBr) 1712, 1805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (2H, s), 8.58 (4H, s); ^{13}C NMR ($CDCl_3$) δ 122.4 (q, J=272.8 Hz), 127.2 (q, J=3.9 Hz), 130.4 (q, J=4.5 Hz), 131.2, 133.1 (q, J=34.4 Hz), 158.2.

4.3. Typical experimental procedure for the synthesis of carboxylic esters using TFBA

A typical experimental procedure is described for the reaction of 3-phenylpropanoic acid with 4-phenyl-2-butanol; to a suspension of $AgClO_4$ (7.7 mg, 0.037 mmol) in dichloromethane (10.0 mL) were added a solution of $TiCl_4$ in toluene (0.50 M, 0.037 mL, 0.019 mmol) and chlorotrimethylsilane (0.118 mL, 0.930 mmol). After the reaction mixture had been stirred for 30 min, a solution of TFBA (740 mg, 2.04 mmol) and 3-phenylpropanoic acid (307 mg, 2.04 mmol) in dichloromethane (7.5 mL) and a solution of 4-phenyl-2-butanol (278 mg, 1.85 mmol) in dichloromethane (2.5 mL) were successively added. The reaction mixture was stirred for 3 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 518 mg (99%) of 1-methyl-3-phenylpropyl 3-phenylpropanoate with an excellent chemoselectivity (>200:1).

4.3.1. 1-Methyl-3-phenylpropyl 3-phenylpropanoate[5b] (1). IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3H, d, J=6.3 Hz), 1.72–1.96 (2H, m), 2.51–2.69 (4H, m), 2.95 (2H, t, J=7.6 Hz), 4.94 (1H, m), 7.11–7.31 (10H, m). Found: C, 80.74; H, 7.99%. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85%.

4.3.2. 3-Phenylpropyl 3-phenylpropanoate[19] (3). IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (2H, m), 2.62

(4H, m), 2.95 (2H, t, J=7.8 Hz), 4.08 (2H, t, J=6.6 Hz), 7.13–7.31 (10H, m). Found: C, 80.35; H, 7.77%. Calcd for $C_{18}H_{20}O_2$: C, 80.56: H,7.51%.

4.3.3. 3-Phenylpropyl cyclohexanecarboxylate[5b] (4). IR (neat) 1732 cm^{-1}; ^1H NMR (CCl_4) δ 1.05–2.40 (13H, m), 2.65 (2H, t, J=8.0 Hz), 4.00 (2H, t, J=6.0 Hz), 7.15 (5H, s). Found: C, 77.89; H, 8.90%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

4.3.4. 1-Methyl-3-phenylpropyl cyclohexanecarboxylate[5b] (5). IR (neat) 1728 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (3H, d, J=6.0 Hz), 1.25–2.25 (13H, m), 2.25–2.80 (2H, m), 4.85 (1H, m), 7.15 (5H, s). Found: C, 78.18; H, 9.07%. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29%.

4.3.5. 3-Phenylpropyl 2,2-dimethylpropanoate[5b] (6). IR (neat) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (9H, s), 1.97–2.03 (2H, m), 2.74 (2H, t, J=7.6 Hz), 4.12 (2H, t, J=6.3 Hz), 7.21–7.34 (5H, m). Found: C, 76.06; H, 9.21%. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

4.3.6. 1-Methyl-3-phenylpropyl 2,2-dimethylpropanoate[5b] (7). IR (neat) 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (9H, s), 1.25 (3H, d, J=6.3 Hz), 1.73–2.00 (2H, m), 2.54–2.74 (2H, m), 4.91 (1H, m), 7.15–7.31 (5H, m). Found: C, 76.70; H, 9.52%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

4.3.7. Benzyl 3-phenylpropanoate[20] (8). IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (2H, t, J=7.8 Hz), 2.96 (2H, t, J=7.8 Hz), 5.10 (2H, s), 7.12–7.40 (10H, m).

4.3.8. Allyl 3-phenylpropanoate (9). IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.66 (2H, t, J=7.8 Hz), 2.97 (2H, t, J=7.8 Hz), 4.57 (2H, td, J=1.3, 5.6 Hz), 5.21 (1H, tdd, J=1.3, 1.7, 10.6 Hz), 5.28 (1H, tdd, J=1.3, 1.7, 17.2 Hz), 5.89 (1H, tdd, J=5.6, 10.6, 17.2 Hz), 7.10–7.35 (5H, m); HR MS: calcd for $C_{12}H_{15}O_2$ ($M+H^+$) 191.1072, found 191.1073.

4.3.9. Cyclohexyl 3-phenylpropanoate[21] (10). IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.19 (8H, m), 1.80 (2H, td, J=5.4, 9.1 Hz), 2.60 (2H, t, J=7.8 Hz), 2.95 (2H, t, J=7.8 Hz), 4.75 (1H, tt, J=4.4, 9.1 Hz), 7.09–7.38 (5H, m).

4.3.10. (−)-Mentyl 3-phenylpropanoate (11). $[\alpha]_D^{28}$=−58.0° (c 1.67, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.62 (3H, d, J=6.9 Hz), 0.68–1.75 (14H, m), 1.78–1.93 (1H, m), 2.53 (2H, t, J=7.8 Hz), 2.87 (2H, t, J=7.8 Hz), 4.59 (1H, dt, J=4.6, 10.9 Hz), 7.05–7.26 (5H, m); HR MS: calcd for $C_{19}H_{29}O_2$ ($M+H^+$) 289.2167, found 289.2177.

4.3.11. (+)-5α-Cholestan-3β-yl 3-phenylpropanoate (12). Mp. 96–98 °C; $[\alpha]_D^{28}$=+13.2° (c 1.00, $CHCl_3$); IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.52–2.02 (46H, m), 2.58 (2H, t, J=7.8 Hz), 2.93 (2H, t, J=7.8 Hz), 4.69 (1H, tt, J=5.6, 11.2 Hz), 7.07–7.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 12.06, 12.20, 18.65, 21.19, 22.55, 22.81, 23.83, 24.19, 27.44, 28.00, 28.23, 28.59, 31.05, 31.97, 33.98, 35.44, 35.78, 36.16, 36.26, 36.73, 39.50, 39.97, 42.57, 44.62, 54.20, 56.25, 56.39, 73.77, 126.15, 128.30, 128.41, 140.61, 172.42; HR MS: calcd for $C_{36}H_{57}O_2$ ($M+H^+$) 521.4358, found 521.4360.

4.3.12. 3-Phenylpropyl benzoate[5b] (13). IR (neat) 1718 cm^{-1}; ^1H NMR (CCl_4) δ 2.23 (2H, m), 2.77 (2H, t, J=8 Hz), 4.27 (2H, t, J=6 Hz), 7.05–7.54 (8H, m), 7.85–8.10 (2H, m). Found: C, 79.69; H, 6.97%. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

4.3.13. 1-Methyl-3-phenylpropyl benzoate[5b] (14). IR (neat) 1716 cm^{-1}; ^1H NMR (CCl_4) δ 1.44 (3H, d, J=6 Hz), 1.74–2.23 (2H, m), 2.55–2.90 (2H, m), 5.15 (1H, m), 7.05–7.54 (8H, m), 7.98 (2H, dd, J=8, 2 Hz). Found: C, 80.47; H, 7.22%. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13%.

4.4. Typical experimental procedure for the synthesis of α,β-unsaturated esters

The same procedure as typical experimental procedure for the catalytic esterification reaction except for using phosphate buffer (pH=7) as a reagent for quenching.

4.4.1. 3-Phenylpropyl (*E*)-crotonate[5b] (15). IR (neat) 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (3H, dd, J=6.9, 1.7 Hz), 1.99 (2H, tt, J=7.6, 6.6 Hz), 2.70 (2H, t, J=7.6 Hz), 4.14 (2H, t, J=6.6 Hz), 5.85 (1H, dq, J=15.0, 1.7 Hz), 6.96 (1H, dq, J=15.0, 6.9 Hz), 7.15–7.31 (5H, m). Found: C, 76.21; H, 8.00%. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%.

4.4.2. 1-Methyl-3-phenylpropyl (*E*)-crotonate (16). IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, d, J=6.3 Hz), 1.70–2.06 (2H, m), 1.87 (3H, dd, J=1.8, 6.9 Hz), 2.50–2.76 (2H, m), 4.99 (1H, tq, J=6.3, 6.3 Hz), 5.84 (1H, qd, J=1.8, 15.4 Hz), 6.96 (1H, qd, J=6.9, 15.4 Hz), 7.10–7.34 (5H, m); HR MS: calcd for $C_{14}H_{19}O_2$ ($M+H^+$) 219.1385, found 219.1387.

4.4.3. 3-Phenylpropyl 3-methyl-2-butenoate[5b] (17). IR (neat) 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (3H, d, J=1.0 Hz), 1.95 (2H, tt, J=7.9, 6.6 Hz), 2.17 (3H, d, J=1.0 Hz), 2.69 (2H, t, J=7.9 Hz), 4.10 (2H, t, J=6.6 Hz), 5.69 (1H, q, J=1.3 Hz), 7.14–7.30 (5H, m). Found: C, 76.86; H, 8.37%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%.

4.5. Typical experimental procedure for the synthesis of lactones from trimethylsilyl ω-(trimethylsiloxy)-carboxylates

A typical experimental procedure is described for the synthesis of pentadecan-15-olide; to a suspension of $AgClO_4$ (16.6 mg, 0.080 mmol) in dichloromethane (90 mL) was added a solution of $TiCl_4$ in toluene (0.5 M, 0.080 mL, 0.040 mmol). After the reaction mixture had been stired for 30 min, a solution of trimethylsilyl 15-(trimethylsiloxy)pentadecanoate (161 mg, 0.400 mmol) and TFBA (145 mg, 0.400 mmol) in dichloromethane (10 mL) was slowly added to the suspension including $TiCl_2(ClO_4)_2$ with a mechanically driven syringe over a 31 h period at room temperature. The reaction mixture was additionally stirred for 3 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture

was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 85.6 mg (89%) of pentadecan-15-olide and 3.8 mg (2%) of diolide.

4.6. Typical experimental procedure for the synthesis of lactones from ω-hydroxycarboxylic acids

A typical experimental procedure is described for the synthesis of octadecan-12-olide; to a suspension of $TiCl_2(OTf)_2$ (10.8 mg, 0.026 mmol) and chlorotrimethylsilane (0.2 mL, 1.57 mmol) in gently refluxing dichloromethane (220 mL) was added a solution of 12-hydroxyoctadecanoic acid (157.6 mg, 0.524 mmol) and TFBA (209.5 mg, 0.578 mmol) in dichloromethane (40 mL) with a mechanically driven syringe over a 5 h period. After addition of the solution, the reaction mixture was concentrated to ca. 20 mL by evaporation of the solvent under reduced pressure and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 135.1 mg (91%) of octadecan-12-olide and 9.4 mg (3%) of diolide.

4.6.1. Dodecan-12-olide[2f] (13-membered ring lactone). IR (neat) 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23–1.48 (14H, m), 1.60–1.73 (4H, m), 2.33–2.38 (2H, m), 4.15 (2H, dd, J=4.0, 5.1 Hz); EI MS: calcd for $C_{12}H_{22}O_2$ (M^+) 198, found 198.

4.6.2. Octadecan-12-olide[12c] (12-hydroxystearic acid lactone). IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, J=6.7 Hz), 1.17–1.80 (28H, m), 2.24 (1H, ddd, J=3.9, 9.0, 12.3 Hz), 2.43 (1H, ddd, J=3.6, 8.1, 12.3 Hz), 4.92 (1H, dddd, J=2.2, 4.3, 6.5, 8.9 Hz); EI MS: calcd for $C_{18}H_{34}O_2$ (M^+) 282, found 282.

4.6.3. Tridecan-13-olide[2f] (14-membered ring lactone). IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19–1.50 (16H, m), 1.58–1.72 (4H, m), 2.35–2.39 (2H, m), 4.14 (2H, dd, J=4.5, 5.3 Hz); EI MS: calcd for $C_{13}H_{24}O_2$ (M^+) 212, found 212.

4.6.4. Tetradecan-14-olide[2f] (15-membered ring lactone). IR (neat) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19–1.48 (18H, m), 1.56–1.73 (4H, m), 2.32–2.37 (2H, m), 4.13 (2H, t, J=4.1, 5.3 Hz); EI MS: calcd for $C_{14}H_{26}O_2$ (M^+) 226, found 226.

4.6.5. Pentadecan-15-olide[2f] (16-membered ring lactone). IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24–1.49 (20H, m), 1.56–1.72 (4H, m), 2.33 (2H, dd, J=6.6, 7.1 Hz), 4.13 (2H, dd, J=5.4, 5.6 Hz); EI MS: calcd for $C_{15}H_{28}O_2$ (M^+) 240, found 240.

4.6.6. Hexadecan-16-olide[2f] (17-membered ring lactone). IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22–1.45 (22H, m), 1.55–1.71 (4H, m), 2.32 (2H, dd, J=6.6, 6.9 Hz), 4.12 (2H, t, J=5.6 Hz); EI MS: calcd for $C_{16}H_{30}O_2$ (M^+) 254, found 254.

4.6.7. (+)-(*E*)-9-Octadecen-12-olide[11] ((*R*)-ricinelaidic acid lactone). $[\alpha]_D^{26}$=+41.3° (c 1.85, $CHCl_3$); IR (neat) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J=6.6 Hz), 1.19–1.71 (20H, m), 2.06–2.55 (6H, m), 4.92–5.00 (1H, m), 5.33–5.53 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 23.4, 24.5, 25.6, 25.7, 26.1, 27.3, 29.1, 29.5, 31.7, 31.8, 33.8, 35.2, 73.8, 124.8, 132.4, 174.4; EI MS: calcd for $C_{18}H_{32}O_2$ (M^+) 280, found 280.

4.6.8. (+)-(*Z*)-9-Octadecen-12-olide[11b,12] ((*R*)-ricinoleic acid lactone). $[\alpha]_D^{28}$=+32.0° (c 1.77, $CHCl_3$); IR (neat) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (3H, t, J=7.0 Hz), 1.10–1.70 (20H, m), 2.06–2.55 (6H, m), 4.92–5.00 (1H, m), 5.13–5.33 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 23.7, 25.3, 26.9, 27.1, 27.5, 29.1, 29.7, 31.7, 32.2, 34.1, 35.0, 37.7, 73.0, 126.3, 134.2, 173.7; EI MS: calcd for $C_{18}H_{32}O_2$ (M^+) 280, found 280.

4.7. Experimental procedure for the synthesis of an 8-membered ring lactone moiety of cephalosporolide D

To a solution of $Hf(OTf)_4$ (28.6 mg, 0.037 mmol) and TFBA (133.8 mg, 0.369 mmol) in acetonitrile (78 mL) at reflux temperature was added a solution of 3-benzyloxy-7-hydroxyoctanoic acid (**20**) (49.2 mg, 0.184 mmol) in THF (4.6 mL) with a mechanically driven syringe over a 15 h period. After the reaction mixture had been stirred for 5 h at reflux temperature, saturated aqueous sodium hydrogencarbonate (1.9 mL) was added at room temperature. The mixture was concentrated by evaporation of the solvent and then it was extracted with diethyl ether, and the organic layer was washed with brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography to afford 30.5 mg (67%) of 3-benzyloxyoctan-7-olide (**21**) and 8.4 mg (17%) of recovered **20** as colorless oils.

4.7.1. 3-Benzyloxyoctan-7-olide (21). IR (neat): 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (3H, d, J=6.3 Hz, 8-H), 1.02–1.33 (1H, m, 5-H), 1.46–1.96 (5H, m, 4-H, 5-H, 6-H), 2.67 (1H, dd, J=6.6, 11.9 Hz, 2-H), 2.71 (1H, dd, J=4.3, 11.9 Hz, 2-H), 3.62–3.77 (1H, m, 3-H), 4.44 (1H, d, J=11.9 Hz, Bn-H), 4.61 (1H, d, J=11.9 Hz, Bn-H), 4.69 (1H, dqd, J=5.3, 6.3, 10.5 Hz, 7-H), 7.14–7.39 (5H, m, Ph); ^{13}C NMR($CDCl_3$): δ 18.9 (5), 21.3 (8), 32.9 (4), 37.7 (2), 38.3 (6), 70.1 (Bn), 75.3 (7), 77.3 (3), 127.5 (Ph), 127.6 (Ph), 128.3 (Ph), 138.1 (Ph), 172.3 (1). Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.15; H, 8.03; HR MS: calcd for $C_{15}H_{21}O_3Na$ ($M+Na^+$) 249.1491, found 249.1539.

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References and notes

1. For a review, see: (a) Mulzer, J. *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 323–380. Acidic esterifications, (b) $BF_3{\cdot}Et_2O$: Marshall, J. L.; Erickson, K. C.; Folsom, T. K. *Tetrahedron Lett.* **1970**, *11*, 4011–4012. (c) H_3BO_3: Lawrance, Jr. W. W. *Tetrahedron Lett.* **1971**, *12*, 3453–3454. (d) $AlCl_3$: Blossey, E. C.; Turner, L. M.; Neckers, D. C. *Tetrahedron Lett.* **1973**, *14*, 1823–1826. (e) Me_3SiCl, Me_2SiCl_2, $MeSiCl_3$, $SiCl_4$: Nakao, R.; Oka, K.; Fukumoto, T. *Bull. Chem. Soc. Jpn* **1981**, *54*, 1267–1268. (f) ZnI_2: Gauthier, J. Y.; Bourdon, F.; Young, R. N. *Tetrahedron Lett.* **1986**, *27*, 15–18. (g) R_2SnCl_2: Kumar, A. K.; Chattopadhyay, T. K. *Tetrahedron Lett.* **1987**, *28*, 3713–3714. (h) $({}^nBu_2XSnOSn{}^nBu_2Y)_2$: Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307–5311. (i) $Sc(OTf)_3$, $Yb(OTf)_3$: Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351–352. (j) $Sc(OTf)_3$/DMAP/DIPC: Greenwald, R. B.; Pendri, A.; Zhao, H. *Tetrahedron: Asymmetry* **1998**, *9*, 915–918. (k) $Sc(OTf)_3$/DMAP/DIPC or EDC: Zhao, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559–7562. (l) $HfCl_4{\cdot}(THF)_2$: Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140–1142. (m) $Ph_2NH^+{\cdot}{}^-OTf$: Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249–5252. (n) 4-Dodecylbenzenesulfonic acid: Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101–10102.
2. (a) $FeCl_3$: Ganem, B.; Small, Jr. V. R. *J. Org. Chem.* **1974**, *39*, 3728–3730. (b) $FeCl_3$: Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129–8133. (c) $CoCl_2$: Ahmad, S.; Iqbal, J. *Tetrahedron Lett.* **1986**, *27*, 3791–3794. (d) $CoCl_2$: Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *57*, 2001–2007. (e) $Sc(OTf)_3$: Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413–4414, see also p 6639, correction. (f) $Sc(OTf)_3$: Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560–4567. (g) $Sc(NTf_2)_3$: Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265–266. (h) $MgBr_2/Et_3N$: Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702–5703. (i) TMSOTf: Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *Chem. Commun.* **1996**, 2625–2626. (j) TMSOTf: Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342–2347. (k) TMSCl: Kumareswaran, R.; Gupta, A.; Vankar, Y. D. *Synth. Commun.* **1997**, *27*, 277–282. (l) Montmorillonite: Li, A.-X.; Li, T.-S.; Ding, T.-H. *Chem. Commun.* **1997**, 1389–1390. (m) $CeCl_3$, $ZnCl_2$: Holton, R. A.; Zhang, Z.; Clarke, P. A.; Nadizadeh, H.; Procter, D. J. *Tetrahedron Lett.* **1998**, *39*, 2883–2886. (n) $CeCl_3$, $YbCl_3$: Clarke, P. A.; Holton, R. A.; Kayaleh, N. E. *Tetrahedron Lett.* **2000**, *41*, 2687–2690. (o) Zeolite: Ballini, R.; Bosica, G.; Carloni, S.; Ciaralli, L.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1998**, *39*, 6049–6052. (p) $TaCl_5$: Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263–3266. (q) $In(OTf)_3$: Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743–1744. (r) $Cu(OTf)_2$: Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611–2614. (s) $Cu(OTf)_2$: Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369–1374. (t) Nafion-H: Kumareswaran, R.; Pachamuthu, K.; Vankar, Y. D. *Synlett* **2000**, 1652–1654. (u) $Bi(OTf)_3$: Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2877–2879. (v) $Bi(OTf)_3$: Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, *66*, 8926–8934. (w) $Bi(OTf)_3$: Carrigan, M. D.; Freiberg, D. A.; Smith, R. C.; Zerth, H. M.; Mohan, R. S. *Synthesis* **2001**, 2091–2094. (x) $BiCl_3$, $Bi(TFA)_3$, $Bi(OTf)_3$: Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851–5854. (y) Yttria–zirconia: Kumar, P.; Pandey, R. K.; Bodas, M. S.; Dongare, M. K. *Synlett* **2001**, 206–209. (z) $LiClO_4$: Nakae, Y.; Kusaki, I.; Sato, T. *Synlett* **2001**, 1584–1586. (aa) $Sc(OTf)_3$/$({}^nBu_2ClSnOSn{}^nBu_2Cl)_2$: Nagano, Y.; Orita, A.; Otera, J. *Tetrahedron* **2002**, *58*, 8211–8217. (bb) HBF_4: Chakraborti, A. K.; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 3521–3525. (cc) $Mg(ClO_4)_2$: Chakraborti, A. K.; Sharma, L.; Gulhane, R.; Shivani, *Tetrahedron* **2003**, *59*, 7661–7668.
3. Parish, R. C.; Stock, L. M. *J. Org. Chem.* **1965**, *30*, 927–929.
4. (a) Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1992**, 2319–2320. (b) Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141–144. See also, (c) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn* **1994**, *67*, 1708–1716. (d) Mukaiyama, T.; Watanabe, K.; Shiina, I. *Chem. Lett.* **1995**, 1–2, see also p 336. (e) Shibata, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1999**, 313–314. (f) Mukaiyama, T.; Shibata, J.; Shimamura, T.; Shiina, I. *Chem. Lett.* **1999**, 951–952. (g) Shiina, I.; Suzuki, M. *Tetrahedron Lett.* **2002**, *43*, 6391–6394. (h) Shiina, I.; Suzuki, M.; Yokoyama, K. *Tetrahedron Lett.* **2002**, *43*, 6395–6398. (i) Shiina, I.; Suzuki, M.; Yokoyama, K. *Tetrahedron Lett.* **2004**, 45, 965–967.
5. (a) Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* **1992**, 625–628. (b) Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1993**, *66*, 1516–1527. (c) Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1993**, 907–910. See also, (d) Mukaiyama, T.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1992**, 1747–1750. (e) Miyashita, M.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1993**, 1053–1054. (f) Miyashita, M.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1994**, *67*, 210–215. (g) Shiina, I.; Miyashita, M.; Nagai, M.; Mukaiyama, T. *Heterocycles* **1995**, *40*, 141–148.
6. (a) Shiina, I.; Miyoshi, S.; Miyashita, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 515–518. (b) Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1994**, 677–680.
7. (a) Shiina, I.; Fukuda, Y.; Ishii, T.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett.* **1998**, 831–832. (b) Shiina, I.; Fujisawa, H.; Ishii, T.; Fukuda, Y. *Heterocycles* **2000**, *52*, 1105–1123.
8. (a) Shoda, S.; Mukaiyama, T. *Chem. Lett.* **1980**, 391–392. (b) Shoda, S. PhD Thesis, the University of Tokyo, 1980.
9. (a) In *Recent progress in the chemical synthesis of antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990. (b) In *Macrolide antibiotics (second edition)*; Omura, S., Ed.; Academic: San Diego, 2002.
10. (a) $(CF_3CO)_2O$: Baker, W.; Ollis, W. D.; Zealley, T. S. *J. Chem. Soc.* **1952**, 1447–1451. (b) $AgClO_4$, $AgBF_4$: Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661–2663. (c) $Hg(OCOCF_3)_2$: Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513–3515. (d) $Hg(OCOCF_3)_2$: Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515–3516.

(e) $BF_3{\cdot}Et_2O$: Scott, L. T. *Synthesis* **1976**, 738–739. (f) $^nBu_2SnO$: Steliou, K.; Szczygielska-Nowosielska, A.; Farve, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578–7579. (g) $^nBu_2SnO$: Steliou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 7130–7138. (h) $^nPr_2BOTf$: Taniguchi, N.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1984**, 1347–1348. (i) DCC, DMAP·HCl: Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395. (j) $(^nBu_2XSnOSn^nBu_2OH)_2$: Otera, J.; Yano, T.; Himeno, Y.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 4501–4504. (k) Hydrous ZrO_2: Kuno, H.; Shibagaki, M.; Takahashi, K.; Honda, I.; Matsushita, H. *Chem. Lett.* **1992**, 571–574. (l) $^nBu_3SnOMe$, $(^nBu_3Sn)_2O$, $(^nBu_3Sn)_2$: White, J. D.; Green, N. J.; Fleming, F. F. *Tetrahedron Lett.* **1993**, *34*, 3515–3518. (m) Zeolite: Ookoshi, T.; Onaka, M. *Tetrahedron Lett.* **1998**, *39*, 293–296. (n) CSA: Trost, B. M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743–3745.

11. (a) Matsuyama, H.; Nakamura, T.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 5218–5223. (b) Narasaka, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 885–888. (c) Seuring, B.; Seebach, D. *Liebigs Ann. Chem.* **1978**, 2044–2073. (d) Gais, H.-J. *Tetrahedron Lett.* **1984**, *25*, 273–276. (e) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183–5189. (f) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755–760.
12. (a) Jadhav, K. S.; Thakur, S. B.; Bhattacharyya, S. C. *Indian J. Chem.* **1978**, *16*, 280–285. (b) Yamada, H.; Ohsawa, S.; Sugai, T.; Ohta, H.; Yoshikawa, S. *Chem. Lett.* **1989**, 1775–1776. (c) Nagarajan, M. *Synth. Commun.* **1999**, *29*, 2467–2475.
13. Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc. Perkin Trans. 1* **1985**, 843–847.
14. Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682–4683.
15. (a) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn* **1995**, *68*, 2053–2060. (b) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Bull. Chem. Soc. Jpn* **1997**, *70*, 267–273. (c) Kobayashi, S.; Iwamoto, S.; Nagayama, S. *Synlett* **1997**, 1099–1101. (d) Suzuki, K.; Yamanoi, S. *Lewis acids in organic synthesis*; Yamamoto, H., Ed.; Wiley: Weinheim, 2000; Vol. 2, pp 849–864. (e) Hara, R.; Takahashi, T. *Lewis acids in organic synthesis*; Yamamoto, H., Ed.; Wiley: Weinheim, 2000; Vol. 2, pp 865–881. We had observed that $ZrCl_2(OTf)_2$ and $HfCl_2(OTf)_2$ were effective catalysts for the synthesis of carboxylic esters in 1992. See, Ref. 5a,b.
16. Recently, Buszek et al. also reported monomer-selective lactonization for the synthesis of an 8-membered ring lactone moiety of octalactins and cephalosporolide D using S-Py ester method. Buszek, K. R.; Jeong, Y.; Sato, N.; Still, P. C.; Muino, P. L.; Ghosh, I. *Synth. Commun.* **2001**, *31*, 1781–1791.
17. Quite recently, we developed an alternative mixed-anhydride method using 2-methyl-6-nitrobenzoic anhydride (MNBA) by the promotion of basic catalysts. These methods promoted by acids or bases could be complementarily utilized for the synthesis of carboxylic esters and lactones according to the stability of substrates and products under the reaction conditions. (a) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 286–287. (b) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535–7539. (c) Shiina, I.; Oshiumi, H.; Hashizume, M.; Yamai, Y.; Ibuka, R. *Tetrahedron Lett.* **2004**, 45, 543–547.
18. (a) Schmeißer, M.; Sartori, P.; Lippsmeier, B. *Chem. Ber.* **1970**, *103*, 868–879. (b) Tabane, Y. *Bull. Chem. Soc. Jpn* **1989**, *62*, 1917–1924.
19. Blum, J.; Zinger, B.; Milstein, D.; Buchman, O. *J. Org. Chem.* **1978**, *43*, 2961–2967.
20. Page, P. C. B.; McKenzie, M. J.; Allin, S. M.; Buckle, D. R. *Tetrahedron* **2000**, *56*, 9683–9695.
21. Kita, Y.; Akai, S.; Yamamoto, M.; Taniguchi, M.; Tamura, Y. *Synthesis* **1989**, 334–337.

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Synthesis of *N*,*N*-dimethyl-2,4-dinitro-5-fluorobenzylamine and its reactions with amino acids and peptides

Zhongfa Liu and Lawrence M. Sayre*

Department of Chemistry, Case Western Reserve University, 10900 Euclid Ave., Cleveland, OH 44106, USA

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Abstract—A practical synthesis is described for *N*,*N*-dimethyl-2,4-dinitro-5-fluorobenzylamine (DMDNFB) and its -d_6 analog as an alternative Sanger's reagent (DNFB), for purposes of amino acid derivatization detectable by positive mode electrospray ionization mass spectrometry. DMDNFB is comparable to DNFB in its efficiency to derivatize amino acids and peptides. Various DMDNP (d_0/d_6) derivatives of (modified) lysine were synthesized to evaluate the potential use of isotope-edited LC-ESI-MS as a tool for structural definition of the posttranslational modification of protein-based lysines.

1. Introduction

The determination of amino acids by high performance liquid chromatography (HPLC) has been dominated by pre or post-column derivatization methods to improve separation arising from greater compatibility with reversed-phase columns and to improve detection by using highly chromophoric or fluorophoric groups.[1–4] Typical amino acid reagents where the derivatization chemistry is well understood include *o*-phthalaldehyde (OPA),[5] 5-dimethylamino-1-naphthalenesulfonyl (dansyl) chloride,[6] 2,4-dinitrofluorobenzene (DNFB, Sanger's reagent),[7,8] phenyl isothiocyanate (PITC),[9] and phenylthiohydantoin (PTH)[10] amino acid derivatives. In addition, coupling of HPLC with mass spectrometry (MS) has been widely explored for analyzing posttranslational modification of protein-derived peptides or amino acids to facilitate structural identification on the basis of mass, especially for resolving co-eluting species due to their different *m*/*z* ratios.[11–14] However, chemical derivatization to permit simultaneous mass and spectral detection of modified amino acids by LC-ESI-MS has not been widely explored.[15]

Recently, labeling of α-amino groups of peptides by a 1:1 mixture of DNFB and its 3,5,6-trideuterio analog was coupled with HPLC electrospray ionization (ESI) MS to differentiate cross-linked peptides arising from post-translational protein modifications.[16] According to this method, the posttranslationally modified protein was first reductively methylated to remove free amino groups, then proteolyzed, and finally the freed α-amino groups were dinitrophenylated. Mono and bis-2,4-dinitrophenyl (DNP) derivatives (cross-linked peptides exhibit two α-amino groups) were separated by phenyl chromatography, and cross-linked peptides in the bis-DNP fraction were individually and unambiguously identified by LC-ESI-MS as 1:2:1 *m*/*z* *m*/*m*+3/*m*+6 triplets in the mass spectrum resulting from the binomial distribution of isotopic label in the bis-DNP derivative.

In cases where posttranslational modifications are rare and spread out over different sequence positions of the same amino acid, detection of the modification would be aided by complete proteolysis to the amino acid stage, thereby pooling the modified amino acid. However, although DNFB-derivatized peptides are readily discerned under ESI positive mode detection conditions because larger peptides are inevitably protonatable, our initial studies on DNFB-labeled amino acids indicated a poor response for most simple amino acids and dipeptides. This was understandable in that 2,4-dinitroarylation of the amino group abolishes the only site with significant proton affinity in these small molecules.

The purpose of the present study was to develop a modified version of Sanger's reagent containing a protonatable site so that the derivatized (modified) amino acid could be readily discerned under ESI positive mode detection, regardless of the nature of the amino acid or modification. Thus, a practical route was devised for synthesis of *N*,*N*-dimethyl-2,4-dinitro-5-fluorobenzylamine (DMDNFB, **1a**) and its -d_6 analog (**1b**). The characteristic UV spectrum would permit verification and quantitation of the peptide/protein

Keywords: Sanger's reagent; Amino acid derivatives; Peptide derivatives; Mass spectrometry.
* Corresponding author. Tel.: +1-216-368-3704; fax: +1-216-368-3006; e-mail address: lms3@cwru.edu

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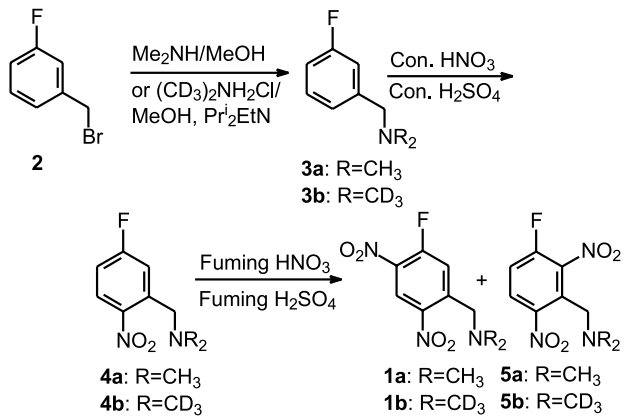
derivatization. When derivatizing a mixture of (modified) peptides or amino acids by a 1:1 mixture of the d_0 and d_6 reagent, the derivatives of interest would appear as either $m/(m+6)$ 1:1 doublets for simple modifications or $m/(m+6)/(m+12)$ 1:2:1 triplets for cross-links in the ESI-MS analysis.

2. Results and discussion

2.1. Preparation of *N*,*N*-dimethyl-2,4-dinitro-5-fluorobenzylamine (DMDNFB, 1a) and its -d_6 analog 1b

There are two alternative strategies to prepare dinitrobenzylamine derivatives: reaction of the corresponding dinitrobenzyl halide with amine,[17] or nitration of benzylamine with fuming sulfuric acid and fuming nitric acid.[18] The former approach is not suitable for preparation of **1a** because treating the intermediate 2,4-dinitro-5-fluorobenzylbromide with dimethylamine would result in reaction at either benzylic or aryl fluoride positions (or both). Thus, compounds **1a** and **1b** were prepared using the second approach (Scheme 1).



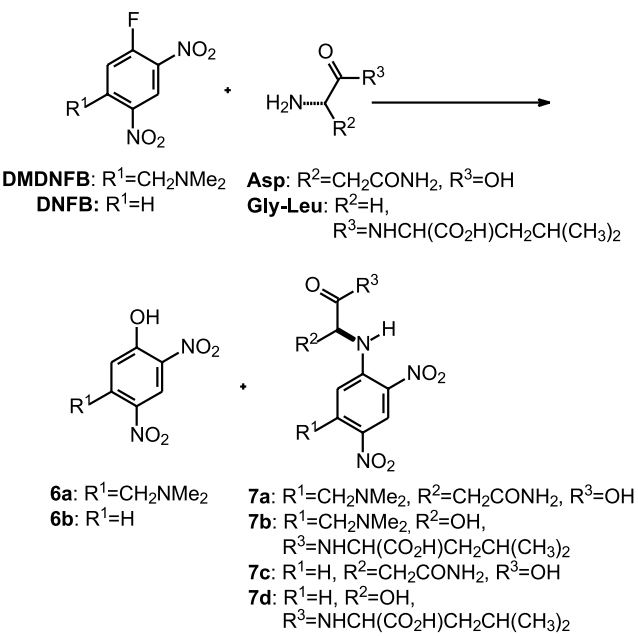
Scheme 1.

Heating 3-fluorobenzylbromide (**2**) with excess dimethylamine in methanol in a sealed tube gave *N*,*N*-dimethyl-3-fluoro-benzylamine (**3a**) in a yield of 85%. Similarly, heating **2** with d_6-dimethylamine hydrochloride in methanol in the presence of diisopropylethylamine (DIPEA) in a sealed tube for 4 days readily afforded the deuterium analog **3b** in a yield of 81%. The nitration was carried out in a stepwise manner. Heating **3a** with concentrated sulfuric acid and nitric acid give a single product in quantitative yield, assigned as *N*,*N*-dimethyl-2-nitro-5-fluorobenzylamine (**4a**) on the basis of ^{19}F couplings[19] observed in the APT ^{13}C NMR spectrum. Compound **4a** was further treated with fuming sulfuric acid and fuming nitric acid to afford **1a** in 72% yield, along with *N*,*N*-dimethyl-2,6-dinitro-3-fluoro-benzylamine (**5a**) in 11% yield. Compounds **1a** and **5a** could be easily separated by silica gel chromatography. We found that the ratio of fuming sulfuric acid to fuming nitric acid was critical for the introduction of the second nitro group. If the ratio is less than 3:1, the yield of **4a** was very low. In the same manner, DMDNFB-d_6 **1b** was prepared starting from **3b** and a 1:1 mixture of DMDNFB-d_0 and DMDNFB-d_6 **1b** was prepared starting from a 1:1 mixture of **3a** and **3b**.

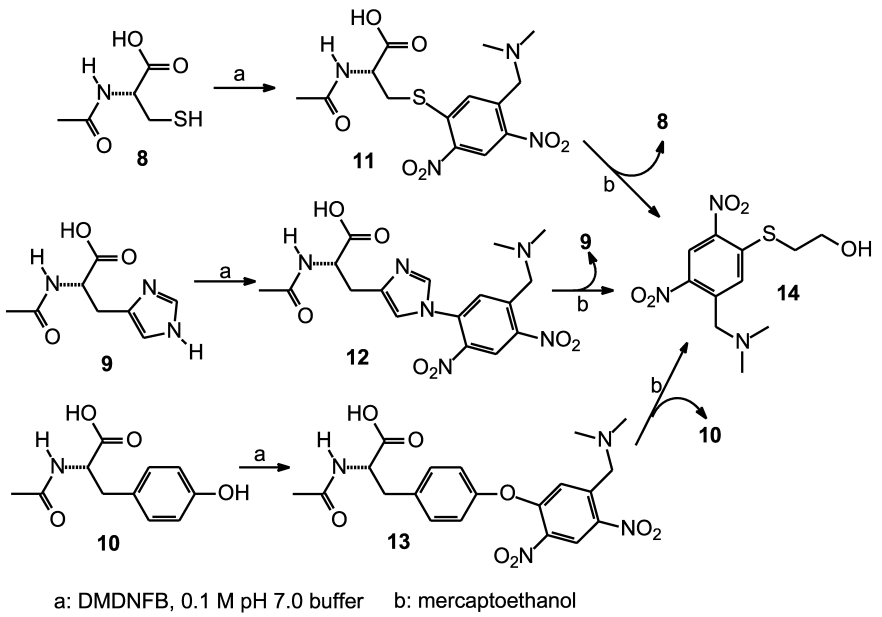
2.2. Reaction of DMDNFB and DNFB with asparagine and glycyl-L-leucine

To evaluate the reactivity of DMDNFB with the α-amino groups of amino acids and peptides under neutral conditions, the reaction of DMDNFB (40 μM) with asparagine (400 μM), the amino acid with the lowest α-amino pK_a, was carried out in pH 7.0, 0.1 M phosphate buffer. UV–Vis spectrometric monitoring indicated that the reaction followed pseudo first order kinetics in the first 2 h, yielding a second order rate constant of 1.76×10^{-3} min^{-1} M^{-1} after factoring out the [Asp] from k_{obs}. Under the same condition, the rate constant for the reaction of DNFB with asparagine was 1.67×10^{-4} min^{-1} M^{-1}. These results demonstrated that DMDNFB is about 10 times more reactive than DNFB toward the α-amino group of asparagine under this condition.

Reactions of DMDNFB (**1a**, free base) and DNFB with asparagine and glycyl-L-leucine were also carried out in an NMR tube and monitored by NMR spectrometry (Scheme 2). The reaction of 20 μmol each of DMDNFB and asparagine in 0.5 mL of a 1:1 mixture of 0.1 M, pH 7.0 phosphate buffer in D_2O and DMF-d_7 at room temperature was complete in 3 h and afforded a more than 90% yield of N^{α}-(5-(dimethylaminomethyl)-2,4-dinitrophenyl)asparagine (**7a**, N^{α}-DMDNP-Asp) and less than 10% of the hydrolysis product N^{α}-(5-(dimethylaminomethyl)-2,4-dinitrophenol (**6a**, DMDNPOH). However, the reaction of DNFB with asparagine under the same reaction condition was relatively slow and afforded an about 50% yield of N^{α}-(2,4-dinitrophenyl)asparagine (**7c**, N^{α}-DNP-Asp) in 4 h. Under the same conditions, the reaction of DMDNFB with Gly–Leu was complete in 1 h and afforded N^{α}-DMDNP-Gly–Leu (**7b**) almost quantitatively. In contrast to the results using pH 7.0 phosphate buffer, when the modification of asparagine (20 μmol) with either DMDNFB or DNFB (20 μM) was conducted in a 1:1 mixture of 5% $NaHCO_3$ in D_2O and DMF-d_7 (0.5 mL), there was no deficit



Scheme 2.



Scheme 3.

in the reaction with DNFB. Thus, the reaction with DMDNFB was complete in 3 h at room temperature and afforded a 81% yield of **7a** and a 18% yield of **6a**, whereas the reaction of DNFB was complete in 3 h and afforded **7c** almost quantitatively. These results demonstrated that DMDNFB is a reasonable alternative reagent to DNFB for labeling α-amino group of amino acids or peptides.

2.3. Reaction of side-chain functional groups of amino acids with DMDNFB and thiolysis of their products with mercaptoethanol

To develop DMDNFB as an alternative N-terminal labeling reagent, the reaction of DMDNFB and amino acids or peptides should lead to N^{α}-DMDNP amino acid or peptide derivatives as final products. However the thiol group of cysteine, the imidazole group of histidine, the phenol group of tyrosine, and the ϵ-amino group of lysine should also react with DMDNFB, as with DNFB. To investigate the reactivity of the first three functional groups toward DMDNFB, the reaction of either N^{α}-acetyl-L-cysteine **8**, N^{α}-acetyl-L-histidine **9**, or N^{α}-acetyl-L-tyrosine **10** (40 mM) with DMDNFB (40 mM) was carried out in 0.1 M pH 7.0 sodium phosphate buffer at room temperature (Scheme 3) and monitored by TLC. The reaction of **8** with DMDNFB was complete in 30 min and the product was N^{α}-acetyl-*S*-DMDNP-L-cysteine **11**. The reaction of **10** with DMDNFB transpired more slowly, and DMDNFB was consumed in 24 h. N^{α}-acetyl-*O*-DMDNP-L-tyrosine **13** was obtained after a column chromatographic purification. However, the ^{1}H NMR spectrum of the residue obtained following workup of the reaction of **9** with DMDNFB for 24 h indicated that only about half of the N^{α}-acetyl-L-histidine was converted to N^{α}-acetyl-N^{τ}-DMDNP-L-histidine **12**. During the purification of **12**, it suffered hydrolytic decomposition to N^{α}-acetyl -L-histidine and DMDNPOH (**6a**) so that we could not obtain a pure sample of **12**.

In the case of amino acid derivatization by Sanger's reagent, it is reported that *S*-DNP-L-cysteine, *O*-DNP-L-tyrosine and N^{τ}-DNP-L-histidine can be reverted to the free amino acids by mild thiolysis using mercaptoethanol.[20] Thus it was expected that mercaptoethanol would revert the DMDNP derivatives **11**–**13** to their precursors **8**–**10**. Thus, mercaptoethanol was added to the above reaction mixtures in situ, and TLC monitoring of these reactions demonstrated **12** and **13** were easily reverted to their corresponding precursors in 1 h. The latter reversion could also be followed by UV–Vis spectrophotometry (Fig. 1). Although **11** was not completely reverted to N^{α}-acetyl-L-cysteine by mercaptoethanol in 1 h at pH 7, the reaction proceeded to completion in 1 h at pH 8. The ϵ-amino group of lysine would be expected to be irreversibly derivatized by DMDNFB along with the α-amino group, so reductive methylation or some other protection strategy would be needed prior to enzymatic hydrolysis if monoderivatization was desired. Overall, by a combination of lysine protection, controlled derivatization, and thiolysis, DMDNP derivatized amino acids or peptides can be limited to the α-amino group.

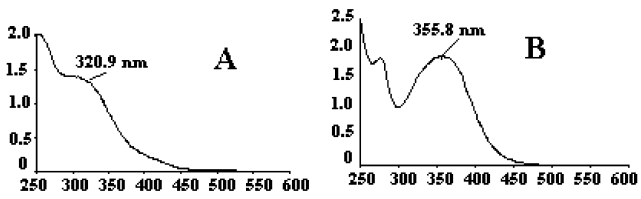
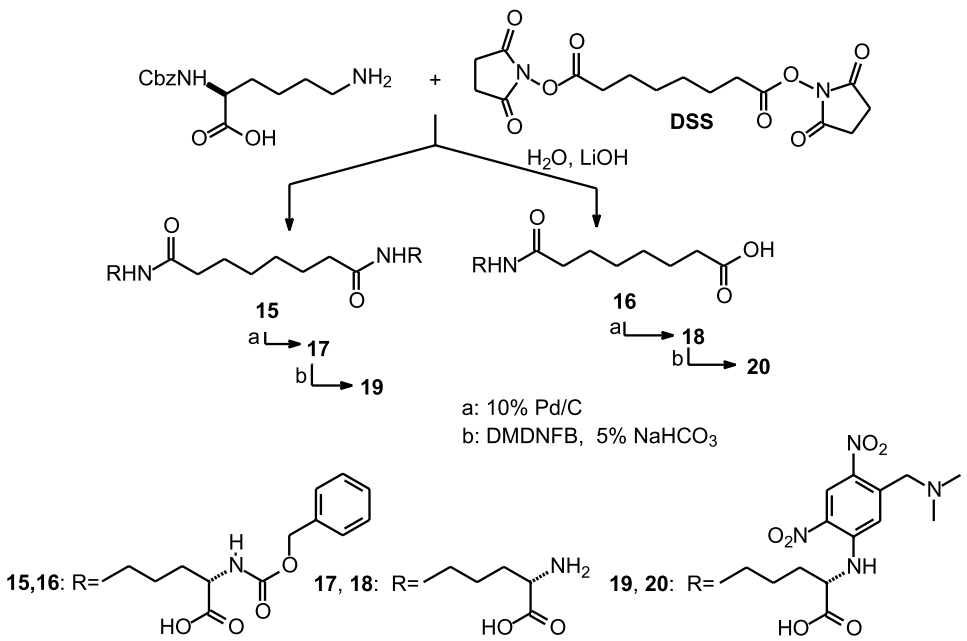


Figure 1. UV–Vis spectrum of (A) N^{α}-acetyl-*O*-DMDNP-tyrosine (0.15 mM) and (B) after treatment with mercaptoethanol for 1 h in 0.1 M pH 7.0 sodium phosphate.

2.4. Synthesis of lysine derivatives of DSS and succinyl chloride and their reactions with DMDNFB studied by isotope-edited ESI-MS

Lysine residues in proteins are major targets for modification by sugars and lipoxidation-derived reactive aldehydes during conditions of physiological oxidative stress.

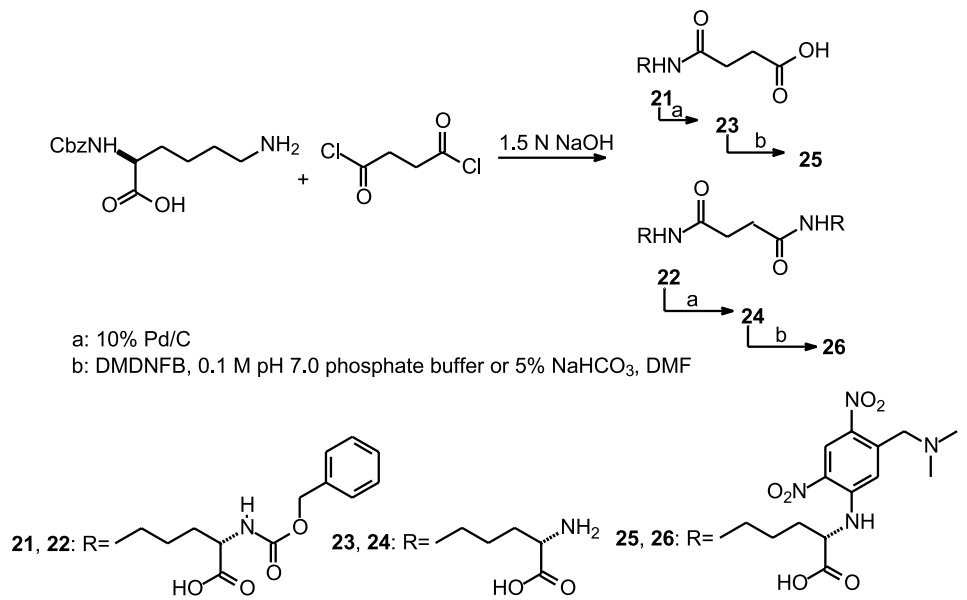


Scheme 4.

To evaluate the reactivity of the α-amino group toward DMDNFB of some modified lysines (with and without cross-linking) that would be generated by hydrolysis of a modified protein sample, we used disuccinimidyl suberate (DSS), a common lysine cross-linking reagent, that would react to give both a cross-link modification, the bis amide **17**, and, under partial hydrolysis conditions, a non-cross-link modification, the mono amide **18** (Scheme 4). Thus, treatment of N^{α}-Cbz-lysine with DSS in a ratio of 3:1 yielded the bis amide **15**, and treatment of N^{α}-Cbz-lysine with DSS in a ratio of 1:3 followed by hydrolysis using 1 M aqueous LiOH yielded the mono amide **16**. The Cbz group was removed from **15** and **16** by hydrogenolysis to give compounds **17** and **18**, respectively.[21]

Although the reaction of **17** or **18** with DMDNFB in a 1:1 mixture of pH 7.0, 0.1 M phosphate buffer and DMF resulted mainly in the hydrolytic by-product DMDNPOH, DMDNP derivatives **19** and **20** were generated, albeit in low yield, when the reactions were carried out in a 1:2 mixture of 5% $NaHCO_3$ and DMF. Thus, using a 1:1 mixture of DMDNFB and DMDNFB-d_6, ESI-MS analysis following work-up as described in the experimental section revealed 1:2:1 triplets with *m*/*z* 877.5/883.6/889.5 (singly charged ion) and *m*/*z* 439.5/442.6/446.1 (doubly charged ion) for the reaction of **17**, as expected for bis-DMDNP derivative **19**, and a 1:1 doublet with *m*/*z* 526.5/532.5 (singly charged ion) for the reaction of **18**, as expected for mono-DMDNP derivative **20**.

One possible explanation for the low yield of dinitrophenylation of compounds **17** and **18** is that the hydrophobic



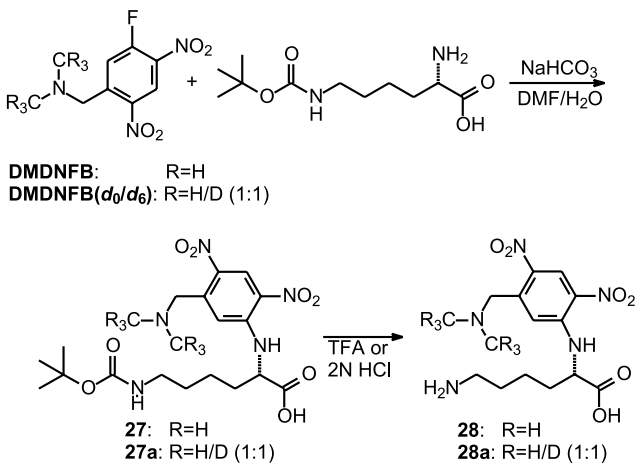
Scheme 5.

environment of the tether is lowering the reactivity of the α-amino group. To test this possibility, it was desirable to use a less hydrophobic tether, and we decided on succinyl (two methylenes in contrast to six methylenes for suberyl). Treatment of N^{α}-Cbz-lysine with succinyl chloride in a ratio of 1:1 in a solution of 1.5 N NaOH afforded a 2:1 mixture of monomer **21** and dimer **22**, which was subjected to hydrogenolysis (Pd/C) to remove the Cbz group to yield mixture of **23** and **24** (Scheme 5). The monomer **23** was washed off the catalyst with methanol and the dimer **24** was washed off the catalyst using 0.1 N HCl. Individual NMR tube scale reactions of monomer **23** and dimer **24** with DMDNFB in a 1:1 mixture of pH 7.0, 0.1 M sodium phosphate buffer in D_2O and DMF-d_7 yielded mono-DMDNP derivative **25** in a yield of 35% and bis-DMDNP derivative **26** in a yield of 30%, whereas the yields increased to 68 and 76%, respectively, using a 1:2 mixture of 5% $NaHCO_3$ in D_2O and DMF-d_7. Based on this result, compounds **25** and **26** were synthesized on a preparative scale in a 1:2 mixture of 5% $NaHCO_3$ and DMF. Attempts to separate a mixture of **25** and **26** on a phenyl superose column used to separate mono and bis-2,4-dinitrophenyl peptide derivatives[16] were unsuccessful. Apparently, the presence of the *N*,*N*-dimethylaminomethyl substituent interferes with the differential affinity of the mono vs. bis-2,4-dinitrophenyl compounds for the phenyl media, at least in the case of **25** and **26**.

2.5. Preparation of N^{α}-(2,4-dinitro-5-(dimethylaminomethyl)phenyl)-L-lysine (N^{α}-DMDNP-lysine, 28) and a 1:1 mixture of N^{α}-DMDNP-lysine and N^{α}-DMDNP-d_6-lysine (28a)

N^{α}-DMDNP-lysine (**28**) was prepared as shown in Scheme 6. Treatment of N^{ϵ}-*t*-Boc-lysine with 1.5 equiv. of DMDNFB yielded N^{ϵ}-*t*-Boc-N^{α}-DMDNP-lysine **27**. Although treatment of **27** with TFA in methylene chloride[22] did not remove the Boc group, it was removed by either heating in TFA at reflux or in 2 N HCl at room temperature, to afford N^{α}-DMDNP-lysine **28**. Also the 1:1 mixture of N^{α}-DMDNP-lysine and N^{α}-DMDNP-d_6-lysine **28a** was prepared using a 1:1 mixture of DMDNFB and DMDNFB-d_6.

The latter mixture will be a convenient lysine surrogate for the use of isotope-edited LC-ESI-MS (positive mode) to monitor the reactions of protein-based lysines with the reactive aldehydes present during physiological oxidative stress. The three advantages are first that the HPLC chromatogram (UV–Vis at 360 nm) will reveal how many species in the incubation mixture contain the lysine moiety. Second, the isotopic pattern in the mass spectrum of each peak will tell how many lysine moieties are contained in the species: compounds containing one N^{α}-DMDNP-lysine would exhibit a *m*/*z* *m*/*m*+6 1:1 doublet in the mass spectrum and compounds containing two N^{α}-DMDNP-lysines would exhibit a 1:2:1 *m*/*z* *m*/*m*+6/*m*+12 triplet in the mass spectrum. Thus it will be easy to distinguish non-cross-link from cross-link modifications and to tell their relative importance. Third, the presence of the *N*,*N*-dimethylaminomethyl basic center will ensure robust ion current signals in the ESI positive mode.



Scheme 6.

The ESI positive mode mass spectrum of the 1:1 d_0:d_6 N^{α}-DMDNP-lysine mixture (**28a**) exhibited a 1:1 *m*/*z* 370.40/376.40 doublet for the expected singly charged (protonated) ions, but also an unexpected 1:2:1 *m*/*z* 739.1/745.2/751.2 triplet, corresponding to a singly protonated non-covalent dimer of the reagent. This latter observation suggests caution in simply interpreting the observation of any *m*/*z* *m*/*m*+6/*m*+12 triplet in terms of a covalent cross-link. Thus, an observed triplet at *m*/*z* 2*x*+1/2*x*+7/2*x*+13 will signal a covalent cross-link only when there is no corresponding *m*/*z* *x*+1/*x*+7 doublet also observed.

3. Conclusions

In this paper, *N*,*N*-dimethyl-2,4-dinitro-5-fluorobenzylamine (DMDNFB, **1a**) and *N*,*N*-dimethyl-d_6-2,4-dinitro-5-fluorobenzylamine (**1b**) were synthesized. Parallel UV–Vis and NMR spectrometric studies on aminolysis of 2,4-dinitrofluorobenzene (DNFB) and DMDNFB by amino acids or peptides demonstrated that DMDNFB was at least as reactive as DNFB under neutral conditions and could form N^{α}-derivatives of amino acids and peptides with comparable efficiency. As with DNFB, DMDNFB also modifies the nucleophilic side-chains of Cys, Tyr, and His, but these adducts can be selectively reversed using mercaptoethanol. A variety of lysine-based derivatives of DMDNFB-d_0 and -d_6 were then prepared to illustrate the potential use of this reagent and isotope edited ESI mass spectrometry to investigate the lysine-based post-translational modification of proteins.

4. Experimental

4.1. General

^{1}H NMR (300 or 200 MHz) and ^{13}C NMR (75.1 or 50.1 MHz) spectra were recorded on Varian Gemini 300 or 200 instruments In all cases, tetramethylsilane or the solvent peak served as internal standard for reporting chemical shifts, which are expressed as parts per million downfield from TMS (δ scale) In the ^{13}C NMR line listings, attached proton test (APT) designations are given as (+) or (−) following the chemical shift Some carboxamide ^{13}C signals were not observed. High-resolution mass spectra

(HRMS) were obtained at 20 eV on a Kratos MS-25A instrument. TLC was performed on glass plates precoated with silica gel $60F_{254}$. Compounds on the developed plate were visualized by short-wavelength UV light (λ=254 nm), by placing the plate in a chamber filled with iodine vapor, or by spraying with ammonium phosphomolybdic acid solution or ninhydrin solution. All preparative column chromatography was performed using 32–63 μm silica gel under nitrogen pressure (flash chromatography). Purity of compounds was assessed by TLC and the lack of detectable extraneous signals in the ^{1}H NMR spectra. The water that was used for all studies was purified by a Millipore system. UV–Vis spectra were obtained using a Perkin–Elmer Lambda 20 spectrophotometer.

3-Fluorobenzylbromide, 2 M dimethylamine in methanol, dimethylamine-d_6 hydrochloride, succinyl chloride, 10% Pd–C, N^{α}-Cbz-lysine, N^{ϵ}-*t*-Boc-lysine, and 2,4-dinitrofluorobenzene (DNFB) were purchased from Aldrich Chemical Company. DSS was purchased from Pierce.

4.2. HPLC-ESI-MS-MS analyses

The reversed phase HPLC with electrospray ionization (ESI) mass spectrometry analysis of DMDNP and DNP amino acid derivatives was performed with a HP1100 equipped with either a Vydac Low TFA C_{18} column (eluent A was 95% H_2O, 5% acetonitrile, and 0.02% TFA and eluent B was 5% H_2O, 95% acetonitrile, and 0.02% TFA; the flow rate was 0.3 mL/min) or a Phenomenex Aqua C_{18} column (eluent A was 100% H_2O, 0.1% formic acid, and 0.02% TFA and eluent B was 90% acetonitrile, 0.1% formic acid, and 0.02% TFA; the flow rate was 0.5 mL/min), where the gradient was 100% A to 100% B over 60 min. The eluent was monitored at 214 nm as channel A and 350 nm as channel B and the UV–Vis spectrum of each peak was obtained from 200 to 600 nm. Electrospray ionization mass spectrometry was performed using a Finnegan LCQ^{deca} (San Jose, CA) in the positive mode using nitrogen as sheath (90 bars) and auxiliary gas (20 bars). The heated capillary temperature was 250 °C, the electrospray voltage was 5.2 kV, and the capillary voltage was set to −4 V. Three scan events were used: (i) 200–1000 *m/z* full scan MS, (ii) data-dependent zoom scan on the most intense ion from the MS full spectrum, and (iii) data-dependent full scan MS/MS on the most intense ion from the MS full spectrum. The MS/MS collision energy was set at 35 V.

4.3. Synthetic compounds

4.3.1. *N*,*N*-Dimethyl-3-fluorobenzylamine (3a).[23] A sealed tube charged with a methanolic solution of dimethylamine (2 M, 3 mL, 6 mmol) and 3-fluorobenzylbromide (378 mg, 2 mmol) was heated at reflux for 24 h. The reaction mixture was cooled and methanol was evaporated. The residue was dissolved in water (8 mL) and adjusted to pH 12 with 1 N NaOH, and the solution was extracted with ether (3×20 mL). The organic layer was combined and dried over anhydrous Na_2SO_4. The ether was evaporated to give **3a** as a colorless oil in a yield of 84.7% (260 mg): ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 6H), 3.41 (s, 2H), 6.94 (td, 1H, *J*=8.5, 2.3 Hz), 7.02–7.08 (2H), 7.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 45.4 (−), 63.9 (+), 113.9 (−, d, *J*=21 Hz), 115.8 (−, d, *J*=21 Hz), 124.5 (−, d, *J*=1.7 Hz), 129.7 (−, d, *J*=8.0 Hz), 141.7 (+, d, *J*=6.8 Hz), 163.0 (+, d, *J*=244 Hz).

4.3.2. *N*,*N*-Dimethyl-3-fluorobenzylamine-d_6 (3b). A sealed tube charged with dimethylamine-d_6 hydrochloride (175 mg, 2 mmol) in methanol (2 mL), diisopropylethylamine (0.70 mL, 4 mmol) and 3-fluorobenzylbromide (189 mg, 1 mmol) was heated to reflux for 96 h. The reaction mixture was cooled and the methanol was evaporated. The residue was dissolved in water (4 mL) and adjusted to pH 12 with 1 N NaOH. Then the aqueous solution was extracted with ether (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give **3b** as a colorless oil (128 mg, 80.5%): ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 2H), 6.94 (td, 1H, *J*=8.5, 2.3 Hz), 7.02–7.08 (2H), 7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 63.8 (−), 114.0 (+, d, *J*=21 Hz), 115.8 (+, d, *J*=21 Hz), 124.6 (+, d, *J*=1.7 Hz), 129.7 (+, d, *J*=8.0 Hz), 141.7 (−, d, *J*=6.8 Hz), 163.0 (−, d, *J*=243.8 Hz); EI HRMS *m/z* calcd for $C_9H_6D_6FN$ M^+ 159.1330, found 159.1330.

4.3.3. *N*,*N*-Dimethyl-2-nitro-5-fluorobenzylamine (4a). Compound **3a** (100 mg, 0.65 mmol) was added to a mixture of sulfuric acid (98%, 0.3 mL) and nitric acid (69%, 0.1 mL) at 50 (C. The mixture was stirred and kept at 100 °C for 2 h, then cooled and poured into ice water (20 mL). The aqueous solution was adjusted to pH 10 with 1 N NaOH and extracted with ethyl acetate (3×30 mL). The organic layer was combined and dried over anhydrous Na_2SO_4 followed by filtration. Ethyl acetate was evaporated in vacuo to give **4a** quantitatively as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6H), 3.75 (s, 2H), 7.06 (m, 1H), 7.48 (dd, 1H, *J*=9.6, 2.7 Hz), 7.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 45.7 (−), 60.2 (+), 114.6 (−, d, *J*=23.3 Hz), 117.5 (−, d, *J*=24.5 Hz), 127.3 (−, d, *J*=9.7 Hz), 139.2 (+, d, *J*=8.4 Hz), 145.2 (+), 165.0 (+, d, *J*=253.5 Hz); EI HRMS *m/z* calcd for $C_9H_{11}FN_2O_2$ (M^+) 198.0805, found 198.0815.

4.3.4. *N*,*N*-Dimethyl-d_6-2-nitro-5-fluorobenzylamine (4b). According to the procedure for the synthesis of **4a**, compound **4b** (pale yellow oil) was prepared quantitatively from **3b**: ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 2H), 7.03 (m, 1H), 7.45 (dd, 1H, *J*=9.6, 2.7 Hz), 7.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 45.0 (+, m), 60.0 (+), 114.6 (−, d, *J*=23.3 Hz), 117.5 (−, d, *J*=24.5 Hz), 127.4 (−, d, *J*=9.7 Hz), 139.2 (+, d, *J*=8.4 Hz), 145.2 (+), 164.9 (+, d, *J*=253.5 Hz); EI HRMS *m/z* calcd for $C_9H_5D_6FN_2O_2$ M^+ 204.1181, found 204.1180.

4.3.5. *N*,*N*-Dimethyl-2,4-dinitro-5-fluorobenzylamine (1a). Fuming nitric acid (1 mL) was added to a solution of **4a** (500 mg, 1.9 mmol) in fuming sulfuric acid (6 mL) and the mixture was heated to 100 °C for 2 h. The reaction mixture was cooled and poured into ice (100 g). The aqueous solution was neutralized to pH 7.0 with 1 N NaOH and extracted with ethyl acetate (5×100 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give a mixture of *N*,*N*-dimethyl-2,4-dinitro-5-fluorobenzylamine **1a** and *N*,*N*-dimethyl-2,6-dinitro-5-fluorobenzylamine **5a** in a ratio of 6:1 based on the integration in the ^{1}H NMR spectrum of the crude product. The mixture was subjected to silica gel chromatography,

eluting with ethyl acetate–hexane (v/v, 4:5) to give **1a** and **5a** as yellow oils in yields of 72.3 and 11.3%, respectively. **1a**: ^{1}H NMR ($CDCl_3$, free base) δ 2.30 (s, 6H), 3.83 (s, 2H), 7.87 (d, 1H, J=11.0 Hz), 9.73 (d, 1H, J=6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 45.7 (−), 60.0 (+), 120.8 (+, d, J=19.3 Hz), 123.7 (−, d, J=1.2 Hz), 144.0 (+), 145.6 (+, d, J=7.6 Hz), 154.5 (+, d, J=19.6 Hz), 157.5 (+, d, J=216.8 Hz); EI HRMS m/z calcd for $C_9H_{10}FN_3O_4$ M^+ 243.0655, found 243.0649. The HCl salt of **1a** was prepared by passing HCl gas through a solution of **1a** in ether: mp 152–154 °C; ^{1}H NMR (methanol-d_4) δ 3.09 (s, 6H), 4.80 (s, 2H), 8.13 (d, 1H, J=10.6 Hz), 9.08 (d, 1H, J=6.9 Hz); ^{13}C NMR (methanol-d_4) δ 44.6 (−), 58.9 (+), 126.2 (−), 126.7 (−, d, J=24.4 Hz), 134.4 (+, d, J=10.1 Hz), 139.3 (+, d, J=9.2 Hz), 146.0 (+, d, J=5.8 Hz), 158.7 (+, d, J=221.0 Hz). **5a**: ^{1}H NMR ($CDCl_3$) 2.16 (s, 6H), 3.71 (s, 2H), 7.34 (t, J=8.2, 9.0 Hz) 7.90 (dd, J=9.0, 4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 45.2 (−), 54.9 (+), 116.7 (d, J=21.0 Hz), 127.4 (−, d, J=9.0 Hz), 131.1 (+), 140.5 (+, d, J=8.3 Hz), 146.6 (+, d, J=2.7 Hz), 155.0 (+, d, J=263.4 Hz); EI HRMS m/z calcd for $C_9H_{10}FN_3O_4$ M^+ 243.0655, found 243.0649. According to the procedure for synthesis of **1a**, the 1:1 mixture of **1a** and *N*,*N*-dimethyl-d_6-2,4-dinitro-5-fluorobenzylamine (**1b**) was prepared using a 1:1 mixture of **4a** and **4b** in a yield of 70.8%.

4.3.6. N^{α}-(2,4-Dinitro-5-(dimethylaminomethyl)-phenyl)glycyl-L-leucine (7b). A solution of **1a** (100 mg) in DMF (2 mL) was added to a suspension of glycyl-L-leucine (50 mg, 0.266 mmol) and sodium bicarbonate (100 mg) in water (1 mL) and the mixture was stirred at room temperature for 1 h. The solution was diluted with water (10 mL) and extracted with ethyl acetate (2×10 mL). Water was evaporated to give a crude product, which was subjected to preparative TLC eluted with methanol–ethyl acetate (1:1, v/v) to give **7b** as a yellow powder in a yield of 95.4%: mp >215 °C (dec); ^{1}H NMR (methanol-d_4) δ 0.91 (d, 6H, J=5.9 Hz), 1.60–1.71 (3H), 2.30 (s, 6H), 3.85 (s, 2H), 4.24 (s, 2H), 4.39 (m, 1H) 7.11(s, 1H), 8.95 (s, 1H); ^{13}C NMR (methanol-d_4) δ 22.2 (+), 23.8 (+), 26.3 (+), 43.3 (+), 46.0 (−), 46.9 (+), 55.0 (−), 62.0 (+), 117.6 (+), 126.6 (+), 131.1 (−), 138.1 (−), 143.7 (−), 148.0 (−), 169.5 (−), 179.8 (−); FAB HRMS m/z calcd for $C_{17}H_{26}N_5O_7$ $(M+H)^+$ 412.1832 found 412.1840.

4.3.7. N^{α}-(2,4-Dinitro-5-(dimethylaminomethyl)-phenyl)-L-asparagine (7a). According to the procedure for the synthesis of **7b**, **7a** was obtained from L-asparagine as a yellow powder in a yield of 85%: mp >200 °C (dec); ^{1}H NMR (methanol-d_4) δ 2.25 (s, 1H), 2.78 (dd, 1H, J=13.9, 6.8 Hz), 2.87 (dd, 1H, J=13.9, 4.6 Hz), 3.81 (s, 2H), 4.53 (t, 1H), 7.17 (s, 1H), 8.94 (s, 1H); ^{13}C NMR (methanol-d_4) δ 39.5 (−), 46.0 (−), 57.1 (−), 60.2 (+), 116.2 (−), 125.3 (−), 131.1 (+), 137.3 (+), 143.3 (+), 148.1 (+), 173.2 (+), 175.8 (+); FAB HRMS m/z calcd for $C_{13}H_{18}N_5O_7$ $(M+H)^+$ 356.1206, found 356.1212.

4.3.8. N^{α}-(2,4-Dinitrophenyl)glycyl-L-leucine (7d). A solution of DNFB (19 μL, 0.15 mmol) in ethanol (0.8 mL) was added to a suspension of glycyl-L-leucine (18.8 mg, 0.1 mmol) and sodium bicarbonate (33.6 mg) in water (0.4 mL) and the mixture was stirred at room temperature for 2 h. Ethanol was evaporated and the aqueous residue was diluted to 4 mL with water and extracted with ether (3×2 mL). The aqueous layer was acidified to pH 2 with 2 N HCl and extracted with ethyl acetate (3×2 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give **7d** as a yellow powder in a yield of 91.8%: mp >240 °C (dec); ^{1}H NMR (methanol-d_4) δ 0.92 (d, 6H, J=5.9 Hz), 1.53–1.69 (3H), 4.22 (s, 2H), 4.37 (td, 1H, J=3.3, 10.0 Hz), 7.02 (d, 1H, J=9.6 Hz), 8.28 (dd, 1H, J=2.7, 9.6 Hz), 9.04 (d, 1H, J=2.6 Hz); ^{13}C NMR (methanol-d_4) δ 22.0 (−), 23.8 (−), 26.3 (−), 43.1 (+), 46.9 (+), 55.0 (−), 116.3 (−), 124.5 (−), 131.0 (−), 132.2 (+), 137.5 (+), 149.3 (+), 164.3 (+), 169.4 (+); FAB HRMS m/z calcd for $C_{14}H_{19}N_4O_7$ $(M+H)^+$ 355.1254 found 355.1263.

4.3.9. N^{α}-Acetyl-*S*-(2,4-dinitro-5-(dimethylaminomethyl)phenyl)-L-cysteine (11). According to the procedure for synthesis of **7b**, **11** was obtained from N^{α}-acetyl-L-cysteine as a yellow powder in 100% yield: ^{1}H NMR (methanol-d_4) δ 2.00 (s, 3H), 2.97 (s, 6H), 3.50 (dd, 1H, J=14.1, 6.6 Hz), 3.65 (dd, 1H, J=14.2, 6.3 Hz), 4.52 (t, 1H, J=6.5 Hz), 4.63 (s, 2H), 8.29 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (methanol-d_4) δ 22.7 (−), 35.4 (+), 44.7 (−), 53.4 (−), 59.3 (+), 125.0 (−), 131.9 (+), 134.2 (−), 145.9 (+), 146.7 (+), 147.1 (+), 173.3 (+), 175.0 (+); FAB HRMS m/z calcd for $C_{14}H_{19}N_4O_7S$ $(M+H)^+$ 387.0974, found 387.0975.

4.3.10. N^{α}-Acetyl-*O*-(2,4-dinitro-5-(dimethylaminomethyl)phenyl)-L-tyrosine (13). According to the procedure for the synthesis of **7b**, **13** was obtained from N^{α}-acetyl-L-tyrosine as a yellow powder in 89.3% yield: ^{1}H NMR (HCl salt in methanol-d_4) δ 1.92 (s, 3H), 2.70 (s, 6H), 2.96 (dd, 1H, J=14.1, 5.7 Hz), 3.21 (dd, 1H, J=13.8, 5.0 Hz), 4.35 (s, 2H), 4.58 (m, 1H), 7.14 (d, 2H, J=8.4 Hz), 7.38 (d, 2H, J=8.4 Hz), 7.89 (s, 1H), 8.87 (s, 1H); ^{13}C NMR (HCl salt in methanol-d_4) δ 22.7 (−), 38.5 (+), 44.7 (−), 55.4 (−), 69.7 (+), 121.4 (−), 124.2 (−), 125.5 (−), 132.8 (−), 135.9 (+), 137.7 (+), 141.0 (+), 143.6 (+), 154.2 (+), 156.2 (+), 172.9 (+), 175.3 (+); FAB HRMS m/z calcd for $C_{20}H_{23}N_4O_8$ $(M+H)^+$ 447.1516, found 447.1513.

4.3.11. *N*,*N*-Dimethyl-2,4-dinitro-5-((2-hydroxyethyl)thio)benzylamine (14). According to the procedure for the synthesis of **7b**, **14** was obtained from mercaptoethanol as a yellow resin in 100% yield: ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 6H), 2.51 (b, 1H), 3.31 (t, 2H, J=6.18 Hz), 3.87 (s, 2H), 3.99 (t, 2H, J=6.24 Hz), 7.97 (s, 1H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.11 (+), 45.78 (−), 59.93 (+), 60.16 (+), 123.26 (−), 128.16 (−), 140.25 (+), 143.72 (+), 144.35 (+); EI HRMS m/z calcd for $C_{11}H_{15}N_3O_5S$ M^+ 301.0732, found 301.0726.

4.3.12. 2-Amino-6-(7-(5-amino-5-carboxypentylaminocarbonyl)heptanoylamino)hexanoic acid (17). Disuccinimidyl suberate (DSS) (50 mg, 0.135 mmol) and N^{α}-Cbz-lysine (151.2 mg, 0.54 mmol) were suspended in DMF (5 mL) and the mixture was stirred at room temperature for 1 h. The reaction mixture was subjected to flash chromatography eluted first with acetone, then with a mixture of acetone and acetic acid (v/v 95:5). The solvent was evaporated and the residue was dissolved in water (20 mL). The aqueous solution was extracted with ethyl acetate (3×10 mL). The combined organic layer was dried

over anhydrous Na_2SO_4 and evaporated to give 2-(benzyloxycarbonylamino)-6-(7-(5-(benzyloxycarbonylamino)-5-carboxypentyl-aminocarbonyl)heptanoylamino)hexanoic acid (**15**) as a white powder in a yield of 73.7% (70 mg): ^{1}H NMR (methanol-d_4) δ 0.91–1.60 (18H),1.88 (m, 2H), 2.15 (t, 4H, J=7.1 Hz), 3.14 (t, 4H, J=6.7 Hz), 4.13–4.20 (m, 2H), 5.05 (s, 4H), 7.30–7.40 (10H); ^{13}C NMR (methanol-d_4) δ 24.4 (+), 26.8 (+), 27.0 (+), 30.0 (+), 32.5 (+), 37.2 (+), 40.2 (+), 55.4 (−), 67.7 (+), 128.9 (−), 129.1 (−), 129.6 (−), 138.3 (+), 158.7 (+), 172.1 (+), 176.3 (+). A solution of **15** (50 mg) in 4.4% methanolic formic acid (2.5 mL) was added to a suspension of Pd–C (10%, 50 mg) in 2.5 mL of 4.4% methanolic formic acid. The mixture was stirred at room temperature for 3 h, then filtered, and the catalyst was washed with methanol (3×5 mL) followed by 1 N HCl (3×5 mL). The filtrate was evaporated to give **17** as a white powder in a yield of 92.9%: ^{1}H NMR (D_2O) δ 1.17–1.27 (8H), 1.37–1.49 (12H), 2.14 (t, 4H, J=7.0 Hz), 3.07–3.16 (6H); ^{13}C NMR (D_2O) δ 22.5 (−), 26.1 (−), 28.6 (−), 28.7 (−), 30.2 (−), 36.6 (−), 39.6 (−), 53.7 (+), 172.9 (−), 178.0 (−); FAB HRMS m/z calcd for $C_{20}H_{38}N_4O_6Na$ 453.2689 $(M+Na)^+$, found 453.2655.

4.3.13. 2-Amino-6-(7-carboxyheptanoylamino)hexanoic acid (18). Disuccinimidyl suberate (DSS) (100 mg, 0.27 mmol) and N^{α}-Cbz-lysine (37.5 mg, 0.135 mmol) was suspended in DMF (5 mL) and the mixture was stirred at room temperature for 1 h. The DMF was removed under high vacuum and the residue was subjected to flash chromatography eluted first with acetone, then with acetone–acetic acid (95:5, v:v). The solvent was removed and the residue was dissolved in a mixture of tetrahydrofuran (THF, 5 mL) and 1 M aqueous LiOH solution (1.7 mL) was added. The reaction mixture was stirred at room temperature for 2 h and then adjusted to pH 3.0 with 2 N HCl. THF was evaporated, the residue was dissolved in water (20 mL), and the aqueous solution was extracted with ethyl acetate (3×10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to give 2-(benzyloxycarbonylamino)-6-(7-carboxyheptanoylamino)-hexanoic acid (**16**) as a white powder in a yield of 95.6% (56.3 mg): ^{1}H NMR (methanol-d_4) δ 1.32–1.36 (4H), 1.47 (m. 2H), 1.58–1.61 (6H), 2.00 (m, 2H), 2.27 (t, 2H, J=7.4 Hz), 2.41 (t, 2H, J=7.2 Hz), 3.23 (t, 2H, J=6.5 Hz), 3.83–3.90 (m, 1H), 5.05 (s, 2H), 7.32 (s, 5H); ^{13}C NMR (methanol-d_4) δ 24.3 (+), 26.3 (+), 27.0 (+), 30.0 (+), 30.1 (+), 33.5 (+), 35.7 (+), 37.1 (+), 40.3 (+), 57.0 (−), 67.5 (+), 128.8 (−), 129.0 (−), 129.5 (−), 138.4 (+), 158.5 (+), 176.2 (+), 176.2 (+), 176.3 (+). A solution of compound **16** (100 mg) in 4.4% methanolic formic acid (5 mL) was added to a suspension of Pd–C (10%, 50 mg) in 5 mL of 4.4% methanolic formic acid. The mixture was stirred at room temperature for 3 h, then filtered, and the catalyst was washed with methanol (3×5 mL). The solvent was evaporated to give **18** as a white powder in a yield of 94.8%: ^{1}H NMR (D_2O) δ 1.34 (4H), 1.47 (m, 2H), 1.58–1.61 (6H), 2.00 (m, 2H), 2.27 (t, 2H, J=7.4 Hz), 2.41 (t, 2H, J=7.2 Hz), 3.23 (t, 2H, J=6.5 Hz), 4.13 (t, 1H, J=7.2 Hz); ^{13}C NMR (D_2O) δ 21.7 (+), 24.2 (+), 25.3 (+), 27.8 (+), 27.8 (+), 27.9 (+), 29.5 (+), 33.9 (+), 35.8 (+), 38.9 (+), 53.0 (−), 177.1 (+), 177.2 (+), 179.3 (+); FAB HRMS m/z calcd for $C_{14}H_{27}N_2O_5$ $(M+H)^+$ 303.1920, found 303.1899.

4.3.14. 6-(3-Carboxylpropionylamino)-2-(5-(dimethylaminomethyl)-2,4-dinitrophenyl-amino)hexanoic acid (25). A solution of succinyl chloride (775 mg, 5 mmol) in acetone (0.5 mL) was added dropwise to a solution of N^{α}-Cbz-lysine (2.1 g, 7.5 mmol) in 5 mL of 1.5 N aqueous NaOH, with maintenance of the pH in the range of 10–11 by periodic addition of 1.5 N NaOH. The mixture was stirred at room temperature for 30 min, acidified with 2 N HCl to pH 2, and extracted with ethyl acetate (50+15+15 mL). The organic layer was combined and dried, and the solvent was removed in vacuo to give 2.4 g of a residue. The ^{1}H NMR spectrum showed the presence of two compounds **21** and **22** in a ratio of 2:1. A solution of the crude mixture (100 mg) in 4.4% methanolic formic acid (5 mL) was added to a suspension of Pd–C (10%, 50 mg) in 5 mL of 4.4% methanolic formic acid. The mixture was stirred at room temperature for 3 h, then filtered, and the catalyst was washed with methanol (3×5 mL). The solvent was evaporated to give 2-amino-6-(3-carboxypropionyl-amino)hexanoic acid (**23**) as a white powder: ^{1}H NMR (D_2O) δ 1.31–1.55 (4H), 1.83 (m, 2H), 2.48–2.59 (4H), 3.16 (t, 2H, J=5.9 Hz), 3.70 (t, 1H, J=6.2 Hz); ^{13}C NMR (D_2O) 21.7 (+), 28.0 (+), 29.9 (+), 30.1 (+), 30.8 (+), 38.9 (+), 54.7 (−), 174.6 (+), 175.0 (+), 177.9 (+). A solution of DMDNFB (24.3 mg, 0.1 mmol) in DMF (0.25 mL) was added to a suspension of **23** (14.7 mg, 0.05 mmol) and $NaHCO_3$ (100 mg) in water (130 μL). The mixture was stirred at room temperature for 2 h and extracted with ethyl acetate (3×5 mL). The aqueous layer was acidified with 2 N HCl (1 mL) and then evaporated to dryness. The residue was washed with water (0.3 mL) to give **25** as a yellow powder: ^{1}H NMR (methanol-d_4) δ 1.43–1.56 (4H), 1.94 (m, 2H), 2.28 (s, 6H), 2.40 (s, 4H), 3.14 (t, 2H, J=6.6 Hz), 3.81 (s, 2H), 4.18 (t, 1H, J=5.43 Hz), 7.14 (s, 1H), 8.95 (s, 1H); ^{13}C NMR (methanol-d_4) δ 24.0 (+), 30.4 (+), 33.4 (+), 34.1 (+), 35.0 (+), 40.3 (+), 46.0 (−), 59.6 (−), 62.1 (+), 117.7 (−), 127.0 (−), 130.5 (+), 137.3 (+), 143.8 (+), 146.1 (+), 147.6 (+), 175.9 (+), 177.5 (+); FAB HRMS m/z calcd for $C_{19}H_{28}N_5O_9$ $(M+H)^+$ 470.1887 found 470.1873.

4.3.15. 6-(3-(5-Carboxy-5-(5-(dimethylaminomethyl)-2,4-dinitrophenylamino)pentyl-carbamoyl)propionyl-amino)-2-(5-(dimethylaminomethyl)-2,4-dinitrophenyl-amino)hexanoic acid (26). Following methanol washing of the catalyst in the preparation of **23**, washing with water and evaporation afforded 2-amino-6-(3-(5-amino-5-carboxy-pentylaminocarbonyl)propionylamino)-hexanoic acid (**24**) as a white powder: ^{1}H NMR (D_2O) δ 1.33–1.55 (8H), 1.81–1.86 (4H), 2.47 (s, 4H), 3.15 (t, 4H, J=7.0 Hz), 3.70 (t, 2H, J=5.9 Hz); ^{13}C NMR (D_2O) 21.7 (+), 28.0 (+), 30.1 (+), 31.4 (+), 38.9 (+), 54.7 (−), 174.6 (+). A solution of DMDNFB (38.9 mg, 0.16 mmol) in DMF (0.4 mL) was added to a suspension of **24** (17.8 mg, 0.04 mmol) and $NaHCO_3$ (100 mg) in water (200 μL). The mixture was stirred at room temperature for 2 h and extracted with ethyl acetate (3×5 mL). The aqueous layer was acidified with 2 N HCl (1 mL) and then water was evaporated. The residue was washed with water (0.3 mL) to give **26** as a yellow powder: ^{1}H NMR (methanol-d_4) δ 1.43–1.51 (8H), 1.97 (m, 4H), 2.28 (s, 12H), 2.39 (s, 4H), 3.14 (t, 4H, J=6.6 Hz), 3.80 (s, 4H), 4.18 (t, 2H, J=5.4 Hz), 7.13 (s, 2H), 8.91 (s, 2H); ^{13}C NMR (methanol-d_4) δ 23.8 (+), 30.2 (+), 32.7 (+), 33.3 (+), 40.2 (+), 46.0 (−), 59.5 (−), 62.1 (+), 117.7 (−),

127.0 (−), 130.4 (+), 137.2 (+), 143.8 (+), 147.6 (+), 174.6 (+), 177.4 (+); FAB HRMS calcd for $C_{34}H_{49}N_{10}O_{14}$ 821.3430, found 821.3519.

4.3.16. N^{ϵ}-*t*-Boc-N^{α}-(2,4-dinitro-5-(dimethylaminomethyl)phenyl)-L-lysine (27). According to the procedure for the synthesis of **7b**, **27** was obtained from N^{ϵ}-*t*-Boc-L-lysine as a yellow powder in a yield of 92.5%: mp >180 °C (dec); ^{1}H NMR (methanol-d_4) δ 1.38 (s, 9H), 1.43–1.47 (4H), 1.95 (m, 2H), 2.30 (s, 6H), 3.00 (t, 2H, J=4.9 Hz), 3.81 (s, 2H), 4.17(t, 1H, J=8.4 Hz), 7.14 (s, 1H), 8.91 (s, 1H); ^{13}C NMR (methanol-d_4) δ 23.8 (+), 28.8 (−), 30.9 (+), 33.4 (+), 41.2 (+), 46.1 (−), 59.5 (−), 62.1 (+), 79.8 (+), 117.7 (−), 127.0 (−), 130.4 (+), 137.1 (+), 143.7 (+), 147.5 (+), 158.5 (+), 177.5 (+). HRMS FAB *m/z* calcd for $C_{20}H_{32}N_5O_8$ $(M+H)^+$ 470.2251, found 470.2247. According to the procedure for synthesis of **7b**, the 1:1 mixture (**27a**) of **27** and N^{ϵ}-*t*-Boc-N^{α}-(2,4-dinitro-5-(dimethyl-d_6-aminomethyl)phenyl)-L-lysine was prepared using a 1:1 mixture of **1a** and **1b** and N^{ϵ}-*t*-Boc-L-lysine in a yield of 89.6%.

4.3.17. N^{α}-(2,4-Dinitro-5-(dimethylaminomethyl)phenyl)-L-lysine (28). Compound **27** (70.5 mg, 0.15 mmol) was dissolved in TFA (10 mL) and heated at reflux for 24 h. TFA was evaporated to give **28** quantitatively as a yellow powder. ^{1}H NMR (methanol-d_4) δ 1.48 (m, 2H), 1.59 (m, 2H), 1.99 (m, 2H), 2.31 (s, 6H), 2.91 (t, 2H, J=7.6 Hz), 3.83 (s, 2H), 4.21 (t, 1H, J=5.0 Hz), 7.13 (s, 1H), 8.90 (s, 1H); ^{13}C NMR (methanol-d_4) δ 23.2 (+), 28.5 (+), 32.8 (+), 40.6 (+), 45.5 (−), 59.1 (−), 61.5 (+), 119.1 (−), 127.3 (−), 130.9 (+), 136.8 (+), 140.6 (+), 147.4 (+), 176.9 (+); HRMS FAB *m/z* calcd for $C_{15}H_{24}N_5O_6$ $(M+H)^+$ 370.1727, found 370.1709. According to the procedure for the synthesis of **28**, the 1:1 mixture (**28a**) of **28** and N^{α}-(2,4-dinitro-5-(dimethylaminomethylene-d_6)-phenyl)-L-lysine was prepared from **27a** in a yield of 97.2%.

4.4. UV–Vis spectrometric monitoring of incubations of either DNFB or DMDNFB with either asparagine or glycyl-L-leucine

A solution of either DNFB or **1a** (DMDNFB) (2 mM) was prepared separately in acetone. A solution of either glycyl-L-leucine or asparagine (400 μM) was prepared separately in 0.1 M phosphate buffer, and the pH was adjusted to 7.0 by 1 N NaOH. Following autozeroing of a cuvette containing 2.94 mL of the latter at 25 °C, 0.06 mL of the acetone solution of either DNFB or DMDNFB was added, and the cuvette was shaken. The reaction was followed by monitoring the formation of the aminolysis product, scanning from 300 to 500 nm, at 20 min intervals for DNFB and 5 min intervals for DMDNFB. The infinity absorbance was determined from the solution of the authentic samples obtained through independent synthesis as described earlier.

4.5. ^{1}H NMR spectrometric monitoring of incubations of either DNFB or DMDNFB with either amino acids or peptides

A solution of either DMDNFB or DNFB (80 mM, 250 μL) in DMF-d_7 was added to a solution of either an amino acid, a peptide or a lysine derivative (80 mM of free amine groups, 250 μL) in either 0.1 M pH 7.0 phosphate buffer or 5% $NaHCO_3$ in D_2O in a NMR tube. The ^{1}H NMR spectrum was taken at the beginning, 10, 30 min, 1, 2, 3, and 24 h.

4.6. Reaction of either N^{α}-acetyl-L-histidine,-L-cysteine, or -L-tyrosine with DMDNFB and thiolysis of their products (mercaptoethanol)

A solution of DMDNFB (40 mM, 0.1 mL) in DMF was added to a solution of either N^{α}-acetyl-L-histidine, -L-cysteine, or -L-tyrosine (40 mM, 0.1 mL) in 0.1 M phosphate buffer at pH 7.0 and the reaction mixture was monitored with thin layer chromatography (TLC). After all the DMDNFB was consumed, mercaptoethanol (1 μL) was added to the reaction mixture, and the reaction was monitored by TLC to see whether the initial products (N^{τ}-DMDNP-N^{α}-acetyl-L-histidine, *S*-DMDNP-N^{α}-acetyl-L-cysteine, or *O*-DMDNP-N^{α}-acetyl-L-tyrosine) were converted to their corresponding precursors. Two of the three initial products were confirmed by comparison to the authentic samples **11** and **13** described above.

4.7. ESI-MS analysis of incubations of 17 or 18 with a 1:1 mixture of DMDNFB-d_0 and DMDNFB-d_6

A solution of DMDNFB (2.43 mg, 0.01 mmol) in DMF (25 μL) was added to a suspension of **17** (1.75 mg, 0.005 mmol) and $NaHCO_3$ (10 mg) in water (13 μL). A solution of DMDNFB (3.89 mg, 0.016 mmol) in DMF (40 μL) was added to a suspension of **18** (2.0 mg, 0.004 mmol) and $NaHCO_3$ (10 mg) in water (20 μL). The two mixtures was stirred at room temperature for 2 h and extracted with ethyl acetate (3×0.5 mL). The aqueous layers were acidified with 2 N HCl (0.1 mL) and then the mixtures were subjected to ESI-MS analysis.

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References and notes

1. Hancock, W. S.; Harding, D. R. K. *CRC Handb HPLC Sep. Amino Acids, Pept., Proteins* **1984**, *1*, 235–262.
2. Lingeman, H.; Underberg, W. J. M. *Detection oriented derivatization techniques in liquid chromatography. Chromatography science series*; Marcel Dekker: New York, 1990; Vol. 48.
3. Riley, C. M.; Stobaugh, J. F.; Lunte, S. M. *Progr. Pharmaceut. Biomed. Anal.* **1994**, *1*, 41–89.
4. Fekkes, D. *J. Chromatogr. B Biomed. Appl.* **1996**, *682*, 3–22.
5. Lindroth, P.; Mopper, K. *Anal. Chem.* **1979**, *51*, 1667–1674.
6. Hsu, K. T.; Currie, B. L. *J. Chromatogr.* **1978**, *166*, 555–561.

7. Sanger, F. *Biochem. J.* **1945**, *39*, 507–515.
8. De Bruin, S. H.; Bucci, E. *J. Biol. Chem.* **1971**, *246*, 5228–5233.
9. Heinrikson, R. L.; Meredith, S. C. *Anal. Biochem.* **1984**, *136*, 65–74.
10. Iskandaranl, Z.; Pietrzyk, D. *J. Anal. Chem.* **1981**, *53*, 489–495.
11. Gutsche, B.; Diem, S.; Herderich, M. *Adv. Exp. Med. Biol.* **1999**, *467*, 757–767.
12. Barr, D. B.; Ashley, D. L. *J. Anal. Toxicol.* **1998**, *22*, 96–104.
13. Palma, M. S.; Itagaki, Y.; Fujita, T.; Hisada, M.; Naoki, H.; Nakajima, T. *Nat. Toxins* **1997**, *5*, 47–57.
14. Knebel, N. G.; Sharp, S. R.; Madigan, *J. Chromatogr. B Biomed. Appl.* **1995**, *673*, 213–222.
15. Johnson, D. W. *Rapid. Commun. Mass. Spectrom.* **2001**, *15*, 2198–2205.
16. Chen, X.; Chen, Y. H.; Anderson, V. E. *Anal. Biochem.* **1999**, *273*, 192–203.
17. Mahmood, S.; Iqbal, M. Z.; Qamar, N. *J. Chem. Soc. Pak.* **1992**, *14*, 80–82.
18. Boyer, J. H.; Pagoria, P. F.; Pillai, T. P.; Pace, M. D.; Stec, D. *J. Chem. Res. Synop.* **1986**, 416–417.
19. Adcock, W.; Dewar, M. J. S.; Gupta, B. D. *J. Amer. Chem. Soc.* **1973**, *95*, 7353–7358.
20. Shaltiel, S. *Biochem. Biophys. Res. Commun.* **1967**, *29*, 178–183.
21. ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442–3444.
22. Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933–3941.
23. Li, S.; Bernstein, E. R.; Seeman, J. I. *J. Phys. Chem.* **1992**, *96*, 8808–8813.

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Concise synthesis of pyrrolophenanthridine alkaloids using a Pd-mediated biaryl coupling reaction with regioselective C–H activation via the intramolecular coordination of the amine to Pd

Takashi Harayama,* Akihiro Hori, Hitoshi Abe and Yasuo Takeuchi

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700-8530, Japan

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Abstract—The concise synthesis of *Amaryllidaceae* alkaloids, such as anhydrolycorinone, anhydrolycorin-7-one, assoanine, and oxoassoanine, which have a pyrrolophenanthridine skeleton, was achieved in moderate yield using the Pd-mediated biaryl coupling reaction of 1-(2-halobenzyl)-2,3-dihydroindole, which applied the regioselective C–H activation method with intramolecular coordination of the benzylamino group to Pd.

1. Introduction

The potentially useful pharmacological activities[1] and unique polycyclic structures of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids (e.g., **1**–**8**) have led to recent interest in developing new synthetic methods for these alkaloids.[2,3] Some of these attempts have involved an intramolecular aryl–aryl coupling reaction with a Pd reagent as the key step, including the dehydrogenation of two arenes with $Pd(OAc)_2$ in acetic acid,[4] a biaryl coupling reaction between a monobromoarene and an arene with a Pd reagent,[3,4a,5] and the intramolecular coupling of a bis-haloarene with a Pd reagent.[6] Recently, we reported a method of synthesizing several benzo[*c*]phenanthridine alkaloids using Pd-assisted aryl–aryl coupling reactions of 2-halo-*N*-naphthylbenzamides via the elimination of a hydrogen halide.[7] To examine the generality of this method, we tried to apply it to the synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids, especially anhydrolycorin-7-one (**3**)[1f] and oxoassoanine (**4**),[8a] which serve as advanced intermediates in the synthesis of other alkaloids.[4b,8b]

In this connection, Cai et al. reported that the reaction of 1-(2-bromobenzoyl)-2,3-dihydroindole (**9a**) using $Pd(OAc)_2$ and K_2CO_3 in DMA in the absence of a phosphine ligand afforded **3** in 55% yield.[5a,9] In our hands, the reaction of 1-(2-iodobenzoyl)-2,3-dihydroindole (**9b**), which is expected to be more reactive than **9a**, under their reaction conditions did not produce **3**, even in the presence of a phosphine ligand. Miki et al. reported that the reaction of 1-(2-bromo-4,5-dimethoxybenzoyl)indole-2,3-dicarboxylate (**10**) with $Pd(PPh_3)_4$ gave no coupling product.[3] Moreover, it has been reported that the biaryl coupling reaction of 1-(2-bromobenzyl)-2,3-diphenylindole (**11**) gave no coupling product,[4a] whereas the reaction of dimethyl 1-(2-bromobenzyl)indole-2,3-dicarboxylate (**12**) with $Pd(PPh_3)_4$ gave a coupling product (**13**).[3] These results seem somewhat contradictory (Scheme 1).

Recently, we developed a method of synthesizing a new skeletal compound, naphthobenzazepine, by regioselective C–H activation using the intramolecular coordination of a benzylamine to Pd.[11] We planned to apply this strategy to the synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids, such as anhydrolycorine (**1**)[1f,12a] and assoanine (**2**).[12b] Interconversion of **1** and **3** or **2** and **4** has already been accomplished by the air oxidation of **1** or **2**, and the $LiAlH_4$ reduction of **3** or **4**.[12] We envisioned that the intramolecular biaryl coupling reaction of 1-(2-halobenzyl)dihydroindole (**A**) using a Pd reagent would afford dihydropyrrolophenanthridine (**C**) directly, via an oxidative addition to Pd(0) and coordination of the amine to Pd(II), followed by the regioselective electrophilic substitution of Pd(II) at the C_7 position of the dihydroindole moiety [forming a four-membered palladacycle (**B**)][13,14] and the reductive elimination of Pd(0), as shown in Scheme 2. The details of the results are the subject of this paper.

2. Results and discussion

First, the Pd-catalyzed coupling reaction of 1-(2-bromobenzyl)-2,3-dihydroindole (**14**)[15] was examined as a preliminary study of the synthesis of these alkaloids

Keywords: Coodination; Palladium; Regioselectivity; Anhydrolycorine; Assoanine.
* Corresponding author. Tel./fax: +81-86-2517963;
e-mail address: harayama@pharm.okayama-u.ac.jp

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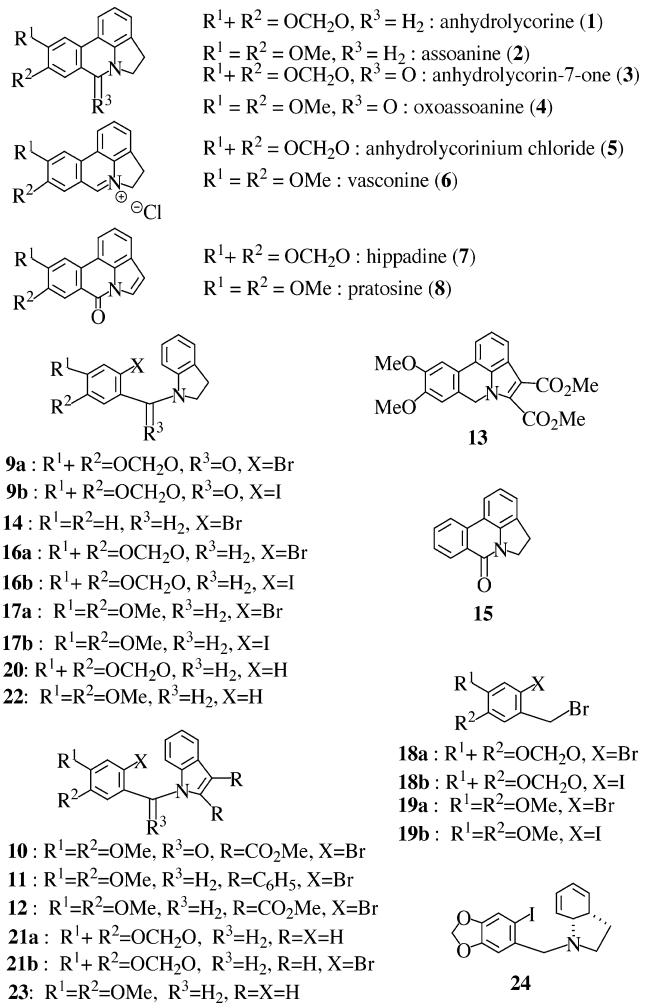
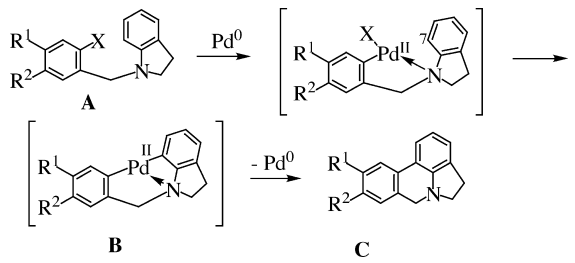


Scheme 1. Pyrrolophenanthridine alkaloids and related compounds.



Scheme 2. Strategy and proposed mechanism for synthesis of dihydropyrrolophenanthridine (**C**) from 1-(2-halobenzyl)dihydroindole (**A**).

(**1**–**4**). The reaction of **14** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in DMF under air gave pyrrolophenanthridone (**15**) in 35% yield, along with 1-benzyl-2,3-dihydroindole (13% yield)[16] and 1-benzylindole (17% yield).[16] These results suggest that **15** was formed via a biaryl coupling reaction and concomitant oxidation, because 1-(2-iodobenzoyl)-2,3-dihydroindole gave **15** in only 8% yield[17] and alkaloids (**1** and **3**) readily undergo oxidation in air.[12] Therefore, this strongly implies that the synthetic strategy shown in Scheme 2 is applicable to the synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids.

Next, to study the synthesis of pyrrolophenanthridine alkaloids, the starting materials (**16a**, **16b**, and **17a**) were prepared from dihydroindole and 2-bromobenzyl bromides (**18a**[18a] and **19a**[18b]) or 2-iodobenzyl bromides (**18b**)[19a] in the presence of *i*-Pr$_2$NEt in dry CH_3CN in 86–91% yield. The starting material (**17b**) was prepared from dihydroindole and 2-iodobenzyl bromide (**19b**)[19b] in ether in 77% yield. The intramolecular coupling reactions of 1-(2-bromobenzyl)dihydroindoles (**16a** and **17a**) using Pd were examined; the results are summarized in Tables 1 and 2. The reaction of **16a** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in DMF under air gave anhydrolycorin-7-one (**3**) in 45% yield (run 1 in Table 1),[12a] and the reaction in CH_3CN did not proceed (run 2 in Table 1). By contrast, the reaction of **16a** under an oxygen atmosphere, which was intended to accelerate the oxidation, afforded **3** in only 21% yield (run 3 in Table 1). In this connection, Knölker et al. recently reported that the reaction of iodo-tetrahydroindole (**24**) with $Pd(PPh_3)_4$ in DMF under air gave **3** in 29% yield via a coupling reaction and oxidation.[2h] The reaction of **16a** in degassed DMF under an Ar atmosphere gave anhydrolycorine (**1**)[12a] and **3**[20a] in 37 and 15% yields, respectively, along with **20** and **21a** (run 4 in Table 1). The reaction of **16a** using Ag_2CO_3 as a base produced only the oxidation product (**21b**) in 58% yield (run 7 in Table 1). The reaction using *i*-Pr$_2$NEt and DBU as a base did not proceed (runs 8 and 9 in Table 1). The reaction of **17a** with $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in DMF under air gave oxoassoanine (**4**)[12b] in 34% yield (run 1 in Table 2). The reaction of **17a** in degassed DMF under an Ar atmosphere gave assoanine (**2**)[20b] and **4** in 28 and 13% yields, respectively, along with **22** and **23** (run 4 in Table 2). The reaction of **16a** and **17a** using PCy_3 as a ligand gave the coupling products in better yield (run 5 in Table 1 and run 5 in Table 2).

To improve the yield, the biaryl coupling reaction of 1-(2-iodobenzyl)-2,3-dihydroindoles (**16b** and **17b**), which are more reactive than bromo compounds, was examined. The results are summarized in Tables 3 and 4. However, the yields were similar or lower than with bromo compounds. Unlike bromo compounds (**16a** and **17a**), with iodo compounds (**16b** and **17b**), Jeffery's conditions[21] gave the coupling products in higher yields (run 6 in Table 3, and run 4 in Table 4).

In conclusion, the concise synthesis of pyrrolophenanthridine (*Amaryllidaceae*) alkaloids was accomplished by applying a strategy utilizing regioselective C–H activation via intramolecular coordination of the benzylamino group to Pd.[11]

3. Experimental

3.1. General

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO A-102 or JASCO FT/IR 350 spectrophotometer, and ^{1}H NMR spectra in deuteriochloroform were recorded on a JNM-MY 60 FT (60 MHz) or a Varian VXR-200 (200 MHz) spectrometer. NMR spectra data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and

Table 1. Results of biaryl coupling reaction of 1-[(6-bromo-1,3-benzodioxol-5-yl)methyl)]-2,3-dihydroindole (**16a**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Base	Temp. (°C)	Time (h)	Yield (%)				
							1	**3**	**20**	**21a**	**21b**
1	B	20	P(*o*-tol)$_3$ (2)	K_2CO_3	125	3	Trace	45	19	6	—
2[c]	B	100	P(*o*-tol)$_3$ (2)	K_2CO_3	125	48	No reaction				
3[d]	C	20	P(*o*-tol)$_3$ (2)	K_2CO_3	125	3	—	21	Trace	8	—
4	A	10	P(*o*-tol)$_3$ (2)	K_2CO_3	125	1.5	37	15	23	16	—
5	A	10	Cy_3P (2)	K_2CO_3	125	1	50	6	17	8	—
6	A	10	*t*-Bu_3P (2)	K_2CO_3	125	8	6	33	—	13	—
7	B	20	P(*o*-tol)$_3$ (2)	Ag_2CO_3	125	5	—	—	—	—	58
8	A	10	P(*o*-tol)$_3$ (2)	*i*-Pr_2NEt	125	9	No reaction				
9	A	10	P(*o*-tol)$_3$ (2)	DBU	125	10	No reaction				
10[e]	B	20	—	K_2CO_3	100	31	—	3	—	—	—

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air, C:O_2) and 200 mol% of base was added.
[b] The molar ratio of the ligand and Pd.
[c] CH_3CN was used as a solvent.
[d] The starting material (**16a**) was recovered in 35% yield.
[e] 100 mol% of *n*-Bu_4NCl and 300 mol% of K_2CO_3 were added. The starting material (**16a**) was recovered in 64% yield.

Table 2. Results of biaryl coupling reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-2,3-dihydroindole (**17a**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Temp. (°C)	Time (h)	Yield (%)			
						2	**4**	**22**	**23**
1[c]	B	20	P(*o*-tol)$_3$ (2)	125	3	Trace	34	11	10
2[d]	B	10	P(*o*-tol)$_3$ (2)	125	7	Trace	25	9	10
3[e]	B	10	P(*o*-tol)$_3$ (2)	160	1	Trace	30	2	17
4	A	10	P(*o*-tol)$_3$ (2)	140	2	28	13	28	18
5	A	10	Cy_3P (2)	125	1	45	13	26	3

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air) and 200 mol% of K_2CO_3 was added.
[b] The molar ratio of the ligand and Pd.
[c] The starting material (**17a**) was recovered in 9% yield.
[d] The starting material (**17a**) was recovered in 21% yield.
[e] DMA was used as a solvent.

the coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out with Merck silica gel (230–400 mesh) and Wako activated alumina (300 mesh). All the experiments were carried out in an argon atmosphere, unless otherwise noted, and the extract was washed with brine, dried over anhydrous K_2CO_3, and filtered, and the filtrate was concentrated to dryness under reduced pressure. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

3.2. Coupling reaction of 1-(2-bromobenzyl)-2,3-dihydroindole (14) with palladium reagent

To a solution of **14** (58 mg, 0.2 mmol) in DMF (1.5 ml) were added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PPh_3 (5.3 mg, 0.02 mmol), and K_2CO_3 (55 mg, 395 mmol), and the

Table 3. Results of biaryl coupling reaction of 1-[(6-iodo-1,3-bezodioxol-5-yl)methyl]-2,3-dihydroindole (**16b**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Temp. (°C)	Time (h)	Yield (%)			
						1	**3**	**20**	**21a**
1	B	20	P(*o*-tol)$_3$ (2)	125	2.5	Trace	43	17	14
2	A	5	P(*o*-tol)$_3$ (2)	125	3.5	34	16	21	12
3	A	5	Cy_3P (2)	125	1.5	48	12	21	12
4	A	5	*n*-Bu_3P (2)	125	3.5	35	10	25	16
5	A	5	*t*-Bu_3P (2)	125	1	41	13	24	13
6	A	5	—	115	3.5	50	11	17	12
7[c]	B	20	—	100	24	Trace	51	19	Trace
8[d]	B	20	—	100	2.3	Trace	47	13	Trace
9	A	5	DPPP	125	2	29	11	27	11

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air) and 200 mol% of K_2CO_3 was added.
[b] The molar ratio of the ligand and Pd.
[c] 100 mol% of *n*-Bu_4NCl and 300 mol% of K_2CO_3 were added.
[d] 100 mol% of *n*-Bu_4NCl and 550 mol% of AcOK were added.

Table 4. Results of biaryl coupling reaction of 1-(2-iodo-4,5-dimethoxybenzyl)-2,3-dihydroindole (**17b**)[a]

Run		Pd $(OAc)_2$ (mol%)	Ligand (L/Pd)[b]	Temp. (°C)	Time (h)	Yield (%)			
						2	**4**	**22**	**23**
1	B	5	P(*o*-tol)$_3$ (2)	125	2	Trace	35	16	13
2	A	5	P(*o*-tol)$_3$ (2)	125	2.5	28	15	25	15
3	A	5	Cy_3P (2)	125	1	24	10	33	4
4[c]	A	5	—	115	4	43	6	22	11
5[d]	A	5	—	155	4	37	6	3	19

[a] The reaction was carried out in degassed DMF under the conditions indicated (A:Ar, B:air) and 200 mol% of K_2CO3 was added.
[b] The molar ratio of the ligand and Pd.
[c] 100 mol% of *n*-Bu_4NCl and 300 mol% of K_2CO_3 were added.
[d] 100 mol% of *n*-Bu_4NCl and 550 mol% of AcOK were added.

reaction mixture was stirred for 1.6 h at 125 °C. Then, the mixture was diluted with AcOEt and the precipitate was removed by filtration. The filtrate was washed with aqueous 5% NaOH solution and brine. The residue was dissolved in $CHCl_3$ and subjected to column chromatography through Al_2O_3. Elution with hexane–AcOEt (200:1) gave a mixture of 1-benzyl-2,3-dihydroindole[16] and 1-benzylindole.[16] Elution with hexane–AcOEt (1:1) gave 4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (**15**) (19 mg, 35%). Moreover, a mixture of 1-benzyl-2,3-dihydroindole and 1-benzylindole was dissolved in $CHCl_3$ and subjected to column chromatography through silica gel. Elution with hexane gave 1-benzyl-2,3-dihydroindole (6 mg, 13%) and successive elution with the same solvent gave 1-benzylindole (9 mg, 17%).

3.2.1. 4,5-Dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (15). Colorless needles, mp 168–170 °C ($CHCl_3$–hexane), (lit.[17] 170–171 °C).

3.2.2. 1-Benzyl-2,3-dihydroindole. Pale yellow oil, (lit.[16] oil). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 2.88–3.44 (4H, m, C_2–H and C_3–H), 4.23 (2H, s, Ar–CH_2N), 6.45–7.33 (9H, m, Ar–H).

3.2.3. 1-Benzylindole. Colorless plates, mp 38.5–40 °C (Et_2O), (lit.[16] 43–44 °C). ^{1}H NMR (60 MHz, $CDCl_3$) δ: 5.33 (2H, s, Ar–CH_2N), 6.55 (1H, d, J=3.4 Hz, C_3–H), 7.04–7.33 (9H, m, Ar–H), 7.62 (1H, d, J=3.4 Hz, C_2–H).

3.3. General procedure for the synthesis of starting materials (16a, 16b and 17a)

To a solution of 2-halobenzyl bromides (**18a**,[18a] **18b**,[19b] and **19a**[18b]) (3.00 mmol) in dry CH_3CN (8 ml) were added dihydroindole (425 mg, 3.60 mmol), Et_4NI (116 mg, 0.45 mmol), and *i*-Pr_2NEt (2.1 ml, 12.3 mmol), and the reaction mixture was stirred for 30 min at 70 °C. The mixture was diluted with AcOEt and the entire organic layer was washed with aqueous 5% NaOH solution and brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography through silica gel.

3.3.1. 1-[(6-Bromo-1,3-benzodioxol-5-yl)methyl]-2,3-dihydroindole (16a). Elution with AcOEt–hexane (1:20) gave **16a** (302 mg, 91%), colorless plates, mp 66–67 °C (Et_2O). IR (KBr) cm^{-1}: 1245, 1040. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.01 (2H, t, J=8.3 Hz, C_3–H), 3.41 (2H, t, J=8.3 Hz, C_2–H), 4.21 (2H, s, Ar–CH_2N), 5.95 (2H, s, $C_{2'}$–H), 6.43 (1H, dd, J=0.9, 7.8 Hz, C_7–H), 6.68 (1H, ddd, J=0.9, 7.4, 7.8 Hz, C_5–H), 6.96 (1H, s, $C_{4'}$–H), 7.03 (1H, s, $C_{7'}$–H), 7.01–7.12 (2H, m, C_4–H and C_6–H). FAB-MS *m*/*z*: 331 $(M)^+$, 333 $(M+2)^+$. Anal. calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; N, 4.22. Found: C, 58.04; H, 4.42; N, 4.28.

3.3.2. 1-[(6-Iodo-1,3-benzodioxol-5-yl)methyl]-2,3-dihydroindole (16b). Elution with AcOEt–hexane (1:10) gave **16b** (324 mg, 86%), colorless needles, mp 74.5–75.5 °C (Et_2O). IR (KBr) cm^{-1}: 1250, 1040. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.02 (2H, t, J=8.1 Hz, C_3–H), 3.40 (2H, t, J=8.1 Hz, C_2–H), 4.15 (2H, s, Ar–CH_2N), 5.96 (2H, s, $C_{2'}$–H), 6.43 (1H, dd, J=1.0, 8.0 Hz, C_7–H), 6.68 (1H, ddd, J=1.0, 7.2, 7.6 Hz, C_5–H), 6.97 (1H, s, $C_{4'}$–H), 7.06 (1H, dd, J=7.6, 8.0 Hz, C_6–H), 7.11 (1H, d, J=7.2 Hz, C_4–H), 7.28 (1H, s, $C_{7'}$–H). FAB-MS *m*/*z*: 379 $(M)^+$. Anal. calcd for $C_{16}H_{14}BrNO_2$: C, 50.68; H, 3.72; N, 3.69. Found: C, 50.91; H, 3.97; N, 3.88.

3.3.3. 1-(2-Bromo-4,5-dimethoxybenzyl)-2,3-dihydroindole (17a). Elution with AcOEt–hexane (1:10) gave **17a** (282 mg, 91%), colorless plates, mp 68–69 °C (Et_2O). IR (KBr) cm^{-1}: 1260, 1030. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.01 (2H, t, J=8.3 Hz, C_3–H), 3.38 (2H, t, J=8.3 Hz, C_2–H), 3.80 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.23 (2H, s, Ar–CH_2N), 6.51 (1H, dd, J=1.0, 7.8 Hz, C_7–H), 6.68 (1H, ddd, J=1.0, 7.2, 7.4 Hz, C_5–H), 7.00 (1H, s, $C_{6'}$–H), 7.05 (1H, s, $C_{3'}$–H), 7.07 (1H, dd, J=7.4, 7.8 Hz, C_6–H), 7.12 (1H, d, J=7.2 Hz, C_4–H). FAB-MS *m*/*z*: 347 $(M)^+$, 349 $(M+2)^+$. Anal. calcd for $C_{16}H_{14}BrNO_2$: C, 58.63; H, 5.21; N, 4.02. Found: C, 58.53; H, 5.08; N, 3.92.

3.3.4. 1-(2-Iodo-4,5-dimethoxybenzyl)-2,3-dihydroindole (17b). To a solution of **19b**[19b] (1.43 g, 4.00 mmol) in ether (10 ml) was added dihydroindole (858 mg, 7.20 mmol) and the reaction mixture was stirred for 1.5 h at rt. After evaporation of solvent, the residue dissolved in $CHCl_3$ was subjected to column chromatography through silica gel. Elution with $CHCl_3$ gave **17b** (1.21 g, 77%), colorless prisms, mp 93–94 °C (Et_2O). IR (KBr) cm^{-1}: 1255, 1025. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.01 (2H, t, J=8.2 Hz, C_3–H), 3.40 (2H, t, J=8.2 Hz, C_2–H), 3.80 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.20 (2H, s, Ar–CH_2–N), 6.50 (1H, dd, J=7.8 Hz, C_7–H), 6.70 (1H, dd, J=7.2, 7.4 Hz, C_5–H), 6.99 (1H, s, $C_{6'}$–H), 7.09 (1H, dd, J=7.4, 7.8 Hz, C_6–H), 7.12 (1H, d, J=7.2 Hz, C_4–H), 7.27 (1H, s, $C_{3'}$–H). FAB-MS *m*/*z*: 395 $(M)^+$. Anal. calcd for $C_{17}H_{18}INO_2$: C, 51.66; H, 4.59; N, 3.54. Found: C, 51.57; H, 4.75; N, 3.47.

3.4. General procedure for the coupling reaction of 1-halobenzyldihydroindole derivatives (16 and 17) in the presence of phosphine ligand

Each compound (**16** or **17**) (0.3 mmol) was reacted with $Pd(OAc)_2$, a phosphine ligand, and a base in dry DMF (8 ml) using $Pd(OAc)_2$ and the phosphine ligand in the ratios indicated in Tables 1 and 2, and 200 mol% of base for the times and temperatures indicated in the tables. Then, the reaction mixture was diluted with AcOEt and the precipitate was removed by filtration. The filtrate was washed with aqueous 5% NaOH solution and brine. The residue from **16** was dissolved in $CHCl_3$ and subjected to column chromatography through Al_2O_3. Elution with hexane–AcOEt (50:1) gave **20** and elution with hexane–AcOEt (30:1) gave **21a**. Moreover, elution with hexane–AcOEt (15:1) gave **1** and elution with AcOEt gave **3**.

3.4.1. Anhydrolycorine (1). Pale yellow prisms, 110–112.5 °C (EtOH), (lit.[20a] 108–111 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.02 (2H, t, J=7.9 Hz, C_4–H), 3.33 (2H, t, J=7.9 Hz, C_5–H), 4.07 (2H, s, C_7–H), 5.97 (2H, s, OCH_2O), 6.64 (1H, s, C_8–H), 6.76 (1H, dd, J=7.3, 7.3 Hz, C_2–H), 7.01 (1H, dd, J=1.0, 7.3 Hz, C_3–H), 7.16 (1H, s, C_{11}–H), 7.28 (1H, dd, J=1.0, 7.3 Hz, C_1–H). Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.49; H, 5.43; N, 5.35.

3.4.2. Anhydrolycorin-7-one (3). Pale brown needles, mp 236–237 °C ($CHCl_3$–MeOH), (lit.[20a] 232–234 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.33 (2H, t, J=8.3 Hz, C_4–H), 4.38 (2H, t, J=8.3 Hz, C_5–H), 6.05 (2H, s, OCH_2O), 7.10 (1H, dd, J=7.6, 7.6 Hz, C_2–H), 7.20 (1H, dd, J=1.2, 7.6 Hz, C_3–H), 7.43 (1H, s, C_{11}–H), 7.64 (1H, dd, J=1.2, 7.6 Hz, C_1–H), 7.82 (1H, s, C_8–H). Anal. calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.46; H, 4.38; N, 5.21.

3.4.3. 1-[(1,3-Benzodioxol-5-yl)methyl]-2,3-dihydroindole (20). Pale yellow oil, (lit.[19a] oil). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.96 (2H, t, J=8.2 Hz, C_3–H), 3.29 (2H, t, J=8.2 Hz, C_2–H), 4.16 (2H, s, Ar–CH_2N), 5.95 (2H, s, $C_{2'}$–H), 6.51 (1H, d, J=7.6 Hz, Ar–H), 6.63–7.11 (6H, m, Ar–H). FAB-MS m/z: 253 $(M)^+$.

3.4.4. 1-[(1,3-Benzodioxol-5-yl)methyl]indole (21a). Colorless needles, mp 82–83 °C (petr. ether). IR (KBr) cm^{-1}: 1235, 1040. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.22 (2H, s, Ar–CH_2N), 5.91 (2H, s, $C_{2'}$–H), 6.53 (1H, d, J=3.4 Hz, C_3–H), 6.59 (1H, d, J=1.4 Hz, $C_{4'}$–H), 6.63 (1H, dd, J=1.4, 7.8 Hz, $C_{6'}$–H), 6.73 (1H, d, J=7.8 Hz, $C_{7'}$–H), 7.10 (1H, ddd, J=1.4, 6.8, 6.8 Hz, C_5–H), 7.12 (1H, d, J=3.4 Hz, C_2–H), 7.18 (1H, ddd, J=1.4, 6.8, 8.2 Hz, C_6–H), 7.30 (1H, dd, J=1.4, 8.2 Hz, C_7–H), 7.64 (1H, dd, J=1.4, 6.8 Hz, C_4–H). FAB-MS m/z: 251 $(M)^+$. Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.32; H, 5.45; N, 5.49.

3.4.5. 1-[(6-Bromo-1,3-benzodioxol-5-yl)methyl]indole (21b). The residue of run 7 in Table 1 was dissolved in $CHCl_3$ and subjected to column chromatography through silica gel. Elution with hexane–AcOEt (20:1) gave **21b**, colorless needles, mp 124.5–125.5 °C (hexane). IR (KBr) cm^{-1}: 1240, 1035. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.29 (2H, s, Ar–CH_2–N), 5.89 (2H, s, $C_{2'}$–H), 6.06 (1H, d, J=3.5 Hz, C_3–H), 6.58 (1H, d, J=3.5 Hz, C_2–H), 7.04 (1H, s, $C_{4'}$–H), 7.12 (1H, s, $C_{7'}$–H), 7.13 (1H, ddd, J=1.0, 7.0, 8.0 Hz, C_5–H), 7.19 (1H, ddd, J=1.0, 7.0, 8.0 Hz, C_6–H), 7.25 (1H, dd, J=1.0, 8.0 Hz, C_7–H), 7.66 (1H, dd, J=1.0, 8.0 Hz, C_4–H). FAB-MS m/z: 329 $(M)^+$, 331 $(M+2)^+$. Anal. calcd for $C_{16}H_{12}BrNO_2$: C, 58.26; H, 3.66; N, 4.24. Found: C, 58.27; H, 3.93; N, 4.11.

The residue from **17** was dissolved in $CHCl_3$ and subjected to column chromatography through silica gel. Elution with hexane–AcOEt (15:1) gave **22**. Successive elution with the same solvent gave **23** and **2**, and elution with AcOEt gave **4**.

3.4.6. Assoanine (2). Pale yellow needles, mp165.5–168 °C (EtOH), (lit.[20b] 175–176 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.03 (2H, t, J=7.8 Hz, C_4–H), 3.34 (2H, t, J=7.8 Hz, C_5–H), 3.90 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.12 (2H, s, C_7–H), 6.67 (1H, s, C_8–H), 6.78 (1H, dd, J=7.4, 7.6 Hz, C_2–H), 7.01 (1H, dd, J=1.0, 7.4 Hz, C_3–H), 7.19 (1H, s, C_{11}–H), 7.34 (1H, dd, J=1.0, 7.6 Hz, C_1–H). FAB-MS m/z: 268 $(M+1)^+$.

3.4.7. Oxoassoanine (4). Colorless needles, mp 271–273 °C ($CHCl_3$–MeOH), (lit.[20b] 270–271 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.43 (2H, t, J=8.3 Hz, C_4–H), 4.04 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 4.49 (2H, t, J=8.3 Hz, C_5–H), 7.20 (1H, dd, J=7.4, 7.6 Hz, C_2–H), 7.28 (1H, d, J=1.0, 7.4 Hz, C_3–H), 7.52 (1H, s, C_{11}–H), 7.80 (1H, d, J=1.0, 7.8 Hz, C_1–H), 7.93 (1H, s, C_8–H). Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.43; H, 5.57; N, 5.03.

3.4.8. 1-(3,4-Dimethoxybenzyl)-2,3-dihydroindole (22). Colorless needles, mp 77–78 °C (petr. ether). IR ($CHCl_3$) cm^{-1}: 1260, 1030. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.97 (2H, t, J=8.0 Hz, C_3–H), 3.33 (2H, t, J=8.0 Hz, C_2–H), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.21 (2H, s, Ar–CH_2N), 6.62–7.14 (7H, m, Ar–H). FAB-MS m/z: 269 $(M)^+$. Anal. calcd for $C_{16}H_{12}BrNO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.78; H, 7.07; N, 5.19.

3.4.9. 1-(3,4-Dimethoxybenzyl)indole (23). Colorless needles, mp 61.5–62.5 °C (hexane). IR (KBr) cm^{-1}: 1255, 1025. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.77 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.25 (2H, s, Ar–CH_2N), 6.53 (1H, d, J=3.6 Hz, C_3–H), 6.66–6.70 (2H, m, $C_{2'}$–H and $C_{6'}$–H), 6.78 (1H, d, J=8.6 Hz, $C_{5'}$–H), 7.10 (1H, ddd, J=6.8, 7.2 Hz, C_5–H), 7.11 (1H, d, J=3.6 Hz, C_2–H), 7.18 (1H, ddd, J=1.4, 7.2, 8.0 Hz, C_6–H), 7.31 (1H, d, J=8.0 Hz, C_7–H), 7.64 (1H, dd, J=1.4, 6.8 Hz, C_4–H). FAB-MS m/z: 267 $(M)^+$. Anal. calcd for $C_{16}H_{12}BrNO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.28; H, 6.26; N, 5.20.

3.5. General procedure for the coupling reaction of 1-(2-iodobenzyl)dihydroindole derivatives (16b and 17b) under phosphine-free conditions (runs 6–8 in Table 3, and runs 4 and 5 in Table 4)

The 1-(2-iodobenzyl)dihydroindole derivative (0.3 mmol) was reacted with 0.05 mol% of $Pd(OAc)_2$, 100 mol% of n-Bu_4NCl, and 300 mol% of K_2CO_3 or 550 mmol% of

AcOK in dry DMF (4 ml) for the times and at temperature indicated in Tables 3 and 4. Then, the reaction mixture was diluted with ether and the precipitates were removed by filtration. Then, the reaction mixture was diluted with AcOEt and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography and the products (**2**, **4**, **22**, and **23**) shown in Tables 3 and 4 were separated by the methods mentioned before.

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References and notes

1. (a) Chattopadhyay, S. C.; Chattopadhyay, U.; Marthur, P. P.; Saini, K. S.; Ghosal, S. *Planta Med.* **1983**, *49*, 252–254. (b) Petti, G. R.; Gaddamidi, V.; Goswani, A.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 796–801. (c) Ghosal, S.; Lochan, R.; Ashutosh, .; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1985**, *24*, 1825–1828. (d) Zee-Cheng, R. K. Y.; Yan, S.-J.; Chen, C. C. *J. Med. Chem.* **1978**, *21*, 199–203. (e) Chen, C. C.; Zee-Cheng, R. K. Y. *Heterocycles* **1981**, *15*, 1275–1283. (f) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003–2007.
2. (a) Hoshino, O. *The alkaloids*; Cordell, G. A., Ed.; Academic: New York, 1998; Vol. 51, pp 323–424. (b) Lewis, J. R. *Nat. Prod. Rep.* **2000**, *17*, 57–84. (c) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 107–110. (d) Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361–7364. (e) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120–9124. (f) Harrowven, D. C.; Lai, D.; Lucas, M. C. *Synthesis* **1999**, 1300–1302, and references cited therein. (g) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595–3607. (h) Knölker, H.-J.; Filali, S. *Synlett* **2003**, 1752–1754.
3. Miki, Y.; Shirokoshi, H.; Matsushita, K. *Tetrahedron Lett.* **1999**, *40*, 4347–4348, and references cited therein.
4. (a) Black, D. C.; Keller, P. A.; Kumar, N. *Tetrahedron* **1993**, *49*, 151–164. (b) Black, D. C.; Keller, P. A.; Kumar, N. *Tetrahedron Lett.* **1989**, *30*, 5807–5808. (c) Itatani, T. *Synthesis* **1979**, 151–152.
5. (a) Shao, H. W.; Cai, J. C. *Chin. Chem. Lett.* **1996**, *7*, 13–14. (b) Kozikowsky, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317–3320. (c) Garden, S. J.; Torres, J. C.; Pinto, A. C. *J. Braz. Chem. Soc.* **2000**, *11*, 441–446.
6. (a) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1993**, *36*, 2597–2600. (b) Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 3859–3862.
7. (a) Harayama, T.; Shibaike, K. *Heterocycles* **1998**, *49*, 191–195. (b) Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. *Synthesis* **2001**, 444–450. (c) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 523–528. (d) Harayama, T.; Akiyama, T.; Nakano, Y.; Nishioka, H.; Abe, H.; Takeuchi, Y. *Chem. Pharm. Bull.* **2002**, *50*, 519–522. (e) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237–241. (f) Harayama, T.; Hori, A.; Nakano, Y.; Akiyama, T.; Abe, H.; Takeuchi, Y. *Heterocycles* **2002**, *58*, 159–164. (g) Harayama, T.; Sato, T.; Nakano, Y.; Abe, H.; Takeuchi, Y. *Heterocycles* **2003**, *59*, 293–301.
8. (a) Llabres, J. M.; Viladoma, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637–2638. (b) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523–1526.
9. Phosphine ligand is generally required for the Heck-type reaction of bromoarene[10] and we could not reproduce Cai's results.[5a]
10. (a) Heck, R. F. *Organic reactions*; Daube, W. G., Ed.; Wiley: New York, 1982; Vol. 27, pp 345–390. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.
11. Harayama, T.; Sato, T.; Hori, A.; Abe, H.; Takeuchi, Y. *Synlett* **2003**, 1141–1144, and references cited therein.
12. (a) Cook, J. W.; Loudon, J. D.; McCloskey, P. *J. Chem. Soc.* **1954**, 4176–4186. (b) Fales, H. F.; Giuffrida, L. D.; Wildman, W. C. *J. Am. Chem. Soc.* **1956**, *78*, 4145–4150.
13. Solé, D.; Valverde, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587–1594.
14. (a) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909–913. (b) Bruce, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 73–86.
15. Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhaker, S.; Pereira, A. M. D. L. *Tetrahedron* **1997**, *53*, 269–284.
16. Kiguchi, T.; Kuninobu, N.; Takahashi, Y.; Yoshida, Y.; Naito, T.; Ninomiya, I. *Synthesis* **1989**, 778–781.
17. Harayama, T.; Toko, H.; Hori, A.; Miyagoe, T.; Sato, T.; Nishioka, H.; Abe, H.; Takeuchi, Y. *Heterocycles* **2003**, *61*, 513–520.
18. (a) Barthel, W. F.; Alexander, B. H. *J. Org. Chem.* **1958**, *23*, 1012–1014. (b) Landais, Y.; Robin, J. P.; Lebrum, A. *Tetrahedron* **1991**, *47*, 3787–3804.
19. (a) Cossy, J.; Tresnard, L.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1925–1933. (b) Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9428–9438.
20. (a) Hara, H.; Hoshino, O.; Umezawa, B. *Tetrahedron Lett.* **1972**, 5031–5034. (b) Parnes, J. S.; Cartner, D. S.; Kurz, L. J.; Flippin, L. A. *J. Org. Chem.* **1994**, *59*, 3497–3499.
21. (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289. (b) Jeffery, T. *Synthesis* **1987**, 70–71. (c) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

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Reductive lithiation of alkoxy-substituted benzyl methyl ethers and connection with cross-coupling reactions

Ugo Azzena,* Giovanna Dettori, Roberta Pireddu and Luisa Pisano

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy

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Abstract—2-and 4-Ethoxymethoxybenzyl methyl ethers were employied as useful starting materials for the synthesis of 1,2- or 1,4-dicarbo-substituted benzenes. The proposed reaction sequence involves connection between the reductive lithiation of benzyl alkyl ethers and the metal-catalyzed cross-coupling reaction of aromatic triflates.

1. Introduction

The arene-catalyzed reductive lithiation of benzyl alkyl ethers is a highly regioselective reaction finding application in the generation of a wide array of benzyllithium organometals.[1–5] Interestingly, the presence of strong electron donor substituents on the aromatic ring does not affect the efficiency of this procedure.[1,4] Indeed, this reaction shows unique features in the generation of stable solutions of methoxy-substituted benzyllithium derivatives both in terms of regioselectivity and mildness of reaction conditions.[6–8]

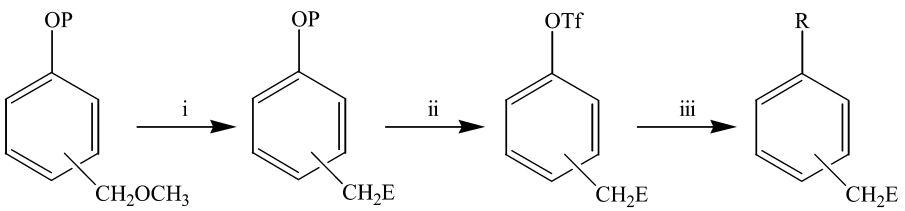
With the aim to expand the synthetic utility of this reaction, and following our interest in the development of highly regioselective strategies for the synthesis of polysubstituted aromatic compounds, we developed a synthetic protocol leading to the synthesis of dicarbo-substituted benzenes by a reaction sequence connecting our reductive lithiation procedure to well known and versatile reactions, i.e. metal-catalyzed cross-coupling reactions of aromatic triflates.[9–14]

To achieve this result, we investigated the reductive lithiation of acetals of 2- and 4-hydroxy-substituted benzyl ethers, planning to complete the reaction sequence through successive hydrolysis of the acetal group and transformation of the resulting phenols into the corresponding triflates, followed by metal-catalyzed cross-coupling reaction of the last compounds (Scheme 1).

2. Results and discussion

2.1. Synthesis of starting materials

The stability of acetal-type phenolic protecting groups, like the methoxymethyl (MOM), towards reduction with alkali metals, has been seldom investigated. We already reported[15] that this type of protecting groups are stable towards reduction with Na metal in aprotic solvents, whilst it was previously reported that, under similar conditions, phenolic acetals cleave with relatively ease, e.g. more easily than the corresponding methyl ethers.[16] In the present work, we investigated the stability, under arene-catalyzed lithiation conditions, of the ethoxymethyl (EOM) group. This protecting group shows distinct advantages over the above mentioned MOM group. Indeed, phenolic ethoxymethyl



Scheme 1. (i) Reductive lithiation and reaction with an electrophile; (ii) acidic hydrolysis and reaction with $(Tf)_2O$; (iii) metal catalyzed cross-coupling reaction.

Keywords: Ethers; Reduction; Lithiation; Cross-coupling.
* Corresponding author. Tel.: +39079229549; fax: +39079229559; e-mail address: ugo@uniss.it

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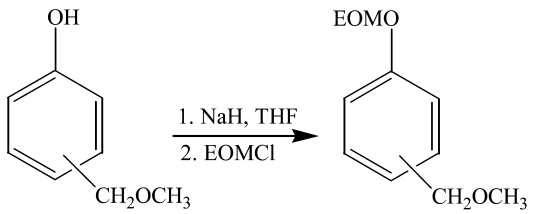
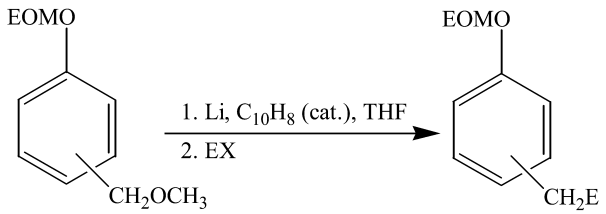
ethers can be easily synthesized reacting phenolates with chloromethyl ethyl ether, which is a cheaper, and much less toxic reagent, than the corresponding chloromethyl methyl ether.

Accordingly, deprotonation of easily available 2- and 4-hydroxybenzyl methyl ether[17] with NaH in dry THF, followed by reaction with chloromethyl ethyl ether, afforded 2- and 4-ethoxymethoxybenzyl methyl ether, **1** and **2**, respectively, in good isolated yields (Scheme 2).



1, 2-CH_2OCH_3, 77%
2, 4-CH_2OCH_3, 85%

Scheme 2. Synthesis of ethoxymethyl ethers of 2-and 4-hydroxybenzyl methyl ether. EOM=$CH_3CH_2OCH_2$.



1, 2-CH_2OCH_3
2, 4-CH_2OCH_3

3-8, 2-CH_2E
9-12, 4-CH_2E

Scheme 3. Reductive lithiation and reaction with electrophiles of ethers **1** and **2**. **3**, **9**: E=H or D; **4**: E=$(CH_3)_2COH$; **5**, **10**: E=PhCHOH; **6**: E=*n*-C_4H_9; 7: E=*n*-$C_{12}H_{25}$; **8**, **12**: E=$(CH_3)_2CH$; **11**, E=*n*-$C_{10}H_{21}$.

Table 1. Reductive lithiation of ethers **1** and **2**, and reaction with electrophiles[a]

Entry	Compoud	*T* (°C)	*t* (h)	EX	Product, E=	Yield (%)[b]
1	**1**	0	1.2	H_2O	**3**, H	>95[c]
2	**1**	0	1.2	D_2O	**3**$_d$, D	>95[c]
3	**1**	0	1.2	$(CH_3)_2CO$[d]	**4**, $(CH_3)_2COH$	56
4	**1**	0	1.2	PhCHO	**5**, PhCHOH	67
5	**1**	0	1.2	*n*-BuBr	**6**, *n*-BuBr	61[e]
6	**1**	0	1.2	*n*-$C_{12}H_{25}Br$	**7**, *n*-$C_{12}H_{25}$	68[e]
7	**1**	0	1.2	*i*-PrBr	**8**, *i*-Pr	56[e]
8	**2**	−10	2.0	H_2O	**9**, H	>95[c]
9	**2**	−10	2.0	D_2O	**9**$_d$, D	92[c]
10	**2**	−10	2.0	PhCHO	**10**, PhCHOH	70
11	**2**	−10	2.0	*n*-$C_{10}H_{21}Br$	**11**, *n*-$C_{10}H_{21}$	85
12	**2**	−10	2.0	*i*-PrBr	**12**, *i*-Pr	72[e]

[a] All reactions were run in the presence of 5 equiv. of Li metal and a catalytic amount of naphthalene (10 mol%).
[b] Isolated yield, unless otherwise indicated.
[c] As determined by ^{1}H NMR spectroscopy.
[d] The electrophile was added at −80 °C.
[e] Yield determined on the corresponding phenol, after acidic hydrolysis of the acetal moiety.

2.2. Reductive metalation reactions

Reductive metalations of ethers **1** and **2** were carried out under Ar with an excess of Li wire in the presence of a catalytic amount of naphthalene in tetrahydrofuran (THF); the results are reported in Table 1 (Scheme 3).

Reaction of a 0.15 M THF solution of ether **1** with 5 equiv. of Li metal in the presence of a catalytic amount of naphthalene (10 mol%) at 0 °C during 1.2 h, furnished a deep red reaction mixture which, upon aqueous work-up, afforded 1-ethoxymethoxy-2-methylbenzene, **3**, in quantitative yield. It is worth noting that we did not observe formation of products of cleavage of the acetal-protecting group, thus showing the stability of the EOM group under reductive electron transfer conditions (Table 1, entry 1). Under these conditions, quantitative formation of an intermediate benzyllithium derivative was evidenced as quenching the reduction mixtures with D_2O (Table 1, entry 2). Similar results were obtained employing di-*tert*-butylbiphenyl (DBB), instead of naphthalene, as an homogeneous electron transfer carrier (not reported in the Table).

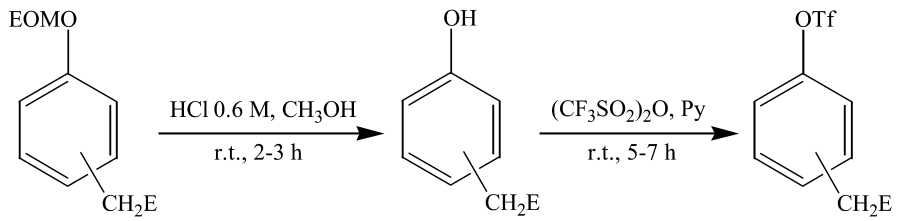
Trapping of this intermediate with acetone or benzaldehyde afforded the corresponding 2-substituted homobenzylic alcohols,[18] **4** and **5**, in satisfactory isolated yields (Table 1, entries 3 and 4).

Furthermore, the organometallic intermediate was successfully trapped with primary or secondary alkyl halides, affording the corresponding 2-alkylated ethoxymethoxybenzenes **6**–**8** in good yields (Table 1, entries 5–7); these compounds were not isolated, but directly hydrolysed to the corresponding phenols (see below).

Similar results were obtained in the reductive lithiation of ether **2**: reduction of a 0.15 M solution of this substrate with 5 equiv. of Li metal and a 10 mol% of naphtahlene was accomplished within 2.0 h at −10 °C, affording 1-ethoxymethoxy-4-methylbenzene, **9**, in quantitative yield (Table 1, entry 8). It is worth noting that reductive cleavage of ether **2** at 0 °C, under otherwise identical reaction conditions, afforded minor amounts (5–10%) of unindefied by products. Intermediate formation of an organolithium reagent was evidenced by quenching the reduction mixture with D_2O (Table 1, entry 9), and this reactive intermediate was efficiently trapped with benzaldehyde, decylbromide, and 2-bromopropane, to afford the corresponding 4-substituted ethoxymethoxybenzenes **10**–**12** in good yields (Table 1, entries 10–12); ether **12** was not isolated, but directly hydrolysed to the corresponding phenol (see below).

2.3. Synthesis of triflates

Mild acidic hydrolysis of compounds **6**–**8** and **11**–**12** (0.6 M HCl in MeOH, rt) allowed the removal of the protecting group, and the corresponding phenols **13**–**17** were obtained in almost quantitative yield. According to a known procedure,[14] reaction of phenols **13**–**17** with trifluoromethanesulfonic anhydride in pyridine afforded triflates **18** (69%), **19** (76%), **20** (70%), **21** (76%), respectively, in good isolated yields (Scheme 4).



6-8: 2-CH_2E
11-12: 4-CH_2E

13-15: 2-CH_2E, > 90%
16, 17: 4-CH_2E, > 90%

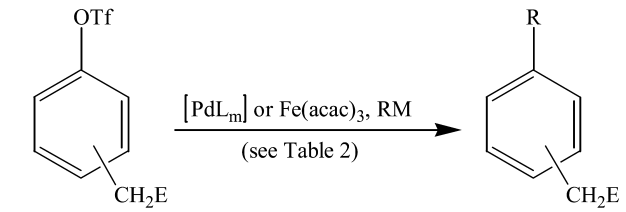
18: 2-CH_2E, 69%
19: 2-CH_2E, 76%
20: 4-CH_2E, 70%
21: 4-CH_2E, 76%

Scheme 4. Synthesis of phenols **13**–**17**, and triflates **18**–**21**. **6**, **13**: E=*n*-C_4H_9; **7**, **14**, **18**: E=*n*-$C_{12}H_{25}$; **8**, **12**, **15**, **17**, **19**, **21**: E=$CH(CH_3)_2$; **11**, **16**, **20**: E=*n*-$C_{10}H_{21}$.

Table 2. Cross-coupling reactions

Entry	Compound	Catalyst (mol%)	RM	Solvent	*T* (°C)	*t* (h)	Product [yield (%)][a]
1	**18**	$PdCl_2(PPh_3)_2$ (5)[b]	PhCCH	DMF	90	16	**22**, 70
2	**19**	$Fe(acac)_3$ (10)	$C_6H_{13}MgBr$	THF/NMP	20	16	**23**, 54
3	**20**	$Pd(PPh_3)_4$ (5)[b]	$PhB(OH)_2$	DME	85	5	**24**, 75
4	**21**	$PdCl_2(PPh_3)_2$ (5)[b]	PhCCH	DMF	90	16	**25**, 79

[a] Isolated yield.
[b] The catalyst was added in two portions (see Section 4).



18, 19: 2-CH_2E
20, 21: 4-CH_2E

22, 23: 2-CH_2E
24, 25: 4-CH_2E

Scheme 5. Cross-coupling reactions. **18**: E=*n*-$C_{12}H_{25}$; **19**, **21**: E=$CH(CH_3)_2$; **20**: E=*n*-$C_{10}H_{21}$; **22**: E=*n*-$C_{12}H_{25}$, R=PhCC, 70%; **23**: E=$CH(CH_3)_2$, R=*n*-C_6H_{13}, 54%; **24**: E=*n*-$C_{10}H_{21}$, R=Ph, 75%; **25**: E=$CH(CH_3)_2$; R=PhCC, 79%.

2.4. Cross-coupling reactions

To test the flexibility of the proposed methodology, triflates **18**–**21** were allowed to react with different coupling reagents in the presence of a Pd or a Fe catalyst. Reaction conditions and yields are reported in Table 2 (Scheme 5).

Good yields were obtained in cross-coupling reactions involving Pd-catalysed coupling reaction of triflates **18** and **21** with phenylacetylene,[19] as well as of triflate **20** with phenyl boronic acid[20] according to known procedures (Table 2, entries 1, 3 and 4, respectively); as a variation, however, we found that adding the catalyst to the reaction mixtures in two successive portions (see Section 4), significantly improved the yields of these reactions.

Furthermore, a satisfactory yield was obtained coupling triflate 19 with $C_6H_{13}MgBr$ in the presence of 10 mol% of $Fe(acac)_3$ in THF/NMP (Table 2, entry 2), under reaction conditions recently described by Fürstner and co-workers.[9]

3. Conclusions

Our results clearly show that reductive metalation of benzyl alkyl ethers is a particularly mild and practical approach to the generation of stable solutions of alkoxy-substituted benzyllithium derivatives. The observed stability of the EOM group under reductive electron transfer conditions, allowed to develop a synthetic protocol connecting our reductive metalation procedure with metal-catalyzed cross-coupling reactions, thus leading to the regioselective synthesis of 1,2- and 1,4-dicarbo-substituted aromatics, with satisfactory overall yields.

4. Experimental

4.1. General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. D_2O was 99.8% isotopic purity. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ (unless otherwise indicated) with $SiMe_4$ as internal standard. $CDCl_3$ for recording spectra of EOM-derivatives was stored over K_2CO_3 in the refrigerator. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of crude reaction mixtures, and comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. Resonances of the CHD protons are usually shifted 0.02–0.04 ppm (δ) upfield relative to the resonances of the corresponding CH_2 protons; the resonances of the arylmethyl CHD carbons

appear as triplet (J=18–20 Hz) shifted 0.3–0.5 ppm (δ) upfield relatively to the corresponding arylmethyl CH_2 carbons. IR spectra were recorded on pure samples. Flash chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey–Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

4.2. Preparation of ethers 1 and 2. General procedure

NaH (1.96 g of a 60% dispersion in mineral oil, 49 mmol) was placed under dry N_2 in a 100 mL two-necked flask equipped with reflux condenser and magnetic stirrer, washed with dry THF (3×10 mL), and suspended in dry THF (30 mL). The mixture was chilled to 0 °C and a solution of the appropriate methyl benzyl ether (5.7 g, 41 mmol) dissolved in THF (15 mL) was added dropwise. The resulting mixture was stirred for 4 h at rt. To this reaction mixture, chilled to 0 °C, a solution of $CH_3CH_2OCH_2Cl$ (4.6 g, 4.5 mL, 49 mmol), dissolved in 10 mL of THF, was slowly added. After stirring overnight at rt, the mixture was quenched by slow dropwise addition of H_2O (20 mL), and the resulting mixture was extracted with Et_2O (3×20 mL). The organic phase was washed brine (10 mL), dried (K_2CO_3) and evaporated. Crude products were purified by distillation, and were characterized as follows.

4.2.1. 1-Ethoxymethoxy-2-methoxymethylbenzene, 1. 6.2 g, 32 mmol, 77%. Colourless oil, bp 125–128 °C/1 mm Hg. (Found: C, 67.12; H, 8.47; $C_{11}H_{16}O_3$ requires C, 67.31; H, 8.23); δ_H (CD_3OD) 1.23 (3H, t, J=7.2 Hz, CH_3), 3.42 (3H, s, OCH_3), 3.76 (2H, q, J=7.2 Hz, OCH_2), 4.53 (2H, s, $ArCH_2$), 5.29 (2H, s, OCH_2O), 7.01 (1H, td, J=7.5, 1.2 Hz, ArH), 7.16 (1H, dd, J=7.5, 1.2 Hz, ArH), 7.27 (1H, td, J=7.5, 1.5 Hz, ArH), 7.37 (1H, dd, J=7.5, 1.5 Hz, ArH); δ_C (DMSO) 6.0, 48.9, 55.8, 61.1, 84.8, 105.7, 113.0, 118.7, 120.4, 120.9, 147.1.

4.2.2. 1-Ethoxymethoxy-4-methoxymethylbenzene, 2. 6.8 g, 35 mmol, 85%. Colourless oil, bp 110–113 °C/1 mm Hg. (Found: C, 67.09; H, 8.50; $C_{11}H_{16}O_3$ requires C, 67.31; H, 8.23); δ_H121(3H, t, J=7.2 Hz, CH_3), 3.36 (3H, s, OCH_3), 3.72 (2H, q, J=7.2 Hz, OCH_2), 4.39 (2H, s, $ArCH_2$), 5.22 (2H, s, OCH_2O), 6.98–7.05 (2H, m, 2×ArH), 7.23–7.28 (2H, m, 2×ArH); δ_C 14.7, 53.3, 60.1, 77.7, 97.8, 114.1, 128.6, 129.5, 161.3.

4.3. Reductive cleavage of ethers 1 and 2, and reaction with electrophiles. General procedure

150 mg of Li wire (22 mg atom, 10 equiv.) was placed under Ar in a 50 mL two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in THF (5 mL). A catalytic amount of naphthalene (28 mg, 0.22 mmol, 10 mol%) was added to the suspended metal, each metal piece was cut into 2–3 smaller pieces with a spatula, and the mixture stirred until a dark green colour appeared. The mixture was chilled to the reported temperature (Table 1) and a solution of the appropriate ether (0.43 g, 2.2 mmol), dissolved in 5 mL of dry THF, was added dropwise. The mixture was stirred for the reported time (Table 1), and a solution of the appropriate electrophile (1.2 equiv.) in THF (2 mL) was slowly added. After stirring for 30 min, the mixture was quenched by slow dropwise addition of H_2O (10 mL, caution), the cold bath removed, and the resulting mixture extracted with Et_2O (3×10 mL). The organic phase was washed with brine (10 mL), dried (K_2CO_3) and the solvent evaporated.

D_2O quenching was performed by slow dropwise addition of 1 mL of the electrophile, followed by aqueous work-up as described above.

Compounds **6**–**8** and **12** were not characterized but directly hydrolysed to the corresponding phenols. Other products were characterized as follows.

4.3.1. 1-Ethoxymethoxy-2-methylbenzene, 3. Purified by flash-chromatography (petroleum ether/AcOEt/Et_3N=7:3:1), colourless oil; R_f=0.75 (petroleum ether/AcOEt/Et_3N=7:3:1); bp 55 °C/1 mm Hg (lit.[21] bp 86–87 °C/8 mm Hg); δ_H122 (3H, t, J=6.9 Hz, CH_3), 2.23 (3H, s, $ArCH_3$), 3.72 (2H, q, J=6.9 Hz, CH_2), 5.24 (2H, s, CH_2), 6.90 (1H, td, J=7.5, 1.5 Hz, ArH), 7.03–7.12 (1H, m, ArH), 7.12–7.16 (2H, m, 2×ArH); δ_C 15.1, 16.3, 64.1, 93.2, 113.9, 121.4, 126.8, 130.7, 157.9.

4.3.2. 1-(2-Ethoxymethoxyphenyl)-2-methylpropan-2-ol, 4. Purified by flash-chromatography (CH_2Cl_2/AcOEt/Et_3N=9.8:0.2:0.1), colourless oil. (Found: C, 69.43; H, 9.12; $C_{13}H_{20}O_3$ requires C, 69.60; H, 9.00); R_f=0.30 (CH_2Cl_2/AcOEt/Et_3N=9.8:0.2:0.1); bp 105 °C/1 mm Hg; ν_{max} 3420 cm^{-1}; δ_H 1.23 (6H, s, 2×CH_3), 1.23 (3H, t, J=7.2 Hz, CH_3), 2.39 (1H, bs, OH), 2.87 (2H, s, $ArCH_2$), 3.72 (2H, q, J=7.2 Hz, CH_2), 5.25 (2H, s, OCH_2O), 6.93–6.99 (1H, m, ArH), 7.13–7.23 (3H, m, 3×ArH); δ_C 15.1, 29.4, 43.7, 64.5, 71.6, 93.5, 114.3, 121.6, 127.1, 127.9, 132.5, 155.8.

4.3.3. 2-(2-Ethoxymethoxyphenyl)-1-phenylethanol, 5. Purified by flash-chromatography (CH_2Cl_2/AcOEt/Et_3N=9:1:0.1), colourless oil. (Found: C, 74.76; H, 7.63; $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40); R_f=0.73 (CH_2Cl_2/AcOEt/Et_3N=9:1:0.1); bp 160 °C/1 mm Hg; ν_{max} 3410 cm^{-1}; δ_H 1.26 (3H, t, J=6.9 Hz, CH_3), 2.43 (1H, bs, OH), 3.01 (1H, dd, J=13.7, 8.4 Hz, ArCH), 3.14 (1H, dd, J=13.7, 4.2 Hz, ArCH), 3.75 (2H, q, J=6.9 Hz, CH_2), 4.98 (1H, dd, J=8.4, 4.2 Hz, ArCHO), 5.24 (1H, d, J=6.9 Hz, OCHO), 5.27 (1H, d, J=6.9 Hz, OCHO), 6.94 (1H, td, J=7.5, 1.5 Hz, ArH), 7.09–7.16 (2H, m, 2×ArH), 7.19–7.40 (6H, m, 6×ArH); δ_C 15.1, 41.0, 64.4, 74.3, 93.3, 114.1, 121.7, 125.7, 127.2, 127.3, 128.0, 128.2, 131.5, 144.4, 155.6.

4.3.4. 1-Ethoxymethoxy-4-methylbenzene, 9. Purified by flash-chromatography (petroleum ether/AcOEt/Et_3N=8:2:1), colourless oil; R_f=0.69 (petroleum ether/AcOEt/Et_3N=8:2:1); bp 70 °C/1 mm Hg (lit.[22] bp 78 °C/4.5 mm Hg); δ_H121(3H, t, J=6.8 Hz, CH_3), 2.29 (3H, s, $ArCH_3$), 3.72 (2H, q, J=6.8 Hz, CH_2), 5.18 (2H, s, OCH_2O), 6.92–6.96 (2H, m, 2×ArH), 7.06–7.10 (2H, m, 2×ArH).

4.3.5. 2-(4-Ethoxymethoxyphenyl)-1-phenylethanol, 10. Purified by flash-chromatography (petroleum ether/CH_2Cl_2/Et_3N=8:2:0.1), colourless oil. (Found: C, 74.81; H, 7.68; $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40); R_f=0.68 (petroleum

ether/CH_2Cl_2/Et_3N=8:2:0.1); ν_{max} 3450 cm^{-1}; δ_H 1.23 (3H, t, J=6.8 Hz, CH_3), 2.03 (1H, bs, OH), 2.92 (1H, dd, J=13.6, 8.4 Hz, ArCH), 2.99 (1H, dd, J=13.6, 4.8 Hz, ArCH), 3.73 (2H, q, J=6.8 Hz, CH_2), 4.82–4.89 (1H, m, CHO), 5.20 (2H, s, OCH_2O), 6.96–7.01 (2H, m, 2xArH), 7.09–7.14 (2H, m, 2×ArH), 7.26–7.36 (5H, m, 5×ArH); δ_C 15.1, 45.2, 64.1, 75.3, 93.2, 116.3, 125.9, 127.5, 128.4, 130.4, 131.2, 143.8, 156.2.

4.3.6. 1-Ethoxymethoxy-4-undecylbenzene, 11. Purified by flash-chromatography (petroleum ether/Et_3N=10:0.1), colourless oil. (Found: C, 78.12; H, 11.46; $C_{20}H_{34}O_2$ requires C, 78.36; H, 11.20); R_f=0.27 (petroleum ether/Et_3N=10:0.1); δ_H 0.89 (3H, t, J=6.6 Hz, CH_3), 1.23 (3H, t, J=7.2 Hz, CH_3), 1.24–1.36 (16H, m, 8×CH_2), 1.52–1.64 (2H, m, CH_2), 2.55 (2H, t, J=8.1 Hz, $ArCH_2$), 3.74 (2H, q, J=7.2 Hz, CH_2O), 5.20 (2H, s, OCH_2O), 6.94–6.99 (2H, m, 2×ArH), 7.06–7.13 (2H, m, 2×ArH); δ_C 14.1, 15.1, 22.7, 29.3, 29.3, 29.5, 29.6, 29.6, 29.7, 31.7, 31.9, 35.1, 64.1, 93.3, 116.1, 129.2, 136.3, 155.4.

4.4. Acidic hydrolysis of acetals 6–8 and 11–12. General procedure

The appropriate acetal (2–5 mmol) was added under Ar to a stirred 0.6 M solution of HCl in MeOH [obtained by adding AcCl (1 mL) to MeOH (20 mL)] chilled to 0 °C. The mixture was stirred at rt for 2–3 h, until complete disappearence of the starting material, as determined by TLC. The mixture was diluted with H_2O (20 mL), and the MeOH evaporated under reduced pressure. The resulting mixture was extracted with Et_2O (4×20 mL), and the organic phase dried ($CaCl_2$) and evaporated. Crude products were purified by flash chromatography and characterized as follows.

4.4.1. 2-Pentylphenol, 13. Purified by flash-chromatography (petroleum ether/AcOEt/AcOH=9:1:0.2), colourless oil. (Found: C, 80.27; H, 10.06; $C_{11}H_{16}O$ requires C, 80.42; H, 9.82); R_f=0.34 (petroleum ether/AcOEt/AcOH=9:1:0.2); ν_{max} 3410 cm^{-1}; δ_H 0.89 (3H, t, J=6.9 Hz, CH_3), 1.24–1.44 (4H, m, 2×CH_2), 1.56–1.70 (2H, m, CH_2), 2.59 (2H, t, J=8.1 Hz, $ArCH_2$), 4.67 (bs, 1H, OH), 6.75 (1H, dd, J=7.8, 1.2 Hz, ArH), 6.86 (1H, td, J=7.5, 1.2 Hz, ArH), 7.04–7.15 (2H, m, 2×ArH); δ_C 14.0, 22.5, 29.4, 29.8, 31.7, 115.1, 120.7, 126.9, 128.5, 130.1, 153.3.

4.4.2. 2-Tridecylphenol, 14. Purified by flash-chromatography (petroleum ether/AcOEt/AcOH=9:1:0.2), colourless oil, which solidifies upon standing; R_f=0.41 (petroleum ether/AcOEt/AcOH=9:1:0.2); mp 43–46 °C (lit.[23] 42.5–43 °C); ν_{max} 3380 cm^{-1}; δ_H 0.87 (3H, t, J=6.9 Hz, CH_3), 1.18–1.40 (20H, m, 10×CH_2), 1.60 (2H, quint, J=7.5 Hz, CH_2), 2.59 (2H, t, J=7.5 Hz, $ArCH_2$), 4.67 (1H, bs, OH), 6.75 (1H, dd, J=8.1, 0.9 Hz, ArH), 6.86 (1H, td, J=7.2, 0.9 Hz, ArH), 7.02–7.14 (2H, m, 2×ArH); δ_C 14.1, 22.7, 29.4, 29.6, 29.6, 29.7, 29.8, 29.9, 31.9, 115.1, 120.7, 127.0, 128.5, 130.1, 153.3.

4.4.3. 2-(2-Methyl)propylphenol, 15. Purified by flash-chromatography (petroleum ether/AcOEt=9.5:0.5), colourless oil, bp 45–50 °C/1 mm Hg (lit.[24] bp 57 °C/10 mm Hg). (Found: C, 80.12; H, 9.76; $C_{10}H_{14}O$ requires C, 79.94; H, 9.41); R_f=0.28 (petroleum ether/AcOEt=9.5:0.5); ν_{max} 3380 cm^{-1}; δ_H 0.92 (6H, d, J=6.8 Hz, 2×CH_3), 1.26 (1H, bs, OH), 1.92 (1H, n, J=6.8 Hz, CH), 2.47 (2H, d, J=6.8 Hz, CH_2), 6.74–6.76 (1H, dd, J=8.0, 1.2 Hz, ArH), 6.85 (1H, td, J=7.6, 1.2 Hz, ArH), 7.05–7.09 (2H, m, ArH).

4.4.4. 4-Undecylphenol, 16. Purified by flash-chromatography (petroleum ether/AcOEt/AcOH=9:1:0.2), colourless oil which solidifies upon standing, mp 52–54 °C (lit.[23] mp 56.5–57 °C); R_f=0.34 (petroleum ether/AcOEt/AcOH=9:1:0.2); ν_{max} 3350 cm^{-1}; δ_H 0.89 (3H, J=6.8 Hz, CH_3), 1.22–1.34 (16H, m, 8×CH_2), 1.53–1.62 (2H, m, CH_2), 2.53 (2H, t, J=8.0 Hz, $ArCH_2$), 4.48 (1H, bs, OH), 6.72–6.78 (2H, m, 2×ArH), 7.02–7.07 (2H, m, 2×ArH); δ_C 14.1, 22.7, 29.2, 29.3, 29.5, 29.6, 29.6, 29.7, 31.7, 31.9, 35.0, 115.0, 129.4, 135.2, 153.3.

4.4.5. 4-(2-Methyl)propylphenol, 17. Purified by flash-chromatography (petroleum ether/AcOEt=9:1), colourless oil, which solidifies upon standing; bp 70–75 °C/1 mm Hg (lit.[25] bp 131 °C/20 mm Hg) R_f=0.28 (petroleum ether/AcOEt=9:1); ν_{max} 3420 cm^{-1}; δ_H 0.87 (6H, d, J=7.2 Hz, 2×CH_3), 1.25 (1H, bs, OH), 1.79 (1H, n, J=7.2 Hz, CH), 2.39 (2H, d, J=7.2 Hz, $ArCH_2$), 6.72–6.77 (2H, m, 2×ArH), 6.98–7.24 (2H, m, 2×ArH).

4.5. Synthesis of trifluoromethanesulfonates 18–21. General procedure

These compounds were synthesized according to a general procedure described in Ref. 14. Crude products were purified by flash chromatography and characterized as follows.

4.5.1. 2-Trydecylphenyl trifluoromethanesulfonate, 18. Purified by flash-chromatography (petroleum ether), colourless oil, bp >150 °C/1 mm Hg. (Found: C, 58.57; H, 7.93; $C_{20}H_{31}F_3O_3S$ requires C, 58.79; H, 7.66); R_f=0.48 (petroleum ether); δ_H 0.90 (3H, t, J=6.6 Hz, CH_3), 1.21–1.39 (20H, m, 10×CH_2), 1.58–1.65 (2H, m, CH_2), 2.71 (2H, t, J=8.1 Hz, $ArCH_2$), 7.23–7.36 (4H, m, 4×ArH); δ_C 14.1, 22.7, 29.3, 29.5, 29.6, 29.6, 29.7, 29.9, 30.0, 31.9, 118.6 (q, J=318 Hz), 121.2, 127.6, 128.2, 131.2, 135.5, 148.0.

4.5.2. 2-(2-Methylpropyl)phenyl trifluoromethanesulfonate, 19. Purified by flash-chromatography (petroleum ether), colourless oil, bp 80–85 °C/1 mm Hg. (Found: C, 46.61; H, 4.91; $C_{11}H_{13}F_3O_3S$ requires C, 46.80; H, 4.65); R_f=0.48 (petroleum ether); δ_H 0.92 (6H, d, J=6.6 Hz, 2×CH_3), 1.93 (1H, n, J=6.6 Hz, CH), 2.58 (2H, d, J=6.6 Hz, $ArCH_2$), 7.21–7.32 (4H, m, 4×ArH); δ_C 22.3, 29.1, 39.3, 119.0 (q, J=318 Hz), 121.2, 127.7, 128.0, 132.1, 134.3, 148.3.

4.5.3. 4-Undecylphenyl trifluoromethanesulfonate, 20. Purified by flash-chromatography (petroleum ether), colourless oil, bp 125–130 °C/1 mm Hg. (Found: C, 56.64; H, 7.32; $C_{18}H_{27}F_3O_3S$ requires C, 56.81; H, 7.17); R_f=0.48 (petroleum ether); δ_H 0.90 (3H, t, J=6.6 Hz, CH_3), 1.21–1.39 (16H, m, 8×CH_2), 1.58–1.65 (2H, m, CH_2), 2.71 (2H, t, J=8.1 Hz, $ArCH_2$), 7.23–7.36 (4H, m, 4×ArH); δ_C 14.1, 22.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 31.3, 31.9, 35.3, 116.8 (q, J=318 Hz), 120.9, 130.0, 143.5, 147.6.

4.5.4. 4-(2-Methylpropyl)phenyl trifluoromethanesulfonate, 21. Purified by flash-chromatography (petroleum ether), colourless oil, bp 85–90 °C/1 mm Hg. (Found: C, 46.67; H, 4.73; $C_{11}H_{13}F_3O_3S$ requires C, 46.80; H, 4.65); R_f=0.37 (petroleum ether); δ_H 0.90 (6H, d, J=6.4 Hz, 2×CH_3), 1.85 (1H, n, J=6.4 Hz, CH), 2.49 (2H, d, J=6.4 Hz, ArCH_2), 7.14–7.23 (4H, m, 4×ArH); δ_C 22.2, 30.2, 44.6, 118.7 (q, J=318 Hz), 120.8, 130.7, 142.3, 147.7; although this triflate was already described,[26] its characterization was not reported.

4.6. Cross-coupling reactions

4.6.1. 1-Phenylethynyl-2-tridecylbenzene, 22. The reaction was run according to a general procedure described in Ref. 18, starting with 0.16 g (0.38 mmol) of **18** and 58 mg (0.57 mmol) of phenyl acetylene in 1.2 mL of dry DMF, in the presence of 0.25 mL (1.7 mmol) of Et_3N and 13 mg (0.019 mmol) of $PdCl_2(PPh)_3$, at 90 °C for 16 h. However, as a variation to the literature procedure, the catalyst was divided in two portions, and the second one was added to the reaction mixtures after 2 h stirring at the reported temperature. The reaction was worked-up as described in the literature, and the crude product purified by flash chromatography (petroleum ether), to afford 97 mg (0.27 mmol, 70%) of 22, as a colourless oil. (Found: C, 90.08; H, 10.36; $C_{27}H_{36}$ requires C, 89.92; H, 10.08); R_f=0.54 (petroleum ether); δ_H 0.90 (3H, t, J=6.9 Hz, CH_3), 1.18–1.42 (20H, m, 10×CH_2), 1.62–1.76 (2H, m, CH_2), 2.86 (2H, t, J= 7.8 Hz, ArCH_2), 7.15–7.26 (3H, m, 3×ArH), 7.30–7.40 (3H, m, 3×ArH), 7.47–7.55 (3H, m, 3×ArH); δ_C 14.1, 22.7, 29.4, 29.6, 29.6, 29.7, 29.7, 30.8, 31.9, 34.8, 88.4, 92.7, 122.5, 123.6, 125.6, 128.1, 128.3, 128.8, 131.4, 132.1, 145.1.

4.6.2. 1-Hexyl-2-(2′-methyl)propylbenzene, 23. The described procedure is a variation of a general one described in Ref. 9. A carefully dried two-necked flask is charged under Ar with 0.20 g (0.71 mmol) of **19**, 12 mg (0.035 mmol) of $Fe(acac)_3$, 5 mL of THF and 0.4 mL of NMP. The red reaction mixture was chilled to 0 °C and 0.43 mL (0.86 mmol) of a 2 M solution of $C_6H_{13}MgBr$ in Et_2O were added dropwise, causing an immediate change from red to dark brown. The reaction was allowed to warm to rt under vigorous stirring, whilst monitored by tlc. After 3 h stirring, 12 mg (0.035 mmol) of $Fe(acac)_3$ and 0.43 mL (0.86 mmol) of a 2 M solution of $C_6H_{13}MgBr$ in Et_2O were successively added, and the resulting mixture was stirred overnight at rt. The mixture was diluted with Et_2O (10 mL), chilled to 0 °C and quenched by dropwise addition of 1 M HCl (10 mL). The resulting mixture was extracted with Et_2O (3×10 mL), and the collected organic phases were washed with H_2O (20 mL), dried ($CaCl_2$) and the solvent evaporated. The residue was purified by flash chromatography (petroleum ether), to afford 84 mg (0.38 mmol, 54%) of **23**, as a colourless oil. (Found: C, 87.67; H, 12.31; $C_{16}H_{26}$ requires C, 87.98; H, 12.02); R_f=0.78 (petroleum ether); δ_H 0.89 (3H, t, J=6.0 Hz), 0.92 (6H, d, J=7.2 Hz, 2×CH_3), 1.20–1.42 (6H, m, 3×CH_2), 1.52–1.60 (2H, m, CH_2), 1.84 (1H, n, J=7.2 Hz, CH), 2.48 (2H, d, J=7.2 Hz, ArCH_2), 2.56–2.61 (2H, m, ArCH_2), 7.08–7.16 (4H, m, 4×ArH); δ_C 14.1, 22.6, 29.5, 29.7, 29.8, 31.3, 31.8, 32.7, 41.9, 125.3, 125.7, 129.0, 130.1, 139.2, 141.0.

4.6.3. 4-Undecylbiphenyl, 24. The reaction was run according to a general procedure described in Ref. 19, starting with 0.396 g (1.04 mmol) of **20** and 0.254 g (2.1 mmol) of phenylboronic acid in 25 mL of DME, in the presence of 5 mL of 2 M aqueous Na_2CO_3, 0.132 g (3.1 mmol) of LiCl, and 60 mg (0.05 mmol) of $Pd(PPh_3)_4$, at 85 °C for 5 h. However, as a variation to the literature procedure, the catalyst was divided in two portions, and the second one was added to the reaction mixtures after 2 h stirring at the reported temperature. The reaction was worked-up as described in the literature, and the crude product was recrystallized from EtOH, to afford 0.240 g (0.78 mmol, 75%) of **24**, mp 45–47 °C. (Found: C, 89.21; H, 10.68; $C_{23}H_{32}$ requires C, 89.53; H, 10.47); δ_H 0.88 (3H, t, J=6.8 Hz, CH_3), 1.24–1.42 (16H, m, 8×CH_2), 1.64 (2H, quint, J=7.6 Hz), 2.64 (2H, t, J=7.6 Hz, ArCH_2), 7.22–7.27 (2H, m, 2×ArH), 7.31 (1H, td, J=7.2, 1.6 Hz, ArH), 7.37–7.44 (2H, m, 2×ArH), 7.49–7.53 (2H, m, 2×ArH), 7.56–7.60 (2H, m, 2×ArH); δ_C 14.1, 22.7, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 31.5, 31.9, 35.6, 126.9, 127.0, 128.7, 128.8, 138.5, 141.2, 142.1.

4.6.4. 1-Phenylethynyl-4-(2′-methyl)propylbenzene, 25. The reaction was run according to a general procedure described in Ref. 18, starting with 0.217 g (0.77 mmol) of **21** and 0.118 g (1.16 mmol) of phenyl acetylene in 2.5 mL of dry DMF, in the presence of 0.50 mL (3.5 mmol) of Et_3N and 27 mg (0.038 mmol) of $PdCl_2(PPh)_3$, at 90 °C for 16 h. However, as a variation to the literature procedure, the catalyst was divided in two portions, and the second one was added to the reaction mixtures after 2 h stirring at the reported temperature. The reaction was worked-up as described in the literature, and the crude product purified by flash chromatography (petroleum ether), to afford 0.142 g (0.61 mmol, 79%) of 25, as a colourless oil. (Found: C, 91.97; H, 7.89; $C_{18}H_{18}$ requires C, 92.24; H, 7.76); R_f=0.43 (petroleum ether); δ_H 0.90 (6H, d, J=6.8 Hz, 2×CH_3), 1.86 (1H, n, J=6.8 Hz, CH), 2.47 (2H, d, J=6.8 Hz, CH_2), 7.10–7.14 (2H, m, 2×ArH), 7.30–7.36 (3H, m, 3×ArH), 7.42–7.46 (2H, m, 2×ArH), 7.50–7.55 (2H, m, 2×ArH); δ_C 22.3, 30.2, 45.3, 88.8, 89.6, 120.4, 123.5, 128.0, 128.3, 129.1, 131.4, 131.5, 142.2.

References and notes

1. Azzena, U.; Carta, S.; Melloni, G.; Sechi, A. *Tetrahedron* **1997**, *53*, 16205–16212.
2. Azzena, U.; Pilo, L.; Piras, E. *Tetrahedron* **2000**, *56*, 3775–3780.
3. Arrica, M. A.; Azzena, U.; Pilo, L.; Piras, E. *Tetrahedron Lett.* **2002**, *43*, 5137–5139.
4. Azzena, U.; Dettori, G.; Idini, M. V.; Pisano, L.; Sechi, G. *Appl. Organomet. Chem.* **2003**, *17*, 851–855.
5. For recent reviews on the arene-catalyzed reductive lithiation procedure, see: Najera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867–926. Yus, M. *Synlett* **2001**, 1197–1205. Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–238. For a recent paper on the mechanism of this reaction, see: Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574–2584.
6. Reductive lithiation of methoxy-substituted benzylic chlorides: Smith, K.; Hou, D. *J. Chem. Soc., Perkin Trans. 1* **1995**,

185–186, and references therein. see also: Gómez, C.; Huerta, F. F.; Yus, M. *Tetrahedron* **1998**, *54*, 1853–1866.
7. Reductive lithiation of alkoxy-substituted trimethylsilyl ethers of benzylic alcohols: Alonso, E.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **1997**, *62*, 417–421, and references therein.
8. Metalation of alkoxy-substitued toluenes: Schlosser, M.; Maccaroni, P.; Marzi, E. *Tetrahedron* **1998**, *54*, 2763–2770.
9. Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863, and references therein.
10. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.
11. Kamikawa, T.; Hayashi, T. *Synlett* **1997**, 163–164.
12. Quesnelle, C. A.; Familloni, O. B.; Snieckus, V. *Synlett* **1994**, 349–350.
13. Ritter, K. *Synthesis* **1993**, 735–762, and references therein.
14. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486.
15. Azzena, U.; Melloni, G.; Pisano, L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 261–266.
16. Birch, A. J. *J. Chem. Soc.* **1947**, 102–105. See also: Cherkasov, A. N.; Pivnitskii, K. K. *Zh. Org. Khim.* **1972**, *8*, 211–212. Cherkasov, A. N.; Pivnitskii, K. K. *Chem. Abs.* **1972**, *77*, 101990t.
17. De Jonge, J.; Bibo, B. H. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1448–1452.
18. For a recent synthesis of 2-hydroxy-substituted homobenzylic alcohols by the reductive lithiation of benzo-1,3-dioxanes, see: Choudhury, P. K.; Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 17373–17382.
19. Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171–1174.
20. Fu, J.-m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665–1668.
21. Mamedov, S.; Alieva, M.; Avanesyan, M. A. *Zh. Obshch. Khim.* **1964**, *34*, 3222–3227. Mamedov, S.; Alieva, M.; Avanesyan, M. A. *Chem. Abs.* **1964**, *62*, 3965f.
22. Hayashi, S.; Furukawa, M.; Fujino, Y.; Ishii, N.; Kamijo, Y. *Chem. Pharm. Bull.* **1972**, *20*, 15–20.
23. Itokawa, H.; Totsuka, N.; Nakahara, K.; Maezuru, M.; Takeya, K.; Kondo, M.; Inamatsu, M.; Morita, H. *Chem. Pharm. Bull.* **1989**, *37*, 1619–1621.
24. Selassie, C. D.; Shusterman, A. J.; Kapur, S.; Verma, R. P.; Zhang, L.; Hansch, C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2729–2733.
25. Bowman, R. S.; Stevens, D. R.; Baldwin, W. E. *J. Am. Chem. Soc.* **1957**, *79*, 87–92.
26. Rivera, I.; Colberg, J. C.; Soderquist, J. A. *Tetrahedron Lett.* **1992**, *33*, 6919–6922.

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Microwave mediated facile one-pot synthesis of polyarylpyrroles from but-2-ene- and but-2-yne-1,4-diones

H. Surya Prakash Rao,[a,*] S. Jothilingam[a] and Hans W. Scheeren[b]

[a]*Department of Chemistry, Pondicherry University, Pondicherry 605 014, India*
[b]*Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld 1, Nijmegen 6525 ED, The Netherlands*

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Dedicated to Professor Goverdhan Mehta, I.I.Sc., Bangalore, on the occasion of his 60th birthday

Abstract—Several pyrrole derivates with multiple aryl substituents were prepared conveniently in a one pot-reaction from but-2-ene-1,4-diones and but-2-yne-1,4-diones via hydrogenation of the carbon–carbon double bond/triple bond followed by amination–cyclization. The reaction could be performed with ammonium formate or alkyl/arylammonium formates under Pd/C in polyethylene glycol-200 (PEG-200) under microwave irradiation. Using this procedure, different aryl-substituted pyrroles were prepared. Furthermore, studies on microwave vs thermal conditions indicate faster heating under microwave conditions was responsible for rate enhancement.

1. Introduction

The pyrrole ring is one of the fundamental heterocycles. It is a widely distributed structural unit in a variety of natural and biologically important molecules such as porphyrins, bile pigments, co-enzymes and alkaloids.[1] Since fundamental molecules for energy trapping from sunlight embody a porphyrin nucleus with four pyrrole units, there has been a continuous quest to synthesize this heterocycle with different substituents efficiently and from readily available starting materials.[2] In recent years, there has been an enhanced interest in the synthesis of pyrrole and its oligomers due to their potential application as conducting materials.[3] Furthermore, pyrrole ring with multiple aromatic ring substitutions have applications as electroluminescent devices.[4] For this reason we became interested in developing a versatile synthesis of pyrrole derivatives from readily available starting materials.

The 2,5-disubstituted pyrroles can be synthesized by the classical Paal–Knorr method involving the reaction of 1,4-butanediones with amines.[5] Even though this procedure is versatile and applicable for the synthesis of a wide variety of pyrrole derivatives, it is limited to the availability of 1,4-diketones. On the other hand, but-2-ene-1,4-diones, the precursors to 1,4-butanediones can be prepared easily from readily available starting materials. For example, 1,4-diarylbut-2-ene-1,4-diones can be prepared by Friedel–Crafts acylation of arenes with fumaroyl chloride.[6] The 1,2,4-triarylbut-2-ene-1,4-diones can be prepared by condensation of benzil and its derivatives with acetophenone.[7] The 1,2,3,4-tetraarylbut-2-ene-1,4-diones can be prepared by deoxygenative dimerization of benzil and its derivatives via carbene intermediates.[8] The 1,4-butanediones can also be prepared by hydrogenation of the triple bond present in the but-2-yne-1,4-diones. The but-2-yne-1,4-diones of interest in the present study, the diaroylacetylenes, can be prepared from the corresponding diaroylethylenes by bromination followed by dehydrobromination.[9]

We reasoned that a simple and versatile route for the synthesis of pyrrole derivatives from 1,4-enediones could be developed if the two steps, viz. reduction and amination–cyclization can be combined in a single pot operation. For this purpose, ammonium formate can be employed as it behaves as a reducing agent of the double bond and also as a source of ammonia. There are several reports in the literature on the utility of ammonium formate as a source of hydrogen in the transfer hydrogenation reaction.[10] In the preliminary communication we disclosed the utility of ammonium formate for one-pot transformation of (*E*)-1,4-diarylbut-2-ene-1,4-diones to 2,5-diaryl-1*H*-pyrroles (Scheme 1).[11] We found that the reaction was greatly accelerated under microwave irradiation and required only 2–3 min. for completion. We also found that polyethylene glycol-200 (PEG-200) can be employed as a convenient solvent for the microwave promoted reactions. Now, we wish to report that this versatile method can be extended for the preparation of 2,5-diaryl and 1,2,5-triaryl-1*H*-pyrrole

Keywords: Pyrrole synthesis; Microwave assisted organic synthesis; Alkyl and aryl ammonium formates; Reduction; Amination–cyclization.
* Corresponding author. Tel.: +91-413-2655991x411; fax: +91-413-2655265; e-mail address: hspr@yahoo.com

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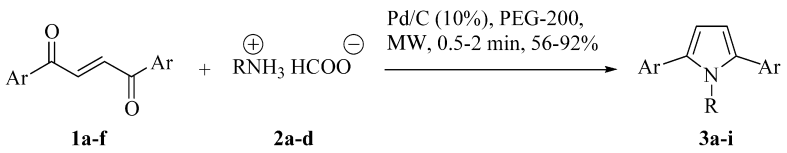


1a-f **2a-d** **3a-i**

1a: Ar = C_6H_5
1b: Ar = 4-ClC_6H_4
1c: Ar = 4-BrC_6H_4
1d: Ar = 4-$CH_3C_6H_4$
1e: Ar = 4-$OCH_3C_6H_4$
1f: Ar = 4-Cl-3-$CH_3C_6H_3$

2a: R = H
2b: R = n-C_4H_9
2c: R = $CH_2C_6H_5$
2d: R = C_6H_5

3a: Ar = C_6H_5, R = H;
3b: Ar = 4-ClC_6H_4, R = H
3c: Ar = 4-BrC_6H_4, R = H
3d: Ar = 4-$CH_3C_6H_4$, R = H
3e: Ar = 4-$OCH_3C_6H_4$, R = H
3f: Ar = 4-Cl-3-$CH_3C_6H_3$, R = H
3g: Ar = C_6H_5, R = n-C_4H_9
3h: Ar = C_6H_5, R = $CH_2C_6H_5$
3i: Ar = R = C_6H_5.

Scheme 1.

derivatives from 1,4-diarylbut-2-yne-1,4-diones and also for the synthesis of 2,3,5-triaryl, 1,2,3,5-tetraaryl and 2,3,4,5-tetraaryl-1*H*-pyrroles. We also report our studies on comparison of yield of the selected pyrrole derivative when synthesized by microwave or conventional heating techniques.

2. Results and discussion

The 1,4-diarylbut-2-ene-1,4-diones (dibenzoyl ethylenes) **1a–f** were smoothly converted into 2,5-diaryl-1*H*-pyrroles **3a–f** when they were subjected to reductive amination–cyclization with ammonium formate **2a** in the presence of 5% Pd/C in PEG-200 under microwave irradiation for 2 min (Scheme 1). In this method the ene-dione was being reduced to the 1,4-dione in the initial transformation via palladium catalyzed catalytic transfer hydrogenation. The resulting 1,4-dione moiety was further transformed into 2,5-diaryl-1*H*-pyrroles in a domino fashion through amination–cyclization by utilizing in situ generated ammonia. The results of the transformation of differently phenyl substituted 1,4-diarylbut-2-ene-1,4-diones **1a–f** to pyrrole derivatives **3a–f** are gathered together in Table 1. It can be seen from the Table that when the reaction was conducted under microwave irradiation in PEG-200 the transformation of 1,4-diphenylbut-2-ene-1,4-dione **1a** into 2,5-diphenyl-1*H*-pyrrole **3a** was over in 30 s whereas the reaction required 30 min for completion in methanol reflux. However, the transformation of 1,4-di(4-methoxyphenyl)-but-2-ene-1,4-dione **1e** into 2,5-di(4-methoxyphenyl)-1*H*-pyrrole **3e** required comparatively longer time both under microwave conditions or under methanol reflux indicating the influence of the electron donating 4-methoxy group in the transformation. The yield of the pyrrole derivative **3e** was 89% under microwave irradiation but only 37% in methanol reflux. In addition to the pyrrole product, the double bond reduced product 1,4-diphenyl-1,4-butanedione was obtained in 45% yield in refluxing in methanol. Prolonged reflux did not increase the yield of the pyrrole product. However, the yield of **3e** rose to 85% when the reaction was conducted in diethylene glycol at 150 °C for 10 min. This result indicated that the reduction of the double bond in **1e** with ammonium formate was efficient and was not affected by the electron donating methoxy substituent on the phenyl ring. On the other hand, subsequent steps in the sequence, the formation of the hemiaminal intermediates and cyclisation to pyrrole rings appears to be highly influenced by the presence of the methoxy group. Amarnath and co-workers made similar observations in the mechanistic studies on Paal–Knorr pyrrole synthesis.[12]

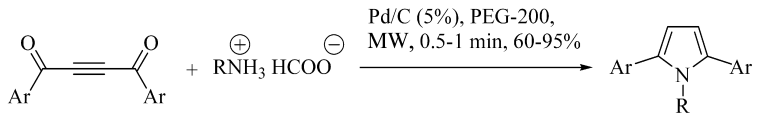
Table 1. Transformation of ene-diones **1a–e** to pyrroles **3a–i**

Entry	Enedione	Formate derivatives	Pyrrole	Time (min)	Power (W)	Yield (%)
1	**1a**	**2a**	**3a**[a]	0.5	200	92
2	**1b**	**2a**	**3b**[b]	1.0	200	80
3	**1c**	**2a**	**3c**[c]	1.0	200	85
4	**1d**	**2a**	**3d**[b]	1.5	200	85
5	**1e**	**2a**	**3e**[d]	2.0	200	89
6	**1f**	**2a**	**3f**[e]	2.0	200	84
7	**1a**	**2b**	**3g**[f]	2.0	200	56
8	**1a**	**2c**	**3h**[g]	2.0	200	63
9	**1a**	**2d**	**3i**[h]	2.0	200	60

[a] Ref. 13.
[b] Ref. 14.
[c] Ref. 15.
[d] Ref. 12.
[e] Ref. 11.
[f] Ref. 16.
[g] Ref. 17.
[h] Ref. 18.

The *N*-alkyl or *N*-aryl pyrrole derivatives **3g–i** was prepared by employing alkyl/aryl ammonium formates **2b–d** as reagents for the reduction, amination–cyclization of enedione **1a**. In general the reaction of alkyl/aryl ammonium formates was found to be difficult and only moderate yields of the pyrrole products **3g–i** were realized in the reaction (Table 1, entry 7–9). Whereas with the microwave heating conditions, the yield of the pyrroles **3g–i** was around 60%, the yield was only about 28% in methanol reflux. It appears that the steric and electronic effects on the amino group of the alkyl/aryl amines play a role in the rate-determining step during the pyrrole formation. Similar to our observation previously, Sammes and Chiu have shown that the Paal–Knorr reaction may follow different pathways depending on whether the reactant is ammonia or an alkyl amine.[19]

Next, we sought to demonstrate utility of the present procedure in the one-pot synthesis of 2,5-disubstituted



4a-f **2a-d** **3a-i**

4a: Ar = C_6H_5
4b: Ar = 4-ClC_6H_4
4c: Ar = 4-BrC_6H_4
4d: Ar = 4-$CH_3C_6H_4$
4e: Ar = 4-$OCH_3C_6H_4$
4f: Ar = 4-Cl-3-$CH_3C_6H_3$

2a: R = H
2b: R = n-C_4H_9
2c: R = $CH_2C_6H_5$
2d: R = C_6H_5

3a: Ar = C_6H_5, R = H
3b: Ar = 4-ClC_6H_4, R = H
3c: Ar = 4-BrC_6H_4, R = H
3d: Ar = 4-$CH_3C_6H_4$, R = H
3e: Ar = 4-$OCH_3C_6H_4$, R = H
3f: Ar = 4-Cl-3-$CH_3C_6H_3$, R = H
3g: Ar = C_6H_5, R = n-C_4H_9
3h: Ar = C_6H_5, R = $CH_2C_6H_5$
3i: Ar = R = C_6H_5

Scheme 2.

Table 2. Transformation of yne-diones **4a–f** to pyrroles **3a–i**

Entry	Ynedione	Formate derivatives	Pyrrole	Time (min)	Power (W)	Yield (%)
1	**4a**	**2a**	**3a**	0.5	200	95
2	**4b**	**2a**	**3b**	1.0	200	92
3	**4c**	**2a**	**3c**	1.0	200	94
4	**4d**	**2a**	**3d**	1.0	200	90
5	**4e**	**2a**	**3e**	1.0	200	91
6	**4f**	**2a**	**3f**	1.0	200	90
7	**4a**	**2b**	**3g**	1.0	200	60
8	**4a**	**2c**	**3h**	1.0	200	65
9	**4a**	**2d**	**3i**	1.0	200	61

pyrroles from 1,4-diphenylbut-2-yne-1,4-diones wherein complete hydrogenation of the triple bond in ynedione to 1,4-dione is followed by an amination cyclization reaction. Thus, in the palladium mediated microwave assisted reaction of ammonium formate with **2a**, 1,4-diarylbut-2-yne-1,4-diones **4a–f** resulted in the 2,5-disubstituted pyrrole derivatives **3a–f** in over 90% yield within one min (Scheme 2). Similar reaction with alkyl/aryl ammonium formate **2b–d** also resulted in the pyrrole derivatives **3g–i** in 60–95% yield (Table 2). It appears that the reactivity of ynediones **4a–f** towards the formation of pyrrole derivatives is similar to enediones **1a–f**. Since there is little difference in the reactivity of similarly substituted ynediones and enediones it can be concluded that hydrogenation of the triple bond to the corresponding fully saturated derivatives is facile and the steps involving amination–cyclization determine the rate of formation of pyrrole derivatives.

Having demonstrated a facile 2,5-diarylpyrrole synthesis from enediones **1a–f** and ynediones **4a–f**, we extended the method for the preparation of pyrroles with multiple aryl substitution. The reaction of (*E*)-1,2,4-triphenylbut-2-ene-1,4-dione (1,2-dibenzoylstyrene) **5a** with ammonium formate **2a** and Pd/C in PEG-200 under microwave irradiation resulted in the known[20] 2,3,5-triphenyl-1*H*-pyrrole **6a** in near quantitative yield within 1 min (Scheme 3; Table 3, entry 1). We conducted this reaction on a 10 mmol scale and found smooth transformation to the pyrrole derivative in 92% yield. Thus, the present procedure is amenable for scaling up. The reaction of **5a** with anilinium formate **2d** resulted in 1,2,3,5-tetraphenyl-1*H*-pyrrole[21] **6b** within 1 min (Scheme 3; Table 3, entry 2). Similarly, the reaction of (*E*)-1,2,3,4-tetraphenylbut-2-ene-1,4-dione (1,2-dibenzoylstilbene) **5b** with ammonium formate furnished 2,3,4,5-tetraphenyl-1*H*-pyrrole[22] **6c** (Scheme 3; Table 3, entry 3). However, the reaction of **5b** with anilinium formate did not yield the expected 1,2,3,4,5-pentaphenyl-1*H*-pyrrole[23] **6d**. The ^{1}H NMR and IR spectra of the crude product from this reaction indicated that reduction of the double bond and formation of imine

Table 3. Transformation of ene-dione **5a**,**b** to pyrroles **6a–c**

Entry	Enedione	Formate derivatives	Pyrrole	Time (min)	Power (W)	Yield (%)
1	**5a**	**2a**	**6a**[a]	1.0	200	95
2	**5a**	**2b**	**6b**[b]	1.0	200	65
3	**5b**	**2a**	**6c**[c]	5.0	200	95

[a] Ref. 20.
[b] Ref. 21.
[c] Ref. 22.

5a,b **2a,d** **6a-d**

5a: $R^1 = R^2 = R^4 = C_6H_5$, R^3 = H
5b: $R^1 = R^2 = R^3 = R^4 = C_6H_5$

2a: R^5 = H
2d: $R^5 = C_6H_5$

6a: $R^1 = R^2 = R^4 = C_6H_5$, $R^3 = R^5$ = H
6b: $R^1 = R^2 = R^4 = R^5 = C_6H_5$, R^3 = H
6c: $R^1 = R^2 = R^3 = R^4 = C_6H_5$, R^5 = H
6d: $R^1 = R^2 = R^3 = R^4 = R^5 = C_6H_5$

Scheme 3.

Table 4. The effect of reaction conditions on the transformation of **5a** to **6a**

S. No.	Vessel	Solvent	Time (min)	Power (W)	Temperature (°C)	Yield (%)
1	Glass (open)[a]	PEG-200	1.0	200	126	96
2	Glass (open)	PEG-200	5.0	–	126	90
3	Teflon (capped)	Methanol	2.0	200	–	96
4	Glass (open)	Ethylene glycol	2.0	200	116	88

[a] The vessel was kept in silica gel bath.

intermediates have occurred but the anticipated cyclization to the pyrrole ring did not take place. It appears that the steric factors play a major role in preventing the open chain intermediates to go through an entropically unfavorable cyclization step.

Next, we sought to find out if there were any non-thermal microwave effects in the conditions employed in the conversion of 1,4-butanediones to the pyrrole derivatives. The transformation of (*E*)-1,2,4-triphenylbut-2-ene-1,4-dione (1,2-dibenzoylstyrene) **5a** to 2,3,5-triphenyl-1*H*-pyrrole **6a** was taken as a representative example. The results in the study are gathered together in Table 4. We found that microwave irradiation at 200 W the temperature of the reaction mixture in PEG-200 reached 126 °C in 1 min (Table 4, entry 1). When the same reaction was conducted in a preheated oil bath maintained at 126 °C it took 5 min. for completion (Table 4, entry 2). However, the yield of the desired product was marginally lower possibly due to decomposition of the product. When the reaction was conducted in methanol in a screw-capped Teflon vessel the reaction took 2 min indicating that methanol is also a good solvent for the reaction (Table 4, entry 3). The microwave-mediated transformation of **5a** to **6a** was equally facile in the high boiling solvent, ethylene glycol (Table 4, entry 4). Thus, similar to the observations made by many groups,[24] in the present transformation microwave energy is used only for rapid heating of the reaction mixture to furnish the desired pyrrole derivatives in near quantitative yield within few min. Even tough the reaction worked well in methanol; obviously, PEG-200 is a better solvent for conducing the microwave-assisted reactions due to precautions one need to take while conducing them in the sealed vessels.

3. Conclusion

In conclusion we have shown that various aryl substituted pyrrole derivatives can be synthesized readily from enediones and ynediones in a microwave mediated one-pot synthesis using ammonium and alkylammonium formates in the presence of palladium. In the future, we plan to use the polyaryl pyrroles for the synthesis of flat dendrimers incorporating the pyrrole core.

4. Experimental

4.1. General

All reagents and solvents were purchased form E-Merck and Sisco Chemicals, India. Microwave reactions were carried out using BPL-Sanyo, India; mono-mode and multi-power (power source: 230 V, 50 Hz, microwave frequency: 2450 MHz) microwave oven. The TLC (pre-coated silica gel 60 F_{254}, Merck) method was used to monitor the progress of the reaction and the products were isolated by short column chromatography on silica gel (100–200 mesh, Acme Synthetic Chemicals, India) using hexanes/dichloromethane (DCM) mixture as the eluent. Melting points were noted using a Gallenkamp melting point apparatus. The IR spectra were recorded as KBr pellets using Bomem MB104 spectrometer. The frequencies at which the ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or in CCl_4:$CDCl_3$ (1:1) with Bruker 300 MHz, Bruker 400 MHz, JEOL 400 MHz or Varian 300 MHz are noted in the spectral data. TMS was used as internal standard. Mass spectra were recorded on HP MS-engine S989A (EI, electron impact, 70 eV). We have given in the experimental section only those spectral data (IR, ^{1}H NMR, ^{13}C NMR or MS), which have not been described in literature.

4.1.1. General procedure for the synthesis of di, tri and tetraarylpyrroles from enediones: 2,5-diphenyl-1*H*-pyrrole (3a). A 25 mL conical flask, charged with enedione **1a** (100 mg, 0.42 mmol), ammonium formate **2a** (267 mg, 4.2 mmol), 5% Pd/C (2 mg) and PEG-200 (2 mL), was irradiated in the microwave oven at 200 W for 30 s. After completion of the reaction (TLC) cooled (rt) contents of the flask were charged on the short column of silica (5 cm×1 cm) and eluted with hexane/DCM (90:10 to 50:50). Removal of solvent from pooled fractions yielded pyrrole **3a** as a white solid (85 mg, 92%). An analytically pure sample was obtained by recrystallization from DCM/hexanes (2:98); mp 142-144 °C (lit:[13] 143 °C). ^{13}C NMR ($CDCl_3$): δ=108.0, 123.8, 126.3, 128.9, 132.6, 133.0 ppm.

4.1.2. 2,5-Di(4-chlorophenyl)-1*H*-pyrrole (3b). Following the above general procedure, enedione **1b** (100 mg, 0.33 mmol) was transformed to pyrrole **3b** with ammonium formate **2a** (206 mg, 3.3 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 1 min. Yield: 76 mg (80%; white solid); mp 180–182 °C (lit.[14] 181 °C). ν_{max}=3460 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=6.50 (d, J=2.7 Hz, 2H), 7.33 (d, J=8.4 Hz, 4H), 7.42 (d, J=8.4 Hz, 4H), 8.44 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ=108.6, 125.0, 129.2, 130.9, 132.3, 132.4 ppm.

4.1.3. 2,5-Di(4-bromophenyl)-1*H*-pyrrole (3c). Following the above general procedure, enedione **1c** (100 mg, 0.25 mmol) was transformed to pyrrole **3c** with ammonium formate **2a** (160 mg, 2.5 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 1 min. Yield: 81 mg (85%, white solid); mp 212–214 °C (lit.[15] 214–216 °C). ^{13}C NMR ($CDCl_3$): δ=108.1, 123.8, 126.4, 128.9, 132.7, 133.1 ppm.

4.1.4. 2,5-Di(4-methylphenyl)-1*H*-pyrrole (3d). Following the above general procedure, enedione **1d** (100 mg, 0.38 mmol) was transformed to pyrrole **3d** with ammonium formate **2a** (238 mg, 3.8 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 1.5 min. Yield: 80 mg (85%, white solid); mp 202–204 °C (lit.[14] 203 °C). ^{1}H NMR ($CDCl_3$): δ=2.35 (s, 6H), 6.45 (br s, 2H), 7.14 (d, J=7.8 Hz, 4H), 7.37 (br d, J=7.8 Hz, 4H), 8.42 (s, br, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ=21.3, 107.5, 123.8, 130.0, 132.0, 132.9, 135.7 ppm.

4.1.5. 2,5-Di(4-methoxyphenyl)-1*H*-pyrrole (3e). Following the above general procedure, enedione **1e** (100 mg, 0.34 mmol) was transformed to pyrrole **3e** with ammonium formate **2a** (213 mg, 3.4 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 2 min. Yield: 84 mg (89%, white solid); mp 230–232 °C (lit.[12] 232 °C).

4.1.6. 2,5-Di(4-chloro-3-methylphenyl)-1*H*-pyrrole (3f). Following the above general procedure, enedione **1f** (100 mg, 0.3 mmol) was transformed to pyrrole **3f** with ammonium formate **2a** (189 mg, 3.0 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 2 min. Yield: 80 mg (84%, white solid); mp 190–192 °C (lit.[11] 190 °C).

4.1.7. 2,3,5-Triphenyl-1*H*-pyrrole (6a). Following the above general procedure, enedione **5a** (1000 mg, 3.2 mmol) was transformed to pyrrole **6a** with ammonium formate **2a** (2019 mg, 32 mmol) and 5% Pd/C (5 mg) in PEG-200 (5 mL) under microwave irradiation at 200 W for 2 min. Yield: 901 mg (95%, white solid); mp 138–140 °C (lit.[20] 135–137 °C).

4.1.8. 2,3,4,5-Tetraphenyl-1*H*-pyrrole (6c). Following the above general procedure, enedione **5a** (500 mg, 1.29 mmol) was transformed to pyrrole **6c** with ammonium formate **2a** (812 mg, 12.9 mmol) and 5% Pd/C (5 mg) in PEG-200 (5 mL) under microwave irradiation at 200 W for 7 min. Yield: 453 mg (95%, white solid); mp 212–214 °C (lit.[22] 214–216 °C). ^{13}C NMR ($CDCl_3$): δ=123.4, 126.1, 126.7, 127.2, 128.0, 128.2, 128.6, 128.9, 130.1, 131.0, 132.9, 135.4, 138.6 ppm.

4.1.9. 1-Butyl-2,5-diphenyl-1*H*-pyrrole (3g). To butylamine (155 mg, 2.1 mmol) and formic acid (0.1 mL, 2.1 mmol) were taken in a 25 mL conical flask at 5 °C, enedione **1a** (100 mg, 0.42 mmol), 5% Pd/C (2 mg) and PEG-200 (2 mL), were added, This reaction mixture was irradiated by microwaves in the microwave oven at 200 W for 2 min. After completion of the reaction (TLC), the mixture was cooled to room temperature and chromatographed on silica (5 cm×1 cm) using hexanes/DCM as the eluent. Removal of solvent from pooled fractions yielded pyrrole **3g** as white solid (65 mg, 56%). An analytically pure sample was obtained by recrystallization from DCM/hexanes (2:98); mp 112–114 °C (lit.[16] 113 °C). ^{1}H NMR ($CDCl_3$): δ=0.50 (t, J=7.3 Hz, 3H), 0.81 (sextet, J=7.3 Hz, 2H), 1.14 (pentet, J=7.3 Hz, 2H), 4.03 (t, J=7.3 Hz, 2H), 6.22 (s, 2H), 7.27 (br t, J=7.2 Hz, 2H), 7.37 (br t, J=7.2 Hz, 4H), 7.42 (br d, J=7.2 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$): δ=13.3, 19.3, 32.7, 44.9, 109.3, 126.8, 128.4, 129.0, 134.2, 136.5 ppm.

4.1.10. 1-Benzyl-2,5-diphenyl-1*H*-pyrrole (3h). Following the above general procedure, enedione **1a** (100 mg, 0.42 mmol) was transformed to pyrrole **3h** with benzyl amine (227 mg, 2.1 mmol), formic acid (0.1 mL, 2.1 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 2 min. Yield: 81 mg, (63%); mp 144–146 °C (lit.[17] 144 °C).

4.1.11. 1,2,5-Triphenyl-1*H*-pyrrole (3i). Following the above general procedure, enedione **1a** (100 mg, 0.42 mmol) was transformed to pyrrole **3i** with aniline (197 mg, 2.1 mmol), formic acid (0.1 mL, 2.1 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 2 min. Yield: 75 mg, (60%); mp 228–230 °C (lit.[18] 229 °C).

4.1.12. 1,2,3,5-Tetraphenyl-1*H*-pyrrole (6b). Following the above general procedure, enedione **5a** (624 mg, 2 mmol) was transformed to pyrrole **6b** with aniline (931 mg, 1 mmol), formic acid (0.45 mL, 10 mmol) and 5% Pd/C (5 mg) in PEG-200 (3 mL) under microwave irradiation at 155 W for 8 min. Yield: 485 mg, (65%); mp 200–202 °C (lit.[21] 200–1 °C).

4.1.13. General procedure for the synthesis of di and triarylpyrroles from ynediones: synthesis of 2,5-diphenyl-1*H*-pyrrole (3a). A 25 mL conical flask, charged with ynedione **4a** (100 mg, 0.43 mmol), ammonium formate (269 mg, 4.3 mmol), 5% Pd/C (2 mg) and PEG-200 (2 mL), was irradiated in the microwave oven at 200 W for 30 s. After completion of the reaction (TLC) the cooled (rt) reaction mixture was loaded on a short column of silica (5 cm×1 cm) and eluted with hexanes/DCM (90:10 to 50:50). Removal of solvent from pooled fractions resulted in pyrrole **3a** as the white solid (89 mg, 95%) after removal of the solvent.

4.1.14. 2,5-Di(4-chlorophenyl)-1*H*-pyrrole (3b). Following the above general procedure, ynedione **4b** (100 mg, 0.33 mmol) was transformed to pyrrole **3b** with ammonium formate (207 mg, 3.3 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 60 s. Yield: 87 mg (92%).

4.1.15. 2,5-Di(4-bromophenyl)-1*H*-pyrrole (3c). Following the above general procedure, ynedione **4c** (100 mg, 0.26 mmol) was transformed to pyrrole **3c** with ammonium formate (161 mg, 2.6 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 60 s. Yield: 90 mg (94%).

4.1.16. 2,5-Di(4-methylphenyl)-1*H*-pyrrole (3d). Following the above general procedure, ynedione **4d** (100 mg, 0.38 mmol) was transformed to pyrrole **3d** with ammonium formate (240 mg, 3.8 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 60 s. Yield: 85 mg (90%).

4.1.17. 2,5-Di(4-methoxyphenyl)-1*H*-pyrrole (3e). Following the above general procedure, ynedione **4e**

(100 mg, 0.34 mmol) was transformed to pyrrole **3e** with ammonium formate (214 mg, 3.4 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 60 s. Yield: 86 mg (91%).

4.1.18. 2,5-Di(4-chloro-3-methylphenyl)-1*H*-pyrrole (3f). Following the above general procedure, ynedione **4f** (100 mg, 0.3 mmol) was transformed to pyrrole **3f** with ammonium formate (190 mg, 3 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 60 s. Yield: 86 mg (90%).

4.1.19. 1-Butyl-2,5-diphenyl-1*H*-pyrrole (3g). To butyl amine (155.9 mg, 2.13 mmol) and formic acid (0.1 mL, 2.13 mmol) taken in a 25 mL conical flask at 5 °C, ynedione **4a** (100 mg, 0.43 mmol), 5% Pd/C (2 mg) and PEG-200 (2 mL) were added. This reaction mixture was irradiated by microwaves in the microwave oven at 200 W for 60 s. After completion of the reaction (TLC) the mixture was cooled to room temperature and chromatographed on silica (5 cm×1 cm) using hexanes/DCM as the eluent. Removal of solvent from pooled fraction yielded pyrrole **3g** as white solid (70 mg, 60%).

4.1.20. 1-Benzyl-2,5-diphenyl-1*H*-pyrrole (3h). Following the above general procedure, ynedione **4a** (100 mg, 0.43 mmol) was transformed to pyrrole **3h** with benzyl amine (228.6 mg, 2.13 mmol), formic acid (0.1 mL, 2.13 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 60 s. Yield: 80 mg, (61%).

4.1.21. 1,2,5-Triphenyl-1*H*-pyrrole (3i). Following the above general procedure, ynedione **4a** (100 mg, 0.43 mmol) was transformed to pyrrole **3i** with aniline (198.7 mg, 2.13 mmol), formic acid (0.1 mL, 2.13 mmol) and 5% Pd/C (2 mg) in PEG-200 (2 mL) under microwave irradiation at 200 W for 60 s. Yield: 82 mg, (65%).

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References and notes

1. (a) Jones, R. A.; Bean, G. P. *The chemistry of pyrroles*; Academic: London, 1977; pp 1–5. (b) Sundberg, R. J. *Comprehensive heterocyclic chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 370. (c) Sundberg, R. J. *Comprehensive heterocyclic chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 149. (d) Boger, D. L.; Boyce, C. W.; Labrili, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54, and references cited therein.
2. *The chemistry of heterocyclic compounds*; Jones, R. A., Ed.; Wiley: Toronto, 1990; part 1 and 2.
3. (a) Tietze, L. F.; Nordmann, G. *Synlett* **2001**, 337. (b) Groenendaal, L.; Meijer, E.-W.; Vekemans, J. A. J. M. In *Electronic materials: the oligomer approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, 1997.
4. Sakon, Y.; Ohnuma, T.; Hashimoto, M.; Saito, S.; Tsutsui, T.; Adachi, C. US Patent 5,077,142 A 19,911,231; **1991** CA 117:16862.
5. (a) Paal, C. *Chem. Ber.* **1884**, *17*, 2756. (b) Knorr, L. *Chem. Ber.* **1884**, *17*, 2863.
6. (a) Conant, J. B.; Lutz, R. E. *J. Am. Chem. Soc.* **1923**, *45*, 1303. (b) Conant, J. B.; Lutz, R. E. *J. Am. Chem. Soc.* **1925**, *47*, 881. (c) Coampaigne, E.; Foye, W. O. *J. Org. Chem.* **1952**, *17*, 1405.
7. Demirdji, S. H.; Haddadin, M. J.; Issidorides, C. H. *J. Heterocycl. Chem.* **1985**, *22*, 495.
8. Wilson, R. M.; Hengge, A. C.; Ataei, A.; Ho, D. M. *J. Am. Chem. Soc.* **1991**, *113*, 7240.
9. Zhang, J.-J.; Schuster, G. B. *J. Am. Chem. Soc.* **1989**, *111*, 7149.
10. (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91. (b) Rao, H. S. P.; Reddy, K. S. *Tetrahedron Lett.* **1994**, *35*, 171.
11. Rao, H. S. P.; Jothilingam, S. *Tetrahedron Lett.* **2001**, *42*, 6595.
12. Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. *J. Org. Chem.* **1991**, *56*, 6924.
13. Patterson, J. N.; Soedigdo, S. *J. Org. Chem.* **1968**, *33*, 2057.
14. Tsuge, O.; Tashiro, M.; Hokama, K.; Yamada, K. *Kogyo Kagaku Zasshi* **1968**, *71*, 1667. CA 70:37587.
15. Alper, H.; Prickett, J. E. *Inorg. Chem.* **1977**, *16*, 67.
16. Schulte, K. E.; Reisch, J.; Walker, H. *Chem. Ber.* **1965**, *98*, 98.
17. Alickmann, D.; Frohlich, R.; Maulitz, A. H.; Wurthwein, E. *Eur. J. Org. Chem.* **2002**, 1523.
18. Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem.* **1999**, *64*, 4204.
19. Chiu, P. K.; Samme, M. P. *Tetrahedron* **1988**, *44*, 3531.
20. Furstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637.
21. Lee, C.; Yang, L.; Hwu, T.; Feng, A.; Tseng, J.; Luh, T. *J. Am. Chem. Soc.* **2000**, *122*, 4992.
22. Sera, A.; Fukumoto, S.; Yoneda, T.; Yamada, H. *Heterocycles* **1986**, *24*, 697.
23. Hong, P.; Yamazaki, H. *J. Organomet. Chem.* **1989**, *373*, 133.
24. Kuhnert, N. *Angew Chem. Int. Ed.* **2002**, *41*, 1863.

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Solid catalysts for the production of fine chemicals: the use of natural phosphate alone and doped base catalysts for the synthesis of unsaturated arylsulfones

Mohamed Zahouily,[a,*] Mohamed Salah,[a] Bouchaib Bahlaouane,[a] Ahmed Rayadh,[a] Abdelaziz Houmam,[b] Emad A. Hamed[b] and Saïd Sebti[c]

[a]*Laboratoire de Catalyse, Synthèse et Environnement, UFR de Chimie Appliquée, Faculté des Sciences et Techniques, Université Hassan II, Mohammadia B. P. 146, 20650 Maroc*
[b]*University of Guelph, Departement of Chemistry and Biochemistry, Guelph, Ontario,Canada, N1G2W1*
[c]*Laboratoire de Chimie Organique Appliquée et Catalyse, Faculté des Sciences, Ben M'Sik B. P. 7955, Casablanca, Maroc*

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Abstract—The inexpensive natural phosphate, both alone and doped with potassium fluoride, is a new basic catalyst for the synthesis of α,β-unsaturated arylsulfones. Activation by water and benzyltriethylammonium chloride has also been investigated. When using an ammonium salt, natural phosphate doped with potassium fluoride is an excellent solid support for the synthesis of α,β-unsaturated arylsulfones, leading to excellent yields in a few minutes.

1. Introduction

Heterogeneous catalysis is an important application of porous solids possessing acid and Lewis basic sites. Studies on solid acid catalysts are enormous. Though little attention is devoted to basic catalysts in comparison with solid acid catalysts, high activities and selectivities are often obtained for many kinds of reaction.[1] Numerous reactions including isomerizations, additions, alkylations and cyclizations are carried out industrially using liquid bases as catalysts. Furthermore, many organic reactions require a stoichiometric amount of liquid bases. The advantages of heterogeneous catalysis over conventional homogeneous reactions is that it provides greater selectivity, enhanced reaction rates, cleaner product and manipulative simplicity. For these reasons, heterogeneous catalysis can be considered as a new attempt to develop the notion of 'clean chemistry'.

Sulfones are important intermediates in organic synthesis.[2] Their importance is due to the fact that arylsulfonyl groups can stabilise adjacent carbanions[3] and may easily be removed by hydrolysis, reduction or elimination[4] and, when appropriate, may be eliminated to introduce carbon–carbon double bonds into organic molecule.[5] Thus they are useful temporary activating groups for alkylation,[6] acylation[7] and addition reactions.[8]

The Knoevenagel condensation of arylsulfones and aldehydes is one of the most popular methods for synthesizing unsaturated arylsulfones. The deprotonation of phenylsulfonylalkanes generally involves strong bases such as sodium hydride,[9] butyl lithium[10] or lithium di-*iso*propylamide (LDA).[11] However, the deprotonation energy strongly depends on the presence of adjacent electron-withdrawing groups such as an ester,[3] nitrile or ketone.[12]

In recent years, the Knœvenagel condensation in heterogeneous media has been carried out in presence of zeolites,[13] organic resins,[14] mixed magnesium–aluminium oxides derived from hydrotalcites,[15] sepiolites,[16] aluminophosphonates oxynitrides (ALPON),[17] and more recently, synthetic phosphate $Na_2CaP_2O_7$.[18]

We have previously investigated the use of natural phosphate to promote organic transformations[19] and have shown that its mildly basic proprieties can be exploited in many synthetic applications.[20] We have also shown that doping with mineral salts increases the activity of natural phosphate.[20]

In continuation of our ongoing program to develop clean and economical processes for the production of fine chemicals, we describe in this paper, the use of natural phosphate (NP) alone and doped with KF as an inorganic

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* Corresponding author. Tel.: +212-61-62-80-76; fax: +212-23-31-53-53; e-mail address: m.zahouily@univh2m.ac.ma

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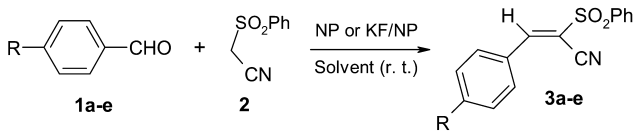

Scheme 1.

support of the Knœvenagel condensation between phenylsulfonylacetonitrile **2** and benzaldehyde or 4-substituted benzaldehydes **1**, at room temperature with a solvent (Scheme 1).

2. Preparation of the catalyst and structural characteristics

Natural phosphate (NP) used in this work was obtained in the Khouribga region (Morocco).[21] Prior to use this material requires initial treatments such as crushing and washing. For use in organic synthesis, the NP is treated by techniques involving attrition, sifting, calcinations (900 °C), washing, and recalcination. These treatments lead to a fraction between 100 and 400 μm that is rich in phosphate and has following chemical composition P_2O_5 (34.24%), CaO (54.12%), F^- (3.37%), SiO_2 (2.42%), SO_3 (2.21%), CO_2 (1.13%), Na_2O (0.92%), MgO (0.68%), Al_2O_3 (0.46%), Fe_2O_3 (0.36%), K_2O (0.04%) and several metals (Zn, Cu, Cd, V, U, Cr) in the range of ppm. The structure of the material is similar to that of fluoroapatite ($Ca_{10}(PO_4)_6F_2$). In sedimentary rocks, phosphates are formed from compounds derived from apatite by partial isomorphic substitution: Ca^{2+}ions by Na^+, Mg^{2+}, Co^{2+}, Fe^{3+}, or Al^{3+}, PO_4^{3-} ions by VO_4^{3-}, SO_4^{2-}, CO_3^{2-} or MnO^{4-}, and F^- by ^-OH or Cl^-. These different substitutions cause distortions of the structure which depends on the nature and the radii of the ions involved. This solid presented a very low surface area (BET) at ca. 1 $m^2\ g^{-1}$.

KF/NP has been prepared by adding 8 g of NP to a 1 g KF aqueous solution. The mixture was stirred, evaporated to dryness and dried at 150 °C for 2 h. The catalyst KF/NP (weight report KF/NP: 1:8)[20c,d] is a grey powder, the colour of NP itself. The IR data shows the presence of some additional H-bonded water at 3250 cm^{-1} and 1636–1675 cm^{-1} for the supported solid. On the other hand, the X-ray diffraction of KF/NP gives a diffraction pattern almost identical to that of NP itself. Peak positions and intensities are essentially unaltered. We showed previously[20] that supporting KF on NP causes the formation of a more open structure which incorporates KF in such a way that crystalline KF is not formed in significant quantities. However, it appears that the basic structure of NP is not destroyed, indicating a less profound interaction of KF with NP than is the case with alumina.[22] The morphology of the solid surface was observed in scanning electron micrograph (SEM) images of KF/NP in comparison with NP. It clearly appears that some modifications have taken place at the surface of the catalyst.

3. Results and discussion

The results for a variety of α,β-unsaturated arylsulfones prepared by Knœvenagel condensation catalyzed by NP alone and doped with KF are summarized in Table 1.

Table 1. Synthesis of products **3** by Knœvenagel condensation using NP and KF/NP

Products	R	Solvent	Yield, % (time, h)[a]	
			NP (5 h)	KF/NP (1 h)
3a	H	MeOH	56	64
3a	H	EtOH	58	60
3a	H	MeOH[b]	60	68
3a	H	EtOH[b]	68	77
3b	NO_2	EtOH	72	82
3b	NO_2	EtOH[b]	87	95
3c	Cl	EtOH	66	75
3c	Cl	EtOH[b]	80	88
3d	Me	EtOH	50	60
3d	Me	EtOH[b]	64	76
3e	OMe	EtOH	46	58
3e	OMe	EtOH[b]	60	70

[a] Yields of pure products isolated by distillation under vacuum and identified by ^1H, ^{13}C NMR, mass spectroscopy and IR spectroscopy.
[b] The solvent/water ratio is 90:10.

In general, the use of NP as heterogeneous catalyst in the Knœvenagel condensation has allowed the isolation of α,β-unsaturated arylsulfones in moderates yields (Table 1). The reactions are relatively slow. Only the isomer of configuration *E* has been isolated.[18]

Solid catalysts become particularly interesting when they can be regenerated. Indeed, in our case, NP was recovered quantitatively by simple filtration and regenerated by calcination for 15 min at 700 °C. The recovered catalyst was reused several times without loss of activity, even after the sixth, cycle product **3a** was obtained in the same yield.

Under similar conditions, the use of NP doped with KF, decreases remarkably the Knoevenagel reaction time (Table 1).

The addition of water slightly increases the reaction yields of the α,β-unsaturated arylsulfones **3** with either catalyst (NP and KF doped NP). For example, the yield of alkene **3a** increases from 64 to 68% in methanol and from 64 to 77% in ethanol when using KF/NP as a catalyst. Various quantities of water have been used. Figure 1 shows that the best results are obtained when 10% of water is added. This activation is probably due to the interaction between water and the solid surface. If a large amount of water is used a thin film of water will be formed between the organic reagents and catalyst which explain the decreasing of the yields (Fig. 1).

The best conditions for synthesizing the alkene **3a** are generalized to **3b**, **3c**, **3d** and **3e** (Table 1).

We clearly show that water increases the catalytic activity of both NP alone and with KF/NP, in all cases. For example, for the alkene **3b**, the yield increases from 72 to 87% and from 82 to 95% for the two catalysts NP alone and KF/NP, respectively. However, under similar conditions, the best catalytic activity was observed with the NP doped by KF (Table 1).

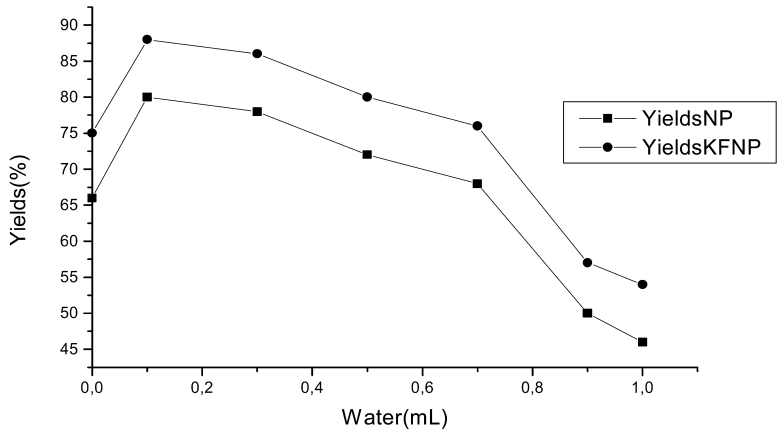

Figure 1. Influence of water in the synthesis of **3a**.

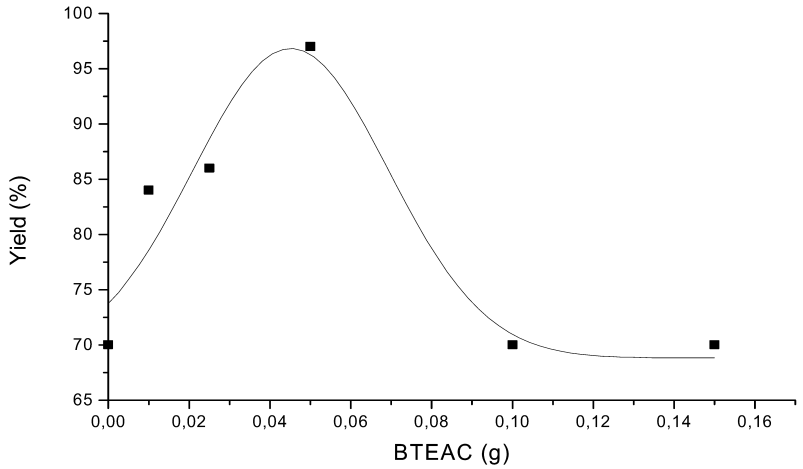

Figure 2. Influence of BTEAC in the synthesis of **3b** (KF/NP catalyst).

It has been shown previously that the addition of an ammonium salt to natural phosphate,[23] fluorapatite,[24] or hydroxyapatite[25] increases the activity of these catalysts. Therefore, we carried out the synthesis of the α,β-unsaturated arylsulfone **3b** with KF/NP in ethanol using different amounts of benzyltriethylammonium chloride (BTEAC). The results obtained after 40 min show that the best yields are obtained with 0.050 g of BTEAC (Fig. 2). Moreover, the kinetic curves for the synthesis of the alkene **3b** in the absence and in the presence of BTEAC clearly show the enhancement of the catalytic activity of KF/NP by addition of the ammonium salt. The yields obtained after 10, 20, 30 and 40 min are 47, 75, 86, and 97% in the presence of BTEAC and 20, 39, 52, and 68% without BTEAC.

Finally, this method was extended to the preparation of several α,β-unsaturated arylsulfones (Table 2). In all cases, the reaction afforded product **3** in high yields. The addition of BTEAC caused a significant increase in the reaction rate (Table 2). Similar effects were observed in the presence of NP alone catalyst (Table 2). It is important to note that BTEAC itself has no catalytic activity and seems to act only as a phase transfer catalyst.

The effect of electron acceptor or donor substituents on the aromatic ring of benzaldehyde in the Knœvenagel condensation was carried out in the reaction of phenylsulfonylacetonitrile **2** and substituted benzaldehyde derivatives (**1a–e**) using NP and KF/NP as catalysts. Results from Tables 1 and 2 show that the presence of electron acceptor groups on the aromatic ring increases the reaction rate proportionally to the value of the Hammet constant. Meanwhile, the presence of electron donor groups decreases the reaction rate, demonstrating the participation of the aldehyde in the controlling step of the reaction.

Table 2. Synthesis of products **3** by Knœvenagel condensation using NP and KF/NP, in the presence and in the absence of BTEAC

Entry	Products	R	Solvent	Yield, % (time, h)[a]	
				NP	KF/NP
1	**3a**	H	EtOH	58 (5)	60 (1)
2	**3a**	H	EtOH[b]	75 (5)	73 (0.8)/91 (1)
3	**3b**	NO_2	EtOH	72 (5)	68 (0.6)/82 (1)
4	**3b**	NO_2	EtOH[b]	85 (3)/94 (4)	86 (0.5)/97 (0.6)
5	**3c**	Cl	EtOH	66 (5)	75 (1)
6	**3c**	Cl	EtOH[b]	86 (4)/93 (5)	77 (0.6)/97 (1)
7	**3d**	Me	EtOH	50 (5)	60 (1)
8	**3d**	Me	EtOH[b]	73 (5)	86 (1)
9	**3e**	OMe	EtOH	46 (5)	58 (1)
10	**3e**	OMe	EtOH[b]	70 (5)	92 (1)

[a] Yields of pure products isolated by distillation under vacuum and identified by ^{1}H, ^{13}C NMR, mass spectroscopy and IR spectroscopy.
[b] BTEAC 0.05 g.

Thus, we estimate that the surface of the catalyst (NP or KF/NP) presents multicatalytic active sites. The basic sites polarize the C–H bond of the active methylene compound. The acidic surface of NP[26] probably coordinates with the oxygen of the carbonyl carbon on which a partial positive charge appears. Consequently, the C–C bond formation is facilitated and the final alkene is obtained by the transfer of a proton followed by dehydration.

The activity of KF/NP/BTEAC seems to be higher than other known catalysts (entry 2–11; Table 3) and slightly lower than ALPON[27] (atomic ratio Al:P:N=1:0.95:0.42; entry 12; Table 3).

Table 3. Comparison of KF/NP/BTEAC with several heterogeneous catalysts in the synthesis of product **3a** by Knœvenagel condensation

Entry	Solid catalyst	Yields (time) [(%) (time/h)] **3a**
1	KF/NP/ BTEAC	91 (1)
2	KF/NP/Water	77 (1)
3	KF/NP	60 (1)
4	NP/ BTEAC	75 (5)
5	NP/water	68 (5)
6	NP	58 (5)
7	$Na_2CaP_2O_7$[18]	58 (1)
8	$Na_2CaP_2O_7$/water[18]	74 (1)
9	Zeolite–CsX[25]	35 (2)
10	MgO[27]	86 (2)
11	Mg–Al-hydrotalcite[27]	71 (2)
12	ALPON[27]	95 (2)[a]

[a] Atomic ratio Al:P:N=1:0.95:0.42.

4. Conclusion

Natural phosphate doped with potassium fluoride is an efficient basic catalyst for the Knoevenagel reaction. Several α,β-unsaturated arylsulfones can be synthesis with high yields using catalytic amounts of KF/NP. This catalyst bring advantages such as high catalytic activity under very mild liquid phase conditions, easy separation of the catalyst by simple filtration, possible recycling of the catalyst, use of non-toxic and inexpensive catalyst and especially, elimination of salts and by-product pollutants. This solid base catalyst then becomes a practical alternative to soluble bases. The addition of an ammonium salt increases the reaction rate for all α,β-unsaturated arylsulfones synthesized and the products were obtained in high yields.

5. Experimental

5.1. General comments

^1H and ^{13}C NMR spectra were recorder at 400 and 100 MHZ, respectively, on a Bruker DRX-400 spectrometer in $CDCl_3$, using $CDCl_3$ as internal standard. The chemical shifts (δ) are expressed in ppm relative to $CDCl_3$ and coupling constant (J) in Hertz. Mass spectra were obtained on VG ZAB-HS mass spectrometer. IR spectra were obtained on a FTIR (ATI Mattson-Genesis Series) and reported in wave numbers (cm^{-1}). Surface area and pore size analysis were carried out at 77 K on a Micromeritics ASAP2010 instrument using nitrogen as adsorbent. X-ray diffraction patterns of the catalysts were obtained on a Philips 1710 diffractometer using Cu K_α radiation and SEM images were taken on a Hitac hi S-2400 microscope. Melting points were determined with a 'Thomas Hoover' melting (capillary method) apparatus and are uncorrected. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM).

All reactions were carried out under atmosphere air. Solvents and starting materials (Aldrich) were used without further purification. The natural phosphate alone and doped by potassium fluoride were prepared according to the method we described previously.[20]

5.2. General procedure for the syntheses of α,β-unsaturated arylsulfones (3a–e)

To a flask containing an equimolar mixture (1 mmol) of aldehyde **1** and phenylsulfonylacetonitrile **2** in solvent (methanol or ethanol: 1 ml), phosphate catalyst (NP or KF/NP) 0.1 g was added and the mixture was stirred at room temperature for a specified time (Tables 1 and 2). The reaction mixture was filtered and the catalyst washed with dichloromethane. After concentration of the filtrate under reduced pressure the residue was subjected to chromatography or distillation under vacuum leading to the α,β-unsaturated sulfone as a solid. The product structure was analysed by ^1H, ^{13}C NMR, mass spectroscopy and IR spectrometry.

The same procedure was used for the reactions carried out with NP or KF/NP (0.1 g) activated with water (0.1 ml) or BTEAC (0.050 g). Water or BTEAC were always added in the last place. In the case of BTEAC, the products were washed with water to eliminate the ammonium salt before purification.

5.3. Identifications of products

5.3.1. α-Phenylsulfonyl cinnamonitrile, 3a. White solid; mp 130–132 °C; R_f (20% AcOEt/hexane) 0.46; ν_{max} (KBr) 3031, 2218, 1578 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.24 (1H, s, =C*H*); 8.03 (2H, d, J=8.4 Hz, *H*Ar); 7.92 (2H, d, J=8.8 Hz, *H*Ar); 7.74–7.70 (1H, m, *H*Ar); 7.64–7.57 (3H, m, *H*Ar); 7.50 (2H, t, J=8.0 Hz, *H*Ar); δ_C (100 MHz $CDCl_3$) 151.5, 137.8, 134.6, 134.1, 131.0, 130.1, 129.7, 129.5, 128.7, 114.8, 113.1; *m/z* (EI): 271 (M^{2+}, 5), 269 (63, M^+), 128 (100), 101 (10), 77 (100), 51 (36%); HRMS (EI): M^+, found 269.0513. $C_{15}H_{11}NO_2S$ requires 269.0511.

5.3.2. α-Phenylsulfonyl 4-nitrocinnamonitrile, 3b. White solid; mp 140–142 °C; R_f (20% AcOEt/hexane) 0.37; ν_{max} (KBr) 3113, 2218, 1596 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.34 (2H, d, J=8.8 Hz, *H*Ar); 8.30 (1H, s, =C*H*Ar); 8.08 (2H, d, J=8.8 Hz, *H*Ar); 8.04 (2H, d, J=7.6 Hz, *H*Ar); 7.77 (1H, t, J=7.6 Hz, *H*Ar). δ_C (100 MHz $CDCl_3$) 151.0, 148.0, 137.4, 136.0, 135.2, 131.5, 129.9, 129.0, 124.5, 115.5, 112.3; *m/z* (EI): 314 (13, M^+), 181 (5), 141 (53), 77 (100), 51 (22), 40 (36%); HRMS (EI): M^+, found 314.0367. $C_{15}H_{10}N_2O_4S$ requires 314.0361.

5.3.3. α-Phenylsulfonyl 4-chlorocinnamonitrile, 3c. White solid; mp 152–154°C; R_f (20% AcOEt/hexane) 0.51; ν_{max} (KBr) 3031, 2227, 1596 cm^{-1}; δ_H (400 MHz

$CDCl_3$) 8.18 (1H, s, =C*H*Ar); 8.02 (2H, d, *J*=8.8 Hz, *H*Ar); 7.87 (2H, d, *J*=8.8 Hz, *H*Ar); 7.75–7.71 (1H, m, *H*Ar); 7.65–7.60 (2H, m, *H*Ar); 7.51–7.46 (2H, m, *H*Ar); δ_C (100 MHz $CDCl_3$) 149.9, 140.5, 137.6, 134.8, 132.1, 129.9, 129.5, 128.7, 128.5, 115.2, 112.9; *m/z* (EI): 305 (30, M^{2+}), 303 (57, M^+), 162 (100), 126 (28), 77 (56), 51 (54), 40 (53); HRMS (EI): M^+, found 303.0128. $C_{15}H_{10}ClNO_2S$ requires 303.0121.

5.3.4. α-Phenylsulfonyl 4-methylcinnamonitrile, 3d. White solid; mp 144–146 °C; R_f (20% AcOEt/hexane) 0.47; ν_{max} (KBr) 3031, 2227, 1596 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.20–7.20 (m, 9H, Ar*H* and 1H, *H*C=C); 2.4 (s, 3H, CH_3); δ_C (100 MHz $CDCl_3$) 159.0, 139.9, 138.2, 135.2, 132.4, 131.3, 131.2, 129.3, 129.2, 114.9, 99.1, 21.5; *m/z* (EI): 285 (20, M^{2+}), 283 (100, M^+), 142 (29), 115 (27), 77 (100); HRMS (EI): M^+, found 283.0669. $C_{16}H_{13}NO_2S$ requires 283.0667.

5.3.5. α-Phenylsulfonyl 4-methoxycinnamonitrile, 3e. White solid; mp 113–115 °C; R_f (20% AcOEt/hexane) 0.23; ν_{max} (KBr) 3022, 2218, 1589 cm^{-1}; δ_H (400 MHz $CDCl_3$) 8.14 (1H, s, =C*H*Ar); 8.01 (2H, d, *J*=7.6 Hz, *H*Ar); 7.92 (2H, d, *J*=8.8 Hz, *H*Ar); 7.69 (1H, t, *J*=7.6 Hz, *H*Ar); 7.60 (2H, t, *J*=7.6 Hz, *H*Ar); 6.98 (2H, d, *J*=8.8 Hz, *H*Ar); 3.89 (3H, s, OCH_3); δ_C (100 MHz $CDCl_3$) 164.5, 151.0, 138.5, 134.3, 133.7, 129.6, 128.4, 122.9, 115.0, 113.7, 110.9, 55.7; *m/z* (EI): 301 (10, M^{2+}), 299 (44, M^+), 157 (100), 77 (33), 51 (10), 40 (16); HRMS (EI): M^+, found 299.0621. $C_{16}H_{13}NO_3S$ requires 299.0616.

References and notes

1. (a) Hattori, H. *Stud. Surf. Sci. Catal.* **1993**, *78*, 35. (b) Hattori, H. *Chem. Rev.* **1995**, *95*, 527. (c) Ono, Y.; Baba, T. *Catal. Today* **1997**, *38*, 321. (d) Bennazha, J.; Zahouily, M.; Sebti, S.; Boukhari, A.; Holt, E. M. *Catal. Commun.* **2001**, *2*, 101. (e) Zahouily, M.; Abrouki, Y.; Rayadh, A. *Tetrahedron Lett.* **2002**, *43*, 7729. (f) Zahouily, M.; Abrouki, Y.; Rayadh, A.; Sebti, S.; Dhimane, H.; David, M. *Tetrahedron Lett.* **2003**, *44*, 2463. (g) Bennazha, J.; Zahouily, M.; Boukhari, A.; Holt, E. M. *J. Mol. Catal. A: Chem.* **2003**, *202*, 247.
2. (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. (b) Trost, B. M. *Bull. Chem. Soc. Jpn* **1988**, *61*, 107. (c) Orita, A.; Yoshioka, N.; Oteru, J. *Chem. Lett.* **1997**, 1023.
3. Zhang, Z.; Liu, G. J.; Wang, Y. L.; wang, W. *Synth. Commun.* **1989**, *19*, 1167.
4. Trost, B. M.; Schmuff, N. R.; Miller, J. *J. Am. Chem. Soc.* **1980**, *102*, 5979.
5. Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 743.
6. (a) Orita, A.; Watanabe, A.; Otera, J. *Chem. Lett.* **1997**, 1025. (b) Patel, P. P.; Welker, M. E.; Liable-Sands, L. M.; Rheingold, A. L. *Organometallics* **1997**, *16*, 4519. (c) Phillips, A. D.; Warren, E. S.; Whitham, G. H. *Tetrahedron* **1997**, *53*, 307.
7. Jacobs, H. K.; Gopalan, A. S. *J. Org. Chem.* **1994**, *59*, 2014.
8. (a) Blades, K.; Lapotre, D.; Percy, J. M. *Tetrahedron Lett.* **1976**, 5895. (b) Giovannini, R.; Petrini, M. *J. Chem. Soc. Chem. Commun.* **1997**, *19*, 12101.
9. (a) Trost, B. M.; Verhœven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 8116. (b) Trost, B. M.; Verhœven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.
10. Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1007.
11. Olson, G. L.; Cheung, H.-O.; Morgan, K. D.; Neukon, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3287.
12. Villemin, D.; Ben Alloum, A. *Synth. Commun.* **1991**, *21*, 63.
13. Croma, A.; Formés, V.; Martin-Aranda, R. M.; García, H.; Primo, J. *Appl. Catal.* **1990**, *59*, 237.
14. Tanabe, K. In *Catalysis by acids and bases*. Imelik, B., et al.Eds.; Elsevier: Amsterdam, 1985; p 1.
15. (a) Croma, A.; Formés, A. V.; Martin-Aranda, R. M.; Rey, F. *J. Catal.* **1992**, *134*, 58. (b) Croma, A.; Formés, V.; Rey, F. *J. Catal.* **1994**, *148*, 205.
16. Croma, A.; Martin-Aranda, R. M. *J. Catal.* **1991**, *130*, 130.
17. (a) Grange, P.; Bastians, Ph.; Conanec, R.; Marchand, R.; Laurent, Y.; Gandia, L. M.; Montes, M.; Fernandes, J.; Odriozola, J. A. *Stud. Surf. Sci. Catal.* **1994**, *91*, 389. (b) Grange, P.; Bastians, Ph.; Conanec, R.; Marchand, R.; Laurent, Y. *Appl. Catal. A* **1994**, *114*, L191. (c) Massinon, A.; Odriozola, J. A.; Bastians, Ph.; Conanec, R.; Marchand, R.; Laurent, Y.; Grange, P. *Appl. Catal.* **1996**, *137*, 9. (d) Climent, M. J.; Croma, A.; Formés, V.; Fran, A.; Guil-López, R.; Iborra, S.; Primo, J. *J. Catal.* **1996**, *163*, 392.
18. Zahouily, M.; Salah, M.; Bennazha, J.; Rayadh, A.; Sebti, S. *Tetrahedron Lett.* **2003**, *44*, 3255.
19. (a) Sebti, S.; Saber, A.; Rhihil, A. *Tetrahedron Lett.* **1994**, *35*, 9399. (b) Sebti, S.; Rhihil, A.; Saber, A.; Hanafi, N. *Tetrahedron Lett.* **1996**, *37*, 6555. (c) Zahouily, M.; Bahlaouan, B.; Solhy, A.; Sebti, S. *React. Kinet. Catal. Lett.* **2003**, *78*, 129.
20. (a) Lazrek, H. B.; Rochdi, A.; Kabbaj, Y.; Taourirte, M.; Sebti, S. *Synth. Commun.* **1999**, *29*, 1057. (b) Alahiane, A.; Rochdi, A.; Taourirte, M.; Redwane, N.; Sebti, S.; Lazrek, H. B. *Tetrahedron Lett.* **2001**, *42*, 3579. (c) Macquarrie, D. J.; Nazih, R.; Sebti, S. *Green Chem.* **2002**, *4*, 56. (d) Abrouki, Y.; Zahouily, M.; Rayadh, A.; Bahlaouan, B.; Sebti, S. *Tetrahedron Lett.* **2002**, *43*, 8951.
21. Natural phosphate (NP) comes Khouribga region (Morocco). It is readily available (raw or treated) from CERPHOS 37, Bd My Ismail, Casablanca, Morocco.
22. (a) Kabashima, H.; Tsuji, H.; Nakata, S.; Tanaka, Y.; Hattori, H. *Appl. Catal. A: General* **2000**, *194*, 227. (b) Campelo, J. M.; Climent, M. S.; Marinas, J. M. *React. Kinet.-Catal. Lett.* **1992**, *47*, 7. (c) Zhu, J. H.; Xu, Q. H. *Acta Chim. Sinica* **1997**, *55*, 474.
23. Sebti, S.; Saber, A.; Rhihil, A.; Nazih, R.; Tahir, R. *Appl. Catal. A* **2001**, *206*, 217.
24. Sebti, S.; Tahir, R.; Nazih, R.; Saber, A.; Boulajaaj, S. *Appl. Catal. A* **2000**, *197*, L187.
25. Sebti, S.; Tahir, R.; Nazih, R.; Saber, A.; Boulajaaj, S. *Appl. Catal. A* **2002**, *228*, 155.
26. Sebti, S.; Rhihil, A.; Saber, A. *Chem. Lett.* **1996**, *8*, 721.
27. Climent, M. J.; Corma, A.; Guil-Lopez, R.; Iborra, S.; Primo, J. *Catal. Lett.* **1999**, *59*, 33.

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A new short synthesis of coumestrol and its application for the synthesis of [6,6a,11a-$^{13}C_3$]coumestrol

Nawaf Al-Maharik and Nigel P. Botting*

School of Chemistry, University of St Andrews, St Andrews, Fife, KY16 9ST, Scotland, UK

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Abstract—A convenient and simple two-step method for the synthesis of coumestrol has been established, which involves a base catalysed condensation of phenyl acetate with benzoyl chloride, followed by demethylation and subsequent tandem intramolecular cyclisation. This method was then employed for the efficient synthesis of multiply ^{13}C-labelled coumestrol.

1. Introduction

Coumestans represent a fully oxidised version of the flavonoid pterocarpans and share the same systematic numbering.[1] A number of coumestans were isolated from *Pueraria* and *Glycyrrhia*.[2] The most common and the most representative, coumestrol **1** (3,9-dihydroxy-6-benzofuro[3,2-*c*][1]benzopyran-6-one), which is related to the coumarins, was isolated from the roots of *Pueraria lubata* and *mirifica*,[3] roots of soybeans,[4] the whole plants of *Tephrosia purpurea*,[5] *Phaseolus coccineus*[6] and *lunatus*.[7] It is found mainly in red clover sprouts, mature alfalfa (lucerne) and alfalfa sprouts, soybean sprouts, and kudzu leaf. However, only small amounts are present in the human diet.[8] Low-coumestrol varieties of alfalfa and red clover are bred for forage and for commercial extraction of other phytoestrogens. Coumestrol **1** is an estrogen agonist that has been shown to be effective in reducing bone loss in model systems.[9] It has a higher binding affinity for the estrogen receptor than genistein,[10] consistent with the receptor binding model that appears to depend upon the phenolic group in the 4′-position of genistein and in the 12′-position of coumestrol. Its useful biological activities have made it an attractive synthetic target. In order to better understand, quantify and deduce the importance of these biological effects there is a need for the development of stable isotopically labelled coumestrol derivatives. Recently multiply ^{13}C-labelled derivatives of isoflavones, a related class of phytoestrogens which includes daidzein and genistein, have been employed as internal standards for LC–MS[11,12] and GC–MS[13] analysis of these compounds in plants and biological fluids resulting in considerable improvements in both sensitivity and reproducibility. Thus, a similarly ^{13}C-labelled version of coumestrol is a key synthetic target and may also have application in the deduction of the metabolic pathway for coumestrol **1** in mammals.

Three methods for the synthesis of coumestrol **1** have been previously described. The first method involved a condensation of methyl-(2-hydroxy-4-methoxyphenyl) glyoxylate and 2,4-dimethoxybenzyl alcohol, followed by photocyclisation, cyclisation and demethylation.[14] The second synthesis was based on a Pd-catalysed coupling reaction of aryl iodides and phenylacetylene, followed by deprotection and $PdCl_2$ catalysed intramolecular carbonylative cyclisation under an atmosphere of CO.[15] In the third procedure, coumestrol was constructed by an annulation onto the corresponding coumarin, forming the furan ring in the last step.[16–18] However, these methods all proved to be poor yielding, and are not suitable for the synthesis of coumestrol labelled with three ^{13}C atoms as is required for an internal standard for LC–MS and GC–MS analysis.[11–13]

In search of a route for preparation of coumestrol containing three ^{13}C-labelled atoms, a new, facile, short and easy procedure has been established. This has then been employed for the synthesis of coumestrol labelled with three ^{13}C atoms located in positions C-6, C-6a and C-11a.

2. Results and discussion

A retrosynthetic analysis illustrates that coumestrol **1** can be constructed by condensation of a phenyl acetate **2** and a benzoyl chloride **3** to give methyl 2,3-bis(2,4-dimethoxyphenyl)-3-oxopropanoate **4**. Demethylation and subsequent

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* Corresponding author. Tel.: +44-1334-463856; fax: +44-1334-463808; e-mail address: npb@st-andrews.ac.uk

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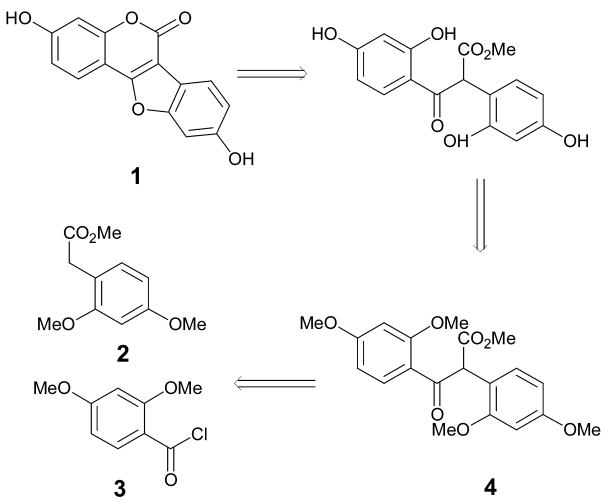
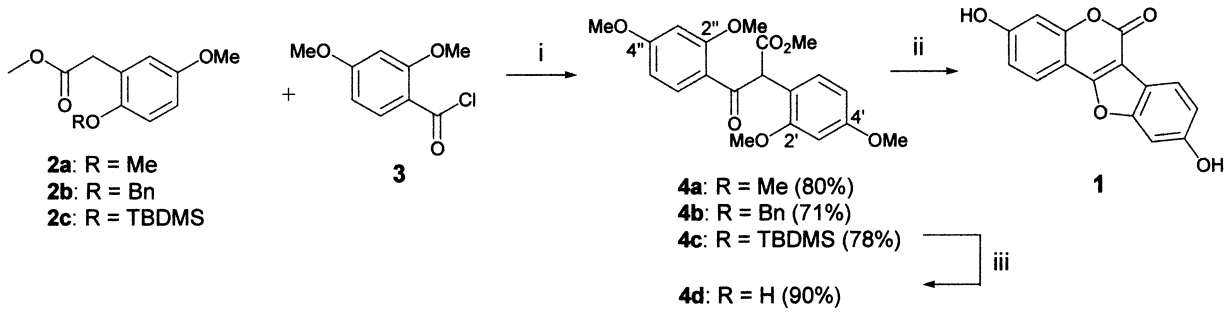


Scheme 1. Retro-synthesis of coumestrol.

C18 Column (150×4.6 mm)) giving a retention time of 8.25 min with a mobile phase of acetonitrile/water (1:1) and a 0.5 mL min^{-1} flow rate.

Treatment of **4b** under the same conditions gave a mixture of compounds, which was shown by ^1H NMR spectroscopy to be a result of only partial removal of the benzyl group. Two steps were required to obtain coumestrol **1** from the silyl protected precursor **4c**. The TBDMS group was first removed with TBAF to give **4d** in 90% yield, which on standard treatment with BBr_3, as for **4a**, gave **1** in almost quantitative yield (Scheme 2).

It was thus clear that use of the two fully methoxylated precursors **2** and **4a** gave the most high-yielding synthesis of coumestrol, superior to any of the previous literature methods. Therefore this procedure was then adapted for the synthesis of [6,6a,11a-$^{13}C_3$]coumestrol **5** starting from



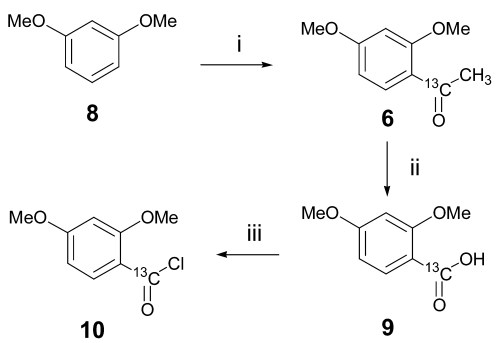
Scheme 2. (i) *n*-BuLi, *i*-Pr_2NH, THF, −78 °C for 2 h then 0 °C for 3 h; (ii) TBAF, THF, 15 min; (iii) 10 equiv. of 1 M BBr_3 in CH_2Cl_2, rt, 72 h (100% from **4a**).

intramolecular cyclisation would then afford coumestrol **1** (Scheme 1). Both the starting materials are amenable to C-labelling as the side chains could be built up using readily available C-labelled precursors, such as [1,2-$^{13}C_2$]acetyl chloride, [1-$^{13}C_1$]acetyl chloride or K^{13}CN.

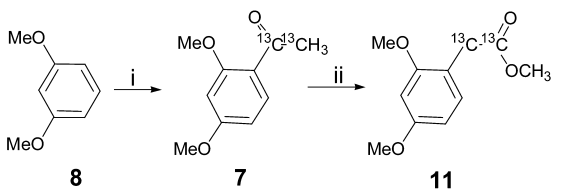
The synthesis of **1** is depicted in Scheme 2, starting from commercially available 2,4-dimethoxybenzoyl chloride **3** and a variety of protected methyl 2-hydroxy-4-methoxyphenyl acetates **2a**–**c**. The conditions for the C-acylation reaction were optimised using three different methyl 2-*O*-substituted 4-methoxyphenylacetates, namely the 2-methoxy **2a**, 2-benzyloxy **2b**, and 2-*tert*-butyldimethylsilyloxy **2c** derivatives, under a range of conditions using dry diethyl ether and dry THF as solvent (Scheme 2). The best results were obtained by reaction of the methyl acetates **2a**–**c** with a slight excess of **3** in the presence of LDA in dry THF at −78 °C and then warming to 0 °C to afford the methyl 2-methoxy-, benzyloxy- and methyl *tert*-butyldimethylsilyloxy 3-oxopropanoates **4a**–**c** in 71–80% yield.

When *O*-demethylation of **4a** was carried out using an excess of BBr_3 in CH_2Cl_2 at room temperature for 72 h a spontaneous tandem intramolecular cyclisation took place as envisaged to afford coumestrol **1** in almost quantitative yield. The product gave identical spectral data to that in the literature. The melting point (360–365 °C (dec)) was a poor indicator of purity due to decomposition of the sample and the wide variation in literature data, encompassing values from 290–293 °C[5] to 385 °C.[16] However, the compound was shown to be pure by reverse phase HPLC (Kingsorb 3μ

2′,4′-dimethoxy[1-$^{13}C_1$]acetophenone **6** and 2′,4′-dimethoxy[1,2-$^{13}C_2$]acetophenone **7**. The two ^{13}C-labelled acetophenones can be readily synthesised from 1,3-dimethoxybenzene **8** through acetylation with commercially available [1-$^{13}C_1$]acetyl chloride or [1,2-$^{13}C_2$]acetyl chloride (Schemes 3 and 4). Firstly, **8** was acetylated with [1-$^{13}C_1$]acetyl chloride using aluminium trichloride in nitroethane to give **6** in 88% yield. Oxidative cleavage of the acetophenone **6** with O_2 using a catalytic amount of $Co(NO_3)_3$ and $Mn(NO_3)_3$ in glacial acetic acid at 110 °C, afforded the 2,4-dimethoxybenzoic[*carboxy*-^{13}C]acid **9** in 75% yield, which on treatment with an excess of oxalyl chloride in CH_2Cl_2 at room temperature resulted in the formation of 2,4-dimethoxy[*carboxy*-^{13}C]benzoyl chloride **10** in 92% yield as indicated by ^1H NMR spectroscopy



Scheme 3. (i) $AlCl_3$, [1-$^{13}C_1$]AcCl, nitroethane, 45 °C, 30 min (88%); (ii) O_2, 0.04 equiv. of $Mn(NO_3)_3$, 0.04 equiv. of $Co(NO_3)_3$, AcOH, 110 °C, 24 h (75%); (iii) 2 equiv. of CO_2Cl_2, a drop of DMF, CH_2Cl_2, rt, 24 h.

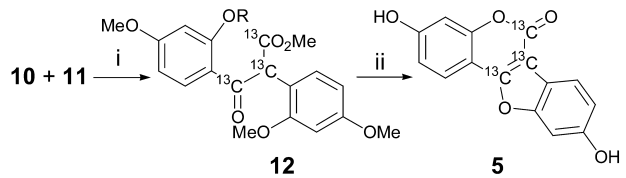


Scheme 4. (i) $AlCl_3$, [1,2-^{13}C]AcCl, nitroethane, 45 °C, 30 min (89%); (ii) TTN, 70% $HClO_4$, MeOH, rt, 2 h (80%).

(Scheme 3). The crude **10** was used in the condensation reaction without further purification.

The other fragment for the condensation reaction, methyl 2′,4′-dimethoxy[1,2-$^{13}C_2$]phenylacetate **11**, was synthesised in 80% yield via oxidative rearrangement of 2′,4′-dimethoxy[1,2-$^{13}C_2$]acetophenone **7** using thallium(III) nitrate (TTN) in MeOH and in presence of 70% $HClO_4$ as reported previously for the unlabelled analogue (Scheme 4).[19]

Condensation between 2,4-dimethoxy[*carboxy*-^{13}C]benzoyl chloride **10** and methyl 2′,4′-dimethoxy[1,2-$^{13}C_2$]-phenylacetate **11**, employing LDA for enolate generation, afforded methyl 2,3-bis(2,4-dimethoxyphenyl)-3-[1,2,3-$^{13}C_3$]oxopropanoate **12** in 83% yield (Scheme 5). Demethylation and subsequent intramolecular cyclisation of **12** using BBr_3 in CH_2Cl_2 resulted in [6,6a,11a-$^{13}C_3$]-coumestrol **5** in almost quantitative yield. The presence of the three ^{13}C-atoms was confirmed by mass spectrometry and by the enhanced signals for C-6,6a and 11a in the ^{13}C NMR spectrum, observed at 157.5, 102.0 and 159.4 ppm, respectively.



Scheme 5. (i) *n*-BuLi, *i*-Pr_2NH, THF, −78 °C for 2 h then 0 °C for 3 h (83%); (ii) 10 equiv. of 1 M BBr_3 in CH_2Cl_2, rt, 72 h (82%).

In conclusion, we have established a simple, two-step, high yielding method for the synthesis of coumestrol **1** from commercially available starting materials. This synthetic route is readily adaptable for the synthesis of different analogues as it is flexible with regard to substitution on both the phenyl acetate and benzoyl chloride. The method has been employed for the synthesis of multiply ^{13}C-labelled coumestrol for use as an internal standard in LC–MS and GC–MS analysis.

3. Experimental

3.1. General

Melting points were determined in open capillary tubes with an electrothermal apparatus and are uncorrected. THF was freshly distilled from sodium/benzophenone. For ^{1}H NMR (300 MHz) spectra the residual peak of $CHCl_3$ (7.26 ppm) and CH_3SOCH_3 (2.59 ppm) were used as internal reference, while for ^{13}C NMR (75 MHz) spectra the central peak of $CDCl_3$ (77.0 ppm) and that of CD_3SOCD_3 (39.95 ppm) were used as reference. Chemical shifts are given in δ and J values in Hz. Peak assignments were performed for the new compounds with the aid of the 2D COSY, GHSQCTOCSY and GHMBC spectra. Mass spectra were recorded at 70 eV. HRMS were recorded on a Finnigan VG AutoSpec instrument. The *O*-substituted methyl 2-hydroxy-4-methoxyphenyl acetates **2a**,[19] **2b**[20] and **2c**[20] were synthesized according to literature procedures.

3.1.1. Methyl 2,3-bis(2,4-dimethoxyphenyl)-3-oxopropanoate (4a). Under an Ar atmosphere, a solution of the acetate **2a** (1.00 g, 4.76 mmol) in dry THF (5 mL) was slowly added at −78 °C to a solution of LDA in THF (20 mL), prepared from diisopropylamine (0.53 g, 0.734 mL, 5.24 mmol) and *n*-BuLi (2.5 M in hexane, 0.21 mL, 5.24 mmol) at 0 °C. The light yellow solution was stirred for 30 min at −78 °C, and then transferred via cannula to a solution of 2,4-dimethoxybenzoyl chloride **3** (1.146 g, 5.71 mmol) in THF (5 mL) at −78 °C. The solution was stirred for 2 h at −78 °C, and then was allowed to warm to 0 °C. After 2 h stirring, the solution was poured into 2% aqueous HCl (20 mL), and extracted with ethyl acetate (3×50 mL). The combined extracts were washed with water (50 mL), dried over $MgSO_4$, and solvent was removed at reduced pressure. The resulting orange viscous oil was subjected to flash chromatography on silica (CH_2Cl_2/EtOAc 97:3) to give title compound **4a** (1.43 g, 80%) as a light yellow solid: mp 107–108 °C; ν_{max} (nujol)/cm^{-1} 1743 (CO_2Me), 1654 (C=O), 1597; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.73 (s, 3H, OCH_3), 3.78 (s, 9H, OCH_3), 3.83 (s, 3H, OCH_3), 5.95 (s, 1H, H-2), 6.37 (d, J=2.4 Hz, 1H, H-3″), 6.43 (dd, J=8.7, 2.4 Hz, 1H, H-5′), 6.43 (d, J=2.4 Hz, 1H, H-3′), 6.52 (dd, J=8.7, 2.4 Hz, 1H, H-5″), 7.04 (d, J=8.7 Hz, 1H, H-6′), 7.91 (d, J=8.7 Hz, 1H, H-6″); ^{13}C NMR ($CDCl_3$, 75 MHz): 52.2 (CO_2CH_3), 55.2 (OCH_3), 55.3 (OCH_3), 55.5 (2×OCH_3), 57.2 (C-2), 98.1 (C-3″), 98.6 (C-3′), 104.2 (C-5′), 105.5 (C-5″), 115.7 (C-1′), 119.7 (C-1″), 130.3 (C-6′), 133.59 (C-6″), 157.8 (C-2′), 160.3 (C-4′), 160.6 (C-4″), 164.8 (C-2″), 170.8 (C-1), 193.0 (C-3); m/z (EI) 374.1361 (M^+, requires 374.1365), 374 (5) and 165 (100); Anal. calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 63.99; H, 5.75.

3.1.2. Methyl 2-(2-benzyloxy-4-methoxyphenyl)-3-(2,4-dimethoxyphenyl)-3-oxopropanoate (4b). Reaction of methyl 2-benzyloxy-4-methoxyphenyl acetate **2b** (0.28 g, 0.97 mmol) sequentially with LDA (1.07 mmol) and **3** (0.214 g, 1.07 mmol), as described for the preparation of **4a**, afforded the title compound **4b** (0.31 g, 71%) as a colorless waxy solid: mp 59–60 °C; ν_{max} (nujol)/cm^{-1} 1734 (CO_2Me), 1664 (C=O), 1604, 834, 737; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.03 (s, 2H, $OCH_2C_6H_5$), 6.08 (s, 1H, C-2), 6.35 (d, J=2.4 Hz, 1H, H-3″), 6.47 (dd, J=8.7, 2.4 Hz, 1H, H-5′), 6.49 (dd, J=8.7, 2.4 Hz, 1H, H-5″), 6.52 (d, J=2.4 Hz, 1H, H-3′), 7.10 (d, J=8.7 Hz, 1H, H-6′), 7.28–7.34 (m, 5H, C_6H_5), 7.87 (d, J=8.7, 2.4 Hz, 1H, H-6″); ^{13}C NMR ($CDCl_3$, 75 MHz): 52.2 (CO_2CH_3), 55.2 (OCH_3), 55.3 (OCH_3), 55.5 (OCH_3), 57.2 (C-2), 70.1 $OCH_2C_6H_5$), 98.2 (C-3″), 99.8 (C-3′), 104.6 (C-5′), 105.5 (C-5″), 116.2 (C-1′), 119.9 (C-1″), 126.9,

127.7, 128.4, 130.3 (C-6′), 133.6 (C-6″), 136.8, 156.9 (C-2′), 160.2 (C-4′), 160.6 (C-4″), 164.7 (C-2″), 170.8 (C-1), 193.1 (C-3); *m/z* (CI$^+$) 451 (M$^+$, 100%), 361 (10), 165 (16); Anal. calcd for $C_{26}H_{26}O_7$: C, 69.32; H, 5.82. Found: C, 68.87; H, 6.13.

3.1.3. Methyl 2-(2-*t*-butyldimethylsilyloxy-4-methoxyphenyl)-3-(2,4-dimethoxyphenyl)-3-oxopropanoate (4c). Reaction of methyl 2-*t*-butyldimethylsilyloxy-4-methoxyphenyl acetate **2c** (0.30 g, 0.968 mmol) sequentially with LDA (1.07 mmol) and **3** (0.214 g, 1.07 mmol), as described for the preparation of **4a**, afforded the title compound **4c** (0.37 g, 78%) as a light yellow wax: ν_{max} (nujol)/cm^{-1} 1736 (CO_2Me), 1670 (C═O), 1600; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.20 (s, 6H, 2×SiCH_3), 0.94 (s, 9H, Si-Bu-*t*), 3.71 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.94 (s, 1H, H-2), 6.37 (d, *J*=2.4 Hz, 1H, H-3″), 6.39 (d, *J*=2.4 Hz, 1H, H-3′), 6.47 (dd, *J*=8.7, 2.4 Hz, 1H, H-5′), 6.52 (dd, *J*=8.7, 2.4 Hz, 1H, H-5″), 7.06 (d, *J*=8.7 Hz, 1H, H-6′), 7.93 (d, *J*=8.7 Hz, 1H, H-6″); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.5 (Si*C*H$_3$), −4.0 (Si*C*H$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 25.6 (SiC(*C*H$_3$)$_3$), 52.1 (CO_2*C*H$_3$), 55.16 (OCH_3), 55.21 (OCH_3), 55.5 (OCH_3), 57.4 (C-2), 98.1 (C-3″), 105.2 (C-3′), 105.5 (C-5″), 105.6 (C-5′), 117.9 (C-1′), 119.7 (C-1″), 130.5 (C-6′), 133.7 (C-6″), 154.1 (C-2′), 159.7 (C-4′), 160.7 (C-4″), 164.9 (C-2″), 170.8 (C-1), 192.7 (C-3); *m/z* (EI) 475.2165 (M$^+$, $C_{25}H_{35}O_7Si$ requires 475.2152), 475 (2), 385 (6) and 165 (100).

3.1.4. Methyl 2-(2-hydroxy-4-methoxyphenyl)-3-(2,4-dimethoxyphenyl)-3-oxopropanoate (4d). Under a N_2-atmosphere, a solution of TBAF (1 M in THF, 3.76 mL, 3.75 mmol) was added to a solution of **4c** (0.80 g, 1.69 mmol) in THF (7 mL) at room temperature. After 15 min, the green solution was poured into water (20 mL), and extracted with ethyl acetate (3×30 mL). The combined extracts were dried over $MgSO_4$, and the solvent was evaporated. The residue was subjected to silica gel chromatography (CH_2Cl_2/EtOAc 95:5) to give the title compound **4d** (0.55 g, 90%) as a white solid: mp 55–56 °C; ν_{max} (nujol)/cm^{-1} 3375 (OH), 1735 (CO_2Me), 1654 (C═O), 1598; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.73 (s, 1H, C-2), 6.42 (d, *J*=2.4 Hz, 1H, H-3″), 6.42 (dd, *J*=8.7, 2.4 Hz, 1H, H-5′), 6.52 (d, *J*=2.4 Hz, 1H, H-3′), 6.54 (dd, *J*=8.7, 2.4 Hz, 1H, H-5″), 7.00 (d, *J*=8.7 Hz, 1H, H-6′), 7.83 (d, *J*=8.7 Hz, 1H, H-6″), 8.29 (s, 1H, 2′-OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.8 (COO*C*H$_3$), 55.2 (OCH_3), 55.5 (OCH_3), 55.6 (OCH_3), 61.1 (C-2), 98.3 (C-3″), 103.8 (C-3′), 105.7 (C-5″), 106.8 (C-5′), 113.6 (C-1′), 119.5 (C-1″), 132.7 (C-6′), 133.9 (C-6″), 156.9 (C-2′), 160.6 (C-4″), 161.0 (C-4′), 165.6 (C-2″), 170.7 (C-1), 196.7 (C-3); *m/z* (EI) 360.120822 (M$^+$, $C_{19}H_{20}O_7$ requires 360.120903), 360 (3%), 342 (9) and 165 (100).

3.1.5. Coumestrol (1). An excess of 1 M BBr_3/CH_2Cl_2 (13.34 mL, 13.34 mmol) was added with stirring to a solution of **4a** (0.5 g, 1.34 mmol) in CH_2Cl_2 (5 mL) at room temperature under Ar. The mixture was stirred for 72 h, then water was added and CH_2Cl_2 was evaporated at reduced pressure. The mixture was refluxed for 3 h. After cooling to room temperature the yellow precipitate was filtered, and the filtrate was extracted with EtOAc (3×30 mL), dried over $MgSO_4$. The combined brown solid was purified by silica gel chromatography (CH_2Cl_2/EtOAc 8:2) to give title compound **1** (0.29 g, 82%) as a light yellow solid: mp 360–365 °C (dec); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.99 (d, *J*=2.1 Hz, 1H, H-4), 7.02 (dd, *J*=8.7, 2.1 Hz, 1H, H-2), 7.04 (d, *J*=8.7, 2.1 Hz, 1H, H-8), 7.25 (d, *J*=2.1 Hz, 1H, H-10), 7.78 (d, *J*=8.7 Hz, 1H, H-7), 7.93 (d, *J*=8.7, 2.4 Hz, 1H, H-1), 10.11 (br s, 1H, 9-OH), 10.77 (br s, 1H, 3-OH); ^{13}C NMR ($CDCl_3$, 75 MHz): 98.6 (C-10), 102.0 (C-6a), 103.0 (C-4), 104.1 (C-1a), 113.7 (C-2), 113.9 (C-10), 114.5 (C-7a), 120.6 (C-7), 122.6 (C-1), 154.6 (C-4a), 155.9 (C-9), 156.9 (C-10a), 157.5 (C-6), 159.4 (C-11a), 161.1 (C-3); Anal. calcd for $C_{15}H_8O_5$: C, 67.17; H, 3.01. Found: C, 66.83; H, 2.78.

3.1.6. 2′,4′-Dimethoxy[1,2-$^{13}C_2$]acetophenone (7). Finely powdered anhydrous $AlCl_3$ (1.68 g, 12.6 mmol) was added to a well-stirred solution of 1,3-dimethoxybenzene **8** (2 g, 14.47 mmol) in freshly distilled nitroethane (10 mL) under a N_2-atmosphere. Then [1,2-$^{13}C_2$]acetyl chloride (1 g, 0.905 mL, 12.58 mmol) was slowly added, and the resulting red solution was stirred at 45 °C for 30 min. The mixture was allowed to cool to room temperature, poured into ice water (100 mL), and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed at reduced pressure, and the orange oily residue was purified by column chromatography (silica, CH_2Cl_2/hexane, 4:1) to afford the title compound **7** (2.03 g, 89%) as a white solid: mp 40–41 °C (Lit[21] mp 39–41 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (dd, *J*=128.1, 6.3 Hz, 3H, H-2), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.44 (dd, *J*=2.4, 1.5 Hz, 1H, H-3′), 6.51 (dd, *J*=8.7, 2.4 Hz, 1H, H-5′), 7.82 (dd, *J*=8.7, 4.2 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.8 (d, *J*=168.7 Hz, C-2), 55.4 (OCH_3), 55.5 (OCH_3), 98.2 (d, *J*=10.8 Hz, C-3′), 105.0 (d, *J*=15.3 Hz, C-5′), 120.5 (d, *J*=132.9 Hz, C-1′), 131.8 (s, C-6′), 161.0 (d, *J*=8.7 Hz, C-2′), 164.5 (C-4′), 197.7 (d, *J*=168.7 Hz, C-1); *m/z* (EI) 182.0852 (M$^+$, $C_8{}^{13}C_2H_{12}O_3$ requires 182.0853), 182 (32%), 166 (100), 151 (6) and 122 (7).

3.1.7. 2′,4′-Dimethoxy[1-$^{13}C_1$]acetophenone (6). The title compound was prepared according to the procedure described for **7**, using [1-$^{13}C_1$]acetyl chloride to give the product as white solid (2.1 g, 88%): 40–41 °C (Lit[21] mp 39–41 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.56 (d, *J*=6.3 Hz, 3H, H-2), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.44 (dd, *J*=2.4, 1.5 Hz, 1H, H-3′), 6.51 (dd, *J*=8.7, 2.4 Hz, 1H, H-5′), 7.82 (dd, *J*=8.7, 3.9 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.8 (d, *J*=169.5 Hz, C-1), 55.4 (OCH_3), 55.5 (OCH_3), 98.2 (C-3′), 105.0 (d, *J*=13.8 Hz, C-5′), 120.5 (d, *J*=132.9 Hz, C-1′), 132.6 (C-6′), 161.0 (d, *J*=8.7 Hz, C-2′), 164.5 (C-4′), 197.7 (C-1); *m/z* (EI) 181.0818 (M$^+$, $C_9{}^{13}C_1H_{12}O_3$ requires 181.0819), 181 (29%), 166 (100), 151 (8) and 122 (6).

3.1.8. 2,4-Dimethoxy[*carboxy*-^{13}C]benzoic acid (9). A solution of the acetophenone **6** (1.0 g, 5.52 mmol), $Mn(NO_3)_3$ (0.064 g, 0.22 mmol), and $Co(NO_3)_3$ (0.064 g, 0.22 mmol) glacial acetic acid (10 mL) was stirred at 110 °C for 24 h under an O_2-atmosphere. The solvent was evaporated at reduced pressure, and the residue was

dissolved in 2 N $NaHCO_3$ (15 mL) at 60 °C, which was extracted with ethyl acetate (3×30 mL). The aqueous solution was acidified with concentrated H_2SO_4, and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting yellow solid was subjected to silica gel chromatography (CH_2Cl_2/EtOAc 97:3) to furnish the title compound **9** (0.76 g, 75%) as a white solid: 105–106 °C (Lit[22] mp 106 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 6.53 (dd, J=2.4, 1.8 Hz, 1H, H-3′), 6.64 (dd, J=9.0, 2.4 Hz, 1H, H-5′), 8.12 (dd, J=9.0, 2.4 Hz, 1H, H-6′), 10.45 (br s, 1H, COOH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.7 (OCH_3), 56.6 (OCH_3), 98.6 (d, J=12.9 Hz, C-3), 106.5 (d, J=17.1 Hz, C-5), 111.3 (d, J=302.1 Hz, C-1), 135.5 (d, J=9.0 Hz, C-6), 159.5 (d, J=8.7 Hz, C-2), 165.1 (C-4), 165.2 (s, COOH); *m/z* (EI) 183.0617 (M^+, $C_8{}^{13}C_1H_{10}O_4$ requires 183.0612), 183 (98%), 166 (100), 154 (26), 136 (58) and 122 (5).

3.1.9. 2,4-Dimethoxy[*carboxy*-^{13}C]benzoyl chloride (10). Oxalyl chloride (1.26 g, 0.86 mL, 9.93 mmol) was added to a solution of the carboxylic acid **9** (0.90 g, 4.92 mmol) in dry CH_2Cl_2 (20 mL) containing a drop of dry DMF under an Ar atmosphere. The solution was stirred at room temperature under light exclusion for 24 h. The solvent was then evaporated at reduced pressure and the yellow orange solid was washed with dry hexane (2×30 mL). Drying in vacuo gave the title compound **10** (0.98 g, 99%) as light yellow solid, which was pure enough (purity ≈90%, as indicated by ^{1}H NMR spectroscopy) to be used in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.46 (t, J=2.4 Hz, 1H, H-3), 6.55 (dd, J=9.0, 2.4 Hz, 1H, H-5), 8.16 (dd, J=9.0, 6.6 Hz, 1H, H-6).

3.1.10. Methyl 2′,4′-dimethoxy[1,2-$^{13}C_2$]phenyl acetate (11). A solution of the acetophenone **7** (1.0 g, 5.49 mmol) in methanol (10 mL) was dropwise added to a well stirred solution of TTN (2.68 g, 6.04 mmol) in methanol (10 mL) containing perchloric acid (5 mL, 70% w/w) under Ar. The reaction mixture was stirred at room temperature for 2 h, and the resulted white precipitate thallium(I) nitrate was removed by filtration and the filtrate was carefully poured into 2 N aq. $NaHCO_3$ (100 mL). The aqueous solution was extracted with CH_2Cl_2 (3×50 mL), washed with brine (2×50 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure, and the orange oily residue was purified by silica gel chromatography (CH_2Cl_2/hexane 4:1) to afford the title compound **11** (0.93 g, 80%) as a light yellow solid: 48–49 °C (Lit[20] mp 50 °C); ν_{max} (nujol)/cm^{-1} 1698 (CO_2Me), 1617, 1590; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.56 (dd, J=129.9, 8.1 Hz, 2H, H-2), 3.68 (d, J=3.9 Hz, 3H, OCH_3), 3.795 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.45 (dd, J=9.0, 2.4 Hz, 1H, H-5′), 6.50 (d, J=2.4 Hz, 1H, H-3′), 7.08 (dd, J=9.0, 2.4 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.0 (d, J=231.5 Hz, C-2), 51.50 (d, J=13.8 Hz, CO_2CH_3), 55.4 (OCH_3), 55.5 (OCH_3), 98.7 (d, J=9.0 Hz, C-3′), 104.1 (d, J=13.2 Hz, C-5′), 115.4 (dd, J=187.6, 11.7 Hz, C-1′), 131.1 (t, J=9.0 Hz, C-6′), 158.9 (d, J=8.7 Hz, C-2′), 160.2 (C-4′), 172.6 (d, J=231.5 Hz, C-1); *m/z* (EI) 212.0960 (M^+, $C_9{}^{13}C_2H_{14}O_4$ requires 212.0959), 212 (34%), 152 (100) and 122 (26).

3.1.11. Methyl 2,3-bis(2,4-dimethoxyphenyl)-3-[1,2,3-$^{13}C_3$]oxopropanoate (12). Condensation of benzoyl chloride **10** (0.50 g, 2.49 mmol) and ^{13}C-labelled acetate **11** (0.44 g, 2.07 mmol) as described for the preparation of **4a**, afforded the title compound **12** (0.65 g, 83%) as a light yellow solid: mp 106–107 °C; ν_{max} (nujol)/cm^{-1} 1700 (CO_2Me), 1623 (C=O), 1591; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.73 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.77 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 5.95 (ddd, J=133.2, 8.7, 6.3 Hz, 1H, H-2), 6.37 (q, J=2.4 Hz, 1H, H-3″), 6.43 (dd, J=9.0, 2.4 Hz, 1H, H-5′), 6.43 (d, J=2.4 Hz, 1H, H-3′), 6.52 (dd, J=8.7, 2.4 Hz, 1H, H-5″), 7.04 (dd, J=8.7, 4.2 Hz, 1H, H-6), 7.91 (dd, J=8.7, 4.2 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$, 75 MHz): 52.2 (OCH_3), 55.2 (OCH_3), 55.3 (OCH_3), 55.5 (2×OCH_3), 57.2 (dd, J=235.6, 162.5 Hz, H-2), 98.1 (d, J=11.7 Hz, C-3″), 98.6 (d, J=8.7 Hz, C-3′), 104.2 (d, J=13.8 Hz, C-5′), 105.5 (d, J=13.8 Hz, C-5″), 115.7 (C-1′), 119.7 (C-1″), 130.3 (C-6′), 133.6 (C-6″), 157. 8 (C-2′), 160.3 (C-4′), 160.6 (C-4″), 164.8 (C-2″), 170.8 (dd, J=235.5, 8.7 Hz, C-1), 193.0 (dd, J=162.5, 8.7 Hz, C-3); *m/z* (EI) 377.147475 (M^+, $C_{17}{}^{13}C_3H_{22}O_7$ requires 377.146618), 377 (4%), 166 (100); Anal. calcd for $C_{17}{}^{13}C_3H_{20}O_7$: C, 63.47; H, 5.66. Found: C, 63.65; H, 5.89.

3.1.12. [6,6a,11a-$^{13}C_3$]Coumestrol (5). The title compound was prepared according to the procedure described for **1**, using **12** to give the product as white solid (0.283 g, 80%): mp 360–365 °C (dec); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.99–7.06 (m, 3H, H-2,4,8), 7.25 (d, J=2.1 Hz, 1H, H-10), 7.78 (d, J=8.7, 2.7 Hz, 1H, H-7), 7.93 (d, J=8.7, 4.2 Hz, 1H, H-1), 10.11 (br s, 1H, 9-OH), 10.77 (br s, 1H, 3-OH); ^{13}C NMR ($CDCl_3$, 75 MHz): 98.6 (C-10), 102.0 (dd, J=348, 251.7 Hz, C-6a), 103.0 (C-4), 104.1 (C-1a), 113.7 (C-2), 113.9 (C-10), 114.5 (C-7a), 120.6 (C-7), 122.6 (C-1), 154.6 (C-4a), 155.9 (C-9), 156.9 (C-10a), 157.5 (dd, J=348, 22.8 Hz, C-6), 159.4 (dd, J=252, 22.8 Hz, C-6), 161.1 (C-3); *m/z* (EI) 271.047053 (M^+, $C_{12}{}^{13}C_3H_8O_5$ requires 271.047238), 132 (44) and 117 (9).

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References and notes

1. Boland, G. M.; Donnelly, D. M. X. *Nat. Prod. Rep.* **1995**, 321–338.
2. Donnelly, D. M. X.; Boland, G. M. *Nat. Prod. Rep.* **1998**, 241–260.
3. Chansakaow, S.; Ishikawa, T.; Sekine, K.; Okada, M.; Higuchi, Y.; Kudo, M.; Chaichantipyuth, C. *Planta Med.* **2000**, *66*, 572–575.
4. Le-Van, N. G. O. *Phytochemistry* **1984**, *23*, 1204–1205.
5. Chang, L. C.; Gerhaeuser, C.; Song, L.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **1997**, *60*, 869–873.
6. O'Neill, M. J.; Adesanya, S. A.; Roberts, M. F. *Phytochemistry* **1984**, *23*, 2704–2705.

7. O'Neill, M.; Adesanya, S. A.; Roberts, M. F.; Pantry, I. R. *Phytochemistry* **1986**, *25*, 1315–1322.
8. Reinli, K.; Block, G. *Nutr. Cancer* **1996**, *26*, 123–148.
9. Draper, C. R.; Edel, M. J.; Dick, I. M.; Randall, A. G.; Martin, G. B.; Prince, R. L. *J. Nutr.* **1997**, *127*, 1795–1799.
10. Shemesh, M.; Lindner, H. R.; Ayolan, N. *J. Reprod. Fertil.* **1972**, *29*, 1–9.
11. Clarke, D. B.; Lloyd, A. S.; Oldfield, M. F.; Botting, N. P.; Needs, P. W.; Wiseman, H. *Anal. Chem.* **2002**, *309*, 158–172.
12. Grace, P. B.; Taylor, J. I.; Botting, N. P.; Fryatt, T.; Oldfield, M. F.; Bingham, S. A. *Anal. Biochem.* **2003**, *315*, 114–121.
13. Grace, P. B.; Taylor, J. I.; Botting, N. P.; Fryatt, T.; Oldfield, M. F.; Al-Maharik, N.; Bingham, S. A. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 1350–1357.
14. Kraus, A. G.; Zhang, N. *J. Org. Chem.* **2000**, *65*, 5644–5646.
15. Hiroya, K.; Suzuki, N.; Yasuhara, A.; Yuya, E.; Kasano, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, *24*, 4339–4346.
16. Emerson, O. H.; Bickoff, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 4381–4388.
17. Kawase, Y. *Bull. Chem. Soc. Jpn* **1959**, *32*, 690–696.
18. Jurd, L. *J. Org. Chem.* **1964**, *29*, 3036–3038.
19. Alesso, E. N.; Aguirre, J. M.; Iglesias, G. Y. M. *Org. Prep. Proced. Int.* **1992**, *24*, 690–692.
20. Theunis, G. A.; Rensburg, H.; Ferreira, D. *Tetrahedron* **2001**, *57*, 7113–7126.
21. Moon, M. W.; Wade, R. A. *J. Org. Chem.* **1984**, *49*, 2663–2669.
22. Chakravarti, D.; Saha, M. *J. Indian Chem. Soc.* **1971**, *48*, 209–216.

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Synthesis, electrochemical and intramolecular charge-transfer properties of 'calix[4]arene-acceptor' diad and triad derivatives

Cheng-Chu Zeng and James Y. Becker*

Department of Chemistry, Ben-Gurion University of the Negev, PO Box 653, Beer-Sheva 84105, Israel

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Abstract—Calix[4]arenes substituted with various acceptor moieties (naphthoquinone (NQ), tetracyanoanthraquinodimethane (TCNAQ)) have been synthesized. In these derivatives the three-dimensional structure of calix[4]arene acts as a weak electron donor (D), connected via a linear sigma spacer to one or two electroactive acceptor (A) units. The electrochemical behavior of these derivatives has been studied by cyclic voltammetry. The UV–Vis spectrum of the TCNAQ triad (A–D–A, **13**) reveals the presence of a weak intramolecular charge transfer absorption band.

1. Introduction

Based on Aviram and Ratner's theoretical proposal[1] of molecular systems containing a covalent linkage between electron donor and acceptor units, D–σ–A ('D' represents electron donor and 'A' stands for electron-acceptor), much attention has been paid to the design and synthesis of systems with potential ability for intramolecular charge transfer. The covalent linkage between TTF and TCNQ moieties has proved to be a great challenge due to the difficult synthetic route and problems with purification.[2,3] As an alternative, systems with other acceptor groups, such as quinone,[4] C_{60},[5] pyridinium[6] and viologen[7] cations, have been studied. Recently, Bryce and co-workers[8b] reported the first readily available, analytically pure and stable TTF–σ–TCNAQ and TCNAQ–σ–TTF–σ–TCNAQ derivatives (e.g., **1** in Scheme 1) by attaching TTF (via a sigma spacer) to moderate acceptor (TCNAQ=teteracyanoanthraquinodimethane) moiety. Compared with TCNQ, the weaker acceptor TCNAQ adopts a 'butterfly' conformation which suppresses the rapid formation of intermolecular charge-transfer complexes during the combination reaction of TCNAQ and functionalized TTF derivatives. On the other hand, TCNAQ still has a reasonably high electron affinity.

In order to obtain improved electrically conducting materials, an increase of dimensionality has also proved to be of a priority in TTF and TCNQ chemistry. A promising strategy is to design nonplanar materials,[9] and to use spiro-conjugation.[10] For example, binaphthalene with a dihedral angle ranging from 60 to 120° as a nonplanar spacer (**3** in Scheme 1)[11] and spiro-cycle (**2** in Scheme 1)[12] as a spiro-conjugation were prepared to achieve increased dimensionality.

Calixarenes[13] have attracted widespread interest in recent years due to their unique combination of properties and structure. Their preparation is remarkably simple; they can be readily modified at both lower or upper rim; abound of conformers and well-defined hydrophobic and hydrophilic regions make calixarenes suitable hosts for neutral and ionic species. Tetranitrotetrapropoxycalix[4]arenes with electron-accepting nitro and electron-donating propoxy substituents have been used as supramolecular materials with second-order nonlinear optical properties.[14]

In the present study we report the synthesis, spectral and redox properties of novel TCNAQ diad **9**, and triads **13** (involving TCNAQ) and **16** (involving naphthoquinone, NQ), based on calyx[4]arene scaffold. In these systems, the three-dimensional calix[4]arene framework is used as a weak electron donor (phenol units) functionalized at the lower rim by different number of pendant tails bearing electron-accepting groups (TCNAQ or NQ). The properties of these new compounds have been investigated by cyclic voltammetry and UV–Vis spectroscopy.

2. Results and discussion

2.1. Synthesis and NMR spectroscopy

The synthesis of TCNAQ-containing calix[4]arene derivatives is outlined in Schemes 2 and 3. Calix[4]arene **4** was

Keywords: Calix[4]arene-sigma-acceptor; Tetracyanoanthraquinodimethane; Napthoquinone; Intramolecular charge transfer; Cyclic voltammetry.
* Corresponding author. Tel.: +972-8-6461197; fax: +972-8-6472943; e-mail address: becker@bgumail.bgu.ac.il

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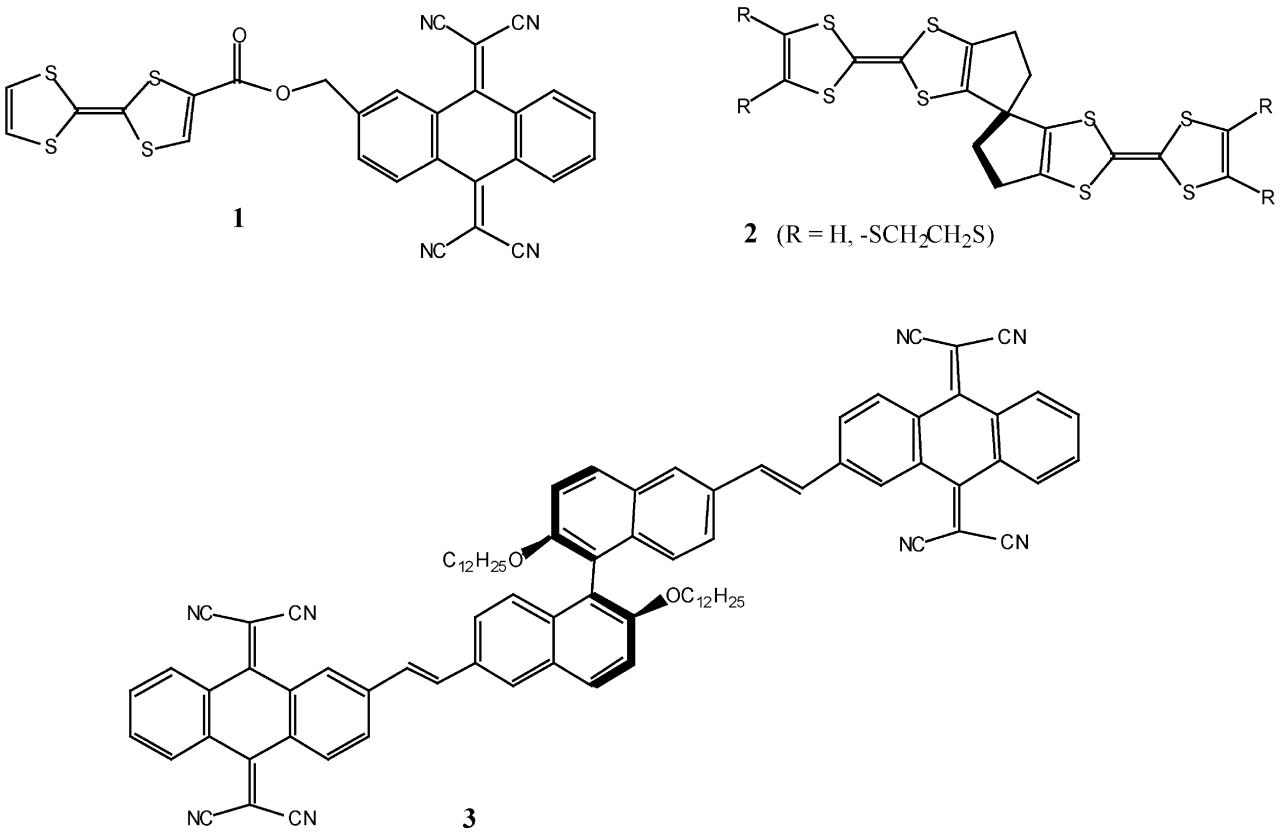
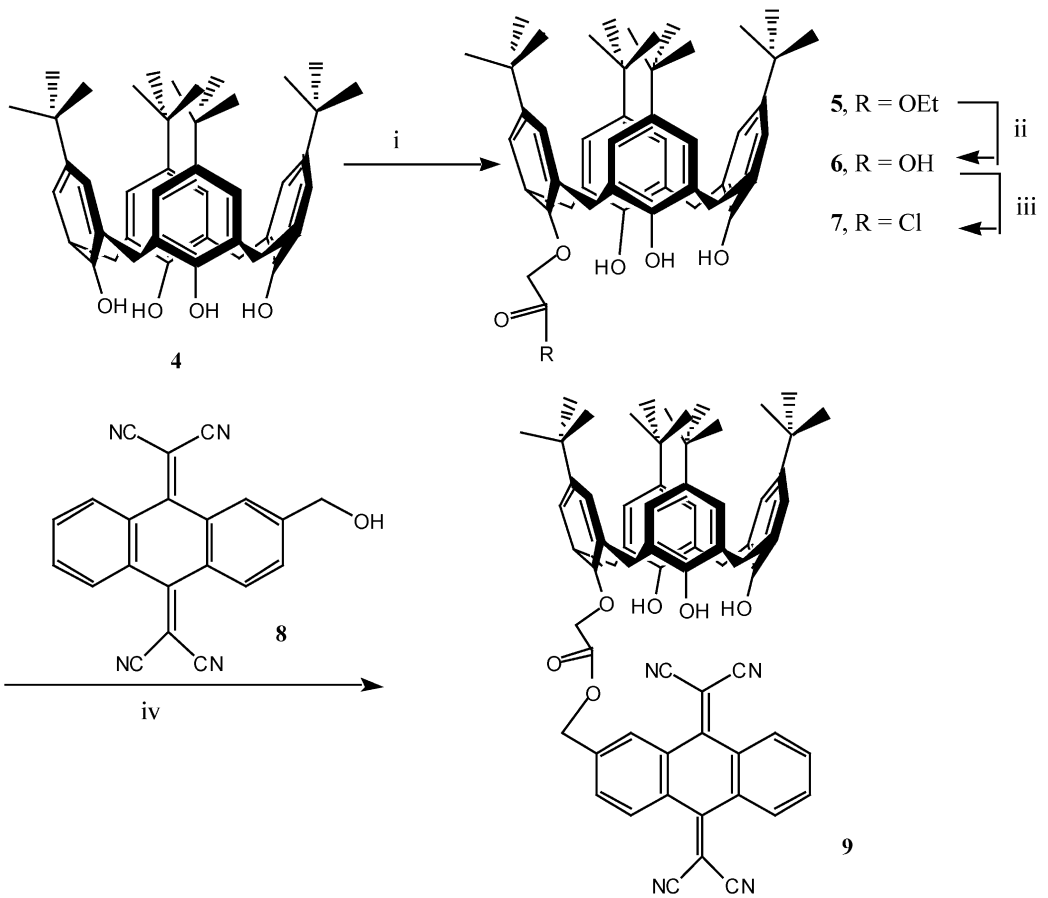
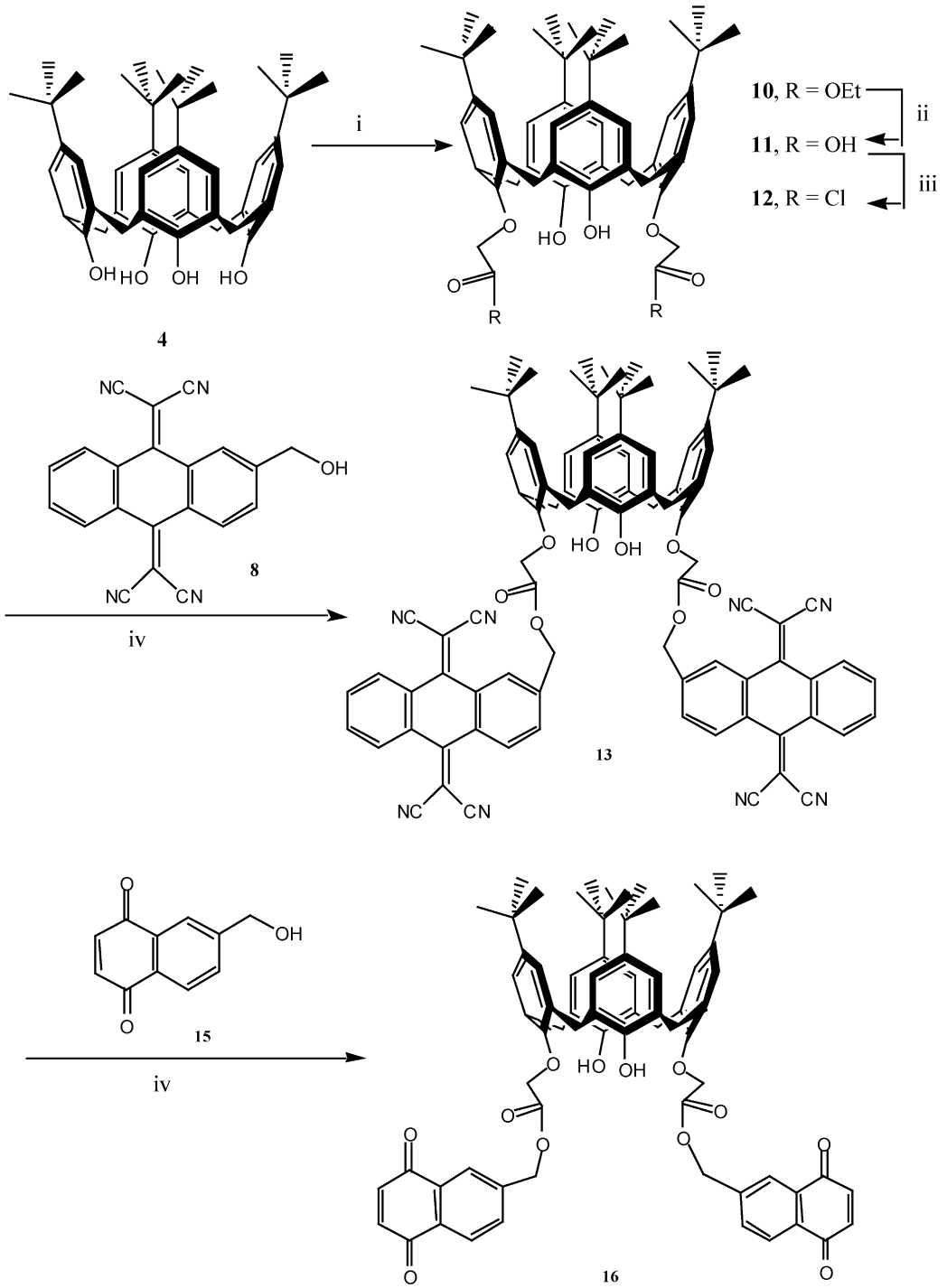


Scheme 1. Selected examples of D–σ–A diads and a D–σ–A–σ–D triad.



Scheme 2. (i) $BrCH_2COOEt/CsF$, DMF (67%); (ii) NaOH, EtOH/water, reflux (54%); (iii) $SOCl_2$, reflux (quant.); (iv) pyridine/CH_2Cl_2, rt (48%).



Scheme 3. (i) $BrCH_2COOEt/K_2CO_3$, CH_3CN, reflux (75%); (ii) NaOH, EtOH/water, reflux (70%); (iii) $SOCl_2$, reflux (quant.); (iv) pyridine/CH_2Cl_2, rt (36 and 48%, respectively).

converted into the corresponding monoacetate **5** and diacetate **10**, respectively, by alkylation with an excess of ethylbromoacetate. The acetates were hydrolyzed to carboxylic acids by refluxing with NaOH in ethanol, followed by acidification with 50% H_2SO_4. Compounds **6** and **11** were subsequently converted to the corresponding acid chlorides **7** and **12**. Condensation with 2-hydroxymethyl-TCNAQ (**8**) in the presence of pyridine, at room temperature, gave the desired TCNAQ diad **9** and triad **13**. Similarly, condensation with hydroxymethyl-NQ (**15**) afforded triad **16**.

Basically, calix[4]arenes exist in four conformers: cone, partial cone, 1,2-alternate and 1,3-alternate. Their structure can be easily distinguished by characteristic ^1H NMR patterns of the $ArCH_2Ar$ methylene protons. For example, cone, partial cone, 1,2-alternate and 1,3-alternate will exhibit a pair of doublets, two pairs of doublets, one singlet and a pair of doublet, and one singlet, respectively.[15] The structure of compounds **9** and **13** were characterized using ^1H and ^{13}C NMR spectroscopy. For triad **13**, the presence of two doublets of the CH_2 bridging groups (at 3.30 and 4.32 ppm) with geminal coupling constants of 13.4 Hz and

Table 1. Oxidation and reduction potentials of calix[4]arenes and related compounds[a]

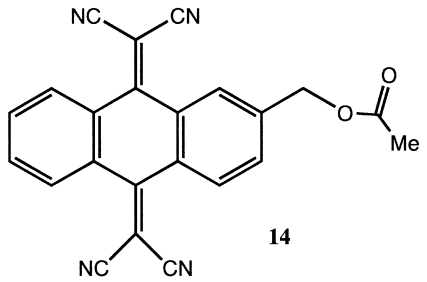
Compound	$-E^{(1)}_{1/2}$	$-E^{(2)}_{1/2}$	E_p(ox)
9	0.34	—	1.52
13	0.33	—	1.39
14	0.34	—	—
10	—	—	1.56
5	—	—	1.57
15	0.70	1.27	—
16	0.69	1.56	1.35

[a] Concentration of substrates: 1 mM; electrolyte: 0.1 M Bu_4NClO_4/CH_2Cl_2; working electrode: glassy carbon; scan rate: 100 mV/s; reference electrode: Ag/AgCl.

31.8 ppm in ^{13}C NMR, is clear evidence for a *cone* conformation.[16] In contrast, the ^1H NMR spectrum of the monoalkylated diad **9** is more complicated and quite different from its precursors **5** or **6**. The chemical shifts of 3.25–3.55 ppm are attributed to four bridging methylene equatorial protons, four doublets with integration of 1:1:1:1 and coupling constants of 13.4, 13.5, 14.3, 13.5 Hz, respectively. This information shows that the four methylene groups are nonequivalent, having different chemical environments. This is also proved by the four carbon signals at 32.78, 32.99, 33.98 and 33.99 ppm observed in the ^{13}C NMR spectrum. On the other hand, the four bridging methylene axial protons exhibit poorly defined signals and there are multiple signals for the methylene protons adjacent to the benzene rings. Dynamic ^1H NMR was also used to confirm the structure. When the temperature increased to 353 K, the bridging methylene axial protons also gave four doublets with coupling constants of 13.4, 13.9, 13.4, 14.3 Hz. The precise reason for such phenomena is unclear, although it may be due to steric interactions between the calix[4]arene moiety and the TCNAQ side chain, which may lead to a spatial distortion of the four phenyl units. Apparently, triad **16** is also in the *cone* conformation because its H NMR spectrum shows one pair of AB doublets.

2.2. Electrochemical properties by cyclic voltammetry

The electrochemical behavior of the redox-active compounds, namely diad **9** and triads **13** and **16** have been studied at room temperature, by cyclic voltammetry (CV) and compared with related derivatives, such as calix[4]arene derivatives 5 and 10, acetoxymethyl-TCNAQ (**14**) and naphthoquinone derivative (**15**). The results are summarized in Table 1 and a typical CV is shown in Figure 1.



14

Upon scanning anodically, diad **9** exhibits one well defined irreversible oxidation wave at 1.52 V (vs. Ag/AgCl), attributed to the oxidation of the phenol units of calix[4]-arene. The measured value of oxidation potential of **9** is slightly less positive (1.52 vs. 1.57 V) than those of calix[4]arene **5**, indicating that there is only a small influence of the chemically linked TCNAQ moiety on the oxidation of the phenol units, but in opposite to the expected direction (any kind of interaction between the phenol units and the TCNAQ electron acceptor moiety should result in a higher oxidation potential). The cathodic scan affords one quasi-reversible wave at $E_{1/2}=-0.33$ V, similar to the value obtained for acetoxymethyl TCNAQ **14**. It seems that there is no effect of the covalently bonded calix[4]arene unit on

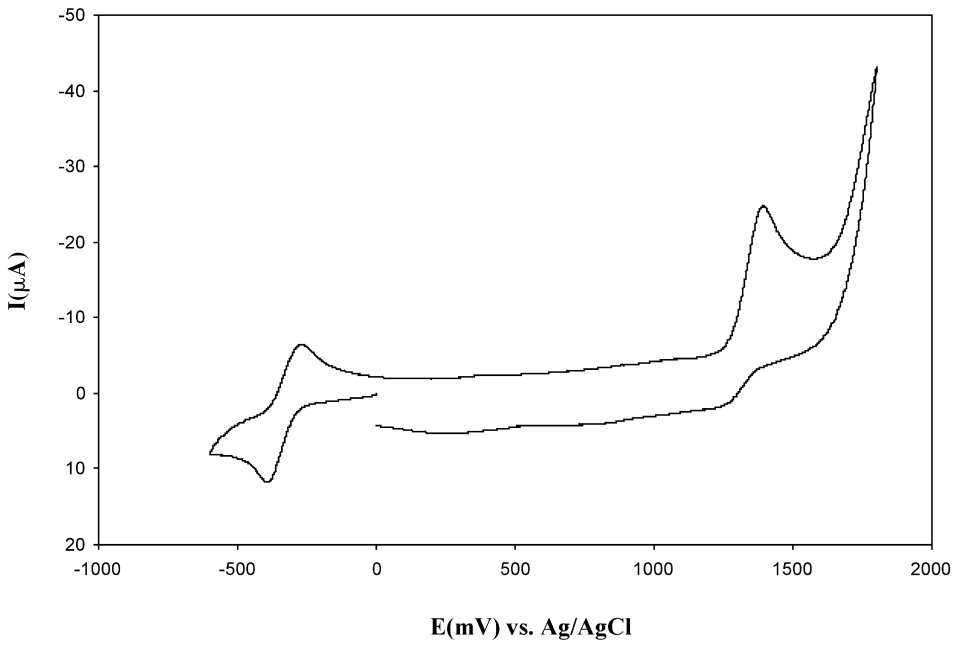


Figure 1. Cyclic voltammogram of triad **13** in 0.1 M $But_4ClO_4-CH_2Cl_2$ solution, at glassy carbon (GC); Scan rate: 100 mV/s. (Only small variations were obtained upon using Pt instead of GC or replacing the solvent by acetonitrile.).

the reduction of the TCNAQ moiety. The voltammogram of triad **13** shows a similar pattern to that of diad **9**, with a quasi-reversible couple $E_{1/2}=-0.34$ V, but with an irreversible oxidation wave at significantly less positive potential, 1.39 V. Here there is a clear influence of the chemically linked TCNAQ unit on the oxidation of the phenol units (again, opposite to the anticipated direction) but no influence of the calixarene moiety on the reduction of the TCNAQ units. As for triad **16**, with two planar NQ moieties, this compound gives an irreversible oxidation wave at 1.35 V, similar to the behavior of triad **13**, but two quasi-reversible redox couples at −0.69 and −1.56 V. Apparently, there is no effect upon reduction at the first redox couple compared with **15**. However, there is an effect on the second redox wave that becomes more negative by 290 mV. This is again in the opposite direction to what would have been expected, because if any kind of interaction (e.g., hydrogen bonding) exists between the anion radical of the NQ moiety in **16** and the phenol units of the calixarene framework, then the second reduction step should be less negative, namely, easier to reduce.

In summary, it seems that no significant change was detected in the reduction of diad **9** and triad **13** with respect to **14**; however, an effect was found in the case of the second reduction step of **16**, compared with **15**. Both triads **13** and **16** show better donor ability than **5** and **10**, exhibiting shifts in the oxidation potentials of the phenol units to less positive potentials by almost 170 mV compared with the 'free' calixarene derivatives (**5** and **10**); a smaller variation (~40 mV) is observed in diad **9**. The reason(s) behind this unexpected phenomenon, where acceptor units attached covalently to calix[4]arene skeleton cause the phenol units to be oxidized more easily, is not clear at this stage.

Previously it has been concluded by controlled potential coulometric analysis[8a,17] that the number of electrons involves in the reduction of TCNAQ is 2. Therefore, it is reasonable to also assume that the reduction wave in the CV of **9** corresponds to two-electron transfer process leading to the corresponding dianion. Similarly, the reduction of **13** consists of four electrons, yielding the corresponding tetraanion. The presence of only one single four-electron reduction wave in **13** indicates that both tetracyano-9,10-anthraquinodimethane moieties behave independently and that each is simultaneously reduced to its dianion. This behavior suggests that the calix[4]arene 'holds' the two TCNAQ units spatially separated preventing any possible interaction between them. Similar observations have also been found in other TCNAQ triad systems with different spacers.[11,18] The case of naphthoquinone derivatives **15** and **16** is different. They both exhibit two redox couples, formally involving 1e transfer each, to electro-generate the corresponding anion radical and dianion. However, the ratio of the current amplitudes between the two reduction processes is not equal to unity because of fast disproportionation of the anion radical, making the ratio usually greater than unity in favor of the first redox couple, depending on scan rate.[19]

As mentioned above, calixarene derivatives are widely used in supramolecular chemistry for the construction of various receptors for charged or neutral guest molecules. Such host–guest interaction can be controlled and detected electrochemically when organic, organometallic or inorganic redox-active centers are incorporated into calix[4]-arene framework. For example, ferrocenium, cobaltocenium and tri(2,2′-bipyridyl)ruthenium(II) ($[Ru(bpy)_3]^{2+}$) moieties were combined with calix[4]arene to recognize cations, anions and neutral species.[20] Calixquinone receptors have been found to enhance electrostatic affinity to cations when the quinone moiety is reduced to its dianion. Similarly, in the case of a quinone-bridged calix[6]arene, in which the quinone unit is quite rigid, it was found[21] that the reduction potential of the quinone moiety is negatively shifted in comparison with reference compounds without the calixarene macrocycle. The newly synthesized compounds **9**, **13** and **16**, with redox-active TCNAQ and NQ moieties, could potentially act as electrochemical sensors for cations when electrostatic interaction is switched on by reduction of the acceptor unit(s). As far as we know, so far, no NQ or TCNAQ unit has been chemically bound to any calixarene skeleton, as ionophore. Therefore, the electrochemical behavior of TCNA Q-calixarene diad **9** and triad **13**, which have stronger acceptor units than **16**, have been studied in the presence of various metallic cations by CV, UV–Vis and ^{1}H NMR spectroscopy. Surprisingly, CV experiments (1 mM substrate, in CH_2Cl_2–0.1 M But_4ClO_4) of the above compounds with metal ions of various ionic radii and charges, such as perchlorate salts of Li^+, Na^+, $Mg^{2+}$and Ba^{2+}, have shown little changes in the voltammograms, indicating that the electrostatic effects between the metal ions studied and the reduced TCNAQ moiety in **9** is very weak. Also, the ^{1}H NMR spectra did not change upon addition of alkali metal perchlorate to solutions of **9** and **13** in CD_3OD. This indicates that binding is probably not taking place in this case. Often the phenolic groups at the lower rim of calixarenes are hydrogen bonding to one another, thus reducing their ability for cations binding. In conclusion, we have found no evidence for cation binding or sensing using NMR or electrochemical methods. At present, it is not clear at which stage receptors **9** and **13** fail.

2.3. UV–Vis spectra

It is well known that calix[4]arene derivatives bearing nitriles on the upper rim and alkoxy groups on the lower rim present nonlinear optical (NLO) properties.[14b] Compared with other NLO-phores consisting of a single π-conjugated system, calix[4]arene can contain up to four D–π–A moieties in one molecule. When the four D–π–A units are symmetrically oriented in one direction (*cone* conformation), the molecular hyperpolarizability (β) value is about three times higher than the value of a derivative with one D–π–A unit. Compounds **9** and **13** could be regarded as D–σ–A systems, in which the TCNAQ moiety is the acceptor and the calix[4]arene unit is the donor. Similar to D–π–A systems, the number of D–σ–A units might be important for the expression of charge transfer (CT) prosperities. Indeed, as evidenced by its UV–Vis spectra, triad **13** which contains two D–σ–A units, exhibits a weak and broad absorption band in the 420–580 nm region, in dichloromethane, in addition to the usual TCNAQ and calix[4]arene absorption bands (Fig. 2), whereas diad **9**

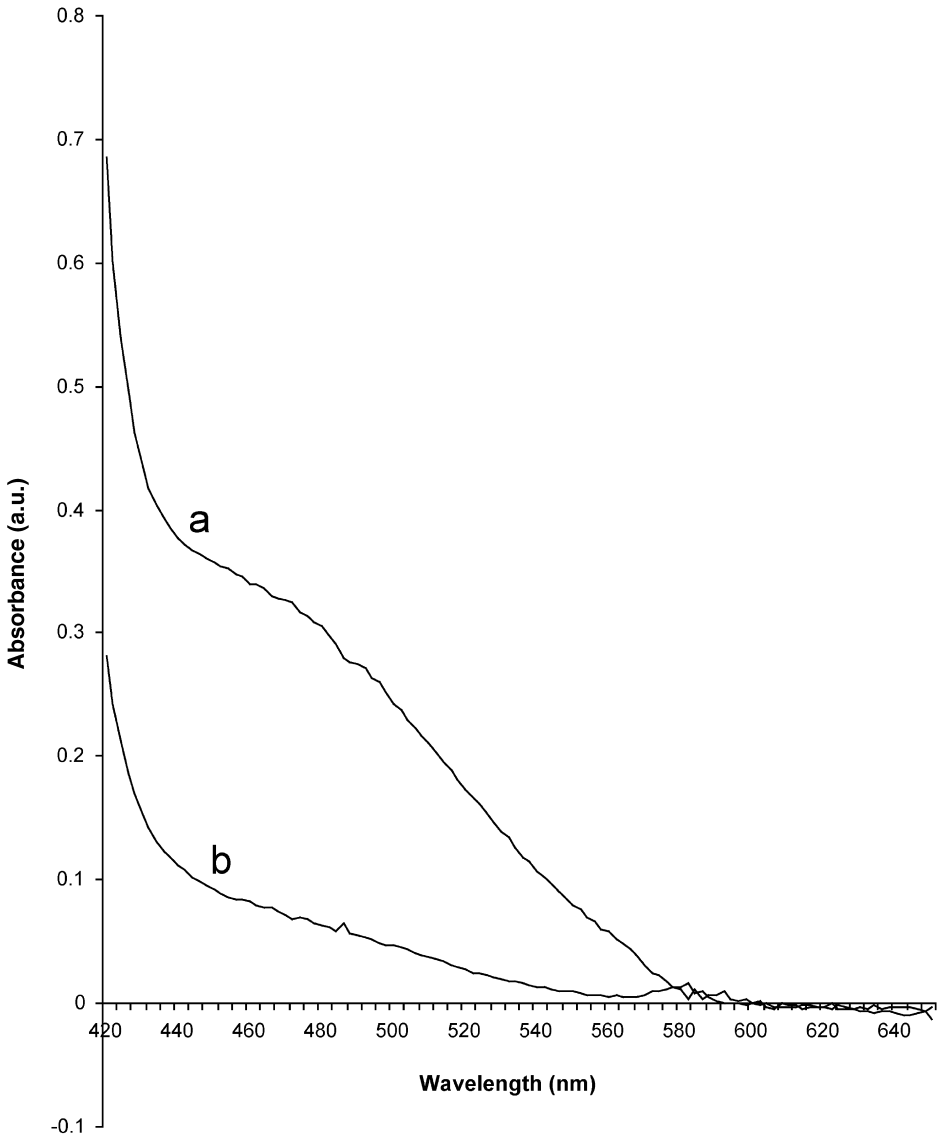


Figure 2. UV–VIS spectrum of compounds (1.4 mM) **13** (a) and **9** (b) in dichloromethane.

which contains only one TCNAQ moiety does not show a CT band under the same conditions. A mixture of 1:2 molar ratios of a TCNAQ derivative **14** and a calix[4]arene derivative **10** does not exhibit a similar absorption band under the same conditions. Also, the intensity of the absorption band of **13** shows a dependence on concentration that is expected for an intramolecular charge transfer process. It is noteworthy that to date, a similar phenomenon of intramolecular charge transfer property was reported[8] only for TCNAQ systems in which the two TCNAQ moieties are chemically linked through a conjugated vinylene bridge to the donor (see compound **3** in Scheme 1). However, there is an example[4e] of such a phenomenon in a *rigid* system involving TTF-σ-quinone diad in which the A and D units are spatially close to each other but lack a conjugation between them. Therefore, the CT phenomenon observed in **13**, which is not a rigid molecule and has two TCNAQ moieties connected by σ bonds to the calixarene framework, is unique. To try to explain the observation of intramolecular CT in this system seems to be a difficult task. Possibly, the two bulky TCNAQ substituents attached to the lower rim of the calix[4]arene scaffold impose a rigid *cone* conformation in **13**, so that the four benzene rings that are oriented in the same direction symmetrically, somehow leading to a spatial interaction between the phenols and the TCNAQ units (which could lie outside the calixarene cone), resulting in intramolecular charge-transfer band. Another possible reason (suggested by a referee) is that a single TCNAQ moiety is able to arrange itself underneath the calixarene ring, whereas in compound **13**, the presence of two TCNAQ moieties will not allow this. Consequently at least one of the TCNAQs must be outside the cone of the calixarene ring, and therefore be in a position to form a charge transfer interaction with the aryl rings.

Triad **16**, which also possesses two D–σ–A units like in **13**, and also has a cone conformation, does not show a charge transfer band. In this case it is not surprising because the electron accepting property of the NQ unit in **16** is quite weak relative to TCNAQ in **13**, as evidenced by their corresponding reduction potentials (Table 1).

Finally, it can be concluded that the relative strength of donor–acceptor affinity, the number of D–σ–A units and the specific orientation of the pending electron accepting group relative to the calixarene framework, maybe among other properties too, could play important roles in the intramolecular charge transfer process that takes place in molecules of type **13**.

3. Conclusion

Novel TCNAQ (diad **9** and triad **13**) and NQ (triad **16**) derivatives covalently linked to the lower rim of calix[4]-arenes have been synthesized. Of the three derivatives, only the UV–Vis spectrum of **13** shows an intramolecular charge transfer band. The redox properties of these derivatives have been investigated using CV measurements and all of them show a clear one irreversible oxidation wave corresponding to the phenolic groups. The TCNAQ derivatives exhibit one quasi-reversible reduction wave whereas the NQ derivative has two. Electrochemical cation recognition has also been studied for **9** and **13** but no binding or sensing was observed.

4. Experimental

All melting points were measured with a melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with a 200 MHz spectrometer (200 MHz ^{1}H frequency, 50 MHz ^{13}C frequency) or 500 MHz spectrometer (500 MHz ^{1}H frequency, 125 MHz ^{13}C frequency). Chemical shifts are given as values (internal standard: TMS). Cyclic voltammograms were measured by Princeton Applied Research Potentiostat/Galvanostat Model 273A equipped with electrochemical analysis software. A one-compartment cylindrical cell, containing 0.1 M Bu_4NClO_4 in dichloromethane (or acetonitrile), and a glassy carbon (GC) working electrode, Pt wire counter electrode and Ag/AgCl (in 2 M NaCl) reference electrode, were employed. Solvents were chemically pure and purified by standard procedures.

Compounds **4**,[22] **5**,[23] **8**,[8a] **10**[24] **11**,[25] **14**[8b] and **15**[26] were synthesized according to literature procedures. Compound **6** was prepared similar to a known procedure,[25] by refluxing a suspension of **5** (2 moles) in ethanol (30 mL)–water (20 mL), containing NaOH (50 moles), for 24 h. The cooled solution was acidified to pH=1 by 50% sulphuric acid. The resulting precipitate was isolated, washed with water, dried under vacuum and recrystallized from ethanol–water to give a white powder, in 55% yield.

4.1. General procedure for the synthesis of compound 9 and 13

A mixture of monoacid **6** (710 mg, 1 mmol) or diacid **11** (764 mg, 1 mmol) and an excess of $SOCl_2$ (40 mmol, 2.9 mL) was stirred under reflux for 3 h. The solvent was distilled off, the residue was dissolved in anhydrous CH_2Cl_2 (5 mL) and the solvent was again evaporated under reduced pressure. This procedure was repeated twice to remove all traces of thionyl chloride. The resulting solid (acyl chloride **7** or **12**) was then dried in a high vacuum for 1 h. The solid was dissolved in 15 mL of dry dichloromethane and was added dropwise a solution of 2-hydroxy-TCNAQ (38.4 mg, 1.1 mmol for **7** or 77 mg, 2.2 mmol for **12**) at room temperature and followed by pyridine (1.1 mmol for **7** or 2.2 mmol for **12**) in 5 mL of dry dichloromethane. The reaction mixture was stirred for 12 h and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and washed with water (20 mL). The separated organic layer was dried over $MgSO_4$. After the evaporation of solvent, the crude product was purified by column chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate with a gradient increase of ethyl acetate to give products **9** and **13** as a yellow powders.

4.1.1. Monoacid 6. Yield: 55% (white powder). Mp: > 270 °C (decomposed); ^{1}H NMR (DMSO-d_6): 1.11 (s, 9H, *t*-Bu), 1.14 (s, 18H, *t*-Bu), 1.16 (s, 9H, *t*-Bu), 3.45 (d, 4H, J=13.6 Hz, ArCH_2Ar), 4.06 (d, 2H, J=14.3 Hz, ArCH_2Ar), 4.34 (d, 2H, J=12.9 Hz, ArCH_2Ar), 4.74 (s, 4H, CH_2O), 7.03 (s, 2H, Ar-*H*), 7.12 (s, 2H, Ar-*H*), 7.19 (s, 2H, Ar-*H*), 7.24 (s, 2H, Ar-*H*), ^{13}C NMR ($CDCl_3$): 30.96, 31.20, 31.70, 33.79, 33.90, 34.03 (C(CH_3)$_3$ and (ArCH_2Ar), 71.84 (OCH_2), 125.11, 125.55, 126.04, 127.55, 127.84, 128.56, 133.76, 142.72, 143.05, 147.66, 150.60, 171.22 (C=O). IR (KBr): ν=3300–2500 (br), 1765, 1480 cm^{-1}. HRMS for $C_{46}H_{58}O_6$: found, (M+1)=707.4290 (calc. 707.4312).

4.1.2. Compound 9. Yield: 48% (yellow powder). Mp: 272–274 °C. ^{1}H NMR ($CDCl_3$): 0.95 (s, 9H, *t*-Bu), 1.10 (s, 9H, *t*-Bu), 1.28 (s, 9H, *t*-Bu), 1.34 (s, 9H, *t*-Bu), 3.28 (d, 1H, J=13.4 Hz, ArCH_2Ar), 3.38 (d, 1H, J=13.5 Hz, ArCH_2Ar), 3.44 (d, 1H, J=14.3 Hz, ArCH_2Ar), 3.53 (d, 1H, J=13.5 Hz, ArCH_2Ar), 4.11–4.71 (br, m, 6H, ArCH_2Ar and ArOCH_2CO), 5.51 (s, 2H, Ar$_{TCAQ}$-CH_2O), 6.65 (s, br, 1H, Ar-O*H*), 6.83 (d, 1H, J=2.43 Hz, Ar-*H*), 6.84 (d, 1H, J=1.84 Hz, Ar-*H*), 6.85 (d, 1H, J=2.38 Hz, Ar-*H*), 7.04 (d, 2H, J=2.44 Hz, Ar-*H*), 7.06 (d, 1H, J=2.40 Hz, Ar-*H*), 7.10 (d, 2H, J=2.0 Hz, Ar-*H*), 7.17 (s, br, 1H, Ar-O*H*), 7.22 (s, br, 1H, Ar-O*H*), 7.62–7.77 (m, 3H, Ar$_{TCAQ}$-H), 8.11–8.35 (m, 3H, Ar$_{TCAQ}$-H), 8.44(s, 1H, Ar$_{TCAQ}$-H), ^{13}C NMR ($CDCl_3$): 30.89, 31.15, 31.40, 31.59 (C(CH_3)$_3$), 32.78, 32.99, 33.99, 33.98 (ArCH_2Ar), 34.08, 34.24, 34.36, 34.53, (C(CH$_3$)$_3$), 65.46 (ArOCH_2), 71.98 (Ar$_{TCAQ}$-CH_2O), 112.87 (CN), 113.12 (CN), 160.10 (C(CN)$_2$), 168.40 (C=O). IR (KBr): ν=3437, 2965, 2230(CN), 1750, 1480 cm^{-1}. MALDI-TOF MS: m/z 1045.38(M+Na$^+$) for $C_{67}H_{66}N_4O_6Na$. HRMS MS: m/z=1023.970: found, for (M+1) for $C_{67}H_{67}N_4O_6$ (calc. 1024.257).

4.1.3. Compound 13. Yield: 36% (orange powder). Mp: 206–208 °C; ^{1}H NMR ($CDCl_3$): 0.95 (s, 18H, *t*-Bu), 1.31 (s, 18H, *t*-Bu), 3.30 (d, 4H, J=13.26 Hz, ArCH_2Ar), 4.33 (d, 4H, J=13.4 Hz, ArCH_2Ar), 4.74 (s, 4H, CH_2OAr), 5.42 (s, 4H, Ar$_{TCAQ}$CH_2OCO), 6.80 (s, 4H, Ar-*H*), 7.07 (s, 4H, Ar-*H*), 7.15 (s, 2H, Ar-O*H*), 7.68–8.25 (m, 12H, Ar$_{TCAQ}$-*H*), 8.42 (d, 2H, Ar$_{TCAQ}$-*H*), ^{13}C NMR ($CDCl_3$): 31.08 (C(CH_3)$_3$), 31.82 (ArCH_2Ar), 34.05 (C(CH_3)$_3$), 65.69 (OCH_2), 72.28 (OCH_2), 112.98 (CN), 113.22 (CN), 125.50, 125.96, 127.17, 127.73, 127.94, 129.87, 130.21, 130.85, 131.77, 132.38, 132.55, 140.83, 142.16, 147.56, 149.45, 150.54, 160.00 (C(CN)$_2$), 160.27 (C(CN)$_2$), 168.37 (C=O). IR (KBr): ν=2950, 2230 (CN), 1757, 1487 cm^{-1}.

MALDI-TOF MS: m/z=1420.37 ($M+Na^+$) for $C_{90}H_{76}N_8O_8Na$. HRMS MS: m/z=1397.542: found, for (M+1) for $C_{90}H_{76}N_8O_8$ (calc. 1397.596).

4.1.4. Compound 16. Yield: 48% (dark brown powder). Mp: 130 °C (decomposed); ^1H NMR ($CDCl_3$): 0.93 (s, 18H, *t*-Bu), 1.27 (s, 18H, *t*-Bu), 3.30 (d, 4H, J=13.2 Hz, ArCH_2Ar), 4.34 (d, 4H, J=13.2 Hz, ArCH_2Ar), 4.83 (s, 4H, CH_2OAr), 5.36 (s, 4H, $Ar_{Quinone}CH_2O$), 6.75 (s, 4H, Ar-*H*), 6.95 (s, 4H, $Ar_{Quinone}$-*H*), 7.02 (s, 4H, Ar-*H*), 7.81–8.06 (m, 6H, $Ar_{Quinone}$-*H*); ^{13}C NMR ($CDCl_3$): 30.87(C(CH_3)$_3$), 31.57(ArCH_2Ar), 33.74(C(CH$_3$)$_3$), 65.59(OCH_2CO), 72.24(COOCH_2), 168.55(COOCH$_2$), 184.47(Naphthoquinone). IR (KBr): ν=1757, 1675, 1485 cm^{-1}; MALDI-TOF MS: m/z 1127.39 ($M+Na^+$) for $C_{70}H_{72}O_{12}Na$, 1143.37($M+K^+$) for $C_{70}H_{72}O_{12}K$.

References and notes

1. Aviram, A.; Ratner, M. *Chem. Phys. Lett.* **1974**, *29*, 277.
2. Segura, J. L.; Martin, N. *Angew. Chem. Int. Ed.* **2001**, *40*, 1372.
3. (a) Bryce, M. R. *J. Mater. Chem.* **2000**, *10*, 589. (b) Panetta, C. A.; Baghdadchi, J.; Metzger, R. M. *Mol. Cryst. Liq. Cryst.* **1984**, *107*, 103.
4. (a) Watson, W. H.; Eduok, E. E.; Kashyap, R. P.; Krawiec, M. *Tetrahedron* **1993**, *49*, 3035. (b) Frenzel, S.; Müllen, K. *Synth. Meth.* **1996**, *80*, 175. (c) Moriarty, R. M.; Tao, A.; Gilardi, R.; Song, Z.; Tuladhar, S. M. *Chem. Commun.* **1998**, 157. (d) Scheib, S.; Cava, M. P.; Baldwin, J. W.; Metzger, R. M. *J. Org. Chem.* **1998**, *63*, 1198. (e) Tsiperman, E.; Regev, T.; Becker, J. Y.; Bernstein, J.; Ellern, A.; Khodorkovsky, V.; Shames, A.; Shapiro, L. *Chem. Commun.* **1999**, 1125.
5. (a) Prato, M.; Maggini, M.; Giacometti, C.; Scorrano, G.; Sandona, G.; Farnia, G. *Tetrahedron* **1996**, *52*, 5221. (b) Llacay, J.; Veciana, J.; Vidal-Gancedo, J.; Bourdelande, J. L.; González-Moreno, R.; Rovira, C. *J. Org. Chem.* **1998**, *121*, 3951. (c) Simonsen, K. B.; Konovalov, V. V.; Konovalova, T. A.; Kawai, T.; Cava, M. P.; Kispert, L. D.; Metzger, R. M.; Becher, J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 657. (d) Martín, N.; Sánchez, L.; Illescas, B.; Pérez, I. *Chem. Rev.* **1998**, *98*, 2527. (e) Illescas, B. M.; Martín, N. *J. Org. Chem.* **2000**, *65*, 5986. (f) Herranz, M.Á.; Illescas, B.; Martín, N. *J. Org. Chem.* **2000**, *65*, 5728.
6. Goldenberg, L. M.; Becker, J. Y.; Levi, O. P-T.; Khodorkovsky, V. Y.; Shapiro, L. M.; Bryce, M. R.; Cresswell, J. P.; Petty, M. C. *J. Mater. Chem.* **1997**, *7*, 901.
7. Simonsen, K. B.; Zong, K.; Rogers, R. D.; Cava, M. P.; Becher, *J. Org. Chem.* **1997**, *62*, 679.
8. (a) Torres, E.; Panetta, C. A. *J. Org. Chem.* **1987**, *52*, 2944–2945. (b) de Miguel, P.; Bryce, M. R.; Goldenberg, L. M.; Beeby, A.; Khodorkovsky, V.; Shapiro, L.; Niemz, A.; Cuello, A. O.; Rotello, V. *J. Mater. Chem.* **1998**, *8*, 71.
9. Kato, H.; Kobayashi, T. *Adv. Mater.* **1993**, *5*, 750.
10. Maslak, P. *Adv. Mater.* **1994**, *6*, 405.
11. Gömez, R.; Segura, J. L.; Martín, N. *J. Org. Chem.* **2000**, *65*, 7566.
12. Tatemitsu, H.; Nishikawa, E.; Sakata, H.; Misumi, S. *Synth. Meth.* **1987**, *19*, 565.
13. (a) Gutsche, C. D. *Calixarenes: monographs in supramolecular chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1989. (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.
14. (a) Kenis, P. J. A.; Noordman, O. F. J.; Schönherr, H.; Kerver, E. G.; Snellink-Ruël, B. H. M.; van Hummel, G. J.; Harkema, S.; van der Vorst, C. P. J. M.; Hare, J.; Picken, S. J.; Engbersen, J. F. J.; van Hulst, N. F.; Vancso, G. J.; Reinhoudt, D. N. *Chem. Eur. J.* **1998**, *4*, 1225. (b) Kelderman, E.; Heesink, G. J. T.; Derhaeg, L.; Verbiest, T.; Klaase, P. T. A.; Verboom, W.; Engbersen, J. F. J.; van Hulst, N. F.; Clays, K.; Persoons, A.; Reinhoudt, D. N. *Adv. Mater.* **1993**, *5*, 925.
15. (a) Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I. *Pure Appl. Chem.* **1988**, *60*, 483. (b) Iqbal, M.; Mangiafico, T.; Gutsche, C. D. *Tetrahedron* **1987**, *43*, 4917. (c) Gutsche, C. D. *Calixarenes*. Royal Society of Chemistry: Cambridge, 1989.
16. Gong, S.-L.; Wang, W.; Chen, Y.-Y.; Meng, L.-Z.; Wan, T. *New J. Chem.* **2002**, *26*, 1827.
17. Kini, A. M.; Cowan, D. O.; Gerson, F.; Mockel, R. *J. Am. Chem. Soc.* **1985**, *107*, 556.
18. Herranz, M. A.; González, S.; Pérez, I.; Martín, N. *Tetrahedron* **2001**, *57*, 725.
19. Bittner, S.; Gorohovsky, S.; Paz-Tal (Levi), O.; Becker, J. Y. *Amino Acids* **2002**, *22*, 71.
20. (a) Beer, P. D.; Hayes, E. J. *Coord. Chem. Rev.* **2003**, *240*, 167–189. (b) Cooper, J. B.; Drew, M. G. B.; Beer, P. D.; Gale, P. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 486–516. (c) Beer, P. D. *Dalton Trans.* **2001**(4), 392–401. Beer, P. D. *Dalton Trans.* **2000**(16), 2721–2728. (d) Beer, P. D.; Chen, Z.; Goulden, A. J.; Grieve, A.; Hesek, D.; Szemes, F.; Wear, T. *J. Chem. Soc. Chem. Commun.* **1994**, 1269–1271. (e) Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud-Neu, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767. (f) Cobben, P. L. H. M.; Egberink, R. J. M.; Bömer, J. R.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573. (g) Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Calixarenes*. Asfari, Z., Bömer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, Holland, 2001; p 365. (h) Andreetti, G. D.; Ugozzoli, F.; Ungaro, R.; Pochini, A. *Inclusion compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: New York, 1991; Vol. 4, p 64.
21. For example: (a) Vataj, R.; Louati, A.; Jeunesse, C.; Matt, D. *Electrochem. Commun.* **2000**, *2*, 769–775. (b) Vataj, R. H.; Louati, A.; Gabelica, V.; Steyer, S.; Matt, D. *J. Electroanal. Chem.* **2002**, *519*, 123–129, and references therein. (c) Komura, T.; Yamaguchi, T.; Kura, K.; Tanabe, J. *J. Electroanal. Chem.* **2002**, *523*, 126–135. (d) Kawaguchi, M.; Ikeda, A.; Shinkai, S. *J. Chem. Soc. Perkin Trans. 1* **1998**, 179–184. (e) Bettega, H. C. Y.; Moutet, J. C.; Ulrich, G.; Ziessel, R. *J. Electroanal. Chem.* **1996**, *406*, 247–250.
22. Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.
23. Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379.
24. Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.
25. Arnaud-Neu, F.; Barrett, G.; Cremin, S.; Deasy, M.; Ferguson, G.; Harris, S. J.; Lough, A. J.; Guerra, L.; McKervey, M. A.; Schwing-weill, M. J.; Schwinte, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1119.
26. Torres, E.; Panetta, C. A.; Heimer, N. E.; Clark, B. J.; Hussey, C. L. *J. Org. Chem.* **1991**, *56*, 3737.

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A versatile approach for the asymmetric synthesis of 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones

Ming-De Chen, Xiang Zhou, Ming-Zhu He, Yuan-Ping Ruan and Pei-Qiang Huang*

Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, Fujian 361005, People's Republic of China

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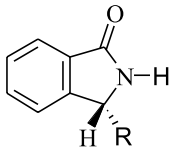
Dedicated to Professor Dr. Khi-Rui Tsai on the occasion of his 90th birthday

Abstract—Based on the use of (*R*)-*p*-benzyloxyphenylglycinol (**10**) as a new oxidatively cleavable chiral auxiliary, a flexible approach to (*R*)-3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones via a diastereoselective reductive-alkylation is developed. The oxidative cleavage of the chiral auxiliary by CAN under mild conditions ensured the access to (*R*)-3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones with *ee* at least 92%.

1. Introduction

3-Alkyl-2,3-dihydro-1*H*-isoindolin-1-ones (isoindolin-1-ones) **1** are the key structural feature of a number of synthetic and naturally occurring bioactive molecules. For example, PD-172938 (**2**) enantiomers show affinity for dopamine D_4 receptor,[1] pazinaclone (DN-2327)[2] (**3**) and pagoclone[3] (**4**) are anxiolytic drug candidates, while lennoxamine (**5**)[4] is an alkaloid isolated from barberries species (Fig. 1). Besides, (*S*)-3-methyl-isoindolin-1-one has been shown to be a valuable chiral auxiliary.[5] Consequently, the chemistry of 3-alkyl-isoindolin-1-ones has attracted much attention currently, and a number of valuable synthetic methods for such compounds have been developed.[6,7]



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However, in contrast to the great progress made in asymmetric synthesis within the last two decades, the methodology for the asymmetric synthesis of simple 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones **1** in high *ee* was rarely explored. Although a flexible approach to 3-aryl substituted 2,3-dihydro-*1H*-isoindolin-1-ones has been reported recently, to the best of our knowledge, (*R*)-3-methyl-isoindolin-1-one (**1a**), first reported by Oppolzer in 1990,[5a] and ten years later by Allin and co-workers,[7] remained the only 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-one (**1**) so far obtained by asymmetric synthesis with high *ee* value.

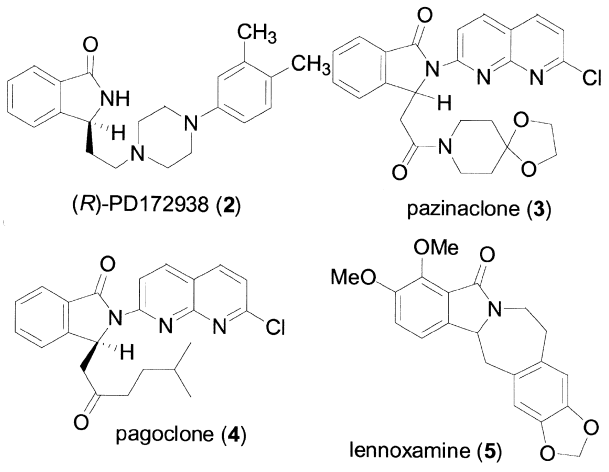

Figure 1.

It is worth mentioning that although four methods[7,9,10] have been reported for the asymmetric synthesis of *N*-substituted 3-alkyl-isoindolin-1-ones **6** starting from (*R*)-phenylglycinol, the removal of the *N*-chiral auxiliary to give **1** could not be achieved in a straightforward and racemization-free manner (vide infra).[6] Consequently, to develop versatile and flexible methods for the asymmetric synthesis of 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones **1** is highly desirable. We herein report a flexible reductive-alkylation approach to 3-alkyl-2,3-dihydro-1*H*-isoindolin-1-ones **1**

Keywords: Isoindolin-1-one; Chiral auxiliary; Benzyloxyphenylglycinol; Asymmetric synthesis.
* Corresponding author. Tel.: +86-592-218-0992; fax: +86-592-218-6400; e-mail address: pqhuang@xmu.edu.cn

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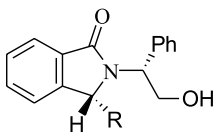
featuring the removal of the chiral auxiliary under racemization free conditions.[11]



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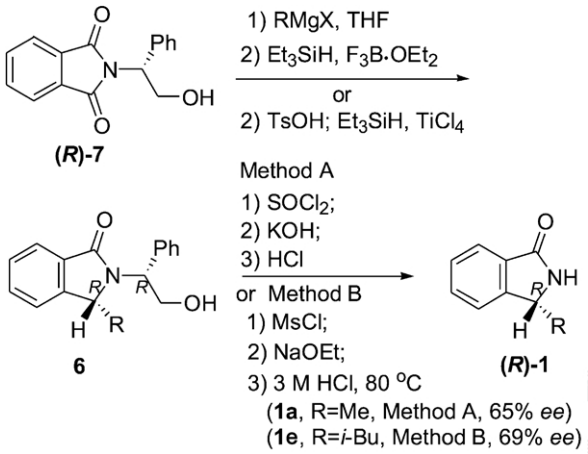
2. Results and discussion

In chiral auxiliary-based asymmetric synthetic methodology, the success of a chiral auxiliary depends, firstly, on its asymmetric induction, and secondly, on the feasibility of its smooth removal from the substrate after asymmetric induction. This is the case of (*R*)-phenylglycinol, a valuable chiral auxiliary gained widespread application in asymmetric syntheses.[12,13] The success of this chiral auxiliary is due partially to the easy cleavage of the benzylic auxiliary under hydrogenolysis conditions.[13] Further development for its cleavage under non-reductive conditions[14–16] has led to the extension of the scope of this chiral auxiliary.

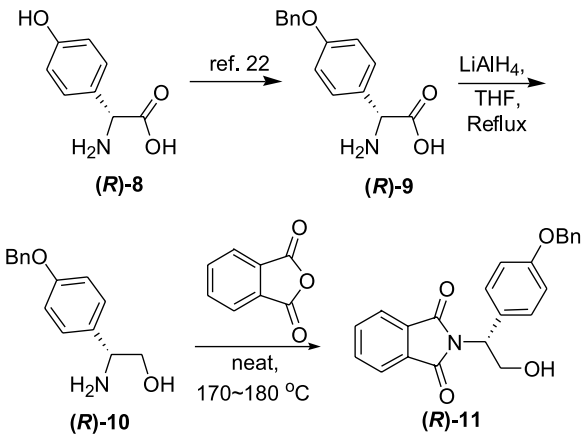
During the asymmetric synthesis of amides or lactams using phenylglycinol as a chiral auxiliary, apart from the widely used dissolving metal reduction method,[17] only two alternative procedures[18] have been used for the removal of benzylic auxiliary group from the nitrogen (e.g., Scheme 1, **6→1**). Recently, inspired from the pioneering work of Meyers,[19] we have developed a versatile and flexible reductive alkylation approach to optically active 3-alkylisoindolin-1-one derivatives (**7→6**, Scheme 1).[10] However, attempted removal of the chiral auxiliary (2-hydroxy-1-phenylethyl group) from the nitrogen of **6** (R=Me, *i*-Bu) by above-mentioned procedures[18] resulted in extensive racemization (Scheme 1). In the recent asymmetric synthesis of 3-aryl-isoindolin-1-ones, Enders and co-workers[8] also noted that attempted cleavage of N–N bond of the chiral auxiliary SAMP under reductive conditions led to either complex mixture or racemization.



Scheme 1.

The easy racemization of the 3-carbon-subsituted isoindolin-1-one systems under acidic, basic or reductive conditions (vide supra), account for the importance of developing a new chiral auxiliary, which is cleavable under mild racemization-free conditions. *N*-*p*-Alkyloxybenzyl group is cleavable under mild oxidative conditions,[20,21] and (*R*)-*N*-*p*-hydroxyphenylglycinol is a cheap and commercially available amino acid. Based on the considerations, we decided to test (*R*)-*N*-*p*-benzyloxylphenylglycinol as a new chiral auxiliary for the asymmetric synthesis of 3-alkylisoindolinones, in hoping that at the end of the synthesis, the *N*-*p*-alkyloxybenzyl group could be removed under racemization-free oxidative conditions.

To this end, cheap and easily available (*R*)-*p*-hydroxyphenylglycine **8** was converted to *O*-benzylether **9** by a known procedure.[22] The reduction of **9** with lithium aluminum hydride in refluxing tetrahydrofuran led to the crude (*R*)-*p*-benzyloxyphenylglycinol (**10**), which was subjected to react with phthalic anhydride without further purification, under solvent-free conditions[23] (170–180 °C, 14–15 h). In this way, (*R*)-**11** {white crystal, mp 132–133 °C (ether), $[\alpha]_D^{20}=+7.4$ (*c* 0.9, $CHCl_3$)} was obtained in 79% yield (Scheme 2).



Scheme 2.

With multi-gram quantities of (*R*)-**11** available, the reductive-alkylation was investigated. The reaction of (*R*)-**11** with 2.5 equiv. of methyl magnesium iodide at −15 to −10 °C led smoothly to the formation of α-hydroxylactam **12a** (Table 1, entry 1) in 98% yield as a 1.2:1 diastereomeric mixture (the stereochemistry was not determined). Although the two diastereomers of **12a** are separable by column chromatography on silica gel, they were unseparated and used in the next step as diastereomeric mixture, since the subsequent reductive dehydroxylation was expected to proceed via the *N*-acyliminium ion intermediate **A**.[24] Indeed, when the diastereomeric mixture of **12a** was subjected to a boron trifluoride etherate mediated triethylsilane reduction,[25,10] diastereoisomer **13a** formed predominately. The two diastereomers **13a**/**14a** were separated by flash chromatography on silica gel, from which the diastereomeric ratio of **13a**/**14a** was determined as 75:25 (Scheme 3).

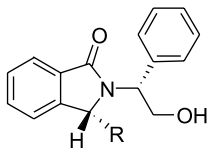
The stereochemistry of the major diastereomer **13a** was tentatively assigned as (3*R*,1′*R*) by the comparison of its ^{1}H NMR spectral data with that of an analogue, de-benzyloxy-**15**, whose structure was determined by a single-crystal X-ray crystallographic analysis.[10] This assignment was

Table 1. Preparation of **13** via the reductive alkylation of **11**

Entry	RMgX	Compounds **12** (yield, %)	Compounds **13/14** (yield, %)	Diastereomeric ratio[a] (**13/14**)
1	MeMgI	**12a** (98)	**13/14a** (98)	75:25
2	EtMgBr	**12b** (88)	**13/14b** (79)	88:12
3	*n*-PrMgBr	**12c** (93)	**13/14c** (96)	81:19
4	*n*-BuMgBr	**12d** (73)	**13/14d** (98)	81:19
5	*i*-BuMgBr	**12e** (89)	**13/14e** (94)	83:17
6	*n*-C_5H_{11}MgBr	**12f** (83)	**13/14f** (67)	73:27
7	*n*-C_7H_{15}MgBr	**12g** (83)	**13/14g** (79)	70:30

[a] Determined by chromatograph separation.

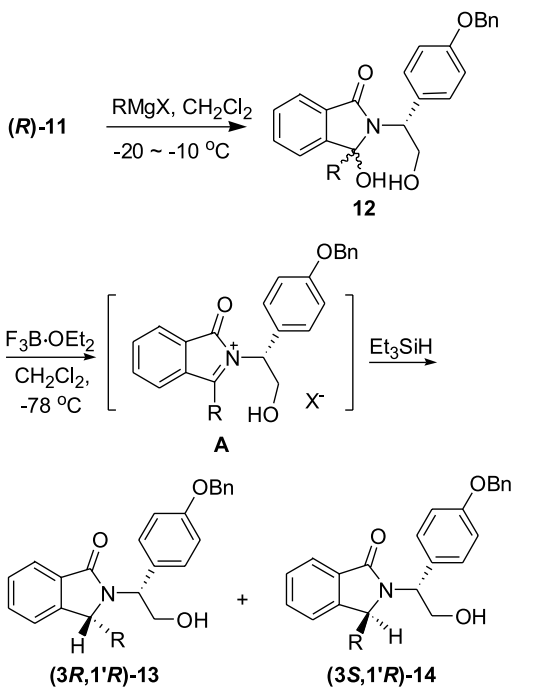
finally confirmed by its transformation into known (*R*)-3-methyl-isoindolin-1-one **1a** (vide infra).



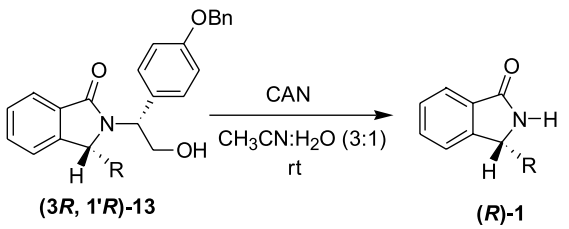
(3*R*,1'*R*)-15

Extension of the same reductive alkylation procedure to other Grignard reagents led to the corresponding products **13b–g** and **14b–g** in diastereoselectivity varied from 70:30 to 88:12 (Table 1, entries 2–7). Although the diastereoselectivity in this step is not high, the easy separation of the diastereomers by flash chromatography on silica gel allows the ready isolation of the diastereomer **13** in pure form.

Next, the key oxidative removal of the chiral auxiliary was investigated. The treatment of *N*-substituted 3-methylisoindolin-1-one (**13a**) with four molar equivalents of ceric ammonium nitrate (CAN)[21] in a mixed solvent system (MeCN–H_2O, 3:1, rt, 30 min.) led smoothly to the desired (*R*)-3-methylisoindolin-1-one (**1a**) as white crystals [mp 112–115 °C; lit.[5c] mp 102–103 °C for (*S*)-**1a**]. By comparing with a racemic sample, the enantiomeric excess of **1a** was determined to 97% based on HPLC analysis on a chiral column (eluent: 2.5% IPA in hexane, λ=270 nm). The specific rotation of the synthesized (*R*)-3-methyl-isoindolin-1-one **1a** {$[\alpha]_D^{20}$=+39.1 (*c* 1.0, MeOH)} is in agreement with that reported by Stevenson and co-workers {$[\alpha]_D^{20}$=−39.8 (*c* 0.6, EtOH) for (*S*)-**1a**},[5c] but different, both in the sense and in the magnitude, from that reported by Allin {$[\alpha]_D^{20}$=−89.7 (*c* 1.7, MeOH) for (*R*)-**1a**, *ca*. 96% *ee*} (Scheme 4).[7]



Scheme 3.



(3*R*, 1'*R*)-13 **(*R*)-1**

Scheme 4.

Following the same procedure as described for **13a**, the oxidative cleavages of **13b–13g** by CAN were performed. The results were listed in Table 2. Except in the case of **13b** (Table 2, entry 2), other 3-substituted isoindolin-1-ones were obtained in high chemical yield and with *ee* % value no less than 92%.

Table 2. Synthesis of (*R*)-**1** by oxidative *N*-deprotection of **13**

Entry	Compounds (*R*)-**1** (yield, %)	*ee* (%) of (*R*)-**1**
1	**1a** (84)	97
2	**1b** (63)	92
3	**1c** (86)	97
4	**1d** (90)	92
5	**1e** (88)	93
6	**1f** (88)	94
7	**1g** (82)	97

In summary, a versatile and flexible approach to (*R*)-3-alkyl-isoindolin-1-ones **1**, in high enantiomeric purity (*ee*≥92%), is developed via a diastereoselective reductive-alkylation procedure.[26] The use of (*R*)-*p*-benzyloxyphenylglycinol (**10**) as a new oxidatively cleavable chiral auxiliary is the key to reach high enantiomeric purity of the 3-alkyl-isoindolin-1-ones **1**. This method is versatile in scope, because various C-3 alkyl substituents can be introduced easily by Grignard reaction. The application of present method to the asymmetric synthesis of 3-alkyl-isoindolin-1-one-based bioactive compounds is in progress.

3. Experimental

3.1. General

All melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian unity+500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by a Bruker Dalton ESquire 3000 plus liquid chromatography-mass Spectrum (ESI direct injection). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (200–300 mesh). Solvent THF was distilled over sodium, with dichloromethane being distilled over P_2O_5.

3.1.1. (*R*)-*N*-[2-Hydroxy-1-(4-benzyloxyphenyl)ethyl]-phthalimide (11). A mixture of phthalic anhydride (0.288 g, 1.943 mmol) and (*R*)-2-hydroxy-1-(4-benzyloxyphenyl)- ethylamine (0.45 g, 1.85 mmol), which obtained by $LiAlH_4$ reduction of known (*R*)-(4-benzyloxyphenyl)-glycinol,[21] was stirred at 170–180 °C for 15 h. The mixture was then cooled to rt, before CH_2Cl_2 was added. The resulting solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel to give **11** (544 mg, yield 79%) as a pale yellow solid. R_f: 0.29 (AcOEt–P.E.=1:2). White crystal. Mp 132~133 °C (ether). $[\alpha]_D^{20}$=+7.4 (*c* 0.9, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3461, 3062, 3033, 2926, 1771, 1707, 1610, 1584, 1512, 1463, 1389, 1363, 1331, 1242, 1179, 1111, 1069, 1013 cm^{-1}. ^{1}H NMR (500 MHz) δ: 2.45 (dd, *J*=4.6, 8.2 Hz, 1H, OH), 4.21 (ddd, *J*=4.6, 5.0, 11.4 Hz, 1H, C*H*$_2$OH), 4.61 (ddd, *J*=8.2, 8.6, 11.4 Hz, 1H, C*H*$_2$OH), 5.03 (s, 2H, OCH_2Ph), 5.42 (dd, *J*=5.0, 8.6 Hz, 1H, C*H*CH$_2$OH), 6.88–7.90 (m, 13H, Ar) ppm. MS (ESI, *m*/*z*): 375 [(M+2H)$^+$, 34], 374 (M+H$^+$, 69), 356 [(M+H–H$_2$O)$^+$, 29], 227 (100), 209 (51). HRESIMS calcd for [$C_{23}H_{19}NO_4$+H]$^+$: 374.1392. Found: 374.1391. Anal. Calcd for $C_{23}H_{19}NO$: C, 73.97; H, 5.13; N, 3.75. Found: C, 74.25; H, 5.32; N, 3.55.

3.2. General procedure for the reductive alkylation of (*R*)-phthalimide derivative (11)

To a cooled (−15 to −10 °C) solution of **11** (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a Grignard reagent (3.0 mmol) in diethyl ether under nitrogen atmosphere. After stirred at the same temperature for 4 h, the reaction was quenched with saturated aqueous solution of ammonium chloride (6 mL) and extracted with dichloromethane (3×30 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuum. Filtration with a short pad of column eluting with ethyl acetate-petroleum ether (1:1) yielded a mixture of two diastereomers **12**. The diastereomeric ratio could be obtained either from flash chromatographic separation or from ^{1}H NMR spectra of the crude mixture.

To a cooled (−78 °C) solution of diastereomer mixture **12** (1.0 mmol) in dry dichloromethane (10 mL) was added dropwise triethylsilane (10 mmol) and boron trifluoride etherate (3.0 mmol) under nitrogen atmosphere. After stirring at −78 °C for 6 h, the mixture allowed to react at rt and stirred overnight. The reaction was quenched by saturated aqueous sodium bicarbonate and extracted with dichloromethane (3×20 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 then concentrated in vacuum. The crude was purified by flash column chromatography on silica gel with ethyl acetate–petroleum ether (1:2) as eluent to give **13**.

3.2.1. (3*R*,1′*R*)-3-Methyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13a). Diastereomeric ratio: 75:25, combined yield 98%. (3*R*,1′*R*)-**13a** (major diastereomer): R_f: 0.27 (AcOEt–P.E.=1:2). Colorless oil. $[\alpha]_D^{20}$=+54.4 (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3366, 2924, 2847, 1664, 1611, 1583, 1510, 1468, 1454, 1468, 1409, 1354, 1300, 1240, 1178, 1079, 1024 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (d, *J*=6.8 Hz, 3H, CH_3), 4.08 (ddd, *J*=3.4, 7.2, 12.4 Hz, 1H, C*H*$_2$OH), 4.35 (q, *J*=6.8 Hz, 1H, NCHMe), 4.44 (ddd, *J*=7.2, 7.9, 12.4 Hz, 1H, C*H*$_2$OH), 4.72 (dd, *J*=3.4, 7.9 Hz, 1H, C*H*CH$_2$OH), 4.85 (dd, *J*=7.2, 7.9 Hz, 1H, OH), 5.03 (s, 2H, OCH_2Ph), 6.88–7.88 (m, 13H, Ar) ppm. MS (ESI, *m*/*z*): 396 (M+Na$^+$, 6), 375 [(M+2H)$^+$, 25], 374 (M+H$^+$, 100). HRESIMS calcd for [$C_{24}H_{23}NO_3$+H]$^+$: 374.1756. Found: 374.1754.

3.2.2. (3*R*,1′*R*)-3-Ethyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13b). Diastereomeric ratio: 88:12, combined yield 79%. (3*R*,1′*R*)-**13b** (major diastereomer): R_f: 0.51 (AcOEt–P.E.=1:1). White solid. Mp 111–113 °C. $[\alpha]_D^{20}$=+51.0 (*c* 0.7, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3366, 3083, 3058, 3027, 2967, 2934, 2878, 1664, 1616, 1491, 1469, 1454, 1421, 1361, 1332, 1301, 1066 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (: 0.56 (t, *J*=7.5 Hz, 3H, CH_3), 1.92–2.12 (m, 2H, CH_2Me), 4.10 (ddd, *J*=3.4, 7.1, 12.4 Hz, 1H, C*H*$_2$OH), 4.40 (dd, *J*=5.1, 7.1 Hz, 1H, OH), 4.45 (ddd, *J*=5.1, 7.9, 12.4 Hz, 1H, C*H*$_2$OH), 4.57 (dd, *J*=3.4, 7.9 Hz, 1H, C*H*CH$_2$OH), 4.98 (t, *J*=7.2 Hz, 1H, NCH), 5.02 (s, 2H, OCH_2Ph), 6.84–6.88 (m, 2H, Ar), 7.22–7.60 (m, 10H, Ar), 7.80–7.88 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 389 [(M+2H)$^+$, 26], 388 (M+H$^+$, 100). HRESIMS calcd for [$C_{25}H_{25}NO_3$+H]$^+$: 388.1913. Found: 388.1909.

3.2.3. (3*R*,1′*R*)-3-*n*-Propyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13c). Diastereomeric ratio: 81:19, combined yield 96%. (3*R*,1′*R*)-**13c** (major diastereomer): R_f: 0.32 (AcOEt–PE=1:2). Colorless oil. $[\alpha]_D^{20}$=+42.4 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3378, 3039, 2954, 2871, 1667, 1611, 1510, 1462, 1411, 1237, 1176, 1023 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) (: 0.80 (t, *J*=6.8 Hz, 3H, CH_3), 1.08–1.20 (m, 1H, $(CH_2)_2$Me), 1.82–2.00 (m, 3H, $(CH_2)_2$Me), 4.08 (ddd, *J*=3.5, 6.0, 12.3 Hz, 1H, C*H*$_2$OH), 4.38 (dd, *J*=6.0, 7.8 Hz, 1H, OH), 4.45 (ddd, *J*=7.8, 8.1, 12.3 Hz, 1H, C*H*$_2$OH), 4.62 (dd, *J*=3.5, 8.1 Hz, 1H, C*H*CH$_2$OH), 4.96 (t, *J*=7.2 Hz, 1H, NCH), 5.02 (s, 2H, OCH_2Ph), 6.88–6.95 (m, 2H, Ar), 7.18–7.22 (m, 2H, Ar), 7.25–7.60 (m, 8H, Ar), 7.80–7.83 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 403 [(M+2H)$^+$, 27], 402

(M+H, 100). HRESIMS calcd for $[C_{26}H_{27}NO_3+H]^+$: 402.2069. Found: 402.2058.

3.2.4. (3*R*,1′*R*)-3-*n*-Butyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13d). Diastereomeric ratio: 81:19, combined yield 98%. (3*R*,1′*R*)-**13d** (major diastereomer): R_f: 0.63 (AcOEt–PE=1:1). White solid. Mp 88–90 °C. $[\alpha]_D^{20}$=+38.0 (*c* 1.1, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3345, 2921, 2852, 1659, 1577, 1540, 1511, 1462, 1421, 1376, 1303, 1241, 1175, 1098, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.80 (t, *J*=7.3 Hz, 3H, CH_3), 1.04–1.28 (m, 4H, $(CH_2)_3Me$), 1.84–2.00 (m, 2H, $(CH_2)_3Me$), 4.10 (ddd, *J*=3.4, 5.1, 12.4 Hz, 1H, C*H*$_2$OH), 4.39 (dd, *J*=3.0, 5.1 Hz, 1H, OH), 4.44 (ddd, *J*=3.0, 8.0, 12.4 Hz, 1H, C*H*$_2$OH), 4.60 (dd, *J*=3.4, 8.0 Hz, 1H, C*H*CH_2OH), 4.98 (t, *J*=7.4 Hz, 1H, NCH), 5.04 (s, 2H, OCH_2Ph), 6.88–6.96 (m, 2H, Ar), 7.16–7.60 (m, 10H, Ar), 7.82–7.84 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 438 (M+Na^+, 5), 417 [(M+2H)$^+$, 31], 416 (M+H^+, 100). HRESIMS calcd for $[C_{27}H_{29}NO_3+H]^+$: 416.2226. Found: 416.2224.

3.2.5. (3*R*,1′*R*)-3-*iso*-Butyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13e). Diastereomeric ratio: 83:17, combined yield, 94%. (3*R*,1′*R*)-**13e** (major diastereomer): R_f: 0.60 (AcOEt–PE=1:1). Colorless oil. $[\alpha]_D^{20}$=+34.2 (*c* 1.2, $CHCl_3$). IR (film) ν_{max}: 3367, 3033, 2955, 2925, 2868, 1666, 1611, 1583, 1510, 1468, 1454, 1413, 1334, 1239, 1177, 1114, 1061, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.70 (d, *J*=6.4 Hz, 3H, CH_3), 0.92 (d, *J*=6.4 Hz, 3H, CH_3), 1.66–1.88 (m, 3H, CH_2CHMe_2), 4.10 (ddd, *J*=3.4, 7.0, 12.4 Hz, 1H, C*H*$_2$OH), 4.33 (dd, *J*=3.2, 7.0 Hz, 1H, OH), 4.43 (ddd, *J*=3.2, 7.8, 12.4 Hz, 1H, C*H*$_2$OH), 4.66 (dd, *J*=3.4, 7.8 Hz, 1H, C*H*CH_2OH), 5.02 (s, 2H, OCH_2Ph), 5.04 (t, *J*=7.9 Hz, 1H, NCH), 6.85–6.90 (m, 2H, Ar), 7.15–7.21 (m, 2H, Ar), 7.28–7.58 (m, 8H, Ar), 7.82–7.84 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 438 (M+Na^+, 36), 417 [(M+2H)$^+$, 24], 416 (M+H^+, 100). HRESIMS calcd for $[C_{27}H_{29}NO_3+H]^+$: 416.2226. Found: 416.2220.

3.2.6. (3*R*,1′*R*)-3-*n*-Pentyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13f). Diastereomeric ratio: 73:27, combined yield 67%. (3*R*,1′*R*)-**13f** (major diastereomer): R_f: 0.63 (AcOEt–P.E.=1:1). White crystal. Mp 104–108 °C. $[\alpha]_D^{20}$=+32.1 (*c* 1.0, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3369, 3034, 2928, 2862, 1665, 1611, 1510, 1465, 1409, 1303, 1240, 1177, 1114, 1021 cm^{-1}. ^1H- NMR (500 MHz, $CDCl_3$) δ: 0.80 (t, *J*=6.9 Hz, 3H, CH_3), 0.68–0.74 (m, 1H, $(CH_2)_4Me$), 1.08–1.22 (m, 5H, $(CH_2)_4Me$), 1.86–2.00 (m, 2H, $(CH_2)_4Me$), 4.10 (ddd, *J*=3.4, 6.1, 12.4 Hz, 1H, C*H*$_2$OH), 4.39 (dd, *J*=3.1, 6.1 Hz, 1H, OH), 4.44 (ddd, *J*=3.1, 7.9, 12.4 Hz, 1H, C*H*$_2$OH), 4.60 (dd, *J*=3.4, 7.9 Hz, 1H, C*H*CH_2OH), 4.95 (t, *J*=7.4 Hz, 1H, NCH), 5.04 (s, 2H, OCH_2Ph), 6.88–6.92 (m, 2H, Ar), 7.18–7.22 (m, 2H, Ar), 7.38–7.60 (m, 8H, Ar), 7.88 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 431 [(M+2H)$^+$, 40], 430 (M+H^+, 100). HRESIMS calcd for $[C_{28}H_{31}NO_3+H]^+$: 430.2382. Found: 430.2381.

3.2.7. (3*R*,1′*R*)-3-*n*-Heptyl-2-[2-hydroxy-1-(4-benzyloxyphenyl)ethyl]-2,3-dihydro-1*H*-isoindolin-1-one (13g). Diastereomeric ratio: 70:30, combined yield 79% (3*R*,1′*R*)-**13g** (major diastereomer): R_f: 0.59 (AcOEt–PE=1:2). White crystal. Mp 104∼105 °C (ether). $[\alpha]_D^{20}$=+31.7 (*c* 0.9, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3371, 3037, 2929, 2858, 1668, 1612, 1511, 1462, 1409, 1238, 1177, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.85 (t, *J*=7.2 Hz, 3H, CH_3), 1.06–1.20 (m, 7H, $(CH_2)_6Me$), 1.20–1.30 (m, 2H, $(CH_2)_6Me$), 1.66–1.78 (m, 1H, $(CH_2)_6Me$), 1.86–1.98 (m, 2H, $(CH_2)_6Me$), 4.12 (ddd, *J*=3.7, 6.8, 11.7 Hz, 1H, C*H*$_2$OH), 4.40 (dd, *J*=6.8, 7.8 Hz, 1H, OH), 4.46 (ddd, *J*=7.8, 7.8, 11.7 Hz, 1H, C*H*$_2$OH), 4.62 (dd, *J*=3.7, 7.8 Hz, 1H, C*H*CH_2OH), 4.98 (t, *J*=7.0 Hz, 1H, NCH), 5.04 (s, 2H, OCH_2Ph), 6.88–6.95 (m, 2H, Ar), 7.18–7.22 (m, 2H, Ar), 7.25–7.45 (m, 6H, Ar), 7.55–7.60 (m, 2H, Ar), 7.84 (d, 1H, Ar) ppm. MS (ESI, *m*/*z*): 480 (M+Na^+, 7), 459 [(M+2H)$^+$, 29], 458 (M+H^+, 100). HRESIMS calcd for $[C_{30}H_{35}NO_3+H]^+$: 458.2695. Found: 458.2695.

3.3. General procedure for the oxidative deprotection of *N*-substituted 3-alkyl-isoindolin-1-ones (13)

To a solution of diastereomeric mixture **13** (1.0 mmol) in a mixed MeCN–H_2O solvent system (3:1, 4 mL) was added ceric ammonium nitrate (2.192 g, 4.0 mmol) at rt. After stirred at the same temperature for 30 min, H_2O (10 mL) was added. The resulting mixture was extracted with ethyl acetate (3×10 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, then dried over anhydrous Na_2SO_4. The crude was purified by flash column chromatography on silica gel with ethyl acetate-petroleum ether (2:1) as eluent to give **1**.

3.3.1. (*R*)-Methyl-2,3-dihydro-1*H*-isoindolin-1-one (1a). Yield 84%. White crystal. Mp 112–115 °C (CH_2Cl_2) [lit.[5c] mp 102–103 °C for (*S*)-**1a**; lit.[6e] mp 118–119 °C for racemic **1a**]. $[\alpha]_D^{20}$=+39.1 (*c* 1.0, MeOH) {lit.[5c] $[\alpha]_D^{20}$=−39.8 (*c* 1.0, MeOH) for (*S*)-enantiomer; lit.[7] $[\alpha]_D^{20}$=−89.7 (*c* 1.7, MeOH) for (*R*)-enantiomer}. IR (KBr, Pellet) ν_{max}: 3193, 3079, 3021, 2923, 1688, 1655, 1540, 1454, 1416, 1260, 1206, 1138, 1084, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.51 (d, *J*=6.8 Hz, 3H, CH_3), 4.54 (q, *J*=6.8 Hz, 1H, CHMe), 6.90 (s, 1H, NH), 7.40–7.60 (m, 3H, Ar), 7.84 (d, *J*=7.50 Hz, 1H, Ar) ppm. MS (ESI, *m*/*z*): 170 (M+Na^+, 77), 148 (M+H^+, 100). HRESIMS calcd for $[C_9H_9NO+H]^+$: 148.0762. Found: 148.0755.

3.3.2. (*R*)-Ethyl-2,3-dihydro-1*H*-isoindolin-1-one (1b). Yield 63%. White crystal. Mp 128–131 °C (CH_2Cl_2) [lit.[27] mp 105 °C for racemic **1b**]. $[\alpha]_D^{20}$=+52.0 (*c* 0.6, MeOH). IR (KBr, Pellet) ν_{max}: 3209, 2961, 2925, 2855, 1690, 1654, 1462, 1421, 1312, 1209, 1143 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.96 (t, *J*=7.4 Hz, 3H, CH_3), 1.66–1.76 (m, 1H, CH_2Me), 1.98–2.06 (m, 1H, CH_2Me), 4.60 (dd, *J*=4.9, 7.6 Hz, 1H, NCH), 7.10 (br s, 1H, NH), 7.42–7.61 (m, 3H, Ar), 7.84 (m, 1H, Ar) ppm. MS (ESI, *m*/*z*): 184 (M+Na^+, 7), 163 [(M+2H)$^+$, 11], 162 (M+H^+, 100). HRESIMS calcd for $[C_{10}H_{11}NO+H]^+$: 162.0919. Found: 162.0918.

3.3.3. (*R*)-*n*-Propyl-2,3-dihydro-1*H*-isoindolin-1-one (1c). Yield 86%. White crystal. Mp 108–109 °C (CH_2Cl_2) [lit.[28] mp 135–136 °C (H_2O) for racemic **1c**]. $[\alpha]_D^{20}$=+57.2 (*c* 0.7, MeOH). R_f: 0.48 (AcOEt–PE=1:1). IR (KBr, Pellet) ν_{max}: 3211, 2958, 2927, 2869, 1680, 1465, 1423, 1306,

745 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.97 (t, J=7.3 Hz, 3H, CH_3), 1.36–1.44 (m, 2H, $(CH_2)_2Me$), 1.48–1.56 (m, 1H, $(CH_2)_2Me$), 1.59–1.68 (m, 1H, $(CH_2)_2Me$), 4.64 (dd, J=4.4, 7.7 Hz, 1H, NCH), 7.40–7.60 (m, 3H, Ar), 7.60 (br s, 1H, NH), 7.83 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 373 [$(2M^+Na)^+$, 17], 351 [$(2M^+H)^+$, 7], 198 ($M+Na^+$, 51), 177 [$(M+2H)^+$, 14], 176 ($M+H^+$, 100). HRESIMS calcd for $[C_{11}H_{13}NO+H]^+$: 176.1075. Found: 176.1068.

3.3.4. (*R*)-*n*-Butyl-2,3-dihydro-1*H*-isoindolin-1-one (1d). Yield 90%. White crystal. Mp 69–71 °C (CH_2Cl_2) [Lit.[6e] mp 88–89 °C for racemic **1d**]. $[\alpha]_D^{20}$=+53.0 (*c* 0.8, MeOH). IR (KBr, Pellet) ν_{max}: 3270, 3078, 2955, 2922, 2852, 1695, 1576, 1540, 1465, 1376, 1203, 1137, 1098 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (t, J=7.1 Hz, 3H, CH_3), 1.22–1.50 (m, 4H, $(CH_2)_3Me$), 1.60–1.70 (m, 1H, $(CH_2)_3Me$), 1.9–2.0 (m, 1H, $(CH_2)_3Me$), 4.61 (dd, 1H, J=4.5, 7.6 Hz, NCH), 6.90 (br s, 1H, NH), 7.20–7.30 (m, 2H, Ar), 7.55 (m, 1H, Ar), 7.85 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 379 [$(2M+H)^+$, 8], 212 ($M+Na^+$, 4), 191 [$(M+2H)^+$, 12], 190 ($M+H^+$, 100). HRESIMS calcd for $[C_{12}H_{15}NO+H]^+$: 190.1232. Found: 190.1229. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.49; H, 7.99; N, 7.68.

3.3.5. (*R*)-*iso*-Butyl-2,3-dihydro-1*H*-isoindolin-1-one (1e). Yield 88%. White crystal. Mp 133–135 °C (CH_2Cl_2) [lit.[29] mp 153 °C (EtOH) for racemic **1e**]. $[\alpha]_D^{20}$=+64.1 (*c* 1.0, MeOH). IR (KBr, Pellet) ν_{max}: 3192, 3075, 2954, 2924, 2863, 1686, 1608, 1467, 1363, 1269, 1203, 1142, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.00 (d, J=6.6 Hz, 3H, CH_3), 1.06 (d, J=6.6 Hz, 3H, CH_3), 1.46–1.53 (m, 1H, CH_2CHMe_2), 1.72–1.78 (m, 1H, CH_2CHMe_2), 1.79–1.88 (m, 1H, CH_2CHMe_2), 4.64 (dd, J=4.0, 9.7 Hz, 1H, NCH), 6.60 (br s, 1H, NH), 7.42–7.58 (m, 3H, Ar), 7.84 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 212 ($M+Na^+$, 4), 191 [$(M+2H)^+$, 13] 190 ($M+H^+$, 100). HRESIMS calcd for $[C_{12}H_{15}NO+H]^+$: 190.1232. Found: 190.1229. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.14; H, 8.14; N, 7.32.

3.3.6. (*R*)-*n*-Pentyl-2,3-dihydro-1*H*-isoindolin-1-one (1f). Yield 88%. White crystal. Mp 56–58 °C (CH_2Cl_2). $[\alpha]_D^{20}$=+49.9 (*c* 0.7, MeOH). IR (KBr, Pellet) ν_{max}: 3218, 3073, 2925, 2855, 1696, 1541, 1465, 1360, 1301, 1260, 1198, 1142, 1086, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.87 (t, J=6.9 Hz, 3H, CH_3), 1.24–1.38 (m, 5H, $(CH_2)_4Me$), 1.41–1.52 (m, 1H, $(CH_2)_4Me$), 1.58–1.70 (m, 1H, $(CH_2)_4Me$), 1.90–1.98 (m, 1H, $(CH_2)_4Me$), 4.61 (dd, J=4.5, 7.6 Hz, 1H, NCH), 7.20 (br s, 1H, NH), 7.41–7.58 (m, 3H, Ar), 7.84 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 407 [$(2M+H)^+$, 4], 205 [$(M+2H)^+$, 16], 204 ($M+H^+$, 100). HRESIMS calcd for $[C_{13}H_{17}NO+H]^+$: 204.1388. Found: 204.1386.

3.3.7. (*R*)-*n*-Heptyl-2,3-dihydro-1*H*-isoindolin-1-one (1g). Yield 82%. Colorless oil. $[\alpha]_D^{20}$=+50.8 (*c* 0.4, MeOH). IR (film) ν_{max}: 3216, 3077, 2927, 2857, 1697, 1611, 1465, 1361, 1307, 1141 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.86 (t, J=7.0 Hz, 3H, CH_3), 1.22–1.34 (m, 9H, $(CH_2)_6Me$), 1.42–1.48 (m, 1H, $(CH_2)_6Me$), 1.60–1.68 (m, 1H, $(CH_2)_6Me$), 1.92–1.94 (m, 1H, $(CH_2)_6Me$), 4.62 (dd, J=4.6, 7.5 Hz, 1H, NCH), 7.40–7.60 (m, 3H, Ar), 7.70 (br s, 1H, NH), 7.82 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 485 [$(2M+Na)^+$, 3], 232 ($M+H^+$, 100). HRESIMS calcd for $[C_{15}H_{21}NO+H]^+$: 232.1701. Found: 232.1691.

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References and notes

1. Belliotti, T. R.; Brink, W. A.; Kesten, S. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499–1502.
2. Wada, T.; Fukuda, N. *Psychopharmacology* **1991**, *103*, 314–322.
3. Kavoussi, R. J.; Pande, A. C.; Lydiard, R. B.; Pap, L.; Pigott, T. A.; Rickels, K. *Int. J. Neuropsychopharmacol.* **2000**, *3*(Suppl. 1). Abst. P. 09.042.
4. Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923–3925.
5. (a) Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015–5018. (b) Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J. *Tetrahedron Lett.* **1995**, *36*, 9533–9536. (c) McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69–79.
6. (a) Hunter, R.; Richards, P. *Tetrahedron Lett.* **2000**, *41*, 3755–3758. (b) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777–4792. (c) Epsztajn, J.; Jozwiak, A.; Koluda, P.; Sadokierska, I.; Wilkowska, I. D. *Tetrahedron* **2000**, *56*, 4837–4844. (d) Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *Synthesis* **2000**, 655–660. (e) Deniau, E.; Enders, D. *Tetrahedron Lett.* **2000**, *41*, 2347–2350. (f) Yoda, H.; Matsuda, K.; Nomura, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 1775–1779. (g) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169–2172. (h) Luzzio, F. A.; Zacherl, D. P. *Tetrahedron Lett.* **1998**, *39*, 2285–2288. (i) Deniau, E.; Enders, D. *Tetrahedron* **2001**, *57*, 2581–2588.
7. Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1715–1721, and references cited therein.
8. Enders, D.; Braig, V.; Raabe, G. *Can. J. Chem.* **2001**, *79*, 1528–1535.
9. (a) Ukaji, Y.; Tsukamoto, K.; Nasada, Y.; Shimizu, M.; Fujisawa, T. *Chem. Lett.* **1993**, 221–224. (b) Pérard-Viret, J.; Prangé, T.; Tomas, A.; Royer, J. *Tetrahedron* **2002**, *58*, 5103–5108.
10. Chen, M. D.; He, M. Z.; Huang, L. Q.; Ruan, Y. P.; Huang, P.-Q. *Chin. J. Chem.* **2002**, *20*, 1149–1153.
11. This work was taken in part from the Master theses of He, M. Z., Xiamen University, China, 2003..
12. For reviews on the use of (*R*)-phenylglycinol as a chiral auxiliary, see: (a) Husson, H. P.; Royer, *J. Chem. Soc. Rev.* **1999**, *28*, 383–394. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873.

13. (a) Eleveld, M. B.; Hogeveen, H.; Schudde, E. P. *J. Org. Chem.* **1986**, *51*, 3635–3642. (b) Andres, C.; Gonzalez, A.; Pedrosa, R.; Perezs-Encabo, A.; Garcia-Granda, S.; Salvado, M. A.; Gomez-Beltran, F. *Tetrahedron Lett.* **1992**, *33*, 4743–4746. (c) Harwood, L. M.; Macro, J.; Watkin, D.; Williams, C. E.; Wong, L. F. *Tetrahedron: Asymmetry* **1992**, *3*, 1127–1130. (d) Harder, T.; Lohl, T.; Bolte, M.; Wagner, K.; Hoppe, D. *Tetrahedron Lett* **1994**, *35*, 7365–7368. (e) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *J. Org. Chem.* **1997**, *62*, 2106–2112. (f) Carrillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716–6721. (g) Steinig, A. G.; Spero, D. M. *J. Org. Chem.* **1999**, *64*, 2406–2410. (h) Adam, W.; Peters, K.; Peters, E. M.; Schambony, S. B. *J. Am. Chem. Soc.* **2000**, *122*, 7610–7611. (i) Cevallos, A.; Rios, R.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4407–4416.
14. (a) Chakraborty, T. K.; Reddy, G. V.; Hussain, K. A. *Tetrahedron Lett.* **1991**, *32*, 7597–7600. (b) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537–5541. (c) Pridgen, L. N.; Mokhallalati, M. K.; Wu, *J. Org. Chem.* **1992**, *57*, 1237–1241. (d) Chen, L.; Trilles, R. V.; Tilley, J. W. *Tetrahedron Lett.* **1995**, *36*, 8715–8718. (e) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179–9190. (f) Delorme, D.; Berthelette, C.; Lavoie, R.; Roberts, E. *Tetrahedron: Asymmetry* **1998**, *9*, 3963–3966. (g) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H. P. *J. Org. Chem.* **2000**, *65*, 6423–6426. (h) Chang, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475–3483.
15. Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185–1187.
16. Agami, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **1999**, *40*, 3709–3712.
17. Julina, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 368–373.
18. (a) Fains, O.; Vernon, J. M. *Tetrahedron Lett.* **1997**, *38*, 8265–8266. (b) Nyzam, V.; Belaud, C.; Zammatio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835–1843.
19. Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662.
20. Greene, T. W.; Wuts, P. G. M. Protective groups in organic chemistry; 2nd ed. Wiley: New York, 1991; p 401.
21. (a) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Jpn* **1985**, *58*, 1413–1420. (b) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001–1002.
22. Ma, D.; Tian, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3493–3496.
23. Kumar, G. B.; Shah, A. C.; Pilati, T. *Tetrahedron Lett.* **1997**, *38*, 3297–3300.
24. For a recent review, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.
25. (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651. (b) Nagai, Y. *Org. Prep. Proc. Int.* **1980**, *12*, 13–48. (c) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235–242. (d) Rolf, D.; Gray, G. R. *J. Am. Chem. Soc.* **1982**, *104*, 3539–3541.
26. During the submission of the present manuscript, Enders and co-workers reported a new flexible approach to (*R*)-3-substituted-2,3-dihydro-1*H*-isoindolin-1-ones based on a new oxidatively cleavable chiral auxiliary, and one more previously unknown enantiomerically enriched (*R*)-3-*tert*-butyl-2,3-dihydro-1*H*-isoindolin-1-one were reported Deniau, E.; Enders, D.; Couture, A.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2003**, *14*, 2253–2258.
27. Helberger, von J. H.; Hevér, D. B. *Justus Liebigs Ann. Chem.* **1938**, *536*, 173–179.
28. Bromberg, O. *Chem. Ber.* **1896**, *29*, 1434–1442.
29. Wöelbling, H. *Chem. Ber.* **1905**, *38*, 3925–3928.

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The β-lactone route to α,β-unsaturated δ-lactones. Total syntheses of (±)-goniothalamin and (−)-massoialactone

Lycia Fournier,[a] Philip Kocienski[b] and Jean-Marc Pons[a,*]

[a]*Laboratoire de Réactivité en Synthèse Organique (RéSO), Faculté des Sciences et Techniques de Saint-Jérôme, UMR-CNRS 6516, 13397 Marseille Cedex 20, France*
[b]*Department of Chemistry, Leeds University, LS2 9JT Leeds, UK*

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Abstract—The HF-induced translactonization of 2′-silyloxy-3-trimethylsilyl-2-oxetanones, obtained through Lewis acid-promoted [2+2] cycloaddition between β-silyloxyaldehydes and trimethylsilylsilylketene, into α,β-unsaturated δ-lactones is applied to the syntheses of (±)-goniothalamin and (−)-massoialactone.

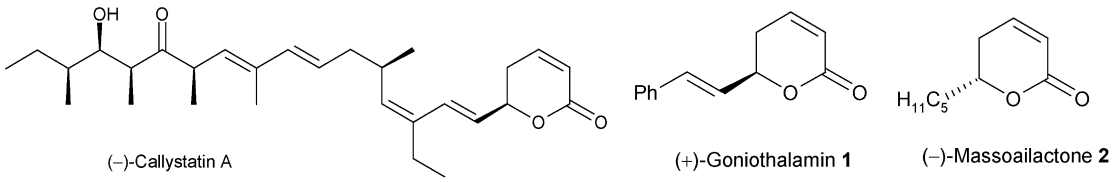
1. Introduction

The α,β-unsaturated δ-lactone (or 5,6-dihydro-2-(*2H*)-pyranone) moiety is present in a number of bioactive natural products such as (−)-callystatin A,[1] (+)-goniothalamin **1**[2] and (−)-massoialactone **2**[3] (Scheme 1). Given its activity, (−)-callystatin A has been the object of wide interest over the past decade and several syntheses or approaches of this molecule have been reported.[4–11]

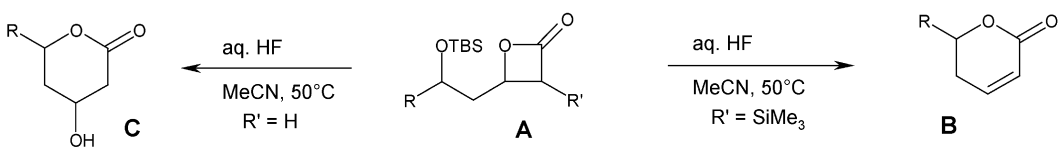
As part of a program directed towards the total synthesis of callystatin A, we recently reported a new route to the α,β-unsaturated δ-lactone moiety.[12] This approach (Scheme 2) is based on a HF-induced translactonization reaction leading, from a β-silyloxy silyl β-lactone **A**, to an α,β-unsaturated δ-lactone **B**. Provided, the β-lactone is desilylated, the reaction can selectively lead to a β-hydroxy δ-lactone **C**. Syntheses of (±)-massoialactone and (±)-prelactone B exemplify the synthetic potential of this new route to the α,β-unsaturated δ-lactone and β-hydroxy δ-lactone moieties.[12] In the present paper, we report full experimental details on the synthesis of a (±)-goniothalamin (**1**) as well as a synthesis of (−)-massoialactone **2**.

2. Synthesis of (±)-goniothalamin (1)

Originally isolated from *Cryptocarya caloneura*,[2] (+)-goniothalamin (**1**), which can also be found in various other sources,[13] was first assigned the (*S*) configuration.



Scheme 1.



Scheme 2.

Keywords: Silylketenes; Lactone; HF; [2+2] Cycloaddition; Translactonization; (−)-Dimethylmalate; Enantioselective.
* Corresponding author. Fax: +33-4-91-28-88-41; e-mail address: jean-marc.pons@univ.u-3mrs.fr

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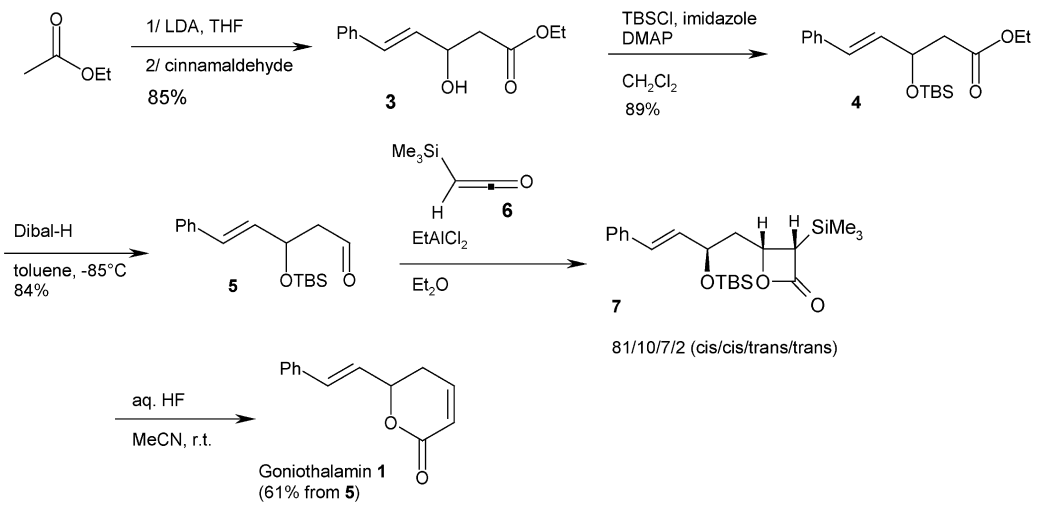


Scheme 3.

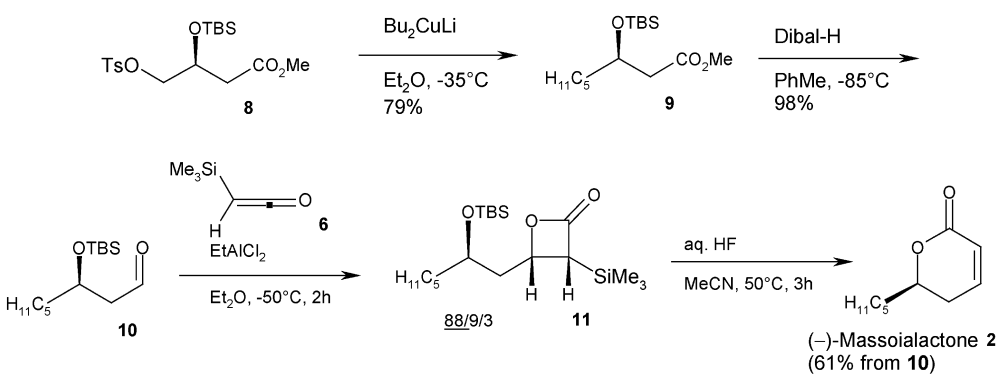
This was later corrected to the (*R*) configuration on the basis of two synthetic studies.[14,15] Interest in the synthesis of goniothalamin was stimulated by its potential as a key intermediate in the synthesis of mevinolic acid analogues. Among the many approaches to goniothalamin,[16,17] several deploy the Wittig reaction for the construction of the exocyclic double bond,[15,18,19] one uses a ring closing metathesis approach for the formation of the endocyclic double bond[20] and one the oxidation of a dihydropyran.[21]

In our synthesis (Scheme 3) the lithium enolate of ethyl acetate added to cinnamaldehyde to yield the corresponding β-hydroxy ester **3** which was protected as its *tert*-butyldimethylsilyl ether without further purification leading to unsaturated ester **4** (76% over the two steps). Ester **4** was then reduced, with Dibal-H at low temperature, to aldehyde **5** (84% yield). In the key step, aldehyde **5** underwent [2+2]-cycloaddition with trimethylsilylketene **6**[22,23] in the presence of $EtAlCl_2$ leading to β-lactones **7** as a mixture of four diastereoisomers (89/10/7/2), which were not purified. In the last step, β-lactones **7** translactonized in the presence of aq. HF in MeCN at room temperature to yield (±)-goniothalamin (**1**) in 61% overall yield for the [2+2] cycloaddition–translactonization sequence. The target molecule was thus obtained in 5 steps and 39% overall yield from cinnamaldehyde.

3. Synthesis of (−)-massoialactone

(−)-Massoialactone (**2**) is the major constituent of the bark oil of *Crytocaria massoia* and was first isolated by Abe in 1937.[3] Over the years, this molecule has received considerable interest and many racemic[12,24–28] and enantioselective[29–39] syntheses have been reported. The shortest and most efficient synthesis of (−)-massoialactone reported to date is by Ramachandran and co-workers who exploited an enantioselective allylboration of hexanal with (+)-*B*-allyldiisopinocampheylborane followed by ring closing metathesis to give the target molecule in 3 steps with 49% yield and 97% ee.[20]

Our synthesis of (−)-massoialactone (Scheme 4) began with the cheap chiral pool molecule (−)-dimethyl malate, which was transformed into ester **8** through BH_3-DMS induced monoreduction, monotosylation and *tert*-butyldimethylsilyl protection to the tosylate **8** as described in the literature (67% over the three steps).[40,41] Treatment of tosylate **8** with the lithium dialkylcuprate generated from *n*-BuLi and CuI led in 79% yield to ester **9** which was reduced with Dibal-H at low temperature to the corresponding aldehyde **10** in 98% yield. The [2+2]-cycloaddition of aldehyde **10** with trimethylsilylketene **6** gave a diastereoisomeric mixture of four β-lactones **11** which were then treated with aq. HF in



Scheme 4.

acetonitrile at 50 °C to give (−)-massoialactone **2** in 61% yield. The target molecule was obtained in 32% overall yield (99% ee) from (−)-dimethyl malate.

4. Conclusion

We have shown that the diastereoselective [2+2]-cycloaddition of β-silyloxy aldehydes with trimethylsilylketene followed by HF-induced translactonization is a useful method for the synthesis of α,β-unsaturated-δ-lactones. The method has delivered short and efficient syntheses of goniothalamin and (−)-massoialactone. Efforts are currently underway to study the mechanism of the formal elimination of Me_3SiOH and to apply this approach to a total synthesis of (−)-callystatin A.

5. Experimental

5.1. General

Reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry argon. Organic extracts were dried over $MgSO_4$ unless otherwise specified and evaporated using a rotary evaporator. Where appropriate, solvents and reagents were dried by standard methods, i.e. by distillation from the usual drying agent prior to use. All reactions were magnetically stirred and were monitored by TLC using precoated aluminium foil sheets. Flash chromatography was performed on 230–400 mesh silica gel. Optical rotations were recorded on a Perkin–Elmer 341 Polarimeter at approximatively 20 °C. Enantiomeric excesses was determined by HPLC on a Chiracel-OB-H 0.46×25 cm column (hexane/isopropanol: 80/20, 1 mL/min). IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer as thin films supported on NaCl plates (absorptions are reported as values in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Brucker AC 200, AC 300 and AC 500 spectrometers in $CDCl_3$. Chemical shifts are reported in ppm relative to residual $CHCl_3$ for ^1H NMR (δ=7.27) and $CDCl_3$ for ^{13}C NMR (δ=77.0).

5.1.1. 3-Hydroxy-5-phenylpent-4-enoic acid ethyl ester (3). A solution of *n*-butyllithium in hexane (1.6 M, 5.2 mL, 8.25 mmol) was added dropwise at −20 °C to a stirred solution of dry diisopropylamine (0.84 g, 8.25 mmol) in dry tetrahydrofuran (10 mL) under argon. After being stirred for 30 min at 0 °C, the reaction mixture was cooled to −70 °C and dry ethyl acetate (0.83 mL, 8.25 mmol) was added dropwise. The resulting solution was stirred for 1 h at −70 °C, becoming very pale yellow. Dry cinnamaldehyde (0.95 mL, 7.5 mmol) was added dropwise to it, and the reaction mixture was stirred at −70 °C for 2 h. The reaction was quenched at −70 °C by addition of glacial acetic acid (0.72 mL, 12.4 mmol) and the resulting gel was diluted with saturated aqueous sodium hydrogen carbonate (8.3 mL) and warmed to room temperature. The resulting suspension was filtered through celite, and the filtrate was washed with ether (15 mL). The aqueous and organic phases were separated, and the aqueous layer was saturated with sodium chloride, prior to extraction with ether (3×10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The yellow residue was purified by flash chromatography (petrol/ether: 70/30) to give alcohol **3** (1.406 g, 6.4 mmol, 85%) as a white solid: mp 39 °C. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.93; H, 7.32. IR=3600–3200, 3024, 1733, 1495, 1400, 1275, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.45–7.23 (5H, m), 6.67 (1H, d, *J*=15.8 Hz), 6.23 (1H, dd, *J*=16.0; 6.1 Hz), 4.74 (1H, q, *J*=5.7 Hz), 4.20 (2H, q, *J*=7.1 Hz), 3.12 (1H, s, OH), 2.66 (1H, 1/2 ABX, J_{AB}=16.2 Hz, J_{AX}=4.7 Hz), 2.64 (1H, 1/2 ABX, J_{AB}=16.2 Hz, J_{BX}=7.5 Hz), 1.29 (3H, t, *J*=7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=172.2 (s), 136.4 (s), 130.7 (d), 129.9 (d), 128.6 (d, 2C), 127.8 (d), 126.5 (d, 2C), 68.9 (d), 60.8 (t), 41.5 (t), 14.2 (q).

5.1.2. 3-(*tert*-Butyldimethylsilyloxy)-5-phenylpent-4-enoic acid ethyl ester (4). A solution of *tert*-butyldimethylsilyl chloride (166 mg, 1.1 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of imidazole (241 mg, 3.6 mmol), ester **3** (200 mg, 0.9 mmol) and 4-dimethylaminopyridine (6 mg, 0.045 mmol) in CH_2Cl_2 (3 mL) under argon and the resulting mixture was stirred at room temperature overnight. The reaction was then quenched with water (2 mL) and extracted with ether (2×5 mL). The combined organic layers were dried, concentrated in vacuo and the residue purified by flash column chromatography (petrol/ether: 90/10) to yield ester **4** (273 mg, 0.8 mmol, 89%) as a colourless oil: IR (film): ν=1736, 1464, 1368, 1252, 1164, 1076, 961, 834, 777 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ=7.40–7.20 (5H, m, H(Ar)), 6.58 (1H, d, *J*=15.9 Hz), 6.20 (1H, dd, *J*=15.9, 6.7 Hz), 4.77 (1H, q, *J*=6.6 Hz), 4.13 (2H, qd, *J*=7.2, 2.0 Hz), 2.64 (1H, 1/2 ABX, J_{AB}=14.5 Hz, J_{AX}=7.8 Hz), 2.52 (1H, 1/2 ABX, J_{AB}=14.5 Hz, J_{BX}=5.5 Hz), 1.27 (3H, t, *J*=7.2 Hz), 0.90 (9H, s), 0.09 (3H, s), 0.07 (3H, s). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=171.0 (s), 136.6 (s), 131.6 (d), 129.9 (d), 128.5 (d, 2C), 126.4 (2C, d), 127.6 (d), 70.7 (d), 60.4 (t), 44.0 (t), 25.7 (3C, q), 18.1 (s), 14.2 (q), −4.3 (q), −5.1 (q).

5.1.3. 3-(*tert*-Butyldimethylsilyloxy)-5-phenylpent-4-enal (5). A solution of diisobutylaluminium hydride in toluene (1.5 M, 0.93 mL, 1.4 mmol) was added dropwise at −85 °C to a stirred solution of the protected ester **4** (265 mg, 0.79 mmol) in dry toluene (7 mL) under argon. The solution was stirred at −90 °C for 1 h, then quenched by dropwise addition of saturated aqueous ammonium chloride (0.5 mL) ($T \leq -75$ °C). The reaction mixture was allowed to warm to room temperature, and saturated aqueous Rochelle salt (potassium sodium tartrate) solution (1.6 mL) was added. The solution was poured into brine (3.2 mL) and then ethyl acetate (4.8 mL) was added. Agitation of the mixture led to formation of a gel. Further Rochelle salt solution (1.6 mL) and ethyl acetate (1.6 mL) were added to the gel, which was left overnight to break down. The resulting two liquid phases were separated, and the aqueous layer was saturated with sodium chloride prior to extraction with ethyl acetate (3×15 mL). The combined organic layers were dried ($MgSO_4$) and then solvent was removed by evaporation. The yellow residue was purified by flash chromatography (petrol/ether: 95/5) to give aldehyde **5** (193 mg, 0.66 mmol, 84%) as a colourless oil: Anal. Calcd for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02. Found: C, 69.80; H, 9.19. IR (film): ν=1724, 1463, 1361, 1253, 1074, 968, 834, 778 cm^{-1}. ^1H NMR

(200 MHz, $CDCl_3$): δ=9.83 (1H, t, J=2.4 Hz), 7.40–7.15 (5H, m, H(Ar)), 6.60 (1H, d, J=15.9 Hz), 6.23 (1H, dd, J=15.9, 6.3 Hz), 4.84 (1H, q, J=6.4 Hz), 2.72 (1H, 1/2 ABMX, J_{AB}=15.8 Hz, J_{AM}=6.8 Hz, J_{AX}=2.6 Hz), 2.63 (1H, 1/2 ABMX, J_{AB}=15.8 Hz, J_{BM}=5.1 Hz, J_{BX}=2.2 Hz), 0.91 (9H, s), 0.11 (3H, s), 0.08 (3H, s). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=201.4 (d), 136.4 (s), 131.3 (d), 130.1 (d), 128.6 (d, 2C), 126.5 (2C, d), 127.8 (d), 69.3 (d), 51.6 (t), 25.8 (3C, q), 18.1 (s), −4.2 (q), −5.0 (q).

5.1.4. (2′*E*)-6-(2′-Phenylvinyl)-5,6-dihydro-2*H*-pyran-2-one 1 [(±)-goniothalamin 1]. To a solution of aldehyde **5** (653 mg, 2.25 mmol) in ether (16 mL) at −50 °C under argon, was added trimethylsilylketene **6** (308 mg, 2.7 mmol) in ether (6 mL). A solution of ethyl aluminium dichloride in hexane (1 M, 2.7 mL, 2.7 mmol) was then added dropwise at that temperature. The reaction was stirred for 2 h between −45 and −30 °C. The mixture was then quenched with water (7 mL) and the aqueous layer extracted with ether (2×12 mL). The organic phases were dried and concentrated to yield the corresponding β-lactone **7** as a 81/10/7/2 (*cis*/*cis*/*trans*/*trans*) mixture of diastereomers. The major *cis* diastereoisomer gave the following ^{1}H NMR spectroscopic data (300 MHz, $CDCl_3$) recorded on the mixture δ=7.50–7.24 (5H, m), 6.57 (1H, d, J=15.9 Hz), 6.17 (1H, dd, J=15.9; 6.8 Hz), 4.88 (1H, m), 4.48 (1H, m), 3.41 (1H, d, J=6.3 Hz), 1.95 (2H, m), 0.93 (9H, s), 0.23 (9H, m), 0.12 (6H, s).

To a solution of this crude mixture of β-lactones in acetonitrile (22 mL) was added aqueous HF (5.4 mL). After 15 min stirring at room temperature, the reaction was extracted with ethyl acetate (4×6 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (petrol/ethyl acetate: 75/25) to give (±)-goniothalamin **1** (276 mg, 1.38 mmol, 61%) as a white solid: mp 80 °C (lit. mp[18] 82 °C) IR (film): ν=1720, 1702, 765, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.45–7.30 (5H, m), 6.93 (1H, td, J=9.9, 4.0 Hz), 6.74 (1H, d, J=16.3 Hz), 6.28 (1H, dd, J=16.0, 6.4 Hz), 6.11 (1H, dt, J=9.9, 1.8 Hz), 5.13 (1H, q, J=7.3 Hz), 2.56 (2H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=163.9 (s), 144.6 (d), 135.8 (s), 133.1 (d), 128.7 (2C)(d), 128.3 (d), 126.7 (2C)(d), 125.6 (d), 121.7 (d), 77.9 (d), 29.9 (t).

5.1.5. (*R*)-(−)-3-(*tert*-Butyldimethylsilyloxy)octanoic acid methyl ester (9). A three-necked round bottom flask with a nitrogen inlet was charged with CuI (1.333 g, 7 mmol) and Et_2O (10 mL). The solution was stirred and cooled at −35 °C before BuLi (1.6 M in hexane, 8.8 mL, 14 mmol) was added. After 1 h, tosylate **8** (486 mg, 1.2 mmol) dissolved in Et_2O (7 mL) was added. The reaction was stopped after 1.5 h (TLC monitoring) by diluting with Et_2O and then adding saturated aqueous NH_4Cl (3.6 mL). The mixture was warmed to room temperature with stirring before the organic layer was separated. The aqueous layer was extracted with EtOAc (3×7 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (12 mL) and brine (12 mL). The organic phase was then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (petrol/ether: 90/10) to give ester **9** (274 mg, 0.95 mmol, 79%) as a colourless oil: $[\alpha]_D$=−20.7 (c=1, $CHCl_3$) (lit.[42] $[\alpha]_D$=−20.77 (c=1.32, $CHCl_3$)).^{1}H NMR (300 MHz, $CDCl_3$): δ=4.13 (1H, quint, J=6.2 Hz), 3.67 (3H, s), 2.44 (2H, d, J=6.2 Hz), 1.50–1.25 (8H, m), 0.94 (3H, t, J=5.7 Hz), 0.92 (9H, s), 0.07 (3H, s), 0.04 (3H, s). ^{13}C NMR (62.9 MHz, $CDCl_3$, lit.[42]): δ=172.2 (s), 69.6 (d), 51.2 (q), 42.6 (t), 37.6 (t), 31.9 (t), 25.7 (3C) (q), 24.6 (t), 22.5 (t), 17.9 (s), 13.8 (q), −4.6 (q), −4.9 (q).

5.1.6. (*R*)-(−)-3-(*tert*-Butyldimethylsilyloxy)octanal (10). A solution of diisobutylaluminium hydride in toluene (1.5 M, 1.3 mL, 1.94 mmol) was added dropwise at −85 °C to a stirred solution of the protected ester **9** (507 mg, 1.76 mmol) in dry dichloromethane (9 mL) under argon. The solution was stirred at −90 °C for 1 h, then quenched by dropwise addition of saturated aqueous ammonium chloride (0.5 mL) ($T\leq$−75 °C). The biphasic mixture was allowed to warm to room temperature, filtrated through a short path of silica gel and the filtrate was washed with dichloromethane. Purification of the crude product by flash chromatography (petrol/ether: 90/10) yielded aldehyde **10** (447 mg, 1.73 mmol, 98%) as a colourless oil: $[\alpha]_D$=−5.3 (c=1.0, $CHCl_3$) (lit.[43] $[\alpha]_D$=−5.3 (c=1.0, $CHCl_3$)) IR (film): ν=1725, 1255, 1101, 836 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.81 (1H, t, J=2.4 Hz), 4.20 (1H, quint, J=5.8 Hz), 2.52 (2H, dd, J=5.8, 2.6 Hz), 1.60–1.33 (8H, m), 0.89 (3H, t, J=6.0 Hz), 0.86 (9H, s), 0.08 (3H, s), 0.06 (3H, s). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=202.0 (d), 68.2 (d), 50.8 (t), 37.8 (t), 31.7 (t), 25.7 (q, 3C), 24.7 (t), 22.5 (t), 17.9 (s), 13.9 (q), −4.5 (q), −4.6 (q).

5.1.7. (*R*)-(−)-6-Pentyl-5,6-dihydro-2*H*-pyran-2-one 2 [massoialactone (2)]. To a solution of aldehyde **10** (447 mg, 1.73 mmol) in ether (12 mL) at −50 °C under argon, was added trimethylsilylketene **6** (237 mg, 2.08 mmol) in ether (3 mL). A solution of ethyl aluminium dichloride in hexane (1 M, 2.1 mL, 2.08 mmol) was then added dropwise at that temperature. The reaction was stirred for 2 h between −45 and −30 °C. The mixture was quenched with water (5 mL) and the aqueous layer extracted with ether (2×15 mL). The organic phases were dried and concentrated in vacuo to yield oxetanones **11** as a mixture of 3 diastereoisomers (*cis*/*trans*/*trans*: 88/9/3). The major cis diastereoisomer gave the following ^{1}H NMR spectroscopic data (300 MHz, $CDCl_3$) recorded on the mixture δ=4.80 (1H, ddd, J=10.6, 6.2, 2.7 Hz), 3.85 (1H, m), 3.38 (1H, d, J=6.2 Hz), 1.90–1.20 (10H, m), 0.92 (9H, s), 0.95–0.80 (3H, m), 0.24 (9H, br s), 0.08 (6H, br s).

To a solution of the crude mixture of oxetanones in acetonitrile (17 mL) was added aqueous HF (4.1 mL). After 4 h stirring at 50 °C, the reaction was extracted with ether (4×10 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (petrol/ethyl acetate: 75/25) to give (−)-massoialactone **2** (178 mg, 1.06 mmol, 61%, with 99% ee): $[\alpha]_D$=−110.7 (c=1, $CHCl_3$). [Lit.[31] $[\alpha]_D$=−110.7 (c=1, $CHCl_3$)]. IR (film): ν=1725, 1630 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.85 (1H, ddd, J=9.7, 5.4, 3.1 Hz), 6.00 (1H, ddd, J=9.7, 2.3, 1.3 Hz), 4.39 (1H, ddt, J=10.5, 7.4, 5.3 Hz), 2.31 (2H, m), 1.80–1.45 (4H, m), 1.42–1.25 (4H, m), 0.90 (3H, t, J=6.9 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=164.6 (s), 145.0 (d), 121.4 (d), 78.0 (d), 34.8 (t), 31.5 (t), 29.3 (t), 24.4 (t), 22.4 (t), 13.9 (q).

References and notes

1. Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859–2862.
2. Hlubucek, J. R.; Robertson, A. V. *Aust. J. Chem.* **1967**, *20*, 2199–2206.
3. Abe, S. *J. Chem. Soc. Jpn* **1937**, *58*, 246.
4. Murakami, N.; Weiqi, W.; Aoki, M.; Tsutsui, Y.; Higuchi, K.; Aoki, S.; Kobayashi, M. *Tetrahedron Lett.* **1997**, *38*, 5533–5536.
5. Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084–9085.
6. Kalesse, M.; Quitschalle, M.; Khandavalli, C. P.; Saeed, A. *Org. Lett.* **2001**, *3*, 3107–3110.
7. Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685–1688.
8. Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. *Org. Lett.* **2002**, *4*, 1023–1026.
9. Marshall, J. A.; Bourdeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751–2754.
10. Enders, D.; Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M. *Chem. Eur. J.* **2002**, *8*, 4272–4284.
11. Kalesse, M.; Khandavalli, P. C.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. Eur. J.* **2003**, *9*, 1129–1136.
12. Fournier, L.; Gaudel-Siri, A.; Kocienski, P. J.; Pons, J. M. *Synlett* **2003**, 107–111, see p 584.
13. Jewers, K.; Davis, J. B.; Dougan, J.; Manchanda, A. H.; Blunden, G.; Kyi, A.; Wetchapinan, S. *Phytochemistry* **1972**, *11*, 2025–2030.
14. Meyers, H. H. *Liebigs Ann. Chem.* **1979**, 484.
15. O'Connor, B.; Just, G. *Tetrahedron Lett.* **1986**, *27*, 5201–5202.
16. Honda, T.; Kametani, T.; Kanai, K.; Tatsuzaki, Y.; Tsubuki, M. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1733–1737.
17. Rahman, S. S.; Wakefield, B. J.; Roberts, S. M.; Dowle, M. D. *J. Chem. Soc. Chem. Commun.* **1989**, 303–304.
18. Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281–288.
19. Bennett, F.; Knight, D. W. *Tetrahedron Lett.* **1988**, *29*, 4625–4628.
20. Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583–586.
21. Chidambaram, N.; Satyanarayana, K.; Chandrasekaran, S. *Tetrahedron Lett.* **1989**, *30*, 2429–2432.
22. Shchukovskaya, L. L.; Pal'chick, R. I.; Lazarev, A. N. *Dokl. Akad. Nausk. SSSR* **1965**, *164*, 357–360.
23. Black, T. H.; Farell, J. R.; Probst, D. A.; Zotz, M. C. *Synth. Commun.* **2002**, *32*, 2083–2088.
24. Hoffmann, R. W.; Landmann, B. *Tetrahedron Lett.* **1983**, *24*, 3209–3212.
25. Mino, T.; Masuda, S.; Nishio, M.; Yamashita, M. *J. Org. Chem.* **1997**, *62*, 2633–2635.
26. Pohmakotr, M.; Jarupan, P. *Tetrahedron Lett.* **1985**, *26*, 2253–2256.
27. Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R.; Williams, D. J. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1355–1362.
28. Carlson, R. M. *J. Org. Chem.* **1975**, *40*, 1610–1616.
29. Marion, F.; Fol, R. L.; Courillon, C.; Malacria, M. *Synlett* **2001**, 138–140.
30. Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445–13450.
31. Sato, M.; Nakashima, H.; Hanada, K.; Hayashi, M.; Honzumi, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 2833–2837.
32. Bonini, C.; Pucci, P.; Racioppi, R.; Viggiani, L. *Tetrahedron: Asymmetry* **1992**, *3*, 29–32.
33. Bennett, F.; Knight, D. W.; Fenton, G. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1543–1547.
34. Takano, S.; Setoh, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 533–534.
35. Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4761–4764.
36. Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4117–4121.
37. Haase, B.; Schneider, M. P. *Tetrahedron: Asymmetry* **1993**, *4*, 1017–1026.
38. Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371–1380.
39. Romeyke, Y.; Keller, M.; Kluge, H.; Grabley, S.; Hammann, P. *Tetrahedron* **1991**, *47*, 3335–3346.
40. Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomiza, S.; Mariwake, T. *Chem. Lett.* **1984**, 1389–1392.
41. Falck, J. R.; Lumin, S.; Lee, S.-G.; Heckmann, B.; Miokowski, C.; Karara, A.; Capdevila, J. *Tetrahedron Lett.* **1992**, *33*, 4893–4896.
42. Schreiber, S. L.; Kelly, S. E.; Porco, J. A., Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210–6218.
43. Kiyooka, S.; Mostofa, A. H. *J. Org. Chem.* **1999**, *64*, 5511–5523.

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Asymmetric synthesis of 3(*S*),17-dihydroxytanshinone

Jiangang Zhang, Wenhu Duan* and Junchao Cai

Shanghai Institute of Materia Madica, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, Shanghai 201203, China

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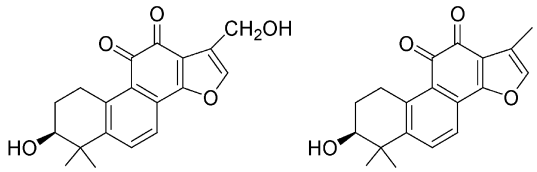
Abstract—The first synthesis of 3(*S*),17-dihydroxytanshinone was achieved by ultrasound promoted Diels–Alder reaction of the protected 3-hydroxymethyl-4,5-benzofurandione with a vinylcyclohexene derivative. Bioassay showed that the synthetic 3(*S*),17-dihydroxytanshinone was active in vitro against HL-60 tumor cell line by MTT method.

1. Introduction

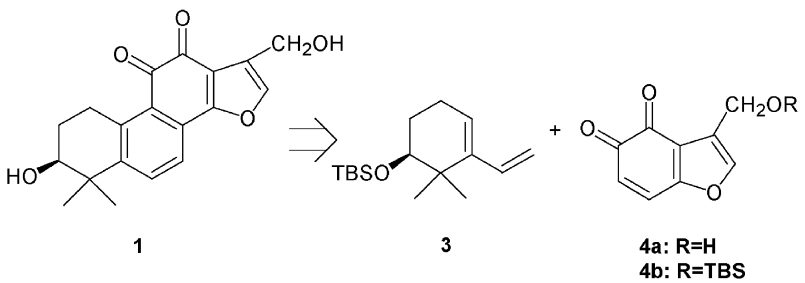
Danshen diterpene quinones exhibit significant cytotoxicity against various tumor cell lines.[1] It is notable that the extract of Dan Shen showed higher activities than the pure natural products.[2] This has led to more intensive search for minor active metabolites.[3] 3,17-Dihydroxytanshinone **1** was isolated from the roots of *Salvia bians* Royle ex Benth. (Labiatae), a native of the Kumaon Himalayan glaciers.[4] It is one of the three known tanshinone diterpene natural products bearing 17-hydroxyl group. However, the authors did not report its absolute configuration and biological activities. Lee and co-workers reported that the absolute stereochemistry of 3-hydroxytanshinone **2**, another natural product isolated from the same plant as **1**, was *S*.[5] According to biosynthesis, 3(*S*),17-dihydroxytanshinone is likely to be the natural one. Its unusual structure and potential biological properties combined to make the compound a challenging synthetic target.



In this paper, we described an asymmetric synthesis of compound **1**.

2. Result and discussion

The retro-synthesis of compound **1** was shown in Scheme 1. The Diels–Alder approach to tanshinone diterpenes was widely employed. Indeed, Lee and co-workers[5] reported the



Scheme 1.

Keywords: Natural product; Antitumor; Tanshinone diterpene; Dihydroxytashinone; Diels–Alder cycloaddition; Ultrasound; Total synthesis.
* Corresponding author. Tel./fax: +86-21-50806032; e-mail address: whduan@mail.shcnc.ac.cn

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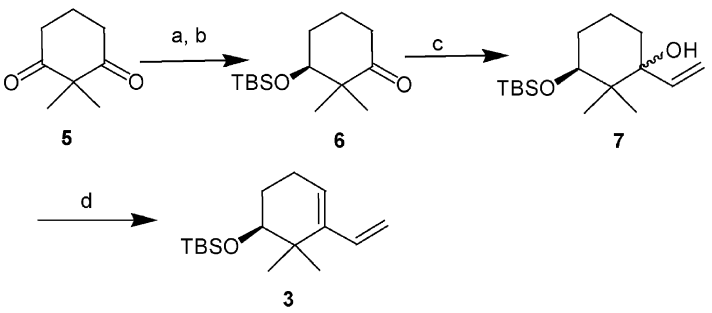


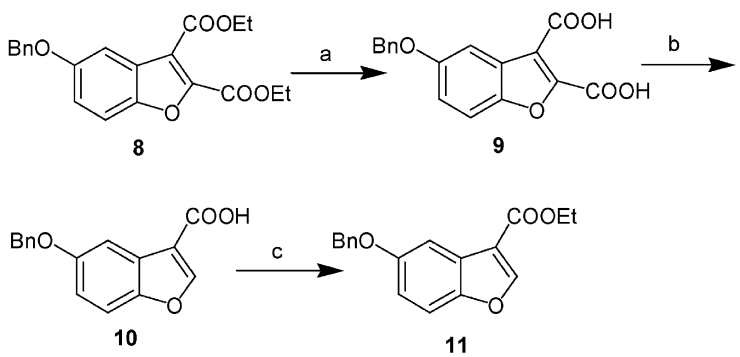
Scheme 2. *Conditions*: (a) Baker's yeast, 25 °C, 18 h, 70%; (b) 1.2 equiv. TBSCl, 1.5 equiv. imidazole, DMF, 25 °C, overnight, 91%; (c) 5 equiv. vinylmagnesium bromide, THF, 0 °C, 2 h; (d) 0.01 equiv. *p*-toluenesulfonic acid, 10 equiv. $MgSO_4$, toluene, reflux, 30 min, 42% two steps.

syntheses of some tanshinone diterpene natural products by ultrasound-promoted Diels–Alder cycloaddition. However, there were few reports on the synthesis of tanshinone diterpenes bearing 17-hydroxyl group.[6]

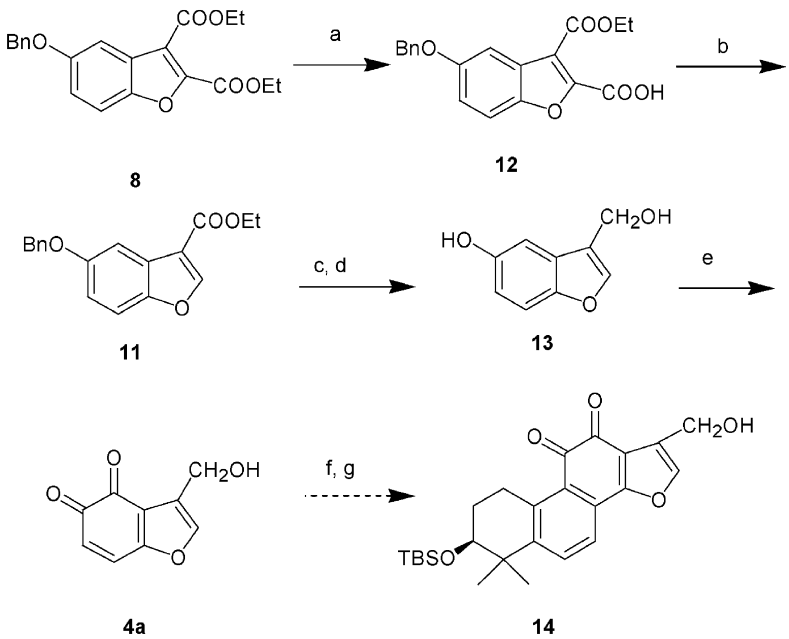
The diene **3** was synthesized from 2,2-dimethyl-1, 3-dicyclohexanone **5**. The starting material **5** was reduced by baker's yeast (70% yield, and >95% ee). Then the hydroxyl group was protected with *t*-butyldimethylsilyl (TBS) according to the conventional procedure to give ketone **6**, the analytical data (including optical rotation) of **6** was identical with that of product in literature.[7] The stereochemistry at C3 of ketone **6** was then assigned to be 'S' as reported in literature. To avoid harsh conditions in synthesis of diene **3** reported by Lee and co-workers in which LDA-mediated triflation, palladium-catalyzed coupling and use of highly toxic tri-*n*-butylstannane were involved, we resorted to a tertiary alcohol dehydration approach. Ketone **6** was treated with vinylmagnesium bromide to give tertiary alcohol **7** in 70% yield. Elimination of the hydroxyl group to form diene was problematic due to acid-sensitive TBS group. After failure with reagents such as $MsCl-Et_3N$, pyridine–$SOCl_2$, and *p*-toluenesulfonic acid, diene **3** was prepared by refluxing **7** with excessive dry magnesium sulfate in the presence of catalytic amount of *p*-toluenesulfonic acid (Scheme 2). The analytical data including optical rotation of diene **3** were identical with that of product in literature.[5] So, the diene **3** possessed S configuration as reported in literature.

With the diene **3** at hand, the next step is to synthesize *o*-quinone **4**, of which compound **11** is the key intermediate, with a synthetic route (Scheme 3) reported by Robins et al. [8] Robin's synthesis of **11** was completed in three steps: first, hydrolysis of benzofuran-2,3-dicarboxylate **8** to give benzofuran-2,3-dicarboxylic acid **9**, and then selective decarboxylation of 2-carboxyl group to benzofuran 3-carboxylic acid **10** and finally esterification of carboxylic acid **10** to afford **11** (Scheme 3).

Although the author reported a moderate yield in monodecarboxylation step, we found that the monodecarboxylation was affected by several factors such as reaction temperature, the quantity of copper, the activation of copper, particle size of copper, and stirring condition, etc. the reaction often encountered either sluggish monodecarboxylation or rapid decarboxylation of two carboxyl groups. We managed to prepare monocarboxylate **11** in a more efficient way (Scheme 4). The 2-carboxylate group of dicarboxylate **8** was selectively hydrolyzed to carboxylic acid **12** when **8** upon reaction with 1 equiv. of sodium hydroxide in ethanol. Then, the 2-carboxyl group of **12** underwent decarboxylation in the presence of copper powder in quinoline at 200 °C to give monocarboxylate **11** in 70% overall yield.[9] 3-Hydroxylmethyl-5-hydroxybenzofuran **13** was then prepared from 3-carboxylate **11** by debenzylation with Pd-catalyzed hydrogenation, and subsequent reduction with $LiAlH_4$ according to our previous work.[6] Cycloaddition of freshly prepared *o*-quinone **4a** from **13** with Fremy's salt with diene **3** was attempted with ultrasonic irradiation to achieve **14**, no cycloaddition product was formed and *o*-quinone **4a** was decomposed. This result was in accordance with our previous findings that *o*-quinone **4a** was very sensitive to temperature, acidic, and



Scheme 3. *Conditions*: (a) NaOH, EtOH, reflux; (b) Cu powder quinoline, 2 h, 200 °C; (c) $SOCl_2$, EtOH.



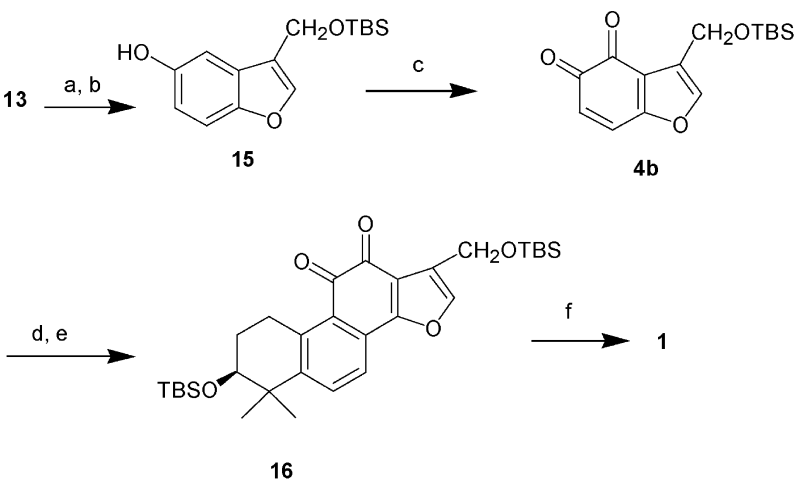
Scheme 4. *Conditions*:(a) 1 equiv. NaOH, EtOH, 2 h, rt; (b) Cu powder, quinoline, 2 h, 200 °C, 70% in two steps; (c) H_2/10% Pd–C, EtOH, 16 h, rt; (d) 5 equiv. $LiAlH_4$, THF, 10 h, 25 °C; (e) Fremy's salt, KH_2PO_4 buffer; (f) 3 equiv. **3**, ultrasonic, 6 h, 5 °C; (g) 1.5 equiv. DDQ, benzene, 10 h, reflux.

basic condition. It is unstable after standing in room temperature for several hours. The instability of *o*-quinone **4a** in fact caused a low overall yield in synthesis of Przewaquinone A.[6] Alternatively, the hydroxyl groups of **13** was protected as its TBS ether.(Scheme 5). The phenolic silyl ether was then selectively cleaved to give **15** upon reflux with potassium carbonate in ethanol (80% yield in two steps).[10] Oxidation of **15** to *o*-quinone **4b** with Fremy's salt was also troublesome. There was no reaction in aqueous methanol and aqueous acetone as the solvents. Finally, the oxidation of **15** to **4b** was achieved with modified phase transfer reaction pioneered by Kende.[11] Compound **16**, the precursor of **1**, was obtained after **3** and **4b** were subjected to ultrasonic irradiation at 5 °C for 6 h followed by aromatization with DDQ. Since the stereochemistry of **3** determined the stereochemistry of **16**, the absolute configuration of **16** was 'S' as in compound **3**. Finally, removal of the TBS protective groups with 15% hydrogen fluoride in acetonitrile[12] gave the target molecule, 3(*S*),17-dihydroxytanshinone, $[\alpha]_D^{20}$ −10° (acetone, *c*=0.4). The data of ^{1}H NMR, IR, MS, and melting point are identical with that of the natural product.[4]

In vitro cytotoxic activity of compound **1** on tumor lines was evaluated by MTT and SRB method, the synthetic 3(*S*),17-dihydroxytanshinone was active against HL60 cell line, the inhibition rate is 62% at 3 μM.

3. Conclusions

We successfully used ultrasound-promoted Diels–Alder cycloaddition to develop a first, concise total synthesis of optically active 3(*S*),17-dihydroxytanshinone (**1**). Chemical



Scheme 5. *Condition*: (a) 3 equiv. TBSCl, 5 equiv. Imidazole, DMF, 16 h, 25 °C; (b) 1.5 equiv. K_2CO_3, 5 equiv. H_2O, EtOH, reflux, 80% in two steps; (c) 5 equiv. Fremy's salt, 10 equiv. TBABr, CH_2Cl_2, KH_2PO_4 buffer, 18 h, 0 °C; (d) 3 equiv. **3**, ultrasonic, 6 h, 5 °C; (e) 1.5 equiv. DDQ, benzene, 10 h, reflux, 28% in three steps; (f) 15% HF, CH_3CN, 3 h, 25 °C, 85%.

synthesis and biological investigations of the analogues of this natural product are in progress.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under nitrogen atmosphere All reagents were purchased from Shanghai Chemical Reagent Company and Acros, and were used without further purification unless otherwise stated. Melting points were uncorrected. Infrared spectra were recorded on a Nicolet Magna 750 spectrometer and only characteristic absorptions were reported. The ^{1}H NMR spectra were measured with a Bruker AM-400 (400 MHz) spectrometer. ^{13}C NMR spectra were measured with an AM-400 (100 MHz) spectrometer. Coupling constants (J values) were reported in Hertz. Chemical shifts were expressed in ppm, using residual solvent as an internal standard. Mass spectra (medium and high resolution) were run on Varian MAT-711 and MAT-95 spectrometers. All solvents were purified and dried prior to use according to standard procedures.[13] 'Petroleum ether' referred to petroleum ether bp, 60–90 °C.

4.2. Synthesis

4.2.1. (−)-(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-1-vinylcyclohexene (3). A solution of **6** (2.00 g, 7.8 mmol) in anhydrous THF (50 mL) was cooled to 0 °C, vinylmagnesium bromide (1.0 M in THF, 39 mL, 39 mmol) was then added dropwise, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated NH_4Cl (50 mL), and the aqueous layer was extracted with ether (3×30 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 40:1) to give **7** (1.60 g), as a mixture of diastereomers. Then **7** was dissolved in dry toluene (80 mL). $MgSO_4$ (10 g, 83 mmol) and *p*-toluenesulfonic acid (9 mg, 0.4 mmol) were added. Then the mixture was refluxed for 30 min, and cooled to room temperature. $MgSO_4$ was then filtered off, the filtrate was washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel eluting with petroleum ether to afford **3** as a colorless oil (0.873 g, 42% from **6**): $[\alpha]_D^{20}$ −14.6° (lit.[5] −15.0°); IR (KBr): 2956, 2856, 1471, 1362, 1256, 1092, 1007, 879, 737, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, J=400 Hz, TMS): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.9 (s, 9H), 0.98 (s, 3H), 1.01 (s, 3H), 1.64–1.68 (m, 2H), 2.01–2.20 (m, 2H), 3.53 (dd, 1H, J=6.3, 6.3 Hz), 4.93 (dd, 1H, J=10.7, 1.9 Hz), 5.27 (dd, 1H, J=17.0, 1.9 Hz), 5.69 (dd, 1H, J=3.6, 3.6 Hz), 6.29 (dd, 1H, J=17.0, 10.7 Hz) ppm. EIMS (m/z): 266 (M^+). HRMS 266.2060, calcd for $C_{16}H_{30}SiO$, 266.2066.

4.2.2. 5-Benzyloxy-benzofuran-2,3-dicarboxylic acid 3-ethyl ester (12). Compound **8** (1.00 g, 2.7 mmol) was dissolved in ethanol (50 mL) at room temperature, and NaOH (0.108 g, 2.7 mmol) in ethanol (14 mL) was added dropwise. After stirring for 2 h, the solution was acidified with HCl (2 M) to pH=4. Ethanol (40 mL) was removed under reduced pressure. The resultant residue was added with water (10 mL), the precipitate formed was collected by filtration, and washed with cold ethanol to give **12** (0.83 g, 2.4 mmol, 90% yield) as a white solid: mp 132–134 °C; IR (KBr): 2984, 1749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 Hz, TMS): δ 1.52 (t, 3H, J=7.1 Hz), 4.61 (q, 2H, J=7.1 Hz), 5.16 (s, 2H), 7.24 (dd, 1H, J=9.3, 2.6 Hz), 7.35–7.48 (m, 5H), 7.49 (d, 1H, J=2.6 Hz), 7.59 (d, 1H, J=9.3 Hz) ppm. EIMS (m/z): 340 (M^+). HRMS 340.0963, calcd for $C_{19}H_{16}O_6$, 340.0947.

4.2.3. 5-Benzyloxy-benzofuran-3-carboxylic acid ethyl ester (11). Compound **12** (1.00 g, 2.94 mmol), copper powder (30 mg, 0.47 mmol) and quinoline (5 mL) were added to a flask. After stirring at 200 °C for 1 h, the mixture was cooled to room temperature. The solution was acidified with conc. HCl (16 mL), and extracted with ether (3×30 mL). The combined extract was washed, respectively, with water (3×30 mL), saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (10:1) to give **11** (0.694 g, 2.36 mmol, 80% yield) as a white crystal: mp 64–66 °C; IR (KBr): 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 1.39 (t, 3H, J=7.1 Hz), 4.38 (q, 3H, J=7.1 Hz), 5.12 (s, 2H), 7.02 (dd, 1H, J=9.2, 2.7 Hz), 7.35–7.50 (m, 6H), 7.59 (d, 1H, J=2.7 Hz), 8.20 (s, 1H) ppm. EIMS (m/z): 296 (M^+). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96%; H, 5.44%. Found: C, 73.20%; H, 5.47%.

4.2.4. 3-Hydroxymethyl-benzofuran-5-ol (13). A mixture of **11** (1.20 g, 4.05 mmol) and 10% palladium on carbon (0.2 g) in ethanol (100 mL) was hydrogenated at room temperature under hydrogen (1 atm) for 16 h. Then, the catalyst was filtered-off, and the solvent was removed in vacuo. The residue was dissolved in anhydrous THF (40 mL) under N_2, and added dropwise to a mixture of $LiAlH_4$ (0.77 g, 20.1 mmol) in THF (40 mL) at room temperature. After stirred for 10 h, ethyl acetate (20 mL) was added to consume the residual $LiAlH_4$, then HCl (2 M, 40 mL) was added to the reaction mixture. The aqueous layer was then separated and extracted with ether (3×30 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (40 mL) and brine (40 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated to dryness, and the residue was purified by flash chromatography on silica gel eluting with petroleum ether/acetone (1:1) to give **13** (0.553 g, 3.36 mmol, 83% yield) as a white crystal: mp 135–136 °C; IR (KBr) 3409, 3201 cm^{-1}; ^{1}H NMR (400 Hz, DMCO-d_6, TMS): δ 4.70 (s, 2H), 6.84 (dd, 1H, J=8.8, 2.6 Hz), 7.11 (dd, 1H, J=2.6 Hz), 7.30 (d, 1H, J=8.8 Hz), 7.67 (s, 1H) ppm. EIMS (m/z): 164 (M^+). Anal. calcd for $C_9H_8O_3$: C, 65.85%; H, 4.91. Found: C, 66.01%; H, 4.91%.

4.2.5. 3-(*tert*-Butyldimethylsilyloxymethyl)-benzofuran-5-ol (15). To a solution of **13** (0.630 g, 3.84 mmol), and imidazole (1.30 g, 19.4 mmol) in anhydrous DMF (10 mL) was added a solution of TBSCl (1.74 g, 11.5 mmol) in

anhydrous DMF (8 mL). The resulting solution was stirred at room temperature for 24 h. $NaHCO_3$ solution (5%, 50 mL) and ether (60 mL) was added, and the aqueous layer was separated and extracted with additional ether (3×30 mL). The combined ether layer was washed with brine (30 mL), dried with Na_2SO_4, and filtered. The solvent was removed in vacuo, the residue was purified by flash chromatograph on silica gel eluting with petroleum ether/ethyl acetate (80:1) to afford a colorless oil. This oil was dissolved in ethanol (32 mL), to which water (0.33 mL, 18 mmol) and K_2CO_3 (0.560 g, 4.06 mmol) were added. The resultant mixture was heated to reflux for 12 h. Then the reaction mixture was cooled to room temperature, and filtered. The filtrate was evaporated to dryness. The residue was purified by flash chromatograph on silica gel eluting with petroleum ether/ethyl acetate (20:1) to give **15** (0.854 g, 3.07 mmol, 80% yield) as a white crystal: mp 72–74 °C; IR (KBr) 3244, 2955, 2854, 1462, 1217, 1070, 924, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS): δ 0.1 (s, 6H), 0.9 (s, 9H), 4.8 (s, 2H), 6.79 (dd, 1H, J=8.8, 2.6 Hz), 6.89 (1H, d, J=2.6 Hz), 7.30 (1H, d, J=8.8 Hz), 7.49 (1H, s) ppm. EIMS (*m*/*z*): 278 (M^+); HRMS 278.1344, calcd for $C_{15}H_{22}SiO_3$, 278.1338.

4.2.6. Oxidize 15 to 3-(*tert*-butyldimethylsilyloxy methyl)-benzofuran-4,5-dione and cycloaddition 3 with 4b to (+)-3(*S*),17-dihydroxytanshinone di-*tert*-butyldimethylsilyl ether (16). A solution of **15** (50 mg, 0.18 mmol) and TBABr (579 mg, 1.8 mmol) in CH_2Cl_2 (20 mL) were cooled to 0 °C in an ice bath, and an ice-cooled aqueous solution of Fremy's salt (300 mg dissolved in 20 mL of 0.1 M KH_2PO_4 buffer adjusted to pH 7) was added dropwise. After the addition, the solution was stirred at 0 °C for 18 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was washed with water (2×20 mL) and brine (3×20 mL), over Na_2SO_4. The solvent was removed under reduced pressure to afford crude **4b** as a red oil, which was unstable at room temperature. Crude **4b** was quickly used in next step without purification. A mixture of crude **4b** and **3** (144 mg, 0.54 mmol) in anhydrous methanol (0.2 mL) was subjected to ultrasonic irradiation at 5 °C for 6 h. Methanol was then removed in vacuo, and the residue was passed through a silica gel plug, eluting initially with petroleum ether to recover unreacted **3** (101 mg, 70% recovery), and then with CH_2Cl_2 to give a mixture of aromatized and dihydro-adducts. This mixture was fully aromatized by refluxing in benzene (5 mL) with DDQ (62 mg, 0.27 mmol) for 10 h. Then the solution was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (8:1) to give **16** as a red crystal (34 mg, 0.06 mmol, 30% yield): mp 184–186 °C; $[\alpha]_D^{20}$ +10 (*c* 0.4, $CHCl_3$); IR (KBr) 2955, 2856, 1697, 1677, 1471, 1387, 1082, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS): δ 0.06 (s, 3H), 0.10 (s, 3H), 0.12 (s, 6H), 0.88 (s, 9H), 0.94 (s, 9H), 1.26 (s, 3H), 1.29 (s, 3H), 1.80–1.85 (m, 1H), 1.86–2.00 (m, 1H), 3.18–3.24 (m, 1H), 3.31–3.40 (m, 1H), 3.70 (dd, 1H, J=8.8, 2.9 Hz), 4.87 (d, 1H, J=1.5 Hz), 7.41 (t, 1H, J=1.5 Hz), 7.59 (d, 1H, J=8.2 Hz), 7.64 (d, 1H, J=8.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.3, −4.8, −4.0, 18.2, 18.4, 25.9, 25.96, 25.98, 26.8, 26.9, 29.3, 40.6, 57.5, 74.8, 117.2, 120.7, 126.0, 127.3, 127.6, 133.8, 141.8, 143.6, 150.0, 162.1, 175.1, 183.3 ppm. EIMS (*m*/*z*): 554 (M^+). HRMS 554.2892, calcd for $C_{31}H_{46}Si_2O_5$, 554.2884.

4.2.7. (−)-3(*S*),17-Dihydroxytanshinone 1. Silyl ether **16** (30 mg, 0.054 mmol) was dissolved in a solution of 40% aqueous HF/CH_3CN (20 mL, 1:4, v/v) and stirred at room temperature for 3 h. Water (20 mL) was then added, and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2/CH_3OH (20:1) to give **1** (15 mg, 0.46 mmol, 85% yield) as red crystals: mp 208–210 °C (lit. 209–210 °C);[4] $[\alpha]_D^{20}$ −10 (*c* 0.4, acetone); IR (KBr): 3553, 3045, 1673, 1658, 1383, 1365, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS): δ 1.32 (s, 3H), 1.35 (s, 3H), 2.15–2.29 (m, 2H), 3.32–3.45 (m, 2H), 3.96 (dd, 1H, J=8.6, 2.8 Hz), 4.70 (s, 2H), 7.33 (s, 1H), 7.50 (d, 1H, J=8.3 Hz), 7.63 (d, 1H, J=8.3 Hz); ^1H NMR (DMSO-d_6, 400 MHz, TMS): δ 1.19 (s, 3H), 1.22 (s, 3H), 1.64–1.78 (m, 1H), 1.82–1.88 (m, 1H), 2.98–3.07 (m, 1H), 3.18–3.26 (m, 1H), 3.52 (dd, 1H, J=8.8, 2.6 Hz), 4.55 (s, 1H), 7.56 (d, 1H, J=8.1 Hz), 7.73 (s, 1H), 7.76 (d, 1H, J=8.1 Hz) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 25.3, 26.2, 26.5, 29.1, 54.6, 72.1, 118.3, 120.4, 126.0, 126.8, 126.9, 134.0, 142.4, 142.5, 149.7, 161.0, 174.7, 182.5 ppm. EIMS (*m*/*z*): 326 (M^+). HRMS 326.1155, calcd for $C_{19}H_{18}O_5$, 326.1154.

References and notes

1. Ryu, S. Y.; Lee, C. O.; Choi, S. U. *Planta Med.* **1997**, *63*, 339–342.
2. Xu, R.-S. Tian Ran Chan Wu Hua Xue; Science: Beijing, 1993; pp 323–334.
3. Luo, H.-W.; Wu, B.-J.; Wu, M.-Y.; Yong, Z.-C.; Niwa, M.; Hirata, Y. *Phytochemistry* **1985**, *24*, 815–817.
4. Khetwal, K. S.; Pathak, R. P.; Vashisht, A.; Pant, N. *J. Nat. Prod.* **1992**, *55*, 947–949.
5. Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn* **1969**, *42*, 3318–3323. Shen, J. X.; Zhang, P. Z.; Qiao, M. *Acta Pharm. Sin.* **1988**, *23*, 545–548. Lee, J.; Li, J.-H.; Oya, S.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5301–5312. Haiza, M.; Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 5008–5013.
6. Duan, W.-H.; Cai, J.-C. *Chin. Chem. Lett.* **1997**, *8*, 205–206.
7. Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273–281.
8. Robins, P. A.; Walker, J. *J. Chem. Soc.* **1952**, 642–649.
9. The analytical data of IR, ^1H NMR, and melting point of Compound **10** was identical with that of literature one.
10. Wilson, N. S.; Keay, B. A. *Tetrahedron Lett.* **1997**, *38*, 187–190.
11. Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *25*, 923–926.
12. Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681–684.
13. Perrin, D. D.; Armargo, W. L. F. Purification of laboratory chemicals; 4th ed. Butterworth-Heinemann: Oxford, 1997.

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Formation of isoxazole derivatives via nitrile oxide using ammonium cerium nitrate (CAN): a novel one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives

Ken-ichi Itoh[†] and C. Akira Horiuchi[*]

Department of Chemistry, Rikkyo (St Paul's) University, 3-34-1 Nishi-Ikebukuro, Toshima-ku, 171-8501 Tokyo, Japan

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Abstract—The reactions of alkenes and alkynes with ammonium cerium(IV) nitrate ($(NH_4)_2Ce(NO_3)_6$, CAN(IV)) in acetone under reflux gave the corresponding 3-acetyl-4,5-dihydroisoxazole and 3-acetylisoxazole derivatives. In the case of acetophenone, 3-benzoyl-4,5-dihydroisoxazole and 3-benzoylisoxazole derivatives were obtained. Reaction of acetone with CAN(IV) afforded the corresponding furoxan (3,4-diacetyl-1,2,5-oxadiazole 2-oxide) as the dimer of nitrile oxide. Moreover, it was found that yields of isoxazole derivatives were improved using ammonium cerium(III) nitrate tetrahydrate ($(NH_4)_2Ce(NO_3)_5{\cdot}4H_2O$, CAN(III))-formic acid. The reaction mechanisms based on nitration and formation of nitrile oxide mediated by CAN(IV) or CAN(III) from acetone or acetophenone are also proposed.

1. Introduction

Isoxazole derivatives are an important class of heterocyclic compounds and their chemical properties have been studied over the years. Isoxazole derivatives have served as a versatile building block in organic synthesis. They can be converted into several important synthetic units such as β-hydroxy ketones,[1–5] γ-amino alcohols,[6] α,β-unsaturated oxime,[7] and β-hydroxy nitriles.[8] For example, the transformation of β-hydroxy ketones is commonly accomplished by reduction of 4,5-dihydroisoxazoles with H_2-Raney Ni,[1] $TiCl_3$,[2] $Mo(CO)_6$,[3] and SmI_2,[4] and oxidation with ozone.[5] In addition, isoxazole derivatives have long been targeted in synthetic investigation for their known biological activities and pharmacological properties such as hypoglycemic,[9] analgesic,[10] anti-inflammatory,[11] and anti-bacterial activity.[12] Recently, Srivastava et al.[13] reported that on evaluation of HIV-inhibitory activity of 5-(2,2-dibromoacetyl)-3-phenylisoxazole, reduction of infected cells was indicated. Two methods have been employed generally to prepare isoxazole derivatives: 1,3-dipolar cycloaddition of alkenes or alkynes with nitrile oxides from the dehydrohalogenation of hydroximoyl chlorides in the presence of triethylamine,[14] and the dehydration of primary nitroalkanes with ethyl chloroformate in the presence of triethylamine.[15] In particular, it is known that the reaction of β-keto esters or α,β-unsaturated ketones with hydroxylamine yields the isoxazole derivatives via intramolcular nitrile oxide cycloaddition (INOC) by a one-pot method.[16,17]

CAN(IV) has been utilized extensively for a variety of oxidative transformations. In addition, it is known that CAN transform several alkenes and aromatic compounds into nitro compounds.[18,19] We have investigated the development of some novel reaction systems using CAN. During the course of our studies, we reported a novel α-iodination of ketones in acetic acid or alcohols,[20] a new alkoxyiodination and nitratoiodination of olefins and α,β-unsaturated esters,[21] and a new α,α′-diiodination of ketones using iodine-CAN(IV).[22] One of our group reported a one-pot synthesis of 4,5-dihydroisoxazole derivatives from alkenes by the use of CAN(IV) or CAN(III) in acetonitrile-formic acid at 57 °C for 48 h.[23] However, the yields of products were unsatisfactory because of the formation of nitroalkene and nitro alcohol from alkene as by-products. Still earlier, we described a novel one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives using ammonium cerium nitrate (CAN).[24] Now, in this paper we report details concerning a new and improved synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives(**1a**–**19a**, **1b**–**19b**) using CAN.

2. Results and discussion

The reaction of alkenes **1**–**13** with CAN(IV) in acetone

Keywords: Ammonium cerium(IV) nitrate; Ammonium cerium(III) nitrate; Formic acid; Isoxazole derivatives; Nitrile oxide.
* Corresponding author. Tel.: +81-3-3985-2397; fax: +81-3-3985-2397; e-mail address: horiuchi@rikkyo.ac.jp
† Present address: College of Science and Technology, Nihon University, 7-24-1 Funabashi-si, Chiba 274-8501, Japan.

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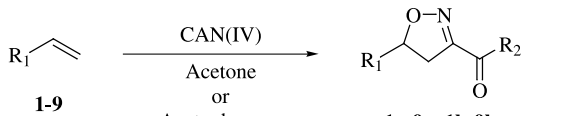


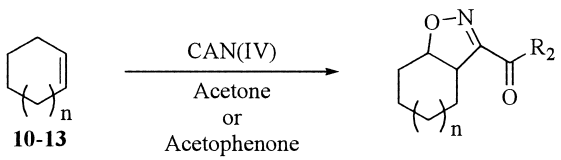
1-9

1a-9a, **1b-9b**
a : R_2=Me
b : R_2=Ph

1 : R_1=n-C_4H_9
2 : R_1=n-C_5H_{11}
3 : R_1=n-C_6H_{13}
4 : R_1=$CH_2C_6H_{11}$
5 : R_1=CH_2Ph
6 : R_1=CH_2SMe
7 : R_1=CH_2CN
8 : R_1=CH_2OPh
9 : R_1=CH_2OCOMe

CAN(IV) : $(NH_4)_2Ce(NO_3)_6$

Scheme 1.



10-13

10 : n=0
11 : n=1
12 : n=2
13 : n=3

10a-13a, **10b-13b**
a : R_2=Me
b : R_2=Ph

Scheme 2.

under reflux gave 3-acetyl-4,5-dihydroisoxazole derivatives (**1a**–**13a**). In the case of acetophenone at 80 °C, 3-benzoyl-4,5-dihydroisoxazole derivatives (**1b**–**13b**) were obtained (Schemes 1 and 2). These results are summarized in Tables 1 and 2. Compound **1a** showed absorption at 1688 (C═O) and 1577 cm^{-1} (C═N) in its IR spectrum. The CI-MS spectrum of **1a** showed an $[M+H]^+$ peak at *m/z* 170. The ^1H NMR spectrum showed a singlet at δ 2.49 (3H, $COCH_3$), and two double doublets at δ 2.76 (1H, *J*=8.4, 17.6 Hz, CH_2) and 3.16 (1H, *J*=11.0, 17.6 Hz, CH_2). The ^{13}C NMR spectra exhibited signals at 193.4, 158.3 and 84.9 ppm, which were assigned as commonly known carbonyl carbon and carbons of the 4,5-dihydroisoxazole ring, respectively. Therefore, compound **1a** was identified to be 3-acetyl-5-butyl-4,5-dihydroisoxazole. Moreover, a similar reaction using alkynes **14**–**19** afforded the corresponding 3-acetyl- and 3-benzoylisoxazole derivatives (**14a**–**19a**, **14b**–**19b**) (Scheme 3). The IR spectrum of **14a** showed absorption at 1705 (C═O) and 1593 cm^{-1} (C═N). The CI-MS spectrum of **14a** showed an $[M+H]^+$ peak at *m/z* 154. The ^1H NMR spectra exhibited a singlet at δ 6.37 (1H). The ^{13}C NMR spectra exhibited signals at 192.5, 175.5, 162.1 and 99.2 ppm, which were assigned as commonly known carbonyl carbon and carbons of the isoxazole ring, respectively. Therefore, compound **14a** was identified to be 3-acetyl-5-propylisoxazole. On the basis of these results,

Table 1. Reaction of alkenes **1**–**13** with CAN(IV) in acetone or acetophenone

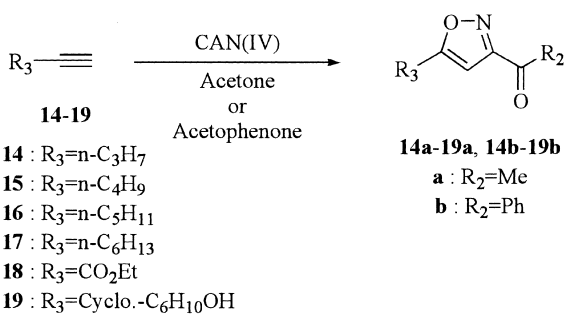
Entry[a]	Substrate	CAN(IV) (mol equiv.)	Solvent	Time (h)	Product (%)[b]
1	1-Hexene (**1**)	1.0	Acetone	15	**1a** (67)
2	1-Heptene (**2**)	1.0	Acetone	14	**2a** (72)
3	1-Octene (**3**)	0.5	Acetone	30	**3a** (47)
4	1-Octene (**3**)	1.0	Acetone	14	**3a** (72)
5	1-Octene (**3**)	1.25	Acetone	8	**3a** (68)
6	1-Octene (**3**)	1.5	Acetone	8	**3a** (62)
7	1-Octene (**3**)	2.0	Acetone	5	**3a** (54)
8	1-Octene (**3**)	4.0	Acetone	5	**3a** (35)
9	Allylcyclohexane (**4**)	1.0	Acetone	10	**4a** (69)
10	Allylbenzene (**5**)	1.0	Acetone	10	**5a** (72)
11	Allylmethylsulfide (**6**)	1.0	Acetone	5	**6a** (33)
12	Allylcyanide (**7**)	1.0	Acetone	15	**7a** (55)
13	Allylphenylether (**8**)	1.0	Acetone	10	**8a** (29)
14	Allylacetate (**9**)	1.0	Acetone	8	**9a** (44)
15	Cyclopentene (**10**)	1.0	Acetone	20	**10a** (47)
16	Cyclohexene (**11**)	1.0	Acetone	30	**11a** (22)
17	Cycloheptene (**12**)	1.0	Acetone	12	**12a** (56)
18	Cyclooctene (**13**)	1.0	Acetone	12	**13a** (59)
19	**1**	1.0	Acetophenone	18	**1b** (68)
20	**2**	1.0	Acetophenone	16	**2b** (78)
21	**3**	0.5	Acetophenone	30	**3b** (50)
22	**3**	1.0	Acetophenone	16	**3b** (77)
23	**3**	1.25	Acetophenone	10	**3b** (73)
24	**3**	1.5	Acetophenone	8	**3b** (68)
25	**3**	2.0	Acetophenone	5	**3b** (62)
26	**3**	4.0	Acetophenone	5	**3b** (27)
27	**4**	1.0	Acetophenone	16	**4b** (67)
28	**5**	1.0	Acetophenone	16	**5b** (54)
29	**6**	1.0	Acetophenone	5	**6b** (18)
30	**7**	1.0	Acetophenone	10	**7b** (60)
31	**8**	1.0	Acetophenone	12	**8b** (39)
32	**9**	1.0	Acetophenone	10	**9b** (66)
33	**10**	1.0	Acetophenone	10	**10b** (73)
34	**11**	1.0	Acetophenone	20	**11b** (49)
35	**12**	1.0	Acetophenone	10	**12b** (57)
36	**13**	1.0	Acetophenone	10	**13b** (71)

[a] Substrate (0.5 mmol), CAN(IV) (0.5–1.0 mmol), and solvent (3.0 ml) were employed under reflux.
[b] Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard. All products were identified by satisfactory spectral data (IR, ^1H NMR, ^{13}C NMR and MS).

Table 2. Reaction of alkynes **14**–**19** with CAN(IV) in acetone or acetophenone

Entry[a]	Substrate	Solvent	Time (h)	Product (%)[b]
1	1-Pentyne (**14**)	Acetone	10	**14a** (31)
2	1-Hexyne (**15**)	Acetone	10	**15a** (45)
3	1-Heptyne (**16**)	Acetone	10	**16a** (45)
4	1-Octyne (**17**)	Acetone	14	**17a** (59)
5	Ethyl acetylenecarboxylate (**18**)	Acetone	12	**18a** (49)
6	1-Ethynyl-1-cyclohexanol (**19**)	Acetone	12	**19a** (68)
7	**14**	Acetophenone	12	**14b** (64)
8	**15**	Acetophenone	12	**15b** (66)
9	**16**	Acetophenone	12	**16b** (71)
10	**17**	Acetophenone	12	**17b** (80)
11	**18**	Acetophenone	8	**18b** (71)
12	**19**	Acetophenone	10	**19b** (49)

[a] Substrate (0.5 mmol), CAN(IV) (0.5 mmol), and solvent (3.0 ml) were employed under reflux.
[b] Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard. All products were identified by satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS).

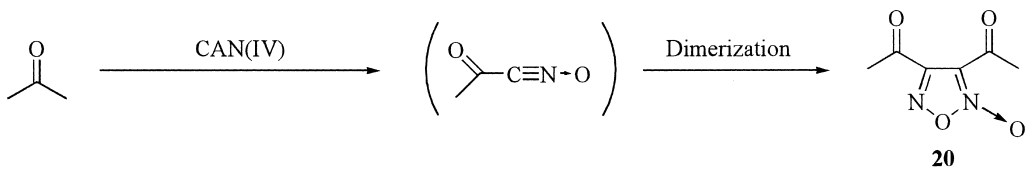


Scheme 3.

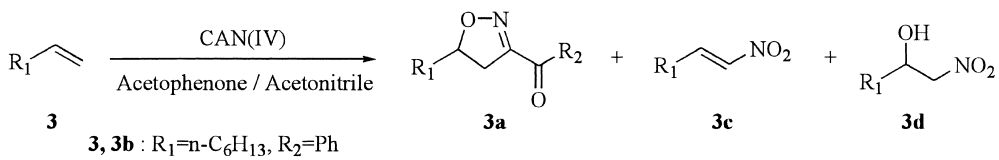
it was found that this reaction gives a novel one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives (**1a**–**19a**, **1b**–**19b**) from dipolarophiles (alkenes **1**–**13** or alkynes **14**–**19**) and acetone or acetophenone using CAN(IV). When substrate (0.5 mmol), CAN(IV) (0.5 mmol: 1.0 mol equiv.), and ketone (3.0 ml) were employed (Table 1, run 4 and 21), 3-acetyl- and 3-benzoylisoxazole derivatives were obtained in good yields of 72 and 77%, respectively. But the yields of isoxazole derivatives were lowered under reaction conditions using excess CAN(IV) (Table 1, run 5–8 and 23–26). It seems that the reaction products or intermediates were further oxidized due to the oxidative power of excess CAN(IV).

It is known that nitrile oxides dimerize to furoxans. If a furoxan is confirmed in this reaction, it is possible to prove the existence of nitrile oxide as an intermediate. The formation of the dimer (3,4-diacetyl-1,2,5-oxadiazole 2-oxide (furoxan) (**20**)) of nitrile oxide generated from acetone was confirmed. As shown in Scheme 4, the reaction of acetone with CAN(IV) gave compound **20**. Its IR spectrum showed absorption at 1718 (C=O) and 1605 cm^{-1} (C=N–O). The CI-MS spectrum of **20** showed an $[M+H]^+$ peak at *m/z* 172. The ^{1}H NMR spectrum showed two singlets at δ 2.74 (3H, $COCH_3$) and 2.63 (3H, $COCH_3$). The ^{13}C NMR spectra exhibited signals at 188.9, 185.5, 153.4 and 111.5 ppm, which were assigned to 1,2,5-oxadiazole 2-oxide, respectively. Therefore, compound **20** was identified to be 3,4-diacetyl-1,2,5-oxadiazole 2-oxide (furoxan). In addition, the formation of nitrile oxide from acetophenone was confirmed in the GC-MS spectra. This result suggests that acetone is converted into the corresponding nitrile oxide via a process, which involves nitration of acetone by cerium(IV) or cerium(III), and then undergoes competitive dimerization, and 1,3-dipolarcycloaddition with the alkenes or alkynes.

In order to investigate the relationship between yields of isoxazole derivatives and ketone as a precursor of nitrile oxide in the presence of CAN(IV), the reaction of 1-octene (**3**) and acetophenone with CAN(IV) in acetonitrile as solvent was carried out (Scheme 5). These results are summarized in Figure 1. From these results, it was found that the yields of isoxazole derivatives depended on the quantity of acetophenone. The reaction of **3** (0.5 mmol) and



Scheme 4. *Reaction conditions*: acetone (3.0 ml) and CAN(IV) (1.0 mmol) were employed under reflux for 10 h.



Scheme 5.

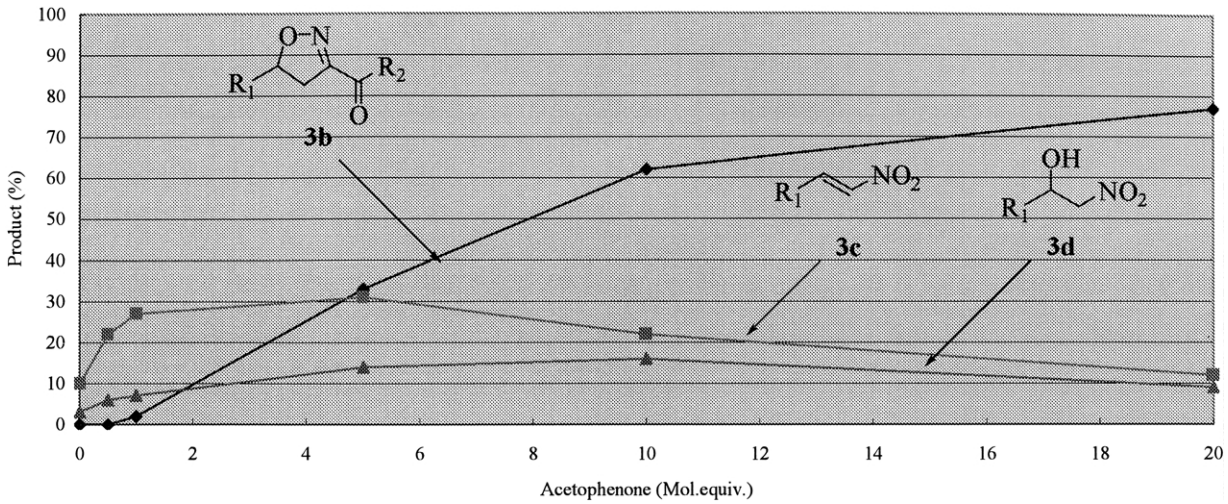
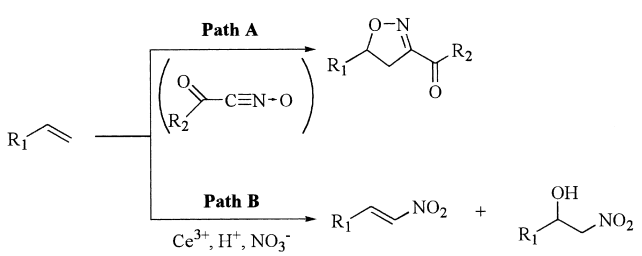


Figure 1. The relationship between acetophenone and products using CAN(IV) Reaction conditions: 1-octene (0.5 mmol), CAN(IV) (0.5 mmol), acetophenone (0–20 mol equiv.), and acetonitrile (3.0 ml) were employed for 20 h under reflux.

acetophenone (2.5 mmol, 5.0 mol equiv.) for 28 h with CAN(IV) in acetonitrile gave **3b**, 1-nitro-1-octene (**3c**),[25] and 1-nitro-2-octanol (**3d**)[25] in 33, 31 and 14% yields, respectively. In the reaction of **3** (0.5 mmol) and acetophenone (10.0 mmol, 20.0 mol equiv.) for 10 h, **3c** (12%), **3d** (9%) and **3b** (77%) as major products were obtained.

Previously, Sugiyama reported that the reaction of several alkenes and a small amount of additive such as cyclohexanone with CAN(IV) in acetonitrile-formic acid gave the corresponding 1-nitroalkenes and 1-nitro alcohols.[25] In this reaction mechanism, Ce^{4+} was at first converted into Ce^{3+} by ketones, and then the nitration of alkenes occurs by Ce^{3+}, proton, and nitrate ion. In the present reaction, it seems that the nitration by CAN(IV) proceeded by a similar reaction mechanism. Ce^{4+} was at first converted into Ce^{3+} by acetone or acetophenone, and the nitration of alkenes or ketones occurs by Ce^{3+}, proton and nitrate ion. From Figure 1, it is seen the nitration of acetone or acetophenone preferentially occurs to the nitration of alkenes under these reaction conditions using excess ketones. Therefore, the formation of nitrile oxide from acetone or acetophenone proceeds, and dipolarophiles (alkenes or alkynes) were consumed in 1,3-dipolar cycloaddition to nitrile oxide. A few by-products such as 1-nitroalkenes and 1-nitro alcohols were obtained. From these results mentioned above, it seems that this reaction proceeds via two reaction pathways: the formation of isoxazole derivatives by 1,3-dipolar cycloaddition of alkenes with nitrile oxide from acetone or acetophenone (Path A), and the formation of 1-nitroalkenes and 1-nitro alcohols from alkenes (Path B) (Scheme 6). Therefore, it seems that the reaction of Path A and B competitively proceeded, and the yields of isoxazole derivatives depended on the quantity of ketone.



Scheme 6.

We further examined the reaction conditions, to improve the yields of the isoxazole derivatives. Recently, Sugiyama

Table 3. Reaction of alkenes **1**–**13** with CAN(III)-formic acid in acetone or acetophenone

Entry[a]	Substrate	CAN(III) (mol equiv.)	Solvent	Time (h)	Product (%)[b]
1	**1**	1.0	Acetone	5	**1a** (74)
2	**2**	1.0	Acetone	5	**2a** (75)
3	**3**	0.5	Acetone	30	**3a** (47)
4	**3**	1.0	Acetone	10	**3a** (84)
5	**3**	1.25	Acetone	8	**3a** (83)
6	**3**	1.5	Acetone	5	**3a** (84)
7	**3**	2.0	Acetone	5	**3a** (83)
8	**4**	1.0	Acetone	10	**4a** (74)
9	**5**	1.0	Acetone	10	**5a** (81)
10	**6**	1.0	Acetone	5	**6a** (50)
11	**7**	1.0	Acetone	8	**7a** (72)
12	**8**	1.0	Acetone	8	**8a** (36)
13	**9**	1.0	Acetone	8	**9a** (46)
14	**10**	1.0	Acetone	5	**10a** (60)
15	**11**	1.0	Acetone	8	**11a** (36)
16	**12**	1.0	Acetone	10	**12a** (68)
17	**13**	1.0	Acetone	10	**13a** (73)
18	**1**	1.0	Acetophenone	12	**1b** (72)
19	**2**	1.0	Acetophenone	15	**2b** (84)
20	**3**	1.0	Acetophenone	15	**3b** (84)
21	**4**	1.0	Acetophenone	15	**4b** (70)
22	**5**	1.0	Acetophenone	16	**5b** (66)
23	**6**	1.0	Acetophenone	5	**6b** (35)
24	**7**	1.0	Acetophenone	10	**7b** (64)
25	**8**	1.0	Acetophenone	12	**8b** (42)
26	**9**	1.0	Acetophenone	10	**9b** (85)
27	**10**	1.0	Acetophenone	10	**10b** (82)
28	**11**	1.0	Acetophenone	20	**11b** (67)
29	**12**	1.0	Acetophenone	10	**12b** (76)
30	**13**	1.0	Acetophenone	10	**13b** (80)

[a] Substrate (0.5 mmol), CAN(III) (0.5 mol), formic acid (10.0 mol) and solvent (3.0 ml) were employed under reflux.

[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard. All products were identified by satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS).

Table 4. Reaction of alkynes **14**–**19** with CAN(III)-formic acid in acetone or acetophenone

Entry[a]	Substrate	Solvent	Time (h)	Product (%)[b]
1	**14**	Acetone	8	**14a** (65)
2	**15**	Acetone	8	**15a** (70)
3	**16**	Acetone	8	**16a** (73)
4	**17**	Acetone	10	**17a** (85)
5	**18**	Acetone	8	**18a** (87)
6	**19**	Acetone	8	**19a** (85)
7	**14**	Acetophenone	8	**14b** (76)
8	**15**	Acetophenone	8	**15b** (77)
9	**16**	Acetophenone	8	**16b** (80)
10	**17**	Acetophenone	8	**17b** (85)
11	**18**	Acetophenone	5	**18b** (76)
12	**19**	Acetophenone	8	**19b** (57)

[a] Substrate (0.5 mmol), CAN(III) (0.5 mol), formic acid (10.0 mol) and solvent (3.0 ml) were employed under reflux.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard. All products were identified by satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS).

reported that the reaction of 1-alkenes (1.5 ml) with CAN(IV) (0.6 mmol) and cyclohexanone (0.5 mmol) as additive in acetonitrile–formic acid (1.0 ml/0.5 ml) at 57 °C for 48 h gave the corresponding 4,5-dihydroisoxazole derivatives.[23] Moreover, this reaction smoothly proceeded by the use of CAN(III) instead of CAN(IV). From Figure 1 and Scheme 6, it was found that the nitration of ketones proceeds by Ce^{3+}, proton and nitrate ion. In the present reaction, we attempted to synthesize the isoxazole derivatives from alkenes with CAN(III)-formic acid instead of CAN(IV) in acetone or acetophenone. The reaction of several alkenes with CAN(III)-formic acid in acetone or acetophenone gave the corresponding 3-acetyl- and 3-benzoyl-4,5-dihydroisoxaole derivatives in preferable yields. These results are summarized in Table 3. The yields of isoxazole derivatives were increased by over 5–20%. For example, the reaction of 1-octene (**3**) with CAN(III)-formic acid in acetone under reflux for 10 h afforded 3-hexyl-5-acetyl-4,5-dihydroisoxazole (**3a**) in 84% yield (Table 3, run 3). Furthermore, in the case of several alkynes, similarly the yields of 3-acetyl- and 3-benzoylisoxaole derivatives were improved. These results are summarized in Table 4. From these results, it is apparent that these reactions using CAN(III)-formic acid efficiently afford the corresponding 3-acetyl- and 3-benzoylisoxazole derivatives in preferable yields. Also, the yields of products were not lowered under the reaction conditions using excess CAN(III) (Table 3, run 4–7). It seems that CAN(III) did not further oxidize the products.

The reaction of 1-octene (**3**) and acetophenone with CAN(III)-formic acid in acetonitrile was carried out, and the relationship between yields of products and ketone in the presence of CAN(III) is shown in Figure 2. The reaction of **3** (0.5 mmol) and acetophenone (2.5 mmol, 5.0 mol equiv.) for 28 h with CAN(III)-formic acid in acetonitrile gave **3b**, 1-nitro-1-octene (**3c**), and 1-nitro-2-octanol (**3d**) in 32, 24 and 13% yields, respectively. In the reaction of **3** (0.5 mmol) and acetophenone (10.0 mmol, 20.0 mol equiv.) for 10 h, **3b**, **3c** and **3d** were given in 82, 10 and 4% yield, respectively. As compared with the results using CAN(IV), the formation of 1-nitrooctene (**3c**) and 1-nitro-2-octanol (**3d**) was inhibited between 5 and 10%. Furthermore, the yields of product were increased by over 5%. From these results, the nitration of ketones or alkenes by Ce^{3+}, proton and nitrate ion was confirmed. Also, it seems that the nitration of ketones (Path A) efficiently proceeds under reaction conditions using CAN(III) without reduction of Ce^{4+} into Ce^{3+}. Since the formation of 1-nitroalkenes and 1-nitro alcohols was inhibited under reaction conditions using CAN(III)-formic acid, the formation of nitrile oxides from acetone or acetophenone smoothly proceeds. Therefore, the yields of isoxazole derivatives were increased.

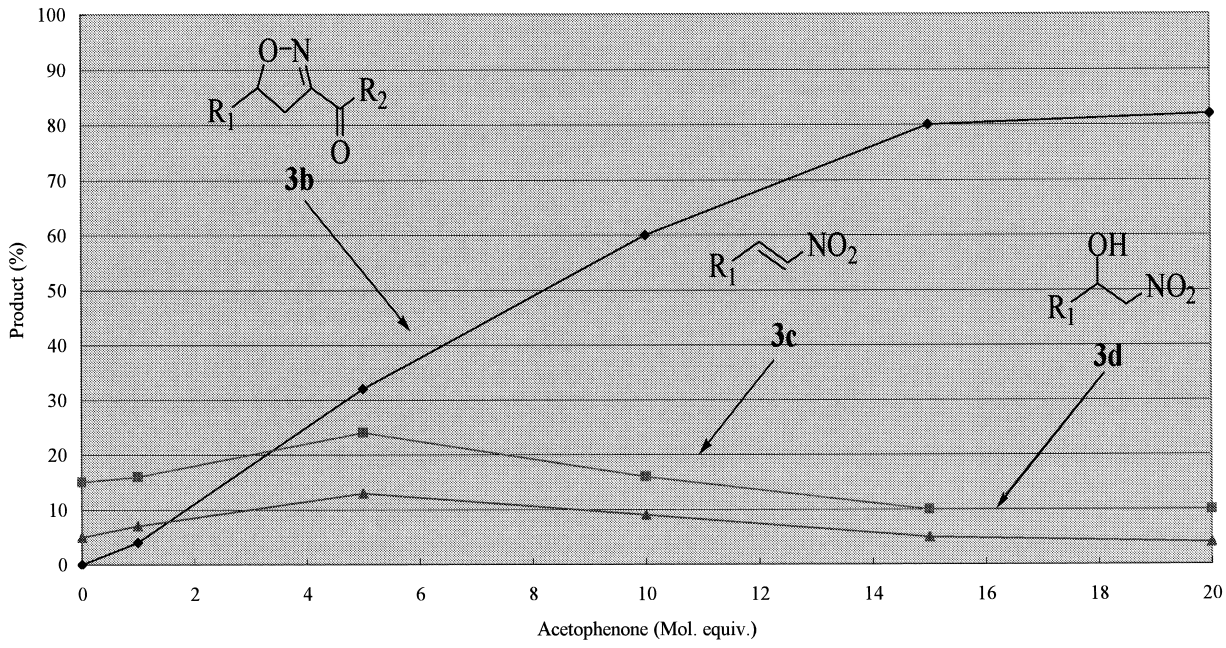
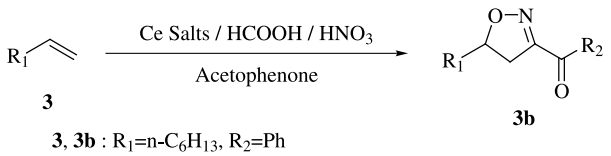


Figure 2. The relationship between acetophenone and products using CAN(III)-formic acid Reaction conditons: 1-octene (0.5 mmol), CAN(III) (0.5 mmol), formic acid (10.0 mol), acetophenone (0–20 mol equiv.), and acetonitrile (3.0 ml) were employed for 20 h under reflux.



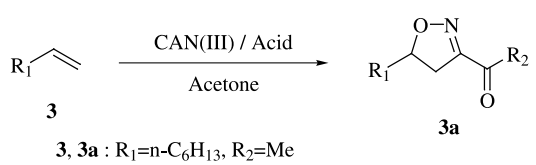
Scheme 7.

In order to investigate the reaction mechanism detailed in the formation of isoxazole derivatives, the reactions of 1-octene (**3**) with several cerium salts–formic acid in acetophenone were carried out (Scheme 7). These results are summarized in Table 5. In this reaction, isoxazole derivatives were not obtained in the absence of cerium salts and formic acid (Table 5, run 1 and 2). Also, the reaction using $Ce(OH)_4$, $Ce(NH_4)_4(SO_4)_2$, $CeCl_3$, and $Ce(CH_3COO)_3$ containing nitric acid gave isoxazole derivatives in 69, 74, 81 and 83% yields, respectively. Also, in the case of using Ce^{3+} salts, the yields of isoxazole derivatives were increased (Table 5, run 2–5). These results show this reaction in the formation of isoxazole derivatives requires Ce^{3+}, nitrate ion, and formic acid. Moreover, in order to clarify the relationship between formation of isoxazole derivatives and formic acid in this reaction mechanism, the reactions of 1-octene (**3**) with CAN(III)-several acids in acetone were carried (Scheme 8). These results are summarized in Table 6. The reaction using acetic acid, propionic acid, and benzoic acid did not proceed. However, the reaction using nitric acid, monochloroacetic acid, oxalic acid, and sulfuric acid gave isoxazole derivatives in 82, 81, 82 and 84% yield, respectively. When CAN(IV) was dissolved in acetone or acetophenone, its solution revealed high acidity. However, the solution dissolving CAN(III) did not reveal the high acidity. Furthermore, this reaction proceeds under reaction conditions using an acid containing the acidity of formic acid or above. From these results, it seems that the proton accomplishes a more essential role for this reaction mechanism than nitration of acetone and acetophenone.

Table 5. Reaction of 1-octene with Ce(IV) and Ce(III) salts in acetophenone

Run[a]	Substrate	Ce salts	Time (h)	Product (%)[b]
1	**3**	—	25	No reaction
2[c]	**3**	$Ce(OH)_4$	25	No reaction
3	**3**	$Ce(OH)_4$	12	**3b** (69)
4	**3**	$Ce(NH_4)_4(SO_4)_2$	12	**3b** (74)
5	**3**	$CeCl_3$	8	**3b** (81)
6	**3**	$Ce(CH_3COO)_3$	8	**3b** (83)

[a] Substrate (0.5 mmol), Ce salts (0.5 mol), formic acid (5.0 mmol), nitric acid (5.0 mmol), and acetophenone (3.0 ml) were employed under reflux.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard.
[c] Substrate (0.5 mmol), Ce salts (0.5 mol), nitric acid (5.0 mmol), and acetophenone (3.0 ml) were employed under reflux. All products were identified by satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS).



Scheme 8.

Table 6. The effect of acid in the formation of isoxazole derivatives

Run	Substrate	Acid	Time (h)	Product (%)[a]
1[b]	**3**	—	70	No reaction
2[c]	**3**	CH_3COOH	25	No reaction
3[c]	**3**	CH_3CH_2COOH	25	No reaction
4[c]	**3**	C_6H_5COOH	25	No reaction
5[c]	**3**	HNO_3	15	**3a** (82)
6[c]	**3**	$ClCH_2COOH$	20	**3a** (81)
7[c]	**3**	$(COOH)_2$	15	**3a** (82)
8[d]	**3**	H_2SO_4	15	**3a** (84)

[a] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard. All products were identified by satisfactory spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS).
[b] Substrate (0.5 mmol), CAN(III) (0.5 mmol), and acetone (3.0 ml) were employed under reflux.
[c] Substrate (0.5 mmol), CAN(III) (0.5 mmol), acid (5.0 mmol) were employed under reflux.
[d] Substrate (0.5 mmol), CAN(III) (0.5 mmol), acid (0.5 mmol) were employed under reflux.

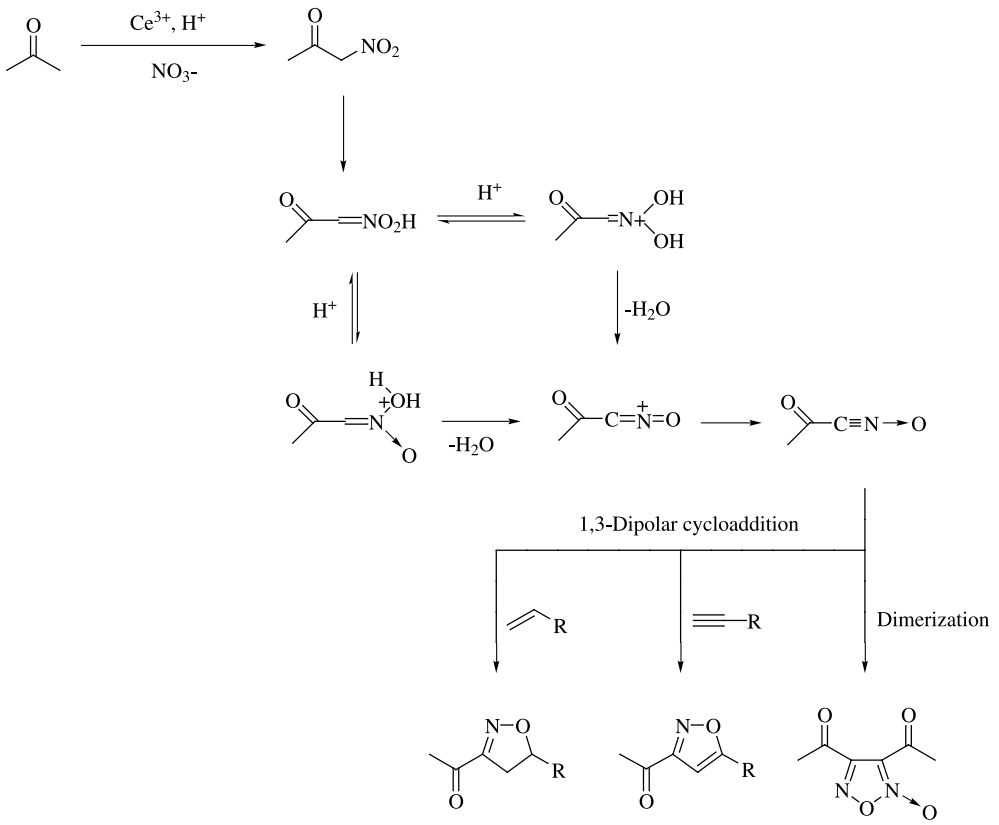
Wade and co-workers[26] reported that acid-catalyzed nitronate cycloaddition reactions gave 4,5-dihydroisoxazole and isoxazole derivatives from nitro compounds and dipolarophiles. In this reaction, nitronic esters were transformed from primary nitro ketones in the presence of nonaqueous protonic and Lewis acids or a strong acid. The protonation of nitronic esters by Lewis acids or a strong acid produced the nitroso cation with dehydration, followed by the formation of nitrile oxide from the nitroso cation. The reaction of nitrile oxide and dipolarphiles afforded the corresponding isoxazole derivatives. On the basis of this reaction mechanism, we proposed the present reaction mechanism in Scheme 9. At first, the nitration of acetone or acetophenone by Ce^{3+}, proton and nitrate ion gave the corresponding nitroketones. In the presence of proton, nitroketones were transformed into nitroso cations, followed by the formation of nitrile oxides from the nitroso cations. Finally, 3-acetyl- and 3-benzoylisoxazole derivatives were obtained by 1,3-dipolar cycloaddition of dipolarophiles (alkenes or alkynes) and nitrile oxide. In the absence of dipolarophiles, nitrile oxide dimerized into furoxan. It is known that nitrile oxides containing an acyl group were obtained from primary nitro compounds[27] and α-hydroxyimino carboxylic acids;[28] however, in this reaction nitrile oxide containing an acyl group was obtained in one-step.

In conclusion, this method is simple and efficient to obtain 3-acetyl- and 3-benzoylisoxazole derivatives. It is particularly noteworthy that this reaction affords a new synthetic method for isoxazole and 4,5-dihydroisoxazole derivatives that is more convenient than the methods used heretofore.

3. Experimental

3.1. General procedure

IR spectra were recorded on a Jasco FT-IR 230 spectrometer. ^{1}H and ^{13}C NMR spectra were measured using a JEOL GSX 400 Model spectrometer in deuteriochloroform solutions with tetramethylsilane used as an internal standard.



Scheme 9. Reaction mechanism.

GC-MS (EI) analyses were performed on a Shimazu GCMS-QP5050 with an ionizing energy of 70 eV. CIMS (*i*-butane reagent gas) were recorded on a Shimazu GCMS-QP5050 with an ionizing energy of 300 eV.

3.2. Synthesis of isoxazole derivatives using CAN(IV)

3.2.1. Typical procedures: reaction of 1-octene (3) with CAN(IV) in acetone. A mixture of 1-octene (**3**) (0.0561 g, 0.5 mmol) and ammonium cerium(IV) nitrate (0.2791 g, 0.5 mmol) in acetone (3.0 ml) was stirred under reflux for 14 h. The reaction mixture was extracted with diethyl ether (30 ml) and washed with aq. sodium hydrogencarbonate solution (2×2.0 ml), saturated aq. NaCl (2×2.0 ml), and water (2×2.0 ml). The ethereal solution was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–diethyl ether (5:1) gave 3-acetyl-5-hexyl-4,5-dihydroisoxazole (**3a**) as a pale-yellow oil (0.0581 g, 59%).

3.2.1.1. 3-Acetyl-5-butyl-4,5-dihydroisoxazole (1a). Pale-yellow oil; IR (NaCl) 1688 and 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.74–4.83 (m, 1H), 3.16 (dd, *J*=11.0, 17.6 Hz, 1H), 2.76 (dd, *J*=8.4, 17.6 Hz, 1H), 2.49 (s, 3H), 1.60–1.74 (m, 2H), 1.34–1.43 (m, 4H), and 0.92 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=193.4, 158.3, 84.9, 36.7, 34.9, 27.3, 26.6, 22.4, and 13.9; CIMS *m/z* 170 $[M+H]^+$; EIMS *m/z* 126 $[M-CH_3CO]^+$ (1), 112 $[M-C_4H_9]^+$ (2), 99 $[M-C_5H_{10}]^+$ (2), 85 $[M-C_6H_{12}]^+$ (4), 55 $[M-C_6H_{12}NO]^+$ (3), 43 $[M-C_7H_{12}NO]^+$ (100); HRMS Found: *m/z* 169.1103 $[M]^+$. Calcd for $C_9H_{15}NO_2$: M, 169.1103.

3.2.1.2. 3-Acetyl-5-pentyl-4,5-dihydroisoxazole (2a). Pale-yellow oil; IR (NaCl) 1688 and 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.74–4.82 (m, 1H), 3.16 (dd, *J*=10.8, 17.4 Hz, 1H), 2.75 (dd, *J*=8.4, 17.4 Hz, 1H), 2.49 (s, 3H), 1.70–1.75 (m, 1H), 1.54–1.60 (m, 1H), 1.31–1.43 (m, 6H), and 0.90 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=193.4, 158.3, 84.9, 36.7, 35.1, 31.5, 26.6, 24.9, 22.5, and 14.0; CIMS *m/z* 184 $[M+H]^+$; EIMS *m/z* 140 $[M-CH_3CO]^+$ (1), 112 $[M-C_5H_{11}]^+$ (2), 99 $[M-C_6H_{12}]^+$ (2), 55 $[M-C_7H_{14}NO]^+$ (3), 43 $[M-C_8H_{14}NO]^+$ (100); HRMS Found: *m/z* 183.1261 $[M]^+$. Calcd for $C_{10}H_{17}NO_2$: M, 183.1259.

3.2.1.3. 3-Acetyl-5-hexyl-4,5-dihydroisoxazole (3a). Pale-yellow oil; IR (NaCl) 1686 and 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.74–4.82 (m, 1H), 3.16 (dd, *J*=11.0, 17.6 Hz, 1H), 2.75 (dd, *J*=8.6, 17.6 Hz, 1H), 2.49 (s, 3H), 1.60–1.74 (m, 4H), 1.34–1.44 (m, 6H), and 0.89 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=193.4, 158.3, 84.9, 36.7, 35.2, 31.7, 29.0, 26.6, 25.1, 22.5, and 14.0; CIMS *m/z* 198 $[M+H]^+$; EIMS *m/z* 154 $[M-CH_3CO]^+$ (1), 136 $[M-CH_3CO-CH_3]^+$ (1), 112 $[M-C_6H_{13}]^+$ (2), 95 $[M-C_6H_{14}O]^+$ (2), 69 $[M-C_8H_{16}O]^+$ (2), 55 $[M-C_8H_{16}NO]^+$ (3), 43 $[M-C_9H_{16}NO]^+$ (100); HRMS Found: *m/z* 197.1428 $[M]^+$. Calcd for $C_{11}H_{19}NO_2$: M, 197.1416.

3.2.1.4. 3-Acetyl-5-cyclohexylmethyl-4,5-dihydroisoxazole (4a). Pale-yellow oil; IR (NaCl) 1686 and 1576 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.83–4.91 (m, 1H), 3.18 (dd, *J*=10.8, 17.4 Hz, 1H), 2.72 (dd, *J*=8.6, 17.4 Hz, 1H), 2.49 (s, 3H), 1.68–1.77 (m, 6H), 1.38–1.45 (m, 2H), 1.21–1.27 (m, 3H), and 0.94–1.17 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=193.4, 158.3, 83.1, 43.1, 37.8, 34.6, 33.5, 33.0, 26.6, 26.4, 26.2, and 26.1; CIMS *m/z* 210 $[M+H]^+$; EIMS *m/z* 166 $[M-CH_3CO]^+$ (1), 126 $[M-C_6H_{11}]^+$ (1), 112 $[M-C_7H_{13}]^+$ (1), 55 $[M-C_9H_{16}NO]^+$ (3), 43

$[M-C_{10}H_{16}NO]^+$ (100); HRMS Found: *m/z* 209.1407 $[M]^+$. Calcd for $C_{12}H_{19}NO_2$: M, 209, 1416.

3.2.1.5. 3-Acetyl-5-benzyl-4,5-dihydroisoxazole (5a). Pale-yellow oil; IR (NaCl) 1686 and 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.21–7.33 (m, 5H), 5.01–5.06 (m, 1H), 3.05–3.13 (m, 2H), 2.83–2.91 (m, 2H), and 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=193.2, 158.2, 136.6, 129.4, 128.7, 127.0, 84.9, 40.9, 36.3, and 26.6; CIMS *m/z* 204 $[M+H]^+$; EIMS *m/z* 203 $[M]^+$ (1), 126 $[M-C_6H_5]^+$ (1), 112 $[M-C_7H_7]^+$ (2), 43 $[M-C_{10}H_{10}NO]^+$ (100); HRMS Found: *m/z* 203.0951 $[M]^+$. Calcd for $C_{12}H_{13}NO_2$: M, 203.0946.

3.2.1.6. 3-Acetyl-5-methylthiamethyl-4,5-dihydroisoxazole (6a). Pale-yellow oil; IR (NaCl) 1687 and 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.97–5.04 (m, 1H), 3.24 (dd, *J*=10.8, 17.7 Hz, 1H), 3.06 (dd, *J*=7.7, 17.7 Hz, 1H), 2.81 (dd, *J*=5.0, 14.1 Hz, 1H), 2.71 (dd, *J*=6.8, 14.1 Hz, 1H), 2.50 (s, 3H), and 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=193.0, 158.2, 83.6, 38.0, 36.6, 26.7, and 16.4; CIMS *m/z* 174 $[M+H]^+$; EIMS *m/z* 173 $[M]^+$ (1), 130 $[M-CH_3CO]^+$ (1), 112 $[M-C_2H_5S]^+$ (12), 61 $[M-C_5H_6NO_2]^+$ (23), 43 $[M-C_5H_8NOS]^+$ (100); HRMS Found: *m/z* 173.0513 $[M]^+$. Calcd for $C_7H_{11}NO_2S$: M, 173.0510.

3.2.1.7. 3-Acetyl-5-cyanomethyl-4,5-dihydroisoxazole (7a). Yellow oil; IR (NaCl) 1687 and 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.99–5.06 (m, 1H), 3.22 (dd, *J*=11.5, 17.8 Hz, 1H), 2.97 (dd, *J*=7.9, 17.8 Hz, 1H), 2.74–2.85 (m, 2H), and 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=192.8, 158.0, 115.2, 77.0, 39.4, 26.7, and 23.7; CIMS *m/z* 153 $[M+H]^+$; EIMS *m/z* 152 $[M]^+$ (2), 138 $[M-CH_3]^+$ (2), 112 $[M-CH_2CN]^+$ (1), 109 $[M-CH_3CO]^+$ (1), 43 $[M-C_5H_5N_2O]^+$ (100); HRMS Found: *m/z* 152.0591 $[M]^+$. Calcd for $C_7H_8N_2O_2$: M, 152.0586.

3.2.1.8. 3-Acetyl-5-phenoxymethyl-4,5-dihydroisoxazole (8a). Pale-yellow oil; IR (NaCl) 1686 and 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.26–7.30 (m, 2H), 6.96–7.00 (m, 1H), 6.88–6.90 (m, 2H), 5.10–5.17 (m, 1H), 4.10 (q, *J*=4.8 Hz, 2H), 3.50 (dd, *J*=11.0, 17.6 Hz, 1H), 3.40 (dd, *J*=7.7, 17.6 Hz, 1H), and 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=193.0, 158.2, 158.1, 129.6, 121.5, 114.7, 81.9, 68.3, 34.2, and 26.8; CIMS *m/z* 220 $[M+H]^+$; EIMS *m/z* 176 $[M-CH_3CO]^+$ (1), 142 $[M-C_6H_5]^+$ (1), 126 $[M-OC_6H_5]^+$ (3), 112 $[M-CH_2OC_6H_5]^+$ (4), 43 $[M-C_{10}H_{10}NO_2]^+$ (100); HRMS Found: *m/z* 219.0904 $[M]^+$. Calcd for $C_{12}H_{13}NO_3$: M, 219.0895.

3.2.1.9. 3-Acetyl-5-acetoxymethyl-4,5-dihydroisoxazole (9a). Pale-yellow oil; IR (NaCl) 1691 and 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.99–5.06 (m, 1H), 4.26 (dd, *J*=3.9, 12.3 Hz, 1H), 4.16 (dd, *J*=5.5, 12.3 Hz, 1H), 3.22 (dd, *J*=11.5, 17.8 Hz, 1H), 2.97 (dd, *J*=7.9, 17.8 Hz, 1H), 2.51 (s, 3H), and 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=192.8, 170.6, 158.0, 81.2, 64.4, 34.1, 26.7, and 20.7; CIMS *m/z* 186 $[M+H]^+$; EIMS *m/z* 142 $[M-CH_3CO]^+$ (1), 126 $[M-C_2H_3O_2]^+$ (5), 112 $[M-C_3H_5O_2]^+$ (5), 43 $[M-C_6H_8NO_3]^+$ (100); HRMS Found: *m/z* 185.0694 $[M]^+$. Calcd for $C_8H_{11}NO_4$: M, 185.0688.

3.2.1.10. 3-Acetyl-4,5-cyclopenta-4,5-dihydroisoxazole (10a). Pale-yellow oil; IR (NaCl) 1688 and 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.05–5.27 (m, 1H), 3.80–3.85 (m, 1H), 2.46 (s, 3H), 2.14–2.19 (m, 1H), 1.90–1.96 (m, 1H), 1.68–1.83 (m, 3H), and 1.28–1.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=193.3, 160.0, 90.8, 49.4, 35.6, 31.4, 27.0, and 23.2; CIMS *m/z* 154 $[M+H]^+$; EIMS *m/z* 153 $[M]^+$ (1), 110 $[M-CH_3CO]^+$ (4), 43 $[M-C_6H_8NO]^+$ (100); HRMS Found: *m/z* 153.0791 $[M]^+$. Calcd for $C_8H_{11}NO_2$: M, 153.0790.

3.2.1.11. 3-Acetyl-4,5-cyclohexa-4,5-dihydroisoxazole (11a). Pale-yellow oil; IR (NaCl) 1686 and 1559 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.52–4.56 (m, 1H), 3.15–3.21 (m, 1H), 2.49 (s, 3H), and 1.14–2.24 (m, 8H); ^{13}C NMR ($CDCl_3$) δ=193.6, 164.3, 83.3, 42.1, 26.8, 25.4, 24.7, 21.4, and 19.7; CIMS *m/z* 168 $[M+H]^+$; EIMS *m/z* 167 $[M]^+$ (1), 150 $[M-OH]^+$ (1), 124 $[M-CH_3CO]^+$ (4), 96 $[M-CH_3CO-C_2H_4]^+$ (3), 55 $[M-CH_3CO-C_4H_8]^+$ (3), 43 $[M-C_7H_{10}NO]^+$ (100); HRMS Found: *m/z* 167.0940 $[M]^+$. Calcd for $C_9H_{13}NO_2$: M, 167.0946.

3.2.1.12. 3-Acetyl-4,5-cyclohepta-4,5-dihydroisoxazole (12a). Pale-yellow oil; IR (NaCl) 1686 and 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.87–4.93 (m, 1H), 3.52–3.58 (m, 1H), 2.47 (s, 3H), and 1.39–2.01 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=193.5, 160.4, 88.2, 48.9, 31.0, 30.3, 28.2, 27.1, 26.7, and 23.8; CIMS *m/z* 182 $[M+H]^+$; EIMS *m/z* 181 $[M]^+$ (1), 138 $[M-CH_3CO]^+$ (3), 43 $[M-C_8H_{12}NO]^+$ (100); HRMS Found: *m/z* 181.1101 $[M]^+$. Calcd for $C_{10}H_{15}NO_2$: M, 181.1103.

3.2.1.13. 3-Acetyl-4,5-cycloocta-4,5-dihydroisoxazole (13a). Pale-yellow oil; IR (NaCl) 1686 and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.50–4.56 (m, 1H), 3.26–3.31 (m, 1H), 2.47 (s, 3H), 196–2.10 (m, 2H), 1.44–1.75 (m, 7H), and 1.22–1.38 (m, 3H); ^{13}C NMR ($CDCl_3$) δ=193.4, 162.7, 88.7, 47.5, 29.8, 27.1, 27.0, 25.6, 25.5, 25.1, and 24.5; CIMS *m/z* 196 $[M+H]^+$; EIMS *m/z* 152 $[M-CH_3CO]^+$ (3), 138 $[M-CH_3CO-CH_2]^+$ (1), 124 $[M-CH_3CO-C_2H_4]^+$ (1), 110 $[M-CH_3CO-C_3H_6]^+$ (1), 96 $[M-CH_3CO-C_4H_8]^+$ (1) 82 $[M-CH_3CO-C_5H_{10}]^+$ (3), 43 $[M-C_9H_{14}NO]^+$ (100); HRMS Found: *m/z* 195.1243 $[M]^+$. Calcd for $C_{11}H_{17}NO_2$: M, 195.1259.

3.2.1.14. 3-Acetyl-5-propylisoxazole (14a). Pale-yellow oil; IR (NaCl) 1705 and 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.37 (s, 1H), 2.78 (t, *J*=7.6 Hz, 2H), 2.64 (s, 3H), 1.71–1.80 (m, 2H) and 1.00 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=192.5, 175.5, 162.1, 99.2, 28.6, 27.3, 20.9 and 13.6; CIMS *m/z* 154 $[M+H]^+$; EIMS *m/z* 153 $[M]^+$ (2), 138 $[M-CH_3]^+$ (1), 110 $[M-CH_3CO]^+$ (1), 43 $[M-C_6H_8NO]^+$ (100); HRMS Found: *m/z* 153.0788 $[M]^+$. Calcd for $C_8H_{11}NO_2$: M, 153.0790.

3.2.1.15. 3-Acetyl-5-butylisoxazole (15a). Pale-yellow oil; IR (NaCl) 1707 and 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.36 (s, 1H), 2.76 (t, *J*=7.7 Hz, 2H), 2.63 (s, 3H), 1.67–1.74 (m, 2H), 1.34–1.45 (m, 2H), and 0.95 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=192.5, 175.6, 162.1, 99.2, 29.5, 27.2, 26.4, 22.1, and 13.6; CIMS *m/z* 168 $[M+H]^+$; EIMS *m/z* 167 $[M]^+$ (1), 152 $[M-CH_3]^+$ (1), 124 $[M-CH_3CO]^+$ (2), 43 $[M-C_7H_{10}NO]^+$ (100); HRMS Found: *m/z* 167.0929 $[M]^+$. Calcd for $C_9H_{13}NO_2$: M, 167.0946.

3.2.1.16. 3-Acetyl-5-pentylisoxazole (16a). Pale-yellow oil; IR (NaCl) 1707 and 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.36 (s, 1H), 2.79 (t, *J*=7.3 Hz, 2H), 2.63 (s, 3H), 1.69–1.76 (m, 2H), 1.33–1.38 (m, 4H), and 0.91 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=192.5, 175.7, 162.2, 99.2, 31.2, 27.2, 27.0, 26.7, 22.3, and 13.9; CIMS *m/z* 182 $[M+H]^+$; EIMS *m/z* 181 $[M]^+$ (1), 166 $[M-CH_3]^+$ (1), 138 $[M-CH_3CO]^+$ (1), 55 $[M-C_7H_{12}NO]^+$ (1), 43 $[M-C_8H_{12}NO]^+$ (100); HRMS Found: *m/z* 181.1097 $[M]^+$. Calcd for $C_{10}H_{15}NO_2$: M, 181.1103.

3.2.1.17. 3-Acetyl-5-hexylisoxazole (17a). Pale-yellow oil; IR (NaCl) 1707 and 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.36 (s, 1H), 2.79 (t, J=7.3 Hz, 2H), 2.63 (s, 3H), 1.67–1.75 (m, 2H), 1.29–1.38 (m, 6H), and 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=192.5, 175.7, 162.1, 99.1, 31.3, 28.7, 27.3, 27.0, 26.7, 22.4, and 14.0; CIMS m/z 196 $[M+H]^+$; EIMS m/z 195 $[M]^+$ (1), 180 $[M-CH_3]^+$ (1), 153 $[M-CH_3CO]^+$ (2), 55 $[M-C_8H_{14}NO]^+$ (1), 43 $[M-C_9H_{14}NO]^+$ (100); HRMS Found: m/z 195.1262 $[M]^+$. Calcd for $C_{11}H_{17}NO_2$: M, 195.1259.

3.2.1.18. Ethyl 3-acetylisoxazolecarboxylate (18a). Colorless needless from EtOH; mp 42.3–435 °C; IR (NaCl) 1710 and 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.25 (s, 1H), 4.48 (q, J=7.1 Hz, 2H), 2.71 (s, 3H), and 1.47 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=190.3, 161.8, 161.4, 155.6, 106.9, 62.2, 26.7, and 13.6; CIMS m/z 184 $[M+H]^+$; EIMS m/z 168 $[M-CH_3]^+$ (1), 140 $[M-CH_3CO]^+$ (1), 138 $[M-C_2H_5O]^+$ (2), 43 $[M-C_6H_6NO_3]^+$ (100); HRMS Found: m/z 183.0530 $[M]^+$. Calcd for $C_8H_9NO_4$: M, 183.0532.

3.2.1.19. 3-Acetyl-6-hydroxy-5-cyclohexylisoxazole (19a). Pale-yellow oil; IR (NaCl) 3400, 1706 and 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.53 (s, 1H), 3.49 (brs, 1H), 2.62 (s, 3H), and 1.17–2.00 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=192.3, 180.0, 161.5, 98.1, 36.1, 27.0, 24.8, 21.3, and 20.4; CIMS m/z 210 $[M+H]^+$; EIMS m/z 194 $[M-CH_3]^+$ (1), 166 $[M-CH_3CO]^+$ (2), 139 $[M-C_5H_{10}]^+$ (1), 110 $[M-C_6H_{11}O]^+$ (2), 98 $[M-C_7H_{11}O]^+$ (2), 55 $[M-C_8H_{12}NO_2]^+$ (100), 43 $[M-C_9H_{12}NO_2]^+$ (100); HRMS Found: m/z 209.1027 $[M]^+$. Calcd for $C_{11}H_{15}NO_3$: M, 209.1052.

3.2.2. Typical procedures: reaction of 1-octene (3) with CAN(IV) in acetophenone. A mixture of 1-octene (**3**) (0.0561 g, 0.5 mmol) and ammonium cerium(IV) nitrate (0.2791 g, 0.5 mmol) in acetophenone (3.0 ml) was stirred at 80 °C for 16 h. The reaction mixture was extracted with diethyl ether (30 ml) and washed with aq. sodium hydrogencarbonate solution (2×2.0 ml), saturated aq. NaCl (2×2.0 ml), and water (2×2.0 ml). The ethereal solution was dried over Na_2SO_4 and concentrated in a vacuum, followed by acetophenone removal by reduced pressure distillation. The resulting oil was chromatographed on silica gel. Elution with hexane–diethyl ether (5:1) gave 3-benzoyl-5-hexyl-4,5-dihydroisoxazole (**3b**) as a pale-yellow oil (0.0829 g, 64%).

3.2.2.1. 3-Benzoyl-5-butyl-4,5-dihydroisoxazole (1b). Pale-yellow oil; IR (NaCl) 1652 and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.17–8.19 (m, 2H), 7.38–7.53 (m, 3H), 4.65–4.74 (m, 1H), 3.32 (dd, J=10.8, 17.4 Hz, 1H), 2.93 (dd, J=8.4, 17.4 Hz, 1H), 1.67–1.75 (m, 2H), 1.28–1.43 (m, 4H), and 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=186.2, 157.8, 136.0, 133.4, 130.3, 128.3, 83.4, 38.8, 35.1, 31.6, 22.6, and 14.0; CIMS m/z 232 $[M+H]^+$; EIMS m/z 231 $[M]^+$ (1), 214 $[M-OH]^+$ (1), 202 $[M-C_2H_5]^+$ (1), 185 $[M-OH-C_2H_5]^+$ (1), 174 $[M-C_4H_9]^+$ (6), 105 $[M-C_7H_{12}NO]^+$ (100), 77 $[M-C_7H_{12}NO-CO]^+$ (45); HRMS Found: m/z 231.1269 $[M]^+$. Calcd for $C_{14}H_{17}NO_2$: M, 231.1259.

3.2.2.2. 3-Benzoyl-5-pentyl-4,5-dihydroisoxazole (2b). Pale-yellow oil; IR (NaCl) 1652 and 1571 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.17–8.20 (m, 2H), 7.42–7.59 (m, 3H), 4.73–4.81 (m, 1H), 3.38 (dd, J=10.8, 17.4 Hz, 1H), 2.98 (dd, J=8.6, 17.4 Hz, 1H), 1.73–1.81 (m, 1H), 1.57–1.66 (m, 1H), 1.26–1.47 (m, 6H), and 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=186.5, 157.8, 135.9, 133.4, 130.3, 128.3, 83.5, 38.8, 35.1, 31.5, 24.9, 22.5, and 14.0; CIMS m/z 246 $[M+H]^+$; EIMS m/z 174 $[M-C_5H_{11}]^+$ (2), 140 $[M-C_6H_5CO]^+$ (2), 105 $[M-C_8H_{14}NO]^+$ (100), 77 $[M-C_8H_{14}NO-CO]^+$ (38); HRMS Found: m/z 245.1399 $[M]^+$. Calcd for $C_{15}H_{19}NO_2$: M, 245.1416.

3.2.2.3. 3-Benzoyl-5-hexyl-4,5-dihydroisoxazole (3b). Pale-yellow oil; IR (NaCl) 1652 and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.17–8.19 (m, 2H), 7.37–7.55 (m, 3H), 4.64–4.72 (m, 1H), 3.31 (dd, J=10.8, 17.4 Hz, 1H), 2.92 (dd, J=8.6, 17.4 Hz, 1H), 1.66–1.71 (m, 1H), 1.50–1.56 (m, 1H), 1.26–1.41 (m, 8H), and 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=186.1, 157.9, 136.0, 133.5, 130.3, 128.3, 83.4, 38.8, 35.2, 31.8, 29.1, 25.3, 22.6, and 14.1; CIMS m/z 260 $[M+H]^+$; EIMS m/z 174 $[M-C_6H_{13}]^+$ (2), 154 $[M-C_6H_5CO]^+$ (2), 105 $[M-C_9H_{16}NO]^+$ (100), 77 $[M-C_9H_{16}NO-CO]^+$ (32); HRMS Found: m/z 259.1587 $[M]^+$. Calcd for $C_{16}H_{21}NO_2$: M, 259.1572.

3.2.2.4. 3-Benzoyl-5-cyclohexylmethyl-4,5-dihydroisoxazole (4b). Pale-yellow oil; IR (NaCl) 1653 and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.18–8.20 (m, 2H), 7.43–7.62 (m, 3H), 4.83–4.91 (m, 1H), 3.40 (dd, J=10.8, 17.4 Hz, 1H), 2.96 (dd, J=8.8, 17.4 Hz, 1H), 1.70–1.83 (m, 6H), 1.44–1.54 (m, 2H), 1.11–1.28 (m, 3H), and 0.95–0.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=186.6, 157.9, 135.9, 133.5, 130.3, 128.3, 81.7, 43.0, 39.5, 34.7, 33.5, 33.0, 26.4, 26.2, and 26.1; CIMS m/z 272 $[M+H]^+$; EIMS m/z 271 $[M]^+$ (2), 254 $[M-OH]^+$ (1), 228 $[M-C_3H_7]^+$ (1), 174 $[M-C_7H_{13}]^+$ (1), 166 $[M-C_6H_5CO]^+$ (1), 105 $[M-C_{10}H_{16}NO]^+$ (100), 77 $[M-C_{10}H_{16}NO-CO]^+$ (32); HRMS Found: m/z 271.1558 $[M]^+$. Calcd for $C_{17}H_{21}NO_2$: M, 271.1572.

3.2.2.5. 3-Benzoyl-5-benzyl-4,5-dihydroisoxazole (5b). Pale-yellow oil; IR (NaCl) 1652 and 1572 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.07–8.11 (m, 2H), 7.38–7.54 (m, 3H), 7.17–7.30 (m, 5H), 4.96–5.03 (m, 1H), 3.29 (dd, J=11.0, 17.6 Hz, 2H), 3.01–3.09 (m, 2H), and 2.90 (dd, J=6.2, 17.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ=186.3, 157.7, 136.1, 135.7, 133.5, 130.2, 129.4, 128.6, 128.3, 126.9, 83.5, 40.8, and 38.2; CIMS m/z 266 $[M+H]^+$; EIMS m/z 265 $[M]^+$ (1), 174 $[M-C_7H_7]^+$ (2), 160 $[M-C_6H_5CO]^+$ (1), 105 $[M-C_{10}H_{10}NO]^+$ (100), 77 $[M-C_{10}H_{10}NOCO]^+$ (49); HRMS Found: m/z 265.1101 $[M]^+$. Calcd for $C_{17}H_{15}NO_2$: M, 265.1103.

3.2.2.6. 3-Benzoyl-5-methylthiamethyl-4,5-dihydroisoxazole (6b). Pale-yellow oil; IR (NaCl) 1654 and 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.17–8.20 (m, 2H), 7.42–7.67 (m, 3H), 4.97–5.05 (m, 1H), 3.47 (dd, J=10.8, 17.6 Hz, 1H), 3.28 (dd, J=7.7, 17.6 Hz, 1H), 2.85 (dd, J=5.1, 14.0 Hz, 1H), 2.76 (dd, J=6.8, 14.0 Hz, 1H), and 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=186.2, 157.7, 135.7, 133.6, 130.2, 128.3, 82.3, 38.6, 38.0, and 16.4; CIMS m/z 236 $[M+H]^+$; EIMS m/z 235 $[M]^+$ (1), 174 $[M-C_2H_5S]^+$ (11), 130 $[M-C_6H_5CO]^+$ (1), 105 $[M-C_5H_8NOS]^+$ (100), 77 $[M-C_5H_5NOS-CO]^+$ (77); HRMS Found: m/z 235.0662 $[M]^+$. Calcd for $C_{12}H_{13}NO_2S$: M, 235.0667.

3.2.2.7. 3-Benzoyl-5-cyanomethyl-4,5-dihydroisoxazole (7b). Yellow oil; IR (NaCl) 1654 and 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.17–8.20 (m, 2H), 7.46–7.64 (m, 3H), 5.01–5.09 (m, 1H), 3.63 (dd, J=11.0, 18.0 Hz, 1H), 3.29 (dd, J=7.0, 18.0 Hz, 1H), and 2.74–2.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=185.5, 158.0, 135.3, 133.9, 130.3, 128.5, 115.5,

76.8, 39.1, and 23.7; CIMS *m/z* 215 $[M+H]^+$; EIMS *m/z* 214 $[M]^+$ (4), 174 $[M-C_2H_2N]^+$ (2), 147 $[M-C_4H_5N]^+$ (6), 105 $[M-C_5H_5N_2O]^+$ (100), 77 $[M-C_5H_5N_2O-CO]^+$ (80); HRMS Found: *m/z* 214.0749 $[M]^+$. Calcd for $C_{12}H_{10}N_2O_2$: M, 214.0742.

3.2.2.8. 3-Benzoyl-5-phenoxymethyl-4,5-dihydroisoxazole (8b). Pale-yellow oil; IR (NaCl) 1653 and 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.19–8.21 (m, 2H), 7.44–7.61 (m, 3H), 7.23–7.30 (m, 2H), 6.86–6.99 (m, 3H), 5.09–5.16 (m, 1H), 4.12 (q, *J*=4.6 Hz, 2H), 3.50 (dd, *J*=11.0, 17.6 Hz, 1H), and 3.40 (dd, *J*=7.7, 17.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=186.2, 158.2, 157.6, 135.7, 133.6, 130.3, 129.5, 128.4, 121.4, 114.6, 80.5, 68.4, and 36.3; CIMS *m/z* 282 $[M+H]^+$; EIMS *m/z* 281 $[M]^+$ (3), 188 $[M-C_6H_5O]^+$ (3), 174 $[M-C_7H_7O]^+$ (4), 105 $[M-C_{10}H_{10}NO_2]^+$ (100), 77 $[M-C_{10}H_{10}NO_2-CO]^+$ (74); HRMS Found: *m/z* 281.1050 $[M]^+$. Calcd for $C_{17}H_{15}NO_3$: M, 281.1052.

3.2.2.9. 3-Benzoyl-5-acetoxymethyl-4,5-dihydroisoxazole (9b). Pale-yellow oil; IR (NaCl) 1654 and 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.05–8.16 (m, 2H), 7.35–7.58 (m, 3H), 4.94–5.01 (m, 1H), 4.25 (dd, *J*=3.7, 12.1 Hz, 1H), 4.16 (dd, *J*=5.5, 12.1 Hz, 1H), 3.41 (dd, *J*=11.4, 17.6 Hz, 1H), 3.16 (dd, *J*=7.5, 17.6 Hz, 1H), and 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=185.5, 170.1, 157.2, 135.2, 133.3, 129.9, 128.0, 79.5, 64.2, 35.7, and 20.2; CIMS *m/z* 248 $[M+H]^+$; EIMS *m/z* 188 $[M-C_2H_3O_2]^+$ (7), 174 $[M-C_3H_5O_2]^+$ (8), 105 $[M-C_6H_8NO_3]^+$ (86), 77 $[M-C_6H_8NO_3-CO]^+$ (51), 43 $[M-C_{11}H_{10}NO_3]^+$ (100); HRMS Found: *m/z* 247.0859 $[M]^+$. Calcd for $C_{13}H_{13}NO_4$: M, 247.0845.

3.2.2.10. 3-Benzoyl-4,5-cyclopenta-4,5-dihydroisoxazole (10b). Pale-yellow oil; IR (NaCl) 1651 and 1566 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.14–8.16 (m, 2H), 7.43–7.60 (m, 3H), 5.23–5.26 (m, 1H), 4.07–4.12 (m, 1H), 2.19–2.24 (m, 1H), 2.01–2.05 (m, 1H), 1.69–1.91 (m, 3H), and 1.39–1.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=186.7, 159.6, 136.5, 133.4, 130.3, 128.3, 89.6, 51.5, 35.7, 31.7, and 23.3; CIMS *m/z* 216 $[M+H]^+$; EIMS *m/z* 215 $[M]^+$ (4), 198 $[M-OH]^+$ (1), 186 $[M-CHO]^+$ (2), 172 $[M-C_2H_3O]^+$ (3), 158 $[M-C_3H_5O]^+$ (3), 144 $[M-C_4H_7O]^+$ (2), 131 $[M-C_5H_8O]^+$ (2), 110 $[M-C_6H_5CO]^+$ (4), 105 $[M-C_6H_8NO]^+$ (100), 77 $[M-C_6H_8NO-CO]^+$ (69); HRMS Found: *m/z* 215.0929 $[M]^+$. Calcd for $C_{13}H_{13}NO_2$: M, 215.0946.

3.2.2.11. 3-Benzoyl-4,5-cyclohexa-4,5-dihydroisoxazole (11b). Pale-yellow oil; IR (NaCl) 1651 and 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.14–8.19 (m, 2H), 7.45–7.64 (m, 3H), 4.57–4.61 (m, 1H), 3.39–3.49 (m, 1H), 2.17–2.23 (m, 1H), 2.04–2.08 (m, 1H), 1.77–1.86 (m, 1H), 1.51–1.64 (m, 3H), and 1.25–2.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=186.9, 163.7, 136.2, 133.5, 130.6, 128.4, 82.1, 44.1, 25.5, 24.9, 21.6, and 19.8; CIMS *m/z* 230 $[M+H]^+$; EIMS *m/z* 229 $[M]^+$ (4), 212 $[M-OH]^+$ (1), 200 $[M-CHO]^+$ (1), 186 $[M-C_2H_3O]^+$ (2), 172 $[M-C_3H_5O]^+$ (2), 158 $[M-C_4H_7O]^+$ (4), 124 $[M-C_6H_5CO]^+$ (5), 105 $[M-C_7H_{10}NO]^+$ (100), 77 $[M-C_7H_{10}NO-CO]^+$ (71); HRMS Found: *m/z* 229.1100 $[M]^+$. Calcd for $C_{14}H_{15}NO_2$: M, 229.1103.

3.2.2.12. 3-Benzoyl-4,5-cyclohepta-4,5-dihydroisoxazole (12b). Pale-yellow oil; IR (NaCl) 1653 and 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.13–8.15 (m, 2H), 7.43–7.62 (m, 3H), 4.90–4.95 (m, 1H), 3.81–3.90 (m, 1H), 1.98–2.02 (m, 2H), 1.83–1.85 (m, 2H), 1.71–1.75 (m, 2H), and 1.45–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=186.9, 160.0, 136.4, 133.4, 130.3, 128.3, 86.7, 50.3, 31.0, 30.5, 28.1, 23.9, and 22.3; CIMS *m/z* 244 $[M+H]^+$; EIMS *m/z* 243 $[M]^+$ (5), 158 $[M-C_5H_9O]^+$ (4), 138 $[M-C_6H_5O]^+$ (4), 105 $[M-C_8H_{12}NO]^+$ (100), 77 $[M-C_8H_{12}NO-CO]^+$ (79); HRMS Found: *m/z* 243.1251 $[M]^+$. Calcd for $C_{15}H_{17}NO_2$: M, 243.1259.

3.2.2.13. 3-Benzoyl-4,5-cycloocta-4,5-dihydroisoxazole (13b). Pale-yellow oil; IR (NaCl) 1652 and 1579 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.14–8.18 (m, 2H), 7.43–7.63 (m, 3H), 4.54–4.60 (m, 1H), 3.54–3.59 (m, 1H), 2.02–2.13 (m, 2H), and 1.27–1.79 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=186.8, 162.3, 136.5, 133.4, 130.3, 128.3, 87.5, 49.1, 29.8, 25.7, 25.5, 25.3, 25.1, and 24.6; CIMS *m/z* 258 $[M+H]^+$; EIMS *m/z* 257 $[M]^+$ (5), 228 $[M-CHO]^+$ (1), 186 $[M-C_4H_7O]^+$ (1), 172 $[M-C_5H_9O]^+$ (2), 152 $[M-C_6H_5CO]^+$ (7), 105 $[M-C_9H_{14}NO]^+$ (100), 77 $[M-C_9H_{14}NO-CO]^+$ (62); HRMS Found: *m/z* 257.1423 $[M]^+$. Calcd for $C_{16}H_{19}NO_2$: M, 257.1416.

3.2.2.14. 3-Benzoyl-5-propylisoxazole (14b). Pale-yellow oil; IR (NaCl) 1663 and 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.28–8.31 (m, 2H), 7.48–7.64 (m, 3H), 6.52 (s, 1H), 2.80 (t, *J*=7.5 Hz, 2H), 1.73–1.84 (m, 2H) and 1.01 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=185.9, 174.4, 161.7, 135.7, 133.7, 130.5, 128.4, 101.6, 28.4, 20.7, and 13.5; CIMS *m/z* 216 $[M+H]^+$; EIMS *m/z* 215 $[M]^+$ (1), 105 $[M-C_6H_8NO]^+$ (100), 77 $[M-C_6H_8NO-CO]^+$ (65); HRMS Found: *m/z* 215.0924 $[M]^+$. Calcd for $C_{13}H_{13}NO_2$: M, 215.0946.

3.2.2.15. 3-Benzoyl-5-butylisoxazole (15b). Pale-yellow oil; IR (NaCl) 1663 and 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.28–8.31 (m, 2H), 7.47–7.63 (m, 3H), 6.51 (s, 1H), 2.82 (t, *J*=7.7 Hz, 2H), 1.69–1.76 (m, 2H), 1.37–1.46 (m, 2H), and 0.95 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=185.9, 174.6, 161.7, 135.7, 133.7, 130.5, 128.4, 101.5, 29.3, 26.1, 22.0 and 13.5; CIMS *m/z* 230 $[M+H]^+$; EIMS *m/z* 229 $[M]^+$ (1), 105 $[M-C_7H_{10}NO]^+$ (100), 77 $[M-C_7H_{10}NO-CO]^+$ (55); HRMS Found: *m/z* 229.1083 $[M]^+$. Calcd for $C_{14}H_{15}NO_2$: M, 229.1062.

3.2.2.16. 3-Benzoyl-5-pentylisoxazole (16b). Pale-yellow oil; IR (NaCl) 1663 and 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.28–8.31 (m, 2H), 7.46–7.62 (m, 3H), 6.51 (s, 1H), 2.80 (t, *J*=7.5 Hz, 2H), 1.69–1.76 (m, 2H), 1.33–1.40 (m, 4H), and 0.89 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=185.7, 174.5, 161.6, 135.7, 133.6, 130.4, 128.2, 101.4, 30.9, 26.9, 26.4, 22.0, and 13.7; CIMS *m/z* 244 $[M+H]^+$; EIMS *m/z* 243 $[M]^+$ (1), 105 $[M-C_8H_{12}NO]^+$ (100), 77 $[M-C_8H_{12}NO-CO]^+$ (49); HRMS Found: *m/z* 243.1246 $[M]^+$. Calcd for $C_{15}H_{17}NO_2$: M, 243.1259.

3.2.2.17. 3-Benzoyl-5-hexylisoxazole (17b). Pale-yellow oil; IR (NaCl) 1663 and 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.28–8.30 (m, 2H), 7.49–7.65 (m, 3H), 6.52 (s, 1H), 2.84 (t, *J*=7.7 Hz, 2H), 1.65–1.79 (m, 2H), 1.19–1.44 (m, 6H), and 0.90 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ=186.1, 174.7, 161.8, 135.8, 133.9, 130.6, 128.5, 101.6, 31.3, 28.7, 27.4, 26.6, 22.4, and 14.0; CIMS *m/z* 258 $[M+H]^+$; EIMS *m/z* 257 $[M]^+$ (1), 105 $[M-C_9H_{14}NO]^+$ (100), 77 $[M-C_9H_{14}NO-CO]^+$ (43); HRMS Found: *m/z* 257.1406 $[M]^+$. Calcd for $C_{16}H_{19}NO_2$: M, 257.1416.

3.2.2.18. Ethyl 3-benzoylisoxazolecarboxylate (18b). Colorless needles from EtOH; mp 51.8–53.5 °C; IR (NaCl) 1665 and 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.26–8.29 (m, 2H), 7.48–7.68 (m, 3H), 7.40 (s, 1H), 4.45 (q, *J*=7.1 Hz, 2H), and 1.42 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$)

δ=184.1, 161.9, 160.9, 156.0, 135.2, 134.2, 130.4, 128.5, 109.8, 62.4, and 13.8; CIMS *m/z* 246 $[M+H]^+$; EIMS *m/z* 246 $[M]^+$ (3), 105 $[M-C_6H_6NO_3]^+$ (100), 77 $[M-C_6H_6NO_3-CO]^+$ (69); HRMS Found: *m/z* 245.0687 $[M]^+$. Calcd for $C_{13}H_{11}NO_4$: M, 245.0688.

3.2.2.19. 3-Benzoyl-6-hydroxy-5-cyclohexylisoxazole (19b). Pale-yellow oil; IR (NaCl) 3437, 1662, and 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.27–8.29 (m, 2H), 7.49–7.66 (m, 3H), 6.70 (s, 1H), 3.50 (brs, 1H), and 1.19–2.02 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=185.9, 178.8, 161.6, 135.6, 134.0, 130.6, 128.5, 100.7, 65.8, 36.5, 30.9, 25.0, 21.5, and 15.2; CIMS *m/z* 272 $[M+H]^+$; EIMS *m/z* 203 $[M-68]^+$ (1), 105 $[M-C_9H_{12}NO_2]^+$ (100), 77 $[M-C_9H_{12}NO_2-CO]^+$ (38); HRMS Found: *m/z* 271.1220 $[M]^+$. Calcd for $C_{16}H_{17}NO_3$: M, 271.1208.

3.2.3. Reaction of acetone with CAN(IV). A reaction mixture of acetone (3.0 ml) and CAN(IV) (0.2971 g, 0.5 mmol) was stirred under reflux for 10 h. The mixture was extracted with diethyl ether (30 ml) and washed with aq. sodium hydrogencarbonate solution (2×2.0 ml), saturated aq. NaCl (2×2.0 ml) and water (2×2.0 ml). The ethereal solution was dried over Na_2SO_4, and concentrated in a vacuum. The resulting oil was 3,4-diacetyl-1,2,5-oxadiazole 2-oxide (**20**).

3.2.3.1. 3,4-Diacetyl-1,2,5-oxadiazole oxide (20). (NaCl) 1718 and 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.74 (s, 3H) and 2.63 (s, 3H); ^{13}C NMR ($CDCl_3$) δ=188.9, 185.5, 153.4, 111.5, 29.2, 28.2; CIMS *m/z* 172 $[M+H]^+$.

3.2.4. Reaction of 1-octene (3) with CAN(III)-formic acid in acetone. A mixture of 1-octyne (**3**) (0.0561 g, 0.5 mmol), ammonium cerium (III) nitrate (0.2741 g, 0.5 mmol), and formic acid (0.2302 g, 5.0 mmol) in acetone (3.0 ml) was stirred under reflux for 10 h. After the usual work up, the resulting oil was chromatographed on silica gel. Elution with hexane–diethyl ether (5:1) gave 3-acetyl-5-hexylisoxazole (**3a**) (0.0670 g, 68%).

3.2.5. Reaction of 1-octene (3) with CAN(III)-formic acid in acetophenone. A mixture of 1-octyne (**3**) (0.0561 g, 0.5 mmol), ammonium cerium(III) nitrate (0.2741 g, 0.5 mmol), and formic acid (0.2302 g, 5.0 mmol) in acetophenone (3.0 ml) was stirred under reflux for 15 h. After the usual work up, the resulting oil was chromatographed on silica gel. Elution with hexane–diethyl ether (5:1) gave 3-benzoyl-5-hexylisoxazole (**3b**) (0.0920 g, 71%).

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References and notes

1. (a) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023–4024. (b) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826–5833. (c) Kim, B. H.; Chung, Y. J.; Ryu, E. J. *Tetrahedron Lett.* **1993**, *34*, 8465–8472.
2. Andersen, S. H.; Sharma, K. K.; Torsell, K. B. G. *Tetrahedron* **1983**, *39*, 2241–2245.
3. Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276–278.
4. Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587–1590.
5. Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123–3126.
6. (a) Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248–5255. (b) Műller, I.; Jäger, V. *Tetrahedron Lett.* **1982**, *23*, 4777–4780.
7. (a) Jager, V.; Grund, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 50–58. (b) Lee, S. Y.; Lee, B. S.; Lee, C.-W.; Oh, D. Y. *J. Org. Chem.* **2000**, *65*, 256–257.
8. (a) Moersch, G. W.; Wittle, E. L.; Neuklis, W. A. *J. Org. Chem.* **1967**, *32*, 1387–1390. (b) Yashiro, A.; Nishida, Y.; Kobayashi, K.; Ohno, M. *Synlett* **2000**, 361–362.
9. Conti, P.; Dallanoce, C.; Amici, M. D.; Micheli, C. D.; Klotz, K.-N. *Bioorg. Med. Chem.* **1998**, *6*, 401–408.
10. Mishra, A.; Jain, S. K.; Asthana, J. G. *Orient. J. Chem.* **1998**, *14*, 151–152.
11. Ko, D.-H.; Maponya, M. F.; Khalil, M. A.; Oriaku, E. T.; You, Z.; Lee, *J. Med. Chem. Res.* **1998**, *8*, 313–324.
12. Kang, Y. Y.; Shin, K. J.; Yoo, K. H.; Seo, K. J.; Hong, C. Y.; Lee, C.-S.; Park, S. Y.; Kim, D. J.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 95–99.
13. Srirastara, S.; Bajpai, L. K.; Batra, S.; Bhaduri, A. P.; Maikhuri, J. P.; Gupta, G.; Dhar, J. D. *Bioorg. Med. Chem.* **1999**, *7*, 2607–2613.
14. Kanemasa, S.; Hayashi, T.; Yamamoto, H.; Wada, E.; Sakurai, T. *Bull. Chem. Soc. Jpn* **1991**, *64*, 3274–3279.
15. Shimizu, T.; Hayashi, Y.; Shibafuchi, H.; Teramura, K. *Bull. Chem. Soc. Jpn* **1986**, *59*, 2827–2831.
16. Katritzky, A. R.; Barczynski, P.; Ostercamp, D. L.; Yousaf, T. I. *J. Org. Chem.* **1986**, *51*, 4037–4042.
17. Martin, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293–297.
18. Itoh, K.; Takahashi, S.; Ueki, T.; Sigiyama, Y.; Talahashi, T. T.; Horiuchi, C. A. *Tetrahedron Lett.* **2002**, *43*, 7035–7037.
19. (a) Chawla, H. M.; Mittal, R. S. *Synthesis* **1985**, 70–72. (b) Ganguly, N.; Sukai, A. K.; De, S. *Synth. Commun.* **2001**, *31*, 301–309.
20. Horiuchi, C. A.; Kiji, S. *Bull. Chem. Soc. Jpn* **1997**, *70*, 421–426.
21. Horiuchi, C. A.; Ochiai, K.; Fukunishi, H. *Chem. Lett.* **1994**, 185–188.
22. Horiuchi, C. A.; Takahashi, E. *Bull. Chem. Soc. Jpn* **1994**, *67*, 271–273.
23. Sugiyama, T. *Appl. Organomet. Chem.* **1995**, *9*, 399–411.
24. Hwu, J. R.; Chen, K.-L.; Ananthan, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1425–1426.
25. Sugiyama, T. *Bull. Inst. Chem. Res., Kyoto Univ.* **1989**, *67*, 120–122.
26. Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. P.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595–4601.
27. Shimizu, T.; Hayashi, Y.; Shibafuchi, H.; Teramura, K. *Bull. Chem. Soc. Jpn* **1984**, *57*, 2531–2534.
28. Arai, N.; Iwakoshi, M.; Tanabe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn* **1999**, *72*, 2277–2285.

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Improvements in Diels–Alder cycloadditions with some acetylenic compounds under solvent-free microwave-assisted conditions: experimental results and theoretical approaches

André Loupy,[a,*] François Maurel[b] and Andrea Sabatié-Gogová[a,†]

[a]*Laboratoire des Réactions Sélectives sur Supports, CNRS UMR 8615, Université Paris-Sud, ICMMO, bâtiment 410, 91405 Orsay Cedex, France*
[b]*ITODYS, CNRS UMR 7086, Université Paris 7-Denis Diderot, 1, rue Guy de la Brosse, 75005 Paris Cedex 5, France*

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Abstract—The Diels–Alder irreversible cycloadditions of 1,3-cyclohexadiene **1**, 3-carbomethoxy-2-pyrone **2** and 2-methoxythiophene **3** with acetylenic dienophiles under solvent-free conditions are described. By strict comparisons with conventional heating under similar conditions, important specific microwave effects are revealed in the two last cases whereas they are absent in the first one. They are discussed in terms of asynchronous mechanisms in agreement with ab initio calculations at the HF/6-31G(d) level indicating dissymmetries in transition states. Specific MW effects can be understood by considering the enhancements in dipole moments from ground states to transition states.

1. Introduction

Coupling solvent-free reactions and microwave (MW) activation allows numerous improvements in organic synthesis.[1–7] Acceleration of chemical reactions under MW radiation can result from either thermal effects due to wave–materials interactions resulting in a rapid and homogeneous raising in temperature, or (and) specific non-purely thermal effects.[4,6,7] These last ones can be connected to organization of polar systems when submitted to an electromagnetic field, leading to decreases in the activation energy[8,9] or increases in the pre-exponential factor in Arrhenius law[10–12] or to microscopic hot spots[13–15] as for instance advocated in sonochemistry.[8]

Among the most popular reactions in organic synthesis, Diels–Alder cycloadditions were currently studied under MW irradiation.[16] Only few strict comparisons between MW and conventional heating (△) under similar sets of conditions are available and describe rather contradictory conclusions.

The possible intervention of specific MW effects is clearly dependent on reaction medium, substrates and mechanisms.[4] With nearly-symmetrical reagents, no or weak MW effects are involved,[16f,g] whereas they are clearly important with a lot of non-symmetrical hetero Diels–Alder reactions[16b,h–l] where often reactions only occurred under MW.

To put into evidence such possible MW effects, one needs a strict comparison of reactions under MW activation or with conventional heating (△) using an oil bath under the similar sets of conditions (time, temperature, pressure…). To this purpose, the Synthewave® 402 reactor from Prolabo operating with focused waves (monomode system)[1] is especially convenient. It allows mechanical stirring of the reaction mixture, the measurement of temperature by infrared detection,[17] its modulation according to emitted power to maintain the temperature constant and a monitoring of profiles of raising in temperature.

Non-catalyzed Diels–Alder cycloadditions are especially suitable cases to be considered under MW activation in solvent-free conditions since they need classically extended heating times in refluxing solvents. To draw unambiguous conclusions on MW activation, further studies need preferably to avoid any thermodynamical equilibrium by retro Diels–Alder reversibility. To this purpose, we consider here some examples of Diels–Alder cycloadditions of different dienes **1**–**3** with activated acetylenic dienophiles. The reactions are irreversible in nature due to expulsion of light small molecules from adducts

Keywords: Microwave irradiation; Solvent-free reaction; Cycloaddition; Activation energy; Dipole moment.
* Corresponding author. Tel.: +33-1-69-15-76-50; fax: +33-1-69-15-46-79; e-mail address: aloupy@icmo.u-psud.fr
† On leave from Department of Organic Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinskeho 9, SK-81237 Bratislava, Slovak Republic.

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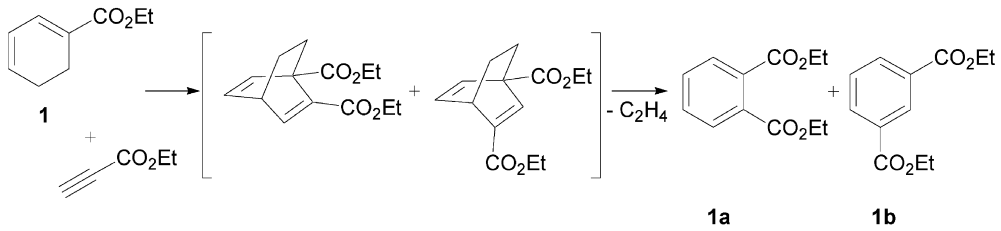
($H_2C{=}CH_2$, CO_2, elemental S) allowing aromatization (Eqs. 1–3). To the best of our knowledge, only one parent case was studied concerning MW enhanced reactions of 1,3-cyclohexadienes and acetylenic compounds but unfortunately without any control blank experiments by conventional heating under similar conditions.[18]

MW reactor. As the vessel is only irradiated in the bottom part, its upper part behaves as a cold wall to avoid removal of the dienophile.

In spite of the absence of any MW specific effects (entries 2/3 and 4/5), the solvent-free procedure constitutes here an



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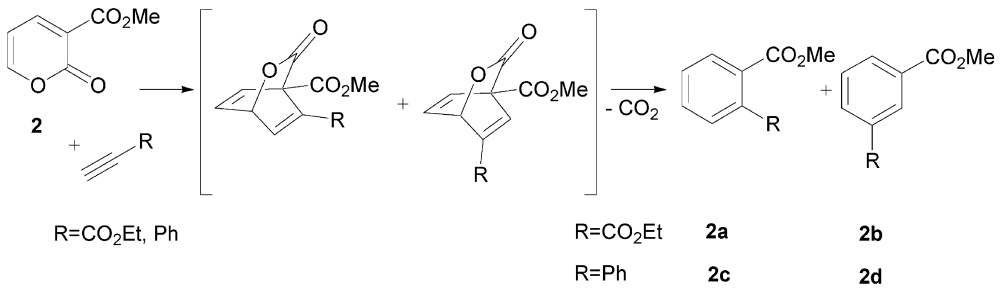

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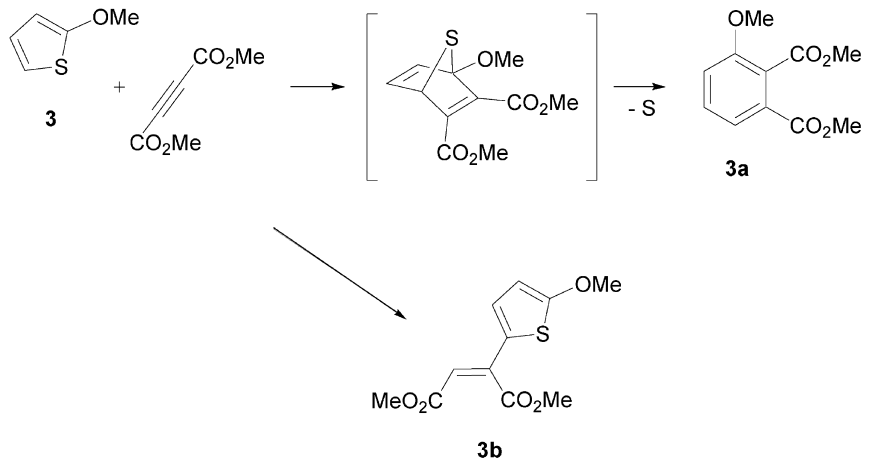


(3)

2. Results

2.1. Reaction of ethyl 1,3-cyclohexadiene carboxylate 1 with ethyl propiolate (EP) (Eq. 1)

In the literature,[19] this reaction was described under very harsh conditions (benzene at 320 °C within 24 h) with a very poor yield (17%) and no selectivity (**1a/1b**=50:50).

When realized either in the absence of solvent or on silica gel as a support in 'dry media' the reaction could be performed at 150 °C (Table 1). Taking into account the boiling point of ethyl propiolate (120 °C), the open system can be used with a rather long tube (roughly 8 cm) inside the undeniable improvement for the reaction (no solvent, atmospheric pressure, shorter reaction times and lower temperatures) with enhanced yields from 17 to 36–37% (entries 2, 3, and 5).

2.2. Reaction of 3-carbomethoxy-2-pyrone 2 with ethyl propiolate or phenyl acetylene (Eq. 2)

Reaction of pyrone **2** with ethyl propiolate was reported by Reed and coll.[20] to occur for 30 h in refluxing xylene with a yield of 50% (**2a/2b**=20:80). With phenyl acetylene as the dienophile, a 60% yield was obtained with a poor selectivity (**2c/2d**=65:35) by extended heating in toluene at 250 °C (in closed vessels) for 24 h. This same experiment was also

Table 1. Reaction of **1** (0.20 g, 1.31 mmol) with ethyl propiolate (0.26 g, 2.63 mmol) at 150 °C under microwave (MW) irradiation or conventional heating (△)

Entry	Activation	Medium	Temperature (°C)	Time (h)	Yield (%)[a] **1a+1b**	**1a/1b**[a]
1	△[19]	Benzene	320	24	17	50:50
2	△	No solvent	150	2.5	36	53:47
3	MW	No solvent	150	2.5	37	52:48
4	△	Silica gel[b]	150	1	25	60:40
5	MW	silica gel[b]	150	1	36	60:40

[a] GC yields and ratios using an internal standard (ethyl diethylmalonate).
[b] 1 g of support for 0.20 g of **1**.

described in xylene at 200 °C for 24 h with a non-specified yield and a conversion of 97% without any subsequent purification.[21]

In our hands, reactions were, therefore, performed either in xylene or solvent-free conditions at atmospheric pressure under microwave or traditional heating for the same times and temperatures (Table 2).

Thanks to important specific MW effects, results obtained under solvent-free conditions (entries 9 and 13) are by far better than the ones previously published under classical conditions (entries 6 and 10) within short reaction times and easier procedures. For instance, with ethyl propiolate, the yield of 80% within 2 h at 120 °C under solvent-free MW assisted conditions constitutes a noticeable improvement to the classical reaction in xylene for 30 h (50%). On another hand, with phenyl acetylene, the yield is equivalent using solvent-free conditions and MW activation within 3 h at 150 °C when compared to the one day procedure in toluene at 250 °C.

In both cases, very important kinetic specific MW effects are evidenced (entries 8/9 and 11/13).

Dealing with selectivity, it appears to be significantly improved by this method in the case of phenyl acetylene since only the regioisomer **2c** is obtained (no traces of **2d** were detectable by GC or NMR). Selectivity is only slightly modified in the case of ethyl propiolate (entries 8 and 9) from **2a/2b**=42:58 (△) to 31:69 (MW).

2.3. Reaction of 2-methoxythiophene 3 with dimethyl-acetylenedicarboxylate (DMAD) (Eq. 3)

According to literature,[22] the progress of this reaction is deeply affected by the nature of the medium. When performed in refluxing xylene, it leads to Diels–Alder cycloaddition (96 h) whereas, when carried out in acetic acid at 100 °C, Michael addition is observed (8 h). In both cases, yields remained very poor (**3a**: 17% and **3b**: 28%, respectively). This reaction was thus performed in xylene, in solvent-free conditions and in acetic acid either under MW activation or in a thermostated oil bath under similar conditions (Table 3).

Serious improvements in yields and experimental conditions are evidenced in both cases when one consider the yields of 65% (entry 20) and 49% (entry 23) obtained, respectively, for **3a** and **3b** when compared to those of 17 and 28% reported in the literature.

It is noticeable that the Michael product consists in a single isomer **3b**. The *E* configuration was confirmed by assignment on the basis of the chemical shifts using NOESY 1D experiment. Irradiation of ethylenic proton at 5.92 ppm increased intensity of proton doublet at 6.86 ppm.

In both cases, important specific MW effects when compared to classical heating are revealed. If this effect seems rather limited for Diels–Alder cycloadditions (MW: 65%, △: 40%), it is much more significant for Michael addition (MW: 49%, △: 4%). Furthermore, the competition between the two processes is highly affected by the mode of activation. Every conditions being equal elsewhere, Michael addition is favored under MW when compared to conventional heating (**3a/3b** is enhanced from 60:40 to 17:83, entries 22/23).

3. Discussion

3.1. Comparisons with literature

Solvent-free conditions lead by far to serious improvements, which can be due to some extent to enhancement in concentration of reagents. They are conducted under easy-to-perform techniques involved in Green Chemistry:

Table 2. Reaction of **2** (0.50 g, 3.25 mmol) with acetylenic compounds (0.45 and 0.46 g, 4.55 mmol) under MW irradiation or conventional heating (△)

Entry	R	Activation	Medium	Temperature (°C)	Time (h)	Yield (%)[a,b]	Products[a,c]
6	CO_2Et	△[20]	Xylene	140	30	50	**2a/2b**=20:80
7		MW	Xylene (3 ml)	120	2	7	**2a/2b**=28:72
8		△	No solvent	120	24	19 (19)	**2a/2b**=(42:58)
9		MW	No solvent	120	2	80 (75)	**2a/2b**=(31:69)
10	Ph	△[20]	Toluene	250	24	60	**2c/2d**=65:35
11		△	No solvent	150	3	19	**2c**
12		△	No solvent	150	24	44 (40)	**2c**
13		MW	No solvent	150	3	64 (62)	**2c**

[a] GC yields and ratios using an internal standard (propyl phtalate when R=CO_2Et and diethyl phtalate when R=Ph).
[b] Yields of isolated products are reported in brackets.
[c] Ratios **2a/2b** and **2c/2d** have been determined by GC and ^1H NMR.

Table 3. Reaction of **3** (0.80 g, 7.02 mmol) with several amounts of DMAD in xylene (1 mL), or without solvent or in acetic acid (15 mL) under MW irradiation or conventional heating (△)

Entry	Activation	Solvent	**3/DMAD**	Temperature (°C)	Time (h)	Yield (%)[a,b]	
						3a	**3b**
14	△[22]	Xylene	1:3	140	96	17	—
15	△	Xylene	1:5	140	2	35	8
16	MW	Xylene	1:5	140	2	50	9
17	△	No	1:3	140	2	21	<2
18	MW	No	1:3	140	2	49	<2
19	△	No	1:5	140	2	40	7
20	MW	No	1:5	140	2	65 (64)	6
21	△[22]	AcOH	1:3	100	8	—[c]	28
22	△	AcOH	1:3	100	2	6	4
23	MW	AcOH	1:3	100	2	10	49 (48)

[a] GC yields using an internal standard (ethyl benzoate).
[b] Yields of isolated products are reported in brackets.
[c] Not reported.

In the first case (Eq. 1), we obtained a yield of 36% either under MW or thermal activations (entries 2 and 3) within 2.5 h in the absence of solvent under atmospheric pressure at 150 °C instead of lower yield (17%) within 24 h in benzene in closed vessels at 320 °C.

In the absence of solvent, the reaction of pyrone **2** (Eq. 2) was now improved up to 80% with ethyl propiolate within 2 h at 120 °C (entry 9) when compared to 50% in refluxing xylene and to 64% with phenyl acetylene (entry 13) within 3 h at 150 °C instead of 60% after 24 h in toluene in closed vessels under pressure at 250 °C.

In the last case (Eq. 3), in the absence of solvent, the yield in cycloadduct is improved up to 65% (entry 20) within 2 h at 140 °C when compared to 17% in refluxing xylene for 96 h. In acetic acid, the Michael adduct is obtained with 49% yield under MW for 2 h at 100 °C (entry 23) instead of 28% after 8 h by conventional heating.

From selectivity point of view, it is noteworthy that:

(i) with cyclohexadiene **1**, the ratios **1a/1b** are nearly identical around 50:50 whatever the conditions examined in the absence or presence of solvent or silica gel and the selectivity remains rather identical;
(ii) with pyrone **2** and ethyl propiolate, the ratios **2a/2b** are slightly affected according to reaction conditions from 20:80 to 42:58 when comparing reactions in xylene and under solvent-free conditions. A slight modification of selectivity is also observed in the absence of solvent under classical heating and under MW (31:69). The most important change lies in the case of reaction **2** with phenyl acetylene as under solvent-free conditions the compound **2c** was obtained specifically instead of a mixture of **2c** and **2d** (65:35) in toluene;
(iii) with thiophene **3**, either in xylene or in dry media, Diels–Alder product **3a** is highly predominant versus Michael adduct **3b**.

We have to quote that, in all these cases, the regioselectivities were not especially affected by MW activation and remained rather the identical as under conventional heating. On the contrary, in the case of reaction of **3** in acetic acid, the regioselectivity **3a/3b** is strongly affected by the mode of activation, starting from 60:40 by conventional heating up to 17:83 by MW under similar sets if conditions (2 h at 100 °C, entries 22 and 23).

3.2. Specific MW effects

The specific MW effects should be the reflect of the modification of polarity during the reaction progress from the ground state (GS) towards the transition state (TS).[4] If there is no development of charges in TS, in an isopolar mechanism, polarity remains unchanged and MW effect will be nil. On the contrary, if charges are developed in asynchronous TS, MW effect should be expected. Such an assumption, connected to the (a)synchronous character of the mechanism, was advanced recently by Cossio, Langa and coll.[23] when considering calculations for cycloadditions predicting asynchronous transition structures in cases where specific MW effects were evidenced and stating that the modifications are related to the relative energies and hardness of the transition structures involved.

It is noteworthy that, during the reactions of pyrone **2** and thiophene **3**, important specific MW effects are involved whereas they are absent in the case of cyclohexadiene **1**.

This important observation could be due to the fact that, in the cases of reactions depicted in Eqs. 2 and 3 under solvent-free conditions, these reactions occurred via asynchronous transition states. On the opposite, the absence of MW effects in case 1 could reflect a synchronous transition state. One can thus state that the possible MW effect should be an experimental indicator of synchronous or asynchronous transition state on the same way as differences in rates did.[24]

3.3. Theoretical calculations

Theoretical approaches can allow justifying these assumptions. Ab initio calculations were carried out at the Hartree–Fock level (HF/6-31G(d)) and Density Functional Theory (B3LYP/6-31G(d)) levels with several aims:

1. optimization of TS geometries to assess the

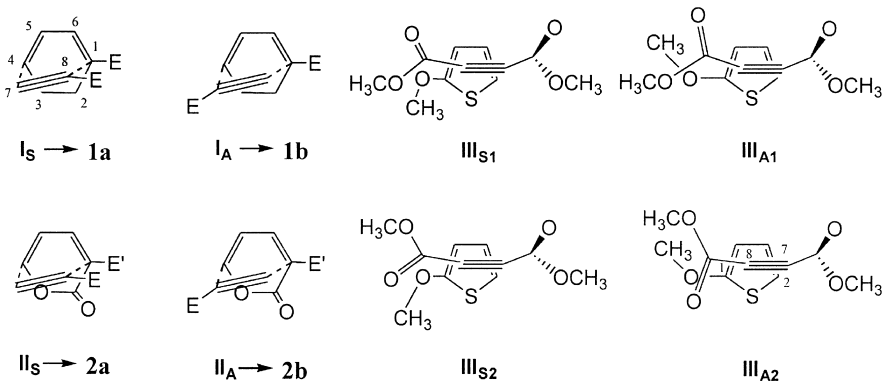


Figure 1. Reagent approaches in reactions depicted in equations 1–3 (E=CO_2Et, E′=CO_2Me).

(a)synchronicity of the mechanism by comparing the relative degrees of the two bonds formation;
2. estimation of activation energies;
3. evaluation of dipole moments in GS and TS as a picture of enhancement in polarity during the reaction progress;
4. orbital frontier analysis to foresee relative reactivities.

3.4. Optimization of transition state geometries and evaluation of activation energies

In the cases of Eqs. 1 and 2 concerning cyclohexadiene **1** and pyrone **2**, two possible approaches were considered where the two esters groups are either *syn* (respectively, $\mathbf{I_S}$ and $\mathbf{II_S}$ for **1** and **2**) or *anti* (respectively, $\mathbf{I_A}$ and $\mathbf{II_A}$) (Fig. 1). In the case of thiophene reaction with DMAD, four possible approaches were considered where the methoxy group of thiophene is either in *syn* or in *anti* conformation (respectively, $\mathbf{III_S}$ and $\mathbf{III_A}$) and one carbonyl group in parallel plane is oriented on the same side of *syn* or *anti* methoxythiophene (respectively, $\mathbf{III_{S2}}$ and $\mathbf{III_{A2}}$) or the contrary (respectively, $\mathbf{III_{S1}}$ and $\mathbf{III_{A1}}$).

Theoretical calculations were carried out to evaluate the structures of the transition states corresponding to these different approaches and to determine the activation energy. The main results of calculations after full optimizations at HF/6-31G(d) level are indicated in Table 4. The values of activation energies were calculated at the DFT level [B3LYP/6-31G(d)] which allows to take into account the correlation effect (see Section 5.1).

From this Table, one can draw a lot of conclusions:

Table 4. Distances between linking bonds and energies of activation for the attacks in Figure 1

	$d_{1,8}$ (Å)	$d_{4,7}$ (Å)	Δd (Å)	$\Delta E^{\#}$ (kcal mol^{-1})
$\mathbf{I_S}$	2.300	2.055	0.245	20.7
$\mathbf{I_A}$	2.162	2.261	−0.099	21.5
$\mathbf{II_S}$	2.376	2.034	0.342	24.4
$\mathbf{II_A}$	2.298	2.085	0.213	22.3
$\mathbf{III_{S1}}$	3.093	1.971	1.122	21.1
$\mathbf{III_{S2}}$	2.889	1.946	0.943	20.8
$\mathbf{III_{A1}}$	3.142	1.955	1.187	20.4
$\mathbf{III_{A2}}$	3.170	1.960	1.210	21.2

In case **I**, the two types of attack lead to rather close values of ΔE, justifying thus the poor selectivity observed (from 50:50 to 60:40 according to reaction medium).
In case **II**, *anti* attack is more largely preferred to *syn* approach by 2.1 kcal mol^{-1}, presumably due to less steric repulsion between the two esters groups. This difference can allow thus an improved selectivity favoring preferential access to **2b**, what is effectively observed with a selectivity of 80:20 in favour of **2b**.

The dissymmetry in TS, when considering the differences in lengths between linking bonds (Δd), is enhanced according to the sequence $\mathbf{III_A}>\mathbf{II_A}>\mathbf{I_A}$. Therefore, the asynchronicity in reactions of thiophene **3** and then pyrone **2** is much more higher than in the case of cyclohexadiene **1**. This prevision is in good agreement with the magnitude of specific MW effects as we observed.

3.5. Case of reaction of pyrone 2 with phenyl acetylene

This case is especially interesting as leading to a single isomer **2c**. Ab initio calculations were performed at the HF/6-31G(d) level for the two possible optimized approaches *syn* and *anti* (Fig. 2).

It was evaluated that *syn* approach is largely preferred to *anti* approach by 5.6 kcal mol^{-1}. We can notice that this high value is perhaps amplified by the possibility of π-stacking between aromatic ring and ester moiety, this phenomenon intervenes at distances 3.5–5 Å[25] and is especially important in solvent-free medium.[26] We can therefore predict the formation of only one isomer (**2c**) resulting from *syn* approach.

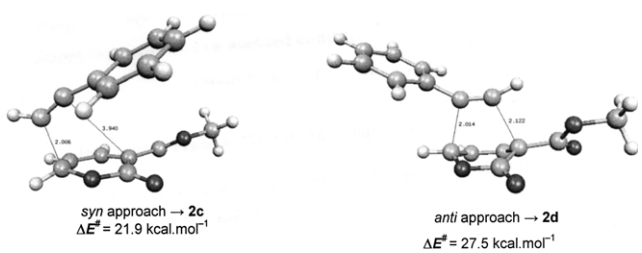


Figure 2. Transition states for the reaction of **2** with phenyl acetylene.

We can also notice the high dissymmetry in the TS (difference in bond lengths between linking atoms Δd=1.934 Å), justifying thus the high degree of asynchronicity for the mechanism and consequently the important MW specific effect.

3.6. Evolution of dipole moments from ground state to transition state

The same calculations as above give access to the values of the dipole moments. We give in Table 5 all of them for starting materials and the different TS. We have to notice the non-nil value for DMAD, which results from the position of the two esters moieties in two perpendicular planes.

In the cases of reactions 2 and 3, large enhancements in dipole moments from GS to TS are foreseen and could consequently give an explanation for the most important MW effects in these cases.

3.7. Frontier orbitals analysis of reagents

Usually in this type of reactions it is possible to justify relative reactivities and selectivities by considering the orbital frontier interactions. So, in Table 6, we indicate the energy levels of the orbitals concerned in the procedures.

The main frontier orbital interactions concern the HOMO of **D** and the LUMO of **E**. The sequence of reactivities connected to these interactions is **3**>**1**>**2**, which differ from the experimental one, i.e., **3**>**2**>**1**. The origin of the discrepancy can be explained as follow: due to the low energy LUMO level of **2**, it is necessary to take into account of the HOMO(**E**)/LUMO(**D**) interaction which can be added to the previous one.

3.8. Case of reaction of thiophene 3: Diels–Alder cycloaddition and Michael addition

In Eq. 4 are represented the two possible pathways (Diels–Alder and Michael reactions) when reacting thiophene **3** with **DMAD** according to reaction conditions leading to, respectively, **3a** and **3b**.

Table 5. Dipole moments of reagents and transition states carried out by HF/6-31G(d) level

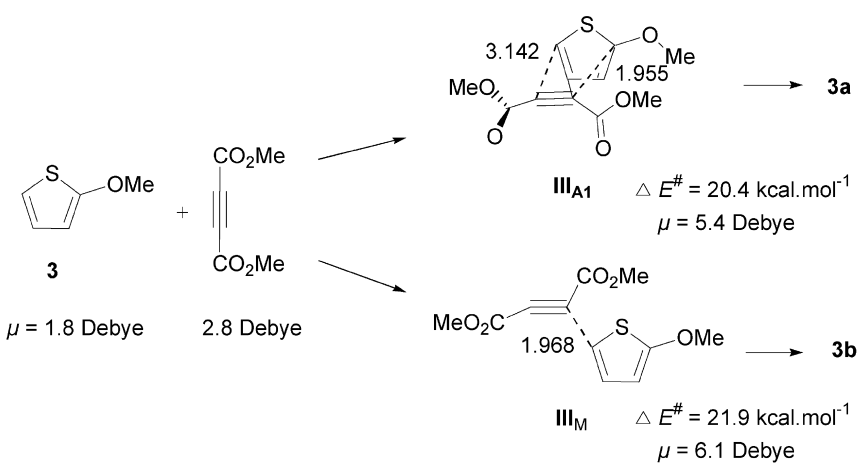
	Ground states		Transition states	
Reaction Eq. 1	**EP**	**1**	$\mathbf{I_S}$	$\mathbf{I_A}$
μ (Debye)	2.2	2.4	0.4	1.9
Reaction Eq. 2	**EP**	**2**	$\mathbf{II_S}$	$\mathbf{II_A}$
μ (Debye)	2.2	3.3	4.8	5.2
Reaction Eq. 3	**DMAD**	**3**	$\mathbf{III_{S1}}$, $\mathbf{III_{S2}}$	$\mathbf{III_{A1}}$, $\mathbf{III_{A2}}$
μ (Debye)	2.8	1.8	5.83, 5.15	5.40, 8.02

When considering the differences in lengths between the newly formed bonds (1.8 and 2.7 cf. Δd in Table 4), an asynchronous mechanism has to be postulated for the Diels–Alder reaction. It could be certainly the reason why this special Diels–Alder cycloaddition is strongly favored under MW conditions when performed in an aprotic solvent or without solvent. The calculations of the relative activation energies $\Delta E^{\#}$ are clearly in agreement with experiments as, respectively, 20.4 and 21.9 kcal mol^{-1} for Diels–Alder (via the approach $\mathbf{III_{A1}}$) and Michael reactions.

When one considers the relative dipole moments of the transition states, the polarity of $\mathbf{III_M}$ is higher than for $\mathbf{III_{A1}}$. Consequently, under MW activation, one can expect an enhancement in Michael addition more important than for Diels–Alder, affecting thus the selectivity in favour of the first one.

In the case of pyrrole, a two steps mechanism has been considered.[27] The Michael addition intermediate should give the cycloaddition in aprotic systems while when a proton transfer is possible the Michael Addition product is observed.

The most important factor affecting the selectivity can be the solvent (xylene and no solvent gives the cycloaddition reaction while acetic acid gives the Michael addition product). We can expect that a protic solvent stabilizes better the more polar transition state, strengthening thus the tendency yet revealed in its absence (the solvent is not included in the calculation).



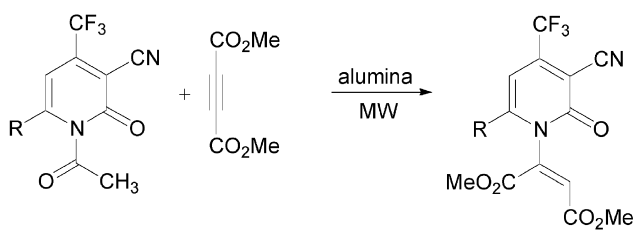
(4)

Table 6. Energy levels of HOMO and LUMO orbitals of the reagents in atomic unities (hartrees)

Compounds		HOMO	LUMO	$\Delta(HOMO_D-LUMO_E)$	$\Delta(HOMO_E-LUMO_D)$
Dienes (D)	**1**	−0.31313	0.09501	0.43623[a]	0.51301[a]
	2	−0.34519	0.06258	0.46829[a]	0.48058[a]
	3	−0.31746	0.14313	0.43096[b]	0.57076[b]
Dienophiles (E)	**EP**	−0.41800	0.12310		
	DMAD	−0.42763	0.11350		

[a] E=EP.
[b] E=DMAD.

Also interesting in the same field is the result observed by Kaishnaiah and Narsaiah[28] who obtained Michael adducts during the reaction of pyridone **4** with DMAD under MW irradiation when carried out on neutral alumina under solvent free conditions instead of the expected Diels–Alder compounds (Eq. 5). Unfortunately, this same experiment was not studied under conventional heating.



(5)

As a coherent interpretation, one can assume that alumina can interact specifically by hydrogen bonding with carbonyl groups from esters moieties as well as acetic acid.

4. Conclusion

Three cases of irreversible Diels–Alder reactions were considered with great success. Solvent-free conditions lead by far to the best results and to easy-to-perform procedures with considerable improvements over classical methods. MW effects are very favorable in the cases of reaction of pyrone **2** and thiophene **3**. The observed specific MW effect is according to the sequence **1**<**3**<**2**, what could be understood by considering the concerted character of the mechanism: **1** may react via a totally concerted mechanism and **2** and **3** via polar non symmetrical ones involving development of charges. All the observations were supported by ab initio calculations taking into account the activation energies, the dissymmetry in TS geometries and enhancements of dipole moment from GS to TS.

In the case of thiophene **3**, an important change in selectivity (competitive Diels–Alder vs Michael reactions) is observed in acetic acid. Under the same conditions, MW strongly favored the Michael addition versus Diels–Alder reaction when compared to conventional heating, presumably via the more polar mechanism. This point could be supported by an increase in the dipole moment from GS to TS in the case of Michael addition. However, the solvent can also certainly contribute to the change in reactivity and selectivity.

5. Experimental

Ethyl 1,3-cyclohexadiene carboxylate **1** was prepared according to a new MW-assisted procedure as an improved and efficient method when compared to classical ones.[29] Pyrone **2**, thiophene **3** and all the dipolarophiles (ethyl propiolate, phenyl acetylene and DMAD) are commercially available.

Reactions were performed by mixing dienes **1**–**3** with dipolarophile in the relative amounts indicated in the Tables 1–3 in a Pyrex tube, which was submitted to MW irradiation in a monomode reactor Synthewave® S402 from Prolabo[1] at temperatures and for reaction times indicated in the Tables. At the end of the reaction, when reactions were carried out up to full conversion of dienes (followed by TLC on Merck silica gel 60 F_{254} plates, using UV light at 254 nm and methylene chloride for detection), the mixture was cooled to room temperature and dissolved in methylene chloride. Crude products were analyzed by capillary gas chromatography (Table 7) using an internal standard (see footnotes in Tables 1–3). ^{1}H NMR spectra were recorded on Bruker AC 400 (400 MHz) in $CDCl_3$ with TMS as reference and then compared with authentic samples. The products **2a**, **2b** and **2c** were purified by flash chromatography using methylene chloride and **3a** and **3b** using ethyl acetate/*n*-pentane (1:5) as eluent.

5.1. Computational details

The reactants **1**, **2**, **3**, **EP** and **DMAD** as well as the corresponding transition states for Diels–Alder reactions were fully optimized without symmetry restrictions (convergence criteria=10^{-4}) with the Hartree–Fock method and using the 6-31G(d) basis set[30] (HF/6-31G(d) calculations). The Gaussian 94 program[31] was used for all calculations. Vibrational frequencies were calculated at the same level of theory to characterize the optimized structures as a minimum or a first-order saddle point on the potential energy surface (the Hessian matrix revealed a single negative eigenvalue for each TS). Previous theoretical studies of cycloaddition have indicated that the activation energies calculated at the Hartree–Fock level are too large, while DFT calculations using the B3LYP hybrid functional[32] have been shown to be in good agreement with experimental activation energy values.[33]

Therefore, the HF/6-31G(d) stationary points were characterized by B3LYP/6-31G(d) single-point calculations (B3LYP/6-31G(d)//HF/6-31G(d) calculations) to obtain more accurate activation energy. The discussion is based on the comparison of experimental results obtained without

Table 7. GC analysis (vector gas is helium (50 kPa) in all cases)

GC column, temperature programme	Compound	rt[a] (min)	Internal standard	rt[a] (min)
OV-1 (12 m×0.22 mm i.d., film thickness 0.1 μm), injector and detector at 250 °C	**1**	4.65	Ethyl diethylmalonate	5.60
80–150 °C[a] with 10 °C min^{-1} then 150–220 °C with 5 °C min^{-1}	**1a**	9.59		
CP-Sil 5CB (25 m×0.32 mm i.d., f. th. 0.12 μm), injector and detector at 280 °C	**2**	5.46	Propyl phthalate	10.36
80–250 °C with 10 °C min^{-1}	**2a**	7.43		
CP-Sil 5CB (idem)	**2**	4.08	Diethyl phthalate	6.50
Injector and detector at 280 °C, 100−250 °C with 10 °C min^{-1}	**2c**	7.29		
OV-1 (12 m×0.22 mm i.d., film thickness 0.1 μm), injector and detector at 280 °C	**3**	2.69	Ethyl benzoate	6.82
50 °C during 2 min then 50–250 °C with 10 °C min^{-1}	**3a**	13.9		

[a] rt, retention time.

solvent at high temperature with computed values on isolated molecule at 0 K. We checked for the reaction **1** that Zero Point Energy (ZPE) corrections reaction do not affect significantly the energy barriers of activation.

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References and notes

1. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213–1234.
2. Varma, R. S. *Green Chem.* **1999**, *1*, 43–55.
3. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851–10870.
4. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223.
5. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
6. For a recent and complete review, see. In *Microwaves in organic synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002.
7. Langa, F.; de la Cruz, P.; de la Hoz, A.; Diaz-Ortiz, A.; Diez-Barra, E. *Contemp. Org. Synth.* **1997**, 373–386.
8. Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363–2366.
9. Lewis, D. A.; Summers, J. D.; Ward, T. C.; McGrath, J. E. *J. Polym. Sci. Part A* **1992**, *30*, 1647–1653.
10. Jacob, J.; Chia, L. H. L.; Boey, F. Y. C. *J. Mater. Sci.* **1995**, *30*, 5321–5327.
11. Binner, J. G. P.; Hassine, N. A.; Cross, T. E. *J. Mater. Sci.* **1995**, *30*, 5389–5393.
12. Shibata, C.; Kashima, T.; Ohuchi, K. *Jpn. J. Appl. Phys.* **1996**, *35*, 316–319.
13. (a) Stuerga, D.; Gaillard, P. *Tetrahedron* **1996**, *52*, 5505–5510. (b) Stuerga, D.; Gaillard, P. *J. Microwave Power Electromag. Energy* **1996**, *31*, 87–113.
14. Maoz, R.; Cohen, H.; Sagiv, J. *Langmuir* **1998**, *14*, 5988–5993.
15. Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Bednarz, Sz. *Tetrahedron* **2003**, *59*, 649–653.
16. (a) Giguere, R. G.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948. (b) Linders, J. T. M.; Kokje, J. P.; Overhand, M.; Lie, T. S.; Maat, L. *Rec. Trav. Chim. Pays-Bas* **1988**, *107*, 449–454. (c) Lei, B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 4609–4610. (d) Stambouli, A.; Chastrette, M.; Soufiaoui, M. *Tetrahedron Lett.* **1991**, *32*, 1723–1724. (e) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raji, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968–6970. (f) Raner, K. D.; Strauss, C. R.; Vyskoc, F.; Mokbei, L. *J. Org. Chem.* **1993**, *58*, 950–953. (g) Laurent, R.; Laporterie, A.; Dubac, J.; Berlan, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* **1992**, *57*, 7099–7102. (h) Garrigues, B.; Laporte, C.; Laurent, R.; Laporterie, A.; Dubac, J. *Liebigs Ann.* **1996**, 739–741, see also 743–741. (i) Diaz-Ortiz, A.; Carrillo, J. R.; Diez-Barra, E.; de la Hoz, A.; Gomez-Escalonilla, M. J.; Moreno, A.; Langa, F. *Tetrahedron* **1996**, *52*, 9237–9248. (j) Motorina, I. A.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1997**, *62*, 2098–2105. (k) Diaz-Ortiz, A.; Carrillo, J. R.; Gomez-Escalonilla, M. J.; de la Hoz, A.; Moreno, A.; Prieto, P. *Synlett* **1998**, 1069–1070. (l) Laporte, C.; Oussaid, A.; Garrigues, B. *Compt. Rendus Acad. Sc., Serie IIC* **2000**, *3*, 321–325. (m) de la Hoz, A.; Diaz-Ortiz, A.; Langa, F. In *Microwaves in organic synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; pp 295–343. (n) Essers, M.; Mueck-Lichtenfeld, C.; Haufe, G. *J. Org. Chem.* **2002**, *67*, 4715–4721. (o) Pinto, D. C. G. A.; Silva, A. M. S. *J. Org. Chem.* **2002**, 4715–4721. (p) Leadbeater, N.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145–3148. (q) Almeida, L. M. P. M.; Carrillo, J. R.; Diaz-Ortiz, A.; de la Hoz, A.; Cavaleiro, J. A. S. *Synlett* **2003**, 1415–1418.
17. Commarmot, R.; Didenot, R.; Gardais, J. F. French Patent 84/03496, 1986; *Chem. Abstr.* **1986**, 105, 17442..
18. Hijji, Y. M.; Wanene, J. *Abstr. Pap. Am. Chem. Soc. 2001* **2001**. 221st ORG-497; *Chem. Abstr.* **2001**, 202999.
19. Wynn, C. M.; Klein, P. S. *J. Org. Chem.* **1996**, *31*, 4251–4252.
20. Reed, J. A.; Schilling, C. L., Jr.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188–2191.
21. Effenberger, F.; Ziegler, T. *Chem. Ber.* **1987**, *120*, 1339–1346.
22. Corral, C.; Lissavetzky, J.; Manzanares, I. *Synthesis* **1997**, 29–31.
23. (a) Diaz-Ortiz, A.; Carrillo, J. R.; Cossio, F. P.; Gomez-Escalonilla, M. J.; de la Hoz, A.; Moreno, A.; Prieto, P. *Tetrahedron* **2000**, *56*, 1569–1577. (b) Langa, F.; de la Cruz, P.; de la Hoz, A.; Espildora, E.; Cossio, F. P.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 2499–2507.
24. Buckle, R. N.; Liu, P. Y.; Roberts, E. W. D.; Burnell, D. J. *Tetrahedron* **1999**, *55*, 11455–11464.
25. Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475–488.

26. Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *34*, 473–476.
27. Domingo, L. R.; Picher, M. T.; Zaragoza, J. *J. Org. Chem.* **1998**, *63*, 9183–9189.
28. Kaishnaiah, A.; Narsaiah, B. *J. Fluorine Chem.* **2002**, *113*, 133–137.
29. Tesson, N.; Deshayes, S. *Org. Prep. Proced. Int.* **2000**, *32*, 41–45.
30. (a) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217–222. (b) Hehre, W. J.; Radom, L.; Schleyer, V. R. P.; Pople, J. A. *Ab initio molecular orbital theory*; Wiley: New York, 1986.
31. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision E.1*; Gaussian, Inc.: Pittsburgh, PA, 1995.
32. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
33. (a) Domingo, L. R.; Arno, M.; Andrés, J. *J. Am. Chem. Soc.* **1998**, *120*, 1617–1618. (b) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036–6043. (c) Sbai, A.; Branchadell, V.; Ortuno, R. M.; Oliva, A. *J. Org. Chem.* **1997**, *62*, 3049–3054. (d) Morao, I.; Lecea, B.; Cossio, F. P. *J. Org. Chem.* **1997**, *62*, 7033–7036.