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Tetrahedron

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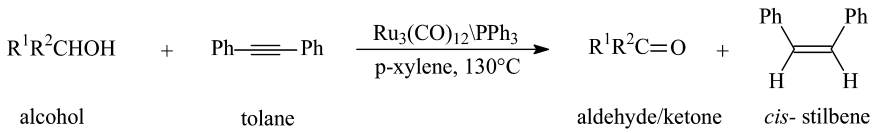
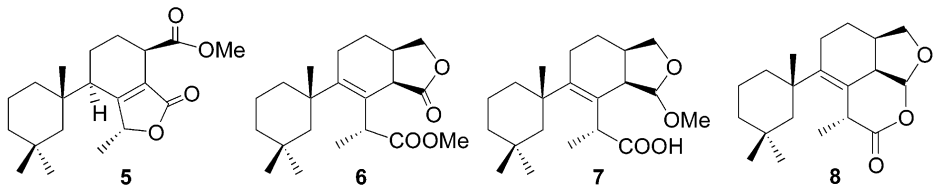
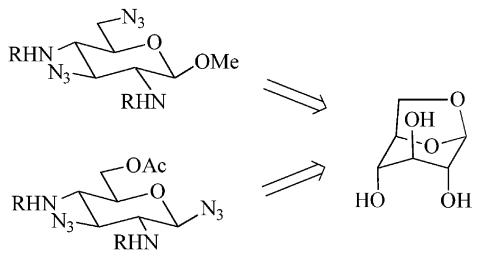
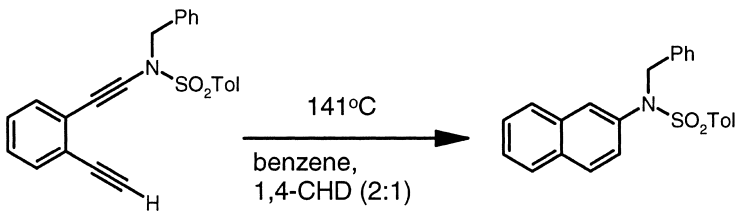
Contents



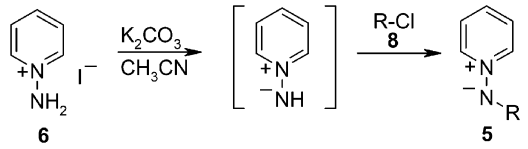
A new dehydrogenation procedure to synthesize aldehydes and ketones from alcohols using triruthenium dodecacarbonyl/ligand as catalyst is described.



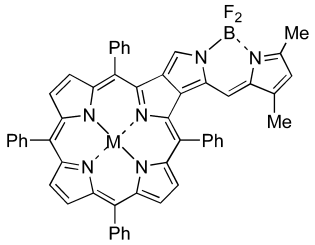




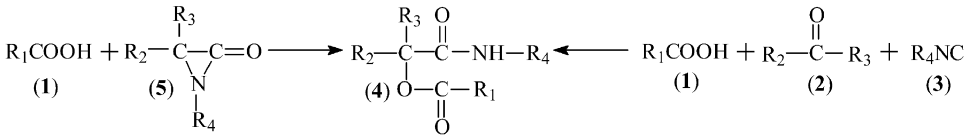
A sulfonamide alkyne substituent leads to an increase in thermal enediyne reactivity.



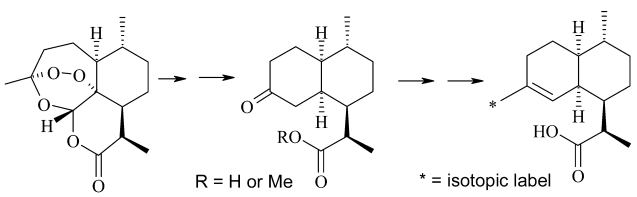
Differently substituted pyridinium *N*-heteroarylaminides **5** have been prepared in one step with good yield from *N*-aminopyridinium iodide **6** and the corresponding heteroaryl chloride **8**.

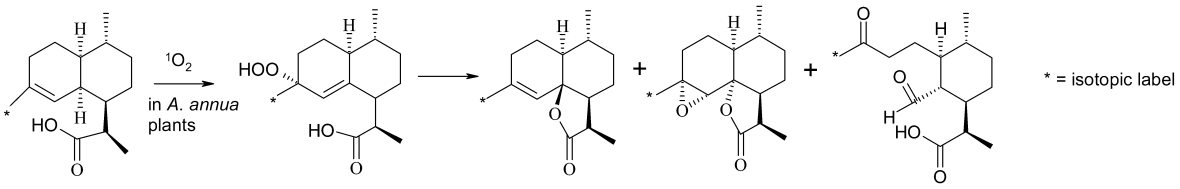


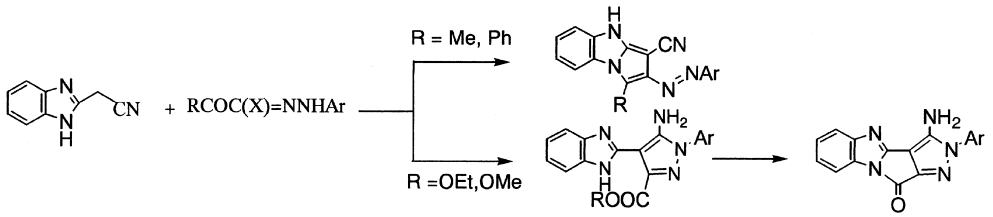
Pyrroloporphyrins react with 2-formylpyrroles to form dipyrromethenoporphyrins that give fused porphyrin-BODIPY® dyads with novel optical spectra upon reaction with BF_3 etherate.

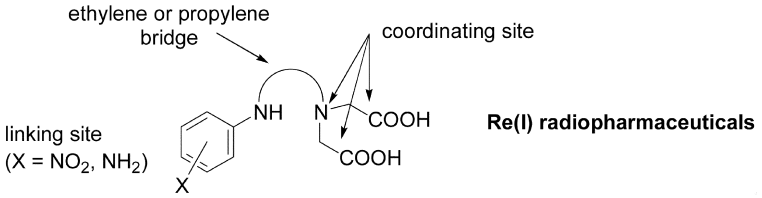


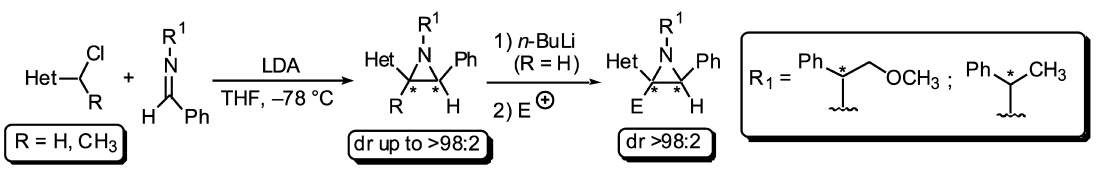
This paper demonstrates that α-lactams (**5**) can function to replace two of the three reactants in the Passerini reaction, the oxo-compound (**2**) and the isonitrile (**3**), to yield, with carboxylic acids (**1**) of a positive pK_a, α-acyloxycarboxamides (**4**).

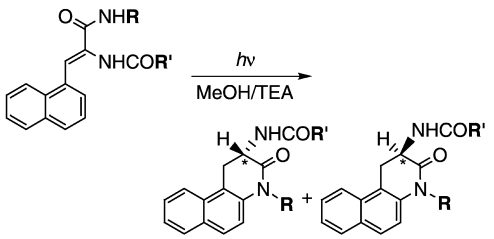




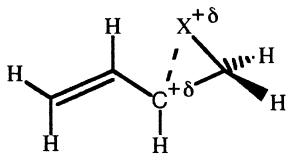




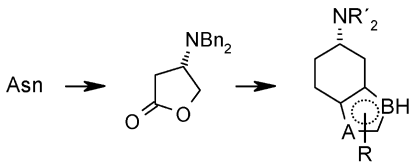




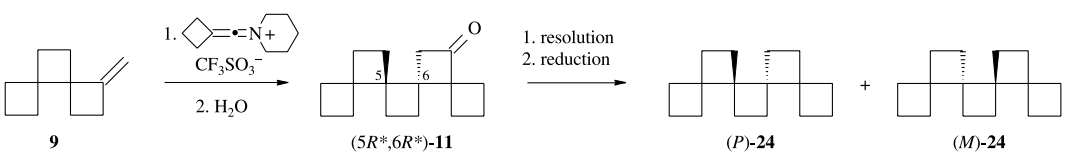
R= (*S*)-*CH(Me)CO_2Me, (*R*)-*CH(Me)CO_2Me; **R'**=Me, Ph



Conformational studies of 1-halo-2-butenylcations (X=F, Cl, Br) have been carried out by means of density functional and ab initio calculations. The presence of an adjacent vinyl group reduces the importance of bridging by halogen atoms as evidenced by geometric and energetic analyses. In several cases, eclipsed conforms were found to be energy minima.

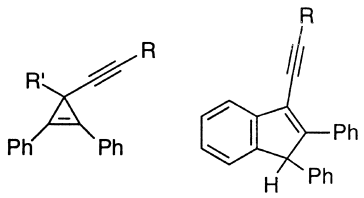


Chemo- and regioselective transformations of asparagine gave access to optically active 5-and 6-amino tetrahydroindolizines when the 3-aminobutyrolactone (*S*)-**2** was employed as a key intermediate. The target compounds were approached by a sequential and regiocontrolled bis-electrophilic attack in the positions 2 and 3 of the pyrrole ring system. Receptor binding experiments showed stereocontrolled receptor recognition leading to the D3 selective agonist (*S*)-**8** with D3 binding that is comparable to the natural neurotransmitter dopamine.

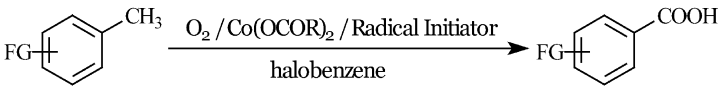


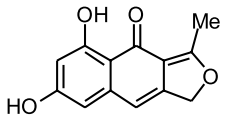
9 (5*R**,6*R**)-**11** (*P*)-**24** (*M*)-**24**

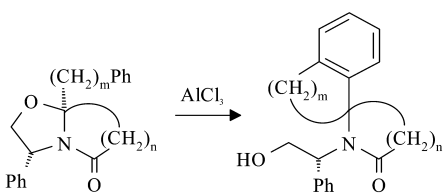
The helical hydrocarbons (*P*)- and (*M*)-**24** were synthesized via a regio- and stereoselective cycloaddition of a trimethylenketeniminium salt to the methylendispirodecane **9** and a subsequent resolution and reduction.



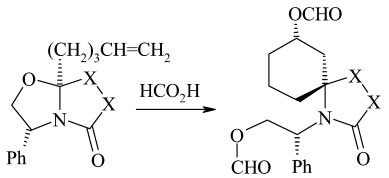
Several 3-alkynylcyclopropenes have been prepared by the reaction of acetylenic nucleophiles with cyclopropenylium salts. Single crystal X-ray structures of four of the cyclopropenes were obtained. The solution-phase thermochemistry of the 3-alkynyl-1,2,3-triphenylcyclopropenes was explored, affording 3-alkynyl-1*H*-indenes in moderate to good yields.







A series of chiral non-racemic 5,5- and 5,6-bicyclic lactams is prepared from (*R*)-phenylglycinol. These are isomerised on treatment with aluminium trichloride in 1,2-dichloroethane to give spiro lactams in high yield and >3:1 diastereoselectivity.



X--X = CH_2-CH_2 or *o*-C_6H_4

Chiral non-racemic bicyclic and tricyclic oxylactams obtained in two steps from *N*-(2-hydroxy-1(*R*)-phenylethyl)-succinimide and -phthalimide are cyclised diastereoselectively in formic acid to give spiro[cyclohexane-1,2′-pyrrolidin]-5′-ones and spiro[cyclohexane-1,1′-isoindolin]-3′-ones, respectively.

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*Corresponding author
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Publisher's Announcement—new Regional Editor for *Bioorganic & Medicinal Chemistry*

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Recent synthetic developments in the nitro to carbonyl conversion (Nef reaction)

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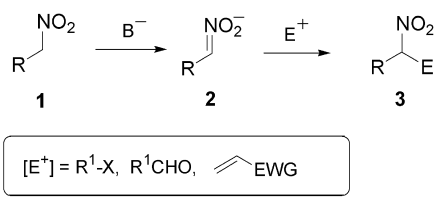
Received 21 October 2003

Contents

1. Introduction

Interconversion of functional groups represents an important aspect in every process leading to the synthesis of structurally-defined compounds. Indeed, many activating groups that promote the formation of carbon–carbon bonds often need to be replaced by other functional entities once they have assisted the main synthetic process. The availability of a consistent number of such transformations for a particular functional group largely contributes to the success and development of the related chemistry. The importance of nitroalkanes **1** in synthesis is mainly due to their easy conversion into the corresponding nitronate anions **2** because of the high electron-withdrawing power of the nitro group that provides an outstanding enhancement of the hydrogen acidity at the α-position (cf. pk_a $MeNO_2$=10).[1–5] Nitronate salts can therefore act as carbon nucleophiles with a range of electrophiles including haloalkanes,[6] aldehydes[7,8] and Michael acceptors,[9] leading to carbon–carbon bond formation (Scheme 1).



Scheme 1. Nitroalkanes as nucleophiles.

Keywords: Nitro compounds; Carbonyl group; Nef reaction.

Abbreviations: BINAP, 2,2′-bis(diphenyphoshino)-1,1′-binaphthyl; BINOL, 1,1′-binaphthalene-2,2′-diol; Bn, benzyl; Boc, *t*-butoxycarbonyl; BY, Baker's yeast; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexylcarbodiimide; DHP, dihydropyran; DIBALH, diisobutylaluminium hydride; DMD, dimethyldioxirane; DMAP, 4-*N*,*N*-dimethylaminopyridine; DMF, dimethylformamide; DMI, 1,3-dimethyl-2-imidazolidinone; DMSO, dimethylsulphoxide; DPPA, diphenylphosphoryl azide; IBX, 1-hydroxy-1,2-benzodioxol-3(1*H*)-one-1-oxide; LiHMDS, lithium 1,1,1,3,3,3-hexamethyldisilazide; MCPBA, *m*-chloroperoxybenzoic acid; MOM, methoxymethyl; Ms, methanesulphonyl; $Ni(acac)_2$, nickel bis(acetylacetonate); NMO, *N*-methylmorpholine-*N*-oxide; $Pd_2(dba)_3$, tris(dibenzylideneacetone)-dipalladium; Phth, phthalimidoyl; PMB, *p*-methoxybenzyl; PPTS, pyridinium *p*-toluenesulphonate; Py, pyridyl; SET, single electron transfer; TBDPS, *t*-butyldiphenylsilyl; TBS, *t*-butyldimethylsilyl; Tf, trifluoromethanesulphonyl; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; THP, tetrahydropyranyl; TMS, trimethylsilyl; TPAP, tetrapropylammonium perruthenate; Ts, *p*-toluenesulphonyl; *p*TSA, *p*-toluenesulphonic acid; TMG, tetramethylguanidine; Tol, *p*-methylphenyl; Tx, 2,3-dimethyl-2-butyl (thexyl).

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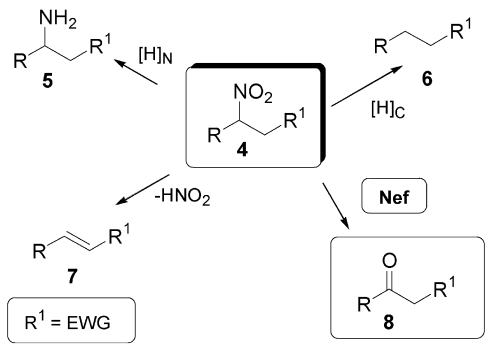


Scheme 2. General transformations of the nitro group.

Once these adducts have been formed, the nitro group can be retained in the molecular framework if this is useful for a further nucleophilic addition or it can be transformed into other functionalities following a defined synthetic strategy (Scheme 2). Reduction of the nitro group in compound **4** allows the preparation of a primary amine **5**, in which a simple modification of the oxidation state of the nitrogen atom is carried out. Alternatively, the nitro group can be removed from the molecule by replacing it with hydrogen giving the corresponding denitrated product **6**[10,11] or by elimination as nitrous acid, introducing a double bond in the molecular structure **7**.[12] A further option consists of the conversion of the nitro group into a carbonyl group **8**.[13] This process is probably the most exploited transformation of the nitro group, since it definitively reverses the polarity of the neighbouring carbon atom from nucleophilic to electrophilic.

The synthetic opportunity offered by this conversion has been focusing the attention on the chemistry of aliphatic nitro compounds since its discovery by Nef in 1894.[14] As a matter of fact, the transformation of sugar nitromethyl groups into aldehydes represents an alternative procedure for the chain elongation of carbohydrates, known for at least half a century as the Sowden protocol.[15] The aim of this review is to collect the new procedures which have appeared in the last decade after the comprehensive report by Pinnick in 1990.[16] In addition, several significant applications of this transformation to the synthesis of pivotal building blocks and important biologically active compounds will be discussed.

2. General aspects of the Nef reaction

The original procedure for the nitro to carbonyl transformation, as described by Nef, was essentially the hydrolysis in strongly acidic conditions of a nitronate salt **9** produced by basic treatment of a nitroalkane (Scheme 3).

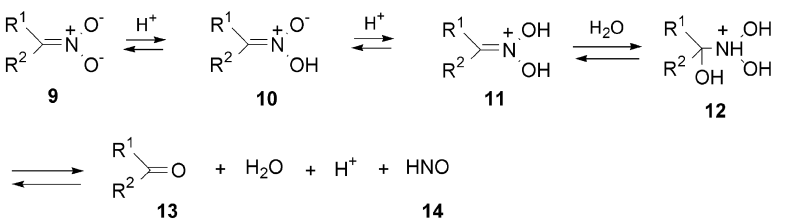
Hydrolysis occurs on a protonated form **11** of the corresponding nitronic acid **10**, giving as intermediate **12** that, by loss of water and hyponitrous acid **14**, gives the carbonyl derivative **13**. The product distribution in this reaction is strongly affected by the acidity level of the system. At pH>1, oximes as well as other hydroxynitroso compounds can be formed in appreciable amounts. For this reason, a rapid acidification of the nitronate salt is required and it is very often operationally desirable to add the nitronate salt to the acid solution. The harsh conditions in which this conversion is usually carried out (pH<1) have spurred the development of alternative methods that can be performed in oxidative, reductive, as well as almost neutral, conditions. It is interesting to note that a common factor in all of the oxidative procedures is the formation of the corresponding nitronate anion as the reactive species; the subsequent cleavage occurs on the carbon–nitrogen double bond to give the carbonyl derivative. Conversely, reductive methods can be carried out both on the nitronate anion or directly on the nitroalkane, even in acidic conditions. An important aspect of this transformation concerns the nature of the nitroalkane used as the substrate. Indeed, secondary nitro compounds are conveniently transformed into ketones, but primary nitro derivatives can be converted into aldehydes or carboxylic acids, depending on the reaction conditions. Particular care must therefore be taken in this reaction, especially when oxidative procedures are chosen to transform primary nitroalkanes into aldehydes. Nitroalkenes that are powerful Michael acceptors can also be used as substrates for the Nef reaction.[17–22] In addition, the conjugate addition of nucleophilic reagents to nitroolefins provides the formation of a nitronate anion as an intermediate that can usually be transformed by a tandem process into the corresponding carbonyl derivative.

3. Recent modifications of the Nef reaction

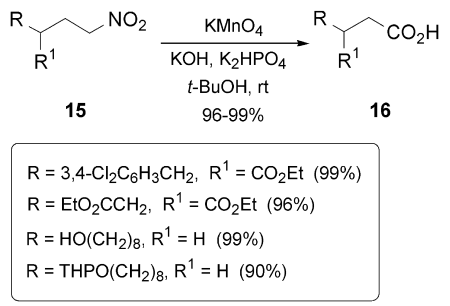
3.1. Oxidative methods

As previously stated, cleavage of the carbon–nitrogen double bond is the key step in almost all of the oxidative methods that are currently used for the Nef reaction. $KMnO_4$ is certainly the most widely used oxidant for this purpose and, in controlled conditions, it is able to convert primary nitro compounds into aldehydes.[23] Buffered permanganate solutions (pH=11) can oxidise primary nitroalkanes such as **15** into alkanoic acids **16** without affecting other functions such as esters, amides, primary alcohols and acetals (Scheme 4).[24]

Dimethyldioxirane (DMD) is a strong oxidising agent readily prepared by the reaction of Oxone® with acetone

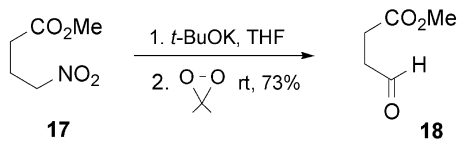


Scheme 3. Mechanism for the original Nef reaction.



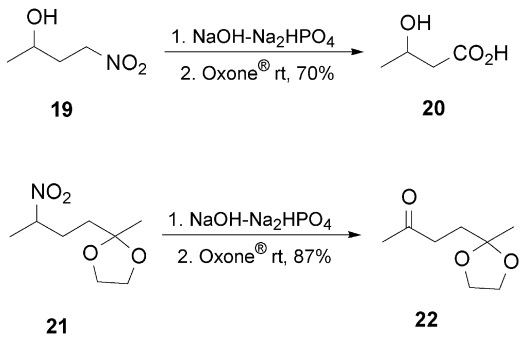
Scheme 4. Permanganate oxidation of primary nitroalkanes to carboxylic acids.

and, among various applications it has been used for the regeneration of the carbonyl group from acetals, hydrazones and other derivatives. DMD attacks nitronate anions obtained from nitro compounds such as **17**, giving the corresponding carbonyl derivative **18** in good yields (Scheme 5).[25]



Scheme 5. Nef reaction using dimethyldioxirane.

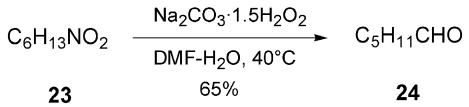
Oxone®, from which DMD derives, is also able to convert nitroalkanes into carbonyl derivatives, but shows less selectivity since primary nitro compounds such as **19** are converted into carboxylic acids **20**. Common protecting groups such as acetals, TBS and acetates are, however, not affected by these conditions as demonstrated for the conversion of nitro compound **21** into ketone **22** (Scheme 6).[26]



Scheme 6. Oxidations with Oxone®.

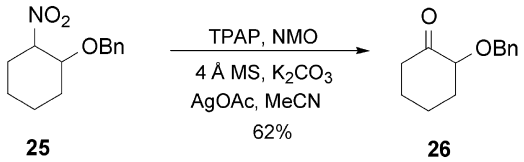
Another peroxide-based system, bis(trimethylsilyl)-peroxide, has also been used for this transformation, but it is applicable only to secondary and benzylic nitro compounds.[27]

Sodium percarbonate ($Na_2CO_3{\cdot}1.5H_2O_2$) can be considered as a stable source of hydrogen peroxide and can be used for the cleavage of carbon–nitrogen double bonds of hydrazones and nitronate salts. This reagent displays a better selectivity than Oxone®, since it converts 1-nitrohexane **23** to hexanal **24** without any overoxidation (Scheme 7).[28]



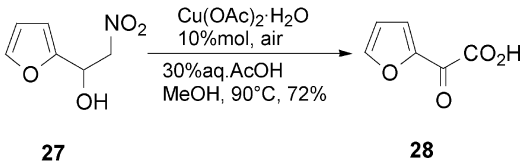
Scheme 7. Reaction of 1-nitrohexane with sodium percarbonate.

Secondary α-alkoxy nitro derivatives such as **25** can be efficiently converted into α-alkoxy ketones **26** using catalytic amounts of tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine-*N*-oxide (NMO). The presence of 4 Å molecular sieves and silver salts is mandatory for the efficiency of the procedure (Scheme 8).[29]



Scheme 8. Nef reaction on nitrocycloalkanones with TPAP.

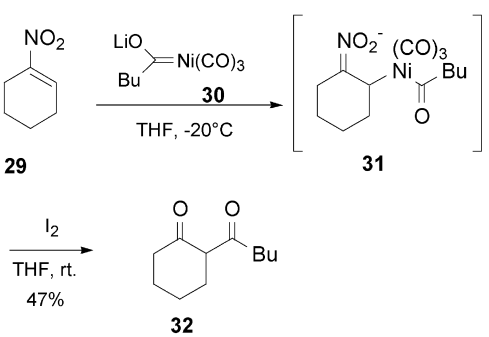
Molecular oxygen is an appealing system to perform oxidations, since it is a cheap, readily available and environmental friendly reagent. Some nitro compounds such as **27** can be transformed into the corresponding carbonyl derivatives **28** when exposed to air in the presence of copper salts (Scheme 9).[30]



Scheme 9. Reaction with O_2 catalyzed by Cu(II) salts.

Metallic copper can also be used for this purpose, but with considerably less efficiency.[31]

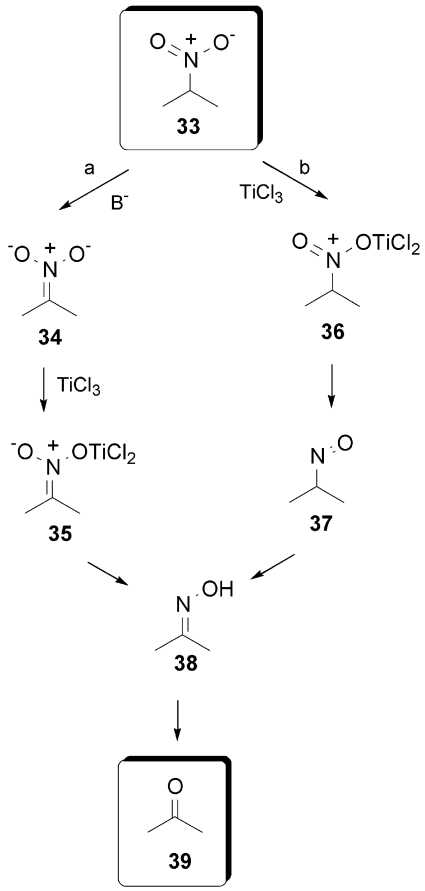
The reaction of nickel acylate complex **30** with nitroalkenes such as **29** gives the corresponding addition products **31** that, by treatment with iodine, affords the 1,3-dicarbonyl derivatives **32**. Iodine provides cleavage of the nickel adduct and of the nitronate anion in a tandem process (Scheme 10).[32]



Scheme 10. Tandem cleavage of the Ni-complex and nitronate salt **31** by iodine.

3.2. Reductive methods

A limited number of reducing agents are currently available for the nitro to carbonyl transformation The most important procedure, known as the McMurry method, employs $TiCl_3$ to reduce nitronate salts **34** (path a) or nitro compounds **33** (path b) into aldehydes or ketones (Scheme 11).[33] A likely intermediate in this process is the oxime **38** that can be obtained by reduction of the titanium nitronate **35** (path a) or the iminium ion **36** that produces the nitroso derivative **37** which tautomerise to the oxime **38** (path b). The oxime **38** is further reduced to the imino derivative and then cleaved to the parent carbonyl compound **39**.

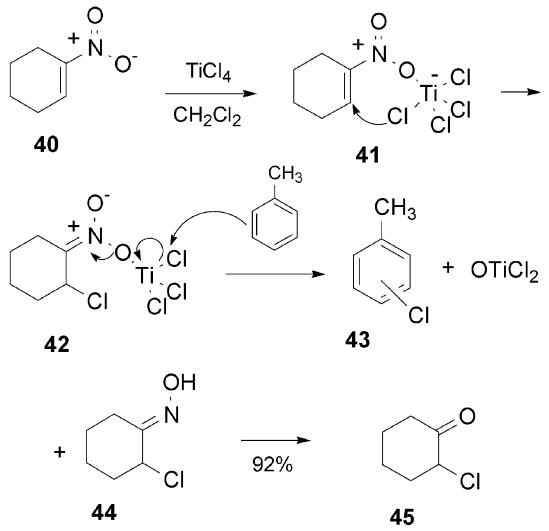


Scheme 11. Mechanism of the Nef reaction using $TiCl_3$.

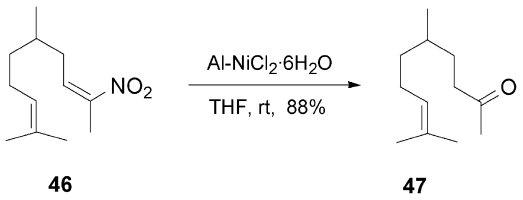
Nitroalkenes such as **40**, can be converted into α-chloroketone **45** using $TiCl_3$ or $TiCl_4$ in the presence of toluene.[34] Titanium tetrachloride attacks the oxygen atom of the nitro group and acts as a chlorinating agent. The intermediate **42** formed by the adduct **41**, is able to chlorinate toluene with a concomitant reduction of the nitro group to the parent oxime **44** that is further reduced to the carbonyl compound **45** (Scheme 12).[35]

Aluminium powder in the presence of $NiCl_2{\cdot}6H_2O$ transforms nitroolefins into carbonyl compounds.[36] Reduction of the nitroalkene **46** to the nitronate probably proceeds through a SET mechanism and is followed by the usual hydrolysis to the carbonyl derivative **47** (Scheme 13).

A similar procedure involves the utilisation of zinc dust–



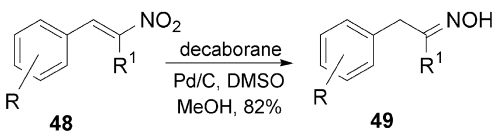
Scheme 12. 2-Chloroketones from nitroalkenes and $TiCl_4$ in the presence of toluene.



Scheme 13. Selective conversion of nitroalkenes into carbonyls by metals.

trifluoroacetic acid[37] or magnesium powder–$CdCl_2$–water in THF.[38] The latter method can be used to transform 6-nitro-Δ^5-steroids into 6-ketosteroids in good yield.

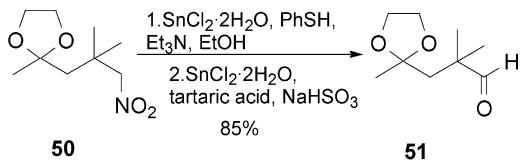
A chemoselective conversion of nitroalkenes **48** to oximes **49** in the presence of aromatic nitro groups can be carried out using decaborane–Pd/C–DMSO in methanol.[39] The role of the DMSO, which is added in an excess of 5 equiv., is not clear, but without this co-reagent only a sluggish conversion occurs (Scheme 14).



R = 3-NO_2, R^1 = H, (82%)
R = 4-Br, R^1 = H, (73%)
R = 4-MeO, R^1 = H, (72%)
R = 3,4-OCH_2O, R^1 = H, (77%)
R = 4-Cl, R^1 = Me, (93%)

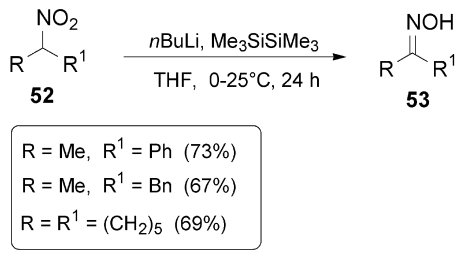
Scheme 14. Synthesis of oximes from nitroalkenes.

The reduction of primary nitroalkanes such as **50** to oximes can be carried out by $SnCl_2{\cdot}2H_2O$ in the presence of thiophenol and triethylamine. Adding a further equivalent of $SnCl_2{\cdot}2H_2O$ and tartaric acid–$NaHSO_3$ to the reaction mixture ensures the reduction of the oxime into the imine, which is rapidly hydrolysed to the aldehyde **51** in good yield (Scheme 15).[40,41]



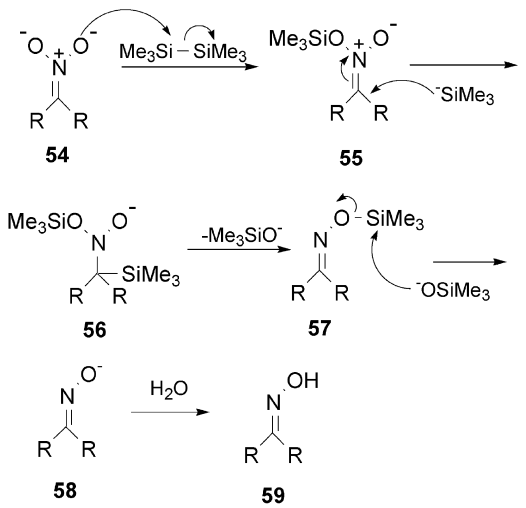
Scheme 15. Nef reaction using tin(II) chloride.

Various metal nitronates of secondary nitroalkanes **52** can be converted into the corresponding oximes **53** by treatment with hexamethyldisilane (Scheme 16).[42]



Scheme 16. Reaction with hexamethyldisilane.

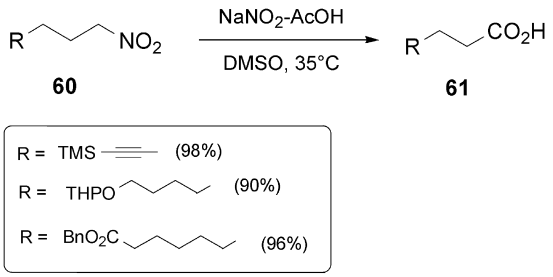
According to the proposed mechanism, hexamethyldisilane acts as a 'counterattack reagent', towards nitronate anion **54** giving a silyl nitronate **55** as the first intermediate. The trimethylsilyl anion attacks the silyl nitronate **55** giving the adduct **56**, that eliminates Me_3SiO^- providing the *O*-silylated oxime **57**. The trimethylsilyloxy anion cleaves derivative **57** to the oxime anion **58**, which upon hydrolysis leads to the formation of the final oxime **59** in a process that closely resembles the Peterson olefination (Scheme 17).



Scheme 17. Mechanism of the Nef reaction using hexamethyldisilane as a counterattack reagent.

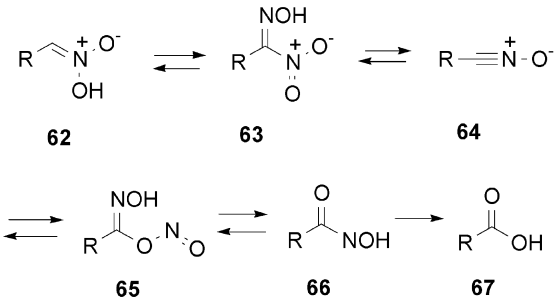
3.3. Other methods

During the course of a multistep synthesis, the number of functional groups present in the molecular framework grows quite rapidly and this dictates the utilisation of ever more selective and mild reagents to carry out chemical transformations. A combination of $NaNO_2$ and acetic acid in DMSO at 35 °C converts primary nitroalkanes **60** into carboxylic acids **61**.[43] The mildness of the reaction conditions makes it possible for some acid- and base-sensitive functions to survive (Scheme 18).



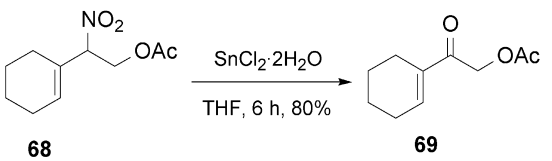
Scheme 18. Reaction of primary nitroalkanes with $NaNO_2$.

In nitrosating conditions the nitronic acid **62** is converted into a nitrolic acid **63** that is in equilibrium with a nitrile oxide **64** (Scheme 19). This reactive intermediate is further nitrosated to derivative **65** and leads to hydroxamic acid **66** that is hydrolysed to the carboxylic acid **67**. It is worth noting that the existence of some of these intermediates has been proved by their isolation (nitrolic acid) or trapping as the cycloadducts (nitrile oxide).



Scheme 19. Mechanism for the Nef reaction using $NaNO_2$.

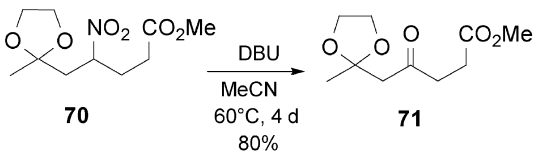
The same reagent can be used to prepare 1-oximino-1-arylacetones starting from 2-nitro-1-arylpropanes.[44] Although α,β-unsaturated nitro compounds are the most popular form of such reactive substrates, β,γ-nitroalkenes can be also prepared, especially when the double bond is inserted into a cyclic structure. These derivatives such as **68** can be transformed into α,β-unsaturated ketones using hydrolytic conditions by activation with $SnCl_2{\cdot}2H_2O$. A stannylnitronate is believed to be the 'activated' intermediate that promotes a subsequent hydrolysis to the final product **69** (Scheme 20).[45]



Scheme 20. $SnCl_2{\cdot}2H_2O$-promoted hydrolysis of β,γ-unsaturated nitroalkenes.

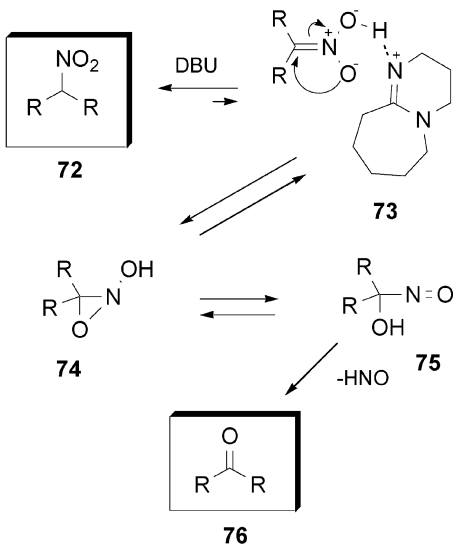
Direct cleavage of the nitronate anion under basic conditions has been only observed on dry activated silica gel and in reactions that involve neighbouring group participation.[46] Some amidine bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are, however, able

to convert secondary nitroalkanes such as **70** into the corresponding ketones **71** when heated at 60 °C in acetonitrile for few days. The procedure shows a consistent degree of chemoselectivity, since primary nitroalkanes are unaffected by these reaction conditions (Scheme 21).[47]



Scheme 21. Nef reaction in basic conditions with DBU.

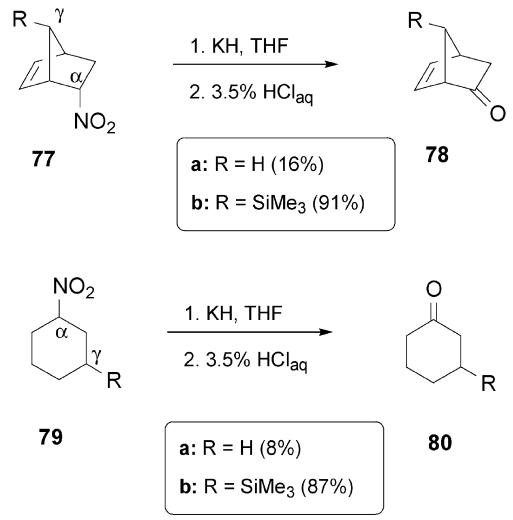
A possible mechanism for this transformation would involve a complex **73**, obtained by reaction of secondary nitroalkane **72** with DBU, that in the absence of water, gives the oxaziridine **74**, and then the hydroxynitroso derivative **75**. The latter intermediate affords the final ketone **76** by elimination of hyponitrous acid (Scheme 22).



Scheme 22. Mechanism for the Nef conversion of a secondary nitroalkane with DBU/MeCN.

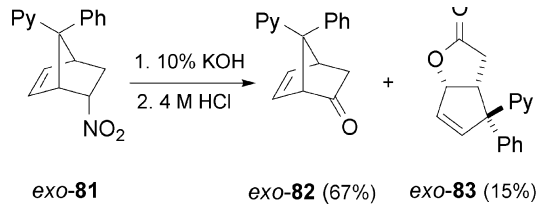
Some nitroalkanes, in spite of a large number of synthetic methods attempting to carry out the Nef reaction, seem to be quite inert towards the nitro to carbonyl conversion. Among the other electronic properties displayed by silicon, the γ-effect has been revealed to be of fundamental importance in order to promote the conversion of some cyclic nitro derivatives into the corresponding ketones (Scheme 23).[48] Under the usual hydrolytic conditions, a negligible amount of the carbonyl derivative **78** is formed when silicon is not present at the γ-position in nitro compound **77**. This behaviour exerted by silicon has been shown to be of general utilisation in the chemistry of nitro compounds as demonstrated for the conversion of **79** into cyclohexanone **80**.[49]

It has recently been observed, however, that the 7-diaryl-5-nitronorbornene *exo*-**81** actually does give as the main product the ketone *exo*-**82** arising from a Nef reaction, along



Scheme 23. Nef reaction promoted by the silicon γ-effect.

with the lactone *exo*-**83** and some unreacted nitro derivative (13%) (Scheme 24).[50]



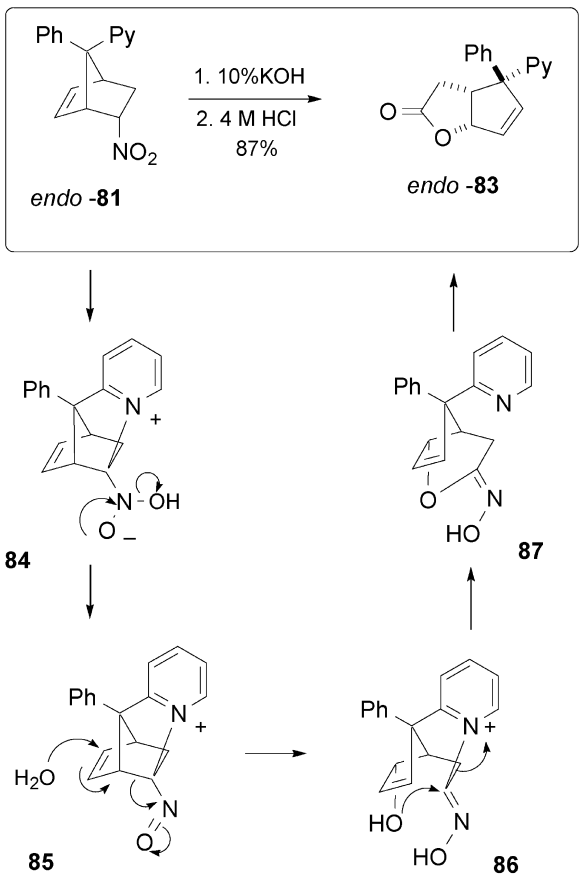
Scheme 24. Nef reaction on a 7-diaryl-5-nitronorbornene.

Interestingly, the reaction of *endo*-**81** under the same conditions affords exclusively *endo*-**83** in 87% yield (Scheme 25). It is conceivable that the presence of the pyridine nitrogen completely suppresses the Nef reaction through coordination with the nitronic acid carbon in the intermediate **84**, leading to the nitroso derivative **85**. Addition of water to the double bond causes a ring cleavage to the oxime **86** that suffers an intramolecular attack by the hydroxy group to give the bicyclic derivative **87**. Further hydrolysis of the oximino group leads to the final bicyclic product *endo*-**83**. This mechanistic hypothesis is also supported by the observation that, with the corresponding norbornanes, lacking the double bond in the bicyclic structure, both the *exo* and *endo* stereoisomers give the norbornanone derivatives in 78 and 53% yields, respectively.

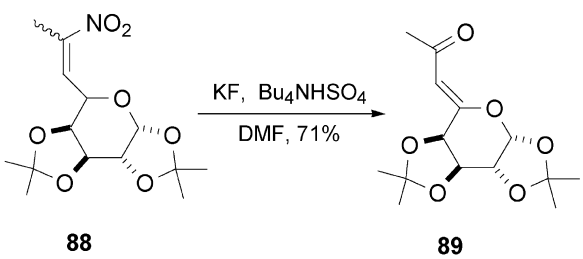
Some sugar nitroolefins such as **88** are converted into the corresponding enol ethers **89** by treatment with a mixture of KF and Bu_4NHSO_4 in DMF at room temperature.[51] A vinylogous Nef-type reaction would probably operate, because of the acidity of the allylic proton in γ-alkoxy-nitroalkenes (Scheme 26). The role played by Bu_4NHSO_4 could have some similarity with a related method that makes use of anhydrous silica gel.[52]

4. Applications of the Nef reaction

The utilisation of nitro compounds for the synthesis of



Scheme 25. Mechanism for the rearrangement of *endo*-**81**.

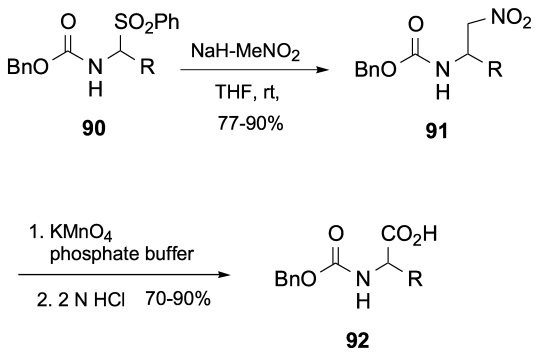


Scheme 26. Nef reaction on sugar nitroolefins.

useful building blocks or in multistep procedures devoted to the preparation of complex molecules is a field that is experiencing a rapid growth. In many of these synthetic pathways, the nitro to carbonyl conversion plays a central role, so that the array procedures to carry out the Nef reaction represents a formidable tool for every organic chemist. In this part of the report, the application of the Nef reaction to the preparation of carbonyl derivatives or in multistep syntheses is presented.

4.1. Oxidative methods

Since primary nitroalkanes are readily converted into carboxylic acids using the Nef reaction, this procedure has often been involved in the synthesis of α-amino acids. The α-amidoalkyl phenyl sulphones **90** can be considered as precursors of reactive *N*-acylimines and therefore react with the anion of nitromethane to give the corresponding adduct **91** (Scheme 27).[53]

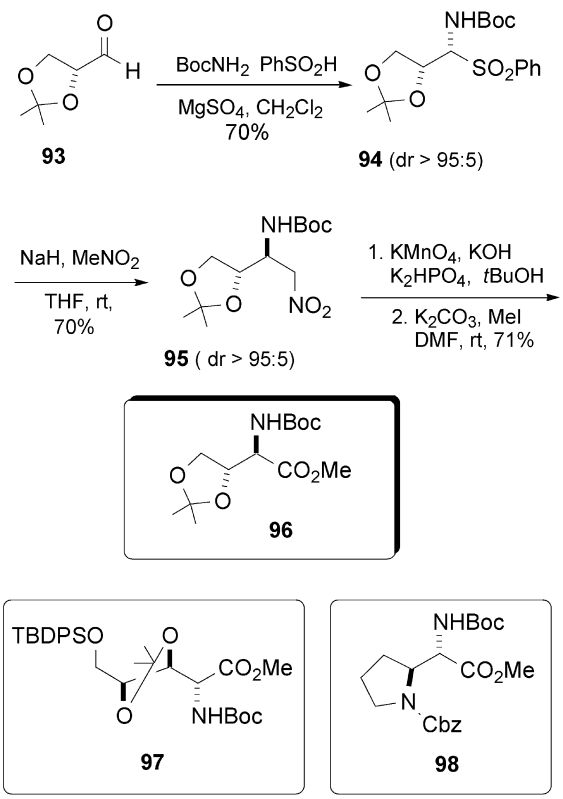


R	**91** (yield %)	**92** (yield %)
$PhCH_2CH_2$	87	90
c-C_6H_{11}	90	88
$Cl(CH_2)_4$	77	85
$C_7H_{14}CH{=}CH(CH_2)_2$	85	72

Scheme 27. Synthesis of α-amino acids.

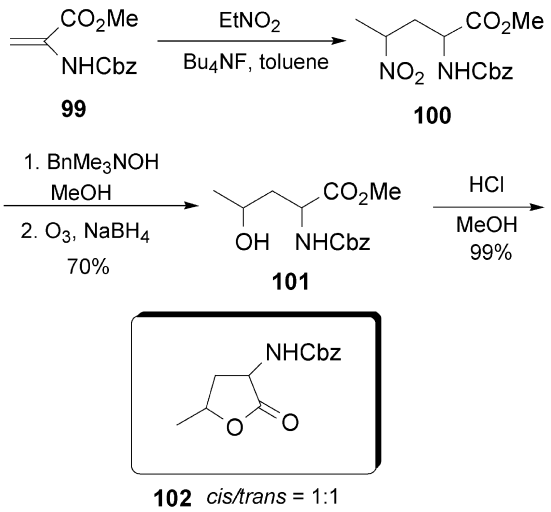
Conversion of the nitro group into carboxylic acids is better realised using $KMnO_4$ in phosphate buffer and leads directly to the *N*-carbobenzoxy α-amino acids **92**. This procedure can be applied to the synthesis of the optically active α-amino acid ester **96** using chiral aldehyde **93**, that can be converted into the α-amidoalkyl phenyl sulphone **94** and then nitro derivative **95** (Scheme 28).[54] The utilisation of other chiral aldehydes allows the preparation of different α-amino acid esters as **97** and **98**.

Michael addition of nitroalkanes to dehydroalanine **99** affords the γ-nitro-α-amino acids such as **100** in racemic



Scheme 28. Synthesis of optically active α-amino acids.

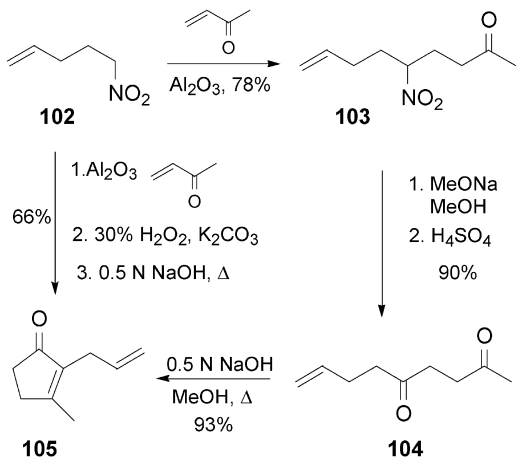
form. These adducts are further elaborated by converting the nitro group into a carbonyl moiety that can be reduced in situ to a diastereomeric pair of γ-hydroxy-α-amino acids **101** in a 1:1 ratio (Scheme 29).[55] The acid-catalysed cyclisation of these hydroxy derivatives gives the 2-amino-lactones **102**.



Scheme 29. Synthesis of 2-aminolactones.

A similar strategy can be used for the preparation of paramagnetic pyrrolidine dienes.[56]

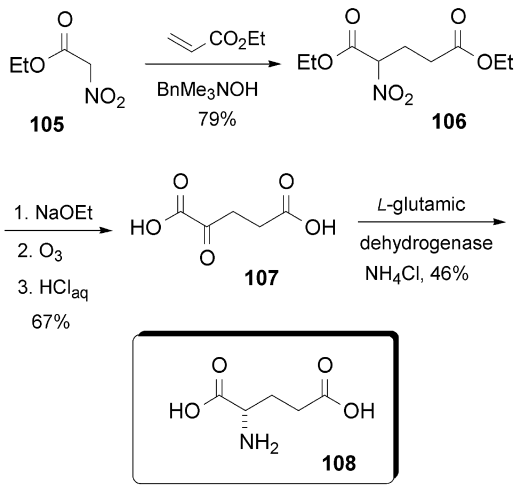
For obvious reasons, it is often advantageous to carry out a synthetic process in a 'one-pot' system, adding the appropriate reagents sequentially to the reaction mixture. Allylrethrone **105** is an important component of an insecticidal pyrethroid and its preparation can be realised in three distinct steps, starting from the nitroalkene **102** and methyl vinyl ketone (Scheme 30).



Scheme 30. Synthesis of allylrethrone.

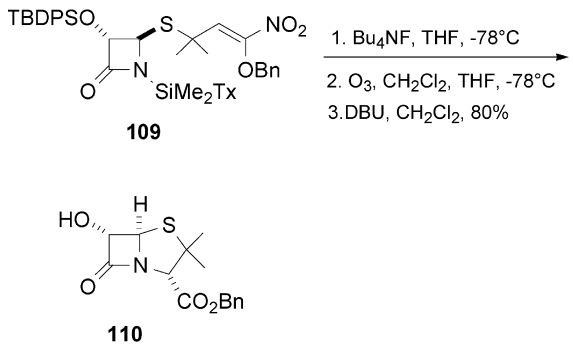
The obtained Michael adduct **103** is converted into the diketone **104** by a hydrolytic Nef reaction and is then cyclised to allylrethrone **105** under basic conditions.[57] Alternatively, the same process can be realised in a one-pot reaction, using hydrogen peroxide to carry out the nitro-to-carbonyl conversion.

Stable-isotope labelled *L*-glutamic acid can be prepared from ^{13}C-enriched compounds, following a strategy involving the conjugate addition of ethyl nitroacetate **105** to ethyl acrylate.[58] Oxidative Nef conversion of the 2-nitroglutarate **106** to diethyl 2-oxoglutarate and ester hydrolysis gives 2-oxoglutaric acid **107**. This diacid is transformed into L-glutamic acid **108** using the commercially available enzyme glutamic dehydrogenase, in the presence of ammonium ions (Scheme 31).



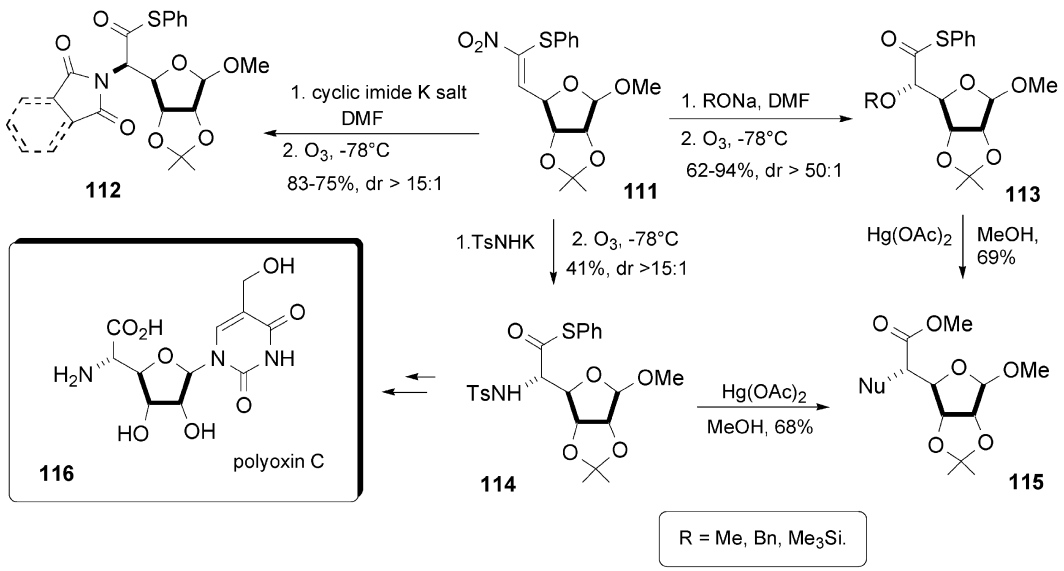
Scheme 31. Synthesis of isotope-labelled L-glutamic acid.

A key step in the stereocontrolled synthesis of a penicillanic acid derivative consists of the intramolecular conjugate addition of a 2-azetidinone nitrogen to a nitroalkene framework in compound **109**.[59] The intermediate nitronate anion obtained is oxidised with ozone to afford a mixture of the *endo* and *exo* epimers that can be completely converted into the more stable *exo* isomer **110** using DBU (Scheme 32).

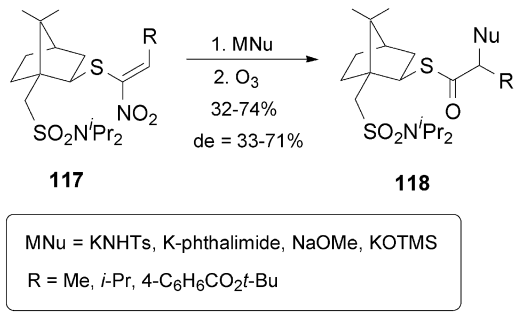


Scheme 32. Synthesis of a penicillanic acid derivative.

The nitroalkene **111** obtained from D-ribose reacts with different nucleophiles with appreciable stereoselectivity.[60] The potassium salts of cyclic imides give a stereochemical outcome which is opposite with respect to sodium alkoxides and TsNHK.[61] Cleavage of the obtained nitronate salts with ozone gives the thiol esters **112**–**114** that can be finally converted into a methyl esters such as **115** using mercuric acetate in methanol (Scheme 33). This strategy can be successfully used for the total synthesis of the nucleoside antibiotic polyoxin C **116**.[62]



Scheme 33. Synthesis of optically active α-substituted methyl esters.



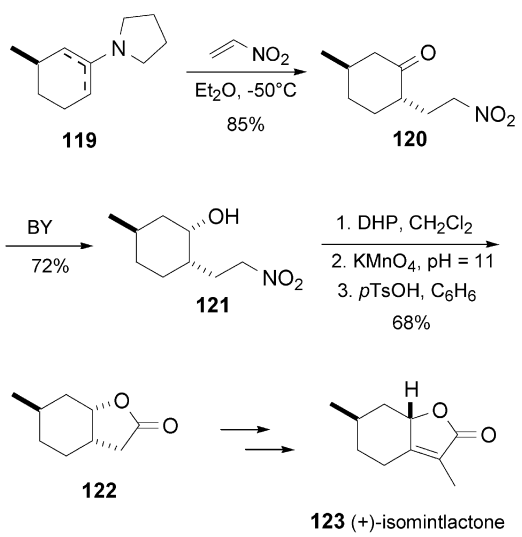
Scheme 34. Synthesis of α-substituted thiol acids.

Optically active nitroalkenes **117** bearing a chiral auxiliary on sulphur react in a similar fashion, but adducts **118** are only obtained with a modest level of diastereoselectivity (Scheme 34).[63]

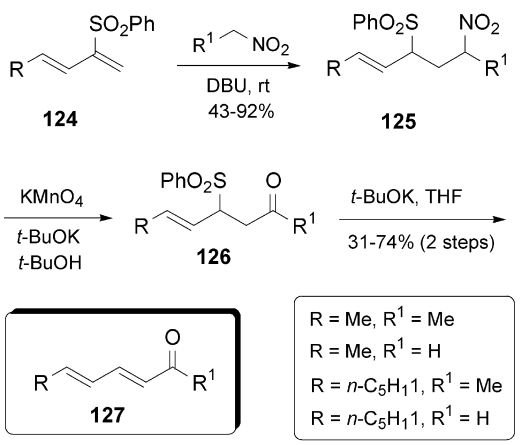
In a related procedure, the addition of diethyl phosphite in the presence of DBU and TMSCl gives trimethylsilyl-α-phosphoryl nitronates that undergo to a Nef reaction using *m*-chloroperoxybenzoic acid. The resulting 1-aryl-2-oxo-alkylphosphonates are useful reagents in the Wadsworth–Horner–Emmons condensations.[64]

Michael addition of the chiral cyclic enamine **119** to nitroethylene is involved in the initial step of the synthesis of optically active (+)-isomintlactone **123**, a constituent of the American peppermint oil.[65] Since the two regioisomers of the enamine **119** are in equilibrium, a single nitro ketone **120** is obtained by the reaction of the more reactive isomer. The compound **120** is reduced to the nitro alcohol **121** using Baker's yeast (BY) and the hydroxy group is protected before the oxidative Nef conversion. Upon removal of the protective group, a spontaneous lactonisation occurs, giving the γ-lactone **122** that can be converted into (+)-isomintlactone **123** in few steps (Scheme 35).

Among the various Michael acceptors, the 2-phenylsulphonyl-1,3-dienes **124** react with nitroalkanes in the presence of DBU to give the nitrosulphones **125**.[66] The



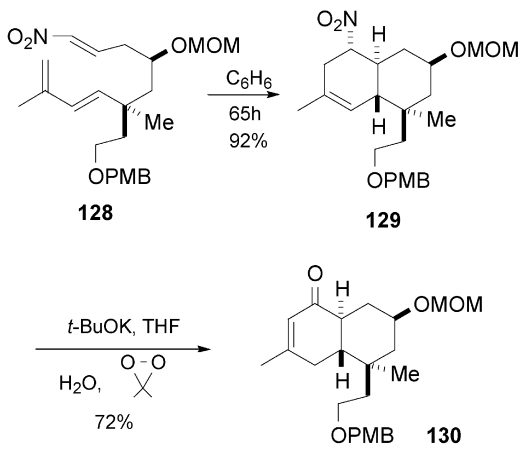
Scheme 35. Synthesis of (+)-isomintlactone.



Scheme 36. Synthesis of conjugated dienones.

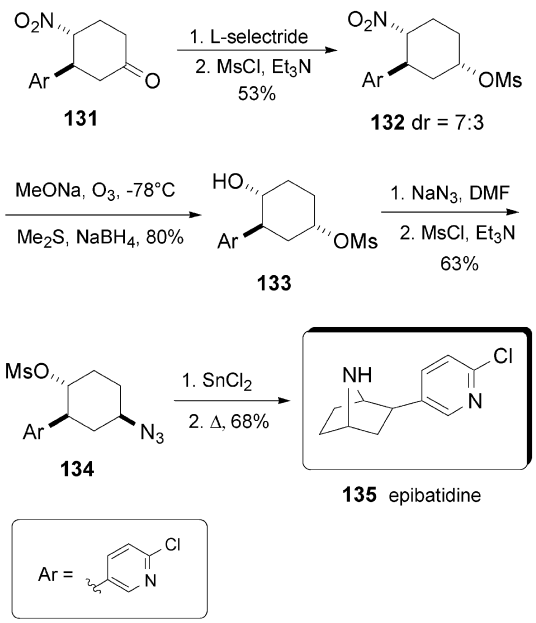
nitro-to-carbonyl conversion on these compounds leads to the keto sulphones **126** that, in basic conditions, eliminate benzenesulphinic acid to afford the conjugated dienones **127** (Scheme 36).

Nitroalkenes are powerful dienophiles in Diels–Alder reactions and react both inter- and intramolecularly to give cycloadducts. For the construction of the AB ring system of the marine alkaloid, norzoanthamine, the nitroalkene **128** is cyclised with outstanding diastereoselectivity.[67] Nef reaction of the obtained cycloadduct **129** with dimethyldioxirane occurs with concomitant double bond migration to give the α,β-unsaturated ketone **130** (Scheme 37).



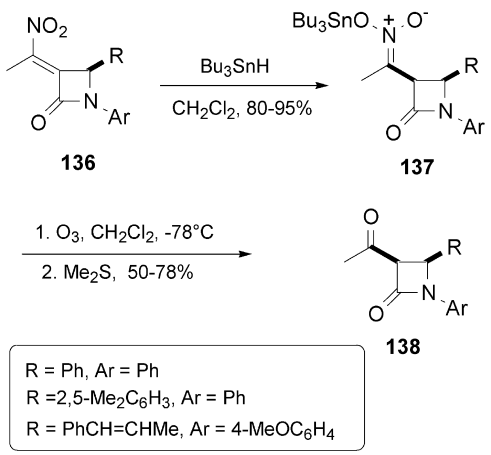
Scheme 37. Synthesis of the AB ring system of norzoanthamine.

The nitrocycloalkanone **131**, obtained from a Diels–Alder reaction, represents an important intermediate towards the total synthesis of racemic alkaloid, epibatidine **135**.[68] A noteworthy feature of the Nef reaction is that the ozonisation of the nitro derivative **132**, followed by treatment with $NaBH_4$, occurs with complete retention of configuration, giving the alcohol **133** in good yield. Further manipulation of this intermediate via **134**, ensures an efficient synthesis of epibatidine **135** (Scheme 38).



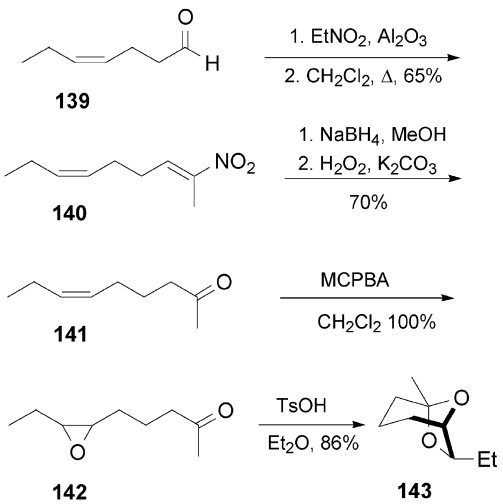
Scheme 38. Synthesis of epibaditine.

The reduction of nitroalkenes such as **136** with Bu_3SnH occurs in neutral conditions, giving the corresponding stannylnitronates **137**.[69] These nitronates can be oxidised to the parent carbonyl derivatives using ozone at low temperatures. This procedure is particularly effective in the synthesis of β-lactam building blocks **138** (Scheme 39).



Scheme 39. Synthesis of β-lactam building blocks.

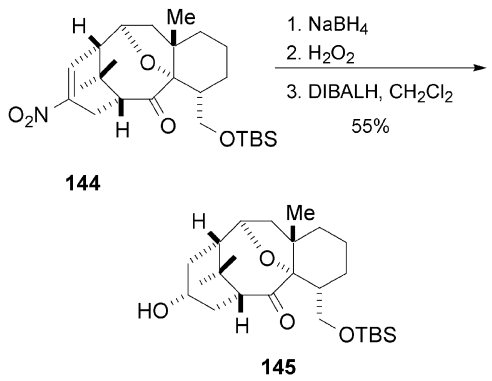
Sodium borohydride reduces a nitroalkene to the corresponding nitronate anion that can be oxidised by hydrogen peroxide to the corresponding carbonyl derivative. This procedure is particularly effective when other unsaturations are present in the molecule and is illustrated for the synthesis of *exo*-brevicomin **143**, the principal pheromone of *Dentroctonus brevicomin*.[70] (*Z*)-4-Heptenal **139** reacts with nitroethane in the presence of Al_2O_3 to give a nitro alcohol that is dehydrated to the corresponding nitroalkene **140** simply by adding dichloromethane and heating at reflux. The nitroalkene **140** is transformed into the unsaturated ketone **141** that, after epoxidation to **142** is converted into *exo*-brevicomin **143** (Scheme 40).



Scheme 40. Synthesis of *exo*-brevicomin.

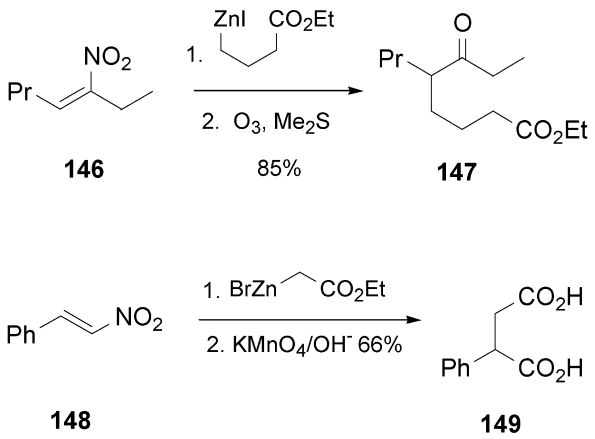
This strategy has also been used for the synthesis of the A-ring of taxane diterpene **145** starting from nitroalkene **144** (Scheme 41).[71,72]

Organometallic addition to nitroalkenes allows the



Scheme 41. Synthesis of the A-ring of taxane diterpenes.

formation of new carbon–carbon bonds and, at the same time, leads to the synthesis of nitronate anions that can be directly converted into carbonyl groups in one-pot reactions. Organozinc reagents add efficiently to nitroolefins **146**, **148** and the obtained nitronates are then oxidised to the parent carbonyl derivatives **147**, **149** (Scheme 42).[73,74]

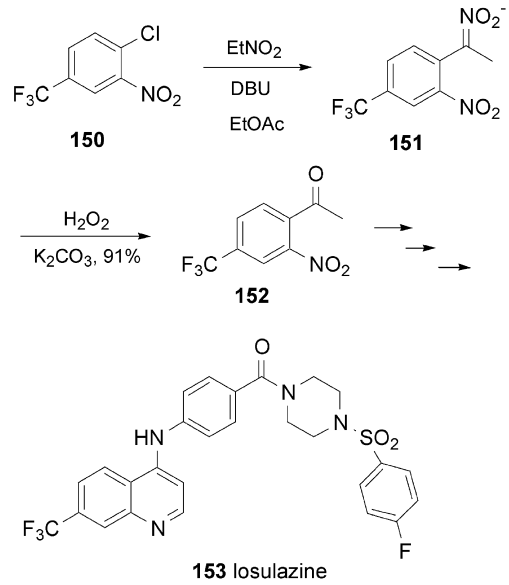


Scheme 42. Coupling of nitroalkenes with organozinc reagents and tandem Nef reaction.

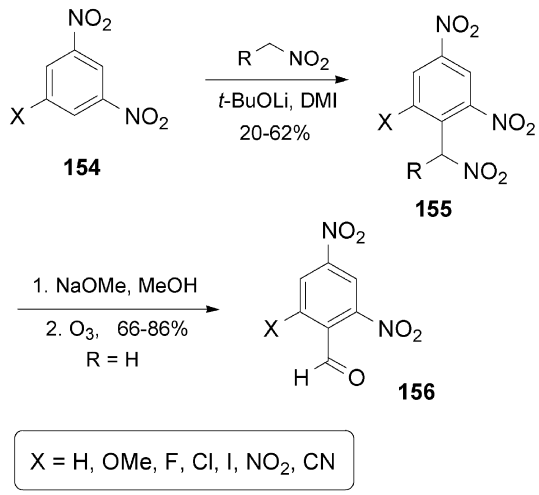
Strongly electron-withdrawing substituents on aromatic derivatives such as **150** greatly facilitate nucleophilic substitutions, so that nitro compounds can add to the ring in the presence of a base such as DBU. The obtained substitution product **151** can undergo a Nef reaction, giving a keto derivative **152**, a key intermediate for the synthesis of the antihypertensive agent, losulazine **153**.[75] The overall procedure can be considered as 'nucleophilic acylation', a synthetic transformation particularly effective on substrates that are not prone to the usual Friedel–Crafts reaction (Scheme 43).

Similarly, primary nitroalkanes react in basic conditions [*t*-BuOLi/1,3-dimethyl-2-imidazolidinone (DMI)] with 1,3-dinitrobenzene and its derivatives **154** to give the corresponding adducts **155**.[76] Various nitromethyl derivatives obtained by this method can be transformed into formyl derivatives **156** by oxidation with ozone (Scheme 44).

The reaction of stabilised carbanions with nitroarenes **157** give rise to the corresponding nitronate anions **158** that, by oxidation, afford the substituted nitroaromatic derivatives.



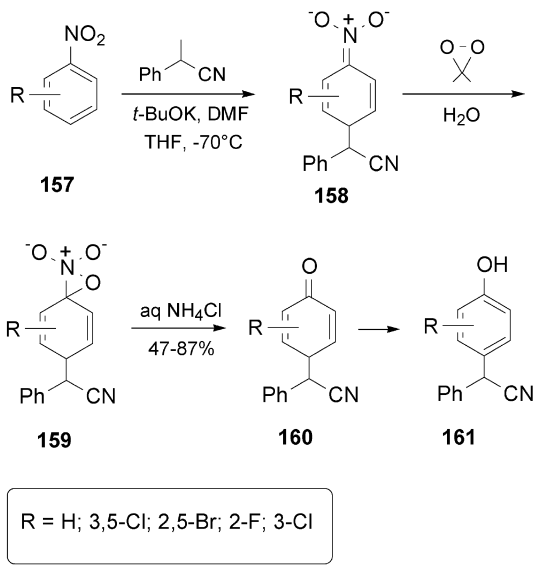
Scheme 43. Nuclephilic acylation on electro-poor aromatics.



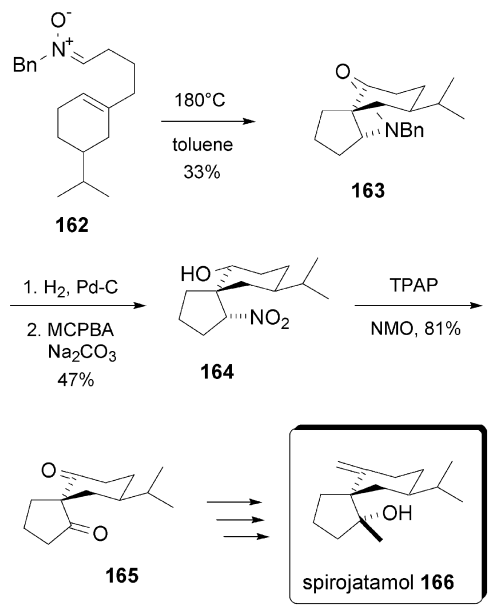
Scheme 44. Synthesis of nitrobenzaldehydes.

When dimethyldioxirane is used as an oxidant for this purpose, however, the intermediate anion is transformed into the corresponding phenol **161**.[77,78] The oxidation is likely to proceed through an oxaziridine **159** that is hydrolysed to the cyclohexadienone **160** that readily tautomerise to the more stable phenol **161** (Scheme 45).[79]

The nitro group is usually introduced in complex molecular frameworks by the reaction of simple or functionalised nitroalkanes with aldehydes or α,β-unsaturated derivatives. Occasionally, the nitro group is generated by the oxidation of amino derivatives and is then converted into a carbonyl group. In a synthetic approach to the spirobicyclic sesquiterpene spirojatamol **166**, the nitrone **162** undergoes an intramolecular cycloaddition to give the tricyclic derivative **163**.[80] This intermediate is first reduced to give an amino alcohol and is then oxidised to the nitro alcohol **164**. A Nef reaction on this nitro alcohol using TPAP–NMO affords the diketone **165** that is then converted into spirojatamol **166** in a few steps (Scheme 46).



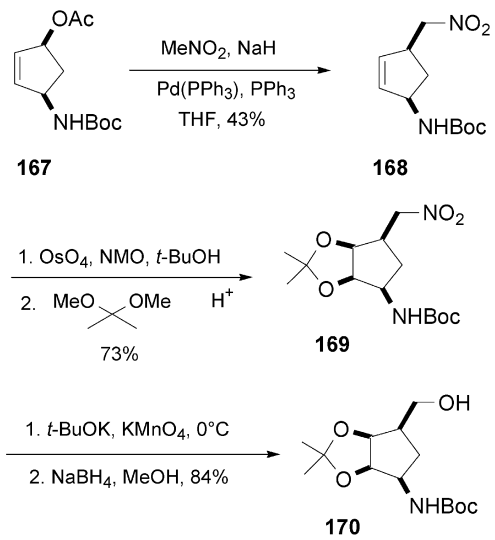
Scheme 45. Synthesis of phenols from nitroarenes.



Scheme 46. Synthetic route to spirojatamol.

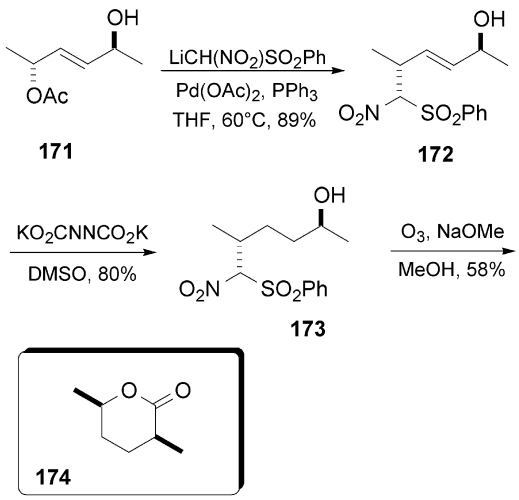
Palladium(0) chemistry represents an alternative method for the introduction of a nitromethyl moiety into a molecule.[81] Allyl acetate **167** reacts with nitromethane in the presence of $Pd(PPh_3)$ to give the corresponding substitution product **168** with retention of the configuration of the acetoxy stereocentre.[82] The nitromethyl group which is introduced acts as a hydroxymethyl synthon, since, after double bond *cis*-dihydroxylation and protection as acetonide **169**, it can be oxidised to the parent aldehyde and then reduced to the alcohol **170** (Scheme 47). The obtained cyclopentyl derivative is a precursor of important carbacyclic nucleosides.[83]

A related procedure can be used for the synthesis of



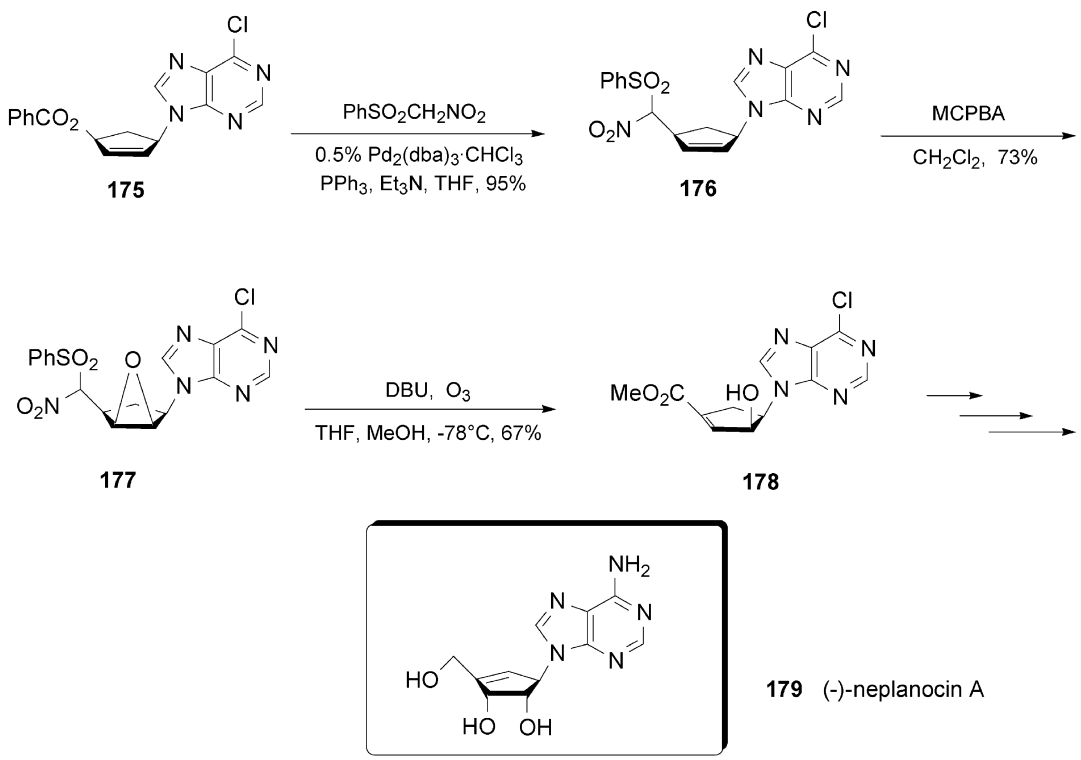
Scheme 47. Synthesis of carbacyclic nucleoside precursors.

enantiomerically enriched lactones, starting from optically active monoacetates such as **171**. These compounds react with the lithium anion of (phenylsulphonyl)nitromethane in the presence of $Pd(OAc)_2$ giving the substitution product **172** with high diastereoselectivity.[84] Reduction of the double bond, to give **173**, and Nef reaction affords the *cis*-lactone **174** that is the major component of the pheromone of the Carpenter bee *Xylocopa hirutissima* (Scheme 48).



Scheme 48. Synthesis of the enantiomerically pure lactone **174**.

The conversion of a (phenylsulphonyl)nitromethyl group into a carboxylic acid is a key step in many processes directed toward the asymmetric synthesis of important biologically active molecules. (−)-Neplanocin A **179** is a carbanucleoside of natural origin that shows some inhibitory properties towards enzymes and is therefore a potentially useful antitumour and antiviral agent.[85,86] A one-carbon unit is introduced into purine **175** by means of $PhSO_2CH_2NO_2$ in the presence of $Pd_2(dba)_3$ and the resulting adduct **176** is converted into the oxirane **177**. The compound **177** undergoes a Nef reaction using ozone in basic conditions to afford the ester **178** that is a key intermediate for the synthesis of (−)-neplanocin A **179** (Scheme 49).

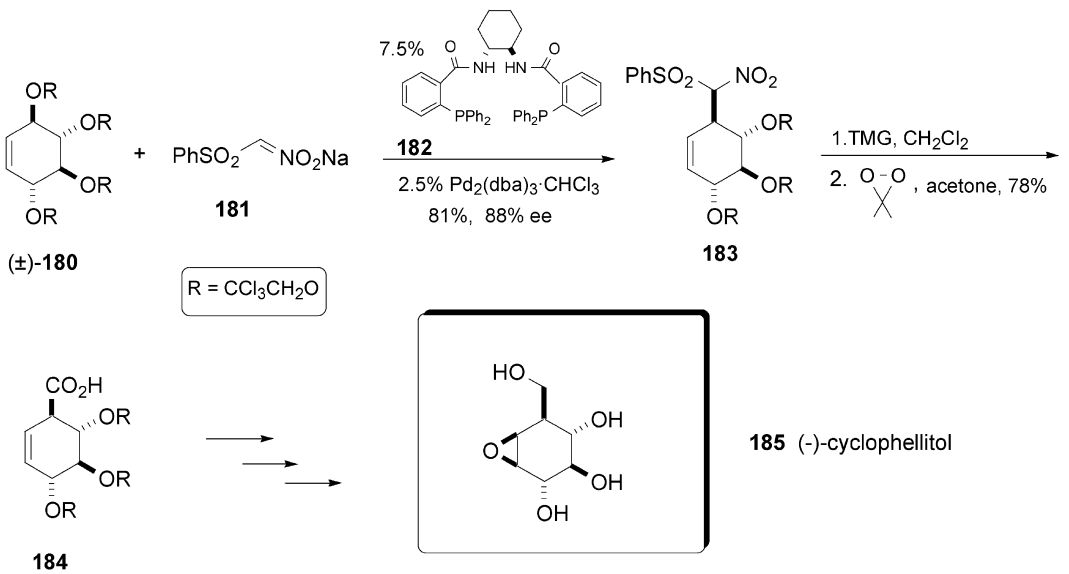


Scheme 49. Synthesis of (−)-neplanocin A.

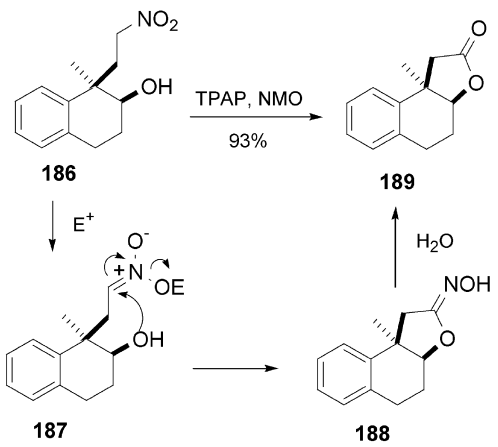
A related strategy can be used for the enantioselective synthesis of other carbanucleosides as (−)-carbovir. The Nef reaction is carried out on a derivative similar to **176** using tetrabutylammonium-oxone buffered with sodium carbonate.[87]

Both enantiomers of the glycosidase inhibitor, cyclophellitol, can be prepared starting from racemic conduriol B **180** using a dynamic kinetic asymmetric transformation.[88] The reaction of **180** with the sodium salt of (phenylsulphonyl)nitromethane **181** in the presence of $Pd_2(dba)_3$ and a chiral ligand **182** affords the corresponding substitution product **183** in satisfactory yield and enantiomeric excess (Scheme 50). The Nef conversion of this derivative is carried out using dimethyldioxirane in basic conditions, leading to the acid **184**, that is transformed into the final product (−)-cyclophellitol **185**, by further synthetic manipulations.

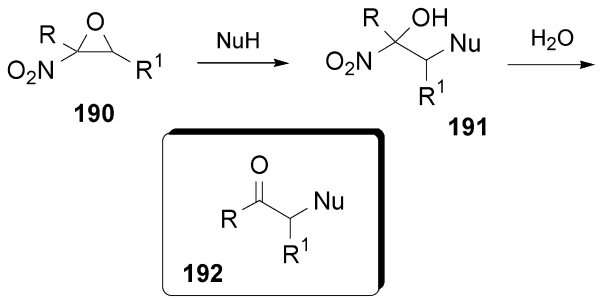
In rigid bicyclic structures, the presence of hydroxy groups in the proximity of the nitro function can lead to unexpected results during oxidation procedures. Oxidation of the nitro alcohol **186** with TPAP–NMO, as well as with other common oxidants, gives the tricyclic lactone **189** in high yield (Scheme 51).[89] This unusual transformation is probably caused by the electrophilic centre of the oxidising



Scheme 50. Synthesis of (−)-cyclophellitol.



Scheme 51. Unusual Nef reaction on bicyclic derivatives.



Scheme 52. Nucleophilic ring opening of α-nitroepoxides.

agent that favours the *aci*-nitro form **187** which allows the attack of the hydroxy group to form the *N*-hydroxyimidate **188**. Hydrolysis of this intermediate affords the final lactone **189**.

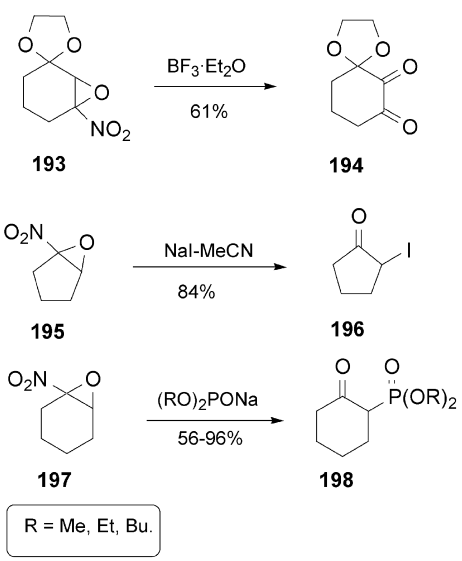
α-Nitroepoxides **190** can be obtained from conjugated nitroalkenes using hydrogen peroxide in basic conditions.[90] Nucleophilic ring opening of these epoxides usually leads to the α-hydroxy nitro intermediates **191** that are prone to a fast hydrolysis to the parent carbonyl compound **192** (Scheme 52).

Some interesting transformations involving these intermediates are depicted in Scheme 53.[91–93]

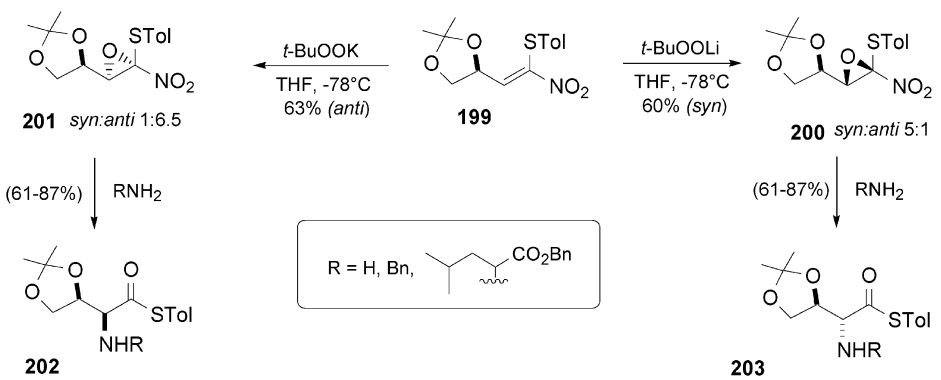
Condensation of (*p*-tolylthio)nitromethane with (*R*)-2,3-*O*-isopropylideneglyceraldehyde affords the corresponding nitroalkene **199** as a single *Z* stereoisomer (Scheme 54). Epoxidation with *t*-BuOOLi leads to the α-nitroepoxide **200**, with a strong preference for the *syn* diastereomer. Conversely, the utilisation of *t*-BuOOK provides a reversal in the diastereoselectivity, with preferential formation of the *anti* diastereomer **201**. Stereospecific opening of the oxirane ring using amino derivatives gives the α-amino *S*-tolyl thioesters **202** and **203** that are amenable to further synthetic transformations.[94–96] This procedure can be successfully extended to other chiral α-hydroxyaldehydes for the preparation of various β-hydroxy-α-amino acid derivatives.[97–100]

Cyclic 2-nitroketones are easily cleaved in different conditions to afford α,ω-difunctionalised systems.[101] When the cleavage is carried out in oxidative conditions, terminal dicarbonyl derivatives are usually obtained in good yield. Potassium persulphate in methanol in the presence of sulphuric acid is able to cleave the 2-nitrocycloalkanones, **204** giving the corresponding α,ω-dicarboxylic acid methyl esters **205** (Scheme 55).[102]

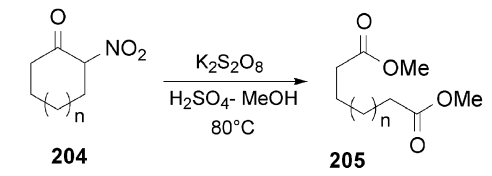
α,ω-Dicarboxylic acids or their methyl monoesters such as **207** can be obtained regioselectively starting from 2-nitrocycloalkanones **206** using Oxone® in buffered



Scheme 53. Synthetic applications of α-nitroepoxides.

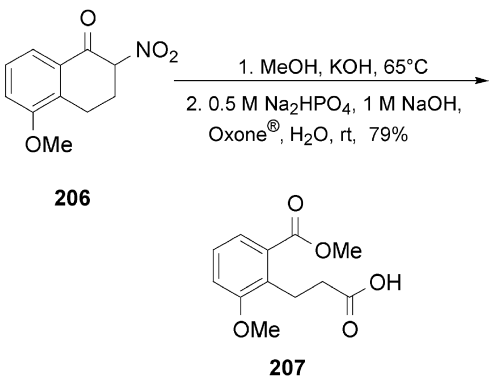


Scheme 54. Nucleophilic ring opening of α-nitroepoxides.



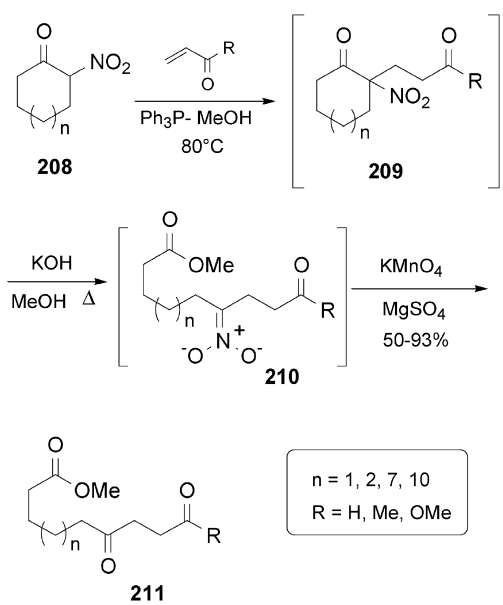
Scheme 55. Oxidative ring cleavage of 2-nitrocycloalkanones using potassium persulphate.

conditions.[103] The carbon atom bearing the nitro group is always converted into a free acid function (Scheme 56).



Scheme 56. Oxidative ring cleavage of 2-nitrocycloalkanones using Oxone®.

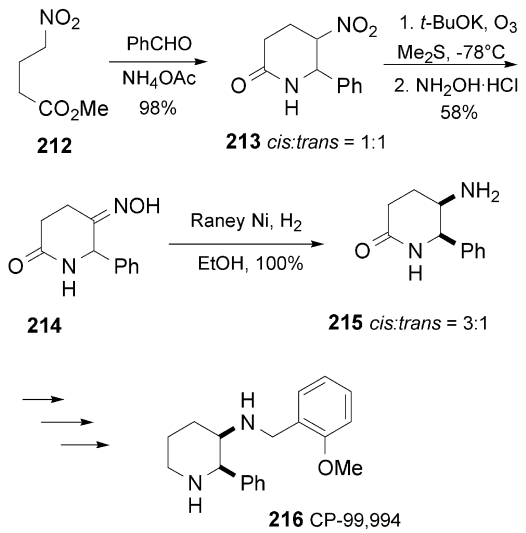
2-Nitroketones form the corresponding nitronate anion in weakly basic conditions, because of the additional activating effect of the carbonyl group.[104] The 2-nitrocycloalkanones **208** therefore, react with enones in the presence of triphenylphosphine to give the Michael adducts **209** that, by the simple addition of a methanolic solution of KOH, are cleaved to the corresponding open-chain nitronate anions **210**.[105,106]



Scheme 57. Synthesis of triketo derivatives.

These intermediates undergo a Nef reaction using $KMnO_4$ to afford the triketo derivatives **211** (Scheme 57). This overall transformation is realised in a one-pot procedure and avoids the isolation of any intermediates.

The utilisation of a Nef protocol can be used to overcome some stereoselectivity troubles occurring during the reduction of a nitro group into the corresponding amine. This procedure is illustrated for the total synthesis of racemic CP-99,994 **216**, a potent substance P antagonist.[107] Condensation of methyl γ-nitrobutyrate **212** with benzaldehyde in the presence of ammonium acetate affords the lactam **213** in good yield, but with no stereoselectivity. Reduction of the nitro group at this stage would provide an equimolar amount of the stereoisomeric amines, which would lower the efficiency of the synthetic process. Oxidative conversion of the nitro group into a carbonyl moiety, however, followed by reaction with hydroxylamine, affords the oxime **214** that, upon reduction with Raney Ni, gives the amine **215** quantitatively and with a better stereoselectivity in favour of the desired *cis* isomer **216** (Scheme 58).



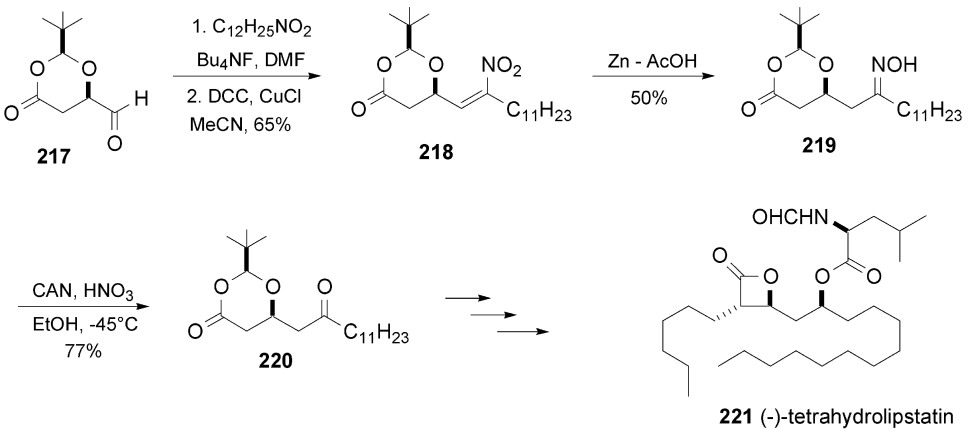
Scheme 58. Synthesis of the substance P antagonist, CP-99,994.

4.2. Reductive methods

Since oximes are known intermediates in the reductive conversion of a nitro group to a carbonyl function, it is sometimes preferable to realise this Nef reaction in two distinct steps, namely nitro-to-oxime conversion, followed by oxime hydrolysis. A recent strategy for the asymmetric synthesis of (−)-tetrahydrolipstatin **221**, a pancreatic lipase inhibitor, utilises the aldehyde **217** as the substrate for a nitroaldol condensation.[108] The obtained nitroalcohol is transformed into the corresponding nitroalkene **218** and then reduced to the oxime **219** using Zn powder in AcOH.

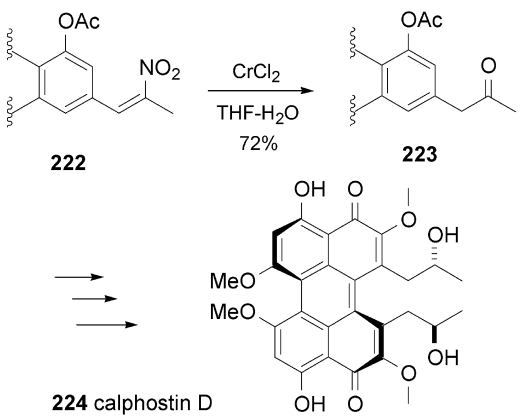
The oxime is cleaved to the parent ketone **220** in oxidative conditions using CAN in the presence of nitric acid (Scheme 59).

A related procedure can be applied en route to the total synthesis of calphostin D **224**, a potent inhibitor of protein



Scheme 59. Nef reaction for the synthesis of (−)-tetrahydrolipstatin.

kinase C.[109] The nitroalkene **222** is directly transformed into the ketone **223** using $CrCl_2$, which avoids the formation of the intermediate oxime (Scheme 60).[110]



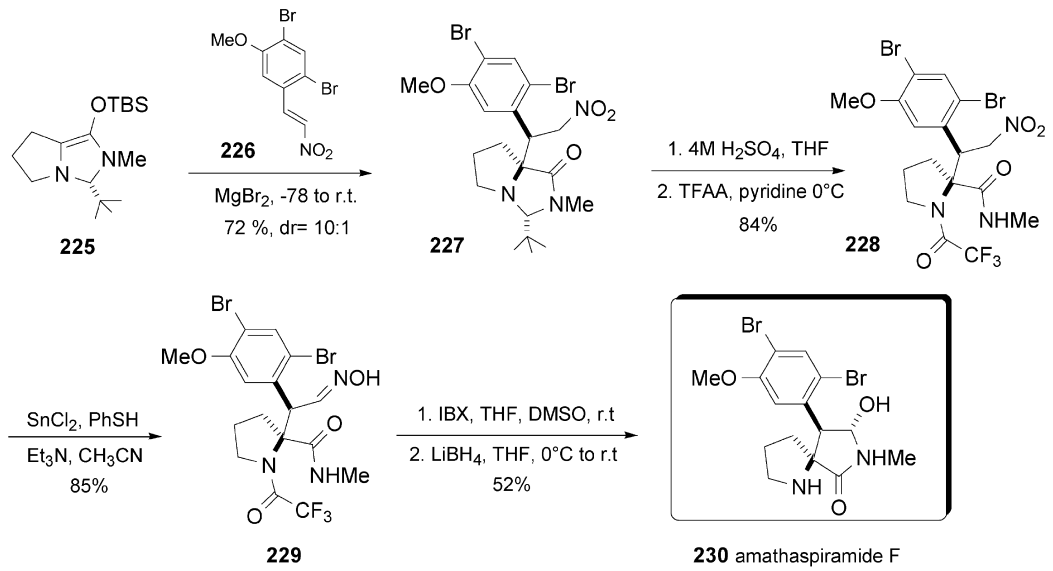
Scheme 60. A key step in the synthesis of calphostin D.

The presence of free amine bases in the molecular structure often makes the Nef conversion a rather troublesome process. It is therefore advisable to protect the amino group as an amide, as demonstrated in the total synthesis of the marine alkaloid, (−)-amathaspiramide F **230** (Scheme 61).[111]

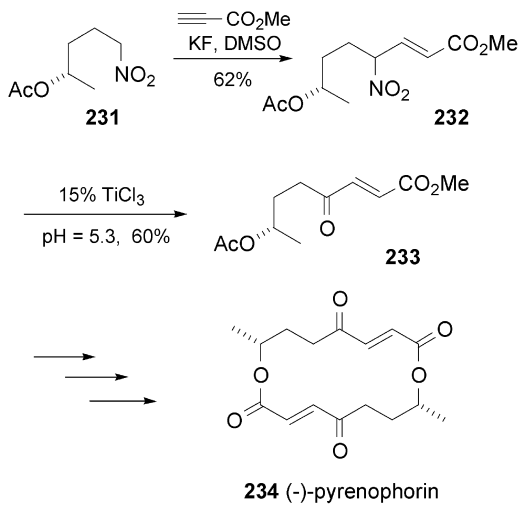
Conjugate addition of the enolate **225** to the nitroalkene **226** affords the product **227** with a high diastereoselectivity, but every attempt to convert the primary nitro group into a carbonyl moiety at this stage does not give any satisfactory results. Hydrolysis of the imidazolidinone ring and protection of the nitrogen as trifluoroacetic amide, however, allows the conversion of **228** into the oxime **229** that, by further functional group manipulations is transformed into amathaspiramide F **230**.

The enedione system is present in a large number of natural products endowed with interesting biological activity. Conjugate addition of the chiral nitroacetate **231** to methyl propiolate gives the corresponding adduct **232** that is converted into the enedione **233** by a classical McMurry reaction.[112] This derivative can be converted into optically active (*R*,*R*)-(−)-pyrenophorin **234**, an antifungal macrolide dilactone (Scheme 62).

A related strategy can be applied to the synthesis of other macrolides featuring enone systems.[113]



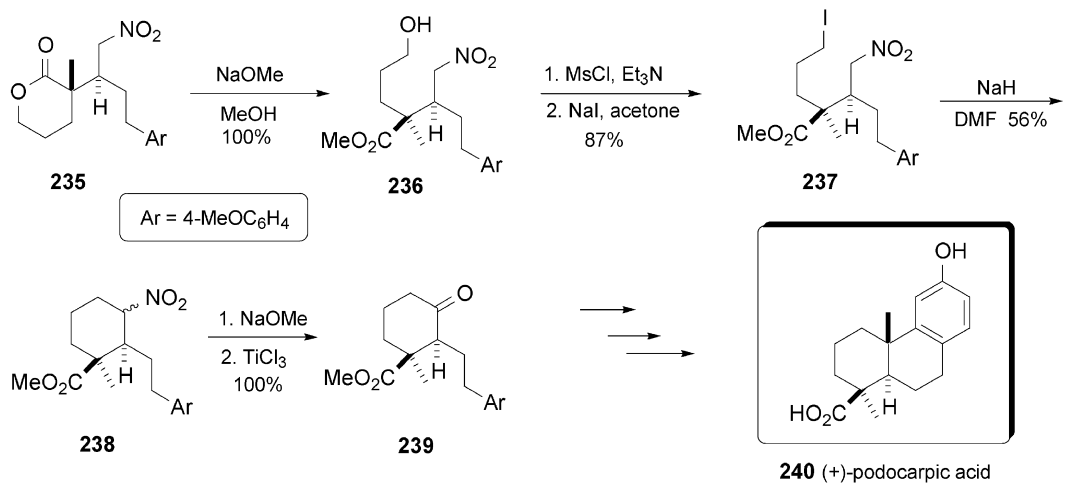
Scheme 61. Nef reaction for the synthesis of amathaspiramide F.



Scheme 62. Synthesis of (−)-pyrenophorin.

conditons to give the nitroalcohol **236**, which is transformed into the corresponding iodide **237** in a two-step process (Scheme 63).[114,115] Intramolecular ring closure, using NaH to generate the nitronate anion, affords the nitrocyclohexane **238** that is converted into the cyclohexanone **239** using the McMurry method. This intermediate can be transformed into (+)-podocarpic acid **240** in a few steps.

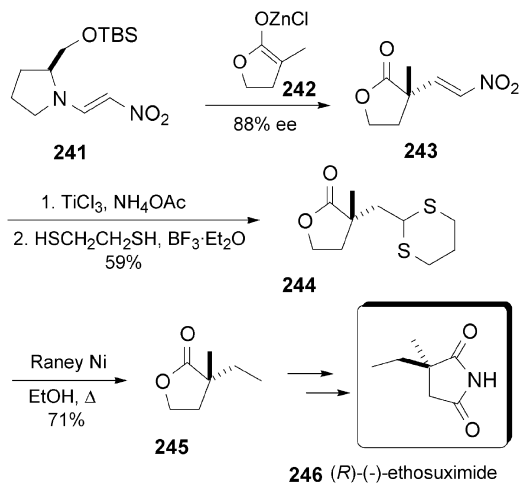
Nitroolefins can be converted directly into carbonyl derivatives using reductive methods. The chiral nitroenamine **241**, obtained from L-proline, reacts with the zinc ester enolate **242**, giving the corresponding lactone **243** in 88% ee (Scheme 64).[116] A reductive Nef reaction using $TiCl_3$ affords an aldehyde that is readily converted into the corresponding thioacetal **244**. Desulphurisation of the thioacetal **244** with Raney Ni leads to the chiral lactone **245** that is transformed in a few steps into the anticonvulsant agent, (*R*)-(−)-ethosuximide **246**.



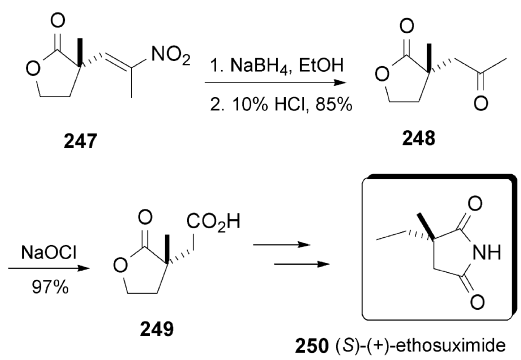
Scheme 63. Synthesis of (+)-podocarpic acid.

Although C-alkylation of nitronate anions is a less common process which respect to nitroaldol condensation, it can be particularly effective in intramolecular reactions. The nitrolactone **235**, obtained by the reaction of a chiral nitroalkene with a Grignard reagent, is opened in basic

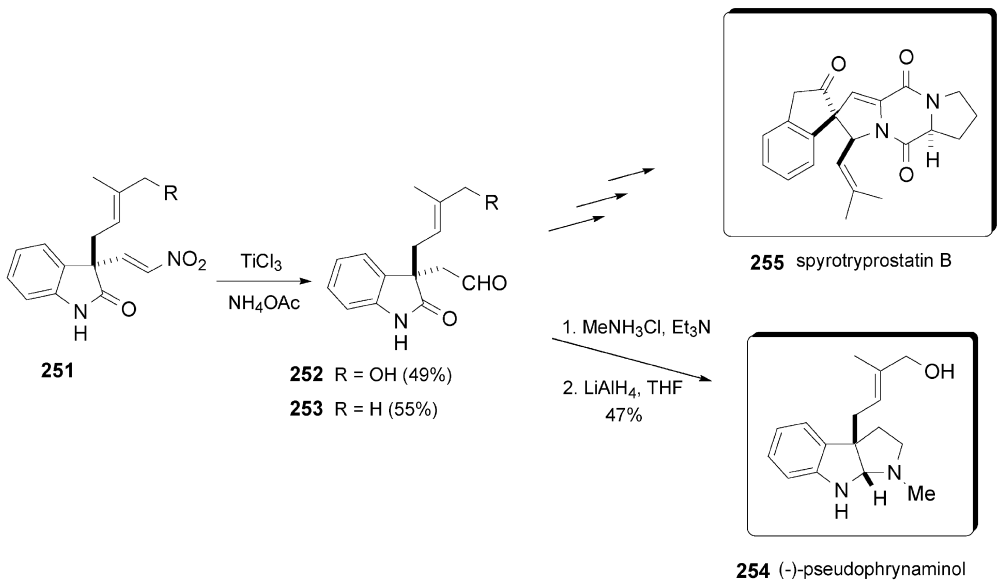
The chiral nitroolefin lactone **247** obtained by a similar procedure can be transformed into the ketone **248** by a tandem nitroolefin reduction-nitronate hydrolysis (Scheme 65). The keto group is cleaved to the parent carboxylic acid **249** by a haloform reaction and ultimately leads to the *S* enantiomer of ethosuximide **250**. The whole process represents a divergent asymmetric synthesis of both enantiomers of ethosuximide, starting from the inexpensive



Scheme 64. Synthesis of (*R*)-(−)-ethosuximide.



Scheme 65. Synthesis of (*S*)-(+)-ethosuximide.

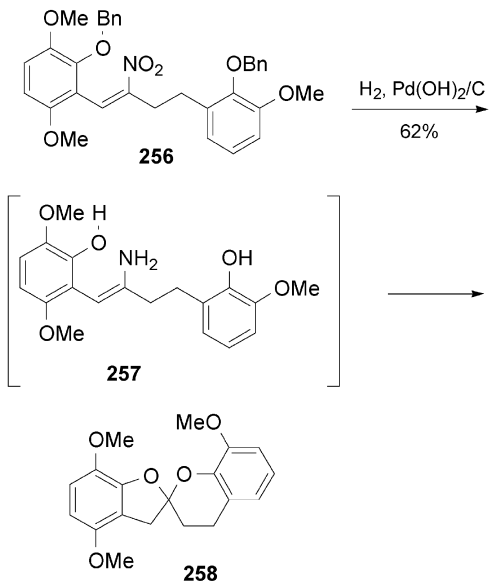


Scheme 66. Syntheses of (−)-pseudophrynaminol and spyrotryprostatin B.

L-proline. This approach follows a related synthesis using both enantiomers of proline as the starting materials.[117]

The final steps towards the total synthesis of the neurotoxin (−)-pseudophrynaminol **254** involve the reductive transformation of the nitroalkene **251** (R=OH) into the aldehyde **252** using $TiCl_3$.[118] Imine formation with methylamine and reductive cyclisation complete the synthesis of (−)-pseudophrynaminol **254** (Scheme 66). The same Nef conversion on the nitroalkene **251** (R=H) gives an aldehyde **253** that, after several steps, can be converted into spirotryprostatin B **255**, a potent antimitotic agent isolated from the fermentation broth of *Aspergillus fumigatus*.[119]

The reduction of nitroalkenes with Pearlman's catalyst [$Pd(OH)_2$/C] initially produces an enamine **257** that is readily hydrolysed to the parent carbonyl compound (Scheme 67).[120,121] In the presence of free hydroxy groups in a suitable position, the spiroketal **258**, which constitutes the core of γ-rubromycin, is directly isolated from nitroalkene **256**.

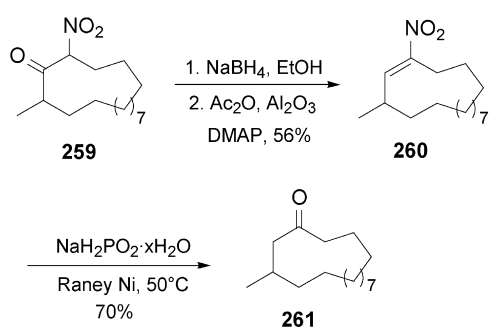


Scheme 67. Synthesis of spiroketal derivatives.

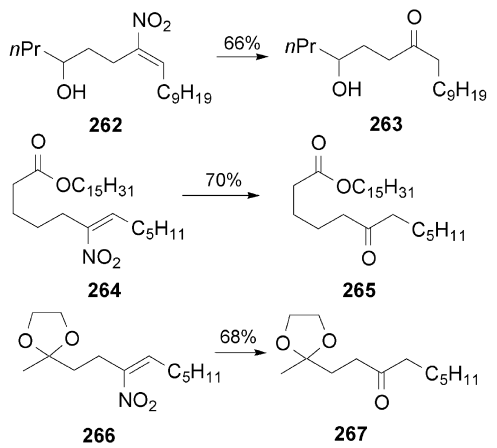
It is highly probable that a similar mechanism occurs in the nitro-to-carbonyl conversion of nitroalkenes using Raney nickel and sodium hypophosphite.[122] This procedure is the key step in the synthesis of several natural products and important synthetic building blocks. The reduction of 2-nitrocyclopentadecanone **259** affords the corresponding nitroalcohol, which is converted into the nitroolefin **260**.[123] This unsaturated compound is converted into muscone **261** using the above-cited procedure (Scheme 68).

Other useful transformations of nitroalkenes **262**, **264** and **266** into ketones **263**, **265** and **267** using Raney-nickel/NaH_2PO_2 are collected in Scheme 69.[124–127]

The cyclopentenone unit is a common motif in a wide array of biologically active substances. Nitromethane reacts with the cyclopentenone **268**, giving a *trans*-substituted nitro derivative that is protected at the carbonyl group as the ketal **269**. A Nef reaction on **269** using $TiCl_3$ gives the aldehyde **270** which is converted via **271** into the compound **272** that shows algicidal properties (Scheme 70).[128]

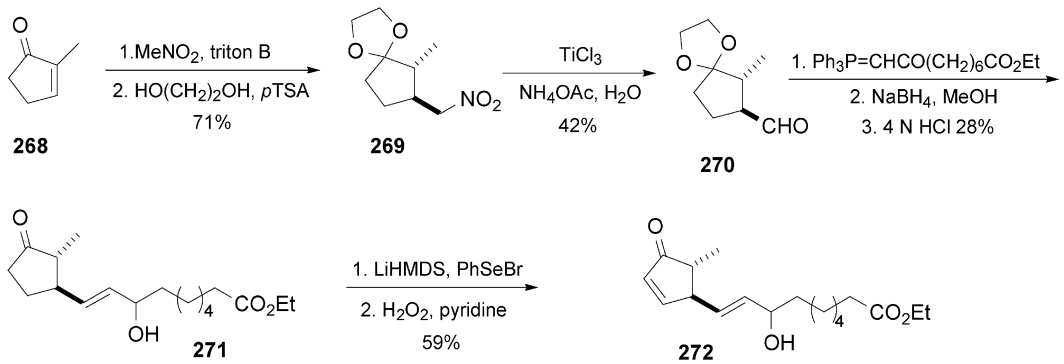


Scheme 68. Synthesis of muscone.

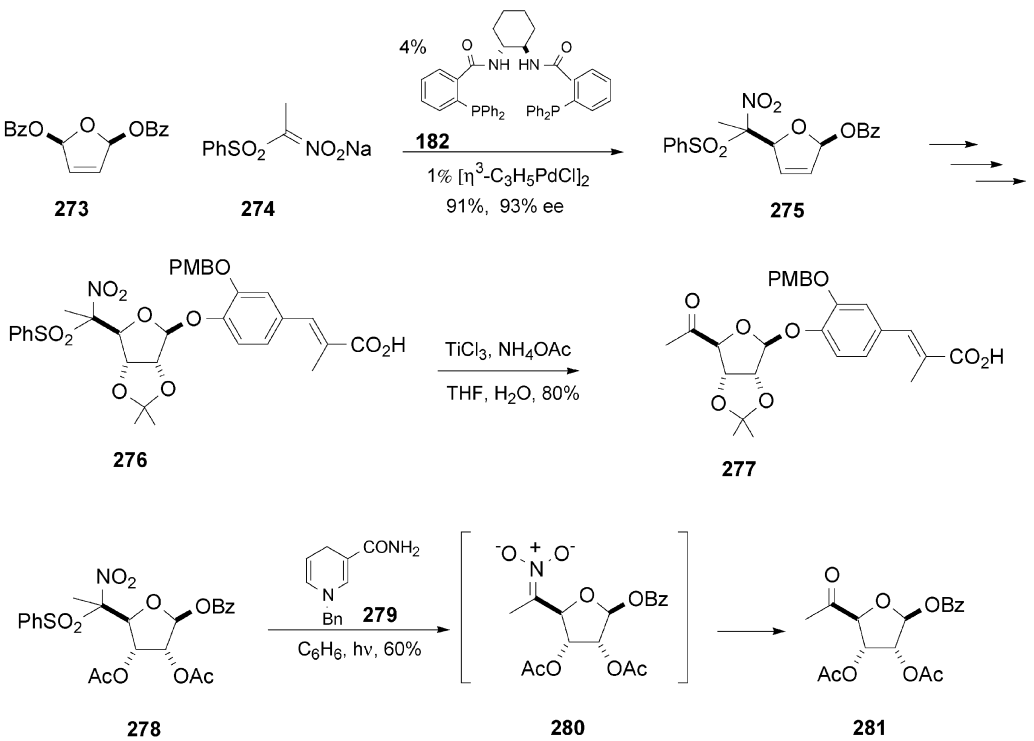


Scheme 69. Nef conversions using $NaH_2PO_2{\cdot}xH_2O$ and Raney nickel.

Reaction of the cyclopentene derivative **273** with the sodium salt of 1-phenylsulphonyl-1-nitroethane **274** in the presence of a chiral catalyst **182** and a Pd species gives the corresponding adduct **275** (Scheme 71). This product, after several steps, is converted into compound **276** that needs to be transformed into the corresponding acyl derivative **277**, an advanced intermediate for the total synthesis of *C*-2 *epi*-hygromycin A.[129,130] Since the nitro compound **276** cannot be converted into its nitronate anion, all oxidative methods are ineffective for the Nef reaction. $TiCl_3$ in buffered solution is, however, able to realise this transformation quite efficiently. In this context, it worth noting that this procedure has been revealed to be rather capricious when applied to other structurally-related cyclopentene derivatives since, the compound **278** fails to give the Nef conversion using $TiCl_3$. The acyl derivative **281** can, however, be obtained in fair yield using



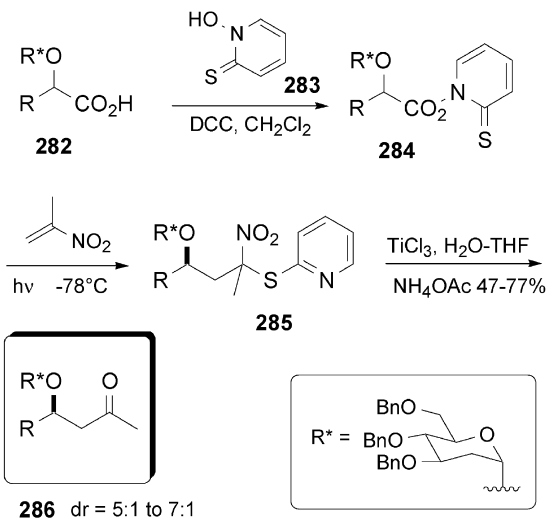
Scheme 70. Synthesis of the algicidal cyclopentenone **272**.



Scheme 71. Use of 1-phenylsulphonyl-1-nitroethane as an acyl anion equivalent.

N-benzylnicotinamide **279** in photochemical conditions. This procedure presumably involves a preliminary desulphonylation that leaves a nitronate anion **280**, which is further reduced by the excess of the nicotinamide to the ketone **281**.[131]

Radical additions to a nitroalkene using Barton's thiohydroxamic protocol provide a rapid entry to thiopyridylnitro derivatives.[132] The α-alkoxy acids **282** bearing a glucal appendage can be transformed with **283** into the corresponding thiohydroxamic anhydrides **284** that react with 2-nitropropene in the usual radical conditions to afford the adducts **285**.[133] A Nef reaction converts these intermediates into the optically active 3-alkoxyketones **286** in good overall yields and diastereomeric ratios (Scheme 72).



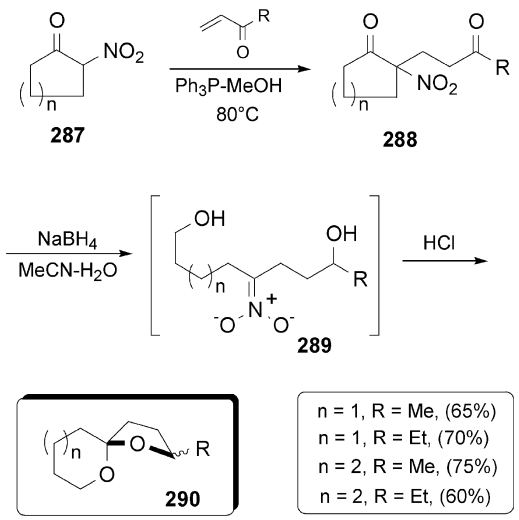
Scheme 72. Nef reaction on thiopyridylnitro derivatives.

4.3. Other methods

Hydrolytic methods, despite the strongly acidic conditions required, are still applied with success in a considerable number of reactions involving the nitro-to-carbonyl conversion. The application of the classical Nef reaction to the synthesis of spiroketal systems represents an interesting example of a cascade reaction.[134] The adducts **288** obtained from 2-nitrocycloalkanones **287** are made to react with $NaBH_4$, leading to the diols **289** by a first tandem retro-Claisen cleavage-reduction of the carbonyl functions. Meanwhile, in basic conditions, the nitro group is converted into the corresponding nitronate anion. Upon quick acidification with HCl, a Nef reaction occurs, followed by a spontaneous spiroketalisation of the intermediate ketodiol, to give the compound **290** as a mixture of *E*/*Z* isomers (Scheme 73).

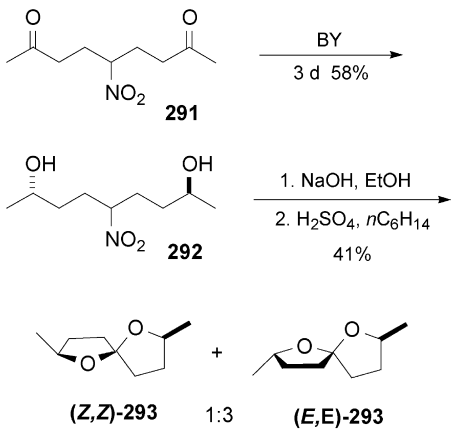
A similar process can be realised stepwise to produce other spiroketal systems.[135]

This procedure can be suitably adapted to the synthesis of spiroketals **293** in an enantiomerically-enriched form, provided that an enantioselective reduction of the carbonyl groups as in the nitroketone **291**, is carried out to give the

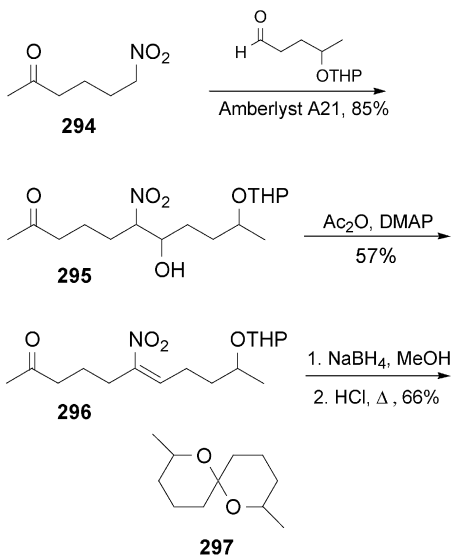


Scheme 73. Synthesis of spiroketals.

optically active alcohols **292**, before the Nef reaction-cyclisation step (Scheme 74).[136,137]



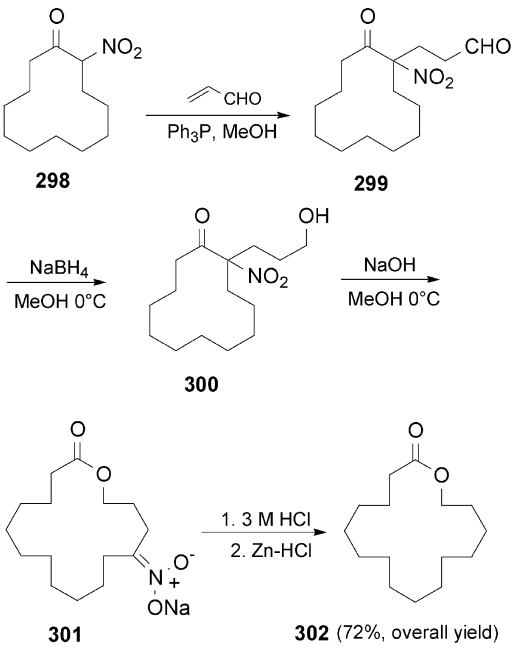
Scheme 74. Enantioselective synthesis of spiroketals.



Scheme 75. Synthesis of spiroketals.

The nitroalkenes such as **296**, obtained from the nitro compound **294** via the nitroalcohol **295**, react with $NaBH_4$ and lead to the formation of nitronate anions that are converted to carbonyl groups and subsequently cyclised to spiroketals **297** (Scheme 75).[138,139]

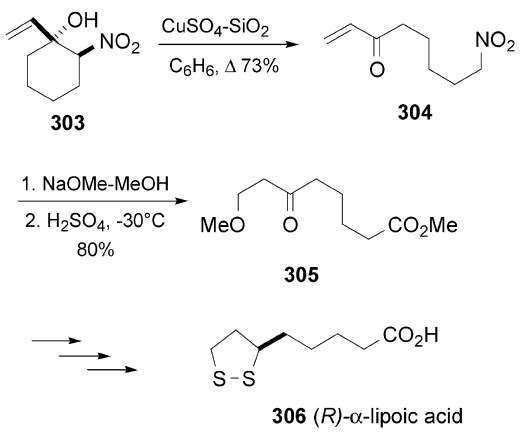
One of the most commonly employed methods for the synthesis of macrocycles involves a ring enlargement reaction of smaller cyclic systems. 15-Pentadecanolide **302**, a component of vegetable musk oils which is of industrial interest, can be prepared starting from 2-nitrocyclododecanone **298** that, upon reaction with acrylaldehyde, gives the adduct **299**.[140,141] Reduction of the aldehyde to **300**, followed by a retro-Claisen process, leads to the 15-membered-ring lactone **301**. Cleavage of the nitronate anion affords a keto derivative that is converted into the macrolide **302** by a Clemmensen reaction (Scheme 76). This process is realised in a one-pot procedure with an overall yield of 72%. A related procedure allows ready access to other macrocycles such as phoracantholide and [10]heterophanes.[142,143]



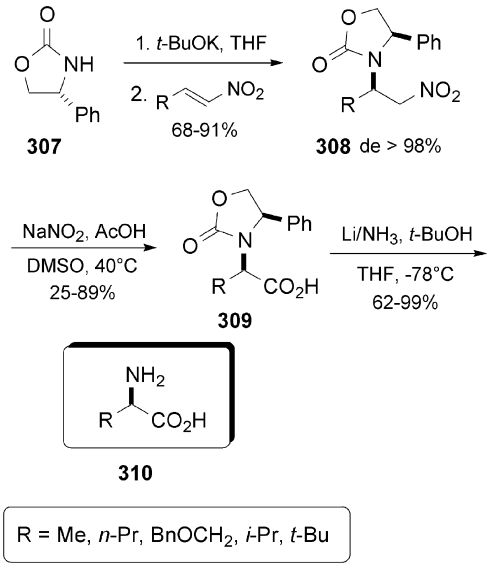
Scheme 76. Synthesis of 15-pentadecanolide.

A retro-Henry reaction on the nitrocyclohexanol **303** affords the open-chain nitroketone **304** that undergoes a tandem Michael addition-Nef reaction upon reaction with NaOMe, followed by acidification with H_2SO_4 to give the ketoester **305**.[144] This derivative is a key intermediate in the synthesis of optically active (*R*)-α-lipoic acid **306** (Scheme 77).

Nucleophilic addition of the potassium salt of optically active 4-phenyl-2-oxazolidinone **307** to nitroalkenes occurs with a high diastereoselectivity giving the nitro derivatives **308** that are amenable to further synthetic transformations.[145,146] The primary nitro group is converted into the carboxylic acids **309** using $NaNO_2$/AcOH in DMSO, followed by reductive cleavage of the oxazolidin-2-one, that leads to the α-amino acids **310** of high enantiomeric purity (Scheme 78).



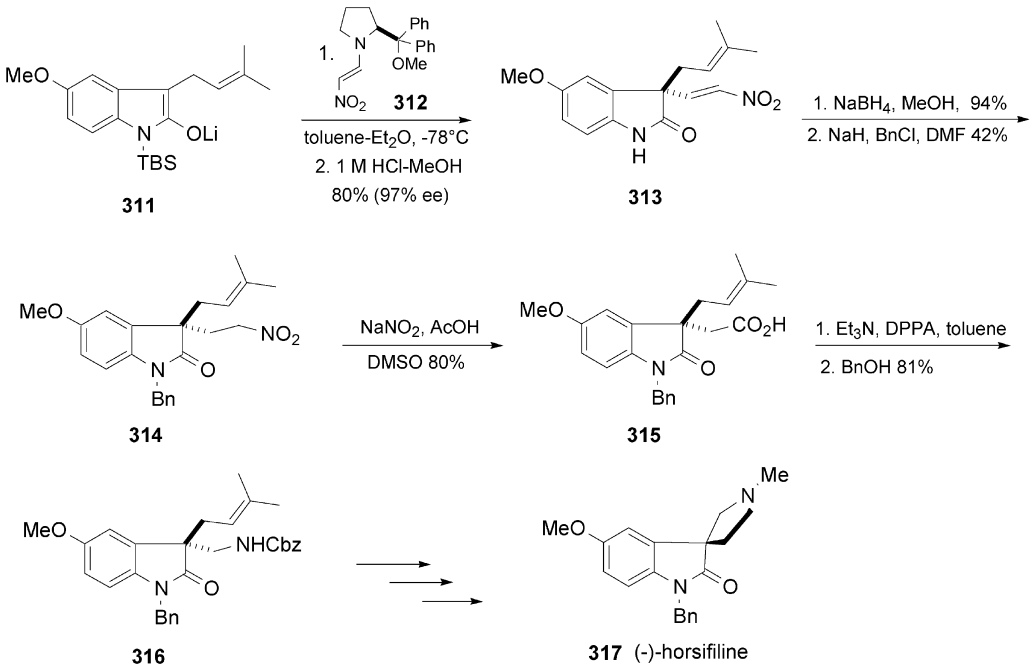
Scheme 77. Synthesis of the ketoester **305**.



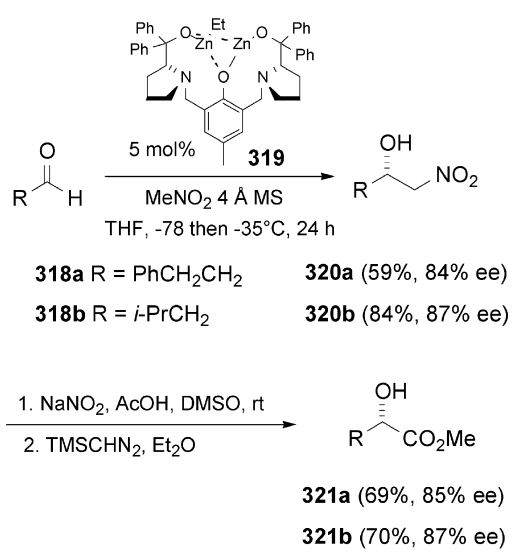
Scheme 78. Synthesis of enantiomerically pure α-amino acids.

The same reagent is used in the total synthesis of (−)-horsfiline **317** an oxindole alkaloid isolated from the Malaysian plant *Horsfildea superba*.[147] The lithium enolate of the oxindole **311** is made to react with the chiral nitroenamine **312** in a 4:1 mixture of toluene/ether giving the nitroalkene **313** in 97% ee. Protection of the indole nitrogen and reduction of the nitroolefin affords the nitroalkane **314** that is converted into the carboxylic acid **315** with $NaNO_2$. A thermal Curtius rearrangement of the acid **315** gives the amine **316** protected as the benzyl carbamate and further synthetic transformations lead to the preparation of (−)-horsfiline **317** (Scheme 79).

Optically active β-nitroalcohols can be obtained by an asymmetric nitroaldol reaction using various chiral catalysts.[148,149] A variety of aldehydes **318** react with nitromethane in the presence of small amounts of a dinuclear zinc catalyst **319**.[150] The obtained β-nitroalcohols **320**, can be transformed into the α-hydroxy acids **321**, by a reaction with the system without any epimerization of the stereogenic centre (Scheme 80). A crucial step in the synthesis of the neuraminidase inhibitor BCX-1812 (RWJ-270201) **324**, is the transformation of the primary



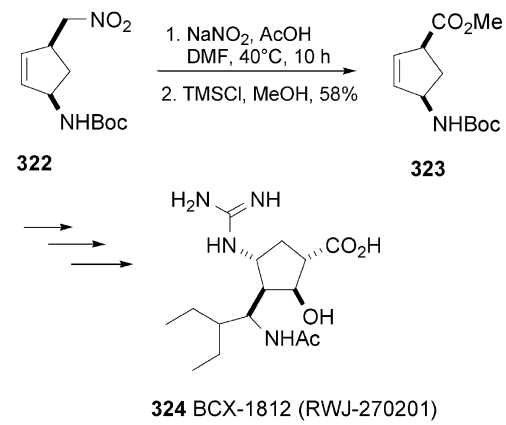
Scheme 79. Synthesis of (−)-horsifiline.



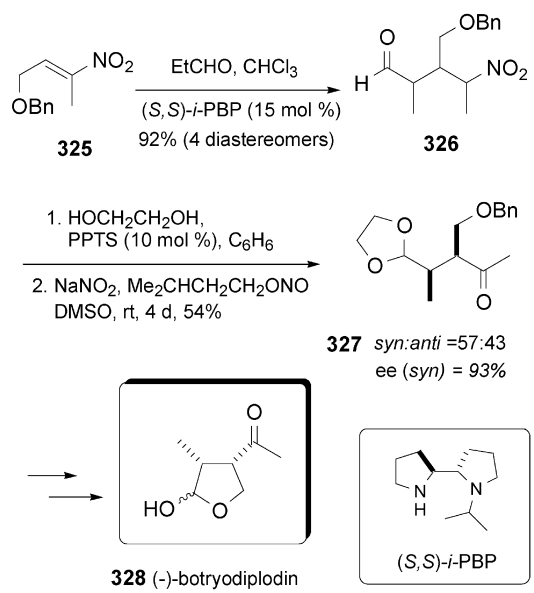
Scheme 80. Synthesis of optically active α-hydroxyacids.

nitroalkane **322** into the ester **323** (Scheme 81).[151] The utilisation of $NaNO_2$/AcOH/DMSO causes, however, a substantial epimerization in the formation of the ester **323**, that can be avoided using DMF as the solvent.

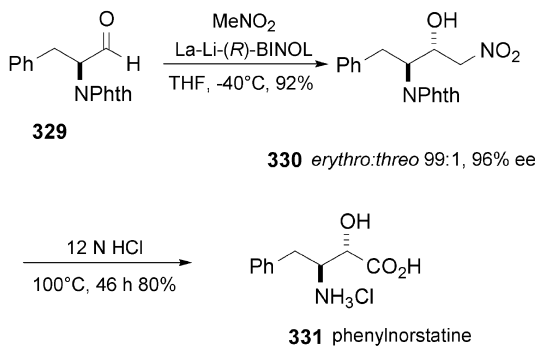
The conjugate addition of propanal to nitroalkene **325**, in the presence of a chiral amine, leads to the formation of the corresponding adduct **326** as a mixture of four diastereomers (Scheme 82).[152] After protection of the carbonyl function as the cyclic acetal, the secondary nitro group can be transformed into the ketone **327** using $NaNO_2$ and isoamyl nitrite in DMSO.[153] The ketone **327** is obtained as a separable mixture of the *syn* (93% ee) and *anti* (74% ee) diastereomers. The *syn* diastereomer is transformed into (−)-botryodiplodin **328**, a compound that exhibits antibiotic and antileukemic activity.



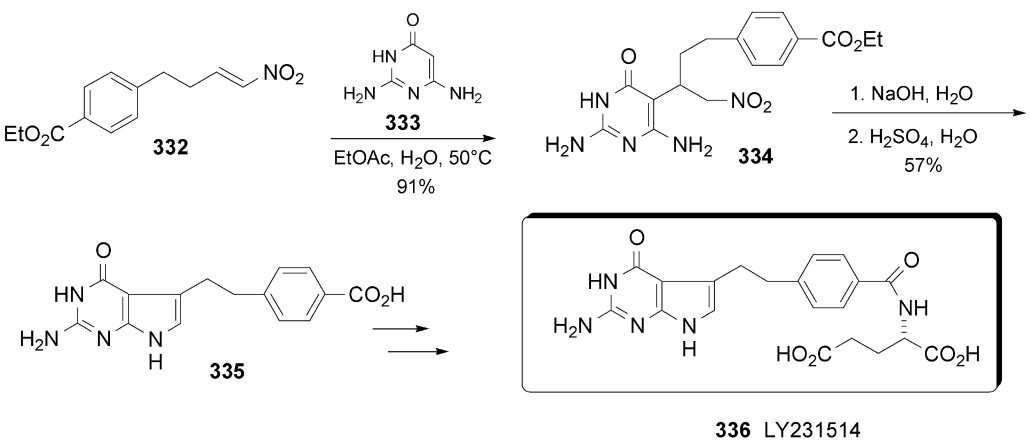
Scheme 81. Synthesis of the neuraminidase inhibitor BCX-1812 (RWJ-270201).



Scheme 82. Synthesis of (−)-botryodiplodin.



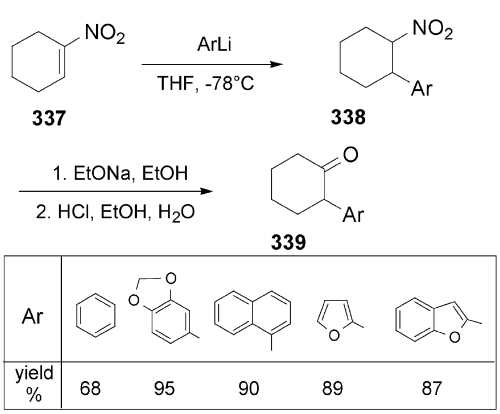
Scheme 83. Synthesis of *erythro*-phenylnorstatine.



Scheme 84. Synthesis of the anticancer agent, LY231514.

The reaction of nitromethane anion with chiral α-amino-aldehydes usually occurs with poor diastereoselectivity. The presence of small amounts of chiral rare earth–Li–BINOL complexes, however, exerts a powerful effect on the diastereoselection (Scheme 83).[154] The α-aminoaldehyde **329** reacts with nitromethane in the presence of La–Li–(*R*)-BINOL as the catalyst (3.3 mol%) to give the nitroalcohol **330** practically as the sole *erythro* diastereomer in 96% ee.

The nitro moiety can be converted into a carboxyl group by prolonged heating at reflux in concentrated HCl that also ensures the removal of the *N*-phthaloyl protecting group (Phth), leading to phenylnorstatine **331**. Rather surprisingly, these harsh conditions do not affect the integrity of the stereocentres present in the molecule.

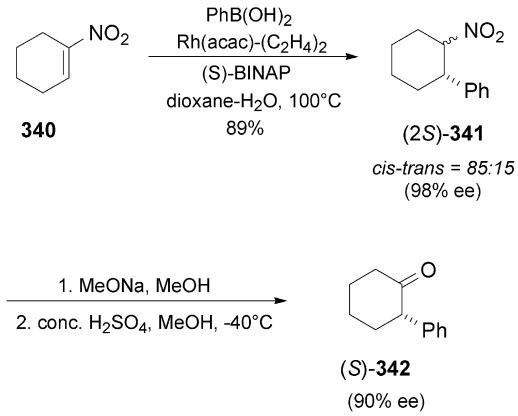


Scheme 85. Synthesis of 2-arylcyclohexanones.

The Nef reaction can be coupled with a ring closure to afford fused pyrroles.[155,156] Pyrimidone **333** adds to the nitro-alkene **332** in a very efficient manner to give the compound **334**. This derivative in hydrolytic conditions is transformed into the corresponding aldehyde that undergoes a fast ring closure to the fused pyrrole **335**. This compound is easily converted into the pyrrolo[2,3-*d*]pyrimidine, LY231514 **336**, a potential inhibitor of folate-dependent enzymes (Scheme 84).

The addition of organometallic reagents to nitroalkenes provides an efficient entry to 2-substituted cycloalkanones and similar derivatives.[157] Aryllithium reagents add to 1-nitro-1-cyclohexene **337**, giving the 2-aryl-1-nitro-cyclohexane derivatives **338**.[158] The nitro group is subsequently transformed into a carbonyl function using common hydrolytic conditions, giving the 2-arylcyclo-hexanones **339** in good yields (Scheme 85). A similar procedure can be applied using Grignard reagents to 3-nitro-5,6-dihydro-4*H*-pyran that directly affords the 2-alkyltetra-hydropyran-3-ones in a one-pot reaction.[159] In this context, it is worth noting that alkyl Grignard reagents can be efficiently added to nitroalkenes in the presence of cerium(III) chloride, which considerably suppresses proton abstraction and redox reactions that usually occur in similar processes.[160]

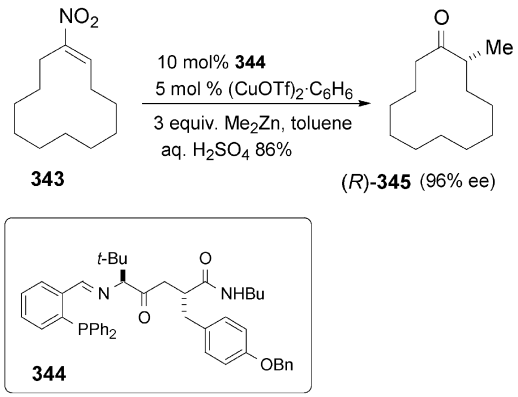
In the presence of chiral catalysts, the organometallic



Scheme 86. Synthesis of optically active 2-phenylcyclohexanone.

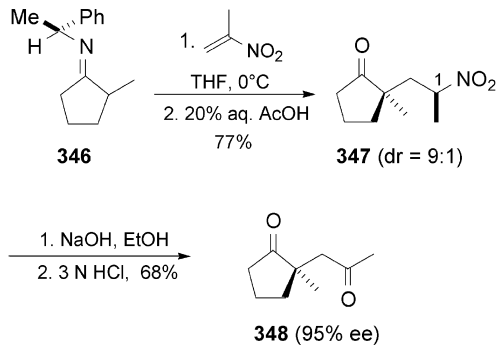
addition to cyclic nitroalkenes produces the corresponding nitro derivatives with variable *cis*/*trans* ratios. Organoboronic acids add to conjugated nitrocycloalkenes such as **340** in the presence of Rh(acac)–$(C_2H_4)_2$/(*S*)-BINAP to give the 2-substituted nitrocycloalkanes **341** that after the Nef conversion, afford the corresponding cycloalkanones **342** in good enantiomeric excesses (Scheme 86).[161]

Similarly, alkylzinc reagents give a conjugate addition to the cyclic nitroalkene **343** in the presence of $(CuOTf)_2{\cdot}C_6H_6$ and a chiral phosphine ligand **344** to afford the corresponding 2-alkyl derivative that undergoes a Nef conversion in hydrolytic conditions.[162] This procedure seems particularly suitable for the enantioselective synthesis of macrocyclic ketones such as (*R*)-2-methylcyclododecanone (*R*)-**345** (Scheme 87).



Scheme 87. Enantioselective synthesis of (*R*)-2-methylcyclododecanone.

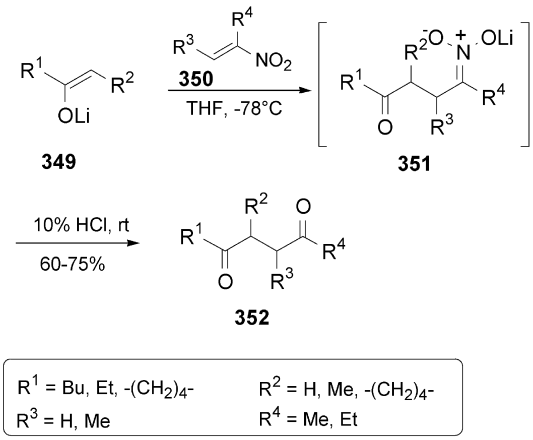
The chiral imine **346** obtained from 2-methylcyclopentanone reacts with 2-nitropropene in a highly regioselective fashion giving a diastereomeric mixture of the C-1 epimeric adducts **347**.[163] Interestingly, the subsequent Nef reaction using $TiCl_3$ gives exclusively the corresponding oxime, while acidic hydrolysis of the nitronate anion affords the diketone **348** in 95% ee (Scheme 88).



Scheme 88. Synthesis of the chiral 1,4-diketone **348**.

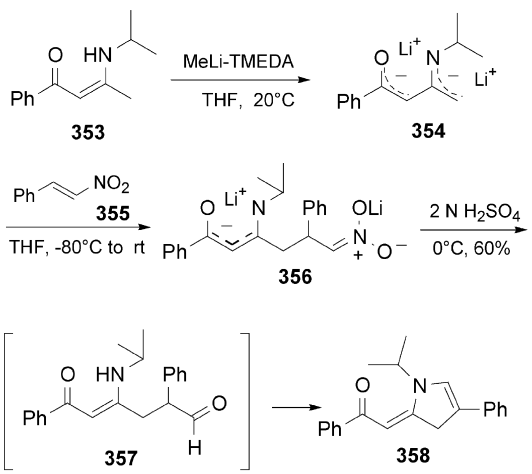
Conjugate addition of lithium ketone enolates **349** to nitroalkenes **350** represents a general method for the direct preparation of 1,4-diketones **352** since the intermediate nitronate anion **351** can be converted directly into a carbonyl group by acid hydrolysis (Scheme 89).[164,165]

The dianion of the β-enaminoketone **354**, prepared from **353**, reacts with nitrostyrene **355** at −80 °C giving the



Scheme 89. Synthesis of 1,4-diketones.

corresponding nitronate adduct **356**.[166] Upon quenching of this intermediate at 0 °C with 2 N H_2SO_4, the aldehyde **357** is formed, followed by a rapid cyclisation to the dihydropyrrole **358** in 60% overall yield (Scheme 90).

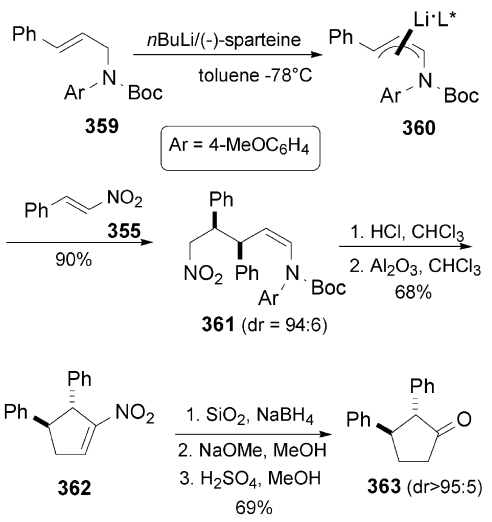


Scheme 90. Synthesis of the dihydropyrrole **358**.

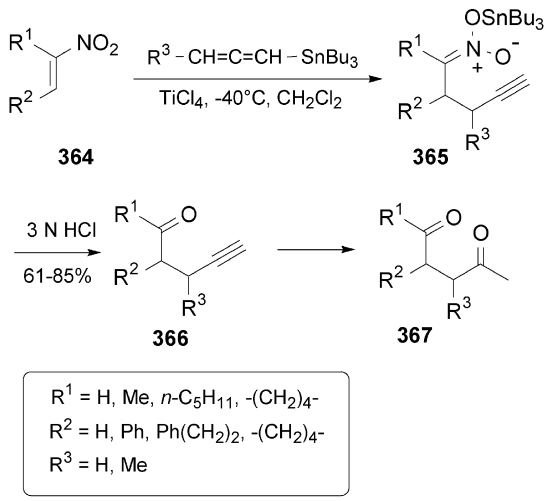
The configurationally-stable organolithium derivative **360** obtained by treatment of the allylic amine **359** with *n*BuLi and (−)-sparteine, adds to the nitroalkene **355** with high diastereomeric and enantiomeric ratios.[167] Hydrolysis of the adduct **361** affords the nitrocycloalkene **362** by an intramolecular nitroaldol-elimination reaction. Conversion of the compound **362** to cyclopentanone **363** is carried out by reduction of the double bond, followed by a Nef reaction in hydrolytic conditions (Scheme 91).

Propargylation of the nitroalkenes **364** can be realised using (tributylstannyl)allenes in the presence of $TiCl_4$.[168] The stannylnitronates **365** that are formed as intermediates can be hydrolysed to the corresponding ketones **366** using 3 N HCl. The obtained α-propargylic ketones **366** are precursors of useful building blocks such as the 1,4-diketones **367** (Scheme 92).

An interesting rearrangement involving a Nef process can be observed in the nitrocyclopropane **368** under strongly



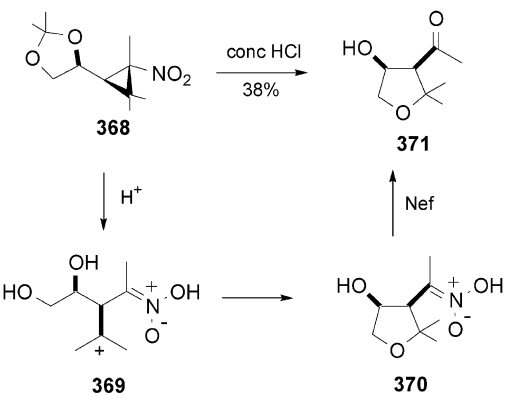
Scheme 91. Synthesis of the optically active cyclopentanone **363**.



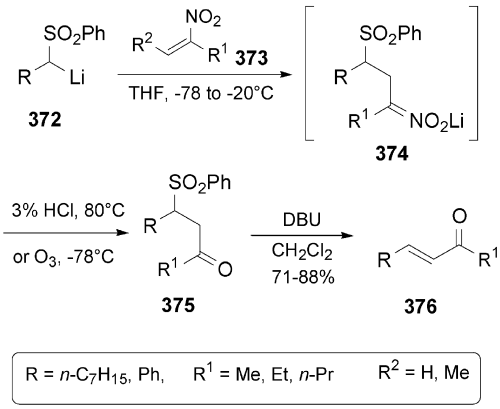
Scheme 92. Nef reaction on α-propargyl stannylnitronates.

acidic conditions (conc. HCl).[169] Cyclopropane ring opening affords the carbenium ion **369** that forms the tetrahydrofuran derivative **370** by intramolecular etherification. Finally, the nitronic acid **370** undergoes a Nef reaction, leading to the keto derivative **371** (Scheme 93).

The α-sulphonyl carbanions **372** add to the nitroalkenes **373** giving, after acid hydrolysis of the intermediate nitronates **374**, the 3-phenylsulfonyl ketones **375**.[170] These derivatives can be transformed into the enones **376** by treatment with DBU that causes elimination of benzenesulphinic acid (Scheme 94).

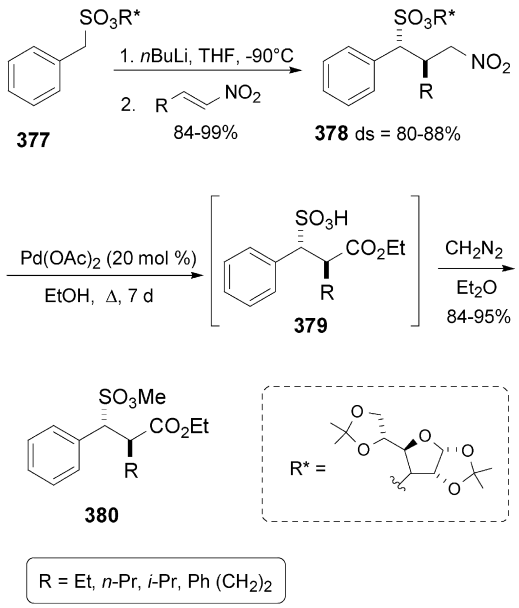


Scheme 93. Rearrangement of the chiral nitrocyclopropane **368**.



Scheme 94. Synthesis of α,β-unsaturated derivatives.

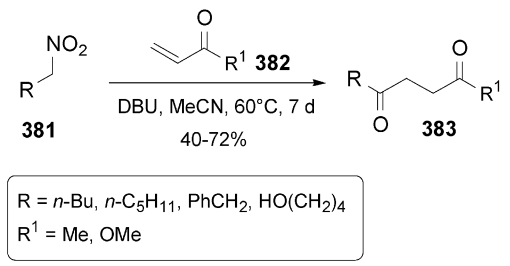
Enantiopure sulphonates **377** bearing a carbohydrate-derived chiral auxiliary can be lithiated at low temperature and then added to nitroalkenes to give the corresponding nitro derivatives **378**.[171] The chiral auxiliary can be subsequently removed in the presence of 20 mol% $Pd(OAc)_2$ in EtOH to afford an intermediate sulphonic acid that also causes the Nef transformation of the primary nitro group into an ethyl carboxylate **379**. The sulphonic acids can be finally methylated using diazomethane to give the diesters **380** (Scheme 95).



Scheme 95. Synthesis of optically active methanesulphonates.

The ability of DBU to promote a conjugate addition of nitroalkanes **381** to enones **382**, as well as a Nef reaction on secondary nitroalkanes, can be effectively used in a tandem process that allows the direct synthesis of γ-diketones and γ-keto esters **383** (Scheme 96).[172]

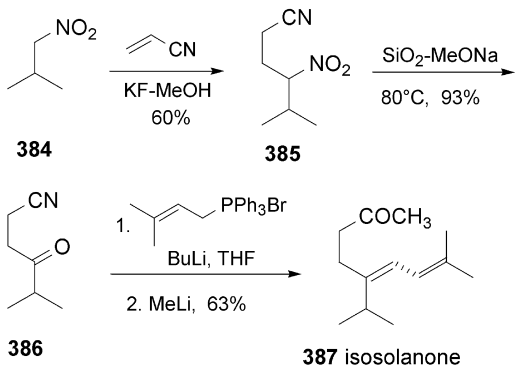
The same transformation can be of course realised in a



Scheme 96. DBU-promoted conjugate addition-Nef reaction.

two-step procedure after isolation of the intermediate γ-nitroketone.[173]

A conjugate addition of the nitroalkane **384** to acrylonitrile represents the first step in the synthesis of terpene isosolanone **387**.[174] The obtained nitrile **385** is converted into the ketonitrile **386** in very good yield using MeONa in dry silica. Wittig olefination and conversion of the cyano group to a methyl ketone using MeLi gives isosolanone **387** as an inseparable diastereomeric mixture (*E*/*Z*, 3:1) (Scheme 97).

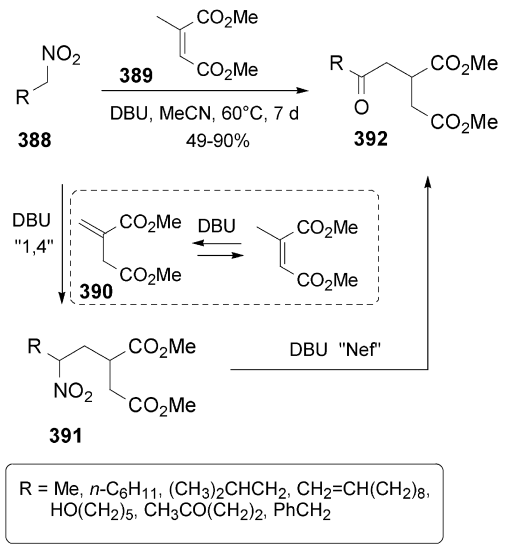


Scheme 97. Synthesis of isosolanone.

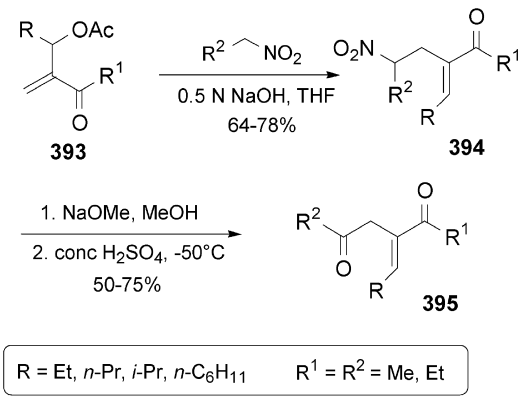
A unusual behaviour can be observed upon reaction of the nitroalkanes **388** with dimethyl citraconate **389** in the presence of DBU.[175] As observed by ^{1}H NMR analysis, in the presence of DBU there is an equilibrium between **389** and its regioisomer **390** that is probably more reactive towards Michael addition with nitroalkanes. The adducts **391** formed by the usual conjugate addition are therefore subsequently transformed into the keto diesters **392** by a Nef reaction (Scheme 98).

Allyl Baylis–Hillman acetates **393** react with nitroalkanes through a conjugate addition–elimination process that leads to the formation of the unsaturated esters **394**.[176] A Nef reaction carried out under hydrolytic conditions on these compounds efficiently affords the (*E*)-alkylidene-1,4-diketones **395** (Scheme 99).

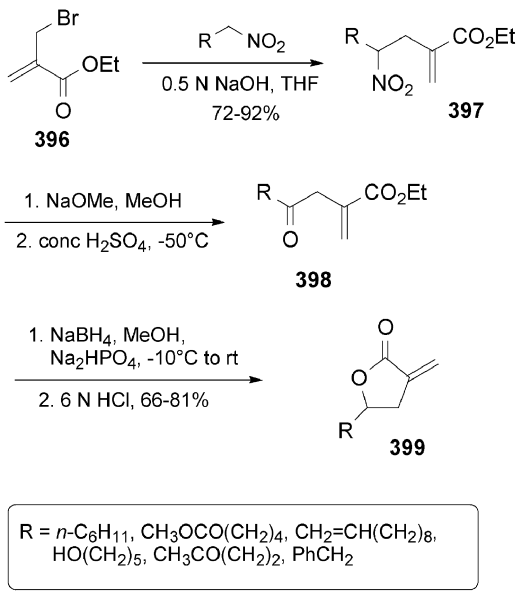
A related procedure involves ethyl (2-bromomethyl)acrylate **396** as a Michael acceptor that behaves similarly to the acetates **393** in the reaction with nitroalkanes, giving the nitro derivatives **397**.[177] The nitro group is best transformed into an hydroxy group by a two-step procedure involving hydrolytic cleavage to **398** and reduction with $NaBH_4$ in the presence of Na_2HPO_4. This transformation is followed by a spontaneous lactonisation to the *exo*-methylene butyrolactones **399** in good overall yields (Scheme 100).



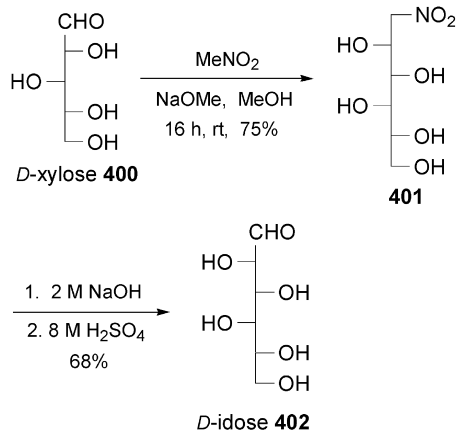
Scheme 98. Synthesis of keto diesters.



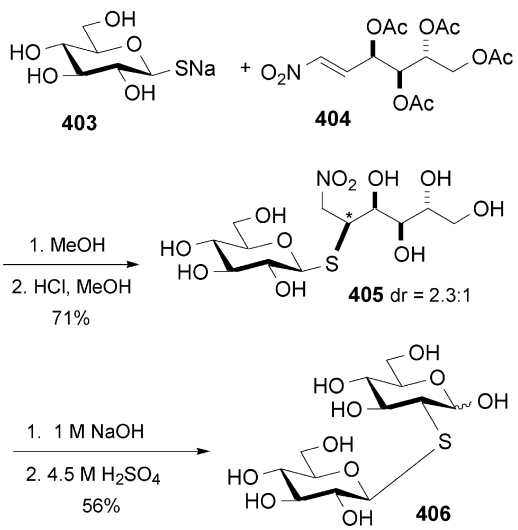
Scheme 99. Synthesis of alkylidene-1,4-diketones.



Scheme 100. Synthesis of *exo*-methylene butyrolactones.



Scheme 101. Synthesis of *D*-idose by chain elongation.



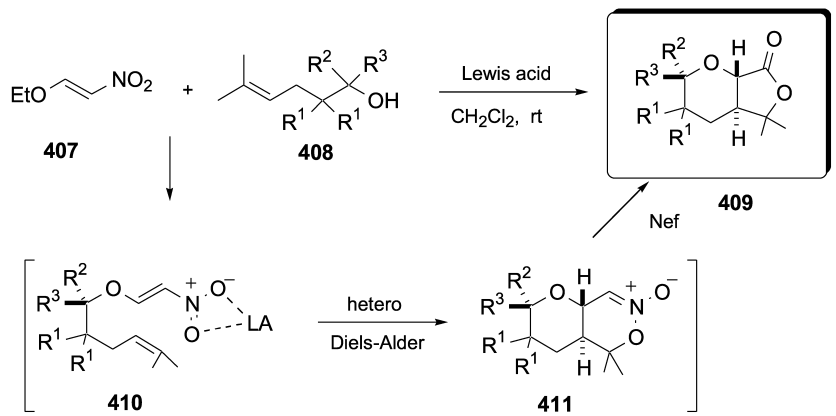
Scheme 102. Synthesis of *S*-glycosylthioglycose **406**.

As previously stated, several structural manipulations in the field of carbohydrate chemistry make use of the Nef reaction as a key step to introduce a carbonyl group in the molecular framework.[15] Reaction of nitromethane with D-xylose **400** produces an epimeric pair of nitrosugars from which 1-deoxy-1-nitro-D-iditol **401** can be recovered in 75% yield after multiple fractional crystallisations.[178] This compound can be transformed into D-idose **402** under classical Nef conditions in 68% yield (Scheme 101).

Conjugate additions to sugar α-nitroalkenes provide a viable method for the synthesis of various disaccharides such as *S*-glycosylthioglycose **406** that shows some enzyme inhibitory properties.[179] The sodium salt of 1-thio-*D*-glucose **403** reacts with the nitroalkene **404**, giving, after deacetylation, the corresponding adduct **405** as a mixture of epimers (Scheme 102).

Hydrolytic Nef reaction on **405** followed by equilibration of the resulting epimeric mixture, allows the isolation by fractional crystallisation of the pure thiodisaccharide **406** in fairy good yield.

The conjugate addition of (*E*)-1-ethoxy-2-nitroethylene **407**, with δ,ε-unsaturated alcohols **408**, leads to the synthesis of *trans*-fused bicyclic γ-lactones **409** in the presence of a catalytic amount of different Lewis acids (Scheme 103).[180] The Michael adduct **410** initially formed, undergoes to a hetero Diels–Alder reaction that produces bicyclic nitronates **411**. The intermediate nitronates **411** can be isolated adding 4 Å molecular sieves to the reaction mixture using $Yb(OTf)_3$ as a catalyst. In the presence of the water of crystallisation, however, a Nef reaction occurs with formation of the bicyclic γ-lactone **409** in a one-pot process.



Lewis acid	R^1	R^2	R^3	**409** yield %
$Ni(ClO_4)_2 \cdot 6H_2O$	H	H	H	72
$Yb(OTf)_3$	Me	H	H	55
$Ni(ClO_4)_2 \cdot 6H_2O$	H	Me	H	68
$Ni(ClO_4)_2 \cdot 6H_2O$	H	Me	Me	51

Scheme 103. Synthesis of bicyclic γ-lactones.

5. Conclusions

The nitro to carbonyl conversion has been firmly established, since its discovery by Nef more than a century ago, as one of the most important functional group transformations. The success of this procedure has been established by the large body of different synthetic protocols that have been set up over the years in order to accomplish this transformation with an increasingly higher level of chemoselectivity. A literature survey shows that a consistent number of syntheses directed towards the preparation of biologically active and industrially important compounds have inserted the Nef reaction into some crucial step of the overall synthetic plan. The originally designed hydrolytic system for this conversion is still largely practised in many synthetic routes in which acid- or base-sensitive groups are not present in the substrate. Hydrolysis of the nitronate anions can be replaced by an oxidative cleavage of the carbon nitrogen double bond using common oxidising agents. On the other hand, by means of a suitable choice of reaction conditions, it is possible to use reducing agents to transform nitroalkenes or their nitronate salts into carbonyl derivatives. In the conjugate additions of nitroalkenes with nucleophiles, a nitronate derivative is often formed as an intermediate. This represents a formidable opportunity to include the Nef conversion in a tandem sequence, with considerable advantages in the efficiency of the whole synthetic process. All these synthetic opportunities to carry out this transformation help in keeping the chemistry of nitro compounds at the very core of organic chemistry.

Acknowledgements

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References and notes

1. Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
2. *Nitro compounds recent advances in synthesis and chemistry*; Feuer, H., Nielsen, A. T., Eds.; VCH: Weinheim, 1990.
3. Ono, N. *The nitro group in organic synthesis*; Wiley-VCH: New York, 2001.
4. *The chemistry of amino, nitroso, nitro and related groups*; Patai, S., Ed.; Wiley: Chichester, 1996.
5. Adams, J. P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2586.
6. Seebach, D.; Lehr, F. *Angew. Chem. Int. Ed.* **1976**, *15*, 505.
7. Rosini, G. *Comprehensive organic synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 321.
8. Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.
9. Perlmutter, P. *Conjugate addition reactions in organic synthesis*; Pergamon: Oxford, 1992.
10. Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705.
11. Rosini, G.; Ballini, R.; Zanotti, V. *Synthesis* **1983**, 137.
12. Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213.
13. Noland, W. E. *Chem. Rev.* **1955**, *55*, 137.
14. Nef, J. U. *Liebigs Ann. Chem.* **1894**, *280*, 264.
15. Petruš, L.; Petrušová, M.; Pham-Huu, D.-P.; Lattová, E.; Pribulová, B.; Turjan, J. *Monat. Chem.* **2002**, *133*, 383.
16. Pinnick, H. W. *Org. React.* **1990**, *38*, 655.
17. Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751.
18. Kabalka, G. W.; Varma, R. S. *Org. Prep. Proc. Int.* **1987**, *19*, 283.
19. Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, *20*, 95.
20. Fuji, K.; Node, M. *Synlett* **1991**, 603.
21. Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. *Nitroalkenes conjugated nitro compounds*; Wiley: Chichester, 1994.
22. Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.
23. Steliou, K.; Poupart, M.-A. *J. Org. Chem.* **1985**, *50*, 4971.
24. Savilles-Stones, E. A.; Lindell, S. D. *Synlett* **1991**, 591.
25. Adam, W.; Makosza, M.; Saha-Möller, C. R.; Zhao, C.-G. *Synlett* **1998**, 1335.
26. Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O. *Synth. Commun.* **1998**, *28*, 3054.
27. Shahi, S. P.; Vankar, Y. D. *Synth. Commun.* **1999**, *29*, 4321.
28. Narayana, C.; Reddy, N. K.; Kabalka, G. W. *Synth. Commun.* **1992**, *22*, 2587.
29. Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 207.
30. Nikalje, M. D.; Sayyed, I.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2000**, *41*, 959.
31. Balogh-Hergovich, É.; Kaizer, J.; Speier, G. *Chem. Lett.* **1996**, 573.
32. Hermanson, J. R.; Gunther, M. L.; Belletire, J. L.; Pinhas, A. R. *J. Org. Chem.* **1995**, *60*, 1900.
33. McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.
34. DeHaan, F. P.; Allen, M. W.; Ang, M. C.; Balacuit, D. B.; Bentley, C. A.; Bergstrand, R. J.; Cho, E. R.; DeHaan, D. O.; Farris, T. E.; Kemnitz, C. R.; Ma, S. K.; Martin, K. A.; Ruiz, R. M.; Sakamoto, D. K.; Sharvit, O.; Strassmaier, T. T.; Uyeda, H. T.; Villahermosa, R. M. *J. Org. Chem.* **1995**, *60*, 8320.
35. Kumaran, G.; Kulkarni, G. H. *Tetrahedron Lett.* **1994**, *35*, 5517.
36. Bezbarua, M. S.; Bez, G.; Barua, N. C. *Chem. Lett.* **1999**, 325.
37. Saikia, A. K.; Barua, N. B.; Sharma, R. P.; Ghosh, A. C. *J. Chem. Res. (S)* **1996**, 124.
38. Bordoloi, M. *J. Chem. Soc., Chem. Commun.* **1993**, 922.
39. Lee, S. H.; Park, Y. J.; Yoon, C. M. *Org. Biomol. Chem.* **2003**, *1*, 1099.
40. Urpí, F.; Villarasa, J. *Tetrahedron Lett.* **1990**, *31*, 7499.
41. Das, N. B.; Sarangi, C.; Nanda, B.; Nayak, A.; Sharma, R. P. *J. Chem. Res. (S)* **1996**, 28.
42. Hwu, J. R.; Tseng, W. N.; Patel, H. V.; Wong, F. F.; Horng, D.-N.; Liaw, B. R.; Lin, R. C. *J. Org. Chem.* **1999**, *64*, 2211.
43. Matt, C.; Wagner, A.; Moiskowski, C. *J. Org. Chem.* **1997**, *62*, 234.
44. Ran, C.; Yang, G.; Wu, T.; Xie, M. *Tetrahedron Lett.* **2003**, *44*, 8061.
45. Das, N. B.; Sarma, J. C.; Sharma, R. P.; Bordoloi, M. *Tetrahedron Lett.* **1993**, *34*, 869.
46. Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3861.
47. Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233.
48. Hwu, J. R.; Gilbert, B. A. *J. Am. Chem. Soc.* **1991**, *113*, 5917.
49. Horng, D.-N.; Chen, K.-L.; Hwu, J. R. *Tetrahedron* **2000**, *56*, 1631.

50. Zimmerman, H. E.; Wang, P. *Helv. Chim. Acta* **2001**, *84*, 1342.
51. Bernal-Montes, J.-C.; Borrachero-Moya, P.; Cabrera-Escribano, F.; Gómez-Guillén, M.; Madrid-Díaz, F.; Moreno-Martínez, J.-M. *Carbohydr. Res.* **1996**, *285*, 49.
52. Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3861.
53. Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449.
54. Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.
55. Crossley, M. J.; Fung, Y. M.; Kyriacopoulos, E.; Potter, J. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1123.
56. Kálai, T.; Balog, M.; Jekö, J.; Hideg, K. *Synthesis* **1999**, 973.
57. Ballini, R. *Synthesis* **1993**, 687.
58. Cappon, J. J.; Baart, J.; van der Walle, G. A. M.; Raap, J.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 158.
59. Barrett, A. G. M.; Sakadarat, S. *J. Org. Chem.* **1990**, *55*, 5110.
60. Barrett, A. G. M.; Weipert, P. D.; Dhanak, D.; Husa, R. K.; Lebold, S. A. *J. Am. Chem. Soc.* **1991**, *113*, 9820.
61. Barrett, A. G. M.; Rys, D. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1009.
62. Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853.
63. Barrett, A. G. M.; Braddock, D. C.; Christian, P. W. N.; Philipauskas, D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 5818.
64. Kim, D. Y.; Lee, K.; Oh, D. Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2451.
65. Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Gazz. Chim. It.* **1995**, *125*, 223.
66. Bäckvall, J.-E.; Ericsson, A. M.; Plobeck, N. A.; Juntunen, S. K. *Tetrahedron Lett.* **1992**, *33*, 131.
67. Williams, D. R.; Brugel, T. A. *Org. Lett.* **2000**, *2*, 1023.
68. Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9297.
69. Palomo, C.; Aizpurua, J. M.; Cossío, F.; García, J. M.; López, M. C.; Oiarbide, M. *J. Org. Chem.* **1990**, *55*, 2070.
70. Ballini, R.; Bosica, G. *Synthesis* **1994**, 723.
71. Magnus, P.; Pye, P. *J. Chem. Soc., Chem. Commun.* **1995**, 1933.
72. Magnus, P.; Booth, J.; Diorazio, L.; Donohoe, T.; Lynch, V.; Magnus, N.; Mendoza, J.; Pye, P.; Tarrant, J. *Tetrahedron* **1996**, *52*, 14103.
73. Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5431.
74. Menicagli, R.; Samaritani, S. *Tetrahedron* **1996**, *52*, 1425.
75. Reid, J. G.; Runge, J. M. R. *Tetrahedron Lett.* **1990**, *31*, 1093.
76. Kawakami, T.; Suzuki, H. *Tetrahedron Lett.* **1999**, *40*, 1157.
77. Adam, W.; Mąkosza, M.; Staliński, K.; Zhao, C.-G. *J. Org. Chem.* **1998**, *63*, 4390.
78. Mąkosza, M.; Surowiek, M. *Tetrahedron* **2003**, *59*, 6261.
79. Adam, W.; Mąkosza, M.; Zhao, C.-G.; Surowiek, M. *J. Org. Chem.* **2000**, *65*, 1099.
80. Tokunaga, Y.; Yagihashi, M.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, 955.
81. Trost, B. M.; Stenkamp, D.; Pulley, S. R. *Chem. Eur. J.* **1995**, *1*, 568.
82. Zhang, D.; Ghosh, A.; Süling, C.; Miller, M. J. *Tetrahedron Lett.* **1996**, *37*, 3799.
83. Rajappan, V. P.; Yin, X.; Schneller, S. W. *Tetrahedron* **2002**, *58*, 9889.
84. Schink, H. E.; Bäckvall, J.-E. *J. Org. Chem.* **1992**, *57*, 1588.
85. Trost, B. M.; Madsen, R.; Guile, S. D. *Tetrahedron Lett.* **1997**, *38*, 1707.
86. Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947.
87. Trost, B. M.; Madsen, R.; Guile, S. D.; Elia, A. E. H. *Angew.Chem. Int. Ed.* **1996**, *35*, 1569.
88. Trost, B. M.; Patterson, D. E.; Hembre, E. J. *Chem. Eur. J.* **2001**, *7*, 3768.
89. Degnan, A. P.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3503.
90. Newman, H.; Angier, R. B. *Tetrahedron* **1970**, *26*, 825.
91. Vankar, Y. D.; Shah, K.; Bawa, A.; Singh, S. P. *Tetrahedron* **1991**, *47*, 8883.
92. Chakraborty, R.; Das, A. R.; Ranu, B. C. *Synth. Commun.* **1992**, *22*, 1523.
93. Kim, D. Y.; Kong, M. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3359.
94. Jackson, R. F. J.; Kirk, J. M.; Palmer, N. J.; Waterson, D.; Wythes, M. J. *J. Chem. Soc., Chem. Commun.* **1993**, 889.
95. Jackson, R. F. J.; Palmer, N. J.; Wythes, M. J. *J. Chem. Soc., Chem. Commun.* **1994**, 95.
96. Jackson, R. F. J.; Palmer, N. J.; Wythes, M. J.; Clegg, W.; Elsegood, M. R. J. *J. Org. Chem.* **1995**, *60*, 6431.
97. Jackson, R. F. J.; Palmer, N. J.; Wythes, M. J. *Tetrahedron Lett.* **1994**, *35*, 7433.
98. Ambroise, L.; Jackson, R. F. W. *Tetrahedron Lett.* **1996**, *37*, 2311.
99. Adams, Z. M.; Jackson, R. F. J.; Palmer, N. J.; Rami, H. K.; Wythes, M. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 937.
100. Dumez, E.; Szeki, A.; Jackson, R. F. W. *Synlett* **2001**, 1214.
101. Ballini, R. *Synlett* **1999**, 1009.
102. Ballini, R.; Bosica, G. *Tetrahedron* **1997**, *53*, 16131.
103. Ballini, R.; Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Synlett* **1998**, 1149.
104. Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E.; Righi, P. *Org. Prep. Proc. Int.* **1990**, *22*, 707.
105. Ballini, R.; Bosica, G.; Gigli, F. *Tetrahedron* **1998**, *54*, 7573.
106. Ballini, R.; Petrini, M.; Polzonetti, V. *Synthesis* **1992**, 355.
107. Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831.
108. Ghosh, A. K.; Fidanze, S. *Org. Lett.* **2000**, *2*, 2405.
109. Hauser, F. M.; Sengupta, D.; Corlett, S. A. *J. Org. Chem.* **1994**, *59*, 1967.
110. Kodukulla, R. P. K.; Trivedi, G. K.; Vora, J. D.; Mathur, H. H. *Synth. Commun.* **1994**, *24*, 819.
111. Hughes, C. C.; Trauner, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4556.
112. Kalita, D.; Khan, A. T.; Saikia, A. K.; Bez, G.; Barua, N. C. *Synthesis* **1998**, 975.
113. Kalita, D.; Khan, A. T.; Barua, N. C.; Bez, G. *Tetrahedron* **1999**, *55*, 5177.
114. Fuji, K.; Zheng, S.-Z.; Node, M.; Hao, X.-J. *Chem. Pharm. Bull.* **1991**, *39*, 202.
115. Hao, X.; Node, M.; Fuji, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1505.
116. Katoh, T.; Nishide, K.; Node, M.; Ogura, H. *Heterocycles* **1999**, *50*, 833.
117. Nishide, K.; Katoh, T.; Imazato, H.; Node, M. *Heterocycles* **1998**, *47*, 839.
118. Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951.
119. Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249.

120. Capecchi, T.; de Koning, C. B.; Michael, J. P. *Tetrahedron Lett.* **1998**, *39*, 5429.
121. Capecchi, T.; de Koning, C. B.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2681.
122. Monti, D.; Gramatica, P.; Speranza, G.; Manitto, P. *Tetrahedron Lett.* **1983**, *24*, 417.
123. Ballini, R.; Marcantoni, E.; Petrini, M. *Liebigs Ann.* **1995**, 1381.
124. Ballini, R.; Bosica, G.; Rafaiani, G. *Helv. Chim. Acta* **1995**, *78*, 879.
125. Ballini, R.; Gil, M. V.; Fiorini, D.; Palmieri, A. *Synthesis* **2003**, 665.
126. Ballini, R.; Bartoli, G. *Synthesis* **1993**, 965.
127. Ballini, R.; Bosica, G. *J. Chem. Res. (S)* **1993**, 435.
128. Crombie, L.; Heavers, A. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2683.
129. Trost, B. M.; Dirat, O.; Dudash, J.; Hembre, E. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3658.
130. Trost, B. M.; Dudash, J.; Dirat, O. *Chem. Eur. J.* **2002**, *8*, 259.
131. Ono, N.; Ramura, R.; Tanikaga, R.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1981**, 71.
132. Barton, D. H. R.; Togo, H.; Zard, S. Z. *Tetrahedron* **1985**, *41*, 5507.
133. Garner, P.; Leslie, R.; Anderson, J. T. *J. Org. Chem.* **1996**, *61*, 6754.
134. Ballini, R.; Petrini, M.; Rosini, G. *Tetrahedron* **1990**, *46*, 7531.
135. Ballini, R.; Bosica, G.; Uselli, A. *J. Heterocycl. Chem.* **1994**, *31*, 259.
136. Occhiato, E. G.; Guarna, A.; De Sarlo, F.; Scarpi, D. *Tetrahedron: Asymmetry* **1995**, *6*, 2971.
137. Bez, G.; Bezbarua, M. S.; Saikia, A. K.; Barua, N. C. *Synthesis* **2000**, 537.
138. Ballini, R.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3159.
139. Ballini, R.; Bosica, G.; Schaafstra, R. *Liebigs Ann. Chem.* **1994**, 1235.
140. Stanchev, S.; Milenkov, B.; Hesse, M. *Tetrahedron Lett.* **1993**, *34*, 6107.
141. Hadj-Abo, F.; Hesse, M. *Helv. Chim. Acta* **1992**, *75*, 1834.
142. Hadj-Abo, F.; Bienz, S.; Hesse, M. *Tetrahedron* **1994**, *50*, 8665.
143. Stanchev, S.; Hesse, M. *Helv. Chim. Acta* **1990**, *73*, 460.
144. Bezbarua, M. S.; Saikia, A. K.; Barua, N. C.; Kalita, D.; Ghosh, A. C. *Synthesis* **1996**, 1289.
145. Sabelle, S.; Lucet, D.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1998**, *39*, 2111.
146. Lucet, D.; Sabelle, S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583.
147. Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699.
148. Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 1236.
149. Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875.
150. Trost, B. M.; Yeh, V. C. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 861.
151. Mineno, T.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 6591.
152. Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901.
153. Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38*, 1418.
154. Sasai, H.; Kim, W.-S.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 6123.
155. Taylor, E. C.; Liu, B. *Tetrahedron Lett.* **1999**, *40*, 4023.
156. Taylor, E. C.; Liu, B. *Tetrahedron Lett.* **1999**, *40*, 4027.
157. Yao, C.-F.; Kao, K.-H.; Liu, J.-T.; Chu, C.-M.; Wang, Y.; Chen, W.-C.; Lin, Y.-M.; Lin, W.-W.; Yan, M.-C.; Liu, J.-Y.; Chuang, M.-C.; Shiue, J.-L. *Tetrahedron* **1998**, *54*, 791.
158. Santos, R. P.; Lopes, R. S. C.; Lopes, C. C. *Synthesis* **2001**, 845.
159. Menicagli, R.; Guagnano, V.; Samaritani, S. *Tetrahedron Lett.* **1995**, *36*, 9531.
160. Bartoli, G.; Bosco, M.; Sambri, L.; Marcantoni, E. *Tetrahedron Lett.* **1994**, *35*, 8651.
161. Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.
162. Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192.
163. Thominiaux, C.; Roussé, S.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2015.
164. Miyashita, M.; Tanaka, D.; Shiratani, T.; Irie, H. *Chem. Pharm. Bull.* **1992**, *40*, 1614.
165. Miyashita, M.; Awen, B. Z. E.; Yoshikoshi, A. *Synthesis* **1990**, 563.
166. Bartoli, G.; Bosco, M.; Dalpozzo, R.; De Nino, A.; Palmieri, G. *Tetrahedron* **1994**, *50*, 9831.
167. Johnson, T. A.; Curtis, M. D.; Beak, P. *Org. Lett.* **2002**, *4*, 2747.
168. Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853.
169. Hübner, J.; Liebscher, J.; Pätzel, M. *Tetrahedron* **2002**, *58*, 10485.
170. Awen, B. Z. E.; Miyashita, M.; Shiratani, T.; Yoshikoshi, A.; Irie, H. *Chem. Lett.* **1992**, 767.
171. Enders, D.; Berner, O. M.; Vignola, N.; Harnying, W. *Synthesis* **2002**, 1945.
172. Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2002**, 2725.
173. Lui, K.-H.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 457.
174. Lee, W. Y.; Jang, S. Y.; Chae, W. K.; Park, O. S. *Synth. Commun.* **1993**, *23*, 3037.
175. Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Gil, M. V. *Synlett* **2002**, 1706.
176. Chamakh, A.; M'hirsi, M.; Villiéras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295.
177. Ballini, R.; Bosica, G.; Livi, D. *Synthesis* **2001**, 1519.
178. Dromowicz, M.; Köll, P. *Carbohydr. Res.* **1998**, *308*, 169.
179. Petrušová, M.; Lattová, E.; Matulová, M.; Petruš, L.; BeMiller, J. N. *Carbohydr. Res.* **1996**, *283*, 73.
180. Wada, E.; Yoshinaga, M. *Tetrahedron Lett.* **2003**, *44*, 7953.

Biographical sketch

Roberto Ballini received an SB degree in Chemistry from the University of Camerino—Italy. After an experience at a Petrolchemical Industry (ENI-ANIC, Ravenna), he began the academic career in 1975 at the University of Camerino as Research Fellowship. Then, he became Assistant Professor in 1978, then promoted to Associate Professor in Organic Chemistry and then full Professor (Organic Chemistry) in 2000. Recent research interests include the chemistry of aliphatic nitrocompounds, the formation and cleavage of C,C bond, the studies and application of heterogeneous catalysis, the synthesis of natural products, and the use of aqueous medium in organic reactions.

Marino Petrini took his Laurea degree in Chemistry in 1980 (University of Camerino). In 1983 he became Research Associate in organic chemistry at the University of Camerino and during the period 1987–88 he has been visiting scientist at the University of Montreal (Professor S. Hanessian). Since 1992 he is Associate Professor in organic chemistry at the University of Camerino. His research interests mainly deal with the following topics: synthesis and reactivity of aliphatic and aromatic nitrocompounds towards the preparation of simple and multiple carbon–carbon bonds; reactivity of organometallic reagents towards carbon and nitrogen electrophiles; synthesis of natural products featured of enhanced biological activity; synthesis and reactivity of functionalised sulfones for the preparation of amino derivatives.

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A novel route to substituted 3-methylidenechroman-2-ones and 3-methylchromen-2-ones

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Abstract—3-Methylidenechroman-2-ones, or their rearrangement products 3-methylchromen-2-ones, were efficiently synthesized by Michael addition of various nucleophiles to 3-diethoxyphosphorylchromen-2-ones followed by Horner–Wadsworth–Emmons reaction of the adducts with formaldehyde. Relative configuration and conformation of the intermediate adducts were studied using NMR spectroscopy and semiempirical PM3 calculations.
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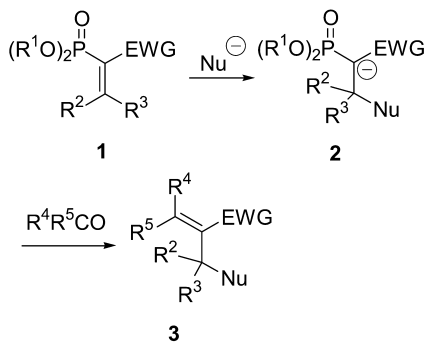
1. Introduction

The synthetic utility of vinylphosphonates **1** containing electron-withdrowing groups in the α-position is well recognized.[1] For example they accept various nucleophiles to give adducts **2** which are excellent reagents for the olefination of carbonyl compounds to yield **3** (Scheme 1). Recently we employed this reaction sequence to synthesize a series of substituted 3-alkylidenedihydro-2-furanones.[2]

Now we present another example showing the potential of this methodology, this time in the synthesis of 3-methylidenechroman-2-ones **7** (3-methylidene-3,4-dihydrocoumarins) or their rearrangement products 3-methylchromen-2-ones **8**.



Scheme 1.

3-Methylidenechroman-2-ones belong to a biologically important class of α-methylidene γ- and δ-lactones.[3] So far, their synthesis has been accomplished by reductive amination of the 3-formylchroman-2-one,[4] elimination of a phenylselenyl residue from 3-phenylselenylmethylchroman-2-one[5] or employing the Claisen rearrangement of α-aryloxymethylacrylates followed by lactonization of the rearrangement product.[6–11] Also, intra- or intermolecular Horner–Wadsworth–Emmons reaction were used to synthesize 2,9*b*-dihydro-1*H*-cyclopenta[c]chromen-4-one[12] or various 3-arylidenechroman-2-ones respectively.[13]

2. Results and discussion

Details of our method are presented in Scheme 2.

The starting 3-diethoxyphosphorylchromen-2-ones **4a**,**b** are known and can be easily prepared by reaction of ethyl diethoxyphosphorylacetate with corresponding aromatic hydroxyaldehydes.[13] On the other hand, additions of nucleophiles to **4**, except 2-([1,3]dioxolan-2-yl)ethylmagnesium bromide,[12] have not been investigated so far. Therefore we decided to test the effectiveness of various nucleophiles **5** in this reaction. Additions of different Grignard reagents in the presence of CuI catalyst, as well as sodium salts of diethyl phosphite and nitromethane proceeded smoothly to give, after standard work up, the crude adducts **6** which were purified by column chromatography. As it turned out, the use of 3 to 5 fold excess of the Grignard reagent improved the yield significantly. Results are given in the Table 1. Unfortunately the sodium salt of diethyl malonate and enamines, generated in situ from carbonyl compound (acetone, cyclohexanone) and proline,

Keywords: Chroman-2-ones; Michael addition; Horner–Wadsworth–Emmons olefination.
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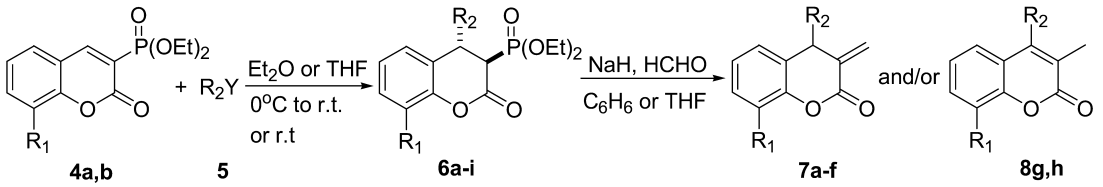

Scheme 2.

Table 1. Synthesis of the adducts **6**, 3-methylidenechroman-2-ones **7** and 3-methylchromen-2-ones **8**

Compound	R_1	R_2Y **5** (equivalents of nucleophile)	**6** Yield (%)[a]	**7** Yield (%)[a]	**8** Yield (%)[a]
a	H	MeMgI (3)	85[b]	71[c]	–
b	OMe	MeMgI (5)	73[b]	68[c]	–
c	H	*n*-BuMgBr (3)	82[b]	58[c]	–
d	OMe	*n*-BuMgBr (5)	91[b]	89[c]	–
e	H	CH_2=CHMgBr (3)	71[d]	55[e]	–
f	OMe	CH_2=CHMgBr (3)	75[d]	50[e]	–
g	H	$(EtO)_2P(O)Na$ (1)	73	–	63[c]
h	OMe	$(EtO)_2P(O)Na$ (1)	50	–	40[c]
i	H	O_2NCH_2Na (1.5)	58	–	–

[a] Yields of pure, isolated products based on **4** or **5**, respectively.
[b] Grignard reagent prepared from the corresponding alkyl halide and magnesium in Et_2O was used.
[c] Reaction was performed in refluxing benzene.
[d] Commercially available vinylmagnesium bromide, 1.0 M solution in THF was used (FLUKA®).
[e] Reaction was performed in THF at rt.

were ineffective as nucleophiles in the addition reactions and only starting materials were recovered. Adducts **6** were always formed as single diastereoisomers. Since, in this type of Michael additions, thermodynamic control is usually observed[2,14] we expected that *trans* isomers would be formed. Careful analysis of ^1H, ^{13}C and ^{31}P NMR spectra of the adducts **6** fully confirmed their structure and the anticipated stereochemistry. This analysis allowed us also to propose the preferred conformation of the dihydropyranone ring with phosphoryl and R_2 groups in *pseudo*-axial positions (Fig. 1). In particular, the $^3J_{H3-H4}$ coupling constants were very small (0.8–1.3 Hz), the $^3J_{P-C11}$ couplings were large (17.1–18.9 Hz), and there was an absence of $^3J_{P-C10}$ couplings. Dihedral angels estimated from these coupling constants, using Karplus equation, had values ~90°, ~150° or ~50° and ~90°, respectively. Characteristic coupling constants for **6a** were as follows: $^3J_{H3-H4}$=1.0 Hz, $^3J_{P-H4}$=12.0 Hz, $^3J_{P-C10}$=0.0 Hz and $^3J_{P-C11}$=18.6.

Interesting features present in the ^1H NMR spectra of all adducts **6**, were that protons of one of the ethoxy groups absorbed at an unexpectedly low frequency, e.g., in **6a**, the methyl protons of one of the ethoxy groups had a chemical shift 0.82 ppm as compared to 1.25 ppm for the other. To rationalize these observations, analysis was performed of the heat of formation dependence on the dihedral angle H3–C3–P–O (rotation around the P–C bond) for **6a**. Global energetic minimum has been identified using PM3 Hamiltonian[15] as implemented in Ampac 6.7.[16] The structure representing this minimum is shown on Figure 2. In this structure, the methyl and phosphoryl groups are in diaxial arrangement, with P–C3–C4-Me dihedral angle around 140°. This is in accord with the presented NMR data. Furthermore, H3–C3–P–O dihedral angle has value of 94°, which gives an almost exactly antiparallel array of P=O and C=O bonds and therefore minimizes interactions between these polar groups. In this arrangement one of the ethoxy groups is placed in the shielding area of the carbonyl bond and/or benzene ring. These results provide a plausible explanation of the observed low chemical shift of the methyl and methylene protons for one of the ethoxy groups in **6a**. We believe that this rationalization is valid also for the other adducts **6**.

Adducts **6a–i** were next employed in Horner–Wadsworth–Emmons olefination of formaldehyde. Best results were obtained using sodium hydride as a base and 3 equiv. of paraformaldehyde in refluxing benzene. In these conditions adducts **6** were transformed into the expected 3-methylidenechroman-2-ones **7** and/or into their rearrangement products 3-methylchromen-2-ones **8**. Only adduct **6i** gave

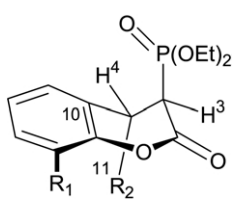

Figure 1. Preferred conformation of the dihydropyranone ring in adducts **6**.

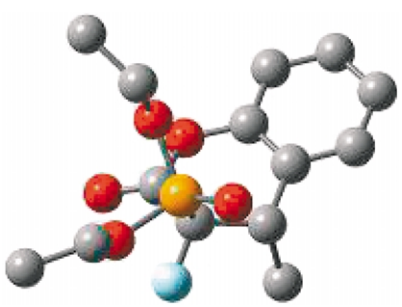

Figure 2. Structure representing global energetic minimum for adduct **6a**.

a complex mixture of products which were difficult to identify. Crude products were purified by column chromatography. Yields are shown in Table 1.

Olefinations performed with adducts **6a**–**d** yielded corresponding 3-methylidenechromanones **7a**–**d**, whereas these performed with adducts **6g**,**h** gave 3-methylchromenones **8g**,**h**, as the only products. On the other hand, reactions with adducts **6e** and **6f** were not chemoselective and mixtures of **7e/8e** and **7f/8f** in 3:7 and 7:3 ratios were obtained, respectively. However, we were pleased to observe that when reactions of **6e**,**f** were performed at room temperature, in THF as a solvent, almost no rearrangement took place and the yields were still good (Table 1). In these conditions adduct **6e** gave a mixture of **7e** and **8e** in 95:5 ratio. This mixture was easily separated by column chromatography to give pure **7e**. Reaction of **6f** gave chromanone **7f** and no detectable amounts of the rearrangement product. Structures of all chromanones **7** and chromenones **8** were unequivocally confirmed by their ^{1}H and ^{13}C NMR spectra.

3. Conclusions

In summary, we have shown that Michael addition of various nucleophiles to 3-diethoxyphosphorylchromen-2-ones **4a**,**b** combined with Horner–Wadsworth–Emmons reaction of the adducts **6** with formaldehyde is a convenient tool for the synthesis of 3-methylidenechroman-2-ones **7** or 3-methylchromen-2-ones **8**. The relative configuration and preferred conformation of the intermediate adducts **6** was also elucidated on the basis of ^{1}H and ^{13}C NMR spectra and semiempirical PM3 calculations.

4. Experimental

4.1. General

Organic solvents and reagents were purified by the appropriate standard procedures.[17] IR spectra were recorded on a Specord M80 spectrometer. ^{1}H NMR (250 MHz), ^{13}C NMR (62.9 MHz) and ^{31}P NMR (101 MHz) spectra were recorded on a Bruker DPX-250 spectrometer with TMS as an internal standard and 85% H_3PO_4 as an external standard, respectively. ^{31}P NMR spectra were recorded using broad band proton decoupling. Column chromatography was performed on FLUKA® silica gel 60 (230–400 mesh).

All Grigard reagents, but vinylmagnesium bromide, were prepared from corresponding alkyl halides and magnesium in Et_2O. Vinylmagnesium bromide was purchased from FLUKA®. 3-Diethoxyphosphorylchromen-2-ones **4a**,**b** were prepared using previously reported procedure.[13]

4.2. General procedure for the preparation of 3-diethoxyphosphorylchroman-2-ones 6a–f

To a solution of chromenone **4** (3.5 mmol) and a catalytic amount of CuI (0.034 g, 0.18 mmol) in Et_2O (20 mL), a solution of Grignard reagent (excesses are given in Table 1) was added dropwise, under argon atmosphere, at 0 °C. When the addition was completed the solution was warmed to room temperature and stirred for 2.5 h. After this time the reaction mixture was quenched with water (2 mL), acidified to pH~1.5 with 10% HCl solution and extracted with $CHCl_3$ (4×10 mL). The organic extracts were washed with water (10 mL) and dried over $MgSO_4$. Evaporation of the solvent gave crude product which was purified by column chromatography and/or by crystallization.

4.2.1. *trans*-3-Diethoxyphosphoryl-4-methylchroman-2-one (6a). Yield 0.89 g, 85%; white prisms (from EtOAc/hexane); mp 110–111 °C; ^{31}P NMR δ (ppm) 19.01; ^{1}H NMR δ (ppm) 0.82 (t, 3H, $^{3}J_{HH}$=7.3 Hz, C H_3CH_2O), 1.22 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.24 (d, 3H, $^{3}J_{HH}$=7.3 Hz, C H_3CH), 3.25 (dd, 1H, $^{2}J_{HP}$=25.0 Hz, $^{3}J_{HH}$=1.0 Hz, CHC H P), 3.38 (ddq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HP}$=9.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3C H HO), 3.61 (ddq, 1H, $^{3}J_{HP}$=12.0 Hz, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{HH}$=1.0 Hz, C H CHP), 3.70 (ddq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{HP}$=7.3 Hz, CH_3CH H O), 4.05 (dq, 2H, $^{3}J_{HP}$=8.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3C H_2O), 6.95–7.22 (m, 4H, C_6H_4); $^{1}H\{^{31}P\}$ NMR δ (ppm) 0.82 (t, 3H, $^{3}J_{HH}$=7.3 Hz, C H_3CH_2O), 1.22 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.24 (d, 3H, $^{3}J_{HH}$=7.3 Hz, C H_3CH), 3.25 (d, 1H, $^{3}J_{HH}$=1.0 Hz, CHC H P), 3.38 (dq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3C H HO), 3.61 (dq, 1H, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{HH}$=1.0 Hz, C H CHP), 3.70 (dq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HH}$=7.3 Hz, CH_3CH H O), 4.05 (q, 2H, $^{3}J_{HH}$=7.0 Hz, CH_3C H_2O), 6.35–7.22 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 15.86 (d, $^{3}J_{CP}$=6.2 Hz, C H_3CH_2OP), 16.21 (d, $^{3}J_{CP}$=6.3 Hz, C H_3CH_2OP), 23.68 (d, $^{3}J_{CP}$=18.6 Hz, C H_3CHCHP), 32.44 (d, $^{2}J_{CP}$=4.4 Hz, CH_3C HCHP), 47.23 (d, $^{1}J_{CP}$=127.8 Hz, CH_3CH C HP), 62.88 (d, $^{2}J_{CP}$=7.1 Hz, CH_3C H_2OP), 63.19 (d, $^{2}J_{CP}$=6.7 Hz, CH_3C H_2OP), 116.68 (s, C_6H_4), 124.95 (s, C_6H_4), 125.61 (s, C_6H_4), 127.84 (s, C_6H_4), 128.51 (s, C_6H_4), 150.89 (s, C_6H_4), 163.75 (d, $^{2}J_{CP}$=6.3 Hz, C=O); IR (cm^{-1}, film) 1772 (C=O), 1260 (P=O), 1028 (P–O). Anal. calcd for $C_{14}H_{19}O_5P$ (298.28) C, 56.38; H, 6.42; P, 10.38. Found C, 56.22; H, 6.48; P, 10.20.

4.2.2. *trans*-3-Diethoxyphosphoryl-8-methoxy-4-methylchroman-2-one (6b). Yield 0.84 g, 73%; light yellow prisms (from EtOAc/hexane); mp 107–108 °C; ^{31}P NMR δ (ppm) 18.53; ^{1}H NMR δ (ppm) 0.91 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.32 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.33 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH), 3.31 (dd, 1H, $^{2}J_{HP}$=25.0 Hz, $^{3}J_{HH}$=0.8 Hz, CHC H P), 3.46 (ddq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HP}$=9.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3CH H O), 3.54–3.67 (m, 1H, C H CHP), 3.79 (ddq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HH}$=7.0 Hz, $^{3}J_{HP}$=7.0 Hz, CH_3C H HO), 3.89 (s, 3H, C H_3O), 4.12 (dq, 2H, $^{3}J_{HP}$=8.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3C H_2O), 6.82–7.11 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 15.49 (d, $^{3}J_{CP}$=6.4 Hz, C H_3CH_2OP), 15.92 (d, $^{3}J_{CP}$=6.3 Hz, C H_3CH_2OP), 23.10 (d, $^{3}J_{CP}$=18.6 Hz, C H_3CHCHP), 32.35 (d, $^{2}J_{CP}$=4.3 Hz, CH_3C HCHP), 46.78 (d, $^{1}J_{CP}$=128.0 Hz, CH_3CH C HP), 55.87 (s, C H_3O), 62.47 (d, $^{2}J_{CP}$=11.0 Hz, CH_3C H_2OP), 62.89 (d, $^{2}J_{CP}$=6.7 Hz, CH_3C H_2OP), 111.05 (s, C_6H_3), 119.02 (s, C_6H_3), 124.67 (s, C_6H_3), 126.36 (s, C_6H_3), 139.84 (s, C_6H_3), 147.15 (s, C_6H_3), 162.89 (d, $^{2}J_{CP}$=6.3 Hz, C=O); IR (cm^{-1}, film) 1756 (C=O), 1216 (P=O), 1068 (P–O). Anal. calcd for $C_{15}H_{21}O_6P$ (328.30) C, 54.88; H, 6.45; P, 9.43. Found C, 54.95; H, 6.58; P, 9.31.

4.2.3. *trans*-3-Diethoxyphosphoryl-4-butylchroman-2-one (6c). Yield 0.89 g, 82%; oil; (eluent EtOAc/hexane=9/

1); ^{31}P NMR δ (ppm) 19.31; ^{1}H NMR δ (ppm) 0.79 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C $H_3(CH_2)_2CH_2$), 0.82 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.19–1.32 (m, 4H, $CH_3(CH_2)_2CH_2$), 1.25 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.47–1.56 (m, 2H, $CH_3(CH_2)_2C$ H_2), 3.33 (dd, 1H, $^{2}J_{HP}$=24.5 Hz, $^{3}J_{HH}$=0.8 Hz, CHC *H* P), 3.36 (m, 1H, CH_3CH *H* O), 3.38 (m, 1H, C *H* CHP), 3.69 (ddq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HH}$=7.0 Hz, $^{3}J_{HP}$=7.0 Hz, CH_3C *H* HO), 4.05 (dq, 2H, $^{3}J_{HP}$=8.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3C H_2O), 6.95–7.21 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 13.45 (s, *C* $H_3(CH_2)_2CH_2$), 15.48 (d, $^{3}J_{CP}$=6.1 Hz, *C* H_3CH_2OP), 15.80 (d, $^{3}J_{CP}$=6.2 Hz, *C* H_3CH_2OP), 21.94 (s, CH_3C $H_2CH_2CH_2$), 28.10 (s, CH_3CH_2C H_2CH_2), 36.32 (d, $^{3}J_{CP}$=17.1 Hz, $CH_3(CH_2)_2C$ H_2), 36.90 (d, $^{2}J_{CP}$=4.3 Hz, *C* HCHP), 45.36 (d, $^{1}J_{CP}$=127.9 Hz, CH *C* HP), 62.45 (d, $^{2}J_{CP}$=7.0 Hz, CH_3C H_2OP), 62.74 (d, $^{2}J_{CP}$=6.7 Hz, CH_3C H_2OP), 116.26 (s, C_6H_4), 123.98 (s, C_6H_4), 124.19 (s, C_6H_4), 128.14 (s, C_6H_4), 128.37 (s, C_6H_4), 150.75 (s, C_6H_4), 163.55 (d, $^{2}J_{CP}$=6.0 Hz, *C*=O); IR (cm^{-1}, film) 1768 (*C=O*), 1224 (*P=O*), 1020 (*P–O*). Anal. calcd for $C_{17}H_{25}O_5P$ (340.36) C, 59.99; H, 7.40; P, 9.10. Found C, 60.17; H, 7.32; P, 9.14.

4.2.4. *trans*-3-Diethoxyphosphoryl-8-methoxy-4-butylchroman-2-one (6d). Yield 1.18 g, 91%; oil; (eluent $CHCl_3$); ^{31}P NMR δ (ppm) 18.83; ^{1}H NMR δ (ppm) 0.86 (t, 3H, $^{3}J_{HH}$=6.8 Hz, C $H_3(CH_2)_2CH_2$), 0.91 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.25–1.39 (m, 4H, $CH_3(CH_2)_2$-CH_2), 1.32 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.51–1.62 (m, 2H, $CH_3(CH_2)_2C$ H_2), 3.37–3.44 (m, 1H, CH_3CH *H* O), 3.39 (dd, 1H, $^{2}J_{HP}$=25.5 Hz, $^{3}J_{HH}$=1.0 Hz, CHC *H* P), 3.44–3.53 (m, 1H, C *H* CHP), 3.79 (ddq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HH}$=7.0 Hz, $^{3}J_{HP}$=7.0 Hz, CH_3C *H* HO), 3.89 (s, 3H, C H_3O), 4.12 (dq, 2H, $^{3}J_{HP}$=8.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3C H_2O), 6.78–7.07 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 13.60 (s, *C* $H_3(CH_2)_2CH_2$), 15.53 (d, $^{3}J_{CP}$=6.4 Hz, *C* H_3CH_2OP), 15.94 (d, $^{3}J_{CP}$=6.3 Hz, *C* H_3CH_2OP), 22.12 (s, CH_3C $H_2CH_2CH_2$), 28.32 (s, CH_3CH_2C H_2CH_2), 36.26 (d, $^{3}J_{CP}$=17.1 Hz, $CH_3(CH_2)_2C$ H_2), 37.23 (d, $^{2}J_{CP}$=4.3 Hz, *C* HCHP), 45.35 (d, $^{1}J_{CP}$=128.3 Hz, CH *C* HP), 55.88 (s, *C* H_3O), 62.64 (d, $^{2}J_{CP}$=7.0 Hz, CH_3C H_2OP), 62.93 (d, $^{2}J_{CP}$=6.7 Hz, CH_3C H_2OP), 111.08 (s, C_6H_3), 120.05 (s, C_6H_3), 124.31 (s, C_6H_3), 125.17 (s, C_6H_3), 140.11 (s, C_6H_3), 147.19 (s, C_6H_3), 163.21 (d, $^{2}J_{CP}$=5.7 Hz, *C*=O); IR (cm^{-1}, film) 1760 (*C=O*), 1216 (*P=O*), 1020 (*P–O*). Anal. calcd for $C_{18}H_{27}O_6P$ (370.39) C, 58.37; H, 7.35; P, 8.36. Found C, 58.19; H, 7.46; P, 8.33.

4.2.5. *trans*-3-Diethoxyphosphoryl-4-vinylchroman-2-one (6e). Yield 0.77 g, 71%; eluent $CHCl_3$/acetone 95/5, white prisms (from AcOEt/hexane); mp 64–68 °C; ^{31}P NMR δ (ppm) 18.66; ^{1}H NMR δ (ppm) 0.91 (t, 3H, $^{3}J_{HH}$=7.3 Hz, C H_3CH_2O), 1.34 (t, 3H, $^{3}J_{HH}$=7.3 Hz, CH_3CH *H* O), 3.49 (dd, 1H, $^{2}J_{HP}$=25.0 Hz, $^{3}J_{HH}$=1.3 Hz, CHC *H* P), 3.79 (qdd, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HH}$=7.3 Hz, $^{3}J_{HP}$=7.3 Hz, CH_3C *H* HO), 4.14 (dq, 2H, $^{3}J_{HP}$=8.0 Hz, $^{3}J_{HH}$=7.3 Hz, CH_3C H_2O), 4.18–4.22 (m, 1H, C *H* CHP), 4.92 (dd, 1H, $^{3}J_{HH}$=17.0 Hz, $^{4}J_{HH}$=1.5 Hz, C *H* H=CH), 5.13 (dd, 1H, $^{3}J_{HH}$=10.3 Hz, $^{4}J_{HH}$=1.0 Hz, CH *H*=CH), 5.89 (2dd, 1H, $^{3}J_{HH}$=17.0 Hz, $^{3}J_{HH}$=10.3 Hz, $^{3}J_{HH}$=6.0 Hz, $^{3}J_{HH}$=6.0 Hz, CH_2=C *H*), 7.05–7.28 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 15.50 (d, $^{3}J_{CP}$=6.1 Hz, *C* H_3CH_2OP), 15.82 (d, $^{3}J_{CP}$=6.3 Hz, *C* H_3CH_2OP), 40.07 (d, $^{2}J_{CP}$=3.5 Hz, *C* HCHP), 44.94 (d, $^{1}J_{CP}$=127.2 Hz, CH *C* HP), 62.67 (d, $^{2}J_{CP}$=7.0 Hz, CH_3C H_2OP), 62.97 (d, $^{2}J_{CP}$=6.7 Hz, CH_3C H_2OP), 116.25 (s, *C* H_2=CHCH), 116.32 (s, C_6H_4), 121.43 (s, C_6H_4), 124.63 (s, C_6H_4), 128.42 (s, C_6H_4), 128.69 (s, C_6H_4), 137.07 (d, $^{3}J_{CP}$=18.5 Hz, CH_2=*C* HCH), 151.00 (s, C_6H_4), 162.85 (d, $^{2}J_{CP}$=5.9 Hz, *C*=O); IR (cm^{-1}, film) 1768 (*C=O*), 1640 (*C=C*), 1256 (*P=O*), 1024 (*P–O*). Anal. calcd for $C_{15}H_{19}O_5P$ (310.29) C, 58.06; H, 6.17; P, 9.98. Found C, 58.17; H, 6.12; P, 9.73.

4.2.6. *trans*-3-Diethoxyphosphoryl-8-methoxy-4-vinylchroman-2-one (6f). Yield 0.89 g, 75%; eluent AcOEt, light yellow prisms (from AcOEt/hexane); mp 60–63 °C; ^{31}P NMR δ (ppm) 18.50; ^{1}H NMR δ (ppm) 0.92 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.33 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 3.44–3.49 (m, 1H, CH_3CH *H* O), 3.49 (dd, 1H, $^{2}J_{HP}$=24.8 Hz, $^{3}J_{HH}$=0.8 Hz, CHC *H* P), 3.79 (ddq, 1H, $^{2}J_{HH}$=10.0 Hz, $^{3}J_{HP}$=7.3 Hz, $^{3}J_{HH}$=7 Hz, CH_3C *H* HO), 3.89 (s, 3H, C H_3O), 4.13 (dq, 2H, $^{3}J_{HP}$=8.0 Hz, $^{3}J_{HH}$=7.0 Hz, CH_3CH *H* O), 4.17–4.21 (m, 1H, C *H* CHP), 4.92 (dd, 1H, $^{3}J_{HH}$=17.0 Hz, $^{4}J_{HH}$=1.5 Hz, C *H* H=CH), 5.13 (dd, 1H, $^{3}J_{HH}$=10.0 Hz, $^{4}J_{HH}$=0.8 Hz, CH *H*=CH), 5.88 (2dd, 1H, $^{3}J_{HH}$=17.0 Hz, $^{3}J_{HH}$=10.3 Hz, $^{3}J_{HH}$=6.0 Hz, $^{3}J_{HH}$=6.0 Hz, CH_2=C *H*), 6.82–7.10 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 15.65 (d, $^{3}J_{CP}$=6.5 Hz, *C* H_3CH_2OP), 16.08 (d, $^{3}J_{CP}$=6.3 Hz, *C* H_3CH_2OP), 40.54 (d, $^{2}J_{CP}$=3.6 Hz, *C* HCHP), 45.05 (d, $^{1}J_{CP}$=127.4 Hz, CH *C* HP), 56.05 (s, *C* H_3O), 62.95 (d, $^{2}J_{CP}$=7.0 Hz, CH_3C H_2OP), 63.26 (d, $^{2}J_{CP}$=6.8 Hz, CH_3C H_2OP), 116.65 (s, *C* H_2=CHCH), 137.02 (d, $^{3}J_{CP}$=18.9 Hz, CH_2=*C* HCH), 111.61 (s, C_6H_3), 120.08 (s, C_6H_3), 122.77 (s, C_6H_3), 124.86 (s, C_6H_3), 140.54 (s, C_6H_3), 147.37 (s, C_6H_3), 162.67 (d, $^{2}J_{CP}$=5.7 Hz, *C*=O); IR (cm^{-1}, film) 1760 (*C=O*), 1680 (*C=C*), 1256 (*P=O*), 1020 (*P–O*). Anal. calcd for $C_{16}H_{21}O_6P$ (340.32) C, 56.47; H, 6.22; P, 9.10. Found C, 56.40; H, 6.13; P, 8.98.

4.3. General procedure for the preparation of 3,4-di-(diethoxyphosphoryl)-chroman-2-ones 6g,h

To a stirred solution of sodium diethylphosphite in THF (10 mL), generated from NaH (0.13 g, 5.40 mmol) and diethylphosphite (0.44 g, 3.20 mmol), a solution of chromenone **4** (3.20 mmol) in THF (10 mL) was added at room temperature, under argon atmosphere. The reaction mixture was stirred for 3 h and water (10 mL) was added. Extraction with CH_2Cl_2 (3×10 mL), drying ($MgSO_4$) and evaporation of the solvent gave a crude product which was purified by column chromatography (eluent $CHCl_3$/MeOH=98/2).

4.3.1. *trans*-3,4-Di-(diethoxyphosphoryl)chroman-2-one (6g). Yield 0.98 g, 73%; oil; ^{31}P NMR δ (ppm) 18.66 (d, $^{3}J_{PP}$=71.7 Hz, *P* CHCHP), 22.79 (d, $^{3}J_{PP}$=71.7 Hz, PCHCH *P*); ^{1}H NMR δ (ppm) 0.93 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.20 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 1.30 (t, 3H, $^{3}J_{HH}$=7.3 Hz, C H_3CH_2O), 1.33 (t, 3H, $^{3}J_{HH}$=7.0 Hz, C H_3CH_2O), 3.59–4.31 (m, 10H, CH_3C H_2O, PC *H* C *H* P), 7.03–7.39 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 15.57 (d, $^{3}J_{CP}$=6.1 Hz, *C* H_3CH_2OP), 15.85 (d, $^{3}J_{CP}$=5.4 Hz, *C* H_3CH_2OP), 15.87 (d, $^{3}J_{CP}$=6.3 Hz, *C* H_3CH_2OP), 16.03 (d, $^{3}J_{CP}$=5.5 Hz, *C* H_3CH_2OP), 35.97 (dd, $^{1}J_{CP}$=141.1 Hz, $^{2}J_{CP}$=3.8 Hz, P *C* HCHP), 40.00 (dd, $^{1}J_{CP}$=126.1 Hz, $^{2}J_{CP}$=3.9 Hz, PCH *C* HP), 63.00 (d, $^{2}J_{CP}$=3.4 Hz, CH_3C

H_2OP), 63.11 (d, $^2J_{CP}$=3.4 Hz, CH_3C H_2OP), 63.26 (d, $^2J_{CP}$=7.2 Hz, CH_3C H_2OP), 63.48 (d, $^2J_{CP}$=6.7 Hz, CH_3C H_2OP), 115.21 (dd, $^3J_{CP}$=7.6 Hz, $^2J_{CP}$=1.3 Hz, C_6H_4), 116.47 (d, $^4J_{CP}$=3.2 Hz, C_6H_4), 124.58 (d, $^5J_{CP}$=3.2 Hz, C_6H_4), 129.31 (d, $^4J_{CP}$=4.4 Hz, C_6H_4), 129.76 (d, $^3J_{CP}$=5.0 Hz, C_6H_4), 151.46 (d, $^3J_{CP}$=5.0 Hz, C_6H_4), 161.87 (dd, $^3J_{CP}$=6.3 Hz, $^2J_{CP}$=1.9 Hz, C=O); IR (cm^{-1}, film) 1768 (C=O), 1200 (P=O), 1232 (P=O), 1016 (P–O), 1026 (P–O). Anal. calcd for $C_{17}H_{26}O_8P_2$ (420.34) C, 48.58; H, 6.23; P, 14.74. Found C, 48.66; H, 6.30; P, 14.87.

4.3.2. *trans*-3,4-Di-(diethoxyphosphoryl)-8-methoxychroman-2-one (6h). Yield 0.72 g, 50%; oil; ^{31}P NMR δ (ppm) 18.20 (d, $^3J_{PP}$=71.7 Hz, P CHCHP), 22.45 (d, $^3J_{PP}$=71.7 Hz, PCHCH P; ^{1}H NMR δ (ppm) 0.95 (t, 3H, $^3J_{HH}$=7.0 Hz, C H_3CH_2O), 1.22 (t, 3H, $^3J_{HH}$=7.1 Hz, C H_3CH_2O), 1.32 (t, 3H, $^3J_{HH}$=7.1 Hz, C H_3CH_2O), 1.33 (dt, 3H, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.6 Hz, C H_3CH_2O), 3.88 (s, 3H, C H_3O), 3.57–4.18 (m, 10H, CH_3C H_2O, PC H C H P), 6.90–7.14 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 15.68 (d, $^3J_{CP}$=6.3 Hz, C H_3CH_2OP), 16.09 (2d, $^3J_{CP}$=5.9 Hz, C H_3CH_2OP), 16.27 (d, $^3J_{CP}$=5.5 Hz, C H_3CH_2OP), 36.36 (dd, $^1J_{CP}$=141.0 Hz, $^2J_{CP}$=3.8 Hz, P C HCHP), 40.02 (dd, $^1J_{CP}$=126.4 Hz, $^2J_{CP}$=4.0 Hz, PCH C HP), 56.13 (s, C H_3O), 63.18 (d, $^2J_{CP}$=2.2 Hz, CH_3C H_2OP), 63.29 (d, $^2J_{CP}$=2.3 Hz, CH_3C H_2OP), 63.45 (d, $^2J_{CP}$=7.2 Hz, CH_3C H_2OP), 63.67 (d, $^2J_{CP}$=6.8 Hz, CH_3C H_2OP), 112.15 (d, $^5J_{CP}$=3.8 Hz, C_6H_3), 116.49 (dd, $^3J_{CP}$=8.2 Hz, $^2J_{CP}$=1.9 Hz, C_6H_3), 121.39 (d, $^3J_{CP}$=5.0 Hz, C_6H_3), 124.64 (d, $^4J_{CP}$=3.2 Hz, C_6H_3), 141.15 (d, $^3J_{CP}$=6.3 Hz, C_6H_3), 147.41 (d, $^4J_{CP}$=3.8 Hz, C_6H_3), 161.59 (dd, $^3J_{CP}$=5.7 Hz, $^2J_{CP}$=1.9 Hz, C=O); IR (cm^{-1}, film) 1764 (C=O), 1200 (P=O), 1276 (P=O), 1044 (P–O), 1080 (P–O). Anal. calcd for $C_{18}H_{28}O_9P_2$ (450.37) C, 48.01; H, 6.27; P, 13.75. Found C, 48.12; H, 6.18; P, 13.65.

4.3.3. Preparation of *trans*-3-diethoxyphosphoryl-4-nitromethylchroman-2-one (6i). A solution of nitromethane (0.24 g, 3.91 mmol) in THF (5 mL) was added to a stirred suspension of NaH (0.11 g, 4.60 mmol) in THF (15 mL), under argon atmosphere, and the reaction mixture was stirred at 40 °C for 15 min. After this time, a solution of chromanone **4a** (1.00 g, 3.55 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred at 50 °C for 2 h. After was cooled to rt, it was acidified to pH~1.5 with 1 N HCl solution. Extraction with $CHCl_3$ (4×15 mL), drying ($MgSO_4$) and evaporation of the solvent yielded a crude product which was purified by column chromatography (eluent, EtOAc) to give pure **6i** (0.71 g, 58%); oil; ^{31}P NMR δ (ppm) 16.99; ^{1}H NMR δ (ppm) 0.96 (t, 3H, $^3J_{HH}$=7.0 Hz, C H_3CH_2O), 1.33 (t, 3H, $^3J_{HH}$=7.5 Hz, C H_3CH_2O), 3.50–3.60 (m, 1H, CH_3CH H O), 3.56 (dd, 1H, $^2J_{HP}$=26.3 Hz, $^3J_{HH}$=1.0 Hz, CHC H P), 3.60–3.64 (m, 1H, C H CHP), 3.79 (ddq, 1H, $^2J_{HH}$=10.0 Hz, $^3J_{HH}$=7.0 Hz, $^3J_{HP}$=7.0 Hz, CH_3C H HO), 4.15 (dq, 2H, $^3J_{HP}$=8.0 Hz, $^3J_{HH}$=7.5 Hz, CH_3C H_2O), 4.52–4.55 (m, 2H, C H_2NO_2), 7.09–7.30 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 15.73 (d, $^3J_{CP}$=6.1 Hz, C H_3CH_2OP), 16.01 (d, $^3J_{CP}$=6.2 Hz, C H_3CH_2OP), 35.80 (d, $^2J_{CP}$=2.7 Hz, C HCHP), 42.85 (d, $^1J_{CP}$=128.3 Hz, CH C HP), 63.36 (d, $^2J_{CP}$=7.1 Hz, CH_3C H_2OP), 63.72 (d, $^2J_{CP}$=6.7 Hz, CH_3C H_2OP), 78.13 (d, $^3J_{CP}$=19.0 Hz, NO_2C H_2CHCHP), 117.09 (s, C_6H_4), 118.22 (s, C_6H_4), 125.42 (s, C_6H_4), 128.68 (s, C_6H_4), 130.31 (s, C_6H_4), 151.36 (s, C_6H_4), 162.04 (d, $^2J_{CP}$=6.3 Hz, C=O); IR (cm^{-1}, film) 1764 (C=O), 1556 (N=O), 1256 (P=O), 1028 (P–O). Anal. calcd for $C_{14}H_{18}NO_7P$ (343.28) C, 48.99; H, 5.29; N, 4.08; P, 9.02. Found C, 49.08; H, 5.34; N, 3.89; P, 8.90.

4.4. General procedure for the preparation of 3-methylidenechroman-2-ones 7a–d and 3-methylchromen-2-ones 8g,h

A solution of 3-diethoxyphosphorylchromanone **6** (1.5 mmol) in benzene (5 mL) was added at room temperature to a suspension of NaH (0.04 g, 1.7 mmol) in benzene (10 mL) and the reaction mixture was stirred under argon atmosphere for 0.5 h. Then paraformaldehyde (0.13 g, 4.5 mmol) was added in one portion. The mixture was refluxed for 1 h, cooled to room temperature, and water (20 mL) was added. Extraction with benzene (2×15 mL), drying ($MgSO_4$) and evaporation of the solvent gave a crude product which was purified by column chromatography.

4.4.1. 3-Methylidene-4-methylchroman-2-one (7a). Yield 0.19 g, 71%, (lit.[10]); oil; (eluent $CHCl_3$/hexane=9/1); ^{1}H NMR δ (ppm) 1.44 (d, 3H, $^3J_{HH}$=7.0 Hz, C H_3CHC), 3.81 (qdd, 1H, $^3J_{HH}$=7.0 Hz, $^4J_{HH}$=2.0 Hz, $^4J_{HH}$=1.0 Hz, CH_3C H C), 5.75 (dd, 1H, $^4J_{HH}$=2.0 Hz, $^2J_{HH}$=1.0 Hz, C H H=CCH), 6.35 (t, 1H, $^4J_{HH}$=$^2J_{HH}$=1.0 Hz, CH H=CCH), 7.08–7.22 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 22.67 (s, C H_3CH), 37.32 (s, CH_3C H), 117.12 (s, C_6H_4), 124.77 (s, C H_2=CCH), 126.77 (s, C_6H_4), 127.03 (s, C_6H_4), 127.12 (s, C_6H_4), 128.25 (s, C_6H_4), 138.01 (s, CH_2=C CH), 150.09 (s, C_6H_4), 163.52 (s, C=O); IR (cm^{-1}, film) 1756 (C=O), 1608 (C=C). Anal. calcd for $C_{11}H_{10}O_2$ (174.20) C, 75.84; H, 5.79. Found C, 75.69; H, 5.71.

4.4.2. 8-Methoxy-3-methylidene-4-methylchroman-2-one (7b). Yield 0.21 g, 68%; oil; (eluent $CHCl_3$/hexane); ^{1}H NMR δ (ppm) 1.42 (d, 3H, $^3J_{HH}$=7.3 Hz, C H_3CHC), 3.79 (qdd, 1H, $^3J_{HH}$=7.3 Hz, $^4J_{HH}$=1.0 Hz, $^4J_{HH}$=0.8 Hz, CH_3C H C), 3.89 (s, 3H, C H_3O), 5.74 (t, 1H, $^2J_{HH}$=$^4J_{HH}$=1.0 Hz, C H H=CCH), 6.34 (dd, 1H, $^2J_{HH}$=1.0 Hz, $^4J_{HH}$=0.8 Hz, CH H=CCH), 6.76–7.10 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 21.71 (s, C H_3CH), 36.62 (s, CH_3C H), 55.04 (s, C H_3O), 109.91 (s, C_6H_3), 117.16 (s, C_6H_3), 123.75 (s, C_6H_3), 126.07 (s, C H_2=CCH), 127.17 (s, C_6H_3), 136.91 (s, C_6H_3), 138.31 (s, CH_2=C CH), 146.70 (s, C_6H_3), 161.95 (s, C=O); IR (cm^{-1}, film) 1756 (C=O), 1660 (C=C). Anal. calcd for $C_{12}H_{12}O_3$ (204.23) C, 70.58; H, 5.92. Found C, 70.67; H, 6.09.

4.4.3. 4-Butyl-3-methylidenechroman-2-one (7c). Yield 0.19 g, 58%; oil; (eluent $CHCl_3$/hexane=7/3); ^{1}H NMR δ (ppm) 0.87 (t, 3H, $^3J_{HH}$=6.8 Hz, C $H_3(CH_2)_2CH_2$), 1.25–1.37 (m, 4H, $CH_3(CH_2)_2CH_2$), 1.58–1.68 (m, 2H, $CH_3(CH_2)_2C$ H_2), 3.58 (td, 1H, $^3J_{HH}$=7.3 Hz, $^4J_{HH}$=1.0 Hz, $CH_3(CH_2)_3C$ H), 5.69 (dd, 1H, $^2J_{HH}$=1.3 Hz, $^4J_{HH}$=1.0 Hz, C H H=CCH), 6.36 (d, 1H, $^2J_{HH}$=1.3 Hz, CH H=CCH), 7.05–7.26 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 13.79 (s, C $H_3(CH_2)_2CH_2$), 22.27 (s, CH_3C $H_2(CH_2)_2$), 28.16 (s, CH_3CH_2C H_2CH_2), 37.54 (s, $CH_3(CH_2)_2C$ H_2), 43.82 (s, CH_2=C C H), 128.05 (s, C H_2=CCH), 136.68 (s, CH_2=C CH), 117.06 (s, C_6H_4), 124.53 (s, C_6H_4), 126.40 (s, C_6H_4), 127.74 (s, C_6H_4), 128.14

(s, C_6H_4), 150.22 (s, C_6H_4), 163.64 (s, C=O); IR (cm^{-1}, film) 1752 (C=O), 1600 (C=C). Anal. calcd for $C_{14}H_{16}O_2$ (216.28) C, 77.75; H, 7.46. Found C, 77.92; H, 7.38.

4.4.4. 4-Butyl-8-methoxy-3-methylidenechroman-2-one (7d). Yield 0.33 g, 89%; oil; (eluent $CHCl_3$); ^{1}H NMR δ (ppm) 0.68 (t, 3H, $^3J_{HH}$=7.0 Hz, C $H_3(CH_2)_2CH_2$), 1.23–1.33 (m, 4H, $CH_3(CH_2)_2CH_2$), 1.59–1.65 (m, 2H, $CH_3(CH_2)_2C$ H_2), 3.56 (t, 1H, $^3J_{HH}$=7.3 Hz, $CH_3(CH_2)_3C$ H), 3.86 (s, 3H, C H_3O), 5.68 (d, 1H, $^2J_{HH}$=1.0 Hz, C H H=CCH), 6.35 (d, 1H, $^2J_{HH}$=1.0 Hz, CH H=CCH), 6.71–7.09 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 13.75 (s, C $H_3(CH_2)_2CH_2$), 22.24 (s, CH_3C $H_2(CH_2)_2$), 28.15 (s, CH_3CH_2C H_2CH_2), 37.26 (s, $CH_3(CH_2)_2C$ H_2), 43.98 (s, CH_2=C C H), 55.93 (s, C H_3O), 127.88 (s, C H_2=CCH), 136.58 (s, CH_2=C CH), 10.78 (s, C_6H_3), 19.12 (s, C_6H_3), 124.47 (s, C_6H_3), 127.48 (s, C_6H_3), 139.42 (s, C_6H_3), 147.64 (s, C_6H_3), 163.01 (s, C=O); IR (cm^{-1}, film) 1748 (C=O), 1664 (C=C). Anal. calcd for $C_{15}H_{18}O_3$ (246.31) C, 73.15; H, 7.37. Found C, 73.11; H, 7.45.

4.4.5. 4-Diethoxyphosphoryl-3-methylchromen-2-one (8g). Yield 0.28 g, 63%; oil; (eluent AcOEt/hexane=9/1); ^{31}P NMR δ (ppm) 13.39; ^{1}H NMR δ (ppm) 1.28 (t, 6H, $^3J_{HH}$=7.0 Hz, $(CH_3CH_2O)_2$), 2.55 (d, 3H, $^4J_{HP}$=3.0 Hz, C H_3C=CP), 4.01–4.22 (m, 4H, $(CH_3C$ $H_2O)_2$), 7.12–8.44 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 15.76 (2d, $^3J_{CP}$=6.2 Hz, C H_3CH_2OP), 16.09 (d, $^3J_{CP}$=6.4 Hz, C H_3C=CP), 40.35 (d, $^3J_{CP}$=3.7 Hz, PC=C C H_3), 62.95 (d, $^2J_{CP}$=7.1 Hz, CH_3C H_2OP), 63.28 (d, $^2J_{CP}$=6.7 Hz, CH_3C H_2OP), 116.58 (s, C_6H_4), 116.62 (s, C_6H_4), 124.88 (s, C_6H_4), 128.68 (s, C_6H_4), 128.92 (s, C_6H_4), 35.55 (d, $^1J_{CP}$=178.9 Hz, P C=CCH_3), 137.29 (d, $^2J_{CP}$=18.3 Hz, PC=C CH_3), 151.26 (s, C_6H_4), 163.23 (d, $^3J_{CP}$=5.7 Hz, C=O); IR (cm^{-1}, film) 1732 (C=O), 1624 (C=C), 1220 (P=O), 1024 (P–O). Anal. calcd for $C_{14}H_{17}O_5P$ (296.26) C, 56.76; H, 5.78; P, 10.45. Found C, 56.61; H, 5.83; P, 10.25.

4.4.6. 4-Diethoxyphosphoryl-8-methoxy-3-methylchromen-2-one (8h). Yield 0.20 g, 40%; oil; (eluent AcOEt/hexane=9/1); ^{31}P NMR δ (ppm) 13.12; ^{1}H NMR δ (ppm) 1.35 (t, 6H, $^3J_{HH}$=7.0 Hz, $(CH_3CH_2O)_2$), 2.63 (d, 3H, $^4J_{HP}$=3.0 Hz, C H_3C=CP), 3.96 (s, 3H, C H_3O), 4.11–4.29 (m, 4H, $(CH_3C$ $H_2O)_2$), 7.03–8.08 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 15.29 (d, $^3J_{CP}$=6.4 Hz, $(C$ $H_3CH_2O)_2P$), 15.39 (d, $^3J_{CP}$=5.8 Hz, C H_3C=CP), 55.25 (s, C H_3O), 61.75 (d, $^2J_{CP}$=5.5 Hz, $(CH_3C$ $H_2O)_2P$), 134.88 (d, $^2J_{CP}$=9.5 Hz, PC=C CH_3), 135.70 (d, $^1J_{CP}$=173.3 Hz, P C=CCH_3), 111.56 (s, C_6H_3), 117.74 (d, $^2J_{CP}$=12.0 Hz, C_6H_3), 118.32 (s, C_6H_3), 122.73 (s, C_6H_3), 140.94 (d, $^3J_{CP}$=13.9 Hz, C_6H_3), 147.41 (d, $^4J_{CP}$=3.8 Hz, C_6H_3), 159.56 (d, $^3J_{CP}$=23.3 Hz, C=O); IR (cm^{-1}, film) 1724 (C=O), 1648 (C=C), 1212 (P=O), 1076 (P–O). Anal. calcd for $C_{15}H_{19}O_6P$ (326.29) C, 55.22; H, 5.87; P, 9.49. Found C, 55.40;, H, 5.73; P, 9.69.

4.5. General procedure for the preparation of 3-methylidenechroman-2-ones 7e,f

A solution of 3-diethoxyphosphorylchromanone **6** (1.5 mmol) in THF (5 mL) was added at room temperature to a suspension of NaH (0.04 g, 1.7 mmol) in THF (10 mL) and the reaction mixture was stirred under argon atmosphere for 0.5 h. Then paraformaldehyde (0.13 g, 4.5 mmol) was added in one portion. The mixture was stirred for 5 h and water (20 mL) was added. Extraction with $CHCl_3$ (2×15 mL), drying ($MgSO_4$) and evaporation of the solvent gave a crude product which was purified by column chromatography (eluent $CHCl_3$/hexane=9/1).

4.5.1. 3-Methylidene-4-vinylchroman-2-one (7e). Yield 0.15 g, 55%; oil; ^{1}H NMR δ (ppm) 4.32–4.39 (m, 1H, CH_2=CHC H), 5.10 (ddd, 1H, $^3J_{HH}$=17.0 Hz, $^2J_{HH}$=1.3 Hz, $^4J_{HH}$=1.0 Hz, CH H=CHCH), 5.29 (ddd, 1H, $^3J_{HH}$=10.0 Hz, $^2J_{HH}$=1.3 Hz, $^4J_{HH}$=1.0 Hz, C H H=CHCH), 5.76–5.90 (m, 1H, CH_2=C H CH), 5.82 (dd, 1H, $^2J_{HH}$=1.5 Hz, $^4J_{HH}$=1.0 Hz, CH H=CCH), 6.49 (dd, 1H, $^2J_{HH}$=1.5 Hz, $^4J_{HH}$=1.0 Hz, C H H=CCH), 7.06–7.32 (m, 4H, C_6H_4); ^{13}C NMR δ (ppm) 46.16 (s, CH_2=CH C H), 117.13 (s, C_6H_4), 117.94 (s, C H_2=CHCH), 123.40 (s, C_6H_4), 124.72 (s, C_6H_4), 127.85 (s, C_6H_4), 128.73 (s, C_6H_4), 129.23 (s, C H_2=CCH), 134.82 (s, CH_2=C CH), 136.80 (s, CH_2=C HCH), 150.33 (s, C_6H_4), 162.90 (s, C=O); IR (cm^{-1}, film) 1760 (C=O), 1608 (C=C), 1660 (C=C). Anal. calcd for $C_{12}H_{10}O_2$ (186.21) C, 77.40; H, 5.41. Found C, 77.58; H, 5.30.

4.5.2. 8-Methoxy-3-methylidene-4-vinylchroman-2-one (7f). Yield 0.19 g, 60%; oil; ^{1}H NMR δ (ppm) 3.89 (s, 3H, C H_3O), 4.31–4.37 (m, 1H, CH_2=CHC H), 5.10 (dt, 1H, $^3J_{HH}$=17.0 Hz, $^2J_{HH}$=$^4J_{HH}$=1.0 Hz, C H H=CHCH), 5.26 (dt, 1H, $^3J_{HH}$=10.0 Hz, $^2J_{HH}$=$^4J_{HH}$=1.0 Hz, CH H=CHCH), 5.79 (ddd, 1H, $^3J_{HH}$=17.0 Hz, $^3J_{HH}$=10.0 Hz, $^3J_{HH}$=6.5 Hz, CH_2=C H CH), 5.80 (dd, 1H, $^4J_{HH}$=1.5 Hz, $^2J_{HH}$=1.0 Hz, C H H=CCH), 6.48 (t, 1H, $^4J_{HH}$=$^2J_{HH}$=1.0 Hz, CH H=CCH), 6.76–7.08 (m, 3H, C_6H_3); ^{13}C NMR δ (ppm) 45.38 (s, CH_2=CH C H), 55.05 (s, C H_3O), 116.76 (s, C H_2=CHCH), 128.67 (s, C H_2=CCH), 133.71 (s, CH_2=C HCH), 135.74 (s, CH_2=C CH), 110.31 (s, C_6H_3), 118.13 (s, C_6H_3), 123.51 (s, C_6H_3), 123.68 (s, C_6H_3), 138.62 (s, C_6H_3), 146.72 (s, C_6H_3), 161.40 (s, C=O); IR (cm^{-1}, film) 1748 (C=O), 1616 (C=C), 1664 (C=C). Anal. calcd for $C_{13}H_{12}O_3$ (216.24) C, 72.21; H, 5.59. Found C, 72.27; H, 5.49.

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References and notes

1. Minami, T.; Mitoyoshiya, J. *Synthesis* **1992**, 333–349.
2. Janecki, T.; Błaszczyk, E. *Synthesis* **2001**, 403–408.
3. Petragnani, N.; Ferraz, H. M. C.; Silva, G. F. J. *Synthesis* **1986**, 157–183.
4. Harmon, A. D.; Hutchinson, C. R. *J. Org. Chem.* **1975**, *40*, 3474–3480.
5. Groutas, W. C.; Felker, D.; Magnin, D. *Synth. Commun.* **1980**, *10*, 355–362.
6. Sunitha, K.; Balasubramanian, K. K.; Rajagopalan, K. *Tetrahedron Lett.* **1984**, *25*, 3125–3126.

7. Sunitha, K.; Balasubramanian, K. K.; Rajagopalan, K. *J. Org. Chem.* **1985**, *50*, 1530–1531.
8. Krishnamoorthy, T. V.; Rajagopalan, K. *Tetrahedron Lett.* **1985**, *26*, 1747–1748.
9. Sunitha, K.; Balasubramanian, K. K.; Rajagopalan, K. *Tetrahedron Lett.* **1985**, *26*, 4393–4394.
10. Drewes, S. E.; Emslie, N. D.; Karodia, N.; Loizou, G. *Synth. Commun.* **1990**, *20*, 1437–1443.
11. Foucaud, A.; Brine, N. *Synth. Commun.* **1994**, *24*, 2851–2861.
12. Bestmann, H. J.; Lehnen, H. *Tetrahedron Lett.* **1991**, *32*, 4279–4282.
13. Falsone, G.; De Nardo, C. M. M.; Darai, M. M. *Z. Naturforsch.* **1993**, *48b*, 1391–1397.
14. March, J. *Advanced organic chemistry*; Wiley: New York, 1992; p 743.
15. Stewart, J. J. P. *Comp. Chem.* **1989**, *10*, 209. see also 211.
16. Ampac 6.7, Semichem; Default convergence criteria were used; Shawnee Mission: Kansas, USA, 2001.
17. Leonard, J.; Lygo, B.; Procter, G. *Advanced practical organic chemistry*; Blackie Academic and Professional: London, 1995; p 54.

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Chemoselective glycosylations using sulfonium triflate activator systems

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Abstract—A novel chemoselective glycosylation sequence is described that employs the recently developed BSP/Tf_2O and DPS/Tf_2O reagent systems to activate thioglycosides. In the first glycosylation event a relatively armed thioglycoside is activated with the BSP/Tf_2O activator system and condensed with an acceptor thioglycoside to yield the thiodisaccharide, which is activated with the more potent DPS/Tf_2O activator in the next glycosylation event. Quenching of (*N*-piperidino)phenyl(*S*-thiophenyl)sulfide triflate, which is formed upon activation of the first thioglycoside, with triethyl phosphite is crucial for a productive glycosylation.
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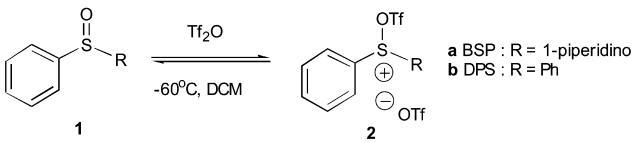
1. Introduction

The concise and efficient preparation of oligosaccharides and glycoconjugates presents a significant challenge in synthetic organic chemistry. Considerable attention in this field has been devoted to the development of efficient chemoselective and orthogonal synthetic strategies.[1] Ever since the observation of Paulsen, in the early 1970's, that the protecting groups on a glycosyl halide significantly influence the rate of anomeric hydrolysis,[2] and the introduction of the armed–disarmed concept by Fraser–Reid,[3] an array of chemoselective condensation procedures have emerged.[4] Apart from the exploitation of the protecting groups, chemoselective condensations have been achieved by taking advantage of the influence of substituent effects, sugar conformation and configuration, solvent effects, and the nature of the anomeric leaving group.[4a,c] Our contributions in this field have been focussed predominantly on the use of thioglycosides.[5] These present an attractive class of donor glycosides since the thiofunction is stable under most conditions used for protecting group manipulations.[6] An additional important asset in chemoselective condensations comprises the fact that thioglycosides can be activated by a range of activator systems of varying thiophilicity.[7] Recently the Crich laboratory launched 1-benzenesulfinyl piperidine (BSP) in combination with trifluoromethanesulfonic anhydride (Tf_2O) as a novel potent thiophilic activator system (**2a**, Scheme 1).[7b] It



Scheme 1. Sulfonium activator species **2a** and **2b**.

was shown that **2a** could be used for the transformation of both armed and disarmed thioglycosides into the corresponding glycosyl triflates, and their ensuing conversion into various disaccharides. Notably, activator system **2a** could be used to promote the highly stereoselective formation of the β-mannosidic linkage, a feat which is normally difficult to attain. We recently reported that no productive glycosylations were obtained using BSP/Tf_2O reagent **2a** in combination with highly disarmed thioglycosides.[8] In contrast, we found that the analogous diphenyl sulfoxide (DPS)-triflic anhydride combination **2b** could activate these unreactive thiosaccharides. These findings prompted us to explore the possibilities for a novel condensation sequence in which the difference in reactivities of the sulfonium activator systems **2a** and **2b** is exploited to attain chemoselective glycosylations using highly disarmed thioglycosides. The full experimental results of our studies are presented here.

2. Results and discussion

The BSP/Tf_2O activation protocol as developed by Crich,[7b] entails the pre-mixing of the donor thioglycoside and the sulfenyl triflate and subsequent addition of the acceptor.

Keywords: Carbohydrates; Glycosylation; Chemoselective; Triflate.
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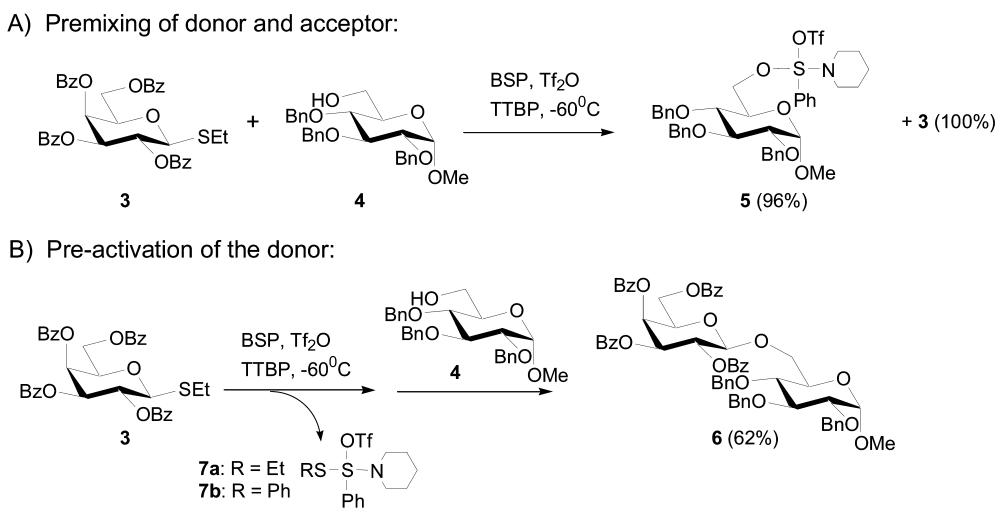
This stepwise protocol was devised to facilitate the intermediate formation of the glycosyl triflate, allowing a more stereoselective condensation reaction. With the objective to attain a chemoselective glycosylation protocol we explored, in a model experiment, whether pre-mixing the donor and acceptor glycosides prior to the addition of the activator would result in a productive glycosylation. Upon treatment of a 1:1 mixture of donor thiogalactoside **3** and glucose acceptor **4**, having an inert anomeric *O*-methyl function, with 1 equiv. of **2a** in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[10] we found that the thiofunction of the thiogalactoside remained unaffected (Scheme 2). The acceptor glucoside on the other hand was transformed into the 6-*O*-benzenesulfinyl piperidine triflate adduct **5**, which proved to be remarkably stable and was isolated in a virtually quantitative yield. The outcome of this experiment agrees with the glycosylation procedure of Gin,[9] in which the analogous DPS/Tf_2O activator system **2b** could activate the anomeric hydroxyl function. Thus, the phenyl-1-piperidinosulfide bis(triflate) **2a** can react with both the hydroxyl function in the acceptor glycoside and with the thiofunction of the donor glycoside depending on their relative nucleophilicities. Pre-activation of the donor galactoside **3** with **2a** at low temperature and subsequent addition of the acceptor **4** did lead to the formation of disaccharide **6**. Accordingly, we followed the Crich activation protocol in our explorative BSP/Tf_2O-mediated chemoselective glycosylations.

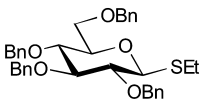
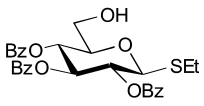
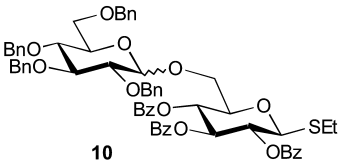
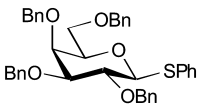
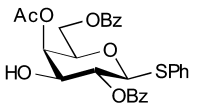
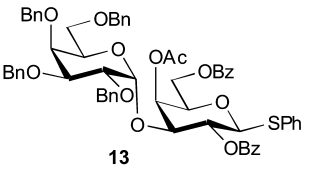
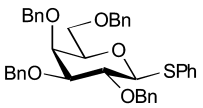
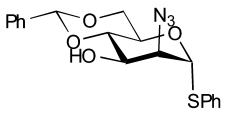
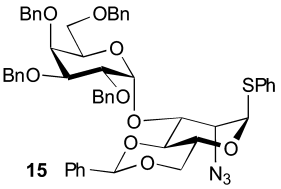
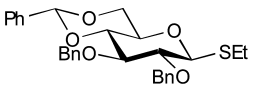
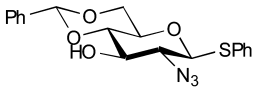
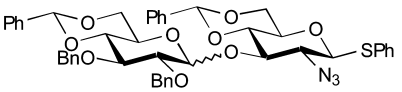
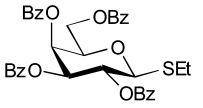
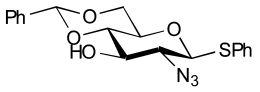
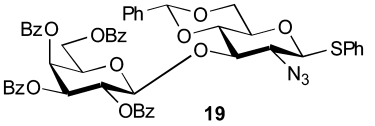
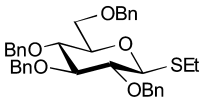
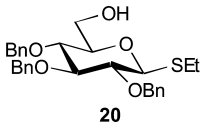
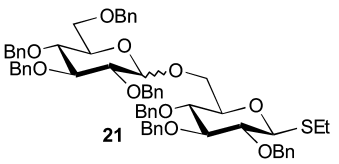
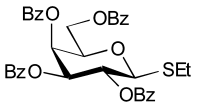
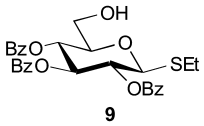
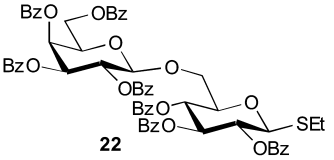
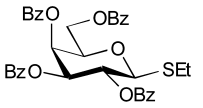
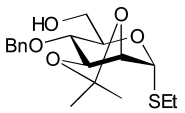
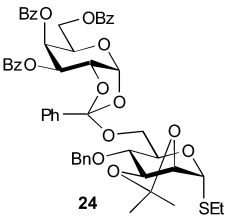
As a first touchstone we investigated the 'classic' condensation of an armed perbenzylated thiodonor with a disarmed perbenzoylated acceptor. Tetrabenzyl thioglucoside **8** was activated by **2a** at −60 °C and condensed with glucoside **9** (Table 1, entry 1). Although the activation and condensation proceeded smoothly as judged by TLC analysis, deterioration of the initially formed disaccharide **10** occurred upon warming of the reaction mixture. It occurred to us that the transiently formed (*N*-piperidino)phenyl(*S*-thioethyl)sulfide triflate **7a** (Scheme 2), generated by the activation of the anomeric phenyl thiofunction with BSP/Tf_2O, is also capable of activating thioglycosides, albeit at higher temperatures. This is supported by the finding of Wong et al.,[11] who use 0.5 equiv. of **2a** to completely activate a highly reactive thiodonor in a chemoselective glycosylation. We therefore set out to exploit the triflate species **7** as an activator for the chemoselective glycosylation of **8** and **9**. Triflate species **7b** was generated by treatment of **2a** with 1 equiv. of thiophenol and used to activate thioglucose **8**. This activation proved to proceed more sluggishly than the BSP/Tf_2O mediated activation of **8** and the ensuing condensation with acceptor **9** led to formation of the thiodisaccharide product **10** in a disappointing yield (44%). Since we were not able to apply the (*N*-piperidino)phenyl(*S*-thiophenyl)sulfide triflate **7b** as an effective activator we returned to the BSP/Tf_2O activator system and decided to scavenge the transiently formed **7** after the condensation event. We selected triethyl phosphite (TEP)[12] as a possible quenching reagent. To investigate the efficacy of TEP as a scavenging reagent we generated triflate species **7b** and treated this with an equimolar amount of TEP prior to the addition of the reactive thioglycoside **8**. In this case the thioacetal function remained intact and the thioglycoside **8** could be quantitatively recovered. Having established that timely addition of the quenching agent TEP prevents decomposition of the thiosaccharide product, we returned to the chemoselective condensation of thiodonor **8** and acceptor **9** (Table 1, entry 1b). Following pre-activation of the glucoside with BSP/Tf_2O at −60 °C and addition of the acceptor the reaction mixture was allowed to warm to −10 °C, after which 1 equiv. of TEP and triethylamine were added to quench (*N*-piperidino)phenyl(*S*-thioethyl)sulfide triflate **7a** and the generated triflic acid, respectively. Thiodisaccharide **10** was now obtained in a satisfactory 78% yield as a mixture of anomers. This successful protocol was next applied to a collection of thiosaccharide donors and acceptors of varying reactivity (Table 1, entries 2–5).

Digalactoside **13** was obtained in a moderate yield of 52% and good α-selectivity by galactosylation of donor **11** with acceptor **12**, which is a relatively strenuous acceptor for both steric and electronic reasons. In a similar manner, armed thiogalactoside **11** was glycosydated with highly disarmed azido thioglucoside **14** to provide the α-linked disaccharide **15** in 73% yield. The conformationally disarmed benzylidene thioglucoside **16** and azido thioglucoside **17** were condensed to give thiosaccharide **18** in an



Scheme 2. Sulfonium activator **2a** can react with both the hydroxyl function of the acceptor (A) and the thiofunction of the donor (B).

Table 1. Chemoselective glycosylations using the BSP/Tf_2O activator system

Entry	Donor	Acceptor	Disaccharide	Product yield (α/β)[a]
1a	 **8**	 **9**	 **10**	1a: 44% (2:1)
1b				1b: 78% (3:1)
2	 **11**	 **12**	 **13**	52% (1:0)
3	 **11**	 **14**	 **15**	73% (1:0)
4	 **16**	 **17**	 **18**	90% (2:1)
5	 **3**	 **17**	 **19**	64% (0:1)
6	 **8**	 **20**	 **21**	0%
7	 **3**	 **9**	 **22**	0%
8	 **3**	 **23**	 **24**	<10%[b]

[a] Anomeric ratio's are determined from the anomeric mixture by ^1H NMR analysis.
[b] Determined in product mixture by NMR analysis.

excellent yield but with a rather disappointing stereoselectivity (α/β 2:1).[7b] Complete chemoselectivity was also achieved when the disarmed perbenzoylated thiogalactoside **3** was glycosylated with glucosazide **17** to give the β-linked dimer **19**. This nicely demonstrates the potential of our chemoselective condensation protocol, since peracylated thioglycosides are mostly employed at the end of a chemoselective glycosylation sequence, because of their low reactivity.[13]

Now that we advantageously applied **2a** for the chemoselective glycosylation of an relatively armed donor and disarmed acceptor we anticipated that the scope of the developed methodology could be extended by decreasing

the difference in reactivity of the donor and acceptor condensation partners. Since the BSP/Tf_2O system is thought to convert the donor thioglycoside in situ to the corresponding anomeric triflate[7b] it should in theory be possible to condense this species with any other thioglycoside, regardless of the reactivity of the acceptor thiofunction, provided that the generated (*N*-piperidino)-phenyl(*S*-thiophenyl)sulfide triflate is timely quenched. However pre-activation of armed donor **8** and reaction with armed acceptor **20** led to an intractable mixture of products and disaccharide **21** was not obtained. The same occurred in the condensations of the disarmed donor **3** with thioglucoside **9** and thiomannoside **23**, although in the latter product mixture little orthoester product (<10%) was detected. Nevertheless, several attempts to optimize these results (longer activation times, lower quenching temperatures) were abortive.

We next focussed on the extension of the chemoselective glycosylation sequence to elongate the obtained thiodisaccharides in a second condensation event. Consequently, we used the more potent DPS/Tf_2O system to activate the disarmed thiodisaccharides and condensed them with a terminal acceptor building block to furnish the target trisaccharides (Scheme 3). Activation of **15** with **2b** and condensation with methyl 2,3,4-tri-*O*-acetyl-α-glucopyranoside (**25**) proceeded uneventfully and gave the expected β-mannose linked trisaccharide **26** in an adequate 64% yield as the sole isomer. Surprisingly, the glycosylation of dimer **19** with the reactive 2,3,4-tri-*O*-benzyl glucose **27** under the same conditions stereoselectively furnished the β-glucoside **28**. This β-selectivity can be explained by the rapid S_N2-like displacement of the intermediate α-triflate, which has also been observed when methanol was used as an acceptor.[14] As a final demonstration the fully protected α-Gal epitope **30**,[15] equipped with an azidopropyl spacer at its reducing end, was assembled by the DPS/Tf_2O mediated condensation of the α-linked digalactoside **13** and the terminal glucosamine building block **29** in 69% yield.

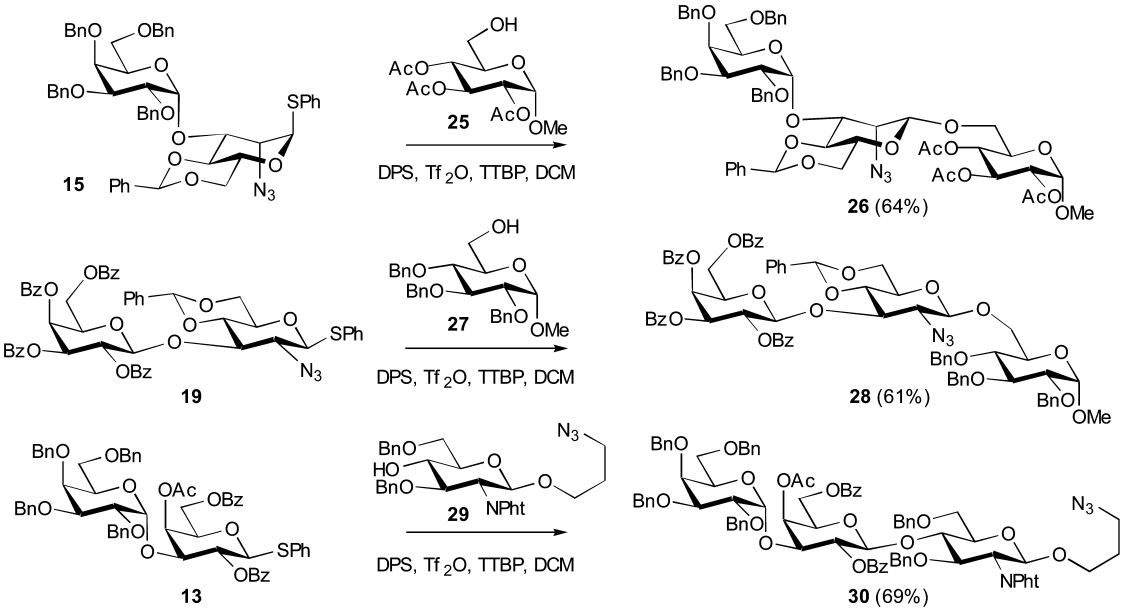
3. Conclusion

A novel chemoselective glycosylation sequence was developed which utilizes thioglycosides and exploits the reactivity difference of the recently developed BSP/Tf_2O and DPS/Tf_2O activator systems. For a productive BSP/Tf_2O mediated chemoselective glycosylation the following requirements have to be fulfilled: (1) the donor glycoside should be pre-activated before addition of the acceptor since the phenyl-1-piperidinosulfide bis(triflate) **2a** can also react with the acceptor hydroxyl function; (2) the donor thioglycoside should be more reactive than the acceptor thioglycoside, to prevent side reactions caused by the transiently formed (*N*-piperidino)phenyl(*S*-thiophenyl/thioethyl)-sulfide triflate **7a/b**; (3) the transiently formed triflate species **7** should be timely quenched with an efficient reagent, here exemplified by the use of triethyl phosphite. The described condensation sequence extends the scope of chemoselective glycosylations towards the use of highly disarmed thioglycosides and can benefit from the advantages inherent to the BSP/Tf_2O mediated glycosylations in the construction of difficult glycosidic linkages. Efforts are currently underway to explore the use of different thio- and seleno-glycosides and to implement the developed methodology in the assembly of more complex oligosaccharides.

4. Experimental

4.1. General methods

Dichloromethane was dried with P_2O_5 and distilled before use. All chemicals (Fluka, Acros, Merck) were used as received. TTBP was synthesized as described by Crich et al.[10] Reactions were performed under an inert atmosphere under strictly anhydrous conditions. Traces of water from the donor and acceptor glycosides, BSP, diphenylsulfoxide and TTBP were removed by co-evaporation with toluene and dichloroethane. Molecular sieves (3 Å) were flame



Scheme 3. DPS/Tf_2O mediated assembly of trisaccharides.

dried before use. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV 400 (400 and 100 MHz). ^{1}H NMR chemical shifts (δ) in $CDCl_3$ are reported relative to tetramethylsilane. ^{19}F NMR chemical shifts (δ) are reported relative to TFA. Mass spectra were recorded on a PE/SCIEX API 165 equipped with an Electrospray Interface (Perkin–Elmer). Optical rotations were recorded on a Propol automatic polarimeter in $CHCl_3$. Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). TLC analysis was conducted on DC-fertigfolien (Schleicher and Schuell, F1500, LS254) or HPTLC aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm), and by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25 g/L.

4.2. General procedure for chemoselective BSP/Tf_2O mediated glycosylations

To a solution of the thiodonor (typically 0.2 mmol, 1.0 equiv.), BSP (1.1 equiv.), TTBP (2.5 equiv.) in dichloromethane (5 mL) was added at −60 °C trifluoromethanesulfonic anhydride (1.1 equiv.). The reaction mixture was stirred for 5 min, after which time a solution of the acceptor thioglycoside (1.1 equiv.) in dichloromethane (1 mL) was added. The mixture was stirred at −60 °C for 1 h, after which it was slowly warmed to −10 °C and quenched by the addition of triethylphosphite (1.0 equiv.) and triethylamine (5 equiv.), followed by saturated aqueous $NaHCO_3$. The organic layer was separated, washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. Purification by silica gel chromatography (ethyl acetate/petroleum ether) gave the thiodisaccharide.

4.2.1. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(benzenesulfinylpiperidine triflate)-α-D-glucopyranoside (5). A mixture of ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-galactoside (**3**), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**), BSP and TTBP were dissolved in DCM and the reaction mixture was cooled to −60 °C. Tf_2O was added and the reaction mixture was warmed to room temperature. The mixture was concentrated to a smaller volume and directly purified by silica gel chromatography (100/0/0 to 0/90/10 petroleum ether/ethyl acetate/methanol) to provide tetra-*O*-benzoyl-1-thio-α-D-galactoside (**3**) and the title compound as a white glassy oil as an 1:1 mixture of sulfur diastereoisomers. R_f 0.25 (10% MeOH in EtOAc); ^{1}H NMR (400 MHz, MeOD): δ=7.72–7.27 (m, 20H, H_{arom}), 4.95–4.85 (m, 3H, C*H*H Bn), 4.75–4.67 (m, 5H, H-1, H-6, CH*H* Bn), 4.59 (m, 1H, H-6), 3.95 (t, 0.5H, *J*=9.6 Hz, H-3), 3.92 (t, 0.5H, *J*=9.6 Hz, H-3), 3.87 (m, 1H, H-5), 3.52 (dd, 0.5H, *J*=3.5, 9.6 Hz, H-2), 3.48 (m, 1H, H-4), 3.40–3.24 (m, 4.5H, H-2, CH_2NCH_2), 3.37 (s, 1.5H, OMe), 3.34 (s, 1.5H, OMe), 1.61 (m, 6H, $CH_2{-}CH_2{-}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.7, 139.3, 139.2 (C_q Bn), 131.7, 131.4 (C_q SPh), 135.9–128.7 (CH_{arom}), 124.9 (J_{CF}=317 Hz, CF_3), 99.4, 99.1 (C-1), 82.7, 82.5 (C-3), 81.0, 80.6 (C-2), 77.0 (C-4), 76.5, 76.4, 75.5, 75.4, 74.9 (CH_2 Bn), 73.8 (C-6), 70.5, 70.3 (C-5), 56.1 (OMe), 51.8 (CH_2NCH_2), 26.9, 26.7, 23.6, 23.5 ($CH_2{-}CH_2{-}CH_2$); ^{19}F NMR (188 MHz, CDCl3): δ=0.96; IR (neat): 1263, 731 cm^{-1}; ES-MS: *m*/*z* 656.1 $[M-OTf]^+$.

4.2.2. Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2,3,4-*O*-benzyl-α-D-glucopyranoside (6). Disaccharide **6** was obtained from ethyl tetra-*O*-benzoyl-1-thio-α-D-galactoside (**3**), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**), following the general coupling procedure in 62% as an colourless oil. R_f 0.40 (25% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09–7.11 (m, 35H, H_{arom}), 5.97 (d, 1H, *J*=2.7 Hz, H-4′), 5.85, (dd, 1H, *J*=8.0, 10.4 Hz, H-2′), 5.60 (dd, 1H, *J*=3.5, 10.4 Hz, H-3′), 4.90 (d, 1H, *J*=10.9 Hz, C*H*H Bn), 4.76 (d, 1H, *J*=8.0 Hz, H-1′), 4.72 (d, 1H, *J*=12.0 Hz, C*H*H Bn), 4.69 (d, 1H, *J*=10.9 Hz, CH*H* Bn), 4.67 (dd, 1H, *J*=6.4, 11.3 Hz, H-6′), 4.58 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.56 (d, 1H, *J*=11.2 Hz, C*H*H Bn), 4.51 (d, 1H, *J*=3.5 Hz, H-1), 4.40 (dd, 1H, *J*=6.8, 11.4 Hz, H-6′), 4.38 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 4.25 (m, 1H, H-5′), 4.21 (dd, 1H, *J*=4.2, 12.7 Hz, H-6), 3.90 (t, 1H, *J*=9.2 Hz, H-3), 3.76 (m, 2H, H-5, H-6), 3.40 (dd, 1H, *J*=3.5, 9.6 Hz, H-2), 3.38 (t, 1H, *J*=9.2 Hz, H-4), 3.21 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.9, 165.6, 165.5, 165.1 (C=O, Bz), 138.7, 138.2, 138.0 (C_q Bn), 129.2, 128.9, 128.6, 128.5 (C_q Bz), 133.5–127.4 (CH_{arom}), 101.9 (C-1′), 97.8 (C-1), 81.8 (C-3), 79.8 (C-2), 77.4 (C-4), 75.4, 74.6, 73.3 (CH_2 Bn), 71.6 (C-3′), 71.3 (C-5′), 69.7 (C-2′), 69.5 (C-5), 68.6 (C-6), 68.0 (C-4′), 61.8 (C-6′), 54.9 (OMe); IR (neat): 1724, 1261, 1068 cm^{-1}; $[\alpha]_D^{23}$ +66.8 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 1065.5 $[M+Na]^+$; HRMS calcd for $C_{62}H_{58}O_{15}NH_4$: 1060.4119. Found: 1060.4120.

4.2.3. Ethyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-2,3,4-*O*-benzoyl-1-thio-β-D-glucopyranoside (10). BSP (27 mg, 0.13 mmol) was dissolved in DCM (5 mL) and cooled to −60 °C. Tf_2O (20 μL, 0.12 mmol) was added followed by thiophenol (11 μL, 0.11 mmol). The reaction mixture was stirred for 5 min, after which ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucoside (**8**, 58 mg, 0.11 mmol) in DCM (1 mL) was added. The mixture was stirred for another 15 min, after which ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside (**9**) was added and the mixture was allowed to warm to room temperature. Standard work-up and purification gave 50 mg (0.048 mmol, 44%) of the title compound as a 2:1 α/β mixture as an slightly yellow oil. The spectroscopic data were in full accord with those previously reported:[5a] R_f 0.80 (25% EtOAc in PE); α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.09–7.12 (m, 52.5H, H_{arom}), 5.88 (t, 1H, *J*=9.4 Hz, H-3α), 5.86 (t, 0.5H, *J*=9.5 Hz, H-3β), 5.53–5.39 (m, 3H, H-2, H-4), 5.00 (m, 15H, H-1, H-1′, CH_2 Bn), 4.12–3.84 (m, 5H), 3.64–3.39 (m, m, 8.5H, H-5, 2×H-6, H-2′, H-3′, H-4′, H-5′, 2×H6′), 2.75–2.63 (m, 3H, CH_2 SEt), 1.25 (m, 4.5H, CH_3 SEt); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.7, 165.4, 165.1 (C=O Bz), 138.9, 138.6, 138.1 (C_q Bn), 129.2, 128.9 (C_q Bz), 133.4–127.4 (CH_{arom}) 103.8 (C-1′β), 97.0 (C-1′α), 84.5, 83.6, 82.2, 81.9, 79.9, 78.6, 78.4, 77.6, 74.8, 74.3, 74.2, 70.8, 70.7, 70.1, 70.0, 69.8, 69.5 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 75.6, 74.9, 74.7, 73.4, 73.3, 73.2 (CH_2 Bn), 68.9, 68.6, 68.3, 66.8 (C-6, C-6′), 24.2 (CH_2 SEt), 14.7 (CH_3 SEt); IR (neat): 1728, 1257, 1089 cm^{-1}; ES-MS: *m*/*z* 1081.4 $[M+Na]^+$; HRMS calcd for $C_{63}H_{62}O_{13}SNH_4$: 1076.4255. Found: 1076.4265.

Disaccharide **10** was also obtained from ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucoside (**8**) and ethyl 2,3,4-tri-*O*-

benzoyl-1-thio-β-D-glucopyranoside (**9**), following the general coupling procedure in 78% as an 3:1 α/β mixture.

4.2.4. Phenyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4-*O*-acetyl-2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside (13). Disaccharide **13** was obtained from phenyl tetra-*O*-benzyl-1-thio-β-D-galactoside (**11**) and phenyl 4-*O*-acetyl-2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside (**12**), following the general coupling procedure in 52% as an colourless oil. R_f 0.80 (33% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12–7.14 (m, 35H, CH_{arom}), 5.67 (d, 1H, *J*=2.8 Hz, H-4), 5.61 (t, 1H, *J*=9.9 Hz, H-2), 5.22 (d, 1H, *J*=3.2 Hz, H-1′), 4.81 (d, 1H, *J*=10.1 Hz, H-1), 4.76 (d, 1H, *J*=11.4 Hz, C*H*H Bn), 4.65 (s, 2H, CH_2 Bn), 4.64 (d, 1H, *J*=12.2 Hz, C*H*H Bn), 4.48 (m, 2H, H-6, C*H*H Bn), 4.36 (m, 4H, H-6, 3×CH*H* Bn), 4.16 (dd, 1H, *J*=3.0, 9.7 Hz, H-3), 3.93 (m, 3H, H-2′, H-5, H-5′), 3.75 (dd, 1H, *J*=2.6, 10.1 Hz, H-3′), 3.44 (dd, 1H, *J*=7.3, 9.6 Hz, H-6′), 3.23 (bs, 1H, H-4′), 3.20 (dd, 1H, *J*=5.2, 9.6 Hz, H-6′), 1.89 (s, 3H, CH_3 Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3, 165.9, 164.8 (C=O), 138.6, 138.5, 138.3 (C_q Bn), 133.4 (C_q SPh), 129.5, 129.4 (C_q Bz), 133.2–127.4 (CH_{arom}), 93.3 (C-1′), 87.0 (C-1), 78.7 (C-3′), 75.5 (C-2′), 74.8 (C-5′), 74.7 (C-4′), 74.3, 74.2, 73.1, 73.0 (CH_2 Bn), 72.7 (C-3), 69.9 (C-5), 69.4 (C-6′), 68.9 (C-2), 65.1 (C-4), 62.7 (C-6), 20.4 (CH_3 Ac); IR (neat): 1724, 1093 cm^{-1}; $[\alpha]_D^{23}$ +90.8 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 1068.1 $[M+Na]^+$; HRMS calcd for $C_{62}H_{60}O_{13}SNH_4$: 1062.4098. Found: 1062.4063.

4.2.5. Phenyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (15). Disaccharide **15** was obtained from tetra-*O*-benzyl-1-thio-β-D-galactoside (**11**) and phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (**17**), following the general coupling procedure in 73% as an yellow oil. R_f 0.80 (25% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.03 (m, 30H, H_{arom}), 5.47 (d, 1H, *J*=3.3 Hz, H-1′), 5.45 (s, 1H, C*H*Ph), 5.41 (bs, 1H, H-1), 4.91 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.87 (d, 1H, *J*=13.1 Hz, C*H*H Bn), 4.69 (d, 1H, *J*=11.9 Hz, CH*H* Bn), 4.59 (d, 1H, *J*=12.6 Hz, C*H*H Bn), 4.56 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.53 (d, 1H, *J*=11.8 Hz, CH*H* Bn), 4.45 (m, 3H, H-3, 2×CH*H* Bn), 4.35 (m, 2H, H-2, H-5), 4.21 (t, 1H, *J*=9.6 Hz, H-4), 4.14 (dd, 1H, *J*=4.8, 10.3 Hz, H-6), 4.00 (m, 3H, H-2′, H-3′, H-5′), 3.87 (bs, 1H, H-4′), 3.79 (t, 1H, *J*=10.3 Hz, H-6), 3.59 (dd, 1H, *J*=6.8, 9.8 Hz, H-6′), 3.46 (dd, 1H, *J*=5.4, 9.8 Hz, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.8, 138.43, 138.38, 137.9, 137.0 (C_q Bn, Ph), 132.9 (C_q SPh), 131.7–126.3 (CH_{arom}), 102.2 (*C*HPh), 98.3 (C-1′), 87.0 (C-1), 79.1 (C-4), 78.0 (C-5′), 75.3 (−2′, 4′), 73.3 (C-3), 74.5, 73.6, 73.5, 71.0 (CH_2 Bn), 70.7 (C-3′), 69.7 (C-6′), 68.3 (C-6), 64.9 (C-2, 5); IR (neat): 2104, 1095 cm^{-1}; $[\alpha]_D^{23}$+66.2 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 930.4 $[M+Na]^+$; HRMS calcd for $C_{53}H_{53}N_3O_9SNH_4$: 925.3846. Found: 925.3853.

4.2.6. Phenyl 3-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-glucopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (18). Disaccharide **18** was obtained from phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucoside (**16**) and phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-glucopyranoside (**17**), following the general coupling procedure in 90% as an α/β-mixture (2:1) as an colourless oil. R_f 0.50 (20% EtOAc in PE); α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61–6.99 (m, 25H, H_{arom}), 5.51 (s, 1H, C*H*Ph), 5.49 (d, 1H, *J*=3.9 Hz, H-1′), 5.45 (s, 1H, C*H*Ph), 4.87 (d, 1H, *J*=11.2 Hz, C*H*H Bn), 4.79 (d, 1H, *J*=11.2 Hz, CH*H* Bn), 4.59 (d, 1H, *J*=10.1 Hz, H-1), 4.58 (d, 1H, *J*=12.4 Hz, C*H*H Bn), 4.42 (d, 1H, *J*=12.3 Hz, CH*H* Bn), 4.36 (m, 2H, H-6, H-6′), 4.11 (m, 1H, H-5′), 4.01 (t, 1H, *J*=9.4 Hz, H-3′), 3.94 (t, 1H, *J*=9.3 Hz, H-3), 3.77–3.69 (m, 3H, H-4, H-6, H-6′), 3.57 (t, 1H, *J*=9.0 Hz, H-4′), 3.48 (m, 3H, H-2, H-5, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.7, 137.6, 137.5, 136.8 (C_q Bn, CHPh), 130.2 (C_q SPh), 134.1–126.0 (CH_{arom}), 102.1 (*C*HPh), 101.4 (*C*HPh), 97.5 (C-1′), 87.3 (C-1), 81.8, 81.4, 78.1, 76.2, 70.3, 63.9 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 75.2, 72.0 (CH_2 Bn), 69.8, 68.5 (C-6, C-6′), 63.0 (C-2); β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61–6.99 (m, 25H, H_{arom}), 5.52 (s, 1H, C*H*Ph), 5.39 (s, 1H, C*H*Ph), 4.88 (d, 1H, *J*=7.3 Hz, H-1′), 4.87 (d, 1H, *J*=11.5 Hz, C*H*H Bn), 4.86 (d, 1H, *J*=11.1 Hz, C*H*H Bn), 4.79 (d, 1H, *J*=11.1 Hz, CH*H* Bn), 4.73 (d, 1H, CH*H* Bn), 4.36 (m, 1H, H-6), 4.10 (m, 1H, H-6′), 3.91 (t, 1H, *J*=9.3 Hz, H-3), 3.74–3.59 (m, 3H, H-4, H-3′, H-4′, H-6′), 3.50 (m, 1H, H-2′), 3.41 (m, 2H, H-2, H-5), 3.25 (m, 1H, H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.4, 138.3, 137.3, 136.9 (C_q Bn, CHPh), 130.5 (C_q SPh), 133.9–126.0 (CH_{arom}), 102.4, 101.5, 101.0 (*C*H Ph, C-1′), 87.1 (C-1), 82.1, 81.2, 81.1, 79.0, 78.1, 70.6, 65.7 (C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.9, 14.7 (CH_2 Bn), 68.7, 68.4 (C-6, C-6′), 64.9 (C-2); IR (neat): 2110, 1089 cm^{-1}; ES-MS: *m*/*z* 816.2 $[M+H]^+$, 838.4 $[M+Na]^+$; HRMS calcd for $C_{46}H_{45}N_3O_9SNH_4$: 833.3220. Found: 833.3233.

4.2.7. Phenyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-glucopyranoside (19). Disaccharide **19** was obtained from phenyl 2,3,4,5-*O*-benzoyl-1-thio-β-D-galactopyranoside (**3**) and phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-glucopyranoside (**17**), following the general coupling procedure in 64% as an slightly yellow oil. R_f 0.50 (25% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04–7.02 (m, 30H, H_{arom}), 5.93 (d, 1H, *J*=2.7 Hz, H-4′), 5.82 (dd, 1H, *J*=8.1, 10.4 Hz, H-2′), 5.58 (s, 1H, C*H*Ph), 5.57 (dd, 1H, *J*=3.4, 10.6 Hz, H-3′), 5.10 (d, 1H, *J*=8.1 Hz, H-1′), 4.42 (d, 1H, *J*=10.1 Hz, H-1), 4.30 (m, 3H, H-6, H-6′, H-6′), 4.02 (t, 1H, *J*=7.3 Hz, H-5′), 3.80 (t, 1H, *J*=9.1 Hz, H-3), 3.78 (t, 1H, *J*=9.1 Hz, H-6), 3.70 (t, 1H, *J*=9.3 Hz, H-4), 3.41 (m, 2H, H-2, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.6, 165.5, 165.4, 165.2 (C=O), 136.8 (Cq CHPh), 133.9–125.9 (CH_{arom}), 130.2, 129.4, 129.2, 129.1 (C_q Bz, SPh), 101.4 (*C*HPh, C-1′), 87.0 (C-1), 81.3 (C-3), 79.2 (C-4), 71.7 (C-3′), 71.4 (C-5′), 70.5 (C-2′), 70.3 (C-5), 68.4 (C-6), 67.8 (C-4′), 64.3 (C-2), 61.2(C-6′); IR (neat): 2111, 1724, 1261, 1091 cm^{-1}; $[\alpha]_D^{23}$ +7.6 (*c*=1.0 $CHCl_3$); ES-MS: *m*/*z* 986.5 $[M+Na]^+$; HRMS calcd for $C_{53}H_{45}N_3O_{13}SNH_4$: 981.3017. Found: 981.3008.

4.2.8. 3,4,6-tri-*O*-benzoyl-α-D-Galactopyranose 1,2-[phenyl {phenyl (3-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-D-mannopyranosid-6-yl)} orthoacetate] (24). The title compound was obtained from 2,3,4,5-*O*-benzoyl-1-thio-β-D-galactopyranoside (**3**) and ethyl 3-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-D-mannopyranoside (**23**) in a 3:1 mixture of donor **3** and orthoester **24** as an yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07–7.23 (m, 25H, H_{arom}), 6.03 (d, 1H, J=5.1 Hz, H-1′), 5.79 (dd, 1H, J=2.7, 4.2 Hz, H-4′), 5.74 (s, 1H, H-1), 5.55 (dd, 1H, J=4.2, 6.0 Hz, H-3′), 4.86 (d, 1H, J=11.2 Hz, C*H*H Bn), 4.60 (m, 2H, H-2′, H-6′), 4.51 (m, 2H, H-5′, CH*H* Bn), 4.35 (m, 1H, H-6′), 4.31 (m, 2H, H-2, H-3), 4.26 (m, 1H, H-5), 3.66 (dd, 1H, J=2.1, 10.5 Hz, H-6), 3.55 (dd, 1H, J=6.2, 10.6 Hz, H-6), 3.51 (dd, 1H, J=6.3, 10.3 Hz, H-4), 2.84 (m, 2H, CH_3 SEt), 1.49 (s, 3H, CH_3 isoprop.), 1.37 (s, 3H, CH_3 isoprop.), 1.25 (t, 3H, J=7.2 Hz, CH_3 SEt). ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.9–165.1 (C=O, Bz), 137.9 (C_q Bn), 136.0 (C_q SPh), 129.5, 129.4–129.4 (C_q Bz), 133.4–126.2 (CH_{arom}), 120.2 (C_q orthoester), 109.5 (C_q isoprop.), 98.1 (C-1′), 84.0 (C-1), 78.4, 76.4, 76.2, 73.1, 70.0, 69.2, 68.7, 66.4 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 72.8 (CH_2 Bn), 63.2, 62.4 (C-6, C-6′), 27.9, 26.3 (CH_3 isoprop.), 24.4 (CH_2 SEt), 14.9 (CH_3 SEt).

4.3. General procedure for the Ph_2SO/Tf_2O mediated glycosylations

To a solution of the thiodisaccharide (0.1 mmol, 1.0 equiv.), Ph_2SO (2.8 equiv.), TTBP (3.0 equiv.) in dichloromethane (4 mL) was added at −60 °C trifluoromethanesulfonic anhydride (1.4 equiv.). The reaction mixture was stirred for 5 min, after which a solution of the acceptor (1.5 equiv.) in dichloromethane (2 mL) was added. The mixture was stirred at −60 °C for 1 h, after which it was slowly warmed to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The glycosides were isolated by silica gel chromatography (ethyl acetate/ petroleum ether).

4.3.1. Methyl 6-*O*-[3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranosyl]-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (26). Trisaccharide **26** was obtained from **15** and **25**, following the general Ph_2SO/Tf_2O coupling procedure in 64% yield as a colourless oil. R_f 0.50 (50% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.01 (m, 25H, H_{arom}), 5.49 (dd, 1H, J=9.3, 9.9 Hz, H-3), 5.41 (bs, 2H, H-1″, C*H*Ph), 4.95 (dd, 1H, J=9.3, 10.3 Hz, H-4), 4.90 (d, 1H, J=4.0 Hz, H-1), 4.89 (d, 1H, C*H*H Bn), 4.88 (d, 1H, C*H*H Bn), 4.86 (dd, 1H, J=4.4, 6.5 Hz, H-2), 4.70 (d, 1H, CH*H* Bn), 4.57 (d, 1H, C*H*H Bn), 4.55 (bs, 1H, H-1′), 4.52 (d, 2H, J=11.7 Hz, CH*H* Bn, C*H*H Bn), 4.42 (d, 1H, J=13.0 Hz, CH*H* Bn), 4.42 (d, 1H, J=11.6 Hz, CH*H* Bn), 4.26 (dd, 1H, J=4.9, 10.5 Hz, H-6′), 4.17 (dd, 1H, J=1.3, 3.4 Hz, H-2′), 4.08 (m, 1H, H-3′), 4.07 (m, 1H, H-4′), 4.01 (m, 1H, H-5), 3.98 (m, 3H, H-2″, H-3″, H-5″), 3.94 (dd, 1H, J=2.0, 10.8 Hz, H-6), 3.88 (bs, 1H, H-4″), 3.81 (t, 1H, J=10.4 Hz, H-6′), 3.54 (dd, 1H, J=6.8, 9.6 Hz, H-6″), 3.50 (dd, 1H, J=7.6, 11.1 Hz, H-6), 3.44 (dd, 1H, J=5.6, 9.7 Hz, H-6″), 3.38 (s, 3H, OMe), 3.34 (m, 1H, H-5′), 2.07 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.97 (s, 3H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.1, 170.0, 169.9 (C=O), 138.8, 138.4, 138.0, 137.0 (C_q Bn, CHPh), 129.3–126.2 (CH_{arom}), 102.1 (*C*HPh), 100.5 (C-1′), 98.4 (C-1″), 96.4 (C-1), 78.2 (C-4′), 78.1, 75.3, 70.5 (C-2″, C-3″, C-5″), 75.1 (C-4″), 74.5 (C-3′), 74.6, 73.6, 73.5, 71.1 (CH_2 Bn), 70.9 (C-2), 70.0 (C-3), 69.5 (C-6″), 69.1 (C-4), 68.8 (C-6), 68.4 (C-6′), 68.1 (C-5), 67.3 (C-5′), 64.3 (C-2′), 55.3 (OMe), 20.7, 20.6 (CH_3 Ac); IR (neat): 2106, 1749, 1223, 1035 cm^{-1}; $[\alpha]_D^{23}$ +9.2 (c=0.60 $CHCl_3$); ES-MS: m/z 1141.9 $[M+Na]^+$; HRMS calcd for $C_{69}H_{67}N_3O_{18}NH_4$: 1135.4763. Found: 1135.4790.

4.3.2. Methyl 6-*O*-[3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosyl]-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (28). Trisaccharide **28** was obtained from **19** and **27**, following the general Ph_2SO/Tf_2O coupling procedure in 61% yield as a colourless oil. R_f 0.55 (33% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.07–7.18 (m, 40H, H_{arom}), 5.94 (bd, 1H, J=3.5 Hz, H-4), 5.83 (dd, 1H, J=8.0, 10.4 Hz, H-2″), 5.58 (dd, 1H, J=10.5, 3.4 Hz, H-3″), 5.57 (s, 1H, C*H*Ph), 5.06 (d, 1H, J=8.0 Hz, H-1″), 4.97 (d, 1H, J=11.0 Hz, C*H*H Bn), 4.87 (d, 1H, J=11.0 Hz, C*H*H Bn), 4.80 (d, 1H, J=11.0 Hz, CH*H* Bn), 4.76 (d, 1H, J=11.0 Hz, C*H*H Bn), 4.63 (d, 1H, J=11.0 Hz, CH*H* Bn), 4.46 (d, 1H, J=3.5 Hz, H-1), 4.50 (d, 1H, J=11.0 Hz, CH*H* Bn), 4.41 (dd, 1H, J=5.8, 11.1 Hz, H-6″), 4.31 (m, 1H, H-6″), 4.28 (m, 1H, H-6′), 4.20 (d, 1H, J=8.1 Hz, H-1′), 4.09 (t, 1H, J=7.2 Hz, H-5″), 4.02 (dd, 1H, J=1.8, 10.8 Hz, H-6), 3.97 (t, 1H, J=9.2 Hz, H-3), 3.78 (m, 1H, H-6′), 3.75 (m, 1H, H-5), 3.70 (m, 1H, H-4′), 3.68 (m, 1H, H-3), 3.65 (dd, 1H, J=4.4, 10.9 Hz, H-6), 3.50 (dd, 1H, J=7.4, 11.0 Hz, H-2), 3.44 (t, 2H, J=9.1 Hz, H-2′, H-4), 3.31 (s, 3H, OMe), 3.29 (m, 1H, H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.7, 165.6, 165.5, 165.3 (C=O), 138.8, 138.3, 138.1, 137.0 (C_q Bn), 133.5–125.9 (CH_{arom}), 129.1, 129.0, 128.8, 128.6 (C_q Bz), 102.8 (C-1′), 101.9 (C-1″), 101.3 (*C*HPh), 98.1 (C-1), 82.0 (C-3), 79.8 (C-2), 79.5 (C-3′), 79.3 (C-4′), 77.7 (C-4), 75.6, 74.7, 73.4 (CH_2 Bn), 71.7 (C-3″), 71.3 (C-5″), 70.2 (C-2″), 69.7 (C-5), 68.7 (C-6), 68.4 (C-6′), 67.8 (C-4″), 66.5 (C-5′), 65.8 (C-2′), 61.3 (C-6″), 55.2 (OMe); IR (neat): 2112, 1728, 1265, 1093, 1070 cm^{-1}; $[\alpha]_D^{23}$ +14.8 (c=0.70 $CHCl_3$); ES-MS: m/z 1340.5 $[M+Na]^+$; HRMS calcd for $C_{75}H_{71}N_3O_{19}NH_4$: 1335.5026. Found: 1335.5004.

4.3.3. 3-Azido-1-*O*-(2,6-di-*O*-benzyl-2-deoxy-phthalimido-β-D-glucopyranosyl)-propanol (29). Ethyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxyphthalimido-1-thio-β-D-glucopyrano-side and 3-azidopropanol (3 equiv.) were condensed following the general coupling protocol in 84% yield. The product (215 mg, 0.38 mmol) was treated with TfOH (96 μL, 1.14 mmol) in the presence of triethyl silane (0.20 mL, 1.26 mmol) in DCM at −78 °C. After 20 min the reaction was quenched by the subsequent addition of MeOH and triethylamine. After the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried and concentrated the mixture was purified by column chromatography to provide the title compound **29** (127 mg, 0.22 mmol, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.79–6.92 (m, 14H, H_{arom}), 5.14 (d, 1H, J=8.3 Hz, H-1), 4,75 (d, 1H, J=12.2 Hz, C*H*H Bn), 4.64 (d, 1H, J=12.0 Hz, C*H*H Bn), 4.58 (d, 1H, J=12.0 Hz, CH*H* Bn), 4.53 (d, 1H, J=12.2 Hz, CH*H* Bn), 4.24 (dd, 1H, J=8.4, 10.8 Hz, H-3), 4.15 (dd, 1H, J=8.4, 10.8 Hz, H-2), 3.81 (m, 4H, H-4, H-6, O–CH_2–CH_2), 3.66 (m, 1H, H-5), 3.45 (m, 1H, H-6), 3.11 (m, 2H, CH_2N_3), 1.66 (m, 2H, CH_2–CH_2–CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.0, 137.6 (C_q Bn), 133.8, 128.4, 128.0, 127.7, 127.6, 127.3, 123.2 (CH_{arom}), 131.4 (C_q, Pht), 98.2 (C-1), 78.6 (C-3), 74.2 (CH_2 Bn), 74.2 (C-5), 74.0 (C-4), 73.6 (CH_2 Bn), 70.3

(O–CH_2–CH_2), 55.2 (C-2), 47.8 (CH_2N_3), 28.7 (OCH$_2$–CH_2–CH_2). ES-MS: *m/z* 595.3 $[M+Na]^+$.

4.3.4. 3-Azido-1-*O*-{4-*O*-[3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl]-3,6-di-*O*-benzyl-2-deoxy-2-phtalimido-β-D-glucopyranosyl}propanol (30). Trisaccharide **30** was obtained from **13** and **29**, following the general Ph_2SO/Tf_2O coupling procedure in 69% yield as a colourless oil. R_f 0.60 (33% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10–6.83 (m, 44H, H_{arom}), 5.54 (m, 2H, H-2′, H-4′), 5.14 (d, 1H, *J*=3.3 Hz, H-1″), 5.00 (d, 1H, *J*=8.5 Hz, H-1), 4.91 (d, 1H, *J*=12.4 Hz, C*H*H Bn), 4.78 (d, 1H, *J*=8.1 Hz, H-1′), 4.74 (d, 1H, *J*=11.4 Hz, C*H*H Bn), 4.63 (s, 2H, CH_2 Bn), 4.62 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.55 (d, 1H, *J*=12.0 Hz, C*H*H Bn), 4.51 (d, 1H, *J*=12.4 Hz, CH*H* Bn), 4.44 (d, 1H, *J*=11.8 Hz, C*H*H Bn), 4.42 (d, 1H, *J*=11.8 Hz, CH*H* Bn), 4.35 (d, 1H, *J*=12.0 Hz, CH*H* Bn), 4.29 (m, 3H, 2×CH*H* Bn, H-3), 4.22 (dd, 1H, *J*=6.5, 11.3 Hz, H-6′), 4.13 (m, 2H, H-6′, H-2), 4.05 (dd, 1H, *J*=8.5, 9.9 Hz, H-4), 3.99 (dd, 1H, *J*=3.4, 10.2 Hz, H-3′), 3.91 (dd, 1H, *J*=3.3, 10.2 Hz, H-2″), 3.85 (bt, 1H, *J*=6.9 Hz, H-5″), 3.75 (m, 1H, O–C*H*H–CH_2), 3.67 (m, 2H, H-5′, H-6), 3.58 (m, 2H, H-6, H-3″), 3.41 (m, 1H, H-5), 3.38 (m, 2H, H-6″, O–CH*H*–CH_2), 3.25 (dd, 1H, *J*=1.2, 2.6 Hz, H-4″), 3.21 (dd, 1H, *J*=5.9, 9.4 Hz, H-6″), 3.08 (m, 2H, CH_2N_3), 1.81 (s, 3H, CH_3 Ac), 1.64 (m, 2H, CH_2CH_2-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.2, 166.0, 164.6 (C=O), 138.7, 138.4, 138.1, 138.0 (C_q Bn), 131.5 (C_q Pht), 129.3, 129.7 (C_q Bz), 133.7–123.2 (CH_{arom}), 100.8 (C-1′), 98.3 (C-1), 94.1 (C-1″), 78.8 (C-3″), 78.3 (C-4), 76.9 (C-3), 75.5 (C-2″), 74.8 (C-4″), 74.7 (C-5), 74.5, 73.5, 73.3, 73.2, 73.1 (CH_2 Bn), 72.3 (C-3′), 71.4 (C-2′), 71.0 (C-5′), 69.8 (C-5″), 69.2 (C-6″), 67.8 (C-6), 65.9 (O–CH_2–CH_2), 65.0 (C-4′), 61.7 (C-6′), 55.7 (C-2), 48.0 (CH_2N_3), 28.8 (CH_2–CH_2–CH_2), 20.4 (CH_3 Ac); IR (neat): 2096, 1712, 1068 cm^{-1}; $[\alpha]_D^{23}$ +39.2 (*c*=0.75, $CHCl_3$); ES-MS: *m/z* 1529.8 $[M+Na]^+$.

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References and notes

1. Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095–1121.
2. (a) Paulsen, H.; Richter, A.; Sinnwell, V.; Stenzel, W. *Carbohydr. Res.* **1974**, *38*, 312–315. (b) Paulsen, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155–224.
3. Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.
4. (a) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc. Perkin Trans. 1* **1998**, 51–65. (b) Baeschlin, D. K.; Green, L. G.; Hahn, M. G.; Hinzen, B.; Ince, S. J.; Ley, S. V. *Tetrahedron: Asymmetry* **2000**, 173–197. (c) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753. (d) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1274–1277. (e) Mong, K.-K. T.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4087–4090. (f) Fridman, M.; Solomon, D.; Yogev, S.; Baasov, T. *Org. Lett.* **2002**, *4*, 281–283.
5. (a) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278. (b) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334. (c) Zuurmond, H. M.; van der Marel, G. A.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 301–302. (d) Duynstee, H. I.; de Koning, M. C.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, *55*, 9881–9898. (e) Sliedrecht, L. A. J. M.; Zegelaar-Jaarsveld, K.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1993**, 335–337.
6. Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205.
7. (a) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067–4069. (b) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020. (c) Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 5175–5178. (d) Ercegovic, T.; Meijer, A.; Magnusson, G.; Ellervik, U. *Org. Lett.* **2001**, *3*, 913–915. (e) See Refs. 4c,5.
8. Codée, J. D. C.; Litjens, R. E. J. N.; Den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519–1522.
9. (a) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597–7598. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279. (c) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 414–417. (d) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947–1950.
10. Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323–326.
11. Mong, K.-K. T.; Lee, H.-K.; Durón, S. G.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 797–802.
12. Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015–4018.
13. Peracylated thioglycosides have been employed for the chemoselective condensation with relatively more disarmed thioglycosides. See for example: (a) Zhu, T.; Boons, G.-J. *Org. Lett.* **2001**, *3*, 4201–4203. (b) See Ref. 8.
14. (a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926–4930. (b) See Ref. 8.
15. For previous syntheses of the α-Gal epitope see: (a) Garegg, P.; Oscarson, S. *Carbohydr. Res.* **1985**, *136*, 207–213. (b) Schaubach, R.; Hemberger, J.; Kinzy, U. *Liebigs Ann. Chem.* **1991**, 607–614. (c) Reddy, G. V.; Jain, R. K.; Bhatti, B. S.; Matta, K. L. *Carbohydr. Res.* **1994**, *263*, 67–77. (d) Vic, G.; Tran, C. H.; Scigelova, M.; Crout, D. H. G. *Chem. Commun.* **1997**, 167–170. (e) Nilsson, K. G. I. *Tetrahedron Lett.* **1997**, *38*, 133–136. (f) Fang, J.; Li, J.; Chen, X.; Zhang, X.; Wang, J.; Guo, Z.; Zhang, W.; Yu, L.; Brew, K.; Wang, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 6635–6638. (g) Hanessian, S.; Huynh, H. K.; Reddy, G. V.; Duthaler, R. O.; Katopodis, A.; Streiff, M. B.; Kinzy, W.; Oehrlein, R. *Tetrahedron* **2001**, *57*, 3281–3290. (h) See Ref. 9d.

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Triruthenium dodecacarbonyl/triphenylphosphine catalyzed dehydrogenation of primary and secondary alcohols

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Abstract—Dehydrogenation of alcohols into aldehydes and ketones by $Ru_3(CO)_{12}/PPh_3$ based homogeneous catalysis has been investigated as an alternative for the classical Oppenauer oxidation. Several catalytic systems have been screened in the Oppenauer-like oxidation of alcohols. A systematic study of various combinations of $Ru_3(CO)_{12}$, mono- and bidentate ligands and hydride acceptors was performed to enable dehydrogenation of primary alcohols to stop at the aldehyde stage. Among many H-acceptors screened, diphenylacetylene (tolane) proved the most suitable judged from its smooth reduction. Electron rich and deficient analogues of tolane have been synthesized and, based on competition experiments between these H-acceptors, a tentative catalytic cycle for the $Ru_3(CO)_{12}/PPh_3$-catalyzed dehydrogenations has been proposed.
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1. Introduction

The ever-growing concern to develop more efficient key transformations in organic synthesis has shifted the focus to catalytic processes. Much effort has been expended on the development of novel transition metal complexes to catalyze the oxidation of alcohols to aldehydes and ketones by a variety of inexpensive and environmentally compatible oxidants such as hydrogen peroxide, molecular oxygen and to a lesser extent sodium hypochlorite.[1] Catalytic methods avoiding stoichiometric amounts of inorganic reagents offer environmental benefits. Here, we report a catalytic methodology for dehydrogenation of alcohols using $Ru_3(CO)_{12}/PPh_3$ as catalyst precursor. As H-acceptor tolane was needed resulting in a less than optimal atom economy.

2. Results and discussion

Various commercially available late transition metal complexes were screened in the catalytic dehydrogenation. Although platinum and palladium are well-known dehydrogenation and hydrogenation catalysts, respectively, and platinum has good β-hydrogen elimination properties, they display little or even no activity in the dehydrogenation of 1-octanol or 1-decanol. Catalysts like $Pd(PPh_3)_2(OAc)_2$, $Pd(PPh_3)_4$, $Ir(PPh_3)_3H(CO)$ and $Rh(PPh_3)_3H(CO)$ in combination with tolane gave similar results and also platinum catalysts like $Pt(PPh)_4$ and $PtCl_2(PPh_3)_2$ were completely inactive. The $RuCl_2(PPh_3)_3$ catalyst, which is very active in the hydrogen transfer to acetone as proposed by Bäckvall et al., showed no catalytic activity in the dehydrogenation of primary alcohols.[2,3a] Only one rare example was published by Oshima in the oxidation of dodecanol.[3b] However, when $Ru_3(CO)_{12}$ was employed as catalyst in combination with triphenylphosphine as ligand (Ru/P atomic ratio=1) and tolane as H-acceptor, aldehydes could be obtained in 60–80% yield together with small amounts of ester. $Ru_3(CO)_{12}$ catalyzed dehydrogenations in the absence of additional ligand are known to solely yield esters.[14,22] Initial oxidation experiments with $Ru_3(CO)_{12}/PPh_3$ have been performed in toluene as solvent in an autoclave at 150 °C. Subsequent experiments demonstrated that the same results could be obtained when the reactions were performed in *p*-xylene at 130 °C in standard glassware equipment. The catalytic system can be generalized as depicted in Scheme 1.

The major by-products of the catalytic dehydrogenation of primary alcohols (RCH_2OH) are the corresponding acids

Keywords: Triruthenium dodecacarbonyl catalyst; Catalytic dehydrogenation; Alcohols; Ligands; Hydride acceptors.
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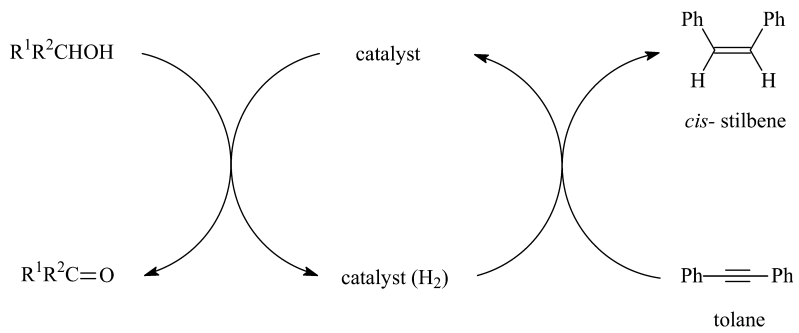
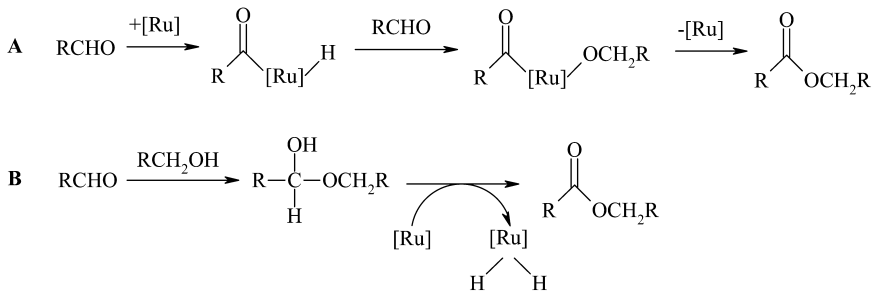


Scheme 1. Irreversible hydrogen transfer from alcohols to tolane (diphenylethyne).



Scheme 2. Proposed pathways towards ester formation.

(RCO_2H) and esters (RCO_2CH_2R). When the reactions are performed under oxygen-free conditions, over-oxidation into the acid is prevented. However, ester formation still occurs. For the ester formation two pathways have been proposed, both starting from the aldehyde (Scheme 2).[4,5]

Product formation might be significantly influenced by variation of the ligands and also the cone or bite angles of the ligands in the catalytically active complex as it has long been recognized that changing the ligands may cause marked changes in the behavior of the free ligands and of their transition metal complexes.[6–10] To our knowledge the exact nature of the coordination of diphosphines at $Ru_3(CO)_{12}$ was not yet studied. Thus, $Ru_3(CO)_{12}$ was tested in combination with several ligands having different cone angles and electronic properties in order to favor aldehyde formation and to suppress the ester formation, the results of which are collected in Table 1.

Table 1. Conversion and yield for monodentate ligands differing in cone angle and electronic properties in the dehydrogenation of 1-octanol[a]

Entry	Ligand	Cone angle	Conv. (%)	$Y_{aldehyde}$[b] (%)	Y_{ester} (%)
1	$P(OEt)_3$	109	73	0	31
2	$P(OPh)_3$	130	68	0	22
3	PPh_3	145	100	80	0
4	$(p\text{-}CH_3C_6H_4)_3P$	145	100	64	8
5	$(p\text{-}CH_3OC_6H_4)_3P$	145	100	60	9
6	$(p\text{-}CF_3C_6H_4)_3P$	145	82	60	3
7	$(o\text{-}CH_3C_6H_4)_3P$	194	93	46	0
8	$(n\text{-}Bu)_3P$	132	42	12	0
9	$(C_6H_{11})_3P$	170	100	11	0
10	tri-(2-Furyl)phosphine	—	75	9	21

[a] All experiments were performed at 100 °C with 1-octanol as substrate in the presence of 5 mol% catalyst, 17 mol% of ligand (Ru/P atomic ratio=0.88) and with 200 mol% of tolane. *p*-Xylene was used as solvent and the reactions were stopped after 4 h.

[b] $Y_{aldehyde}$=yield$_{ald}$=conversion×selectivity$_{aldehyde}$.

With PPh_3, $(p\text{-}CH_3OC_6H_4)_3P$ or $(o\text{-}CH_3C_6H_4)_3P$ as ligand a fair amount of desired aldehyde and only a very small amount of ester were formed. The other ligands tested gave lower conversions or more ester.

Ligands with different bite angles were also tested in combination with $Ru_3(CO)_{12}$. The results of these experiments are collected in Table 2.

The bidentate ligands tested did not suppress the ester formation and did not yield aldehyde. The yield of ester formation depends on the bite angle as demonstrated by the results in Figure 1. Increasing flexibility of a ligand backbone raises the chance of an arm-off η^1 coordination (entries 4, 5 and 6 compared to 1, 2, and 3). Ligands with good chelating properties display high and very similar catalytic activities within a range of bite angles from 72 to 92°. Lower activity is afforded by potentially non-chelating

Table 2. Conversion and yield for bidentate ligands differing in bite angles in the dehydrogenation of 1-octanol[a]

Entry	Ligand	Bite angle	Conv. (%)	Y_{ester}[b]	$Y_{aldehyde}$
1	$Ph_2PCH_2PPh_2$	72	100	50	0
2	$Ph_2P(CH_2)_2PPh_2$	83	100	47	0
3	$Ph_2P(CH_2)_3PPh_2$	92	100	47	0
4	$Ph_2P(CH_2)_4PPh_2$	97	72	12	0
5	$Ph_2P(CH_2)_5PPh_2$	—	85	22	0
6	$Ph_2P(CH_2)_6PPh_2$	—	88	26	0
7	Diphenyl-2-pyridylphosphine	—	80	0	30
8	2,2′-Dipyridyl	—	100	0	50

[a] All experiments were performed in *p*-xylene at 130 °C with 1-octanol as substrate in the presence of 5 mol% catalyst, 5 mol% of bidentate ligand (Ru/P atom ratio=1.5) and 200 mol% of tolane. Furthermore, all experiments were performed in *p*-xylene and were stopped after 5 h.

[b] Fifty percent yield corresponds to 100% conversion of 1-octanol (RCH_2OH) into ester (RCO_2CH_2R).

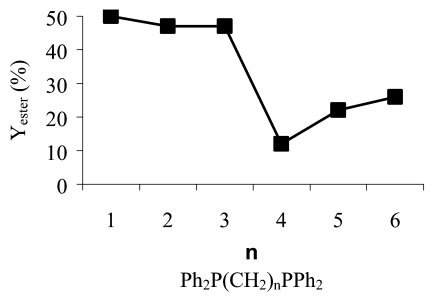


Figure 1. Effect of bite angle on ester formation in the ligand series $Ph_2P(CH_2)_nPPh_2$. For reaction conditions see Table 2.

The conversion and selectivity to the aldehyde were nearly the same when a Ru/P atomic ratio of 0.5 or 0.88 was chosen. Lower Ru/P atomic ratios rendered the reaction slower and the selectivity lower. Presumably, excess of ligand is blocking free coordination sites on the catalyst and consequently retards the reaction. The optimal amount of PPh_3 would be in between a Ru/P atomic ratio of 0.5 and 0.88. Due to the small difference in selectivity between the two ratios, all other experiments where performed with a Ru/P ratio of 0.88. Furthermore, the optimum amount of tolane was found to be 200 mol%. Less tolane led to lower reaction rates and more ester formation. Larger amounts

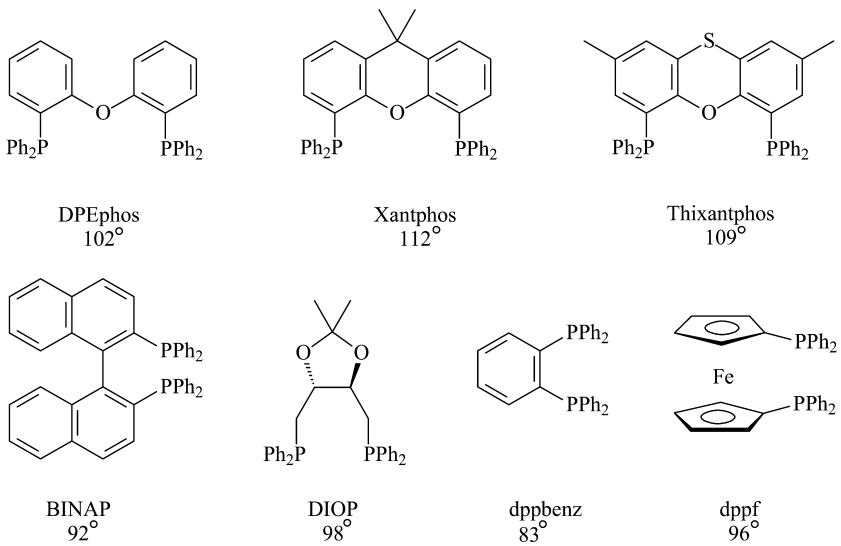


Figure 2. Additional bidentate ligands screened for $Ru_3(CO)_{12}$-catalyzed dehydrogenation of 1-octanol including their bite angles.

ligands. Less ester formation seems to go hand in hand with a slower reaction.

Several other bidentate ligands screened like DPEphos, xantphos, thixantphos, BINAP, DIOP, dppbenz and dppf (see Figure 2 for structures and bite angles) in equimolar amounts with respect to the Ru-catalyst did not give satisfactory results and no clear trends in the conversion rate or yield of the aldehyde could be observed.

From the results collected in Tables 1 and 2, it can be concluded that ester formation is almost completely suppressed when $Ru_3(CO)_{12}$ is used as catalyst in combination with PPh_3 as ligand (cone angle 145°). The effect of the amount of PPh_3 on the ester formation was also investigated (Table 3) in the aforementioned conditions. The Ru/P atomic ratio was changed in every experiment. Furthermore, all experiments were performed in *p*-xylene and were stopped after 5 h.

Table 3. Conversion and yields in the dehydrogenation of 1-octanol searching for the optimal amount of PPh_3[a]

Ru/P ratio	Conv. (%)	Y_{ald} (%)	Y_{ester} (%)	S_{ald} (%)
0.88	100	59	0	59
0.5	100	62	0	62
0.25	88	41	0	47

[a] Reaction conditions as in Table 1.

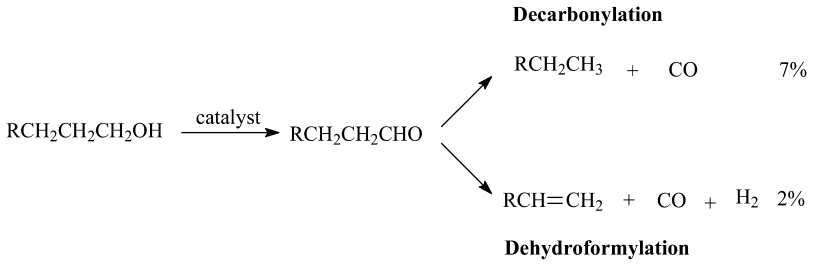
(400 mol%) diminished reaction rates but did not affect the selectivity. The observation that lower concentrations of the H-acceptor led to more ester formation indicates that tolane is not only acting as a H-acceptor but is also playing the role of ligand. Ester formation could also be suppressed by keeping the alcohol concentration as low as possible, that is, working under substrate starving conditions. This was accomplished by adding the alcohol over a period of 1 h to a mixture of 5 mol% $Ru_3(CO)_{12}$, 17 mol% PPh_3 (Ru/P atomic ratio of 0.88) and 200 mol% of tolane.

To widen the scope of the $Ru_3(CO)_{12}/PPh_3$ catalyzed dehydrogenations, several primary and secondary alcohols

Table 4. Oxidation of primary and secondary alcohols with $Ru_3(CO)_{12}$[a]

Entry	Substrate	Catalyst (mol%)	Temp. (°C)	Time (h)	Conv. (%)	*Y* (%)
1[b]	1-Octanol	5	130	5	100	80
2	1-Octanol	5	130	5	100	59
3	1-Decanol	5	130	5	100	54
4	Geraniol	5	100	4	100	82
5	(*S*)-Citronellol	5	130	5	100	77
6	Benzyl alcohol	5	100	4	100	71
7	*p*-Methoxy-benzyl alcohol	5	100	4	100	99
8	Cinnamyl alcohol	5	100	2	100	90
9	2-Decanol	0.5	100	4	94	92
10	Cholesterol	5	150	12	100	94
11	4-*t*-Butyl-cyclohexanol	0.5	130	12	100	88

[a] See Section 4 for the reaction conditions.
[b] Slow addition experiment.



Scheme 3. Consecutive reactions observed during the dehydrogenation of primary alcohols.[11,12]

have been subjected to oxidation, see Table 4. For the dehydrogenation of primary alcohols, 17 mol% PPh_3 was always used to suppress ester formation. In contrast, from secondary alcohols ketones can be produced with relatively high rates and selectivities. In these oxidations, no ligand is needed to suppress side reactions and lower concentrations of the catalyst can be used.

The yield of 1-octanal could be enhanced from 59 to 80% when the alcohol was slowly added to the catalyst (entries 1 and 2). Alcohols containing functional groups like double bonds could be oxidized, leaving the double bond intact (entries 4, 5, 8 and 10). When primary alcohols are oxidized, a considerable loss of material takes place except in the case of *p*-methoxybenzyl or cinnamyl alcohol. Part of the product loss may result from dehydroformylation and decarbonylation of the aldehyde as a consequence of the high temperature (see Scheme 3). When 1-dodecanol was oxidized, these consecutive reactions accounted for ~10% loss. When lower boiling alcohols depicted in Table 4 were oxidized, the decarbonylated and dehydroformylated products evaporated from the reaction mixture before analysis. Also high boiling aldol condensation products might have been formed although no experimental evidence was found. However, the undesired decarbonylation and dehydroformylation as well as aldol condensation reactions can only occur when the primary alcohols are first oxidized into the aldehydes. In the case of entries 7 and 8, decarbonylation and dehydroformylation are prevented due to conjugation between carbonyl and the carbon–carbon double bond or aromatic ring.

There is also some evidence for coordination of the formed ester molecules to the metal center of the catalyst. When half the amount of catalyst was used less material was missing than with double the amount of catalyst. However, attempts to release material from the catalyst by adding strongly coordinating ligands, like cyanide or by phosphine ligands failed. So it remains unclear what the fate of the missing material is.

All alcohols containing unsubstituted ethylene or acetylene groups, yielded a substantial number of by-products and were not further investigated. Even alcohols with substituted acetylenes like 6-phenyl-5-hexyn-3-ol yielded mixtures of products. The hydride has the option to transfer intra- or intermolecularly either to the triple bond of 6-phenyl-5-hexyn-3-ol or to that of the actual H-acceptor tolane.

Another aspect investigated is the performance of alternatives to tolane as H-acceptor. Tolane is initially transformed into *cis*-stilbene that slowly isomerizes to *trans*-stilbene at elevated temperatures. Both isomers are difficult to separate from the product. For this reason other cheap H-acceptors like nitrobenzene, *m*-dinitrobenzene, azobenzene, phenazine, diisopropyl azodicarboxylate, *tert*-butylperoxide, dehydrolinalol, nicotinamide and analogues were screened. The results with these alternative H-acceptors are, however, disappointing. Surprisingly, when tolane was replaced by 1-phenylpropyne, high yields of ester and only small amounts of the aldehyde were obtained, indicating that small changes in H-acceptor may have a dramatic effect on the selectivity. Furthermore, it also suggests that tolane is not only acting as H-acceptor but is also suppressing ester formation efficiently. Subsequently, other substituted analogues of tolane with electron withdrawing or electron releasing substituents have been synthesized. These analogues might provide information about the catalytic cycle. In this cycle, the H-acceptor has to coordinate to the metal center first. After coordination, a hydride is transferred from the metal center to the H-acceptor. Electron rich H-acceptors coordinate well to the metal center but are poor hydride acceptors. The opposite is true for electron deficient H-acceptors. Electron deficient compounds would take up the hydride easily but do not coordinate very well.

For this reason, the MeO (electron rich) and CF_3 (electron deficient) substituted analogues of tolane have been synthesized.[13] Both substituted tolane analogues could be isolated in 80% yield and were studied in the dehydrogenation of 1-octanol.

The reactions performed at 130 °C in *p*-xylene as solvent in the presence of the catalytic system $Ru_3(CO)_{12}/PPh_3$ (Ru/P atomic ratio of 0.88) were stopped after 5 h. The results of the experiments with different H-acceptors are collected in Table 5.

In the catalytic systems, tolane is the best H-acceptor followed by the electron rich 4-MeO-tolane. Both tolane and 4-MeO-tolane coordinate better to the metal center than 4-CF_3-tolane does. Due to the considerably lower fraction of complexed 4-CF_3-tolane, the overall rate of hydride insertion is lower compared to that of the other two

Table 5. $Ru_3(CO)_{12}/PPh_3$ catalyzed dehydrogenation of 1-octanol with tolane and substituted analogues

H-acceptor	Conv. alcohol (%)	Yield aldehyde (%)
Tolane	100	72
4-MeO-tolane	93	61
4-CF_3-tolane	50	22

H-acceptors. The difference between tolane and the electron rich 4-MeO-tolane may originate from the more difficult H-uptake by the latter, despite its easier complexation. In addition, experiments with equimolar mixtures of two H-acceptors were conducted and the catalyst performance after 5 h reaction time is collected in Table 6.

Table 6. $Ru_3(CO)_{12}/PPh_3$ catalyzed dehydrogenation of 1-octanol with equimolar mixtures of H-acceptors

H-acceptor	Conv. alcohol (%)	Yield aldehyde (%)
Tolane/4-MeO-tolane	93	58
Tolane/4-CF_3-tolane	56	22
4-MeO-tolane/4-CF_3-tolane	100	70

Compared to the oxidations with tolane, 4-MeO-tolane or the mixture of tolane and 4-MeO-tolane, the reaction with a mixture of 4-MeO-tolane and 4-CF_3-tolane is surprisingly fast. The conversion of 4-CF_3-tolane into 4-CF_3-stilbene is even faster than those of tolane or 4-MeO-tolane into the corresponding stilbene compounds, see Table 7.

Table 7. Conversion of mixtures of H-acceptor in the $Ru_3(CO)_{12}/PPh_3$ catalyzed dehydrogenation

H-acceptor mixture[a]	Conv. (%)
Tolane/4-MeO-tolane	46/51
4-MeO-tolane/4-CF_3-tolane	35/64

[a] Molar ratio is 1, but total ratio tolane/substrate is 2.

The conversions of tolane and 4-MeO-tolane are comparable indicating that both compounds are comparable in coordinating and accepting the hydride. The higher conversion of 4-CF_3-tolane with respect to 4-MeO-tolane indicates that both H-acceptors play an important but different role in the dehydrogenation of the alcohols. First, the electron rich 4-MeO-tolane will coordinate to the metal center and this increases the electron density on the metal center. As a result the electron deficient 4-CF_3-tolane can coordinate and will then be reduced very fast. The asymmetry introduced by the substituents on the hydride acceptor may also play an important role in the coordinating and hydride accepting properties of the H-acceptor. Unfortunately, the effect of a symmetrically disubstituted tolane was not studied and this leaves room for speculation.

Furthermore, experiments were performed with a radical scavenger to determine whether the oxidation of alcohols is a one or a two-electron process. Standard reaction conditions were used with the exception that in these experiments 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added as a radical scavenger. The results are comparable to the experiments, which were performed under standard reaction conditions without radical scavenger. Hence, it can be concluded that the oxidation is not of a radical nature.

Attempts to unravel the mechanistic pathway of the catalytic reaction were also initiated. Ruthenium complexes formed during the $Ru_3(CO)_{12}/PPh_3$ catalyzed dehydrogenation of 1-octanol in combination with tolane as H-acceptor precipitated from the reaction mixture. The MALDI-TOF MS spectrum of the solid showed 4 different molar masses, see Figure 3.

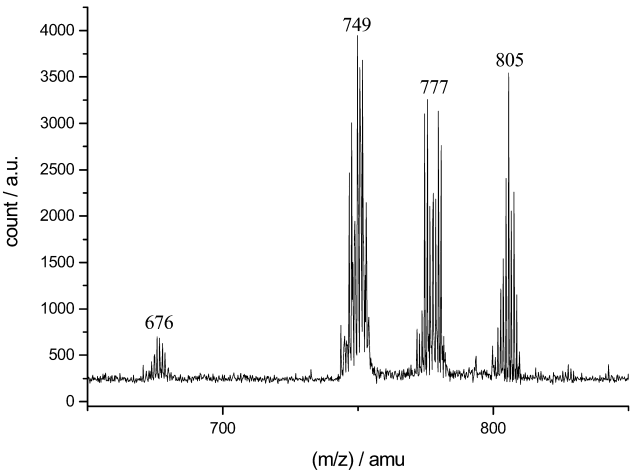


Figure 3. MALDI-TOF MS spectrum obtained from a ruthenium complex isolated during $Ru_3(CO)_{12}/PPh_3$ catalyzed dehydrogenation of 1-octanol.

In this particular case, crystals were grown from one isolated Ru-complex. The X-ray structure of these crystals revealed a mass of 804 corresponding to the structure depicted in Figure 4. The analyzed crystals turned out to be a dichloromethane solvate of the Ru-complex. The molecular structure of the Ru-complex is very similar to that observed in the benzene solvate reported earlier by Yamazaki and Taira.[22]

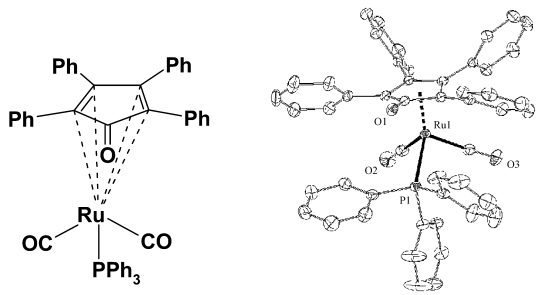
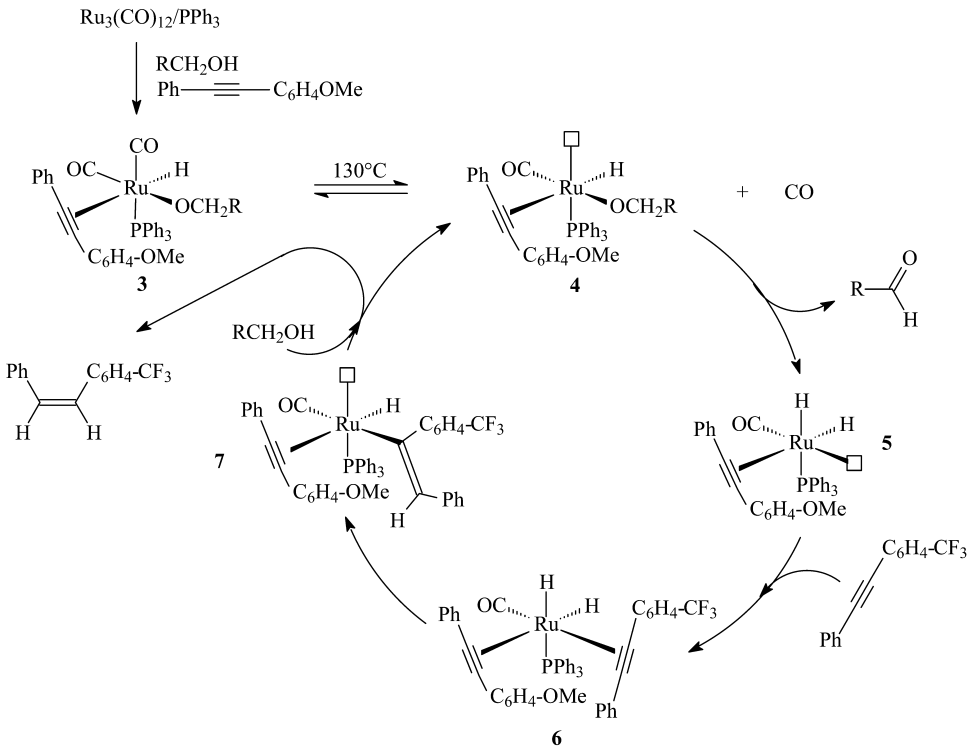


Figure 4. X-ray structure of the isolated ruthenium complex from $Ru_3(CO)_{12}/PPh_3$ catalyzed dehydrogenation of 1-octanol. H atoms and solvent molecule are omitted for clarity. Displacement ellipsoids are drawn at the 50% probability level.

In this complex tetracyclone, formally composed of two tolane molecules and one carbon monoxide molecule as depicted in Figure 4, acts as a ligand. An envelope structure is adopted by the tetracyclone ring. The carbonyl carbon atom is located 0.236(2) Å from the least-squares plane through the atoms of the diene system, who all lie within 0.03(2) Å of this plane. The distances between the diene carbons are similar in length (C–C 1.44–1.45 Å, observed range: 1.438(3)–1.453(3) Å; the C–C (carbonyl) bonds are significantly longer: 1.480(3) and 1.482(3) Å), indicating delocalization of the double bonds over the four atoms. The isolated ruthenium complex has been investigated for its catalytic activity. Unfortunately, it turned out that this complex is not the active species in the catalytic cycle and hence, its formation is expected to reduce the activity of the catalytic system.

Since little mechanistic information about the $Ru_3(CO)_{12}$ catalyzed reactions is available, it was difficult to obtain information about the catalytic cycle. Nevertheless, based



Scheme 4. Proposed catalytic cycle for the $Ru_3(CO)_{12}$ catalyzed dehydrogenations.

on the results obtained so far, particularly those from the competition experiments with the electron rich and electron deficient tolane analogues, a tentative catalytic cycle can be proposed, see Scheme 4.

Before entering the catalytic cycle, the $Ru_3(CO)_{12}$ metal cluster is proposed to be defragmented into the mono-metallic complex **3** by PPh_3, the electron rich 4-MeO-tolane and the alcohol. Due to high temperature, a CO molecule is released generating a free coordination site in **4**. β-Hydride elimination from the alkoxide gives rise to a ruthenium hydride species **5** and one aldehyde or ketone molecule is released. Subsequently, the electron deficient 4-CF_3-tolane can coordinate to the metal center **6** due to the higher electron density on the metal induced by the electron rich 4-MeO-tolane. One hydride is inserted in the 4-CF_3-tolane ligand and a free coordination site is generated in **7**. Concomitant reductive elimination from the 4-CF_3-tolane followed by oxidative addition of an alcohol molecule restores ruthenium complex **4** and in this way the catalytic cycle is closed.

3. Conclusions

In contrast to the classical Oppenauer and the Oppenauer-like oxidation presented by Bäckvall,[2,3] it was found that the dehydrogenations of primary and secondary alcohols are catalyzed by $Ru_3(CO)_{12}$ in the presence of tolane as H-acceptor.[23] Screening experiments with several ligands demonstrated that ester formation is almost completely suppressed with triphenylphosphine as ligand and the selectivity towards the aldehyde never exceeded 80%. For the dehydrogenation of primary alcohols, additional ligand (PPh_3) is needed to suppress ester formation. Non-conjugated aldehydes often give decarbonylation and dehydroformylation as consecutive reaction.

No PPh_3 and less $Ru_3(CO)_{12}$ are needed for the oxidation of secondary alcohols and still high conversions and selectivities for ketones are obtained.

Taking into account all the experimental results a catalytic cycle has been proposed.

4. Experimental

4.1. General

All starting materials were obtained from commercial suppliers and used as received. All reactions were performed under an atmosphere of dry argon. Analytical thin layer chromatography was performed on Kieselgel 60 F-254 precoated silica gel plates. Visualization was accomplished with UV light or iodine vapour. Column chromatography was performed on Merck silica gel 60 or on Merck aluminum oxide 90. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a 400 MHz NMR (Varian Mercury, 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR), or on a 300 MHz NMR (Varian Gemini, 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR). Proton chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS), whereas the carbon chemical shifts are reported in ppm downfield of TMS using the resonance of the deuterated solvent as internal standard. The phosphorus shifts were referenced to 85% H_3PO_4. IR-spectra were recorded on a Perkin Elmer ATR-IR Spectrum One. MALDI-TOF-spectra were obtained on a PerSeptive Biosystems Voyager DE PRO spectrometer using α-cyano-4-hydroxycinnamic acid

as a matrix. GC analyses were performed using a Zebron ZB-35 or a Chirasil-Dex-CB column on a Perkin Elmer Autosystem in combination with a flame ionization detector. Conversion and yields were determined by using 1,3,5-tri-*tert*-butylbenzene as internal standard. GC/MS measurements were obtained with a Shimadzu GC/MS-QP5000 using a Zebron ZB-35 column.

4.1.1. $Ru_3(CO)_{12}$ catalyzed dehydrogenations of primary alcohols with monodentate ligands, general procedure. All monodentate ligands were obtained from Aldrich, Acros or Strem. All catalytic oxidation experiments were performed in a dry, oxygen-free argon atmosphere. A typical experiment was performed as follows. An oven-dry 40 mL Radley carousel reaction tube was flushed with argon before it was charged with $Ru_3(CO)_{12}$ (61.2 mg, 0.096 mmol), tolane (684 mg, 3.84 mmol) as H-acceptor and triphenylphosphine (85.6 mg, 0.326 mmol) as metal ligand. Alcohol (1.92 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 81 mg, 0.33 mmol) dissolved in *p*-xylene (2.50 mL) were added to the mixture. A small aliquot was taken from the alcohol/internal standard solution for GC analysis. The reaction tube was placed in a 12 tube Radley reaction carousel and the mixture was heated and stirred with a magnetic stirrer for several hours. Small aliquots of reaction mixture were taken for GC analysis. The products were characterized by GLC and GC/MS by comparison with authentic samples. The conversions and yields were determined with GLC (Tables 1, 2 and 4).

4.1.2. $Ru_3(CO)_{12}$ catalyzed dehydrogenations of primary alcohols with bidentate ligands, general procedure. All bidentate ligands were obtained from Aldrich, Acros or Strem. In a typical experiment, the oven-dry 40 mL Radley carousel reaction tube was charged with $Ru_3(CO)_{12}$ (61.2 mg, 0.096 mmol), tolane (684 mg, 3.84 mmol) and 0.096 mmol bidentate ligand. 1-Octanol (250 mg, 1.92 mmol) and internal standard (1,3,5-tri-*tert*-butylbenzene, 81 mg, 0.33 mmol) dissolved in *p*-xylene (2.50 mL) were added to the mixture. GC analysis was performed after 5 h as described above.

4.1.3. $Ru_3(CO)_{12}$ catalyzed dehydrogenations of secondary alcohols, general procedure. The procedure was analogous to that of the primary alcohols with monodentate ligands (see Section 4.1.1). In all of the examples, no ligand was added.

4.1.4. Octanal. 1-Octanol was dehydrogenated according to the procedure described above. The product was characterized (GC) by comparison with an authentic sample. After 5 h, octanal was obtained in 80% yield after bulb-to-bulb distillation. Spectral data were in accordance with the literature.

4.1.5. Benzaldehyde. Benzyl alcohol was dehydrogenated according to the procedure described above. The product was characterized (GC) by comparison with an authentic sample. After 5 h, benzaldehyde was obtained in 71% yield after bulb-to-bulb distillation. Spectral data were in accordance with the literature data.

4.1.6. 2-Decanone. 2-Decanol was dehydrogenated according to the procedure described above. The product was characterized (GC) by comparison with an authentic sample. After 5 h, 2-decanone was obtained in 92% yield after bulb-to-bulb distillation. Spectral data were in accordance with the literature data.

4.1.7. 4-Cholestene-3-one. Cholesterol was dehydrogenated according to the procedure described above. The product was characterized (GC) by comparison with an authentic sample. The yield was determined with GLC. Purification of the reaction mixture by flash column chromatography (silica gel, with dichloromethane/diethyl ether (20:1)) yielded 4-cholestene-3-one as a light brown/white powder (94%). The spectral data was in accordance with literature data.[15]

4.1.8. Screening of H-acceptors. Analogous to the general procedure, the dehydrogenation of 1-octanol was performed with 2 equiv. of the alternative H-acceptors. All reactions were stopped after 5 h. The conversion was monitered by GC analysis.

4.1.9. 4-Methoxy-diphenylethyne. A mixture of phenylacetylene (6.0 g, 58.74 mmol), 4-iodoanisole (11.7 g, 53.42 mmol), CuI (1.0 g, 5.25 mmol), dichlorobis(triphenylphosphine)palladium (II) (1.5 g, 2.14 mmol) and triethylamine (65 mL, 466 mmol) was stirred at RT. After stirring overnight, the mixture was poured into H_2O (200 mL) and extracted with diethyl ether (200 mL). The organic layer was washed successively with H_2O (100 mL) and brine (100 mL) before drying ($MgSO_4$). Evaporation of the solvent followed by bulb-to-bulb distillation under reduced pressure (150 °C/0.03 Torr), gave 4-methoxy-diphenylethyne (8.4 g, 81%) as a light yellow solid. The spectral data was in accordance with literature data.[17] Mp 58 °C (lit.[17] 52–54 °C).

4.1.10. 4-Trifluoromethyl-diphenylethyne. A mixture of phenylacetylene (2.50 g, 24.48 mmol), 4-iodobenzotrifluoride (5.50 g, 20.22 mmol), CuI (0.5 g, 2.63 mmol), dichlorobis(triphenylphosphine)palladium (II) (0.70 g, 0.10 mmol) and triethylamine (30 mL, 220 mmol) was stirred at RT. After stirring overnight, the mixture was poured into H_2O (100 mL) and extracted with diethyl ether (100 mL). The organic layer was washed successively with H_2O (50 mL) and brine (50 mL) before drying ($MgSO_4$). Evaporation of the solvent followed by bulb-to-bulb distillation under reduced pressure (150 °C/0.03 Torr), gave 4-trifluoromethyl-diphenylethyne (3.9 g, 78%) as an off-white solid. Mp 97 °C (lit.[24] 104–106 °C, dec.). The spectral data was in accordance with literature data.[16]

4.1.11. Dehydrogenation in the presence of equimolar mixtures of H-acceptor. Analogous to the general procedure, the dehydrogenation of 1-octanol was performed with a 1 to 1 mixture of H-acceptor (total 2 equiv. of H-acceptor). All reactions were stopped after 5 h. The conversion was monitored by GC analysis (Tables 5–7).

4.1.12. Dehydrogenation in the presence of radical scavenger. The dehydrogenation of 1-octanol was performed according to the general procedure including 2,6-di-*tert*-butyl-4-methylphenol (427 mg, 1.94 mmol). The conversion was monitored by GC analysis.

4.1.13. Isolation of $(Ph_4C_5O)Ru(CO)_2PPh_3$ formed during the dehydrogenation of 1-octanol. After the dehydrogenation of 1-octanol according to the standard procedure, the reaction mixture was allowed to cool to room temperature overnight. A yellow solid had precipitated. Removal of the mother liquor by filtration yielded a yellow solid that was purified by column chromatography (silica gel, CH_2Cl_2) and crystallized from CH_2Cl_2:hexane, the product was obtained as a few yellow crystals. ^{1}H NMR ($CDCl_3$): δ=7.44–6.94 (m, 35H); ^{13}C NMR ($CDCl_3$): δ=202.2, 202.1, 133.5, 133.1, 133.0, 132.6, 132.6, 132.1, 131.2, 130.3, 130.1, 130.0, 128.2, 128.1, 127.6, 126.7, 125.9, 105.6, 105.5, 81.8; ^{31}P NMR ($CDCl_3$): δ=39.0; IR (ATR): ν=3051, 2006, 1951, 1605, 1575, 1498, 1486, 1445, 1435, 1401, 1312, 1091, 1072, 1029, 1001, 838, 805, 757, 740, 727, 708, 690 cm^{-1}. MALDI-TOF *m/z* 777, 749, 805. R_f=0.22 (CH_2Cl_2). Mp 205 °C (dec.).

4.2. Crystals structure determination of $(Ph_4C_5O)Ru(CO)_2PPh_3$

A yellow crystal having approximate dimensions of 0.27×0.42×0.54 mm^3 mounted on top of a glass capillary was used for X-ray study. The data were collected on a Nonius KappaCCD diffractometer. A correction for absorption was considered unnecessary. Reduced-cell calculations did not indicate higher lattice symmetry. All data were collected at 150 K using graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The structure was solved by automatic Patterson methods (DIRDIF99).[18] The structure was refined on F^2, using full-matrix least squares techniques (SHELXL97).[19] Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for Crystallography.[20] Validation, geometrical calculations and illustrations were performed with PLATON.[21]

The crystal structure has been deposited at the Cambridge Crystallographic Data Center as (η4-2,3,4,5-tetraphenyl-2,4-cyclopentadien-1-one)-dicarbonyl-triphenylphosphine-ruthenium(0) dichloromethane solvate and allocated the deposition number CCDC 223319.

Crystal data: $C_{49}H_{35}O_3PRu{\cdot}CH_2Cl_2$, M=888.74, tetragonal, space group $I4_1/a$ (No. 88), a=22.1040(1), c=33.2826(2) Å, V=16261.44(14) Å^3, Z=16, D_{calc}=1.452 g cm^{-3}, μ(Mo Kα)=0.600 mm^{-1}, F(000)=7264, T=150 K.

Data collection and refinement: θ_{min}, θ_{max}=1.8, 27.5°, data set (*hkl*-range)=−28:28, −28:28, −43:42, total data=123,055, total unique data=9325 (R_{int}=0.050), number of refined parameters=514, final R=0.0312 [for 8043 $I > 2\sigma(I)$], final $wR2$=0.0803, goodness of fit=1.03, min. and max. residual density=−0.86, 0.68e Å^{-3}.

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References and notes

1. Sheldon, R. A.; van Santen, R. A. *Catalytic oxidations: principles and applications*; World Scientific: Singapore, 1995; p 239.
2. Aranyos, A.; Csjernyik, G.; Szabo, K.; Bäckvall, J.-E. *Chem. Commun.* **1999**, 351.
3. (a) Wang, G.-Z.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1992**, 337. (b) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.
4. Ito, T.; Horino, H.; Koshiro, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn* **1982**, *55*, 504.
5. Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885.
6. Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
7. Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. *Pure Appl. Chem.* **1999**, *71*, 1443.
8. Dierkes, P.; Van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.
9. Van der Veen, L. A.; Keeven, P. H.; Schoenmaker, G. C.; Reek, J. N. H.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 872.
10. Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. *CATTECH* **2000**, *3*, 164.
11. Chatt, J.; Shaw, B. L.; Field, A. E. *J. Chem. Soc.* **1964**, 3466.
12. Beck, C. M.; Rathmill, S. E.; Jung Park, Y.; Chen, J.; Crabtree, R. H. *Organometallics* **1999**, *18*, 5311.
13. Shirakawa, E.; Yoshida, H.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 3759.
14. (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (b) Blum, Y.; Reshef, D.; Shvo, Y. *Tetrahedron Lett.* **1981**, *22*, 1541. (c) Shvo, Y.; Blum, Y.; Reshef, D.; Maritmenzin, M. *J. Organomet. Chem.* **1982**, *226*, C21.
15. Almeida, M. L. S.; Kočovsky, P.; Bäckvall, J.-E. *J. Org. Chem.* **1996**, *61*, 6587.
16. Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 271.
17. Mouriès, V.; Waschbüsch, R.; Carran, J.; Savignac, P. *Synthesis* **1998**, 1544.
18. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; García-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. *The DIRDIF99 program system*; Technical Report of the Crystallography Laboratory, University of Nijmegen: The Netherlands, 1999.
19. Sheldrick, G. M. *SHELXL97, Program for crystal structure refinement*; University of Göttingen, 1997.
20. *International tables for crystallography*; Wilson, A. J. C., Ed.; Kluwer Academic: Dordrecht, 1992; Vol. C.
21. Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7.
22. Yamazaki, S.; Taira, Z. *J. Organomet. Chem.* **1999**, *578*, 61.
23. A significant solvent effect has been observed for these reactions. Apolar solvents such as *p*-xylene, decaline, polar solvents like NMP, DMA and DMSO and polar protic solvents like phenol and 3-ethyl-3-pentanol were studied. With phenol the best results were obtained (48% yield, 64% selectivity at 100 °C, 1 h).
24. Kiplinger, J. L.; King, M. A.; Fechtenkötter, A.; Arif, A. M.; Richmond, T. G. *Organometallics* **1996**, *15*, 5292.

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Conformational analysis and absolute stereochemistry of 'spongian'-related metabolites

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Abstract—New degraded and rearranged diterpenoids, **5**–**8**, have been isolated from the Antarctic sponge *Dendrilla membranosa*. The structure and relative stereochemistry of these compounds were determined by spectroscopic data. The absolute stereochemistry of **5** was determined by spectroscopic data using a chiral reagent. Conformational studies allowed us to assign also the absolute stereochemistry of **6**–**8**, as well as those previously isolated spongian-derived metabolites with known relative stereochemistries.
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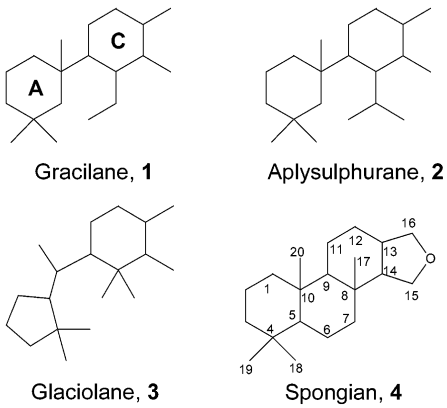
1. Introduction

Sponges are known to be a rich source of highly functionalized terpenoids[1] with degraded and rearranged carbobicyclic frameworks, such as **1**–**3**, hypothetically derived from a common spongian skeleton precursor **4**. Gracilin A[2] (isolated from *Spongionella gracilis*, Dictyoceratida), aplysillolides A and B, (*Aplysilla glacialis*, Dendroceratida) are examples[3] of naturally occurring diterpenoids belonging to the gracilane skeletal class; aplysulphurin,[4,5] tetrahydroaplysulphurins[5,6] (*Aplysilla sulphurea*), cadlinolides A and B[3] (*A. glacialis*) are aplysulphurane derivatives and glaciolide[7] (*A. glacialis*) is representative of the glaciolane skeleton. The gracilane skeleton is common to sponges of the orders Dictyoceratida and Dendroceratida while aplysulphurane and glaciolane-derived metabolites have only been found in species of the order Dendroceratida.

Dendrilla membranosa, a slow-growing sponge which has no spicules or mucus and that has not been observed to be preyed upon,[8] appears to be chemically defended,[8,9] and four related bioactive diterpenoids were previously isolated from it: 9,11-dihydrogracilin,[8,10] membranolide,[8,11] dendrillin,[9] and dendrinolide.[12]

Continuing with our interest in benthic organisms from the Antarctic[13–19] we have decided to restudy[11] the Antarctic sponge *D. membranosa* in order to isolate its minor metabolites. In this work we report on the structure of four new diterpenoids, **5**–**8**. Compound **5** is a nor-diterpene gracilane skeleton derivative while **6**–**8** are C-20 aplysulphurane-type diterpenes. The presence of a methyl butyrolactone moiety on **5** allowed us to apply a recently reported method[20] to determine the absolute configuration of **5**, and the conformational analysis of **5**–**8** allowed to establish the absolute stereochemistry of **6**–**8**, as well as that of the known spongian-derived metabolites related to gracilane **1** and aphysulphurane **2** backbone.



2. Results and discussion

D. membranosa was collected off King George Island (South Shetlands), Antarctic. From the crude extract the new compounds **5**–**8** were obtained together with the already described membranolide,[8,11] and polyrhaphin D,[21] after flash chromatography followed by gel filtration and successive HPLC.

Keywords: Sponges; Dendroceratida; Stereochemistries; Diterpenes.
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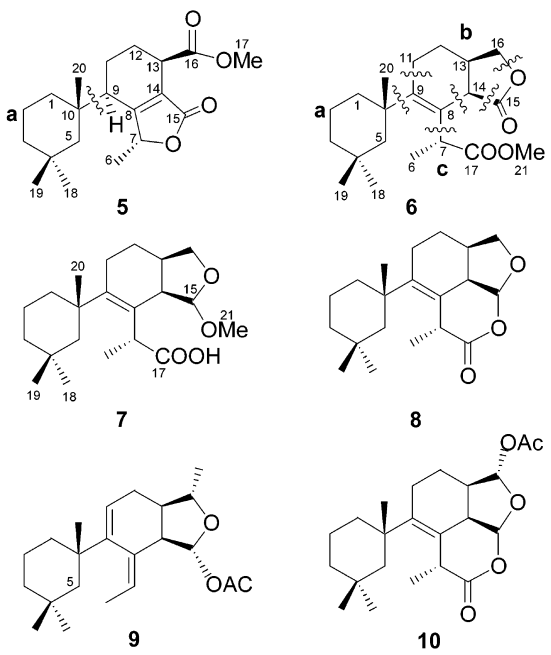


Compound **5** (HREIMS $[M+1]^+$ 335.2197 (calcd for $C_{20}H_{31}O_4$, 335.2222)) was isolated as a colorless oil. The ^{13}C NMR spectrum, Table 1, showed signals for 20 carbons, and DEPT spectral data indicated the presence of five methyl groups, one of them (C-17) attached to oxygen, six methylene groups, three methine carbons (one bearing oxygen), two quaternary olefinic carbons, two carbonyls, and two sp^3 quaternary carbons. ^1H NMR spectrum, Table 1, showed four methyl singlets, one of them as a methoxy group at δ 3.37, a signal for a secondary methyl group at δ 1.05 (d, J=6.5 Hz), a quartet at δ 4.92 (1H, q, J=6.5 Hz), a broad doublet of doubles at δ 3.50 (1H, dd, J=2.9, 2.9 Hz), and complex signals between δ 2.10 and 0.75.

The presence of a deshielded methylene carbon at around 52 ppm in **5** (entry 5, Table 1) called our attention, and the HMBC long-range correlations of this carbon with three angular methyl groups indicate that it corresponds to an isolated methylene. This led us to suspect that ring A contained in gracilane and aplysulphurane skeletons was present in **5**. A similar chemical shift of 52.7 ppm was observed[2] for the corresponding C-5 of gracilin A, **9**. The comparison of the ^{13}C NMR chemical shifts of the remaining carbon atoms of ring A of **5** with that of gracilin A[2] corroborated a fragment **a** moiety. These arguments are also applicable to compounds **6**–**8**. The C-5 chemical shift of naturally occurring metabolites related to gracilane and aplysulphurane skeletons seems very useful in assisting structural elucidation, and it is noteworthy that this has never been pointed out previously.

The presence of a methyl ester group was confirmed by the HMBC correlation between H_3-17 and C-16. One of the two remaining oxygens given by the molecular formula was a carbonyl and the other has to be attached to C-7, while both must be involved in a methyl substituted lactone ring. This lactone was established as α,β-unsaturated by the HMBC correlations between H_3-6/C-8 and H-7/C-8, C-14, which is

Table 1. ^1H and ^{13}C NMR data of compounds **5**–**8** (500 MHz, δ ppm, (J) Hz, $CDCl_3$)

No.	**5**		**6**		**7**		**8**	
	δ_H[a]	δ_C[a]	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	0.70 ddd (4.3, 13.0, 13.0) 1.30 m	35.9	β: 2.18 br d (12.8) α: 1.28 m	39.0	β: 2.17 m α: 1.30 m	39.1	1.89 m 1.08 m	39.9
2	1.38 m 1.31 m	18.9	β: 2.00 m α: 1.51 m	19.9	1.85 m 1.50 m	20.1	1.49 m	20.5
3	0.90 m 1.30 m	38.8	1.16 m 1.37 m	39.9	1.17 ddd (3.8, 13.1, 13.1) 1.35 ddd (3.8, 3.8, 13.0)	40.0	1.17 m 1.29 m	39.5
4		30.8		31.1		31.5		31.6
5	β: 1.12 d (13.5) α: 0.77 d (13.1)	51.7	β: 1.80 br d (14.1) α: 1.03 d (14.1)	50.9	β: 1.80 d (12.1) α: 1.00 m	50.8	β: 1.24 d (13.7) α: 1.78 d (13.7)	51.2
6	1.05 d (6.5)	19.2	1.18 d (7.0)	16.4	1.23 d (7.0)	15.7	1.37 d (7.4)	14.3
7	4.92 q (6.5)	79.7	4.28 q (7.0)	41.0	4.20 q (7.0)	41.5	4.14 d (7.4)	40.6
8		166.8		125.3		127.7		122.8
9	1.57 m	47.4		146.3		144.5		147.0
10		37.5		41.6		39.6		39.6
11	β: 1.50 m α: 1.30 m	21.6	β: 1.60 m α: 2.36 ddd (3.5, 3.5, 15.5)	27.1	β: 1.90 m α: 2.20 ddd (4.3, 4.3, 15.7)	27.7	β: 1.89 m α: 2.46 ddd (4.7, 4.7, 11.9)	26.8
12	1.16 m 2.07 dddd (2.8, 2.8, 5.7, 13.2)	25.4	1.43 m 1.74 m	31.3	1.30 m 1.60 m	30.7	0.89 m 1.89 m	25.5
13	3.50 dd (2.9, 2.9)	37.0	2.58 m	34.2	2.30 m	37.9	2.62 m	37.5
14		127.7	3.62 d (8.6)	41.0	2.70 dd (8.1, 2.9)	48.9	3.00 m	41.6
15		171.2		176.5	4.74 d (2.9)	113.0	6.00 d (5.8)	103.4
16		172.1	4.12 dd (1.0, 9.2) 4.39 dd (6.6, 9.1)	74.5	3.76 d (8.5) 4.10 dd (8.5, 5.4)	74.8	3.58 dd (8.9, 8.9) 4.15 dd (8.8, 8.8)	72.9
17	3.37s	51.4		175.2		178.1		172.4
18	0.83s	35.1	0.81s	26.2	0.88s	26.9	0.74s	27.5
19	0.86s	26.9	0.86s	33.0	0.86s	33.0	0.88s	32.8
20	0.74s	19.9	1.07s	31.2	1.03s	30.7	1.12s	31.8
21			3.71s	52.0	3.20s	54.9		

[a] C_6D_6.

consistent with the IR absorptions at 1757 and 1735 cm^{-1} for ester functionalities. Since the IR spectrum revealed no absorption for additional unsaturations, the molecule is tricyclic.

COSY correlated fragment H-9–H_2-11–H_2-12–H-13 and HMBC correlations of H-9 with C-8, C-14 fixed the position of the lactone ring and allowed us to link the ester appendage to C-13 in agreement with the deshielded chemical shift of H-13 and the HMBC long-range correlation between H-12 and C-16. The C-9/C-10 linkage of both six-membered rings was secured by the HMBC correlation of the downfield H-9 with C-20, C-10 and C-5. This completes the overall planar structure of **5**.

The relative stereochemistry of **5** was assigned on the basis of 2D NOESY experiments, coupling constants and molecular mechanics calculations, Figure 1. In 2D NOESY (C_6D_6) experiments H-7 shows NOE with H_3-20 and H-5β, while H-9 shows NOE with H_3-6 and H-5α. Additional NOE effects of H_3-20 with H-11β and H_3-19 were observed, establishing a β configuration for Me-20, Me-19 and H-7, and an α stereochemistry for H-9 and Me-6. The small *J*-value of H-13 (J=2.9 Hz) observed is an equatorial disposition for H-13. Thus, the stereochemistry of the carboxylate group on C-13 is axial.

Molecular mechanics calculations were performed[22] in order to find a minimized structure for **5** compatible with the NOEs observed. The minimized structure (Fig. 1) consists of a trimethylcyclohexane moiety, ring A, in a chair conformation equatorially linked at C-10 to a bicyclic system formed by a cyclohexene carboxylate ring C fused to a methyl γ-lactone residue. Conformation **5** is consistent with the observed NOEs and allowed us to establish the relative configuration as 7R^*, 9R^*, 10S^* and 13R^*. The configurations at C-9 and C-10 of **5** are coincident with those of the 9,11-dihydrogracilin A whose relative configurations were determined by X-ray analysis of an 8-keto derivative.[10]

Compound **5** is the first example of a degraded diterpenoid belonging to the gracilane skeleton that possesses a lactone function between C-7 and C-15 instead of the oxane ring between C-15 and C-16. The presence of a γ-methyl butenolide moiety on compound **5** allowed us to use the method described by Latypov et al.[20] to determine the absolute configuration of **5**. *R* and *S* 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) were used to form complexes with the γ-methyl butenolide moiety of compound **5**. NMR analysis of the Δδ of H-7 of the two complexes gave clear evidence to assign the absolute stereochemistry of C-7 as *R* (Table 2). This information, together with the NOESY data, implied that C-9 and C-13 are *R* and C-10 is *S*.

Table 2. $\delta_{H\text{-}7}$ of compound **5** with *R* and *S* TFAE at 233 K

n equiv. of (*R*) or (*S*)-TFAE	δ_R	δ_S	$\Delta(\delta_R-\delta_S)$
6	5.23509	5.26778	−0.03269
12	5.19413	5.24010	−0.04597
24	5.14964	5.21106	−0.06142

Compound **6** (HREIMS $[M]^+$ 348.2300 (calcd for $C_{21}H_{32}O_4$, 348.2300)) was isolated as a colorless oil. The ^{13}C NMR data, Table 1, indicated the presence of 21 carbons in the molecule, one of them being a methoxy group (C-21). As aforementioned, the ^1H and ^{13}C NMR spectroscopic data (Table 1) of **6** suggested that it possesses the same A ring (fragment **a**), which was corroborated by HMBC correlations.

COSY NMR experiments allowed the correlation H_2-11-H_2-12-H-13-H_2-16 and H-14-H-13 fragment **b**; and H_3-6-H-7 fragment **c**. The long-range HMBC correlation of the secondary methyl group H_3-6 with C-17 confirmed the presence of the methyl ester group at C-7 in fragment **c**. According to the degree of unsaturation, the molecule is tricyclic and, once again, taking into account the number of oxygens of the molecular formula, and the fact that molecule must possess an oxymethylene, this and the remaining oxygen must be involved in a lactone ring. From biogenetic considerations, HMBC correlations and comparison of the ^1H NMR and ^{13}C NMR data with those of the related compound tetrahydroaplysuphurin-1, **10**,[5] the structure was concluded to be as depicted in **6**.

The ^1H and ^{13}C NMR data of compound **7** are very similar to those of compound **6**, the main difference between them being the substitution of the carbonyl group of the lactone ring of **6** (δ_C 176.2, C-15) for a hemiketal carbon at δ_C 113.0. The presence of the methoxy group at C-15 was confirmed by HMBC correlation between H_3-21 and C-15. The downfield chemical shift of C-17 at δ 178.1 ppm and an IR broad absorption at 3100 cm^{-1} and a band at 1731 cm^{-1}

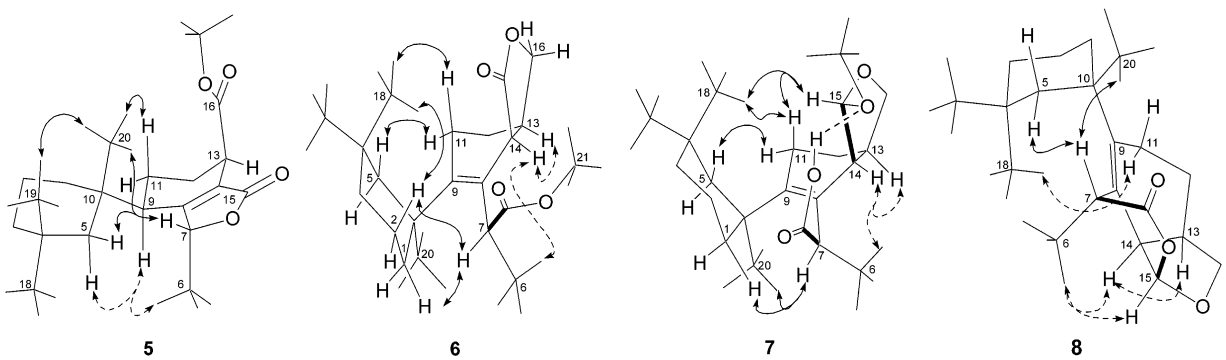


Figure 1. Selected NOEs of compounds **5**–**8**.

indicate that compound **7** must have a carboxylic acid instead of the methylester of **6**.

Compound **8** (HREIMS $[M]^+$ 318.21167 (calcd for $C_{20}H_{30}O_3$, 318.2194)) can be seen as a derivative of **7** by the loss of methanol as a consequence of an intramolecular displacement of the hemiketalic methoxy group by the free carboxylic acid to give the corresponding δ-lactone **8**. This was corroborated by the presence of a hemiketal proton at C-15 (δ_H 6.00; δ_C 103.4), one oxygen less in the molecular formula and the similarity between the ^1H and ^{13}C NMR data and those of **7**.

From the biogenetic point of view, the aplysulphurane and gracilane skeletons have been hypothesized[23] to arise from a common spongian skeleton precursor **4**, Scheme 1, by migration of the C-17 methyl group and cleavage of the C-5–C-6 bond. Assuming that the C-10 chiral centre of the related compounds **6**–**8** is not involved in that process, we could expect them to have an identical C-10 configuration.

2D NOESY experiments showed strong NOEs between H-7/H-1β and H-11α/H-5β for compounds **6** and **7**, whereas **5** and **8** shows NOE between H-7/H5β and H-7/H-5α, respectively. These NOEs indicate that ring A in compound **8** must adopt a different disposition, Figure 1, with respect to the bicyclic moiety from that of **6** and **7** in order to preserve the same configuration at C-10. This was corroborated by molecular mechanics calculations and a study of the coupling constants. The minimized structures **6**–**8**, as represented in Figure 1, were obtained, and the comparison of the well-resolved *J*-values of selected protons of these compounds with the theoretical coupling constants given by the program[22] proved to be in good agreement. For example, the *J*-values of H_2-16 (1.6, 6.4 Hz) and H-14 (8.6 Hz) of **6**; the *J*-values of H_2-16 (0.9, 4.3 Hz), H-14 (8.3 Hz) and H-15 (5.9 Hz) of **7**; and the *J*-values of H-15 (6.6 Hz) of **8** have to be compared with the *J*-values of the respective protons given in Table 1. The conformations **6**–**8**, Figure 1, fulfill additional observed NOEs H_3-6/H-14; H-13/H-14; H-7/H-2β; H_3-18/H-2β and H-11β/H_3-18 in **6**; H_3-6/H-14; H-14/H-13; H-15/H-11β, H_3-18; H-7/H_3-20 and H-11β/H_3-18 in **7**; H_3-6/H-14, H-15; H-14/H-13; H-7/H_3-20; and H-11α/H_3-18 in **8**.

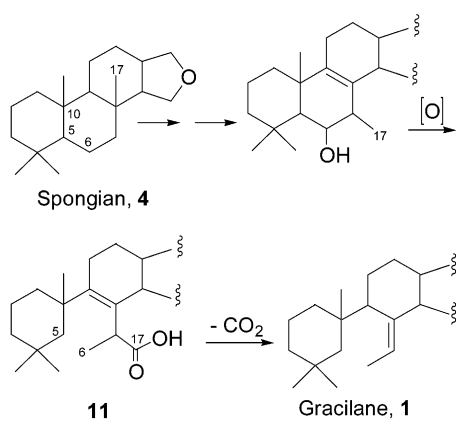
In compounds **6**–**8** the cyclohexane ring has a chair conformation with Me-18 and the bicyclic residues in axial positions. The *cis*-fused cyclohexene ring C of the bicyclic moiety of **6** and **7** adopted a similar twisted half boat arrangement. However, in **6**, the five-membered ring has an envelope conformation with the endocyclic atoms arranged in an almost ideal plane, whereas in compound **7**, that shows H-bond interaction of the proton of the acid with the oxygen of the methoxy group at C-15 on the furane ring, it was a partial envelope with C-16 out of the ideal plane through the remaining atoms of the ring.

In compound **5** ring A has a chair conformation with Me-19 and Me-20 in a 1,3-diaxial disposition. This change in the conformation of ring A of **5** with respect to that of ring A of compounds **6**–**8**, which places both H_3-19 and H_3-20 methyl groups in an equatorial configuration, explains a ^{13}C chemical shift (data in $CDCl_3$ in experimental) difference of about 7 ppm of Me-18 and Me-19 in these compounds: from $\delta_{C\text{-}18}$ 35.8 and $\delta_{C\text{-}19}$ 27.7 for compound **5** to values of δ 26.5 and 33.0 for C-18 and C-19, respectively, for compounds **6**–**8**, entries 18 and 19, Table 1.

The configuration at C-10 of compounds **6**–**8** is coincident with the *S* configuration at C-10 of **5**. All these considerations allowed us to propose the absolute stereochemistries: 7*R*,10*S*,13*R*,14*R* for **6**; 7*R*,10*S*,13*R*,14*R*,15*S* for **7**; and 7*R*,10*S*,13*R*,14*R*,15*R* for **8**, as depicted in Figure 1.

Compound **7** is biogenetically interesting because a free acid such as **11** has been proposed[22] as an intermediate in the biogenesis of the gracilane skeleton by the loss of CO_2, Scheme 1. The finding of the acid **7** as a naturally occurring metabolite supports this hypothesis, and the conservation of the chirality at C-10 as *S* in compounds **5**–**8**, which is coincident with that of the respective C-10 of spongian marine skeleton,[24] gives additional support for the biogenetic origin of these compounds from the spongian precursor, and suggests that most of the spongian-derived marine diterpenes with a given relative stereochemistry should have an absolute configuration identical with that of **5**. For instance, tetrahydroaplysulphurin-1, **10**,[4,6] and related compounds,[3–5,25] membranolide,[8,11] gracilin-A[2,10,26] and related compounds,[3,25] whose relative stereochemistries were solved by single-crystal X ray diffraction analysis or by other means.

Compound **5** is the first non-annonaceous naturally occurring metabolite containing a γ-methyl butenolide moiety to which the method described by Latypov et al.[20] was applied to solve the absolute configuration.



Scheme 1. Biogenesis of the gracilane skeleton via acid **11**.

3. Experimental

3.1. General procedures

Optical rotations were measured on a Perkin–Elmer model 343 Plus polarimeter using a Na lamp at 25 °C. IR spectra were obtained with a Perkin–Elmer 1650/FTIR spectrometer in $CHCl_3$ solutions. ^1H NMR and ^{13}C NMR, HSQC, HMBC and COSY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^1H NMR and at 125 MHz for ^{13}C NMR. Two-dimensional NMR spectra were obtained with the standard Bruker

software. EIMS and HRMS data were taken on a Micromass Autospec spectrometer. HPLC separations were performed with a Hewlett Packard 1050 (Jaigel-Sil semipreparative column, 10 μm, 20×250 mm) with hexane–EtOAc mixtures. The gel filtration column (Sephadex LH-20) used hexane–MeOH–CH_2Cl_2 (3:1:1) as solvent. Merck Si gels 7734 and 7729 were used in column chromatography. The spray reagent for TLC was H_2SO_4–H_2O–AcOH (1:4:20).

3.2. Biological material

D. membranosa (1.0 kg) was collected by SCUBA diving off King George Island (South Shetlands, Antarctic) at −35 m.

3.3. Extraction and isolation

Wet samples were extracted with acetone at room temperature, and were concentrated to give a dark residue (26.1 g). The extract was chromatographed by flash chromatography on silica gel. The fraction eluted with hexane–EtOAc (8:2) (1.19 g) was chromatographed on an LH-20 column to give a complex mixture that was further separated on HPLC to give compounds, **5** (4.1 mg), **6** (1.5 mg), and **8** (1.6 mg) and the known compounds membranolide[8,11] (53.0 mg), and polyrhaphin D[13] (0.8 mg). From the fraction eluted with hexane–EtOAc (6:4) (1.03 g) compound **7** (3.7 mg) was isolated after LH-20 column and HPLC.

3.3.1. Compound 5. Colorless oil; $[\alpha]_D^{25}$=+70 (*c*, 0.27, $CHCl_3$); IR ν_{max} (film) 1757, 1735 cm^{-1}; ^1H and ^{13}C NMR (C_6D_6), see Table 1; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (3H, s, H-18), 0.91 (3H, s, H-20), 0.97 (3H, s, H-19), 1.05 (1H, m, H-2), 1.09 (1H, m, H-3), 1.10 (1H, m, H-5α), 1.15 (1H, m, H-1), 1.40 (1H, m, H-5β), 1.41 (1H, m, H-3), 1.44 (3H, d, *J*=6.6 Hz, H-6), 1.50 (1H, m, H-1), 1.50 (1H, m, H-2), 1.57 (1H, dddd, *J*=2.9, 2.9, 2.9, 12.4 Hz, H-12), 1.69 (1H, m, H-11), 1.80 (1H, m, H-11), 2.19 (1H, m, H-9), 2.22 (1H, dddd, *J*=2.6, 2.9, 5.5, 13.1 Hz, H-12), 3.41 (1H, dd, *J*=2.8, 2.8 Hz, H-13), 3.69 (3H, s, H-17), 5.27 (1H, q, *J*=6.6 Hz, H-7); ^{13}C NMR ($CDCl_3$ 125.7 MHz) δ 19.4 (CH_3, C-6), 19.9 (CH_2, C-2), 20.8 (CH_3, C-20), 22.1 (CH_2, C-11), 25.8 (CH_2, C-12), 27.7 (CH_3, C-19), 31.5 (C, C-4), 35.8 (CH_3, C-18), 36.8 (CH_2, C-1), 37.2 (CH, C-13), 38.4 (C, C-10), 39.4 (CH_2, C-3), 48.5 (CH, C-9), 52.2 (CH_2, C-5), 52.6 (CH_3, C-17), 81.0 (CH, C-7), 127.2 (C, C-14), 168.9 (C, C-8), 172.7 (C, C-15), 172.9 (C, C-16); EIMS *m/z* 335 $[M+1]^+$ (<1), 319 $[(M-Me]^+$ (<1), 210 (100); HREIMS $[M+1]^+$ 335.2197 (calcd for $C_{20}H_{31}O_4$, 335.2222), $[M-Me]^+$ 319.1817 (calcd for $C_{19}H_{27}O_4$, 319.1909).

3.3.2. Compound 6. Colorless oil; $[\alpha]_D^{25}$=−30 (*c*, 0.10, $CHCl_3$); IR ν_{max} (film) 1768, 1730 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 348 $[M]^+$ (13), 316 $[M-MeOH]^+$ (100), 301 $[M-MeOH-Me]^+$ (41), 273 (87); HREIMS $[M]^+$ 348.2300 (calcd for $C_{21}H_{32}O_4$, 348.2300), $[M-MeOH]^+$ 316.1987 (calcd for $C_{20}H_{28}O_3$, 316.2038), $[M-MeOH-Me]^+$ 301.1799 (calcd for $C_{19}H_{25}O_3$, 301.1803).

3.3.3. Compound 7. Colorless oil; $[\alpha]_D^{25}$=+12 (*c*, 0.25, $CHCl_3$); IR ν_{max} (film) 3100, 1731 cm^{-1}; ^1H and ^{13}C NMR in $CDCl_3$, see Table 1; EIMS *m/z* 318 $[M-CH_3OH]^+$ (6), 303 $[M-CH_3-CH_3OH]^+$ (3), 274 $[M-CO_2-CH_3OH]^+$ (18), 259 (16), 245 (14), 150 (56), 69 (100); HREIMS 318.2266 (calcd for $C_{20}H_{30}O_3$, 318.2195), 303.1995 (calcd for $C_{19}H_{27}O_3$, 303.1960), 274.2338 (calcd for $C_{19}H_{30}O$, 274.2297), 259.2140 (calcd for $C_{18}H_{27}O$, 259.2062), 245.1954 (calcd for $C_{17}H_{25}O$, 245.1905).

3.3.4. Compound 8. Unstable colorless oil; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 318 $[M]^+$ (1), 274 $[M-CO_2]^+$ (25), 259 (23), 245 (26) 69 (100); HREIMS $[M]^+$ 318.2116 (calcd for $C_{20}H_{30}O_3$, 318.2194), $[M-CO_2]^+$ 274.2293 (calcd for $C_{19}H_{30}O$, 274.2296).

3.3.5. Preparation of the 2,2,2-trifluoro-1-(9-anthryl) ethanol complexes of 5. Compound **5** (1.0 mg, 3.0 μmol) and $CDCl_3$ (0.5 mL) were placed in a 5 mm NMR tube with increasing amounts of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (0, 6, 12 and 24 equiv.). The same experimental procedure was followed for the production of the corresponding (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol complexes. The ^1H NMR spectrum for each complex with each concentration was recorded at 233 K.

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References and notes

1. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcole, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2003**, *20*, 1–48, and references cited therein.
2. Mayol, L.; Piccialli, V.; Sica, D. *Tetrahedron Lett.* **1985**, *26*, 1357–1360.
3. Tischler, M.; Andersen, R. J.; Choudhary, M. I.; Clardy, J. *J. Org. Chem.* **1991**, *56*, 42–47.
4. Karuso, P.; Skelton, B. W.; Taylor, W. C.; White, A. H. *Aust. J. Chem.* **1984**, *37*, 1081–1093.
5. Karuso, P.; Bergquist, P. R.; Cambie, C. R.; Buckleton, J. S.; Clark, R. G.; Rickard, C. E. F. *Aust. J. Chem.* **1986**, *39*, 1643–1653.
6. Buckleton, J. S.; Bergquist, P. R.; Cambie, C. R.; Clark, R. G.; Karuso, P.; Rickard, C. E. F. *Acta Crystallogr. Sect. C* **1987**, *43*, 2430–2432.
7. Tischler, M.; Andersen, R. J. *Tetrahedron Lett.* **1989**, *30*, 5717–5720.
8. Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1987**, *52*, 296–298.
9. Baker, B. J.; Kopitzke, R. W.; Yoshida, W. Y.; McClintock, J. B. *J. Nat. Prod.* **1995**, *58*, 1459–1462.
10. Puliti, R.; Fontana, A.; Cimino, G. *Acta Crystallogr.* **1993**, *C49*, 1373–1376.
11. Manríquez, V.; San-Martín, A.; Rovirosa, J.; Darias, J.; Peters, K. *Acta Crystallogr. Sect. C* **1990**, *46*, 2486–2487.

12. Fontana, A.; Scognamiglio, G.; Cimino, G. *J. Nat. Prod.* **1998**, *60*, 475–477.
13. Cueto, M.; Darias, J.; San-Martín, A.; Rovirosa, J. *J. Nat. Prod.* **1998**, *61*, 1466–1468.
14. Cueto, M.; Darias, J.; San-Martín, A.; Rovirosa, J. *Tetrahedron* **1998**, *54*, 3575–3580.
15. Cueto, M.; Darias, J.; San-Martín, A.; Rovirosa, J. *J. Nat. Prod.* **1998**, *61*, 17–21.
16. Seldes, A.; Romero, M.; Gros, E. G.; Darias, J.; Rovirosa, J.; San-Martín, A. *Ser. Cient. INACH* **1990**, *40*, 81–97.
17. Cueto, M.; Darias, J.; San-Martín, A.; Rovirosa, J. *J. Nat. Prod.* **1997**, *60*, 279–281.
18. Cueto, M.; Darias, J. *Tetrahedron* **1996**, *52*, 5899–5906.
19. Seldes, A.; Deluca, M. E.; Gros, E. G.; Rovirosa, J.; San-Martín, A.; Darias, J. *Z. Naturforsch.* **1990**, *45*, 83–86.
20. Latypov, S.; Franck, X.; Jullian, J.-C.; Hocquemiller, R.; Figadère, B. *Chem. Eur. J.* **2002**, *8*, 5662–5666.
21. Bobzin, S. C.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 3902–3907.
22. *PCModel (version 7.0)*; Serena Software: Bloomington, IN.
23. Mayol, L.; Piccialli, V.; Sica, D. *Tetrahedron* **1986**, *42*, 5369–5376.
24. Arnó, M.; González, M. A.; Zaragozá, R. J. *Tetrahedron* **1999**, *55*, 12419–12428.
25. Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1986**, *51*, 2601–2603.
26. Poiner, A.; Taylor, W. C. *Aust. J. Chem.* **1990**, *43*, 1713–1727.

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Synthesis of polynitrogenated analogues of glucopyranoses from levoglucosan

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Abstract—Polynitrogenated analogues of glucopyranoses were synthesised from levoglucosan. These compounds are useful intermediates for the synthesis of new aminoglycoside mimetics.
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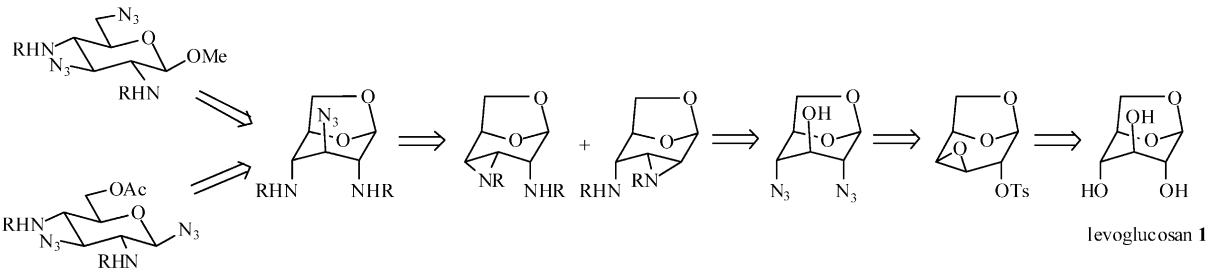
1. Introduction

A large class of aminoglycosides (such as Kanamycin, Neomycin, Tobramycin, Gentamicin) has been known over 50 years for their antibacterial activities.[1] Their mechanism of action has also been elucidated.[2] These natural products bind to ribosomal RNA of bacteria, thereby interfering with the protein biosynthesis. Despite the established bactericidal properties of aminoglycoside antibiotics, their therapeutic use is limited; their internal administration at high doses results in clinical side effects.[1] More recently, these substances have attracted attention for their antiviral applications by interacting with the viral RNA molecules.[3] The development of new antiviral agents is necessary for fighting these diseases owing to the appearance of resistant mutant strains. The aminoglycosides have been synthetically modified in ongoing efforts to discover new antiviral and antitumor agents.[4,5] Wong and co-workers have also synthesised new aminoglycoside mimetics containing motifs that recognize viral RNA.[5] We have been interested in finding an easy access to di-, tri- and tetranitrogenated analogues of glucopyranose. These compounds will be used as building blocks for the synthesis of new aminoglycoside mimetics. A number of syntheses of tetranitrogenated compounds has been reported starting from a variety of carbohydrate derivates, but they are often lengthy and yields are unsatisfactory.[6] Moreover, they could also be very interesting for the synthesis of LPA[7] analogues and for the elaboration of macromolecular organised dendrimers.[8]

2. Results and discussion

As illustrated in Scheme 1, a retrosynthetic scheme was planned starting from levoglucosan **1**, readily available on multi-gram scale using our recently easy preparation of by a solid-supported, solvent-free, microwave assisted procedure.[9] The preparation of these polynitrogenated compounds was considered via opening of epoxides and aziridines with azide ions. The preparation of 2,3,4-trinitrogenated glucopyranoside could be carried out via the formation 2,3 or 3,4-aziridine intermediates. According to Fürst–Plattner rules,[10] these two types of aziridines might



Scheme 1. Retrosynthetic scheme.

Keywords: Levoglucosan; Aziridine; Azidolysis.
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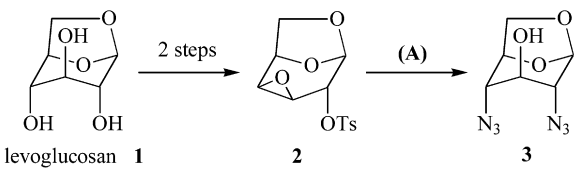
be opened by a nucleophile (azide ions in our case) in C-3 position leading to the same product.

Starting from levoglucosan **1**, the epoxide **2** is readily obtained in two steps (61% overall yield) using the Grindley procedure.[11] Conversion of epoxide **2** to diazido compound **3** has been previously described by Paulsen and co-workers[12] but requires three steps in 40–60% overall yield. We anticipated that **3** could be obtained in one step using a microwave assisted reaction with azide nucleophiles. It has been shown that microwave heating provided improvement (better yields and decrease in reaction times) in many synthetic reactions.[13] However, to the best of our knowledge, the use of azide ions under microwave irradiation has never been reported. Preliminary attempts to open epoxide **2** with NaN_3 in the presence of various Lewis acids were disappointing. However, using an excess[14] of LiN_3 (4 equiv.), in the presence of alumina, in DMF/toluene concentrated medium, the compound **3** resulting by successive trans diaxial attack at C-4 and then C-2 positions was obtained in a gratifying 90% yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (A) LiN_3 (4 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene, MW, 20 min, 90%.

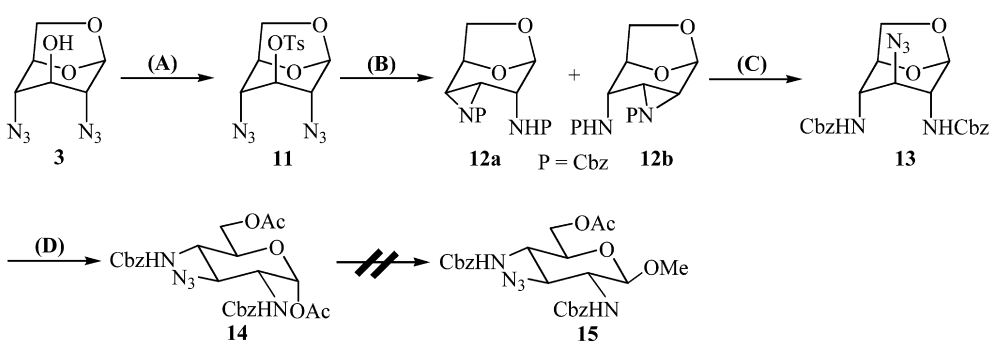
Table 1.

Starting material	Product	Yield (%)
4	**3**	70
5	**8**	85
6	**9**	90
7	**10**	85

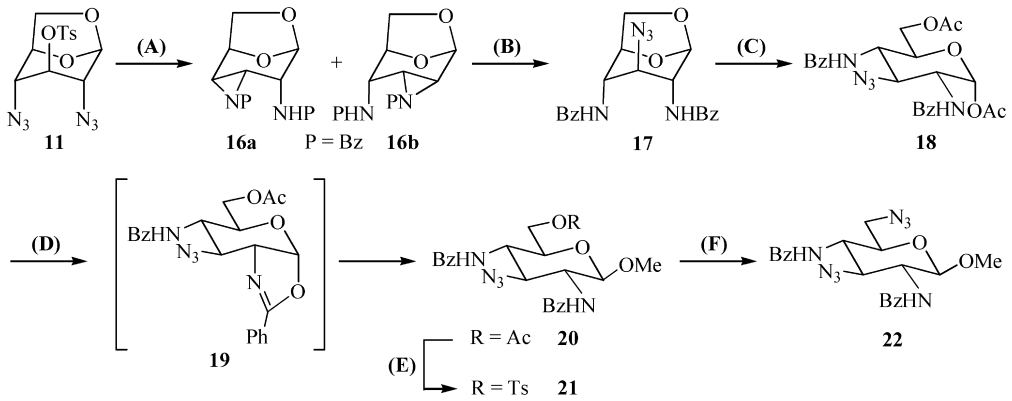
Such experimental conditions (LiN_3 (3 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene) were also successfully applied onto dianhydropyranoses **5**, **6**, **7** according to Fürst–Plattner rules (see Table 1). Starting from the dianhydropyranose **4**, the diazide **3** can be also obtained in the same conditions in 70% yield.

With diazide **3** in hands, the access to 2,3,4-trinitrogenated glucopyranoside via the formation 2,3 or 3,4-aziridine intermediates was envisaged. From **3**, tosylate **11** was obtained in nearly quantitative yield by reaction with *N*-tosylimidazole in the presence of sodium methoxide. Catalytic hydrogenation of **11** on Pd/C led to the expected mixture of the two 2,3 and 3,4-aziridines which was directly treated with benzyl chloroformate, to give the corresponding carbamates **12a** and **12b** (65% yield; two steps) as an inseparable mixture. Azidolysis (LiN_3 2 equiv., Al_2O_3 in DMF/toluene, microwave irradiation for 12 min at 120 °C) of **12a** and **12b** mixture led, as anticipated and according to Fürst–Plattner rules, to one compound (55% yield) having the D-gluco configuration **13**. Acetolysis of **13** was done in CF_3COOH/Ac_2O medium giving the diacetate **14**. Unfortunately, several attempts for the transformation into methyl glucoside **15** were unsuccessful (Scheme 3).

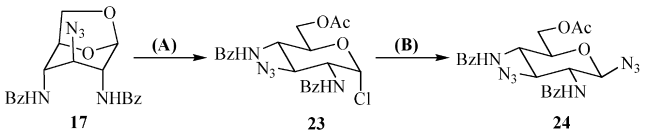
Another protecting group was then considered for obtaining the tetranitrogenated compound: after reduction of **11**, the mixture of aziridines was benzoylated giving **16a** and **16b** (Scheme 4). Azidolysis of the mixture led to the trinitrogenated compound **17** (88% yield), which was in turn acetolysed to give diacetate **18** in 90% yield. By treatment with trimethylsilyl triflate for 40 min, the oxazolidine **19** was formed and directly converted in one pot, by addition of methanol, into methyl 6-*O*-acetyl-3-azido-2,4-benzamido-2,3,4-trideoxy-β-D-glucopyranoside **20** in 80% yield. The β configuration was ascertained by a large coupling constant between H-1 and H-2 ($J_{1,2}$=8 Hz). The tetrasubstituted nitrogen compound **22** was finally obtained, from **20**, in 3 steps: MeONa catalytic deacetylation of the 6 position followed by tosylation gave the



Scheme 3. *Reagents and conditions*: (A) TsIm (1.5 equiv.), MeONa (2 equiv.), CH_3CN, 0 °C to rt, 12 h, 90%; (B) (i) Pd/C, H_2, EtOAc/EtOH (1:1), rt, 6 h; (ii) CbzCl (3 equiv.), Et_3N, CH_2Cl_2, 0 °C to rt, 15 h, 65% in two steps; (C) LiN_3 (2 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene (1:1), MW, 120 °C, 12 min, 55%; (D) CF_3COOH, Ac_2O, 0 °C to rt, 2 days, 90%.



Scheme 4. *Reagents and conditions*: (A) (i) Pd/C, H_2, EtOAc/EtOH (1:1), rt, 6 h; (ii) Bz_2O (3 equiv.), DMAP cat., pyridine/CH_2Cl_2 (1:1), rt, 16 h, 83% in two steps; (B) LiN_3 (2 equiv.), Al_2O_3 (3 equiv. in weight), DMF/toluene (1:1), MW, 10 min, 88%; (C) CF_3COOH, Ac_2O, 0 °C to rt, 3 days, 90%; (D) TMSOTf (1.1 equiv.), $ClCH_2CH_2Cl$, 50 °C, 30 min, then MS 4 Å, rt, 1 h, then MeOH (10 equiv.), rt, 2 h, 80%; (E) (i) MeONa (0.1 equiv.), MeOH/toluene (1:1), rt, 12 h; (ii) TsCl (2 equiv.), DMAP, CH_2Cl_2/Et_3N (1:1), rt, 12 h, 62% in two steps; (F) LiN_3 (1.5 equiv.), DMF, 80 °C, 3 h, 82%.



Scheme 5. *Reagents and conditions*: (A) AcCl, MeOH, 0 °C, rt, 36 h, 80%; (B) LiN_3 (2 equiv.), DMF, 80 °C, 2 h, 77%.

crystalline ester **21** which was heated in DMF with LiN_3. Methyl 3,6-diazido-2,4-dibenzamido-2,3,4,6-tetradeoxy-β-D-glucopyranoside **22** was isolated in 51% overall yield from **20** (and 13% from levoglucosan **1** in 12 steps).

The tetrasubstituted analogue **24** was also synthesised from **17**. By treatment in Veyrieres conditions[15] (AcCl, MeOH, 0 °C, 36 h), chloride **23** was easily formed in 80% yield; the azidolysis of anomeric chloride by LiN_3 in DMF led to crystalline diazide **24** in 77% yield (Scheme 5).

In conclusion, the syntheses of tetranitrogenated analogues of glucopyranoses **22** and **24** were achieved in 12 and 9 steps, respectively, from levoglucosan **1** via a common intermediate **17** in satisfactory overall yields.

3. Experimental

3.1. General methods

The microwave reactor was a monomode system (Synthewave 402 from Prolabo Society) with focused waves. All reactions were performed in a cylindrical pyrex vessel. A continuous mechanical stirring provided a good homogeneity of the materials. The temperature was controlled all along the reaction and evaluated by an infrared detector which indicated the surface temperature. Automatic control of the irradiation (power or temperature) as well as data processing was followed by a computer system. Lithium azide was prepared by the protocol described in the literature.[16] Aluminium oxide (90 active, neutral, activity I) was used in microwave reactions. Methanol was distilled from magnesium/iodine. 1,2-Dichloroethane and acetonitrile were distilled over CaH_2 prior to use. Flash column chromatography was performed using 35–70 μ silica gel (60) purchased from S.D.S. Company. ^1H et ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively, or at 300 and 75 MHz, or 400 and 100 MHz. Chemical shifts are reported in ppm relative to TMS as internal standard. Optical rotations were determined operating at the sodium D line with a Perkin–Elmer 241C polarimeter. Melting points were measured on Büchi b-450 and are uncorrected. IR spectra were recorded with an FTIR spectrometer. Mass spectra were recorded by navigator LC/MS (source AQA) for electrospray ionisation. Elemental analyses were carried out by Laboratoire de Micro-Analyse ICSN-Gif sur Yvette.

3.1.1. 1,6-Anhydro-2,4-diazido-2,4-dideoxy-β-D-glucopyranose (3). Lithium azide (1.3 g, 26.92 mmol) and aluminium oxide (6 g, 3 equiv. in weight) were added to a solution of **2** (2 g, 6.73 mmol) in DMF/toluene (12 mL, 3:1). This mixture was submitted to microwave irradiation for 20 min (*P*: 120–240 W, *T*: 125 °C). After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) to afford the compound **3** (1.323 g, 90%) as pale yellow oil: R_f 0.45 (EtOAc/heptane 1:1), IR ν_3)=2100 cm^{-1}, ^1H NMR δ (250 MHz, $CDCl_3$): 5.51 (s, 1H, H-1), 4.62 (d, 1H, H-5, *J*=5 Hz), 4.14 (d, 1H, H-6, *J*=8 Hz), 3.78–3.86 (m, 2H, H-6′, H-3), 3.5 (d, 1H, H-4), 3.4 (d, 1H, H-2), ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 101 (C-1), 74.6 (C-5), 70.8 (C-3), 67.0 (C-6), 62.8, 62.7 (C-2, C-4). ESI-MS *m/z* 235 $[M+Na]^+$, 273 $[M-H+Na+K]^+$, 447 $[2M+Na]^+$.

3.1.2. 1,6-Anhydro-3-azido-3-deoxy-β-D-mannopyranose (9). Lithium azide (81 mg, 1.66 mmol) and aluminium oxide (0.36 g, 3 equiv. in weight) were added to a solution of **6** (120 mg, 0.83 mmol) in DMF/toluene (4 mL, 1:1). This mixture was submitted to microwave irradiation for 20 min (*P*: 120–240 W, *T*: 125 °C). After cooling, the reaction mixture was filtered through a pad of silica gel with a mixture of CH_2Cl_2/MeOH (9:1) and the filtrate concentrated under vacuum to afford the compound **9** (140 mg, 90%) as pale yellow oil: R_f 0.32 (CH_2Cl_2/MeOH 9:1), ^1H NMR δ (250 MHz, CD_3OD): 5.28 (s, 1H, H-1), 4.81 (sl, 1H, OH, H echangeable), 4.41 (d, H-5, *J*=5 Hz), 4.10 (d, 1H, H-6, *J*=7 Hz), 3.95 (d, H-6′, *J*=7 Hz), 3.86 (m, 1H, H-4), 3.77

(m, 1H, H-2), 3.67 (dd, 1H, H-3, J=7, 5 Hz). ^{13}C NMR δ (62.5 MHz, CD_3OD): 101.0 (C-1), 75.2 (C-5), 69.3 (C-4), 66.8 (C-2), 63.9 (C-6), 63.2 (C-3). ESI-MS m/z 210 $[M+Na]^+$; 248 $[M-H+Na+K]^+$.

3.1.3. 1,6-Anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-gluco-pyranose (10). Compound **10** was obtained from **7** by the same experimental protocol than compound **3**. 3 equiv. of lithium azide were used. Compound **10**: pale yellow oil, 85% yield. R_f 0.4 (EtOAc/heptane 1:1), IR ν_3)=2100 cm^{-1}, ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.3–7.5 (m, 5H, H-Ar), 5.48 (s, 1H, H-1), 4.70 (s, 2H, CH_2Ph), 4.62 (d, H-5, J=5.5 Hz), 3.95 (d, H-6, J=7.5 Hz), 3.91 (m, 1H, H-4), 3.70 (dd, H-6′, J=7.5, 5.5 Hz), 3.38 (m, 1H, H-3), 3.24 (d, 1H, H-2, J=3 Hz), 2.52 (sl, 1H, OH, H echangeable). ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 136.0, 128.6, 128.4, 128.3 (C-Ar), 101.1 (C-1), 78.7 (C-4), 75.1 (C-5), 71.9 (*C*H_2Ph), 70.4 (C-3), 66.3 (C-6), 62.8 (C-2). MS (ESI) m/z 300 $[M+Na]^+$; 316 $[M+K]^+$.

3.1.4. 1,6-Anhydro-2,4-diazido-2,4-dideoxy-3-*O*-tosyl-β-D-glucopyranose (11). To a solution of **3** (6.7 g, 31.9 mmol) in dry CH_3CN (150 mL) was added *N*-tosyl-imidazole (10.5 g, 47.85 mmol). The mixture was stirred at 0 °C and then sodium methoxide (3.5 g, 63.8 mmol) was added. After 12 h at rt, the reaction was neutralised with 1 N HCl. The material was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford the compound **11** (10.45 g, 90%) as white crystals: mp 61–62 °C, R_f 0.55 (EtOAc/heptane 1:1), $[\alpha]_D^{25}$=−3 (*c* 1, $CHCl_3$), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.83 (d, 2H, H-Ar, J=8 Hz), 7.42 (d, 2H, H-Ar, J=8 Hz), 5.47 (s, 1H, H-1), 4.65 (d, 1H, H-3, J=5 Hz), 4.42 (m, 1H, H-5), 4.13 (d, 1H, H-6, J=8 Hz), 3.84 (dd, 1H, H-6′, J=8, 5 Hz), 3.57 (s, 1H, H-4), 3.27 (s, 1H, H-2), 2.48 (s, 3H, CH_3 Ts), ^{13}C NMR δ (50 MHz, $CDCl_3$): 146.2, 132.5, 130.5, 128.0, (C-Ar), 99.8 (C-1), 76.2 (C-3), 73.6 (C-5), 65.9 (C-6), 59.4 (C-4), 59.1 (C-2), 21.8 (CH_3 Ts). ESI-MS m/z 427 $[M-H+Na+K]^+$; 755 $[2M+Na]^+$. Anal. calcd for $C_{13}H_{14}N_6O_5S$: C, 42.62, H, 3.85, N, 22.94, S, 8.75. Found: C, 42.89, H, 3.71, N, 23.04, S, 8.66.

3.1.5. 1,6-Anhydro-3,4-benzyloxycarbonylepimino-2-benzyl-oxycarboxamido-2,3,4-trideoxy-β-D-allopyranose (12a) and 1,6-anhydro-2,3-benzyloxycarbonyl-epimino-4-benzyloxycarboxamido-2,3,4-trideoxy-β-D-allopyranose (12b). Pd/C (0.85 g) was added to a solution of **11** (8.05 g, 22.055 mmol) in EtOAc/EtOH (60 mL, 1:1). The mixture was stirred under hydrogen atmosphere (4 bar) during 6 h. The reaction mixture was filtered through a pad of celite with EtOH and the filtrate concentrated under vacuum. The resulting crude material was dissolved in CH_2Cl_2 (45 mL); DMAP (0.8 g, 6.56 mmol) and triethylamine (20 mL) were added. After being stirred at 0 °C, benzyl chloroformate (10 mL, 70 mmol) was added dropwise. After 20 h at rt, the reaction was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford a mixture of the compound **12a/12b** (5.88 g, 65%) as white crystals: R_f 0.39 (EtOAc/heptane 1:1), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.20–7.45 (m, 10H, H-Ar), 5.63, 5.81 (m, 2NH), 5.59 (d, H-1a, J=9 Hz), 5.17 (s, H-1b), 5.04–5.15 (m, 4H, 2CH_2Ph Cbz), 4.71 (d, H-5a), 4.36 (d, H-5b), 3.82–4.04 (m, H-6, H-4b, H-2a), 3.63–3.82 (m, H-6′), 2.84–3.05 (m, H-2b, H-3a), 2.67–2.82 (m, H-3b, H-4a), ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 155.8, 161.9 (C=O), 136.4, 135.4, 128.7, 128.6, 128.3, 128.1 (C-Ar), 101.5 (C-1b), 96.8 (C-1a), 76.1 (C-5b), 69.3 (C-5a), 68.8, 67.1 (2OCH_2Ph Cbz), 66.4 (C-6), 47.6 (C-4b), 47.4 (C-2a), 36.7 (C-4a), 36.2 (C-2b), 35.2 (C-3b), 34.7 (C-3a). ESI-MS m/z 433 $[M+Na]^+$; 449 $[M+K]^+$; 471 $[M-H+Na+K]^+$; 843 $[2M+Na]^+$. Anal. calcd for $C_{22}H_{22}N_2O_6$: C, 64.38, H, 5.40, N, 6.83. Found: C, 64.42, H, 5.31, N, 6.66.

3.1.6. 1,6-Anhydro-3-azido-2,4-dibenzyloxycarboxamido-2,3,4-trideoxy-β-D-glucopyranose (13). In pyrex tube for MW, a mixture of aziridines **12a/12b** (3.53 g, 8.63 mmol) was dissolved in DMF/toluene (20 mL, 1:1); lithium azide (1.05 g, 17.26 mmol) and aluminium oxide (10.6 g, 3 equiv. in weight) were added. This mixture was submitted to microwave irradiation for 10 min (*P*: 60–150 W, *T*: 125 °C). After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford the compound **13** (2.67 g, 55%) as white crystals: mp 109 °C, R_f 0.54 (EtOAc/heptane 1:1), $[\alpha]_D^{25}$=−5 (*c* 1, $CHCl_3$), ^{1}H NMR δ (400 MHz, $CDCl_3$): 7.15–7.45 (m, 10H, H-Ar), 6.10, 6.35 (m, 2NH), 5.39 (s, 1H, H-1), 5.00–5.25 (m, 4H, 2CH_2Ph Cbz), 4.44 (s, 1H, H-5), 4.23 (s, 1H, H-6), 3.50–3.95 (m, 4H, H-2, H-3, H-4, H-6′), ^{13}C NMR δ (62.5 MHz, $CDCl_3$): 156.0, 156.1 (C=O), 136.0, 129.0, 128.5, 128.3 (C-Ar), 100.5 (C-1), 75.2 (C-5), 67.3 et 68.1 (2OCH_2Ph Cbz), 66.3 (C-6), 61.8 (C-3), 51.2, 51.4 (C-2, C-4). ESI-MS m/z 476 $[M+Na]^+$; 514 $[M-H+Na+K]^+$; 929 $[2M+Na]^+$. Anal. calcd for $C_{22}H_{23}N_5O_6$: C, 58.27, H, 5.11, N, 15.44. Found: C, 58.56, H, 4.96, N, 15.56.

3.1.7. 1,6-Di-*O*-acetyl-3-azido-2,4-dibenzyloxycarboxamido-2,3,4-trideoxy-α-D-glucopyranose (14). To a solution of **13** (2.045 g, 4.514 mmol) in acetic anhydride (20 mL) was added dropwise trifluoroacetic acid (1.1 mL) at 0 °C. After 2 days at rt, the reaction was quenched by the addition of ethanol then concentrated in vacuo. The resulting crude material was purified by column chromatography (SiO_2, EtOAc/heptane 1:1) and recrystallized from ethanol to afford the compound **14** (2.255 g, 90%) as white crystals: mp 148–150 °C, R_f 0.41 (EtOAc/heptane 1:1), $[\alpha]_D^{25}$=+44 (*c* 1, acetone), ^{1}H NMR δ (400 MHz, $CDCl_3$): 7.02–7.51 (m, 10H, H-Ar), 6.12 (s, 1H, H-1), 5.80, 5.91 (m, 2NH), 4.75–5.22 (m, 4H, 2CH_2Ph Cbz), 4.35 (m, 1H, H-3), 4.00–4.24 (m, 4H, H-2, H-5, H-6, 6′), 3.64 (m, 1H, H-4), 2.00, 2.15 (s, 3H, CH_3 Ac), ^{13}C NMR δ (100 MHz, $CDCl_3$): 170.7, 169.1 (C=O Ac), 156.4 (2C=O Cbz), 136.0, 135.7, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1 (C-Ar), 91.1 (C-1), 69.9 (C-5), 67.8, 67.5 (2OCH_2Ph Cbz), 62.6 (C-6), 61.9 (C-3), 53.6, 53.0 (C-2 et C-4), 20.9, 20.7 (2CH_3 Ac). ESI-MS m/z 578 $[M+Na]^+$; 616 $[M-H+Na+K]^+$. Anal. calcd

for $C_{26}H_{29}N_5O_9$: C, 56.21, H, 5.26, N, 12.61. Found: C, 56.37, H, 5.08, N, 12.61.

3.1.8. 1,6-Anhydro-2-benzamido-3,4-benzoylepimino-2,3,4-tri-deoxy-β-D-allopyranose (16a) and 1,6-anhydro-4-benzamido-2,3-benzoylepimino-2,3,4-trideoxy-β-D-allo-pyranose (16b). Pd/C (0.1 g) was added to a solution of **11** (0.875 g, 2.4 mmol) in EtOAc/EtOH (8 mL, 1:1). The mixture was stirred under hydrogen atmosphere (4 bar) during 6 h. The reaction mixture was filtered through a pad of celite with EtOH and the filtrate concentrated under vacuum. The resulting crude material was dissolved in pyridine/CH_2Cl_2 (25 mL, 1:1), DMAP (30 mg, 0.24 mmol) and benzoic anhydride (1.7 g, 7.515 mmol) were added at 0 °C. After 16 h at rt, the reaction mixture was concentrated under vacuum. The resulting crude material was purified by column chromatography (SiO_2, EtOAc/heptane 7:3) and recrystallized from a mixture of ethyl acetate and heptane to afford a mixture of the compound **16a/16b** (0.7 g, 83%) as white crystals: R_f 0.49 (EtOAc/heptane 8:2), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.95–8.10 (m, 2H, H-Ar), 7.80–7.92 (m, 2H, H-Ar), 7.37–7.55 (m, 6H, H-Ar), 7.60, 7.31 (m, 2NH), 5.73 (s, H-1a), 5.34 (s, H-1b), 4.80 (m, H-5a), 4.44–4.61 (m, H-2a, H-5b), 3.93–4.12 (m, H-6, H-4b), 3.78–3.90 (m, H-6′), 3.35 (m, H-3b), 3.29 (m, H-3a), 2.88 (m, H-4a), 2.83 (m, H-2b), ^{13}C NMR δ (75 MHz, $CDCl_3$): 167.0, 167.1, 177.5, 177.9 (C=O), 133.4, 133.3, 132.7, 131.9, 131.8, 129.0, 128.8, 128.6, 127.2 (C-Ar), 101.5 (C-1b), 96.8 (C-1a), 76.1 (C-5b), 69.3 (C-5a), 66.4 (C-6), 47.6 (C-4b), 47.4 (C-2a), 36.7 (C-4a), 36.2 (C-2b), 35.2 (C-3b), 34.7 (C-3a). ESI-MS *m/z* 373 $[M+Na]^+$; 389 $[M+K]^+$. Anal. calcd for $C_{20}H_{18}N_2O_4$: C, 68.56, H, 5.18, N, 8.00. Found: C, 68.37, H, 5.11, N, 7.85.

3.1.9. 1,6-Anhydro-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-β-D-glucopyranose (17). In pyrex tube for MW, a mixture of aziridines **16a/16b** (1 g, 2.856 mmol) was dissolved in DMF/toluene (6 mL, 1:1); lithium azide (0.3 g, 5.712 mmol) and aluminium oxide (3 g, 3 equiv. in weight) were added. This mixture was submitted to microwave irradiation for 10 min (*P*: 60–150 W, *T*: 120 °C). After cooling, the reaction mixture was diluted with EtOAc, filtered through a pad of silica gel and the filtrate concentrated under vacuum. The crude product was recrystallized from a mixture of ethyl acetate and heptane to afford the compound **17** (2.8 g, 88%) as white crystals: mp 195–197 °C, R_f 0.56 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+13$ (*c* 1, $CHCl_3$), ^{1}H NMR δ (300 MHz, $CDCl_3$): 7.62–7.73 (m, 4H, H-Ar), 7.46–7.57 (m, 2H, H-Ar), 7.32–7.43 (m, 4H, H-Ar), 6.71, 6.44 (m, 2NH), 5.60 (s, 1H, H-1), 4.67 (d, 1H, H-5, *J*=5 Hz), 4.46 (d, 1H, H-6, *J*=8 Hz), 4.30 (d, 1H, H-2, *J*=8 Hz), 4.20 (d, 1H, H-4, *J*=7 Hz), 4.05 (m, 1H, H-3), 3.92 (dd, 1H, H-6′, *J*=5, 8 Hz), ^{13}C NMR δ (75 MHz, $CDCl_3$): 167.5, 162.7 (C=O), 133.8, 131.9, 128.6, 127.3 (C-Ar), 101.0 (C-1), 75.1 (C-5), 66.7 (C-6), 60.3 (C-3), 50.8, 50.9 (C-2, C-4). Anal. calcd for $C_{20}H_{19}N_5O_4$: C, 61.06, H, 4.87, N, 17.80. Found: C, 61.09, H, 4.89, N, 17.67.

3.1.10. 1,6-Di-*O*-acetyl-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-α-D-glucopyranose (18). To a solution of **17** (0.8 g, 2.05 mmol) in acetic anhydride (70 mL) was added dropwise trifluoroacetic acid (3 mL) at 0 °C. After 3 days at rt, the reaction was quenched by the addition of ethanol then concentrated in vacuo. The resulting white solid was recrystallized from a mixture of ethyl acetate and heptane to afford the compound **18** (0.9 g, 90%) as white crystals: mp 211 °C (decomposition), R_f 0.48 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+32$ (*c* 1, acetone), ^{1}H NMR δ (300 MHz, Acetone D): 8.23 (d, 1H, NH, *J*=9 Hz), 8.11 (d, 1H, NH, *J*=8 Hz), 7.75–7.95 (m, 4H, H-Ar), 7.35–7.60 (m, 6H, H-Ar), 6.33 (d, 1H, H-1, *J*=4 Hz), 4.69 (t, 1H, H-3, *J*=11 Hz), 4.40–4.58 (m, 2H, H-2, H-5), 4.25–4.39 (m, 2H, H-4 et H-6), 4.15 (dd, 1H, H-6′, *J*=2, 12 Hz), 2.00, 2.15 (s, 3H, CH_3 Ac), ^{13}C NMR δ (62.5 MHz, Acetone D): 169.1, 170.3 (C=O Ac), 167.6, 162.7 (C=O Bz), 134.9, 134.7, 131.9, 128.7, 128.6, 127.8, 127.6 (C-Ar), 90.6 (C-1), 70.8 (C-5), 63.1 (C-6), 60.7 (C-3), 52.2, 52.8 (C-2, C-4), 20.3, 20.5 ($2CH_3$ Ac). Anal. calcd for $C_{24}H_{25}N_5O_7$: C, 56.21, H, 5.26, N, 12.61. Found: C, 56.37, H, 5.08, N, 12.61.

3.1.11. Methyl 6-*O*-acetyl-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-β-D-glucopyranoside (20). TMSOTf (0.36 mL, 1.793 mmol) dissolved in dry 1,2-dichloroethane (8 mL) was added dropwise under argon to a solution of **18** (0.807 g, 1.63 mmol) in dry 1,2-dichloroethane (30 mL). The mixture was stirred at 50 °C until completion as monitored by TLC (30 min); the oxazolidine **19** was formed (at this stage, this compound can be isolated). Molecular sieves (0.5 g) were added. After 1 h at rt, methanol (0.7 mL, 16.3 mmol) was added. The reaction was quenched by addition of triethylamine (0.4 mL). The reaction mixture was filtered through a pad of celite with EtOAc/toluene and the filtrate concentrated under vacuum. The crude product was recrystallized from a mixture of ethyl acetate and heptane to afford the compound **20** (0.61 g, 80%) as white crystal: mp 242 °C (decomposition), R_f 0.48 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+20$ (*c* 1.09, DMSO), ^{1}H NMR δ (300 MHz, DMSO D): 8.63–8.83 (m, 2H, 2NH), 7.75–7.95 (m, 4H, H-Ar), 7.37–7.63 (m, 6H, H-Ar), 4.65 (d, 1H, H-1, *J*=9 Hz), 4.13–4.37 (m, 2H, H-5, H-6), 4.00–4.13 (m, 1H, H-6′), 3.73–4.00 (m, 3H, H-2, H-3, H-4), 3.40 (s, 3H, CH_3 OMe), 2.05 (s, 3H, CH_3 Ac), ^{13}C NMR δ (62.5 MHz, DMSO D): 170.1 (C=O Ac), 166.4, 166.7 (C=O Bz), 134.2, 134.0, 131.4, 131.3, 128.8, 127.2 (C-Ar), 101.2 (C-1), 72.8 (C-5), 63.0 (C-3), 62.9 (C-6), 55.9 (CH_3 OMe), 54.4 (C-2), 50.8 (C-4), 20.5 (CH_3 Ac). Anal. calcd for $C_{23}H_{25}N_5O_6$: C, 58.18, H, 5.09, N, 14.13. Found: C, 57.95, H, 5.17, N, 13.78.

3.1.12. Methyl 3-azido-2,4-dibenzamido-2,3,4-trideoxy-6-*O*-tosyl-β-D-glucopyranoside (21). The compound **20** (1.2 g, 2.42 mmol) was dissolved in toluene/methanol (40 mL, 1:1). A solution (2 M) of sodium methoxide in methanol (1 mL, 0.242 mmol) was added. After being stirred for 12 h at room temperature, the reaction mixture was neutralised with DOWEX AG50W-X8 (H^+) resin then filtered through a pad of celite. The filtrate was concentrated under vaccum. The crude material was dissolved in Et_3N/CH_2Cl_2 (20 mL, 1:1). DMAP (30 mg, 0.242 mmol) and *p*-toluenesulfonyl chloride (0.74 g, 3.88 mmol) were added. After being stirred for 12 h at rt, the reaction mixture was filtered through a pad of silica gel with a mixture of CH_2Cl_2/MeOH (9:1) then concentrated under reduce pressure. The crude product was recrystallized from the mixture of acetone and heptane to afford the compound **21** (0.875 g, 62%) as white crystal: mp 165 °C (decomposition), R_f 0.46

(EtOAc/heptane 6:4), $[\alpha]_D^{25}=+17$ (*c* 1, acetone), ^{1}H NMR δ (300 MHz, acetone D): 8.13 (t, 2H, 2NH, *J*=9 Hz), 7.80–7.95 (m, 4H, H-Ar), 7.76 (d, 2H, H-Ar, *J*=8 Hz), 7.45–7.60 (m, 6H, H-Ar), 7.35 (d, 2H, H-Ar, *J*=8 Hz), 4.86 (d, 1H, H-1, *J*=9 Hz), 4.59 (t, 1H, H-3, *J*=10.5 Hz), 4.28 (m, 1H, H-6), 4.06–4.21 (m, 2H, H-5, H-6), 3.94 (m, 1H, H-4), 3.82 (m, 1H, H-2), 3.41 (s, 3H, CH_3 OMe), 2.35 (s, 3H, CH_3 Ts), ^{13}C NMR δ (75 MHz, Acetone D): 167.6, 167.8 (C=O Bz), 146.0, 135.8, 135.3, 133.9, 132.6, 132.4, 131.0, 129.4, 129.0, 128.4, 128.3 (C-Ar), 102.0 (C-1), 73.8 (C-5), 70.2 (C-6), 63.2 (C-3), 56.6 (C-2), 56.4 (CH_3 OMe), 52.6 (C-4), 21.4 (CH_3 Ts). Anal. calcd for $C_{28}H_{29}N_5O_7S$: C, 58.02, H, 5.04, N, 12.08, S, 5.53. Found: C, 58.19, H, 4.92, N, 11.78, S, 5.59.

3.1.13. Methyl 3,6-diazido-2,4-dibenzamido-2,3,4,6-tetra-deoxy-β-D-glucopyranoside (22). Lithium azide (60 mg, 1.191 mmol) was added to a solution of **21** (0.46 g, 0.794 mmol) in DMF (4 mL). After being stirred for 3 h at 80 °C, the reaction mixture was filtered through a pad of silica gel with EtOAc then concentrated under reduce pressure. The crude material was recrystallized from a mixture of acetone and heptane to afford the compound **22** (0.295 g, 82%) as white crystal: mp 241 °C (decomposition), R_f 0.56 (EtOAc/heptane 6:4), $[\alpha]_D^{25}=-49$ (*c* 1.1, DMSO), ^{1}H NMR δ (300 MHz, DMSO D): 8.60–8.90 (m, 2H, 2NH), 7.75–7.95 (m, 4H, H-Ar), 7.40–7.65 (m, 6H, H-Ar), 4.69 (d, 1H, H-1, *J*=9 Hz), 4.15–4.35 (m, 1H, H-5), 3.72–4.00 (m, 3H, H-2, H-3, H-4), 3.40–3.60 (m, 1H, H-6), 3.42 (s, 3H, CH_3 OMe), 3.20–3.40 (m, 1H, H-6′), ^{13}C NMR δ (75 MHz, DMSO D): 166.5, 166.7 (C=O Bz), 134.0, 133.8, 131.5, 131.4, 128.3, 127.3, 127.2 (C-Ar), 101.1 (C-1), 74.7 (C-5), 62.9 (C-3), 55.9 (CH_3 OMe), 54.5 (C-2), 51.8 (C-4), 51.2 (C-6). Anal. calcd for $C_{21}H_{22}N_8O_4$: C, 55.99, H, 4.92, N, 24.88. Found: C, 55.97, H, 4.97, N, 25.09.

3.1.14. 6-*O*-Acetyl-3-azido-2,4-dibenzamido-2,3,4-tri-deoxy-α-D-glucopyranosyl chloride (23). To a solution of **17** (1.224 g, 3.165 mmol) in acetyl chloride (100 mL) was added dropwise methanol (1.05 mL) at 0 °C. After 24 h at rt, methanol (1 mL) was also added dropwise. After 12 h, the mixture was evaporated under reduce pressure. The crude product as white solid was recrystallized from a mixture of acetone and heptane to afford the compound **23** (1.19 g, 80%) as white crystal: mp 147 °C (decomposition), R_f 0.73 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=+78$ (*c* 1, acetone), ^{1}H NMR δ (300 MHz, acetone D): 8.10–8.40 (m, 2H, 2NH), 7.75–8.05 (m, 4H, H-Ar), 7.35–7.65 (m, 4H, H-Ar), 6.51 (d, 1H, H-1, *J*=4 Hz), 4.58–4.80 (m, 2H, H-3, H-5), 4.45–4.58 (m, 2H, H-2, H-4), 4.38 (dd, 1H, H-6, *J*=5, 12.5 Hz), 4.22 (dd, 1H, H-6′, *J*=2, 12.5 Hz), 2.05 (s, 3H, CH_3 Ac). ^{13}C NMR δ (75 MHz, Acetone D): 170.8 (C=O Ac), 168.0, 168.2 (C=O Bz), 135.3, 134.9, 132.6, 132.5, 129.2, 128.3, 128.2 (C-Ar), 95.6 (C-1), 72.5 (C-5), 63.5 (C-6), 60.5 (C-3), 55.6 (C-2), 52.4 (C-4), 20.7 (CH_3 Ac). Anal. calcd for $C_{22}H_{22}$ ClN_5O_5: C, 55.99, H, 4.70, N, 14.84, O, 16.95. Found: C, 56.21, H, 4.75, N, 14.77, O, 16.71.

3.1.15. 6-*O*-Acetyl-3-azido-2,4-dibenzamido-1,2,3,4-tetra-deoxy-β-D-glucopyranosyl azide (24). Lithium azide (0.23 g, 4.628 mmol) was added to a solution of **23** (1.09 g, 2.314 mmol) in DMF (4 mL). After being stirred for 2 h at 80 °C, the reaction mixture was filtered through a pad of silica gel with EtOAc then concentrated under vacuum. The crude material was recrystallized from acetone to afford the compound **24** (0.85 g, 77%) as white crystal: mp 178 °C (decomposition), R_f 0.62 (EtOAc/heptane 8:2), $[\alpha]_D^{25}=-59$ (*c* 1.64, DMSO), ^{1}H NMR δ (250 MHz, DMSO D): 8.90 (d, 1H, NH, *J*=8 Hz), 8.80 (m, 1H, NH), 7.75–7.97 (m, 4H, H-Ar), 7.35–7.65 (m, 6H, H-Ar), 4.98 (d, 1H, H-1, *J*=9 Hz), 3.75–4.45 (m, 6H, H-2, H-3, H-4, H-5, H-6, 6′), 2.05 (s, 3H, CH_3 Ac). ^{13}C NMR δ (62.5 MHz, DMSO D): 169.9 (C=O Ac), 166.6, 166.7 (C=O Bz), 133.9, 133.7, 131.5, 131.4, 128.2, 127.1 (C-Ar), 87.7 (C-1), 74.7 (C-5), 64.6 (C-6), 54.0 (C-2), 50.5 (C-4), 20.5 (CH_3 Ac). Anal. calcd for $C_{22}H_{22}N_8O_5$: C, 55.23, H, 4.63, N, 23.42. Found: C, 55.22, H, 4.77, N, 23.53.

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References and notes

1. Koeda, T.; Umemura, K.; Yokota, M. In *Aminoglycoside antibiotics*; Umezawa, H., Hooper, R., Eds.; Springer: Berlin, 1982; pp 267–356.
2. (a) Tanaka, N. Mechanism of action of aminoglycoside antibiotics. *Handbook of experimental pharmacology*; Springer: New York, 1982; Vol. 62. p 221. (b) Cundliffe, E. Recognition sites for antibiotics within rRNA. In *The ribosome*; Hill, W. E., et al. Eds.; American Society of Microbiology: Washington, DC, 1990; p 479. (c) Noller, H. F. *Annu. Rev. Biochem.* **1991**, *60*, 191.
3. (a) Moazed, D.; Noller, H. F. *Nature* **1987**, *327*, 389. (b) von Ahsen, U.; Noller, H. F. *Science* **1993**, *260*, 1506. (c) Walter, F.; Vincens, Q.; Westhof, E. *Curr. Opin. Chem. Biol.* **1999**, *3*, 694. (d) Michael, K.; Tor, Y. *Chem. Eur. J.* **1998**, *4*, 2091.
4. (a) Baker, T. J.; Luedtke, N. W.; Tor, Y.; Goodman, M. *J. Org. Chem.* **2000**, *65*, 9054. (b) Luedtke, N. W.; Baker, T. J.; Goodman, M.; Tor, Y. *J. Am. Chem. Soc.* **2000**, *122*, 12035. (c) Hui, Y.; Ptak, R.; Paulman, R.; Pallansch, M.; Chang, C.-W. T. *Tetrahedron lett.* **2002**, *43*, 9255. (d) Seeberger, P. H.; Baumann, M.; Zhang, G.; Kanemitsu, T.; Swayze, E. E.; Hofstadler, S. A.; Griffey, R. H. *Synlett* **2003**, 1323.
5. (a) Alper, P. B.; Hendrix, M.; Sears, P.; Wong, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 1965. (b) Wong, C.-H.; Hendrix, M.; Manning, D. D.; Rosenbohm, C.; Greenberg, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 8319. (c) Wong, C.-H. *Acc. Chem. Res.* **1999**, *32*, 376–385. (d) Sucheck, S. J.; Greenberg, W. A.; Tolbert, T. J.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1080.
6. (a) Reckendorf, W. M.; Wassiliadou-Micheli, N. *Chem. Ber.* **1974**, *107*, 1188. (b) Ali, Y.; Richardson, A. C. *J. Chem. Soc.* **1969**, 320. (c) Baer, H. H.; Rajabalee, F. *Carbohydr. Res.* **1970**, *12*, 241. (d) Baer, H. H.; Bayer, M. *Carbohydr. Res.* **1970**, *14*, 114. (e) Baer, H. H.; Neilson, T. *Can. J. Chem.* **1965**, *43*, 840.
7. van den Berg, R. J. B. N.; Noort, D.; van der Marel, G. A.; van Boom, J. H.; Benschop, H. P. *J. Carbohydr. Chem.* **2002**, *21*, 167.
8. (a) Dubber, M.; Lindhorst, K. *J. Chem. Soc. Chem. Commun.*

1998, 1265. (b) McGeary, R. P.; Jablonkai, I.; Toth, I. *Tetrahedron* **2001**, *57*, 8733. (c) Lundquist, J. J.; Toone, E. *J. Chem. Rev.* **2002**, *102*, 555. (d) Chow, H.-F.; Mong, T. K.-K.; Nongrum, M. F.; Wan, C.-W. *Tetrahedron* **1998**, *54*, 8543.

9. Bailliez, V.; de Figueiredo, R. M.; Olesker, A.; Cleophax, J. *Synthesis* **2003**, *7*, 1015.
10. Williams, N. R. *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 109.
11. Grindley, T. B.; Reimer, G. J.; Kralovec, J. *Can. J. Chem.* **1987**, *65*, 1065.
12. (a) Paulsen, H.; Koebernick, H. *Chem. Ber.* **1976**, *109*, 104. (b) Paulsen, H.; Koebernick, H.; Stenzel, W.; Köll, P. *Tetrahedron Lett.* **1975**, *18*, 1493.
13. (a) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
14. The use of an excess of LiN_3 is necessary; with 2 or 3 equiv. a mixture of mono- and di-azido compounds was obtained.
15. Désiré, J.; Veyrières, A. *Carbohydr. Res.* **1995**, *268*, 177.
16. Hofman-Bang, N. *Acta. Chem. Scand.* **1957**, *11*, 581.

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Synthesis and thermal cyclization of an enediyne-sulfonamide☆

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Abstract—The synthesis of an enediyne sulfonamide by alkylidene carbene rearrangement is reported. The compound cyclizes thermally to give the Bergman product, which was prepared independently for comparison. Like other σ-acceptor substituents at the enediyne alkyne termini, such as fluoride, oxonium or ammonium groups, the sulfonamide moiety enhances the reactivity for thermal Bergman cyclization as shown by the cyclization kinetic of the title compound.
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1. Introduction

Apart from the ring strain, the Bergman cyclization is quite sensitive to substituent effects.[1] Substituents at the alkyne termini are generally more effective than at the vinyl positions,[2] but heteroarene anellation can have a large effect on the energetics, too.[3–5] Morokuma et al.[6] have predicted that electron acceptor substituents at the terminal alkyne carbons of an enediyne should facilitate its thermal cyclization. This prediction was narrowed to strong σ-acceptors and/or π-donors by Schreiner et al.[7] A doubly fluoro-substituted enediyne was expected to undergo an exothermic Bergman cyclization, which was recently confirmed experimentally by Sander et al.[8] Other structures predicted to show enhanced reactivity in thermal cyclizations are enediynes with protonated yne-ol (onium-ion) or protonated yne-amine (ammonium-ion) sub-structure.[9] These structures are not stable and have, to the best of our knowledge, not been reported in the literature so far. We describe here the synthesis of the first stabilized enediyne with yne-amine substructure and its properties in thermal cyclization.[10]

2. Results and discussion

Yne-amines are very sensitive to hydrolysis.[11,12] This prohibits the characterization and property investigation of yne-amine substituted enediynes. Therefore yne-sulfonamide structures were selected as target compounds. They are stable and crystalline due to the strong electron acceptor properties of the sulfone moiety.[13] The required σ-acceptor effect of the nitrogen atom on the enediyne system remains, while the π-donating character of the nitrogen atom is reduced similar to an ammonium ion.[14] For the synthesis of sulfonamide benzoenediynes two general routes can be envisaged: the coupling of an alkyne sulfonamide to a 1-bromo-2-ethynyl-benzene by the Sonogashira–Hagihara method (see Scheme 1, route 1), or the formation of the carbon–nitrogen bond by either copper-catalyzed N-alkynylation of a sulfonamide[15] (see Scheme 1, route 2) or the reaction of alkynyl-phenyl-iodonium triflate salts with sulfonamides[16] (see Scheme 1, route 3). A Sonogashira–Hagihara coupling of ethynyl sulfonamides has not been reported in the literature so far and all of our initial attempts to couple *N*-Ts,*N*-Bn-ethynylamine[17] or its tri-methyl-tin derivative to iodo- or bromoarenes in transition-metal mediated processes failed under various reaction conditions. The copper-catalyzed N-alkynylation of sulfonamides was recently described to be less efficient than the N-alkynylation of lactams.[15] Therefore, the target enediyne was prepared via the alkynyl-phenyl-iodonium triflate salt.

Starting material **1** was prepared following a modified literature procedure.[18] The TMS-alkyne was transformed with iodosobenzene into the phenyl iodonium triflate in 64% yield. The iodonium salt was then reacted in toluene with lithium *N*-Bn,*N*-Ts-amide to give sulfonated, benzylated alkyneamide **4** in 46%. The same reaction in THF was much less efficient. Mechanistically, this step consists most likely of an addition of the lithium amide to the alkyne in β position giving a alkyldiene-carbene iodonium ylide, which eliminates phenyl iodide. The so formed alkylidene carbene rearranges by movement of the bromoaryl moiety to **4**. To complete the enediyne system, an alkyne must be introduced at the position of the remaining bromine

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Keywords: Enediyne; Yne-amine; Carbene rearrangement; Thermal cyclization.
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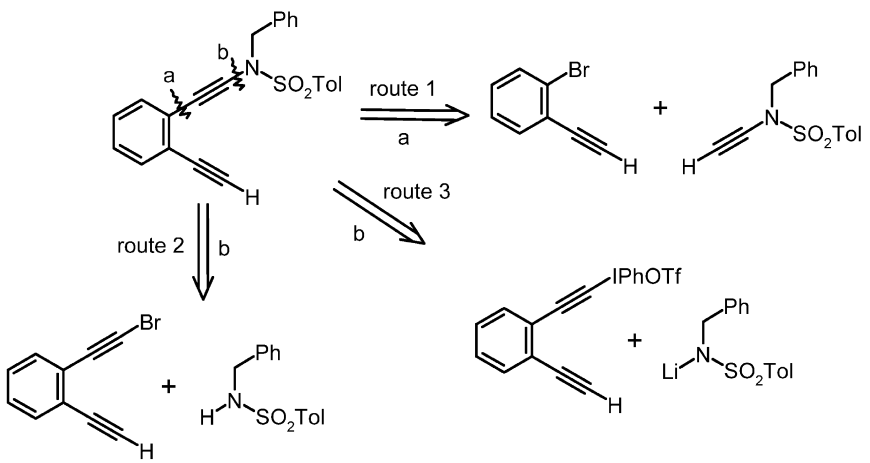
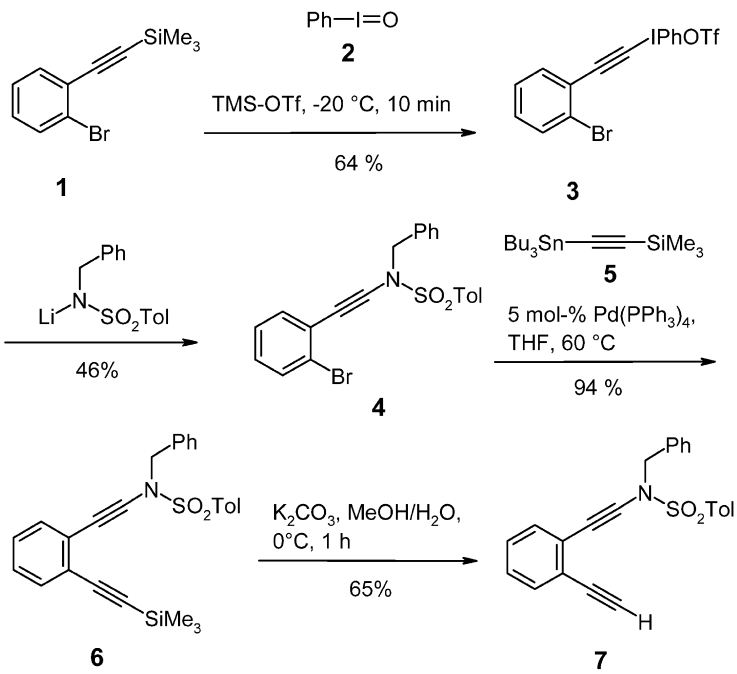
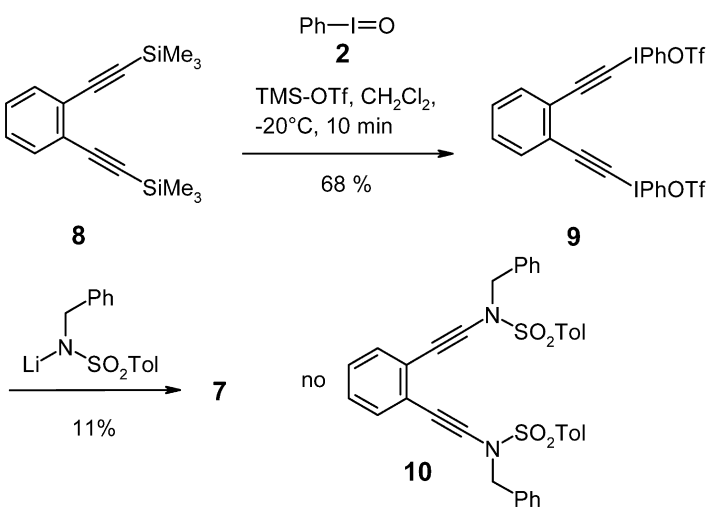


Scheme 1.



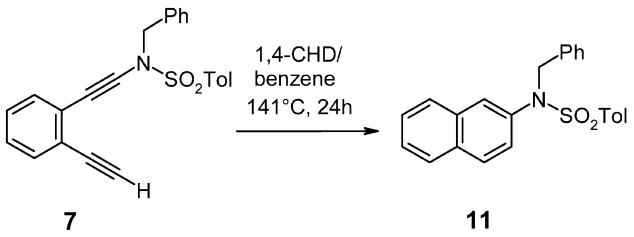
Scheme 2.



Scheme 3.

substituent. Standard Sonogashira–Hagihara coupling conditions with TMS-acetylene lead to decomposition of **4**, but a base-free Stille-type coupling protocol with **5** gave enediyne **6** in good yield. Finally, the TMS group was removed with K_2CO_3 in MeOH/water to give **7** in moderate yield.[19] Our attempts to prepare a twofold substituted enediyne-bis-sulfonamide[20] were not successful. The bis-iodoniumphenyl triflate **9** did not undergo a twofold rearrangement if treated with lithiated *N*-Bn,*N*-Ts-amine. Only compound **7** could be identified as reaction product, although in poor yield. A decreased ability of the substituted aryl moiety to undergo the rearrangement from the alkylidene carbene to the alkyne may explain the observation (Schemes 2 and 3).[21]

The thermal cyclization reaction of **7** was investigated by heating solutions of the compound (c=1.6×10^{-2} mol/l) in benzene/cyclohexadiene (ratio 2/1) to 141 °C. The conversion of the starting material and product formation was followed by HPLC analysis of the reaction mixture (Scheme 4).[22] The expected Bergman cyclization product **11** was synthesized independently from **12** for comparison using standard transformations (see Scheme 5 and Section 3 for details).



7 **11**

Scheme 4.

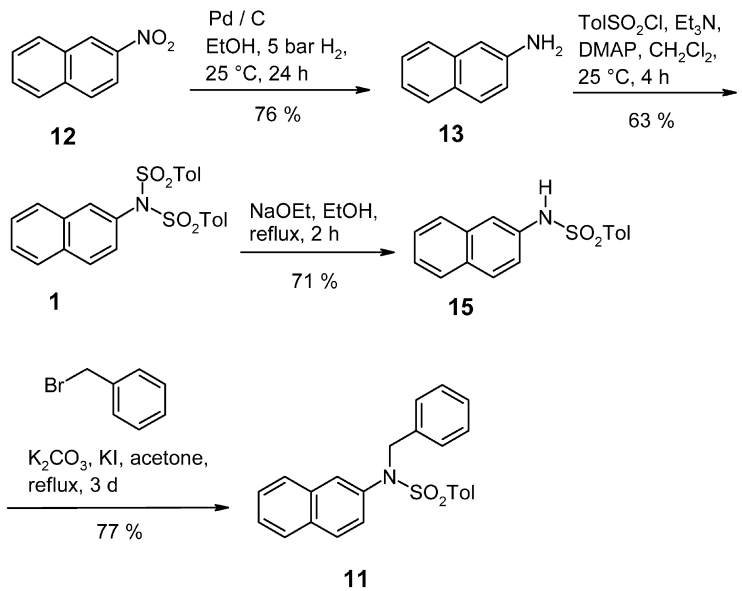
The HPLC analysis confirmed the formation of **11** from **7**, by identical retention times, UV- and mass spectra to the independently prepared material. A kinetic analysis of the reaction following the consumption of the starting material under pseudo first order conditions revealed a rate constant of k=2.66×10^{-4} s^{-1} which corresponds to a half life time of τ=44 min of the compound at this reaction temperature.[23] For the parent enediyne system benzo-1,2-diyne an activation energy for thermal cyclization of E_a=105.1 kJ/mol has been reported. This corresponds to a rate constant of k=9.77×10^{-5} s^{-1} and a half life of τ=118 min at 141 °C. Although the steric hindrance for a cyclization is significantly increased in **7** due to the large *N*-benzyl and *N*-tosyl substituents,[24] the reactivity of **7** is comparable or even higher than that of benzo-1,2-diyne. This supports the theoretical prediction[7] that σ-acceptor substituents at the terminal alkyne carbon atoms of an enediyne increase the thermal reactivity of the system. The alkyne sulfonamide substituent described here adds another option to electronically modify thermal enediyne reactivity.

3. Experimental

3.1. General

All ^{1}H NMR spectra were recorded at 400 MHz, all ^{13}C NMR spectra at 100 MHz in $CDCl_3$ unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbons. CC means column chromatography on silica gel. PE means petrol ether with a boiling range of 60–70 °C. EA means ethyl acetate. All reactions were carried out under nitrogen atmosphere.

3.1.1. (2-Bromophenylethynyl)trimethylsilane (1). After stirring a mixture of $PdCl_2(PPh_3)_2$ (351 mg, 0.50 mmol), CuI (191 mg, 1 mmol) and 1,2-dibromobenzene (1.21 ml, 2.36 g, 10 mmol), dissolved in 5 ml of THF and 5 ml of triethylamine at room temperature for 10 min, ethynyltrimethylsilane (1.55 ml, 1.08 g, 10 mmol) was added. The reaction mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, and washed with aqueous NH_4Cl. The combined organic phases were dried over Na_2SO_4, the solvent was removed and CC with hexanes gave **1** as a yellow oil (1.47 g, 58%).



12 **13** **1** **15** **11**

Scheme 5.

R_f=0.34 (hexanes). All spectroscopic data are identical to the ones reported in the literature.[18]

3.1.2. (2-Bromophenylethynyl)phenyliodonium triflate (3). To a stirred suspension of iodosobenzene (1.57 g, 7.14 mmol) in 50 ml of CH_2Cl_2, TMS-OTf (1.39 ml, 1.59 g, 7.14 mmol) and then **1** (1.80 g, 7.14 mmol) were added via syringe at −20 °C over 10 min. After warming to room temperature, the reaction mixture was concentrated and 15 ml of cold ether was added. The precipitated solid was filtered off and washed with cold ether. The residue was dried under reduced pressure to give a colorless solid (2.43 g, 64%). Mp: 94–95 °C. IR (KBr): $\tilde{\nu}$=2929 cm^{-1}, 2859, 2374, 2342, 2165, 1688, 1634, 1465, 1436, 1263, 1178, 1037, 990, 755, 735, 678, 649, 580, 522. UV/Vis (CH_3CN): λ_{max} (log ε)=209 nm (3.873), 249 (3.520). ^1H NMR (250 MHz, $CDCl_3$): δ=7.26–7.37 (m, 3H), 7.50–7.69 (m, 5H), 8.16–8.21 (m, 2H). ^{13}C NMR (60 MHz, $CDCl_3$): δ=36.4 (C_{quat}), 105.7 (C_{quat}), 117.3 (C_{quat}), 122.1 (C_{quat}), 126.6 (C_{quat}), 127.4 (+), 130.3 (C_{quat}), 132.4 (+), 132.5 (+), 132.7 (+), 132.8 (+), 134.2 (+), 135.1 (+), 137.5 (+). MS (ESI) *m/z* (%): 385 (97) [$M^+-CF_3SO_3$], 383 (100) [$M^+-CF_3SO_3$], 258 (18) [$M^+-CF_3SO_3-I$], 256 (19) [$M^+-CF_3SO_3-I$]. $C_{15}H_{10}BrF_3IO_3S$ (534.11): calcd C 33.80 H 1.70; found C 33.61 H 1.71.

3.1.3. *N*-Benzyl-*N*-(2-bromophenylethynyl)-4-methylbenzenesulfonamide (4). To a solution of *N*-benzyl-4-methylbenzene-sulfonamide (0.94 g, 3.58 mmol) in 50 ml of toluene, *n*-buli (2.70 ml, 4.30 mmol, 1.6 M in hexane) was added via syringe at 0 °C. After stirring for 30 min at this temperature **3** (2.29 g, 4.30 mmol) was added in small portions. The reaction mixture was stirred overnight, the solvent was removed and the residue was dissolved in Et_2O. The organic phase was washed with H_2O, brine and was dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel with 7:3 hexanes/Et_2O to give **4** as a colorless solid (0.72 g, 46%). R_f=0.34 (7:3 hexanes/Et_2O). Mp: 87–88 °C. IR (KBr): $\tilde{\nu}$=2923 cm^{-1}, 2852, 2231, 1596, 1429, 1368, 1173, 762. UV/Vis (CH_3CN): λ_{max} (log ε)=207 nm (4.996), 258 (4.144). ^1H NMR: δ=2.44 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 7.05–7.51 (m, 11H), 7.82–7.85 (m, 2H). ^{13}C NMR: δ=21.7 (+), 55.8 (−), 70.6 (C_{quat}), 87.2 (C_{quat}), 124.4 (C_{quat}), 125.2 (C_{quat}), 126.9 (+), 127.8 (+), 128.4 (+), 128.5 (+), 128.6 (+) 129.0 (+), 129.8 (+), 132.2 (+), 132.5 (+), 134.3 (C_{quat}), 134.7 (C_{quat}), 144.7 (C_{quart}). MS (CI) *m/z* (%): 459 (100)/457 (94) [$M+NH_4^+$], 442 (39)/440 (37) [$M+H^+$], 288 (37) [$M-C_7H_7SO_2+H^+$]/286 (38) [$M-C_7H_7SO_2+H^+$]. $C_{22}H_{18}BrNO_2S$ (439.02): calcd C 60.01 H 4.12 N 3.18; found C 59.51 H 4.08 N 3.00.

3.1.4. *N*-Benzyl-4-methyl-*N*-(2-trimethylsilanyl-ethynyl-phenyl-ethynylbenzenesulfonamide (6). To a solution of **4** (388 mg, 0.88 mmol), $Pd(PPh_3)_4$ (53 mg, 0.12 mmol) and CuI (7 mg, 0.01 mmol) in 5 ml of THF, trimethylstannyl ethynylsilane (116 mg, 0.30 mmol) was added, and the reaction mixture was stirred at 60 °C for 2 d. The solvent was removed and CC with 7:3 hexanes/Et_2O gave **6**, as a light yellow oil (376 mg, 94%). R_f=0.45 (7:3 hexanes/Et_2O). IR (film): $\tilde{\nu}$=3055 cm^{-1}, 2987, 2306, 2234, 1741, 1265, 739. UV/Vis (CH_3CN): λ_{max} (log ε)=230 nm (4.633), 246 (4.588), 288 (4.164). ^1H NMR (250 MHz, $CDCl_3$): δ=0.19 (s, 9H, $Si(CH_3)_3$), 2.42 (s, 3H, CH_3), 4.62 (s, 2H, CH_2), 7.12–7.46 (m, 11H), 7.76–7.84 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6): δ=21.7 (+), 56.2 (−), 70.5 (C_{quat}), 87.1 (C_{quat}), 98.1 (C_{quat}), 103.6 (C_{quat}), 124.2 (C_{quat}), 125.7 (C_{quat}), 126.9 (+), 127.8 (+), 128.1 (+), 128.4 (+), 128.6 (+), 128.9 (+), 129.7 (+), 131.0 (+), 132.7 (+)), 134.6 (C_{quat}), 135.0 (C_{quat}), 144.6 (C_{quat}). MS (EI) *m/z* (%): 457 (24) [M^+], 302 (13) [$M-C_7H_7SO_2^+$], 91 (100). $C_{27}H_{27}NO_2SSi$ (457.15): calcd C 70.86 H 5.95 N 3.06; found C 70.02 H 6.17 N 2.98.

3.1.5. *N*-Benzyl-*N*-(2-ethynyl-phenylethynyl)-4-methylbenzenesulfonamide (7). Compound **6** (156 mg, 0.34 mmol) was dissolved in 20 ml of methanol and K_2CO_3 (140 mg, 1.01 mmol) was added. After stirring for 1 h at room temperature, the reaction mixture was diluted with EtOAc and washed three times with H_2O. The organic phase was dried over Na_2SO_4 and the solvent was removed. The residue was purified by CC with 9:1 hexanes/Et_2O to yield **7** as a light yellow oil (85 mg, 65%). R_f=0.18 (9:1 hexanes/Et_2O). IR (film): $\tilde{\nu}$=3283 cm^{-1}, 3065, 3033, 2925, 2233, 2108, 1923, 1597, 1366, 1170, 1088, 1021, 799, 759, 653, 598. UV/Vis (CH_3CN): λ_{max} (log ε)=227 nm (4.715), 254 (4.281), 261 (4.240). ^1H NMR (300 MHz, $CDCl_3$): δ=2.43 (s, 3H, CH_3), 3.12 (s, 1H, CH), 4.63 (s, 2H, CH_2), 7.14–7.45 (m, 11H), 7.81–7.85 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.6 (+), 55.9 (−), 70.2 (C_{quat}), 80.7 (C_{quat}), 82.2 (+), 86.9 (C_{quat}), 123.3 (C_{quat}), 126.2 (C_{quat}), 127.0 (+), 127.8 (+), 128.3 (+), 128.4 (+), 128.5 (+), 128.9 (+), 129.7 (+), 130.9 (+), 132.4 (+), 134.5 (C_{quat}), 134.8 (C_{quat}), 144.6 (C_{quat}). MS (EI, 70 eV) *m/z* (%): 91 (100) [$C_7H_7^+$], 155 (15) [$CH_3C_6H_4SO_2^+$], 230 (6) [$M^+-CH_3C_6H_4SO_2$], 385 (3) [M^+]. HRMS $C_{24}H_{19}NO_2S$: calcd 385.1137; found 385.1138±0.8 ppm.

3.1.6. 2-Naphthyl-amine (13). 2-Nitronaphthalene (**12**, 2.00 g, 11.56 mmol) was dissolved in 50 ml of ethanol and Pd/C (50 mg, 10% Pd) was added. The reaction mixture was stirred at room temperature at a H_2 pressure of 5 atm for 24 h. After filtration and removal of the solvent, the residue was recrystallized from hexanes to give **13** as a yellow solid (1.25 g, 76%). All spectroscopic data are identical to the ones reported in the literature.[25] *Caution*: Compound **13** is a cancer inducing substance!

3.1.7. 4-Methyl-(4-benzenesulfonyl)-*N*-naphthalen-2-ylbenzenesulfonamide (14). A mixture of **13** (1.25 g, 8.74 mmol), 4-methyl-benzene-sulfonyl chloride (5.03 g, 26.4 mmol), triethylamine (9.00 ml, 6.48 g, 64 mmol) and *N*,*N*-dimethyl-amino-pyridine (53 mg, 0.44 mmol) in 50 ml of CH_2Cl_2 were stirred at room temperature for 4 h. The reaction mixture was extracted with 1 N HCl, H_2O and brine. The combined organic phases were dried over Na_2SO_4, the solvent was removed and the residue was recrystallized from ethanol to give **14** as a colorless solid (2.48 g, 63%). Mp: 165–166 °C. IR (KBr): $\tilde{\nu}$=3061 cm^{-1}, 2923, 2231, 1919, 1596, 1493, 1370, 1169, 1085, 928, 661, 550, 482. UV/Vis (CH_3CN): λ_{max} (log ε)=197 nm (5.097), 224 (5.074). ^1H NMR (300 MHz, $CDCl_3$): δ=2.48 (s, 6H, CH3), 7.08 (dd, *J*=8.7 Hz, *J*=2.2 Hz, 1H), 7.31–7.38 (m, 4H), 7.48–7.60 (m, 3H), 7.74–7.89 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.8 (+), 126.9 (+), 127.7 (+), 127.8 (+), 128.3 (+), 128.5 (+), 128.7 (+), 128.9 (C_{quat}), 129.0

(C_{quat}), 129.2 (+), 129.4 (C_{quat}) 129.7 (+), 130.0 (+), 131.5 (+), 131.8 (C_{quat}), 133.2 (+), 133.7 (+), 136.3 (C_{quat}), 136.7 (+), 144.8 (C_{quat}), 145.2 (+), 145.6 (C_{quat}). MS (EI, 70 eV) *m/z* (%): 451 (81) [M+], 296 (100) [$M-C_7H_7SO_2^+$], 155 (10) [$C_7H_7SO_2^+$], 139 (59) [$C_7H_7SO^+$], 91 (63) [$C_7H_7^+$]. $C_{24}H_{21}NO_4S_2$ (451.56): calcd C 63.84 H 4.69 N 3.10; found C 63.79 H 4.71 N 3.11.

3.1.8. 4-Methyl-*N*-naphthalen-2-ylbenzenesulfonamide (15). Sodium (1.20 g, 52.17 mmol) was added to 30 ml of ethanol. After completion of the reaction, **14** (0.45 g, 1.00 mmol) was added and the reaction mixture was refluxed for 2 h, then diluted with H_2O and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, the solvent was removed and the residue was recrystallized from ethanol to give **14** as a colorless solid (0.21 g, 71%). All spectroscopic data are identical to the ones reported in the literature.[26]

3.1.9. *N*-Benzyl-4-methyl-*N*-naphthalen-2-ylbenzenesulfonamide (11). To a mixture of **15** (0.1 g, 0.34 mmol) and benzyl bromide (0.12 ml, 0.17 g, 1.01 mmol) in 5 ml of acetone, K_2CO_3 (0.14 g, 1.01 mmol) and KI (0.06 g, 0.34 mmol) were added and the reaction mixture was refluxed for 3 d. After cooling to room temperature the resulting precipitate was filtered off and washed with acetone. The filtrate was evaporated and the residue was recrystallized from ethanol to give **11** as a colorless solid (0.10 g, 77%). All spectroscopic data are identical to the ones reported in the literature.[27]

Acknowledgements

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References and notes

1. For one of the first experimental reports of electronic effects on the Bergman cyclization, see: Schmittel, M.; Kiau, S. *Chem. Lett.* **1995**, 953–954.
2. (a) Jones, G. B.; Warner, P. M. *J. Am. Chem. Soc.* **2001**, *123*, 2134–2145. (b) Plourde, G. W., II; Warner, P. M.; Parrish, D. A.; Jones, G. B. *J. Org. Chem.* **2002**, *67*, 5369–5374.
3. (a) Kim, C. S.; Russell, K. C. *J. Org. Chem.* **1998**, *63*, 8229–8234. (b) Kim, C. S.; Diez, C.; Russell, K. C. *Chem. Eur. J.* **2000**, *6*, 1555–1558. (c) Nath, M.; Huffmann, J. C.; Zaleski, J. M. *Chem. Commun.* **2003**, 858–859.
4. For a recent report on computer design of new enediyne based anticancer drugs, see: Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2000**, *122*, 8245–8264.
5. Effect of *ortho*-substituents in benzannelated enediynes: (a) Alabugin, I. V.; Manoharan, M.; Kovalenko, S. V. *Org. Lett.* **2002**, *4*, 1119–1122. (b) Alabugin, I. V.; Manoharan, M. *J. Phys. Chem. A* **2003**, *107*, 3363–3371.
6. Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907–1911.
7. Prall, M.; Wittkopp, A.; Fokin, A. A.; Schreiner, P. R. *J. Comput. Chem.* **2001**, *22*, 1605–1614.
8. Wenk, H. H.; Balster, A.; Sander, W.; Hrovat, D. A.; Borden, W. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 2295–2298.
9. Amino-enediynes show a little lower reactivity than the parent system in calculations. Because ammonium has no π-donor and only σ-acceptor properties, the ammonium-enediyne has a relatively low barrier for cyclization and an almost thermoneutral reaction energy as predicted from calculations. Doubly substituted bis-ammonium-enediynes are far less reactive, because of the repulsion of the positively charged groups of the *ortho*-ammonium substituents in the cyclization product. See Ref. 7 for a systematic computational study.
10. For a recent report on synthesis and thermal cyclization of structurally related 3-aza-3-ene-1,5-dienes, see: (a) Nadipuram, A. K.; David, W. M.; Kumar, D.; Kerwin, S. M. *Org. Lett.* **2002**, *4*, 4543–4546. The nitrogen atom in these enediynes is part of a imidazole ring and therefore of different electronic influence. Enediynes with amide or amine not adjacent to the alkyne termini: (b) Banfi, L.; Guanti, G.; Rasparini, M. *Eur. J. Org. Chem.* **2003**, 1319–1336. (c) Basak, A.; Mandal, S.; Das, A. K.; Bertolasi, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 873–877.
11. Brandsma, L. Preparative Acetylenic Chemistry; 2nd ed. Elsevier: Amsterdam, 1988; p 187ff.
12. Brandsma, L. *Recl. Trav. Chim. Trav. Chim. Pays-Bas* **1971**, *90*, 1098–1100.
13. Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 489–492.
14. The positive charge of the ammonium group should contribute to the σ-acceptor properties of the substituents. This effect is missing in sulfonamides. Their activation effect on the enediyne system is therefore expected to be smaller.
15. Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369.
16. Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 2426–2430.
17. The alkyne was synthesized in two steps from TMS-ethynylphenyliodonium triflate and *N*-Ts,*N*-Bz-amine, followed by deprotection of the TMS group with fluoride. See supporting information for details. Synthesis of the TMS-ethynylphenyliodonium triflate, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. (b) Stang, P. J. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; pp 67–98.
18. Huynh, C.; Linstrumelle, G. *Tetrahedron* **1988**, *44*, 6337–6344.
19. Other conditions were tried: TBAF in THF/water gave only very slow conversion and even poorer yield.
20. Theory predicts a significantly reduced thermal reactivity for a bis-ammonium enediyne, because of strong repulsion of the *ortho* ammonium moieties in the cyclization product. In the case of a bis-sulfonamide at least the contribution from charge to repulsion is omitted.
21. Compound **7** may have been obtained from **9** by one addition of a lithium amide and rearrangement to the alkyne amide. The second iodoniumphenyl moiety was hydrolyzed upon work up.
22. The analytical method follows previously described procedures: (a) Choy, N.; Kim, C.-S.; Ballestero, C.; Artigas, L.; Diez, C.; Lichtenberger, F.; Shapiro, J.; Russell, K. C. *Tetrahedron Lett.* **2000**, *41*, 6955–6958. (b) Wisniewski Grissom, J.; Calkins, T. L.; McMillen, H. A.; Jiang, Y. *J. Org. Chem.* **1994**, *59*, 5833–5835. (c) Kim, C.-S.; Russell, K. C. *J. Org. Chem.* **1998**, *63*, 8229–8234.

23. The derived rate constant describes the thermal conversion of **7**. HPLC analyses showed that the Bergman cyclisation product is the main product of the thermolysis. HPLC-MS shows side products in minor amounts.
24. For a recent study on the effect of the steric influence of functional groups at the termini of acylic enediynes on the Bergman cyclization temperature, see: Rawat, D. S.; Zaleski, J. M. *Chem. Commun.* **2000**, 2493–2494.
25. Roesler, A.; Pfleiderer, W. *Helv. Chim. Acta* **1997**, *80*, 1869–1881.
26. Hellwinkel, D.; Lenz, D. R. *Chem. Ber.* **1985**, *118*, 66–85.
27. Buzniak, J.; Skulksi, L.; Wybraniec-Bugaj, J. *Pol. J. Chem.* **1981**, *55*, 1923–1927.

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An easy preparation of pyridinium *N*-heteroarylaminides

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Abstract—Differently substituted pyridinium *N*-heteroarylaminides have been prepared in one step with good yield from *N*-aminopyridinium iodide and the corresponding heteroaryl chloride.
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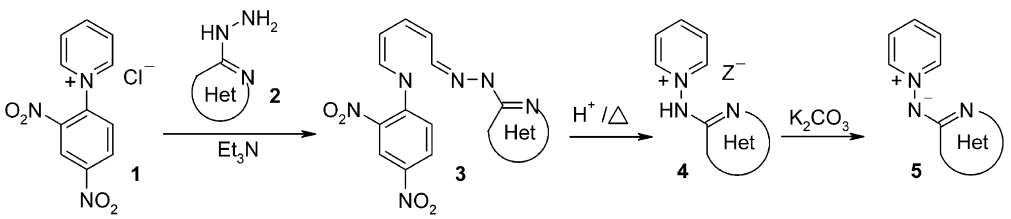
For many years conjugated heterocyclic *N*-ylides, a subgroup of mesomeric betaines,[1] have been widely used as building blocks for the synthesis of fused heterocyclic systems and natural products, due to its 1,3-dipolar character,[2] that allows cycloaddition processes to take place efficiently. Today, cycloimmonium ylides are involved in a wide range of synthetically useful reactions, mainly in the field of heterocyclic chemistry.[3]

The chemistry of pyridinium *N*-(2′-heteroaryl)aminides **5** (Scheme 1) has been developed in the last few years taking advantage of its structure, in which a positively charged pyridinium ring coexists with a 2-aminoheteroaryl negatively charged moiety. This peculiar structure would selectively direct the attacking electrophiles, thus allowing easy and selective halogenations on the heteroaryl moiety.[4–6] Moreover, N-alkylation process takes place regioselectively over the aminide nitrogen, by the partial blockage of the heteroaryl α-nitrogen, via an intramolecular hydrogen bond.[4] The N–N bond reduction of the resulting pyridinium salts should allow the preparation of the corresponding amines[4,7] or polyamines.[8] When N-alkylation was performed with α-haloesters or α-haloketones, pyrido[1,2-*a*]pyrimidin-4-ones and imidazo[1,2-*a*]pyridines were respectively obtained by a cascade heterocyclisation process.[9] Finally, intramolecular radical arylations of *N*-haloazinylpyridinium *N*-aminides afforded dipyridopyrazole and pyridopyrazolepyrazine derivatives.[10]

The synthesis of *N*-aminide intermediates **5** has been traditionally performed by attack of the corresponding 2-heteroaryl hydrazine **2** to 2,4-dinitrophenyl pyridinium chloride **1** (see Scheme 1) generating the hydrazone **3**, which is again closed to a pyridinium derivative by acid catalysis, to produce the salt **4** and from there, by treatment with base, the *N*-aminides were obtained. This method, adapted from the scheme described by Beyer[11] is suitable for available heteroaryl derivatives, usually the simpler pyridylhydrazines.

Alternatively, an easy method can be used for various π-deficient heterocycles, by simply treating the *N*-aminopyridinium iodide **6**[12] with the corresponding 2-chloroheteroaryls **8** in the presence of base. The method generates the pyridinium *N*-aminides **5** in only one step, and makes a suitable alternative to prepare a diversity of those useful intermediates. The methodology has been applied to the synthesis of *N*-vinyl,[13] *N*-imidoyl[14] and fluorinated *N*-aromatic iminopyridinium ylides.[15]



Scheme 1.

Keywords: Pyridinium *N*-aminides; *N*-ylides.
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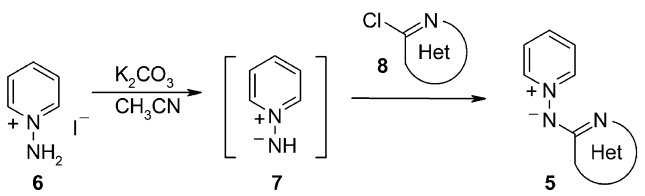
1. Results and discussion

Different α-chloroheterocycles **8a**–**o** were reacted with the *N*-iminopyridinium ylide **7**, generated at room temperature from the readily available *N*-aminopyridinium iodide **6**[12] and anhydrous potassium carbonate in acetonitrile (Scheme 2), to produce the corresponding pyridinium *N*-heteroarylaminides **5a**–**o**. A set of commercial 2-(and 4-)chloropyrimidines, 2-chloropyrazines and 3-chloropyridazines, were chosen, having additional chlorine atoms on the heterocyclic ring, in order to obtain new halogenated ylides as useful starting materials in our in course studies on radical[10] processes and palladium catalysed reactions.[16]



Scheme 2.

The nucleophilic substitution process works well using simpler halodiazines such as 2-chloropyrimidine and 2-chloropyrazine, yielding aminides such as **5g** and **5m**, in only 4 h and with improved yields (95 and 72) in comparison over those obtained using the traditional ANRORC process, followed by treatment with base[4] (72 and 64%, see Table 1). However, with 2-chloropyridine the reaction did not take place, and after 48 h reflux, only the starting materials were recovered. As in other S_NAr reactions, electron-withdrawing groups make the heterocyclic ring of the electrophile more π-deficient, facilitating the attack of the nucleophile. In this way, good yields in *N*-(pyridin-2′-yl)pyridinium aminides were obtained with 2,6-dichloropyridine, 3-nitro and 5-nitrochloropyridines and almost quantitative yields employing dichlorodiazines (see Table 1). The worse result was obtained for compound **5e**, having a phenyl group, which probably increases the electronic density in the diazine ring, making the S_NAr process more difficult. A considerable improvement was also obtained in the synthesis of *N*-(2′-benzothiazol-2′-yl)pyridinium aminide **5p**, previously reported in a 45% yield.[11]

In conclusion, we describe herein a mild and efficient method to prepare a series of pyridinium *N*-heteroarylaminides **5** in good to excellent yields from the suitable α-haloheterocycle **8** and a stoichiometric amount of

Table 1. Compounds **5a**-**p** obtained

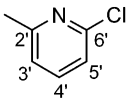
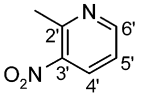
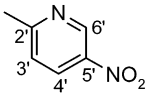
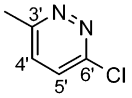
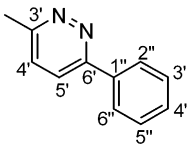
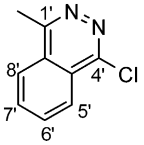
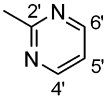
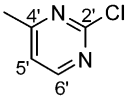
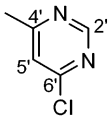
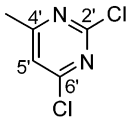
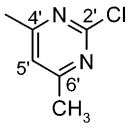
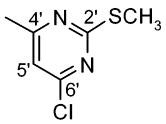
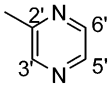
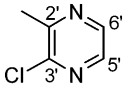
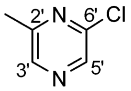
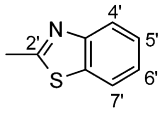
Compound	Het	Reaction time (h)	Reaction temperature	Yield (%)
5a		4	Reflux	65
5b		24	Room temp.	70
5c		4	Room temp.	75[a]
5d		15	Room temp.	91
5e		4	Reflux	53
5f		10	Reflux	77
5g		4	Reflux	95[b]
5h		20	Room temp.	95

Table 1 (*continued*)

Compound	Het	Reaction time (h)	Reaction temperature	Yield (%)
5i		20	Room temp.	85
5j		7	Room temp.	75
5k		24	Room temp.	98
5l		24	Room temp.	88
5m		4	Reflux	72[b]
5n		20	Room temp.	95
5o		20	Room temp.	77
5p		24	Reflux	90[b]

[a] This compound was obtained by nitration of *N*-(pyridin-2′-yl)pyridinium aminide in 25% yield.[4]
[b] These compounds were obtained by the classical procedure (see Scheme 1) in 72% (**5g**), 64% (**5m**), and 45% (**5p**) overall yield.[11]

commercial 1-aminopyridinium iodide **6**. This one-step procedure represents a clear improvement to previously described methodologies.

2. Experimental

All melting points were determined in open capillary tubes, on a Gallenkamp MFB-595-010M and are uncorrected. IR spectra were obtained on a Perkin–Elmer FTIR 1725X spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 or 500 MHz spectrometer at room temperature. Chemical shifts are given in ppm (δ) downfield from TMS. Coupling constants (J) are in hertz (Hz), and signals are described as follows: s, singlet; d, doublet; t, triplet; br., broad; m, multiplet; ap., apparent etc. The assignment of proton and carbon resonances has been made on the basis of double resonance and two-dimensional H,C-correlated experiments; HSQC and HMBC spectra have been recorded when necessary on a Varian Mercury VX-300 NMR System. Elemental analyses were carried out on a Heraeus Rapid CHN analyzer and are within 0.4% of the theoretical values for all new compounds described. All reagents were obtained from commercial sources and used without further purification. Solvents used were purified and dried by standard procedures. Column chromatography was carried out with silica gel 60 (40–63 μm, Merck) columns or Biotage Flash (KP-Sil, 60 Å, 32–63 μM) cartridges, using the eluent reported for each case.

2.1. Preparation of pyridinium aminides 5

General method. Potassium carbonate (1.86 g, 13.5 mmol) was added to a solution of the *N*-aminopyridinium iodide **6** (1 g, 4.5 mmol) in acetonitrile (20 mL) and the reaction mixture was vigorously stirred for 45 min at room temperature to give a purple solution of compound **7**. Over this solution, the corresponding α-chloroheterocycle **8** (4.7 mmol) in acetonitrile (5 mL) was added. The mixture was either stirred at room temperature or refluxed (see Table 1) until no starting material was detected by TLC. The inorganic salts were filtered through zelite, the filtrate was evaporated in vacuo and the product was purified by chromatography on silica gel using ethanol as eluent, crystallized from the suitable solvent and identified.

The following compounds were prepared according the general method.

2.1.1. *N*-(6′-Chloropyridin-2′-yl)pyridinium aminide (5a). Yellow solid (601 mg, 65%, ethanol–ethyl acetate), mp 110–112 °C. Anal. calcd for $C_{10}H_8ClN_3$: C, 58.41; H, 3.92; N, 20.43. Found: C, 58.68; H, 4.02; N, 20.44; ν_{max} (KBr) 1586, 1430, 767 cm^{-1}; δ_H (500 MHz. CD_3OD) 8.73 (2H, dd, *J*=7.1, 1.2 Hz, *H*2(6)); 8.03 (1H, tt, *J*=7.7, 1.2 Hz, *H*4); 7.80 (2H, dd, *J*=7.7, 7.1 Hz, *H*3(5)); 7.27 (1H, dd, *J*=8.4, 7.3 Hz, *H*4′); 6.34 (1H, d, *J*=8.4 Hz, *H*3′ or 5′); 6.32 (1H, d, *J*=7.3 Hz, *H*3′ or 5′); δ_C (125 MHz. CD_3OD) 165.7 (*C*2′), 149.5 (*C*6′), 144.6 (*C*2(6)), 140.1 (*C*4′), 138.2 (*C*4), 128.3 (*C*3(5)), 110.1 (*C*3′ or 5′), 109.4 (*C*3′ or 5′).

2.1.2. *N*-(3′-Nitropyridin-2′-yl)pyridinium aminide (5b). Deep orange solid (681 mg, 70%, methanol), mp 257–258 °C. Anal. calcd for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.66; H, 3.77; N, 25.66; ν_{max} (KBr) 1602, 1543, 1479, 1426, 1241 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.63 (2H, dd, *J*=6.8, 1.3 Hz, *H*2(6)); 8.30 (1H, dd, *J*=8.1, 1.8 Hz, *H*4′); 8.25 (1H, tt, *J*=7.7, 1.3 Hz, *H*4); 7.93 (3H, m, *H*3(5) and 6′); 6.40 (1H, dd, *J*=8.1, 4.6 Hz, *H*5′); δ_C (75 MHz. DMSO-d_6) 158.3 (*C*2′), 154.1 (*C*6′), 144.1 (*C*2(6)), 138.8 (*C*4), 135.2 (*C*4′), 127.5 (*C*3(5)), 127.3 (*C*3′), 107.6 (*C*5′).

2.1.3. *N*-(5′-Nitropyridin-2′-yl)pyridinium aminide (5c). Orange solid (729 mg, 75%, methanol), mp 220–222 °C (lit.[4]216–218 °C); ν_{max} (KBr) 1597, 1547, 1488, 1426, 1275 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.69 (2H, dd, *J*=7.0, 1.3 Hz, *H*2(6)); 8.61 (1H, d, *J*=2.7 Hz, *H*6′); 8.26 (1H, tt, *J*=7.7, 1.3 Hz, *H*4); 7.98 (1H, dd, *J*=9.5, 2.7 Hz, *H*4′); 7.94 (2H, dd, *J*=7.7, 7.0 Hz, *H*3(5)); 6.40 (1H, d, *J*=9.5 Hz, *H*3′); δ_C (75 MHz. DMSO-d_6) 165.6 (*C*2′), 147.9 (*C*6′), 143.3 (*C*2(6)), 139.4 (*C*4), 131.3 (*C*5′), 130.5 (*C*4′), 127.4 (*C*3(5)), 109.4 (*C*3′).

2.1.4. *N*-(6′-Chloropyridazin-3′-yl)pyridinium aminide (5d). Yellow solid (845 mg, 91%, ethanol–ethyl acetate), mp 154–155 °C. Anal. calcd for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 52.09; H, 3.26; N, 27.13; ν_{max} (KBr) 1577, 1474, 1414, 1341, 1149 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.79 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.22 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 7.93 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5)); 7.18 (1H, d, *J*=9.4 Hz, *H*5′); 6.83 (1H, d, *J*=9.4 Hz, *H*4′); δ_C (75 MHz. CD_3OD) 164.9 (*C*3′), 145.6 (*C*2(6)), 144.9 (*C*6′), 140.3 (*C*4), 129.9 (*C*5′), 128.9 (*C*3(5)), 122.3 (*C*4′).

2.1.5. *N*-(6′-Phenylpyridazin-3′-yl)pyridinium aminide (5e). Yellow solid (592 mg, 53%, ethanol–ethyl acetate), mp 160–161 °C. Anal. calcd for $C_{15}H_{12}N_4$: C, 72.56; H, 4.87; N, 22.57. Found: C, 72.27; H, 4.87; N, 22.28; ν_{max} (KBr) 1592, 1474, 1449, 1412, 1337, 1153 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.82 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.11 (1H, tt, *J*=7.7, 1.3 Hz, *H*4); 7.85 (2H, dd, *J*=7.7, 6.9 Hz, *H*3(5)); 7.80 (2H, dd, *J*=8.2, 1.5 Hz, *H*2″(6″)); 7.62 (1H, d, *J*=9.5 Hz, *H*5′); 7.40 (2H, dd, *J*=8.2, 6.9 Hz, *H*3″(5″)); 7.36 (1H, tt, *J*=6.9, 1.5 Hz, *H*4″); 6.85 (1H, d, *J*=9.5 Hz, *H*4′); δ_C (75 MHz. CD_3OD) 165.0 (*C*3′), 151.4 (*C*6′), 145.9 (*C*2(6)), 139.9 (*C*4), 138.8 (*C*1″), 130.1 (*C*3″(5″)), 129.7 (*C*4″), 129.0 (*C*3(5)), 127.5 (*C*5′), 127.0 (*C*2″(6″)), 119.8 (*C*4′).

2.1.6. *N*-(4′-Chlorophthalazin-1′-yl)pyridinium aminide (5f). Yellow solid (889 mg, 77%, ethanol–ethyl acetate), mp 157–159 °C. Anal. calcd for $C_{13}H_9ClN_4$: C, 60.83; H, 3.53; N, 21.83. Found: C, 60.64; H, 3.69; N, 21.73; ν_{max} (KBr) 1512, 1483, 1406, 1359, 1138 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.85 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.40 (1H, m, *H*5′ or *H*8′); 8.26 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 8.01 (1H, m, *H*5′ or *H*8′); 7.96 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5); 7.87 (2H, m, *H*6′ and *H*7′); δ_C (75 MHz. CD_3OD) 162.0 (*C*1′), 146.2 (*C*2(6)), 143.5 (*C*4′), 140.6 (*C*4), 133.3 (*C*6′ or *C*7′), 133.0 (*C*6′ or *C*7′), 129.0 (*C*3(5)), 127.8 (*C*4′a), 125.3 (*C*5′ or *C*8′), 125.2 (*C*5′ or *C*8′), 124.4 (*C*8′a).

2.1.7. *N*-(Pyrimidin-2′-yl)pyridinium aminide (5g). Yellow solid (735 mg, 95%, ethyl acetate), mp 151–153 °C (lit.[4]150–152 °C); δ_H (300 MHz. CD_3OD) 8.71 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.20 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 8.11 (2H, d, *J*=4.8 Hz, *H*4′(6′)); 7.91 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5)); 6.38 (1H, t, *J*=4.8 Hz, *H*5′); δ_C (75 MHz. CD_3OD) 169.4 (*C*2′), 159.2 (*C*4′(6′)), 145.8 (*C*2(6)), 139.9 (*C*4), 128.8 (*C*3(5)), 109.0 (*C*5′).

2.1.8. *N*-(2′-Chloropyrimidin-4′-yl)pyridinium aminide (5h). Yellow solid (883 mg, 95%, ethanol–ethyl acetate), mp 134–136 °C. Anal. calcd for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 52.32; H, 3.52; N, 27.26; ν_{max} (KBr) 1618, 1587, 1474, 1335, 977 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.65 (2H, dd, *J*=6.9, 1.4 Hz, *H*2(6)); 8.27 (1H, tt, *J*=7.6, 1.4 Hz, *H*4); 7.94 (2H, dd, *J*=7.6, 6.9 Hz, *H*3(5)); 7.65 (1H, d, *J*=6.2 Hz, *H*6′); 6.25 (1H, br.d, *J*=6.2 Hz, *H*5′); δ_C (75 MHz. CD_3OD) 168.9 (*C*4′), 160.8 (*C*2′), 153.8 (*C*6′), 145.2 (*C*2(6)), 141.2 (*C*4), 128.6 (*C*3(5)), 105.8 (*C*5′).

2.1.9. *N*-(6′-Chloropyrimidin-4′-yl)pyridinium aminide (5i). Yellow solid (790 mg, 85%, ethanol–ethyl acetate), mp 167–168 °C. Anal. calcd for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 52.47; H, 3.47; N, 27.01; ν_{max} (KBr) 1619, 1574, 1448, 1336, 1066, 974 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.66 (2H, dd, *J*=6.9, 1.4 Hz, *H*2(6)); 8.26 (1H, tt, *J*=7.8, 1.4 Hz, *H*4); 7.92 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5)); 7.81 (1H, s, *H*2′); 6.30 (1H, br.s, *H*5′); δ_C (75 MHz. CD_3OD) 168.9 (*C*4′), 158.6 (*C*2′), 156.7 (*C*6′), 145.2 (*C*2(6)), 141.1 (*C*4), 128.6 (*C*3(5)), 104.5 (*C*5′).

2.1.10. *N*-(2′,6′-Dichloropyrimidin-4′-yl)pyridinium aminide (5j). Yellow solid (814 mg, 75%, ethanol–ethyl acetate), mp >190 °C, dec. Anal. calcd for $C_9H_6Cl_2N_4$: C, 44.84; H, 2.51; N, 23.24. Found: C, 45.15; H, 2.64; N, 23.06; ν_{max} (KBr) 1618, 1574, 1460, 1391, 1146, 989 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.69 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.33 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 7.99 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5)); 6.30 (1H, br.s, *H*5′); δ_C (75 MHz. CD_3OD) 169.7 (*C*4′), 160.5 (*C*2′), 156.9 (*C*6′), 145.2 (*C*2(6)), 141.8 (*C*4), 128.9 (*C*3(5)), 103.4 (*C*5′).

2.1.11. *N*-(2′-Chloro-6′-methylpyrimidin-4′-yl)pyridinium aminide (5k). Yellow solid (972 mg, 98%, hexane–ethyl acetate), mp 144–146 °C. Anal. calcd for $C_{10}H_9ClN_4$: C, 54.43; H, 4.11; N, 25.39. Found: C, 54.11; H, 4.03; N, 25.17; ν_{max} (KBr) 1597, 1457, 1267, 1177 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.68 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.30 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 7.97 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5)); 6.13 (1H, br.s, *H*5′); 2.21 (3H, s, C*H*$_3$); δ_C (75 MHz. CD_3OD) 169.6 (*C*4′), 164.3 (*C*6′), 160.5 (*C*2′), 145.3 (*C*2(6)), 141.1 (*C*4), 128.7 (*C*3(5)), 103.4 (*C*5′); 22.8 (*C*H$_3$).

2.1.12. *N*-(6′-Chloro-2′-methylsulfanylpyrimidin-4′-yl)pyridinium aminide (5l). Yellow solid (998 mg, 88%, hexane–ethyl acetate), mp 158–160 °C. Anal. calcd for $C_{10}H_9ClN_4S$: C, 47.53; H, 3.59; N, 22.17; S, 12.69. Found: C, 47.30; H, 3.51; N, 22.03; S, 12.35 ν_{max} (KBr) 1617, 1541, 1447, 1369, 1214 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.72 (2H, dd, *J*=7.0, 1.3 Hz, *H*2(6)); 8.31 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 7.97 (2H, dd, *J*=7.8, 7.0 Hz, *H*3(5)); 6.06 (1H, br.s, *H*5′); 2.08 (3H, s, CH_3); δ_C (75 MHz. CD_3OD) 172.2 (*C*4′), 168.4 (*C*2′), 156.9 (*C*6′), 145.8 (*C*2(6)), 141.3 (*C*4), 128.5 (*C*3(5)), 99.6 (*C*5′); 13.7 (CH_3).

2.1.13. *N*-(Pyrazin-2′-yl)pyridinium aminide (5m). Yellow solid (557 mg, 72%, ethyl acetate), mp 158–159 °C (lit.[4] 157–159 °C); δ_H (300 MHz. CD_3OD) 8.82 (2H, dd, *J*=7.0, 1.2 Hz, *H*2(6)); 8.21 (1H, tt, *J*=7.8, 1.2 Hz, *H*4); 7.93 (2H, dd, *J*=7.8, 7.0 Hz, *H*3(5)); 7.86 (1H, d, *J*=1.5 Hz, *H*3′); 7.61 (1H, dd, *J*=3.1, 1.5 Hz, *H*6′); 7.45 (1H, d, *J*=3.1 Hz, *H*5′); δ_C (75 MHz. CD_3OD) 162.0 (*C*2′), 145.3 (*C*2(6)), 141.9 (*C*6′), 139.9 (*C*4), 136.8 (*C*3′), 129.5 (*C*5′), 128.9(*C*3(5)).

2.1.14. *N*-(3′-Chloropyrazin-2′-yl)pyridinium aminide (5n). Yellow solid (883 mg, 95%, ethanol–ethyl acetate), mp 197–199 °C. Anal. calcd for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 52.25; H, 3.52; N, 27.13; ν_{max} (KBr) 1612, 1559, 1474, 1443, 1397, 1045 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.68 (2H, dd, *J*=6.8, 1.3 Hz, *H*2(6)); 8.22 (1H, tt, *J*=7.7, 1.3 Hz, *H*4); 7.91 (2H, dd, *J*=7.7, 6.8 Hz, *H*3(5)); 7.49 (1H, d, *J*=2.8 Hz, *H*6′); 7.21 (1H, d, *J*=2.8 Hz, *H*5′); δ_C (75 MHz. CD_3OD) 159.7 (*C*2′), 146.4 (*C*2(6)), 141.2 (*C*6′), 140.9 (*C*4), 136.6 (*C*3′), 129.2 (*C*3(5)), 128.1 (*C*5′).

2.1.15. *N*-(6′-Chloropyrazin-2′yl)pyridinium aminide (5o). Yellow solid (715 mg, 77%, ethanol–ethyl acetate), mp 184–186 °C. Anal. calcd for $C_9H_7ClN_4$: C, 52.31; H, 3.41; N, 27.11. Found: C, 52.45; H, 3.47; N, 27.15; ν_{max} (KBr) 1618, 1555, 1465, 1445, 1389, 984 cm^{-1}; δ_H (300 MHz. CD_3OD) 8.78 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.21 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 7.93 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5)); 7.70 (1H, s, *H*3′); 7.36 (1H, s, *H*5′); δ_C (75 MHz. CD_3OD) 161.9 (*C*2′), 147.8 (*C*6′), 145.1 (*C*2(6)), 140.1 (*C*4), 134.0 (*C*3′), 128.7 (*C*3(5)), 126.0 (*C*5′).

2.1.16. *N*-(Benzothiazol-2′-yl)pyridinium aminide (5p). Yellow solid (919 mg, 90%, hexane–ethyl acetate), mp 170–172 °C (lit.[11] 167–169 °C); δ_H (300 MHz. CD_3OD) 9.07 (2H, dd, *J*=6.9, 1.3 Hz, *H*2(6)); 8.16 (1H, tt, *J*=7.8, 1.3 Hz, *H*4); 7.92 (2H, dd, *J*=7.8, 6.9 Hz, *H*3(5)); 7.52 (1H, dd, *J*=7.8, 1.3 Hz, *H*7′); 7.22 (1H, dd, *J*=8.0, 1.6 Hz, *H*4′); 7.17 (1H, ddd, *J*=8.0, 7.0, 1.3 Hz, *H*5′); 6.97 (1H, ddd, *J*=7.8, 7.0, 1.6 Hz, *H*6′); δ_C (75 MHz. CD_3OD) 176.9 (*C*2′), 153.8 (*C*3′a), 143.9 (*C*2(6)), 139.2 (*C*4), 131.5 (*C*7′a), 128.7 (*C*3(5)), 126.4 (*C*5′), 121.7 (*C*6′), 121.4 (*C*7′), 117.8 (*C*4′).

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References and notes

1. Ollis, D. W.; Stanforth, S. P. *Tetrahedron* **1985**, *41*, 2239–2329.
2. *1,3-Dipolar cycloaddition chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.
3. Vaquero, J. J.; Alvarez-Builla, J. *Adv. Nitrogen Heterocycl.* **2000**, *4*, 159–250.
4. Carceller, R.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J.; Fajardo, M.; Gomez-Sal, P.; Gago, F. *Tetrahedron* **1994**, *50*, 4995–5012.
5. Burgos, C.; Delgado, F.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **1995**, *51*, 8649–8654.
6. García de Viedma, A.; Martínez-Barrasa, V.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J. *J. Org. Chem.* **1999**, *64*, 1007–1010.
7. Martínez-Barrasa, V.; Delgado, F.; Burgos, C.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2000**, *56*, 2481–2490.
8. Reyes, M. J.; Delgado, F.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2002**, *58*, 8573–8579.
9. De la Rosa, R.; Martinez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2000**, *41*, 5837–5840.
10. Núñez, A.; García de Viedma, A.; Martinez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Synlett* **2002**, 1093–1096.
11. Beyer, H.; Thieme, E. *J. Prakt. Chem.* **1966**, *31*, 293–303.
12. Gösl, R.; Meuwesen, A. *Org. Synth.* **1973**, *5*, 43–45.
13. Sasaki, T.; Kanematsu, K.; Kakehi, A. *J. Org. Chem.* **1972**, *37*, 3106–3110.
14. Kakehi, A.; Ito, S.; Uchiyama, K.; Konno, Y.; Kondo, K. *J. Org. Chem.* **1977**, *42*, 443–448.
15. Banks, R. E.; Hitchen, S. M. *J. Fluorine Chem.* **1978**, *12*, 159–166.
16. García-Cuadrado, D.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Synlett* **2002**, 1904–1906.

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Synthesis and characterization of β-fused porphyrin-BODIPY® dyads

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Abstract—Novel dyads in which a porphyrin ring is directly fused through two β-pyrrolic carbons to a BODIPY® moiety have been prepared using a stepwise approach starting from the copper(II) complex of pyrrolo[2,3-*c*]-5,10,15,20-tetraphenylporphyrin. Formylation and reaction with 3,5-dimethylpyrrole afforded **8**; subsequent BF_2 complexation gave the TPP-BODIPY® dyad in reasonable yields. Demetalation in TFA/H_2SO_4 led to the corresponding free base **12**, opening the way to the subsequent preparation of the Zn complex **13**. Both **12** and **13** exhibited complex optical spectra with an intensely red-shifted Q-band. Luminescence spectra displayed a very intense band around 700 nm making these species suitable as near-IR dyes and sensors in biological media. Optical analyses of **12**, using the INDO/SCI technique, were performed to obtain information to establish the origin of the novel optical properties. These studies showed that the optical properties of **12** cannot be attributed to deformation of the molecular skeleton, but derive from the increased extension of the conjugation between the TPP and BODIPY® π-systems.
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1. Introduction

The exploitation of organic compounds in electronic and optoelectronic devices is one of the most exciting and challenging themes of research, with potential for enormous improvements in the performance of such devices. The discovery of the electrical conducting properties of polyacetylene[1] by Heeger, MacDiarmid and Shirakawa, who were awarded the 2000 Nobel Prize for Chemistry, can be considered the starting point of this field of research. Since their initial report, continuous effort has been focussed on the preparation of molecules to be used as organic conducting or optical materials. New organic compounds have been successfully employed in different technological applications,[2] although several problems still confine these molecular devices to the laboratory curiosity category and prevent their introduction into a marketplace dominated by silicon-based devices. Organic compounds should have molecular properties, such as stability, optical and redox properties, tailored for the subsequent application, and it is important to control the solid state aggregation of the organic material in the solid film, which is in several cases critical for the performances of the device.[3]

The presence of a highly delocalized π-electron system in a molecule such as a porphyrin provides a variety of advantages for their application. Indeed, one of the ways to enhance the use of porphyrins in optolectronic devices is to further expand the existing π-system.[4] Porphyrins are particularly appealing because of the richness of their properties, and because expertise is available to modify these useful platforms to build more complex molecular architectures.[5] We have been involved in this field of research and have reported the preparation of porphyrin arrays, and in particular oligoporphyrin systems where the macrocycles are covalently fused at their β-pyrrolic positions,[6] and the strong electronic interaction within the macrocycles results in a unique photophysical behavior.[6b] Similar fused arrays have been proposed as molecular wires[5,7] Our attention has been focused on heterodyads, in which a porphyrin and a different chromophore are fused through their π-aromatic systems by sharing two adjacent β-carbons.[8]

Keywords: Fused porphyrins; Porphyrin dyads; BODIPY; Optical spectra; INDO/SCI theory.
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Among the different chromophores, 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY®) and related dyes have been used for several applications,[9] because of their stability, high absorption and emission bands and the independence of the optical properties from the pH of the solution. BODIPY® fluorophores have strong absorption and high fluorescence quantum yields with emission maxima from 490 to 650 nm.

BODIPY® dyes were first prepared by Treibs and Kreuzer in 1968.[10] Solutions of the alkyl-substituted derivatives have a green, fluorescein-like fluorescence. When substituents that introduce additional conjugation are added to the parent molecule, both the absorption and emission spectra of the derivatives can shift to significantly longer wavelengths.[11] Hence one would expect that a BODIPY® dye that is partly conjugated with the aromatic system of a porphyrin macrocycle might result in absorption and emission spectra significantly red-shifted beyond 650 nm. Examples of dyes in which BODIPY® units are fused to benzene rings have been described,[12] but analogues directly fused to porphyrin chromophores have not. BODIPY®-molecules appended to porphyrins[13] and to 21-thia- and 21-oxa-porphyrins[14] (in which the BODIPY® units are attached via unrestricted phenylalkynyl linkers) have been reported.

The fused pyrroloporphyrin[15] represents the natural starting material for rational synthesis of new π-extended molecules in which BODIPY® and porphyrin moieties are directly fused at their β-pyrrolic positions. Herein we describe the synthesis and photophysical characterization of porphyrin-BODIPY® dyads **12** and **13**. Optical properties of **12** have been investigated by use of the INDO/SCI technique, to provide information on the spectroscopic signature of these species.

2. Experimental

2.1. General

5,10,15,20-Tetraphenylporphyrin (H_2TPP) and its metal derivatives were synthesized according to the literature.[16] The Cu and Ni complexes of 2-nitroTPP were also prepared according to the literature.[17] N_2O_4 gas was prepared by reacting HNO_3 with zinc metal.[17] Melting points were measured on a Thomas/Bristoline microscopic hot stage apparatus and are uncorrected. ^{1}H NMR spectra were obtained in deuteriochloroform solution at 300 MHz using a General Electric QE 300 spectrometer; chemical shifts are expressed in ppm relative to residual $CHCl_3$ (at 7.258 ppm) in the deuterated solvent, unless otherwise stated. All chemicals were obtained from commercial suppliers and used without further purification. THF was distilled from Na/benzophenone and toluene was distilled from calcium hydride prior to use. Elemental analyses were performed at the Midwest Microlab., Inc., Indianapolis, IN. Mass spectra (MALDI-TOF) were obtained at the Facility for Advanced Instrumentation, University of California, Davis, CA. Electronic spectra were measured in dichloromethane using a Hitachi U-2000 spectrophotometer or a Hewlett–Packard 8450A spectrophotometer (Davis) and a Perkin–Elmer Lambda 16 spectrophotometer (Bologna). Uncorrected emission and corrected excitation spectra were obtained with a Perkin–Elmer LS50 spectrofluorimeter. The fluorescence lifetimes (uncertainty, ±5%) were obtained with an Edinburgh single-photon counting apparatus, in which the flash lamp was filled with N_2. Emission spectra in a rigid, transparent 2-methylcyclohexane matrix at 77 K were recorded using quartz tubes immersed in a quartz Dewar filled with liquid N_2. Fluorescence quantum yields were determined using H_2TPP (Φ=0.11) in deaerated toluene[18] as a reference. In order to allow comparison of emission intensities, corrections for the different absorbance[19] and phototube sensitivity were performed. A correction for a difference in the refractive index was introduced when necessary.

2.1.1. Copper(II) 5,10,15,20-tetraphenyl[(2,3-c)pyrroloformyl]porphyrin (4). The β-fused-di-α-free-pyrroloporphyrin **1**[14] (0.60 g, 0.841 mmol) was dissolved in trimethylorthoformate (30 mL, 0.274 mol) and treated with TFA (30 mL, 0.393 mol). The reaction was allowed to stir under argon at 0 °C for 10 min and at room temperature for 30 min (TLC monitoring). Next, cold water was added and the mixture was stirred for 2 h before 500 mL of saturated aq. Na_2CO_3 was added and stirring was continued for another 1 h. The organic layer was then separated and was washed with H_2O twice. The title porphyrin **4** (0.522 g, 83%) was recrystallized from CH_2Cl_2/MeOH. Mp>300 °C. UV/vis λ_{max} (CH_2Cl_2) 432 nm (ε 239,000), 558 (16,700), 604 (15,300), 658 (8600). MS *m*/*z* 741.6 (M^+). Anal. calcd for $C_{47}H_{29}CuN_5O\cdot H_20$: C, 75.14; H, 4.01; N, 9.21. Found: C, 75.03; H, 4.08; N, 8.98.

2.1.2. Nickel(II) 5,10,15,20-tetraphenyl[(2,3-c)pyrroloformyl]porphyrin (5). The title compound was obtained as described above (0.312 g scale, 96%), starting from β-fused-di-α-free pyrroloporphyrin **3**. Mp>300 °C. UV/vis λ_{max} (CH_2Cl_2) 432 nm (ε 137,700), 552 (12,300), 596 (12,200), 658 (3300). ^{1}H NMR ($CDCl_3$): δ 6.14 (d, 1H, *J*=3.6 Hz), 6.95 (s, 1H), 7.68 (br, 10H), 7.78 (br, 5H), 8.08 (br, 5H), 8.14 (s, *J*=7.2 Hz, 1H), 8.51 (d, *J*=4.8 Hz, 1H), 8.60 (s, 1H), 8.66 (d, *J*=4.8 Hz, 1H), 8.73 (d, *J*=5.1 Hz, 1H), 8.80 (d, *J*=5.4 Hz), 9.83 (s, 1H). MS *m*/*z* 738.1 (M^+). Anal. calcd for $C_{47}H_{29}N_5ONi\cdot 0.5H_2O$: C, 75.53; H, 4.04; N, 9.37. Found: C, 75.96; H, 3.88; N, 9.03.

2.1.3. Copper(II) 5,10,15,20-tetraphenyldipyrrometheno-porphyrin hydrochloride (9). The formylpyrroloporphyrin **4** (98.4 mg, 0.132 mmol) was dissolved in 25 mL of CH_2Cl_2 and degassed with argon for 5 min. 2,4-Dimethylpyrrole (0.02 g, 0.210 mmol) was added to the reaction mixture followed by TFA (0.20 mL, 0.261 mmol). The reaction mixture was stirred for 1 day (TLC monitoring). Washing with saturated $NaHCO_3$ afforded the unstable dipyrromethenoporphyrin free base, and is not recommended. Workup involved an aqueous work up using brine and the organic layer (CH_2Cl_2) was collected, reduced in volume (to 50 mL) using a rotary evaporator and compound **9** precipitated from solution as the hydrochloride after addition of MeOH and further concentration (97 mg, 90%). Mp>300 °C. Anal. calcd for $C_{53}H_{37}ClCuN_6$: C, 74.29; H, 4.35; N, 9.81. Found: C, 74.34; H, 4.66; N, 9.49.

2.1.4. Nickel(II) 5,1015,20-tetraphenyldipyrromethenoporphyrin hydrochloride (10). This complex was obtained (81 mg, 73%) as described above using the nickel(II) formylpyrroloporphyrin **5**. Mp>300 °C. UV/vis λ_{max} (CH_2Cl_2) 424 nm (ε 48,800), 530 (25,300), 686 (16,400). MS calcd for $C_{53}H_{36}N_6Ni$ *m/z* 814.2. Found: *m/z* 813.9 (M^+). ^1H NMRs ($CDCl_3$): δ 1.91 (s, 3H), 2.25 (s, 3H), 5.37 (s, 1H), 5.75 (s, 1H), 6.92 (d, *J*=1.8 Hz, 1H), 7.19 (s, 2H), 7.60 (m, 8H), 7.68 (s, 5H), 7.93 (m, 5H), 8.24 (d, *J*=5.1 Hz, 2H), 8.53 (d, *J*=4.5 Hz, 2H), 8.58 (d, *J*=4.2 Hz, 1H), 8.72 (d, *J*=4.8 Hz, 1H). Anal. calcd for $C_{53}H_{37}ClN_6Ni{\cdot}H_20$: C, 73.16; H, 4.52; N, 9.66. Found: C, 72.88; H, 4.98; N, 9.42.

2.1.5. Copper(II) dipyrromethenoporphyrin BF_2 complex (8). The copper(II) dipyrromethenoporphyrin hydrochloride **9** (100 mg, 0.121 mmol) was dissolved in toluene (10 mL) and degassed for 5 min. Triethylamine (0.10 mL, 0.82 mmol) and boron trifluoride etherate (0.10 mL, 0.79 mmol) were added and the reaction mixture was allowed to stir for 1 day (TLC monitoring) under an argon atmosphere. The reaction mixture was worked up with 5% HCl and water and the organic layer was collected and reduced in volume. This organic phase was then passed through a silica plug (3:1 CH_2Cl_2/cyclohexane) to remove baseline impurities. The eluent was then collected and concentrated. Upon addition of MeOH, **8** precipitated and was collected (71 mg, 65%). Mp>300 °C. MS calcd for $C_{53}H_{35}BCuF_2N_6$ *m/z* 867.2. Found: *m/z* 868.6 (M^+).

2.1.6. Metal-free dipyrromethenoporphyrin (11). A solution of **8** (0.230 g, 0.280 mmol) in 5 mL of CH_2Cl_2 was sonicated for 5 min. A mixture of TFA/2% sulfuric acid (10 mL/0.2 mL) was added and the reaction mixture was stirred vigorously for 2 min and then poured into a mixture of ice/water. The aqueous phase was extracted with CH_2Cl_2 (3×250 mL), washed with a saturated solution of $NaHCO_3$ and then with H_2O. The organic phase was evaporated and the residue was chromatographed on an alumina (Brockmann Grade V) column (eluting with CH_2Cl_2/cyclohexane 3/1). The main green band was collected and evaporated to yield compound **11** which was further recrystallized from CH_2Cl_2/cyclohexane (100.7 mg, 47%). Mp>300 °C. MS calcd for $C_{53}H_{38}N_6$ *m/z* 758.3. Found: *m/z* 759.9. ^1H NMR ($CDCl_3$): δ −2.29 (s, 2H), 2.01 (s, 3H), 2.27 (s, 3H), 5.49 (s, 1H), 5.84 (s, 1H), 6.84 (s, 1H), 7.18 (s, 5H), 7.78 (m, 5H), 8.15 (m, 10H), 8.24 (d, *J*=7.5 Hz, 2H), 8.44 (d, *J*=5.1 Hz, 2H), 8.60 (d, *J*=10.5 Hz, 1H), 8.73 (d, *J*=5.1 Hz, 1H). Anal. calcd for $C_{53}H_{38}N_6{\cdot}0.5H_2O$: C, 82.90; H, 5.12; N, 10.94. Found: C, 83.22; H, 5.17; N, 10.87.

2.1.7. Metal-free dipyrromethenoporphyrin BF_2 complex (12). Metal-free dipyrromethenoporphyrin **11** (48.9 mg, 0.0644 mmol) was dissolved in toluene (5 mL) and degassed for 5 min. Triethylamine (0.10 mL, 0.817 mmol) and boron trifluoride etherate (0.100 mL, 0.789 mmol) were added and the reaction mixture was stirred for 1 day (TLC monitoring) under an argon atmosphere. The reaction mixture was worked up with 5% HCl and H_2O and the organic layer was collected and reduced in volume. The reduced organic phase was then passed through a silica gel plug (3:1 CH_2Cl_2/cyclohexane) to remove baseline impurities. The product was observed to be unstable in solution and on an alumina TLC. The eluent was then collected and concentrated. Upon addition of MeOH, **12** precipitated (22 mg, 42%). Mp>300 °C. MS calcd for $C_{53}H_{37}BF_2N_6$ *m/z* 806.3. Found: *m/z* 806.4 (M^+). ^1H NMR ($CDCl_3$): δ −2.12 (s, 1H), 2.36 (s, 3H), 2.56 (s, 3H), 5.35 (s, 1H), 6.10 (s, 1H), 6.93 (d, *J*=1.8 Hz, 1H), 7.76 (br, 2H), 7.88 (br, 8H), 8.20 (s, 5H), 8.26 (br, 5H), 8.58 (d, *J*=5.1 Hz, 2H), 8.66 (d, *J*=4.5 Hz, 2H), 8.78 (d, *J*=4.2 Hz, 1H), 8.86 (d, *J*=4.8 Hz, 1H).

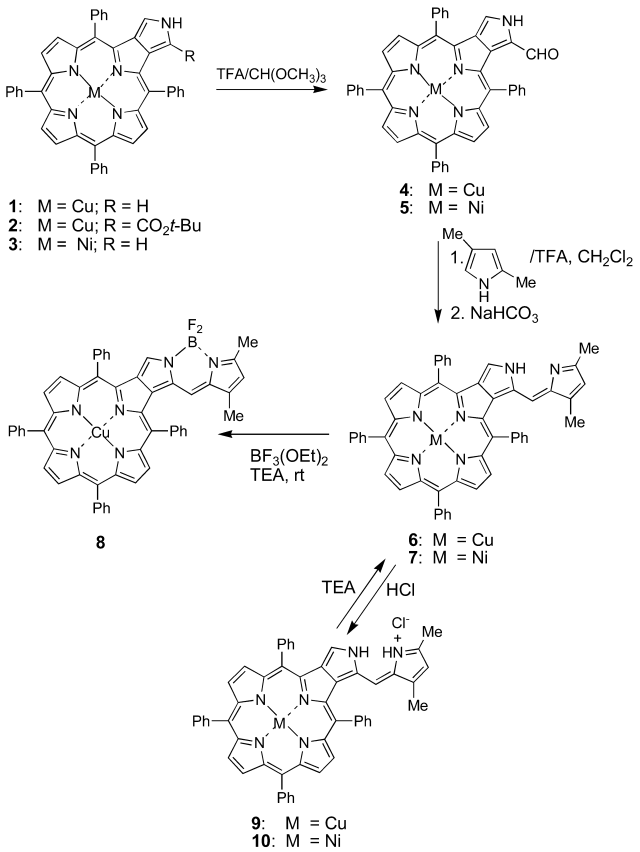
2.1.8. Zinc(II) dipyrromethenoporphyrin BF_2 complex (13). Zinc acetate (25 mg, 0.136 mmol) was added to metal-free dipyrromethenoporphyrin BF_2 complex, **12** (20 mg, 0.025 mmol) dissolved in toluene (5 mL). The reaction mixture was stirred overnight (TLC monitoring). At the end of this time the solution was pinkish-red in color. The reaction mixture was poured into H_2O and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The organic layers were then collected and passed through a silica gel plug to remove baseline impurities. The organic layer was then reduced in volume and after addition of cyclohexane, compound **13** precipitated (15 mg, 68%). Mp>300 °C. MS calcd for $C_{53}H_{35}BF_2N_6Zn$ *m/z* 868.2. Found: *m/z* 868.2 (M^+). ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H), 2.56 (s, 3H), 5.18 (s, 1H), 6.07 (s, 1H), 7.10 (d, *J*=1.8 Hz, 1H), 7.75 (br, 5H), 7.86 (br, 5H), 8.18 (m, 5H), 8.24 (br, 5H), 8.54 (d, *J*=4.8 Hz, 2H), 8.81 (d, *J*=6.6 Hz, 2H), 8.84 (s, 1H), 8.90 (d, *J*=4.8 Hz, 1H). Anal. calcd for $C_{53}H_{35}BF_2N_6Zn{\cdot}2H_20$: C, 70.25; H, 4.34; N, 9.27. Found: C, 70.06; H, 4.66; N, 9.35.

3. Results and discussion

3.1. Synthesis

The synthetic pathway leading to the formation of **8** is presented in Scheme 1. The first step is the formation of **4** from the pyrroloporphyrin **1**. The formylation reaction of pyrroles is generally carried out by the Vilsmeier reaction ($POCl_3$ and DMF); however, the Vilsmeier reagent is known to react at the β-positions of tetraarylporphyrins.[20] We carried out the reaction using TFA and trimethylorthoformate, in order to selectively functionalize the pyrrole moiety. In theory, this methodology can afford diformylated species and it has been used to prepare 2,5-diformylpyrroles[21] or 1,9-diformyldipyrromethanes from their corresponding di-α-free precursors.[22] Furthermore the TFA and $HC(OMe)_3$ system has also been used by Montforts et al.[23] to regioselectively formylate unhindered β-positions of deuteroporphyrin. In our case, the reaction of **1** with TFA/$HC(OMe)_3$ gave only one formylation product. No bis- or di-formylated derivatives were observed by mass spectrometry. The ^1H NMR spectrum confirmed that the substitution took place at the α-position of the fused pyrrole ring (the α-proton peak at 6.95 ppm integrated as one proton). Metal-free formylpyrroloporphyrin [obtained by treatment with TFA/H_2SO_4 (not shown)] is stable. Free-base pyrroleporphyrins are very unstable.[15b]

A different route for **4** is available in which the starting material is the pyrroloporphyrin *t*-butyl ester **2**. Cleavage of the *t*-butyl ester protecting group, decarboxylation of the subsequent carboxylic acid group and formylation of the



Scheme 1. Synthesis of CuTPP-BODIPY® **8**.

fused pyrrole moiety take place in a one-pot reaction. The overall yield of the reaction was somewhat lower (43%) and for this reason formylation of the α,α′-di-unsubstituted pyrroloporphyrin was preferred.

Acid-catalyzed condensation of **4** with 2,4-dimethylpyrrole gave dipyrromethenoporphyrin **6**. The reaction was quite similar to the synthesis of dipyrromethanoporphyrins obtained by condensing α-alkyl-ester pyrroloporphyrin and 5-acetoxypyrroles under slightly acidic conditions (Montmorillonite clay K-10).[15] The free base dipyrromethene derivative **6** was obtained after washing the reaction mixture with saturated $NaHCO_3$ solution. Preferably the reaction product was isolated as the protonated form **9**. The free base **6** is less stable than **9** and it was prone to decomposition over time (especially after being exposed to light and air); for this reason analytically pure compounds were characterized in their protonated forms. UV–visible spectra of **6** and **9** are reported in Figure 1. These species can be easily interconverted in solution by addition of acid or bases. It is worth mentioning that the absorption attributed to the dipyrromethene unit for **9** is similar to that observed for the BODIPY® derivative **8**, while the same band has a significant blue shift (~30 nm) in the case of **6**. In most cases, the protonated dipyrrometheno-porphyrins were characterized as the hydrochloride salts, due to anion exchange of the salt product with chloride from a brine wash. The same behavior was observed when the reaction was carried out on Ni complex **5** to give **7** and **10**.

The complexation of boron trifluoride etherate by the

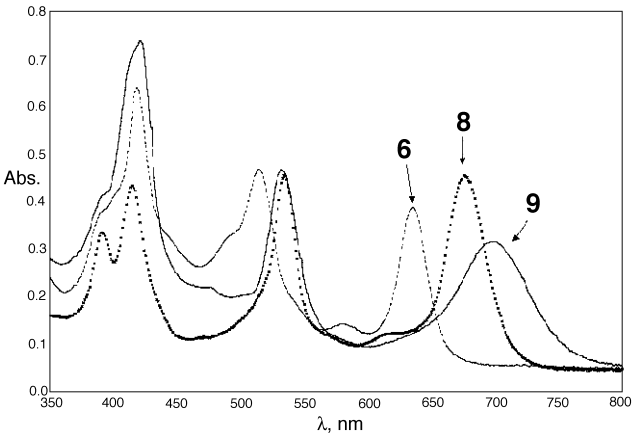
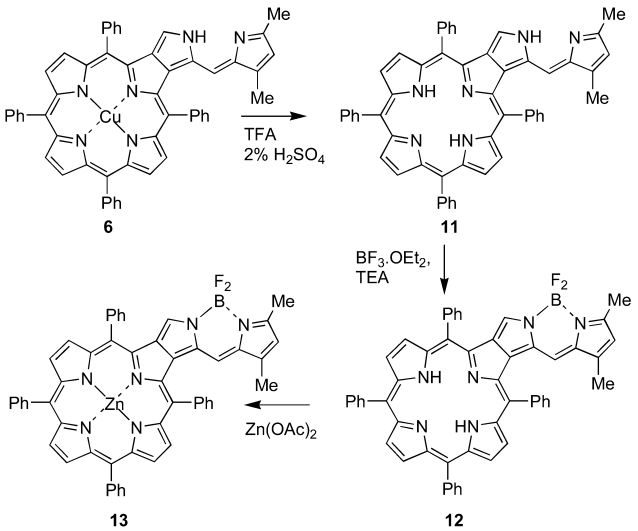


Figure 1. UV–visible spectra of **6**, **8** and **9** in CH_2Cl_2.

dipyrromethene moiety of **6** to yield the BODIPY® complexes was accomplished under basic conditions. Although a similar reaction was carried out by Burgess et al.[24] at higher temperatures (70 °C) using toluene as solvent, the BF_3 complexation took place rapidly at room temperature in 65% yield (Scheme 1). A color change from green to red attested to the fast complexation reaction. The reaction flask was shielded from light and was purged with argon to minimize any decomposition of the dipyrromethenoporphyrin. The corresponding BF_2 complex was stable under the same conditions. The free base (M=2H) fused dipyrromethenoporphyrin **11** and its BF_2 complex **12** were synthesized from the copper dipyrromethenoporphyrin **8** (Scheme 2). The copper dipyrromethenoporphyrin **8** was demetalated with 2% H_2SO_4 in TFA to give the free base dipyrromethenoporphyrin **11** which was unstable and prone to decomposition upon exposure to light and air. The instability of the metal-free dipyrromethenoporphyrin **11** caused its synthesis from the corresponding free base formyl-pyrroloporphyrin to be unsuccessful. The zinc dipyrromethenoporphyrin BF_2 complex **13** was synthesized by metalation with $Zn(OAc)_2$ in toluene in 68% yield (Scheme 2).



Scheme 2. Synthesis of ZnTPP-BODIPY® **13**.

3.2. Photophysical properties

The absorption spectra of **12** and **13** show three quite intense bands in the 300–750 nm region (Table 1 and Fig. 2). The same behavior is observed for the Cu complex **8**. These spectra are different from those expected by the addition of the spectra of TPP and of BODIPY® units. In particular, in the region around 400 nm, **8**, **12** and **13** present a structured transition with a molar absorption coefficient much lower than that typically observed in this spectral region for TPPs. At longer wavelengths, two transitions with similar intensities are present with energies and absorption coefficients only slightly dependent upon metalation. On the contrary, while BODIPY® units have a narrow transition whose energy is related to its substituents, typically with $\varepsilon \approx 100{,}000\ M^{-1}\ cm^{-1}$, the TPPs present in this region a set of Q-bands, less intense and more strongly dependent upon metalation.

Table 1. Photophysical data in CH_2Cl_2 of the porphyrin-BODIPY® systems studied

Compound	λ_{max} (nm)	ε ($M^{-1}\ cm^{-1}$)	λ_{max} (nm)	τ (ns)	Φ
8	390	53,000	–	–	–
	412	72,200			
	531	78,300			
	675	80,000			
9	410	10,600	–	–	–
	529	78,900			
	695	60,300			
11	393	55,200	690	7.0	0.076
	425	41,000			
	529	53,000			
	598	27,200			
	631	28,600			
	680	18,500			
12	388	51,500	693	4.2	0.04
	413	44,500			
	531	65,000			
	640	58,250			
13	392	55,000	714	1.6	0.053
	415	64,000			
	539	80,500			
	676	61,000			

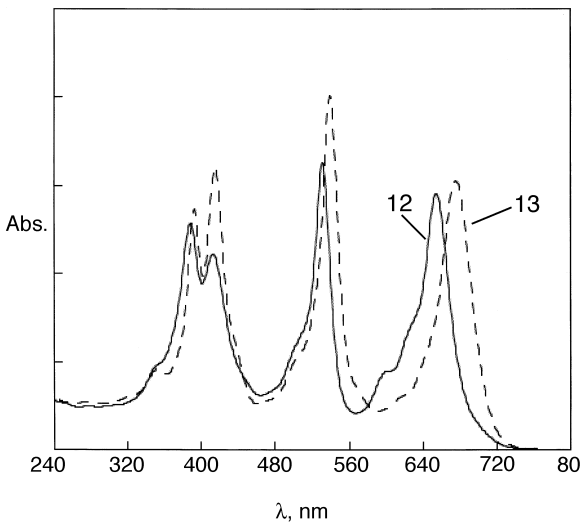


Figure 2. Absorption spectrum of **12** and **13** (dashed line) in CH_2Cl_2 at room temperature.

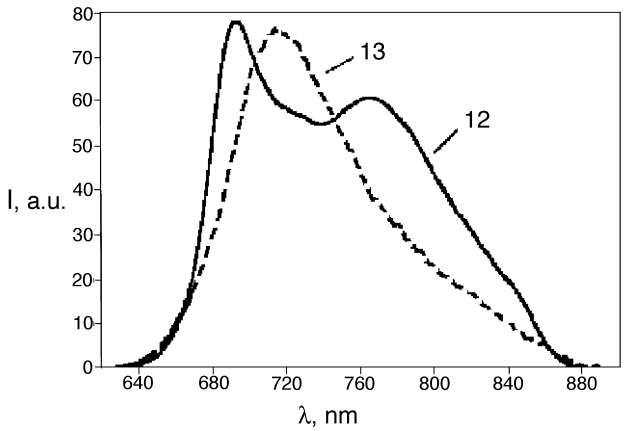


Figure 3. Fluorescence spectrum of **12** and **13** (dashed line) in CH_2Cl_2 at room temperature.

It is interesting to note that, while for porphyrins on going from the free base to their Zn complexes an increase of the energy of the lowest transition is observed, the reverse behavior is encountered on going from **12** to **13**. The same pattern is observed in the luminescence spectra (Fig. 3 and Table 1), where **12** and **13** show a fluorescence band in the region around 700 nm.

The excitation spectra strictly match the absorption analogs, indicating that excitation over all the 240–700 nm region leads to the population of the fluorescent excited state with unitary efficiency, independently of the nature of the chromophore involved in the absorption process. The low Stokes-shift observed between the lowest absorption and the fluorescence band indicates that the distortion occurring in going from the ground state to the fluorescent excited state is also low, suggesting a small charge transfer character in the latter state. It should be noted that the fluorescence quantum yields observed, although not very high, are still of interest because of their spectral location; new fluorescent labels and sensors in the near IR region are of great interest for biological and biotechnological applications. Compounds **6** and **8**, did not show any fluorescence band both at room temperature and at 77 K ($\Phi < 10^{-5}$).

For all the compounds studied, no phosphorescence was observed even at 77 K; we believe it to lie in a region outside the instrumental range (900 nm being the upper limit).

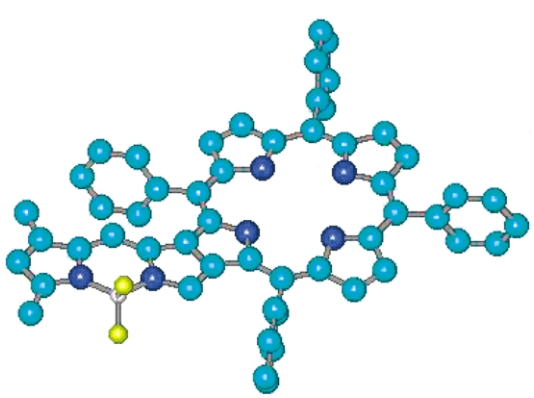


Figure 4. PM3 optimized geometry of **12**. Hydrogen atoms are not shown.

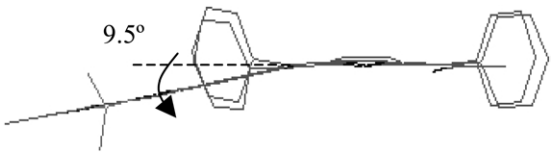
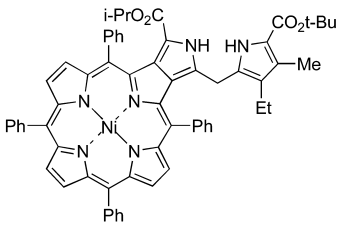


Figure 5. View of **12** showing the angle between the H_2TPP and BODIPY® units.

3.3. Optical properties

To further investigate the optical properties of the TPP-BODIPY® species we performed semi-empirical Hartree–Fock calculations. Starting from a planar configuration, we optimized the geometry of **12** by using the PM3 method.[25] The optimized geometry configuration is shown in Figure 4. This structure is not planar (Fig. 5) and an angle of 9.5° is found between the H_2TPP ring and the BODIPY® moiety; furthermore the H_2TPP macrocycle presents some deviations from planarity. These results are in good accord with features observed in the X-ray structure of the similar dipyrromethanoporphyrin **14**.[15b]



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Optical properties of **12**, in the optimized geometry, were obtained by using the intermediate neglect diatomic overlap/spectroscopic parametrization (INDO/S) method[26] followed by a converged configuration interaction (CIS). In the CIS calculation, we considered only single excitations from the highest occupied molecular orbitals of **12** to the lowest unoccupied molecular orbitals. Figure 6 shows the calculated absorption spectrum for **12**. Here, an arbitrary Gaussian broadening of the transition energies has been used and no vibronic replicas have been included. A remarkably good agreement with experimental data is found. The minor blue-shift of the calculated absorption peaks with respect to the measured ones is typical of INDO/SCI calculations.[27] The calculated absorption spectrum of **12** also shows a large decrease in the molar absorpion coefficient of the Soret band with respect to the H_2TPP molecule, as observed in the experimental spectrum.

In order to understand the features of the calculated spectrum, we also report (in Fig. 6) the absorption spectra of the separate H_2TPP and BODIPY® fragments as obtained from the optimized geometry of **12** (that is, keeping the geometry calculated for **12**). The H_2TPP and BODIPY® fragments, even in this slightly distorted geometry, present absorption peaks similar to those of the isolated molecules and consequently the presence of a distortion in **12** is not responsible for the appearance of the low energy (640 nm) absorption peak. The appearance of the low energy absorption peak is mainly due to the increased extension of the π-conjugation along the entire molecule. This is

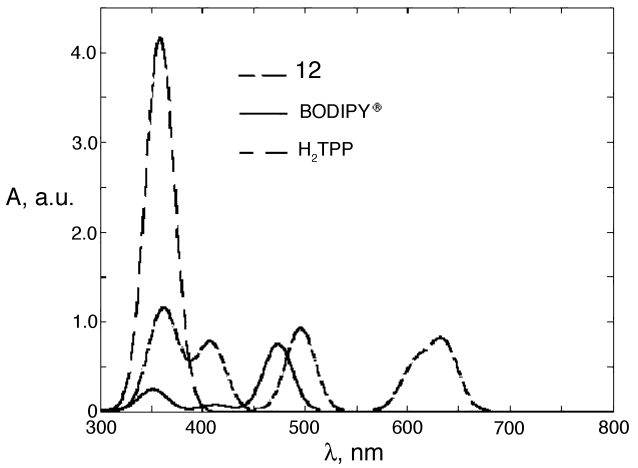

Figure 6. Calculated absorption spectra of **12** and of the separate TPP and BODIPY® molecules in the optimized geometry for **12**. An artificial broadening of the levels has been considered in order to better compare with experimental results.

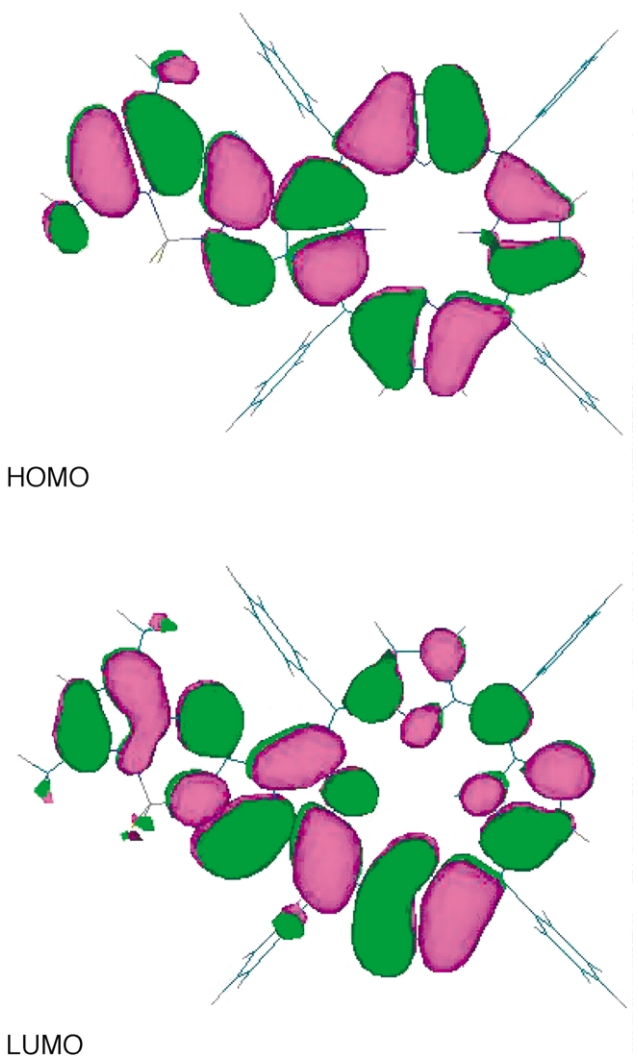

Figure 7. Calculated HOMO and LUMO wavefunctions for **12**. The INDO/S method was used, assuming a PM3 optimized geometry.

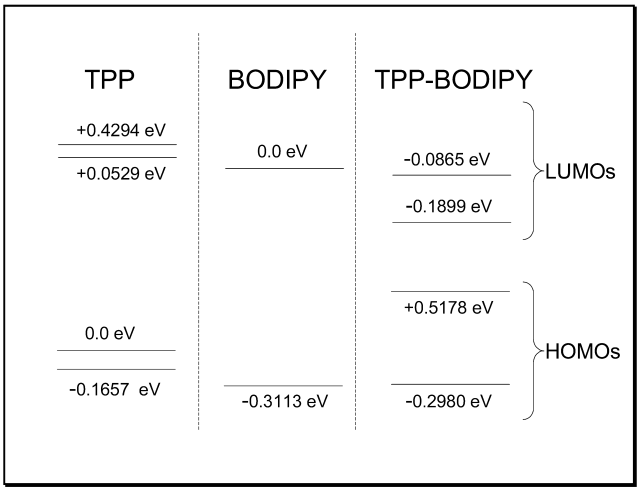

Figure 8. HOMO and LUMO energy levels for **12** and for the isolated H_2TPP and BODIPY® molecules. In order to emphasize the energy difference between levels we set the zero of the energy for LUMO levels with that of the BODIPY® LUMO, while for HOMO levels the zero energy is the TTP HOMO.

shown in Figure 7, in which we plot the HOMO and LUMO of **12**.

Clearly, the HOMO/LUMO wavefunctions extend over the entire complex. In Figure 8, we report the calculated levels for isolated H_2TPP and BODIPY® molecules and also for **12**. HOMO as well as LUMO levels of H_2TPP and BODIPY® are very close in energy (within 0.31 eV for the HOMOs and within 0.087 eV for the LUMOs), which results in a strong interaction between these orbitals. This interaction pushes the HOMO level of **12** toward higher energy while the LUMO level is pushed toward lower energies. This leads to an overall reduction of the HOMO–LUMO gap of **12** with respect to that of the isolated molecules. Indeed, a close inspection of the excited states reveals that the lowest excited state of **12** (640 nm) is mainly composed by the HOMO and LUMO levels which are completely delocalized along the entire molecule. Similar behavior was observed for β-fused oligoporphyrin system where the extension of the π-conjugation resulted in the appearance of a low energy peak around 700 nm.[6] The comparison between **11** and **12** is shown in Figure 9. Again

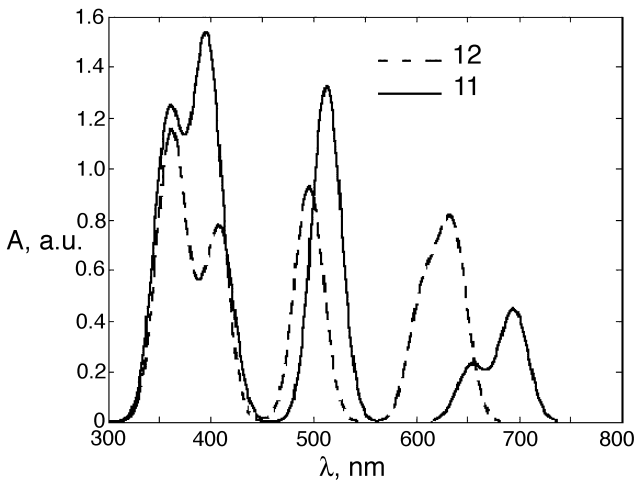

Figure 9. Calculated absorption spectra of **11** and **12** (dashed line).

there is a good accord with the experimental observation that the absence of the BF_2 group increases the intensity of the high energy absorption peaks while the low energy one is reduced.

3.4. Conclusions

Synthetic methodology has been developed for the preparation of dyes in which a porphyrin macrocycle is directly fused to a BODIPY® moiety through two β-pyrrolic carbons. The optical spectra of the resulting dyads show bands in the 300–750 nm region, and characterized by a reduction of the absorbance of the Soret band and the presence of an absorption band of similar intensity around 650 nm. A fluorescence band was observed in the region around 700 nm, with a low Stokes-shift observed between the lowest absorption and the fluorescence band. This behavior is different from the linear superimposition of the spectra of isolated components of the dyad and cannot be ascribed to deformation of the molecular skeleton of both moieties. To obtain further information on the origin of these optical features, we carried out a INDO/SCI calculation on **12**. These studies showed that the optical properties of **12** derived from an increased extension of the π-conjugation along the entire molecule.

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References and notes

1. Shirakawa, H.; Louis, E. J.; MacDiarmid, A. G.; Chiang, C. K.; Heeger, A. J. *Chem. Commun.* **1977**, 578.
2. (a) Metzger, R. M. *Acc. Chem. Res.* **1999**, *32*, 950. (b) Würthner, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 1037. (c) Vilan, A.; Cahen, D. *Trends Biotechnol.* **2002**, *20*, 22, and references therein.
3. Kraft, A. *Chem. Phys. Chem.* **2001**, *2*, 163.
4. Tsuda, A.; Osuka, H. *Science* **2001**, *293*, 79.
5. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: Boston, MA, 2000.
6. (a) Vicente, M. G. H.; Jaquinod, L.; Smith, K. M. *Chem. Commun.* **1999**, 1771. (b) Paolesse, R.; Jaquinod, L.; Della Sala, F.; Nurco, D. J.; Prodi, L.; Montalti, M.; D'Amico, A.; Di Carlo, A.; Lugli, P.; Smith, K. M. *J. Am. Chem. Soc.* **2000**, *122*, 11295.
7. (a) Lu, T. X.; Reimers, J. R.; Crossley, M. J.; Hush, N. S. *J. Phys. Chem.* **1994**, *98*, 11878. (b) Reimers, J. R.; Lü, T. X.; Crossley, M. J.; Hush, N. S. *Chem. Phys. Lett.* **1996**, *256*, 353. (c) Reimers, J. R.; Hall, L. E.; Crossley, M. J.; Hush, N. S. *J. Phys. Chem. A* **1999**, *103*, 4385.
8. Wang, H. J. H.; Jaquinod, L.; Nurco, D. J.; Vicente, M. G. H.; Smith, K. M. *Chem. Commun.* **2001**, 2646.
9. (a) Haugland, R.P.; Kang, H.C. Chemically Reactive Dipyrrometheneboron Difluoride Dyes. U.S. Patent 4,774,339, 1988.(b) Molecular Probes Inc., Eugene, OR.

10. Treibs, A.; Kreuzer, F.-H. *Liebigs Ann. Chem.* **1968**, *718*, 203.
11. Rurack, K.; Kollmannsberger, M.; Daub, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 385.
12. Wada, M.; Ito, S.; Uno, H.; Murashima, T.; Ono, N.; Urano, T.; Urano, Y. *Tetrahedron Lett.* **2001**, *42*, 6711.
13. Li, F.; Yang, S. I.; Ciringh, Y.; Seth, J.; Martin, C. H., III; Singh, D. L.; Kim, D.; Birge, R. R.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 10001.
14. Kumaresan, D.; Agarwal, N.; Gupta, I.; Ravikanth, M. *Tetrahedron* **2002**, *58*, 5347.
15. (a) Jaquinod, L.; Gros, C.; Olmstead, M. M.; Antolovich, M.; Smith, K. M. *Chem. Commun.* **1996**, 1475. (b) Gros, C. P.; Jaquinod, L.; Khoury, R. G.; Olmstead, M. M.; Smith, K. M. *J. Porphyrins Phthalocyanines* **1997**, *1*, 201.
16. Smith, K. M. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Amsterdam, 1975.
17. Shea, K. M.; Jaquinod, L.; Smith, K. M. *J. Org. Chem.* **1998**, *63*, 7013.
18. Seybold, P. G.; Gouterman, M. *J. Mol. Spectrosc.* **1969**, *31*, 1.
19. Credi, A.; Prodi, L. *Spectrochim. Acta, A* **1998**, *54*, 159.
20. Jaquinod, L. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: Boston, MA, 2000; Vol. 1, p 201.
21. Tardieux, C.; Bolze, F.; Gros, C. P.; Guilard, R. *Synthesis* **1998**, 267.
22. Clezy, P. S.; Fookes, C. J. R.; Liepa, A. J. *Aust. J. Chem.* **1972**, *25*, 1979.
23. Montforts, F.; Scheurich, G.; Meier, A.; Haake, G.; Hoper, F. *Tetrahedron Lett.* **1991**, *29*, 3477.
24. Burghart, A.; Kim, H.; Welch, M.; Thoresen, L. H.; Reibenspies, J.; Burgess, K. *J. Org. Chem.* **1999**, *64*, 7813.
25. Stewart, J. J. *J. Comput. Chem.* **1989**, *10*, 221.
26. (a) Ridley, J. E.; Zerner, M. C. *Theor. Chem. Acta* **1973**, *32*, 111. (b) Ridley, J. E.; Zerner, M. C. *Theor. Chem. Acta* **1976**, *42*, 223.
27. (a) Gigli, G.; Lomascolo, M.; Cingolani, R.; Barbarella, G.; Zambianchi, Z.; Antolini, L.; Della Sala, F.; Di Carlo, A.; Lugli, P. *Appl. Phys. Lett.* **1998**, *73*, 2414. (b) Rawlings, D. C.; Davidson, E. R.; Gouterman, M. *Theor. Chim. Acta* **1982**, *61*, 227. (c) Baker, J. D.; Zerner, M. C. *Chem. Phys. Lett.* **1990**, *175*, 192.

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A direct link between the Passerini reaction and α-lactams☆

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Abstract—α-Lactams (aziridinones) can function to replace two of the three reactants, the oxo-compound and the isonitrile, in the Passerini reaction. Four α-lactams (**5a-d**) were reacted with mono- and dicarboxylic acids of positive pK_a values to give 2-acyloxycarboxamides (**4**) and bis-2-acyloxycarboxamide products **12** and **13**, respectively. The same compounds were also prepared via the Passerini reaction. Acids with a negative pK_a decarbonylate α-lactams to give immonium salts. The main path of the reaction depends on the pK_a of the acid component, the reactivity of the α-lactam, and the reaction conditions.
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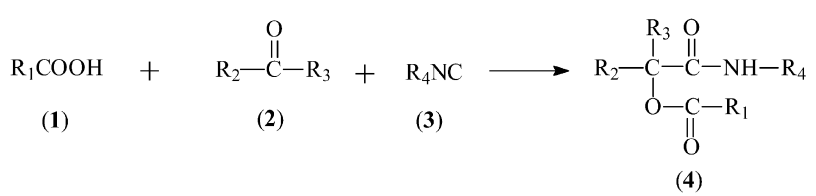
1. Introduction

In 1921, Mario Passerini reported[2] that the one-pot, three-component reaction between a carboxylic acid (**1**), an aldehyde or ketone (**2**), and an isonitrile (**3**) yields α-acyloxycarboxamides (**4**) (Scheme 1). The yields of type **4** products reported by Passerini himself varied between 14[3] and 87%,[4] depending on the substituents in the reactants. Since then, this reaction, named the Passerini reaction, has been used widely, as documented in several extensive reviews[5–8].

About 40 years later, the synthesis of α-lactams (aziridinones) (**5**) has been achieved, and their reactions studied[9]. α-Lactams are the first stable representatives of three-membered ring carbonyl compounds to have been isolated in pure state. As summarized in a 1968 review[9] and in later published reports, ionic aprotic nucleophiles, such as *tert*-butoxide,[10] phenyl magnesium bromide,[11] or lithium aluminum hydride[12] effect ring-opening with cleavage of the lactam bond (the 1–2 bond), to give α-amino acid derivatives (**6**), while non-ionic protic nucleophiles, such as water, *tert*-butyl alcohol, benzylamine, glycine ethyl ester, α-toluenethiol, etc. cause ring-opening with cleavage of the 1–3 bond, to yield α-substituted carboxamides (**7**)[10] (Scheme 2). There are, however, a number of published reports,[13–16] which contradict the above general rule of ring-opening of stable α-lactams. The reactions of α-lactams with amines appear to be especially complicated, the products often being mixtures derived from competing modes of ring-opening. The factors governing regioselectivity in nucleophilic ring-opening of stable α-lactams have not been fully enumerated to date, although substantial progress has been made.[17,18] While unsubstituted aziridinone itself is still unknown, and appears to be unstable, the structural prerequisites that lend stability to this class of compounds are a tertiary alkyl substituent in position 1 and a tertiary alkyl or aryl substituent in position 3.

The predominant general path of thermal decomposition of most stable α-lactams prepared to date is fragmentation into an aldehyde or ketone (**2**) and an isonitrile (**3**), via the



Scheme 1. The Passerini reaction.

☆ See Ref. 1.

Keywords: Aziridinones; Maleic anhydride; Mono- and dicarboxylic acids; Nucleophilic substitution; Passerini reaction.
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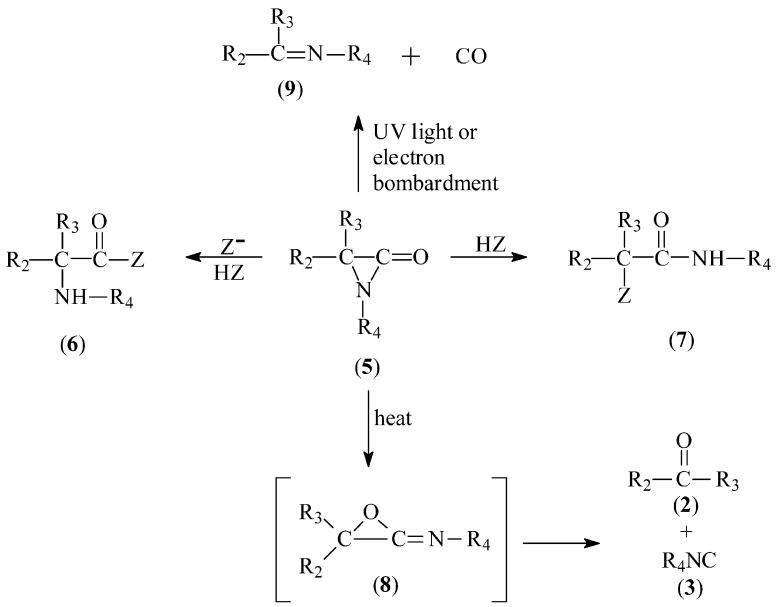


Scheme 2. Nucleophilic ring cleavage of α-lactams, and their thermal, photolytic, and electron bombardment induced decomposition.

imino-oxirane intermediate **8**[19] (Scheme 2). This thermal decomposition path of α-lactams is in sharp contrast with their electron impact-induced fragmentation,[20–22] ultraviolet photolysis,[23] and reaction with strong, non-aqueous mineral acids (e.g., HCl in ether[24]), all of which lead to Schiff bases (**9**) or their salts (**10**), and carbon monoxide (Scheme 2). An imino-oxirane intermediate (**8**) has also been postulated in the oxidation of ketenimines (**11**) with peracids,[25,26] which yields oxo-compounds (**2**) and isonitriles (**3**), along with minor amounts (~20%) of α-acyloxycarboxamides (**4**) (Scheme 3).

2. Results and discussion

2.1. Reaction of α-lactams with monocarboxylic acids

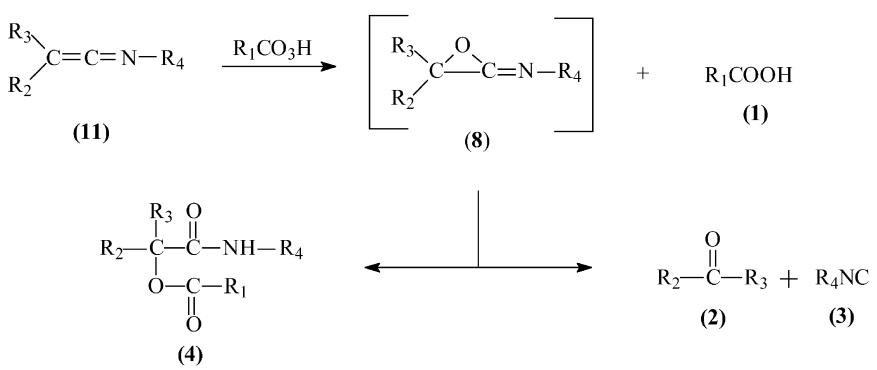
Heretofore, it went unnoticed that there is a connection between α-lactams and the Passerini reaction.[27]

For this study, we have chosen four α-lactams for their greatly varying thermal stability and reactivity, viz. 1-*tert*-butyl-3,3-dimethylaziridinone (**5a**),[10] 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**),[28] 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**),[20] and 1,3-di-*tert*-butylaziridinone (**5d**)[29] and five monocarboxylic acids, viz. acetic acid (**1a**), pivalic acid (**1b**), benzoic acid (**1c**), *trans*-cinnamic acid (**1d**), and trifluoroacetic acid (**1e**), as well as hydrofluoric acid.

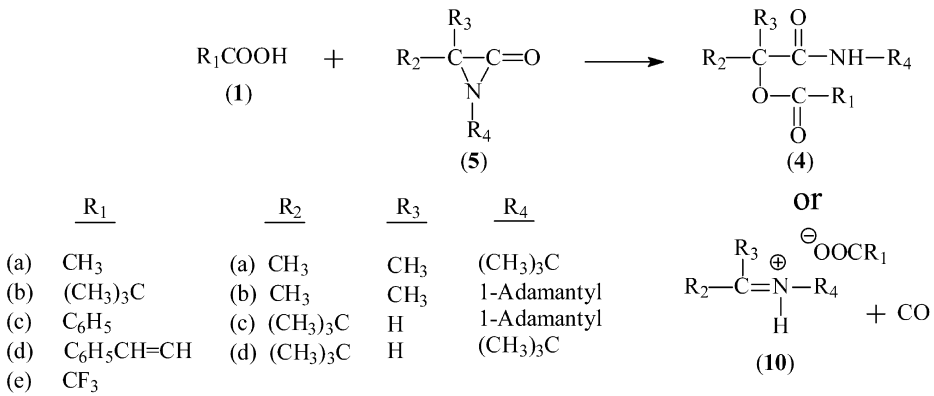
We have found that α-lactams readily react with carboxylic acids (**1**) to give α-acyloxycarboxamides (**4**) (Scheme 4), that is, α-lactams are capable of replacing two of the three reactants in the Passerini reaction (the aldehyde or ketone and the isonitrile), and the yields are comparable. An important advantage of this new synthesis of α-acyloxycarboxamides (**4**) is that it obviates the necessity of working with the repulsive-smelling isonitriles. Naturally, all the reactions have to be performed under sufficiently mild conditions to preclude the concurrent spontaneous decomposition of the α-lactam. The yields of products (**4**) from the reaction of α-lactams **5a**-**d** with monocarboxylic acids **1a**-**e** and from the Passerini reaction are listed in Table 1.

2.2. Reaction of α-lactams with dicarboxylic acids

The reaction described above can also be extended to dicarboxylic acids. Thus, α-lactams **5a** and **5b** with maleic



Scheme 3. The oxidation of ketenimines with peracids.



Scheme 4. The reaction of α-lactams with monocarboxylic acids.

acid, and α-lactams **5a-d** with succinic acid gave bis-Passerini products **12** and **13**, respectively. The same compounds can also readily be prepared by the Passerini reaction (Scheme 5).

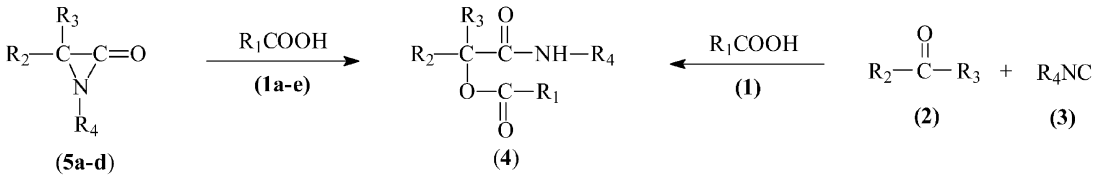
We reported earlier[30] that treatment of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**) with maleic acid in dioxane solution yields di-(*N*-1-adamantylneopentylidenimmonium) maleate (**14**), mp 191 °C (dec.), along with carbon monoxide, rather than a bis-Passerini product (Scheme 6). Whether the reaction of α-lactams with acids yields a Passerini product or an immonium salt depends on three factors: (1) the pK_a of the acid, (2) the relative reactivity of the α-lactam, (3) the reaction conditions. Of these, the first factor is the most determining one.

Ordinary saturated or unsaturated aliphatic and aromatic mono- and dicarboxylic acids react with α-lactams to give the Passerini product, while strong non-aqueous mineral acids, such as hydrochloric acid, hydrobromic acid, and *p*-toluenesulfonic acid cause decarbonylation with the formation of immonium salts (Scheme 7). If water is present, the immonium salts are hydrolyzed to an aldehyde or ketone and an amine.[24]

We concur with the observation of Bott,[24b] that even though ordinary amide-resonance is diminished in α-lactams because of the small-ring strain, it still contributes significantly to their stability. If *N*-protonation suppresses this amide-resonance, α-lactams decompose immediately and quantitatively, even at room temperature (Scheme 7).

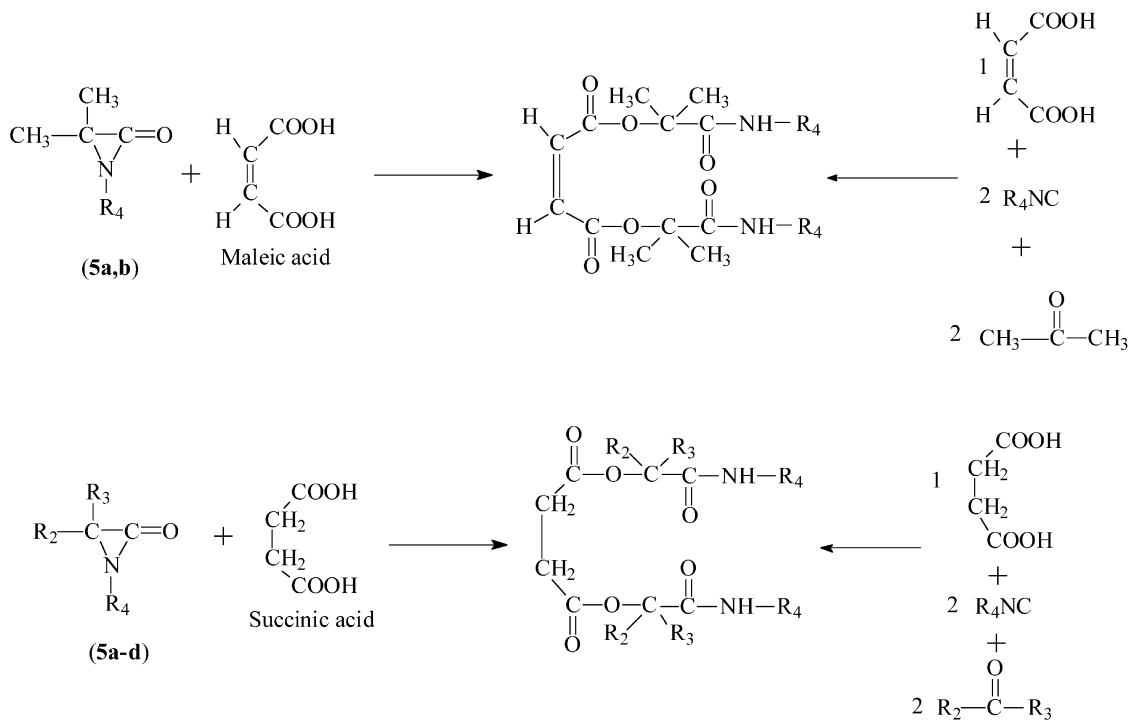
According to the evidence presented in this paper, the protonating power of carboxylic acids with a positive pK_a is

Table 1. The yields of products from the reaction of α-lactams

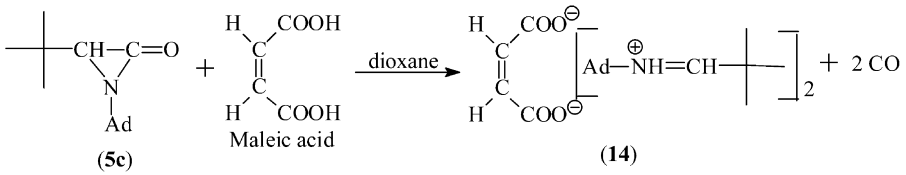


	R_1	R_2	R_3	R_4	Yield[a] (%)	Yield[b] (%)
4a	CH_3	CH_3	CH_3	t-C_4H_9	37	66
4b	t-C_4H_9	CH_3	CH_3	t-C_4H_9	66	45
4c	C_6H_5	CH_3	CH_3	t-C_4H_9	67	76
4d	$C_6H_5CH{=}CH$	CH_3	CH_3	t-C_4H_9	84	54
4e	CF_3	CH_3	CH_3	t-C_4H_9	66	47
4f	CH_3	CH_3	CH_3	1-Ad	81	50
4g	t-C_4H_9	CH_3	CH_3	1-Ad	74	29
4h	C_6H_5	CH_3	CH_3	1-Ad	75	32
4i	$C_6H_5CH{=}CH$	CH_3	CH_3	1-Ad	60	23
4j	CF_3	CH_3	CH_3	1-Ad	41	75
4k	CH_3	t-C_4H_9	H	1-Ad	63	57
4l	t-C_4H_9	t-C_4H_9	H	1-Ad	36	54
4m	C_6H_5	t-C_4H_9	H	1-Ad	58	68
4n	$C_6H_5CH{=}CH$	t-C_4H_9	H	1-Ad	74	75
4o	CF_3	t-C_4H_9	H	1-Ad	Decarbonylates	70
4p	CH_3	t-C_4H_9	H	t-C_4H_9	67	42
4q	t-C_4H_9	t-C_4H_9	H	t-C_4H_9	80	81
4r	C_6H_5	t-C_4H_9	H	t-C_4H_9	38	45
4s	$C_6H_5CH{=}CH$	t-C_4H_9	H	t-C_4H_9	65	33
4t	CF_3	t-C_4H_9	H	t-C_4H_9	Decarbonylates	72

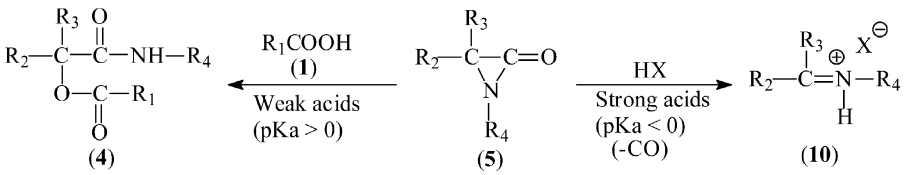
[a] Monocarboxylic acids.
[b] Passerini reaction.



Scheme 5. The reaction of α-lactams with dicarboxylic acids and the corresponding Passerini reactions.

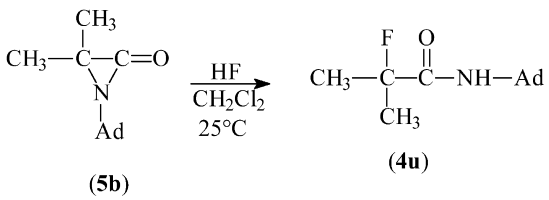


Scheme 6. Reaction of 1-(1-adamantyl)-3-*t*-butylaziridinone (**5c**) with maleic acid.



Scheme 7. Dependence of the product on the pK_a of the acid (see also Table 2).

insufficient to lead to decarbonylation, instead it leads to a Passerini product by nucleophilic substitution at C-3 (Scheme 7). Thus, while α-lactam **5b** reacts with hydrofluoric acid at room temperature to give 2-fluoro-2-methyl-*N*-(1-adamantyl)propanamide (**4u**) in good yield (Scheme 8), treatment of α-lactam **5c** with aqueous hydrobromic acid at room temperature leads to decarbonylation and a good yield of pivalaldehyde, isolated as the semicarbazone, and a nearly quantitative yield of 1-adamantanamine (Scheme 9).

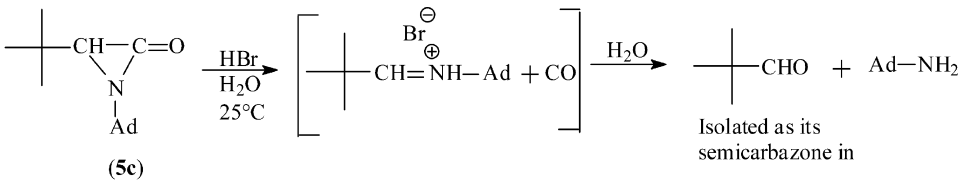


Scheme 8. Reaction of α-lactam **5b** with hydrofluoric acid.

It appears that the acid-strength where the turning point in the reaction path occurs is around a pK_a of zero. So, the acids in the left column of Table 2 will give a Passerini product with α-lactams, while those in the right-side column will

Table 2. The pK_a values of selected acids[31]

'Weak acid'	pK_a	'Strong acid'	pK_a
Pivalic acid	5.03	Benzenesulfonic acid	−0.6
Acetic acid	4.8	Methanesulfonic acid	−1.2
trans-Cinnamic acid	4.44	Sulfuric acid	−5.0
Benzoic acid	4.2	*p*-Toluenesulfonic acid	−6.6
Succinic acid	4.16, 5.61	Hydrochloric acid	−7
Formic acid	3.8	Hydrobromic acid	−9
Phthalic acid	3.51, 4.82	Hydroiodic acid	−10
Hydrofluoric acid	3.2		
Maleic acid	1.83, 6.07		
Trifluoroacetic acid	0.2		



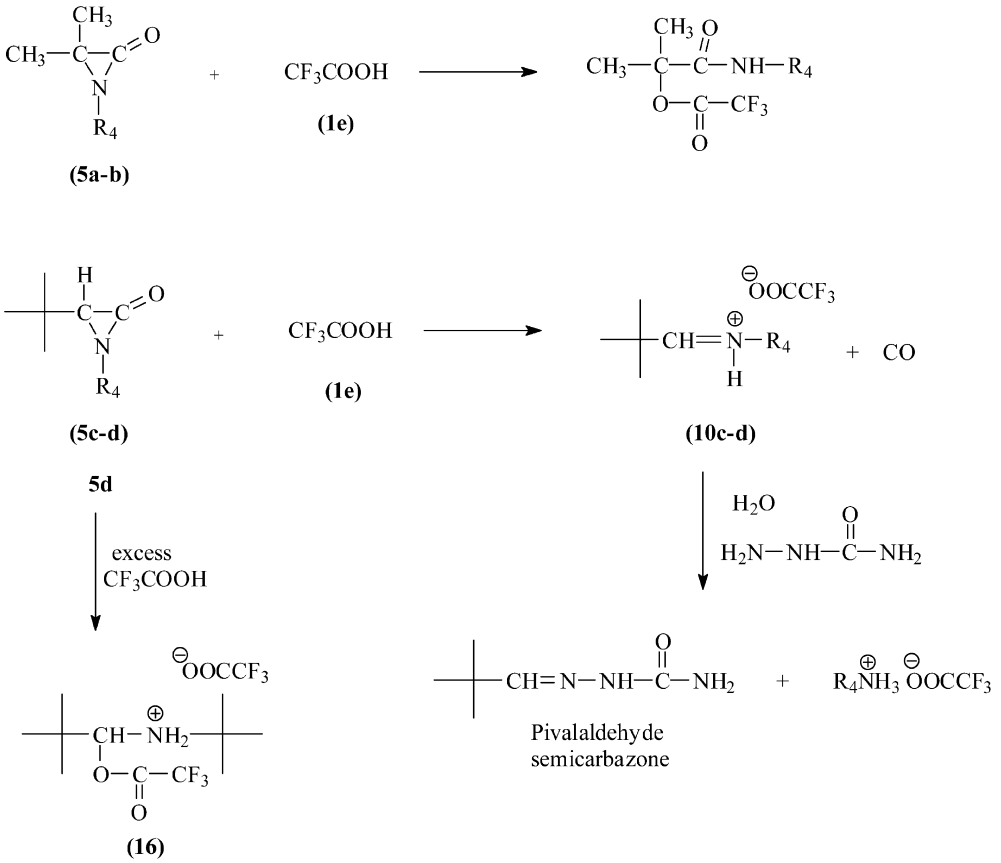
Scheme 9. Reaction of α-lactam **5c** with hydrobromic acid.

cause decarbonylation as the predominant reaction path. Trifluoroacetic acid (**1e**), the pK_a of which is at or near the turning point, gives both, depending on the relative reactivity of the α-lactam. Thus, the two more reactive α-lactams (**5a**, **5b**) give Passerini products (**4e**, **4j**), while the two less reactive ones (**5c**, **5d**) decarbonylate upon treatment with trifluoroacetic acid to immonium trifluoroacetates **10c-d**. After work-up, 1-adamantan ammonium trifluoroacetate (**15c**) was isolated from **5c** and *tert*-butyl ammonium trifluoroacetate (**15d**) or *N*-*tert*-butyl-2,2-dimethyl-1-(trifluoroacetyl)oxypropan-1-aminium trifluoroacetate (**16**) was isolated from **5d**, in excellent yield.

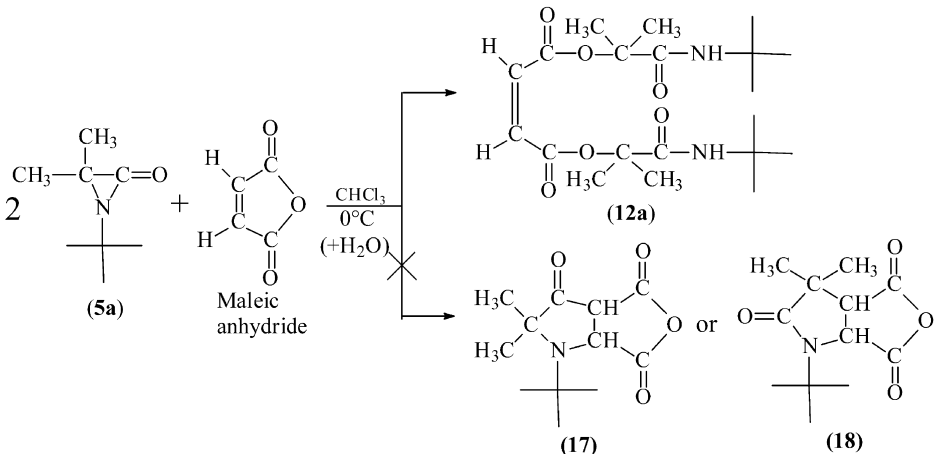
In separate experiments, both hydrolysis products, pivalaldehyde and 1-adamantanamine, were isolated from **5c**, the former as its semicarbazone. Pivalaldehyde semicarbazone was also isolated from the reaction of **5d** with CF_3COOH and subsequent hydrolysis of the intermediate salt **10d** (Scheme 10). Because of the low boiling point of *tert*-butylamine (bp 44–46 °C), it was removed with the solvent upon evaporation.

2.3. Reaction of α-lactams with maleic anhydride

It has been reported[32] that maleic anhydride is an excellent 'dipolarophile' in 1,3-dipolar cycloaddition reactions. We found indeed that α-lactam **5a** undergoes smooth and rapid reaction with maleic anhydride, even at 0 °C in $CHCl_3$. However, the product isolated after chromatography on alumina is not a 3+2=5 type cycloadduct (**17** or **18**), but the bis-Passerini product di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (**12a**), representing a 2:1 addition without decarbonylation, even if the two reactants are applied in an equimolar ratio (Scheme 11). It should be noted that this product is obtained even when freshly vacuum-sublimed maleic anhydride is used. This same product was also readily obtained from α-lactam **5a** and maleic acid, and by the Passerini reaction from maleic acid, acetone, and *tert*-butyl isonitrile (Scheme 5), cf. Section 4. This result is the more surprising since α-lactam **5a** has been reported to undergo successful 1,3-dipolar cycloaddition reaction with three different 'dipolarophiles', viz. phenylisocyanate,[33] diphenylketene,[34] and *N*,*N*-dimethylformamide.[35]



Scheme 10. Reactions of α-lactams **5a-d** with trifluoroacetic acid.



Scheme 11. The reaction of α-lactam **5a** with maleic anhydride.

We include these results here because they represent a striking example of an α-lactam leading to a bis-Passerini product, even though no mechanistic investigation was undertaken to date to fully account for the reaction. It is evident, however, that the absence of a strong acid preserves the α-lactam ring from decarbonylation so that it can undergo nucleophilic ring-opening. Under comparable conditions (0–25 °C, in $CHCl_3$ or CCl_4 solution), α-lactams **5b-d** do not react with maleic anhydride. When a 2:1 mixture of α-lactam **5b** and maleic anhydride is heated to 70 °C for 10 min in carbon tetrachloride solution, the characteristic α-lactam carbonyl band in the IR at ~1840 cm^{-1} completely disappears. However, under these forced conditions, several parallel reactions occur simultaneously and concurrently:

(a) Passerini reaction, leading to a low yield (17%) of the bis-Passerini product (**12b**),
(b) spontaneous thermal decomposition of the α-lactam, leading to acetone (not isolated) and 1-adamantyl isonitrile (26%),
(c) formation of a bright purple dye (~51%) which stays at the top of the silica gel column during chromatography and was not investigated further.

As we reported earlier,[30] α-lactam **5c** also reacts with maleic anhydride, but only at 80 °C, and under the more severe conditions required for this reaction, decarbonylation occurs and the products are *N*-(1-adamantyl) maleamic acid (**19**), pivalaldehyde (**20**), and carbon monoxide (Scheme 12). The details of this complicated reaction have been studied, and a four-step mechanism, based on acid-catalyzed decarbonylation and hydrolysis, has been proposed.[30] Control experiments on **5a-d** with benzoic and succinic anhydride under comparable conditions (0–25 °C, in $CHCl_3$ or CCl_4 solution) led to no detectable reaction.

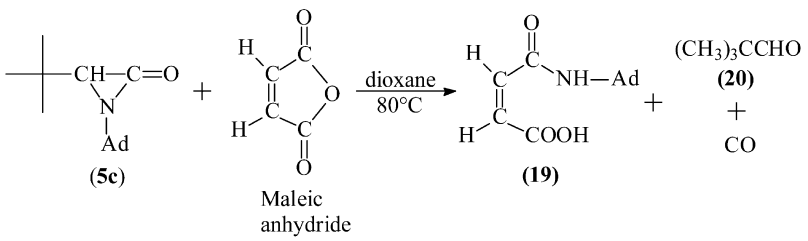
3. Conclusions

α-Lactams **5a-d** react with ordinary aliphatic and aromatic mono- and dicarboxylic acids and hydrofluoric acid to give Passerini products **4** and **12-13**, whereas reaction with stronger acids leads to immonium salts, for example, **10** with concomitant decarbonylation, in agreement with an earlier report.[24] The major path of the reaction depends on a combination of three factors:

(1) the pK_a of the acid: a positive pK_a favors Passerini product formation, while a negative pK_a leads to decarbonylation.
(2) the relative reactivity of the α-lactam: higher reactivity favors Passerini product.
(3) the reaction conditions: milder reaction conditions favor Passerini product.

An advantage of this synthesis of α-acyloxycarboxamides from α-lactams is that it obviates the necessity of working with the repulsive-smelling isonitriles.

α-Lactams **5a** and **5b** also react with maleic anhydride to give the bis-Passerini product **12a** and **12b**, respectively, rather than a cycloadduct (**17** or **18**).



Scheme 12. The reaction of α-lactam **5c** with maleic anhydride.

4. Experimental

Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz Bruker instrument with tetramethylsilane as internal standard. Chemical shifts are reported in ppm (δ). IR spectra were measured on a Perkin–Elmer Spectrum 1000 FT-IR. Microanalyses were preformed by Atlantic Microlab Inc., Norcross, GA. Mass spectra (MS) were recorded on a Hewlett–Packard GC–MS GCD system. For column chromatography, JT Baker Silica gel (40 μm) was used. Thin layer chromatography (TLC) was preformed with Analtech silica gel glass backed plates (250 μm). The aziridinones were prepared by the method of Scrimin et al.[36] except where noted otherwise.

4.1. Reactions of α-lactams with carboxylic acids

4.1.1. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with acetic acid. *N*-*tert*-Butyl-2-acetoxy-2-methylpropanamide (4a). The toluene solution of the α-lactam 1-*tert*-butyl-3,3-dimethylaziridinone[10] (**5a**) (0.565 g, 0.004 mol) was cooled to 0 °C and 2 equiv. of acetic acid (0.48 g, 0.008 mol) dissolved in toluene (2 mL) was added dropwise. After stirring for 1 h, the reaction mixture was washed with 5% sodium bicarbonate and twice with water (20 mL). The organic layer was dried with sodium sulfate and the solvent removed under reduced pressure to afford crude product **4a** (0.430 g, 53.4%). After recrystallization from 3 mL of *n*-heptane, a white solid **4a** (0.30 g, 37%) with mp 78–79 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.45. IR (CCl_4) ν: 3430, 2955, 1739, 1680, and 1505 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.55 (s, 6H), 2.02 (s, 3H), and 5.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 22.1, 24.4, 51.1, 81.8, 169.2, 172.2. MS: *m*/*z* 201, 186, 158, 144, 129, 115, 102, 101, 88, 86, 61, 59, 58, 57, 43 (base peak).

4.1.2. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with pivalic acid. *N*-*tert*-Butyl-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4b). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.318 g, 2.25 mmol) in 25 mL of toluene at 0 °C was added 0.689 g (6.75 mmol) of pivalic acid in 10 mL of anhydrous toluene. The solution was stirred overnight slowly coming to rt for 20 h then was washed with 4×35 mL of 5% $NaHCO_3$ and 2×35 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.46 g of a white solid. After flash chromatography (95% *n*-hexane/5% ethyl acetate), 0.36 g (66%) of a solid (**4b**) with mp 49–50 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3446, 2973, 2935, 1739, 1687 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9H), 1.35 (s, 9H), 1.59 (s, 6H), 5.86 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.1, 28.6, 39.1, 50.8, 81.6, 172.4, 176.3. MS: *m*/*z* 243, 228, 186, 185, 171, 158, 144, 114, 103, 102, 86, 85, 59, 58, 57 (base peak), 41. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.28; H, 10.47; N, 5.78.

4.1.3. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with benzoic acid. *N*-*tert*-Butyl-2-benzoyloxy-2-methylpropanamide (4c). The toluene solution of the α-lactam 1-*tert*-butyl-3,3-dimethylaziridinone (**5a**) (0.565 g, 0.004 mol) was cooled to 0 °C and 2 equiv. of benzoic acid (0.98 g, 0.008 mol) dissolved in toluene (2 mL) was added dropwise. After stirring for 1 h, the reaction mixture was washed with 5% sodium bicarbonate and twice with water (20 mL). The organic layer was dried with sodium sulfate and the solvent removed under reduced pressure to afford crude product **4c** (0.81 g, 77.0%) with mp 88–89 °C. After recrystallization from *n*-heptane (1.5 mL), 0.70 g (66.5%) of a white solid with mp 89–90 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3435, 3050, 2955, 1722, 1680, 1505 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.72 (s, 6H), 5.89 (s, 1H), and 7.44 (t, 2H, *J*=7.7 Hz), 7.56 (t, 1H, *J*=7.5 Hz), 7.97 (d, 2H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 24.7, 28.8, 51.2, 82.5, 128.7, 129.6, 130.7, 133.4, 164.9, and 172.3. MS: *m*/*z* 263, 205, 191, 164, 146, 123, 105 (base peak), 77, 59, 57. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.26; H, 8.00; N, 5.22.

4.1.4. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with *trans*-cinnamic acid. *N*-*tert*-Butyl-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4d). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.318 g, 2.25 mmol) in 25 mL of toluene at 0 °C was added 1.00 g (6.75 mmol) of *trans*-cinnamic acid in 10 mL of anhydrous toluene. The solution was stirred overnight slowly coming to rt for 18.5 h then was washed with 4×35 mL of 5% $NaHCO_3$ and 2×35 mL of distilled water, dried with Na_2SO_4, filtered and rotary-evaporated to give 0.60 g of a yellow solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.55 g (84%) of a white solid (**4d**) with mp 102–104 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.50. IR (CCl_4) ν: 3447, 3030, 2975, 1722, 1688, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H), 1.68 (s, 6H), 5.87 (s, 1H, exchangeable in D_2O), 6.43 (d, 1H, *J*=16.0 Hz), 7.41 (q, 3H, *J*=2.6 Hz), 7.54 (quintuplet, 2H, *J*=2.6 Hz), 7.68 (d, 1H, *J*=16.0 Hz). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.6, 51.0, 81.9, 118.3, 128.1, 129.0, 130.5, 134.2, 145.4, 165.1, 172.2. MS: *m*/*z* 231, 217, 190, 175, 172, 145, 131 (base peak), 103, 77, 59, 57, 51, 41. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.32; H, 7.94; N, 4.83.

4.1.5. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with trifluoroacetic acid. *N*-*tert*-Butyl-2-methyl-2-trifluoroacetoxypropanamide (4e). 1-*tert*-Butyl-3,3-dimethylaziridinone (**5a**) (0.565 g, 0.004 mol) was dissolved in toluene (30 mL). A solution of trifluoroacetic acid (0.92 g, 0.008 mol) in toluene (2 mL) was added dropwise at 0 °C. After stirring for 1 h, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the toluene was removed under reduced pressure to afford 0.47 g (83%) of an oil which partially solidified after 2 days. 0.37 g (65.5%) of pure **4e** was obtained by sublimation (40–50 °C, 11 mm), mp 46–47 °C. TLC (90% *n*-hexane/10% isopropyl alcohol) R_f=0.45. IR (CCl_4) ν: 3454, 2970, 1793, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.70 (s, 6H), 5.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.7, 28.5, 51.5, 87.0, 114.3 (q, *J*=286.5 Hz), 155.0 (q, *J*=42.0 Hz), 169.9. MS: *m*/*z* 255, 240, 184, 155, 126, 114, 98, 86, 69, 57 (base peak), 41. Anal. Calcd for $C_{10}H_{16}NO_3F_3$: C, 47.06; H, 6.32; N, 5.49. Found: C, 47.32; H, 6.51; N, 5.57.

4.1.6. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with acetic acid. *N*-(1-Adamantyl)-2-acetoxy-2-methylpropanamide (4f). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone[28] (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 0.502 g (8.35 mmol) of acetic acid. The solution was stirred for 2.5 h then was washed with 3×10 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.51 g of a white solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.38 g (81%) of a white solid (**4f**) with mp 157–158 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.20. IR (CCl_4) ν: 3439, 2910, 2848, 1750, 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.59 (s, 6H), 1.69 (s, 6H), 2.00 (s, 6H), 2.07 (s, 6H), 5.67 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 22.0, 24.3, 29.5, 36.4, 41.4, 51.6, 81.7, 169.1, 171.9. MS: *m/z* 279, 236, 222, 219, 178, 176, 150, 135 (base peak), 102, 93, 79, 59, 43, 41. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.05; H, 9.16; N, 4.91.

4.1.7. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with pivalic acid. *N*-(1-Adamantyl)-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4g). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 0.853 g (8.35 mmol) of pivalic acid. The solution was stirred for 4 h then was washed with 4×40 mL of 5% $NaHCO_3$ and 2×40 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.88 g of an oil. After flash chromatography (92.5% *n*-hexane/7.5% ethyl acetate), 0.40 g (74%) of a white solid (**4g**) with mp 65–67 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.41. IR (CCl_4) ν: 3438, 2910, 2852, 1739, 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (s, 9H), 1.59 (s, 6H), 1.69 (s, 6H), 1.99 (s, 6H), 2.08 (s, 3H), 5.75 (bs, 1H, exchangeable in D_2O). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.2, 29.5, 36.4, 39.1, 41.5, 51.4, 81.6, 172.2, 176.3. MS: *m/z* 321, 306, 263, 236, 219, 220, 192, 163, 150, 144, 135 (base peak), 107, 103, 93, 85, 79, 67, 59, 57, 41. Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 71.01; H, 9.94; N, 4.29.

4.1.8. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with benzoic acid. *N*-(1-Adamantyl)-2-benzoyloxy-2-methylpropanamide (4h). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 1.02 g (8.35 mmol) of benzoic acid in 10 mL of benzene. The solution was stirred for 3 h then was washed with 4×40 mL of 5% $NaHCO_3$ and 2×40 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.54 g of a white solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.43 g (75%) of a white solid (**4h**) with mp 105–106 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.24. IR (CCl_4) ν: 3441, 2910, 2852, 1730, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.68 (s, 6H), 1.73 (s, 6H), 2.02 (s, 6H), 2.08 (s, 3H), 5.78 (bs, 1H, exchangeable in D_2O), 7.47 (t, 2H, *J*=7.0, 8.0 Hz), 7.59 (t, 1H, *J*=7.0 Hz), 8.00 (d, 2H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 24.6, 29.5, 36.4, 41.5, 51.7, 82.3, 128.5, 129.5, 130.7, 133.2, 164.8, 171.9. MS: *m/z* 341, 283, 240, 219, 193, 192, 191, 164, 135 (base peak), 105, 77, 59. Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 74.02; H, 8.03; N, 4.04.

4.1.9. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with *trans*-cinnamic acid. *N*-(1-Adamantyl)-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4i). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 1.24 g (8.35 mmol) of *trans*-cinnamic acid in 10 mL of benzene. The solution was stirred for 5 h then was washed with 4×40 mL of 5% $NaHCO_3$ and 2×40 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.60 g of a light yellow solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.37 g (60%) of a white solid (**4i**) with mp 125–126 °C was obtained. TLC (85% *n*-hexane/15% ethyl acetate) R_f=0.39. IR (CCl_4) ν: 3438, 3064, 3029, 2910, 2851, 1722, 1686, 1637 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.68 (s, 12H), 2.03 (s, 6H), 2.08 (s, 3H), 5.74 (bs, 1H, exchangeable in D_2O), 6.42 (d, 1H, *J*=16.0 Hz), 7.40 (s, 3H), 7.53 (s, 2H), 7.68 (d, 1H, *J*=16.0 Hz). ^{13}C NMR ($CDCl_3$): δ 25.0, 29.8, 36.7, 41.8, 52.0, 82.2, 118.7, 128.5, 129.3, 130.9, 134.6, 145.7, 165.5, 172.3. MS: *m/z* 367, 309, 238, 219, 190, 175, 150, 145, 135 (base peak), 131, 107, 103, 93, 91, 79, 77, 59, 41. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.21; H, 8.13; N, 3.71.

4.1.10. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with trifluoroacetic acid. *N*-(1-Adamantyl)-2-methyl-2-trifluoroacetoxypropanamide (4j). To a solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**) (0.89 g, 0.004 mol) in 10 mL of ether at 0 °C, trifluoroacetic acid (0.570 g, 0.005 mol) was added. The solution was stirred for 3 h. The ether was removed under reduced pressure to afford crude *N*-(1-adamantyl)-2-methyl-2-trifluoroacetoxypropanamide **4j** (81.9%). After flash chromatography (70% *n*-hexane/30% ethyl acetate), 0.54 g (40.6%) of a white solid with mp 100–102 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.42. IR (CCl_4) ν: 3445, 2920, 2860, 1795, 1693 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.67 (t, *J*=2.7 Hz, 6H), 1.70 (s, 6H), 1.97 (d, *J*=2.7 Hz, 6H), 2.08 (s, 3H), 5.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 29.6, 36.4, 41.5, 52.2, 87.0, 114.4 (q, *J*=287.0 Hz), 155.4 (q, *J*=42.4 Hz), 169.7. MS: *m/z* 333, 219, 192, 176, 155, 135 (base peak), 107, 93, 69, 41. Anal. Calcd for $C_{16}H_{22}NF_3O_3$: C, 57.65; H, 6.65; N, 4.20. Found: C, 57.79; H, 6.67; N, 4.02.

4.1.11. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with acetic acid. *N*-(1-Adamantyl)-2-acetoxy-3,3-dimethylbutanamide (4k). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**)[20] (0.990 g, 0.004 mol) was dissolved in benzene (30 mL). Acetic acid (0.480 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% Na_2CO_3 (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4k** (88%). After flash chromatography (90% *n*-hexane/10% ethyl acetate), pure *N*-(1-adamantyl)-2-acetoxy-3,3-dimethylbutanamide was obtained (63%), mp 138–140 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.33. IR (CCl_4) ν: 3435, 3092, 3037, 2910, 2852, 1752, 1691 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.01 (s, 9H), 1.67 (s, 6H), 1.99 (s, 6H), 2.07 (s, 3H), 2.14 (s, 3H), 4.56 (s, 1H), 5.45 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 26.7, 29.8, 32.0, 34.4, 36.7, 42.0, 52.3, 81.5, 167.6, 170.1. MS: *m/z* 307, 251, 232, 207, 178, 150, 135 (base peak), 120, 93, 79, 57, 43. Anal. Calcd for

$C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.10; H, 9.53; N, 4.66.

4.1.12. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with pivalic acid. *N*-(1-Adamantyl)-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4l). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**) (0.75 g, 0.003 mol) was dissolved in benzene (30 mL). Pivalic acid was added (0.61 g, 0.006 mol) and the reaction was refluxed for 2 h. The reaction mixture was then washed with 5% $NaHCO_3$ (30 mL), and twice with H_2O (20 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure, to give a crude oil which solidified (0.95 g, 90.5%). Crude 4 l was flash chromatographed (90% *n*-hexane/10% ethyl acetate) to obtain pure *N*-(1-adamantyl)-2-(2,2-dimethylpropanoyloxy)-3,3-dimethylbutanamide (0.38 g, 36.2%), mp 90–92 °C. TLC (80% *n*-hexane/20% ethyl acetate): R_f=0.64. IR (CCl_4) ν: 3437, 2910, 1742, 1687 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.02 (s, 9H), 1.26 (s, 9H), 1.67 (s, 6H), 1.98 (s, 6H), 2.07 (s, 3H), 4.68 (s, 1H), 5.48 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 27.2, 29.4, 34.2, 36.3, 38.9, 41.6, 51.8, 80.6, 167.6, 176.5. MS: *m/z* 349, 293, 249, 232, 208, 172, 163, 135 (base peak), 117, 85, 70, 57. Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.26; H, 10.15; N, 4.05.

4.1.13. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with benzoic acid. *N*-(1-Adamantyl)-2-benzoyloxy-3,3-dimethylbutanamide (4m). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**) (0.75 g, 0.003 mol) was dissolved in benzene (30 mL). Benzoic acid (0.73 g, 0.006 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4m** (0.86 g, 77.5%). After flash chromatography (95% *n*-hexane/5% ethyl acetate), pure **4m** (0.645 g, 58.2%) was obtained, mp 163–165 °C. TLC (80% *n*-hexane/20% ethyl acetate): R_f=0.67. IR (CCl_4) ν: 3436, 2911, 2852, 1734, 1688, 1513 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.14 (s, 9H), 1.66 (s, 6H), 1.99 (s, 6H), 2.06 (s, 3H), 4.93 (s, 1H), 5.55 (s, 1H), 7.48 (m, 2H), 7.63 (m, 1H), 8.10 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.4, 34.4, 36.3, 41.6, 52.0, 81.5, 128.7, 133.4, 165.2, 167.2. MS: *m/z* 369, 313, 283, 269, 240, 208, 192, 177, 135 (base peak), 105, 79, 77, 70. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.79; H, 8.62; N, 3.69.

4.1.14. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with *trans*-cinnamic acid. *N*-(1-Adamantyl)-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4n). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**) (0.75 g, 0.003 mol) was dissolved in benzene (30 mL). *trans*-Cinnamic acid (0.89 g, 0.006 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4n** (1.04 g, 100%). After recrystallization from 6 mL hot *n*-heptane, a white solid (0.77 g, 74.0%) with mp 122–123 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3429, 3060, 2910, 1732, 1687, 1638, 1549, 1512 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.67 (s, 6H), 2.00 (s, 6H), 2.07 (s, 3H), 4.82 (s, 1H), 5.54 (bs, 1H), 6.50 (d, J=16.0 Hz, 1H), 7.44 (m, 3H), 7.55 (dd, J=3.7 Hz, 2H), 7.76 (d, J=16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 29.4, 34.2, 36.3, 41.6, 52.0, 81.1, 117.2, 128.3, 129.1, 130.7, 134.1, 146.0, 165.7, 167.3. MS (ES): *m/z* 417.9 (M+23), 395.8, 380.9, 313.1, 245.0. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.95; H, 8.39; N, 3.33.

4.1.15. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with acetic acid. *N*-*tert*-Butyl-2-acetoxy-3,3-dimethylbutanamide (4p). 1,3-di-*tert*-Butylaziridinone[29] (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). Acetic acid (0.48 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4p** (0.90 g, 98.1%) as an oil which solidified overnight. After recrystallization from 1 mL of *n*-hexane, 0.61 g (66.5%) of a white solid was obtained, mp 62–63 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.44. IR (CCl_4) ν: 3440, 2965, 1738, 1683, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (s, 9H), 2.11 (s, 3H), 4.64 (s, 1H), 5.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 26.4, 28.8, 34.2, 51.4, 81.2, 167.7, 169.9. MS: *m/z* 229, 214, 186, 173, 157, 131, 129, 87, 75, 57 (base peak), 43.

4.1.16. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with pivalic acid. *N*-*tert*-Butyl-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4q). 1,3-di-*tert*-Butylaziridinone (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). Pivalic acid (0.817 g, 0.008 mol) was added and the reaction refluxed for 30 min. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4q** (0.91 g, 83.8%). Crude **4q** was flash chromatographed (95% *n*-hexane/5% ethyl acetate) to obtain pure *N*-*tert*-butyl-2-(2,2-dimethylpropanoyloxy)-3,3-dimethylbutanamide (**4q**) (0.869 g, 80%), mp 87–88 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.48. IR (CCl_4) ν: 3427, 3370, 2955, 2860, 1735, 1667, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.99 (s, 9H), 1.24 (s, 9H), 1.30 (s, 9H), 4.66 (s, 1H), and 5.59 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.5, 27.3, 28.8, 34.4, 39.0, 51.3, 80.8, 167.8, and 176.7. MS: *m/z* 271, 256, 215, 199, 172, 157, 143, 130, 102, 85, 71, 57 (base peak), 41.

4.1.17. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with benzoic acid. *N*-*tert*-Butyl-2-benzoyloxy-3,3-dimethylbutanamide (4r). 1,3-di-*tert*-Butylaziridinone (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). Benzoic acid (0.98 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4r** (0.92 g, 79%). After recrystallization from *n*-heptane/ethyl acetate (5 mL/2 mL), 0.44 g (37.6%) of a white solid with mp 128–129 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.68. IR (CCl_4) ν: 3440, 3380, 3060, 2965, 2870, 1720, 1685, 1598, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.32 (s, 9H), 4.91 (s, 1H), 5.70 (s,

1H), 7.47 (m, 2H), 7.59 (m, 1H), 8.09 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.6, 51.4, 81.7, 128.8, 129.8, 133.6, 165.4, 167.6. MS: *m/z* 291, 276, 253, 235, 219, 192, 177, 143, 130, 105 (base peak), 87, 77, 70, 57, 41.

4.1.18. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with *trans*-cinnamic acid. *N*-*tert*-Butyl-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4s). 1,3-di-*tert*-Butylaziridinone (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). *trans*-Cinnamic acid (1.19 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4s** (1.22 g, 96.2%). After recrystallization from methylene chloride/*n*-heptane (1 mL:3 mL), 0.83 g (65.4%) of a white solid was obtained, mp 97–98 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.46. IR (CCl_4) ν: 3440, 2960, 2868, 1715, 1680, 1633, 1505 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.33 (s, 9H), 4.81 (s, 1H), 5.70 (s, 1H), 6.50 (d, 1H, *J*=16.0 Hz), 7.38 (m, 3H), 7.54 (m, 2H), 7.74 (d, 1H, *J*=16.0 Hz). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.4, 51.4, 81.2, 117.3, 128.4, 129.1, 130.8, 134.2, 146.2, 165.8, 167.7. MS: *m/z* 317, 261, 245, 231, 218, 175, 162, 149, 131 (base peak), 103, 77, 70, 57, 41.

4.1.19. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with 1 equiv. of trifluoroacetic acid. 1-Adamantan ammonium trifluoroacetate (15c). Dropwise, over a period of 5 min, a solution of trifluoroacetic acid (0.659 g, 5.78 mmol) in 5 mL of THF was added to a solution of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**) (1.43 g, 5.78 mmol) in 20 mL of THF at 0 °C. The solution stirred for 3 h slowly reaching a temperature of 10 °C and then the THF was removed under reduced pressure to give 1.77 g of a white solid. It was recrystallized from hot *n*-heptane/isopropyl alcohol (15 mL:5 mL) to give 1.26 g (82%) of 1-adamantan ammonium trifluoroacetate (**15c**), mp 298–300 °C. IR (KBr) ν: 2914, 1668, 1541, 1455, 1365 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.59 (dd, 6H, *J*=10.0 Hz), 1.77 (s, 6H), 2.06 (s, 3H), 8.03 (bs, 3H, exchanges in D_2O). ^{13}C NMR (DMSO-d_6) δ 28.4, 35.2, 50.9, 117.1 (q, *J*=299.0 Hz), 158.6 (q, *J*=31.0 Hz). Anal. Calcd for $C_{12}H_{18}F_3NO_2$: C, 54.33; H, 6.84; N, 5.28. Found: C, 54.35; H, 6.76; N, 5.27.

4.1.20. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with trifluoroacetic acid followed by hydrolysis. To 0.36 g (1.46 mmol) of 1-(1-adamantyl)-3-*tert*-butylaziridinone in 10 mL of benzene was added a solution of trifluoroacetic acid (0.347 g, 3.04 mmol) in 5 mL of benzene and it stirred at rt for 66 h (immediately upon addition of trifluoroacetic acid gas evolution was observed). The benzene was removed under reduced pressure to yield a solid to which 9 mL of hexane was added and the mixture was stored at −20 °C for several hours. It was then filtered to give 0.481 g of a white solid, which was added to a solution of semicarbazide hydrochloride (0.186 g, 1.67 mmol) and sodium acetate (0.151 g, 1.84 mmol) in 10 mL of water and stirred at rt for 7.5 h. It was then cooled down in an ice-bath for 15 min. The reaction mixture was filtered over a sintered disc Büchner funnel and the solid washed with 5 mL of ice–cold water to give 0.200 g of crude pivalaldehyde semicarbazone which was recrystallized from 5 mL of hot water to give 0.160 g (77%) of pure product, mp 186–188 °C (reported[37] mp 191 °C). TLC, IR, and MS were identical with those of an authentic sample prepared from pivalaldehyde and semicarbazide hydrochloride.

To the filtrate was added $NaHCO_3$ until pH=8 and stirred for 1 h at 0 °C. It was then filtered to give 0.135 g (61%) of pure adamantanamine, mp 203–205 °C. TLC, IR, and MS were identical with those of an authentic sample of adamantanamine (Aldrich).

4.1.21. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with 1 equiv. of trifluoroacetic acid. *tert*-Butyl ammonium trifluoroacetate (15d). Dropwise over a period of 5 min, a solution of trifluoroacetic acid (0.650 g, 5.7 mmol) in 5 mL of THF was added to a solution of 1,3-di-*tert*-butylaziridinone (**5d**) (0.96 g, 5.7 mmol) in 15 mL of THF at 0 °C. The solution stirred for 3 h slowly reaching a temperature of 10 °C and then the THF was removed under reduced pressure to give 1.22 g of a white solid. It was recrystallized from hot *n*-heptane/isopropyl alcohol (3 mL/1 mL) to give 0.87 g (82%) of *tert*-butyl ammonium trifluoroacetate (**15d**), mp 185–187 °C. ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 9H), 8.04 (bs, 3H). ^{13}C NMR (DMSO-d_6) δ 27.0, 50.8, 117.1 (q, *J*=299.0 Hz), 158.6 (q, *J*=31.6 Hz). MS: *m/z* 97, 69, 58, 45. Anal. Calcd for $C_6H_{12}F_3NO_2$: C, 38.50; H, 6.42; F, 30.48; N, 7.49. Found: C, 38.67; H, 6.49; F, 30.75; N, 7.47.

4.1.22. *tert*-Butyl ammonium trifluoroacetate (15d). To a solution of *tert*-butylamine (1.76 g, 0.024 mol) in 27 mL of THF is added trifluoroacetic acid (2.96 g, 0.026 mol) in one portion at rt. It is stirred for 17 h then evaporated to dryness to give 3.8 g of a white solid. It was recrystallized from *n*-heptane/isopropyl alcohol (24 mL/7 mL) to give 3.2 g (71%) of a white solid (**15d**), mp 187–189 °C. ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 9H), 8.04 (bs, 3H). ^{13}C NMR (DMSO-d_6) δ 27.0, 50.8, 117.1 (q, *J*=299.0 Hz), 158.6 (q, *J*=31.6 Hz). MS: *m/z*. 97, 69, 58, 45.

4.1.23. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with 2 equiv. of trifluoroacetic acid. *N*-*tert*-Butyl-2,2-dimethyl-1-(trifluoroacetyloxy)propan-1-aminium trifluoroacetate (16). Dropwise, a solution of trifluoroacetic acid (0.91 g, 0.008 mol) in 10 mL of benzene was added to a solution of 1,3-di-*tert*-butylaziridinone (**5d**) (0.68 g, 0.004 mol) in 5 mL of benzene at 10 °C. The resulting mixture was stirred overnight and then filtered to yield pure **16** (74%), mp 119–120 °C. IR (KBr) ν: 2990, 1785, 1691, 1485 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.36 (s, 9H), 4.78 (s, 1H), 8.33 (s, 2H, exchangeable in D_2O). ^{13}C NMR ($CDCl_3$) δ 23.8, 25.5, 36.4, 51.0, 60.9, 115.1 (q, *J*=291.0 Hz), 161.3 (q, *J*=36.0 Hz), 182.9. Anal. Calcd for $C_{13}H_{21}F_6NO_4$: C, 42.28; H, 5.73; F, 30.87; N, 3.79; O, 17.33. Found: C, 42.42; H, 5.73; N, 3.77.

4.1.24. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with trifluoroacetic acid followed by hydrolysis. To 0.611 g (3.6 mmol) of 1,3-di-*tert*-butylaziridinone in 20 mL of benzene is added a solution of trifluoroacetic acid (0.912 g, 8 mmol) in 10 mL of benzene and is stirred at rt for 3 days (immediately upon addition of trifluoroacetic acid gas

evolution was observed). The benzene was removed under reduced pressure to yield a solid to which 6 mL of hexane was added and the mixture was stored at −20 °C for overnight. The precipitate was then filtered to give 0.97 g of a white solid, which was subsequently added to a solution of semicarbazide hydrochloride (0.491 g, 4.4 mmol) and sodium acetate (0.397 g, 4.84 mmol) in 20 mL of water and stirred at rt for 2 days. It was then cooled down in an ice-bath for 15 min. The reaction mixture was filtered over a sintered disc Büchner funnel and the solid washed with 5 mL of ice–cold water to give 0.270 g (52%) of pure pivalaldehyde semicarbazone, mp 186–188 °C. TLC, IR, and MS were identical with those of an authentic sample prepared directly from authentic pivalaldehyde and semicarbazide hydrochloride. No effort was made to isolate the other hydrolysis product, *tert*-butylamine.

4.1.25. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with maleic acid. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (12a). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.317 g, 2.25 mmol) in 17 mL of toluene at 0 °C was added 0.130 g (1.125 mmol) of maleic acid in 15 mL of THF. The solution was stirred for 15 h slowly coming to rt. The solvents were evaporated under reduced pressure and the residue was taken up into 50 mL of methylene chloride and washed with 3×30 mL of 5% $NaHCO_3$ and 2×30 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.36 g of a white solid. After flash chromatography (60% *n*-hexane/40% ethyl acetate), 0.33 g (73%) of a white solid (**12a**) with mp 148–149 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.36. IR (CCl_4) ν: 3448, 3401, 2973, 1731, 1687, 1642 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (s, 18H), 1.61 (s, 12H), 6.26 (s, 2H), 6.30 (bs, 2H, exchangeable in TFD). ^{13}C NMR ($CDCl_3$): δ 24.6, 28.6, 51.2, 83.2, 130.2, 163.4, 171.3. MS: *m*/*z* 398, 383, 343, 326, 299, 256, 228, 160, 143 (base peak), 114, 87, 58, 57, 41.

4.1.26. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with maleic acid. Di[2-methyl-*N*-(1-adamantyl) propanamido-2-]maleate (12b). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.366 g, 1.67 mmol) in 25 mL of benzene at rt was added 0.097 g (0.835 mmol) of maleic acid in 8 mL of THF. The solution was stirred for 20 h and the solvents were evaporated under reduced pressure to give an oil which was taken up into 60 mL of benzene and washed with 3×30 mL of 5% $NaHCO_3$ and 2×30 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.47 g of a white solid. After flash chromatography (75% *n*-hexane/25% ethyl acetate), 0.39 g (84%) of a white solid (**12b**) with mp 205–206 °C was obtained. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.33. IR (CCl_4) ν: 3439, 3394, 2910, 2852, 1732, 1684, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.61 (s, 12H), 1.68 (s, 12H), 2.02 (s, 12H), 2.07 (s, 6H), 6.16 (s, 2H, exchangeable in D_2O), 6.24 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.7, 29.5, 36.4, 41.3, 52.0, 83.1, 130.2, 163.3, 171.1. Anal. Calcd for $C_{32}H_{46}N_2O_6$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.26; H, 8.27; N, 4.93.

4.1.27. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone with succinic acid. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)succinate (13a). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.317 g, 2.25 mmol) in 25 mL of toluene at 0 °C was added 0.133 g (1.12 mmol) of succinic acid in 6 mL of THF. The solution was stirred overnight slowly coming to rt for 19 h then was washed with 4×35 mL of 5% $NaHCO_3$ and 2×35 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.40 g of an oil which crystallized upon standing. After flash chromatography (65% *n*-hexane/35% ethyl acetate), 0.29 g (65%) of a white solid (**13a**) with mp 106–108 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.34. IR (CCl_4) ν: 3446, 3402, 2966, 2929, 1745, 1686, 1637 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 18H), 1.59 (s, 12H), 2.62 (s, 4H), 5.94 (bs, 2H). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.6, 29.7, 51.1, 82.2, 170.6, 171.9. MS: *m*/*z* 401, 385, 345, 301, 242, 228, 215, 187, 160, 142, 114, 101, 86, 69, 59, 58, 57, 41. Anal. Calcd for $C_{20}H_{36}N_2O_6$: C, 59.98; H, 9.06; N, 6.99. Found: C, 60.03; H, 9.08; N, 6.90.

4.1.28. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) and succinic acid. Di[2-methyl-1-(1-adamantyl)propanamido-2-]succinate (13b). To a solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**) (0.48 g, 0.002 mol) in 15 mL of THF at 0 °C, succinic acid (0.12 g, 0.001 mol) was added. The solution stirred for 7.5 h. THF was removed under reduced pressure. The residue was dissolved in methylene chloride (30 mL) and washed with 5% $NaHCO_3$ (15 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude di[2-methyl-1-(1-adamantyl)propanamido-2]succinate (**13b**) (68.5%). After washing with hot *n*-heptane and ethyl acetate, a white solid with mp 216–218 °C was obtained. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.34. IR (CCl_4) ν: 3420, 2900, 2838, 1735, 1678 cm^{-1}. (KBr) ν: 3390, 2900, 2840, 1730, 1663 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.55 (s, 12H), 1.64 (s, 12H), 1.97 (s, 12H), 2.04 (s, 6H), 2.58 (s, 4H), and 5.76 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 24.7, 29.6, 29.8, 36.5, 41.4, 51.9, 82.2, 170.7, 171.8. Anal. Calcd for $C_{32}H_{48}N_2O_6$: C, 69.04; H, 8.69; N, 5.03. Found: C, 68.90; H, 8.80; N, 5.15.

4.1.29. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone with succinic acid. Di[3,3-dimethyl-1-(1-adamantyl)butanamido-2-]succinate (13c). To a solution of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**) (1.63 g, 0.0066 mol) in 20 mL of dioxane succinic acid (0.35 g, 0.003 mol) was added. The solution was refluxed for 10 h. Dioxane was removed under reduced pressure and the residue was taken up into 25 mL of ethyl acetate and washed with 5% $NaHCO_3$ (20 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford 0.81 g (44%) of crude **13c** which was recrystallized twice from isopropyl alcohol (17 and 11 mL) to give 0.22 g (12.0%) of a white solid (**13c**) with mp 244–246 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.58. IR (CCl_4) ν: 3420, 2900, 2840, 1735, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.7 and 2.0 (s, 30H), 2.65 (s, 4H), and 4.65 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.1, 29.6, 34.1, 36.5, 41.6, 52.2, 81.8, 167.0, 171.3. High resolution MS: *m*/*z* 612, 556, 500, 435, 379, 347, 321, 264, 209, 135 (base peak), 107, 79, 57. Anal. Calcd for $C_{36}H_{56}N_2O_6$: C, 70.55; H, 9.21; N, 4.57. Found: C, 70.34; H, 9.27; N, 4.39.

4.1.30. Reaction of 1,3-di-*tert*-butylaziridinone with succinic acid. Di(3,3-dimethyl-1-*tert*-butylbutanamido-2-)succinate (13d). To a solution of 1,3-di-*tert*-butylaziridinone (**5d**) (2.99 g, 0.0177 mol) in 30 mL of THF, succinic acid (0.95 g, 0.008 mol) was added. The solution was refluxed for 6 h. Dioxane was removed under reduced pressure and the residue was taken up into 40 mL of ethyl acetate and washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford 1.89 g (51.8%) of crude **13d** which was recrystallized from 12 mL of hexane/ethyl acetate. It was filtered and the filtrate was evaporated to give 1.35 g of a sticky solid which was recrystallized twice from *n*-heptane to give 0.89 g (24.4%) of solid **13d** with mp 156–157 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3443, 2967, 2876, 1746, 1686 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.32 (s,18H), 2.7 (s, 4H), 4.6 (s, 2H), and 5.65 (s, 2H).

4.2. Passerini reactions

4.2.1. Passerini reaction between acetic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-acetoxy-2-methylpropanamide (4a). To a solution of acetic acid (1.80 g, 0.03 mol) in acetone (10 mL), *tert*-butyl isonitrile (2.49 g, 0.03 mol) was added. The solution was seeded with *p*-toluene sulfonic acid and sat overnight. The excess acetone was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate removed under reduced pressure to afford crude **4a** (3.03 g, 75.2%). After recrystallization from 10 mL *n*-heptane, a white solid (2.66 g, 66%) with mp 78–79 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.42. IR (CCl_4) ν: 3430, 2955, 1739, 1680, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.55 (s, 6H), 2.02 (s, 3H), and 5.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 22.1, 24.4, 51.1, 81.8, 169.2, 172.2. MS: *m*/*z* 201, 186, 158, 144, 129, 115, 102, 101, 88, 86, 61, 59, 58, 57, 43 (base peak). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.76; H, 9.53; N, 6.96.

4.2.2. Passerini reaction between pivalic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4b). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol), pivalic acid (2.04 g, 0.02 mol), and a catalytic amount of *p*-toluene sulfonic acid in 10 mL of acetone was stirred overnight at room temperature. The excess acetone was removed under reduced pressure and the remaining residue was dissolved in 20 mL of methylene chloride. This solution was washed with 5% $NaHCO_3$ (20 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4b** (2.20 g, 45.2%), a light yellow oil which crystallized upon standing. After recrystallization from 3.5 mL of *n*-heptane, a white solid with mp 50–51 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.40. IR (CCl_4) ν: 3430, 2960, 1730, 1680, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (s, 9H), 1.31 (s, 9H), 1.55 (s, 6H), 5.82 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.1, 28.6, 39.1, 50.8, 81.6, 172.4, 176.3. MS: *m*/*z* 243, 228, 186, 185, 171, 158, 144, 114, 103, 102, 86, 85, 59, 58, 57 (base peak), 41. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.35; N, 5.76. Found: C, 64.34; H, 10.48; N, 5.76.

4.2.3. Passerini reaction between benzoic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-benzoyloxy-2-methylpropanamide (4c). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol), benzoic acid (2.44 g, 0.02 mol), and a catalytic amount of *p*-toluene sulfonic acid in 10 mL of acetone was stirred overnight at room temperature. The excess acetone was removed under reduced pressure and the remaining residue was dissolved in 30 mL of ethyl acetate. This solution was washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford crude **4c** (5.27 g, 100%). After recrystallization from 5 mL of carbon tetrachloride, a white solid (1.63 g, 30.9%) with mp 88–89 °C was obtained. The mother liquor was evaporated to yield 2.40 g (45.5%) of a nearly pure second crop with mp 80–84 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3435, 3050, 2955, 1722, 1680, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.72 (s, 6H), 5.89 (s, 1H), 7.44 (t, 2H, *J*=7.7 Hz), 7.56 (t, 1H, *J*=7.5 Hz), 7.97 (d, 2H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 24.7, 28.8, 51.2, 82.5, 128.7, 129.6, 130.7, 133.4, 164.9, and 172.3. MS: *m*/*z* 263, 205, 191, 164, 146, 123, 105 (base peak), 77, 59, 57. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.37; H, 7.98; N, 5.27.

4.2.4. Passerini reaction between *trans*-cinnamic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4d). To a solution of *trans*-cinnamic acid (1.00 g, 0.00675 mol) in an excess amount of acetone (10 mL), *tert*-butyl isonitrile (0.561 g, 0.00675 mol) dissolved in 2 mL of acetone was added dropwise at room temperature. The reaction mixture was stirred for 6 days. The excess acetone and unreacted *tert*-butylisonitrile were removed under reduced pressure. The residue was dissolved in 30 mL of methylene chloride, washed with 2×30 mL of 5% $NaHCO_3$, 3×50 mL of distilled water, the organic layer dried with Na_2SO_4, and the methylene chloride was removed under pressure to yield 1.06 g (54.3%) of **4d**, mp 96–98 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4): 3446, 3085, 3064, 3030, 2950, 1720, 1693, 1635. ^1H NMR ($CDCl_3$): δ 1.37 (s, 9H), 1.68 (s, 6H), 5.86 (bs, 1H), 6.42 (d, *J*=16.0 Hz, 1H), 7.40–7.53 (m, 5H), 7.67 (d, *J*=16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.7, 51.0, 81.9, 118.3, 128.2, 129.0, 130.5, 134.2, 145.4, 165.1, 172.2. MS: *m*/*z* 231, 217, 190, 175, 172, 145, 131 (base peak), 103, 77, 59, 57, 51, 41.

4.2.5. Passerini reaction between trifluoroacetic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-methyl-2-trifluoroacetoxypropanamide (4e). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 5 mL of acetone was added dropwise to a solution of trifluoroacetic acid (3.42 g, 0.03 mol) in 10 mL of acetone at −10 °C over a period of 10 min. The ice-bath was then removed and the solution stirred at rt for 2 days. Excess acetone was evaporated under reduced pressure to yield 6.36 g of a light yellow oil which was taken up into 30 mL of ethyl acetate and washed with 30 mL of 5% $NaHCO_3$, 2×20 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 3.30 g (64.7%) of a light yellow oil which solidified after 3 days. It

was purified by vacuum sublimation (40–50 °C at 11 mm) to give 2.4 g (47%) of a white solid **4e**, mp 45–46 °C. TLC (90% *n*-hexane/10% isopropyl alcohol) R_f=0.45. IR (CCl_4) ν: 3454, 2970, 1793, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.70 (s, 6H), 5.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.7, 28.5, 51.5, 87.0, 114.3 (q, J=286.5 Hz), 155.0 (q, J=42.0 Hz), 169.9. MS: *m/z* 255, 240, 184, 155, 126, 114, 98, 86, 69, 57 (base peak), **41**. Anal. Calcd for $C_{10}H_{16}F_3NO_3$: C, 47.06; H, 6.32; N, 5.49. Found: C, 47.32; H, 6.51; N, 5.57.

4.2.6. Passerini reaction between acetic acid, acetone and adamantyl isonitrile. *N*-(1-Adamantyl)-2-acetoxy-2-methylpropanamide (4f). To a solution of acetic acid (0.405 g, 0.00675 mol) in an excess amount of acetone (10 mL), adamantyl isonitrile (1.09 g, 0.00675 mol) dissolved in 10 mL of acetone was added dropwise at room temperature. The reaction mixture was stirred for 5 days. The excess acetone was removed under reduced pressure. The residue was dissolved in 30 mL of methylene chloride, washed with 2×30 mL of 5% $NaHCO_3$, 3×50 mL of distilled water, the organic layer dried with Na_2SO_4, and the methylene chloride was removed under reduced pressure to yield 0.93 g (49.5%) of pure **4f**, mp 154–156. TLC (90% ethyl acetate/10% hexane) R_f=0.20. IR (CCl_4): 3403, 2920, 2854, 1750, 1688. ^1H NMR ($CDCl_3$): δ 1.59 (s, 6H), 1.69 (s, 6H), 2.00 (s, 6H), 2.07 (s, 6H), 5.67 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 22.0, 24.3, 29.5, 36.4, 41.4, 51.6, 81.7, 169.1, 171.9. MS: *m/z* 279, 236, 222, 219, 178, 176, 150, 135 (base peak), 102, 93, 79, 59, 43, 41.

4.2.7. Passerini reaction between pivalic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4g). To a solution of pivalic acid (0.633 g, 0.0062 mol) in an excess amount of acetone (20 mL), adamantyl isonitrile (1.00 g, 0.0062 mol) dissolved in 10 mL of acetone was added dropwise at room temperature over a period of 10 min. A catalytic amount of *p*-toluenesulfonic acid was added and the reaction was stirred for 7 days. The excess acetone was removed under reduced pressure. The residue was dissolved in 50 mL of methylene chloride, washed with 4×30 mL of 5% $NaHCO_3$, 3×30 mL of distilled water, dried with Na_2SO_4, and the methylene chloride was removed under reduced pressure to yield 1.14 g of a yellow solid. It was flash chromatographed (92.5% *n*-hexane/7.5% ethyl acetate) to give a white solid (**4g**) 0.57 g (28.6%), mp 63–65 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.32. IR (CCl_4) ν: 3438, 2910, 2852, 1739, 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (s, 9H), 1.59 (s, 6H), 1.69 (s, 6H), 1.99 (s, 6H), 2.08 (s, 3H), 5.75 (bs, 1H, exchangeable in D_2O). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.2, 29.5, 36.4, 39.1, 41.5, 51.4, 81.6, 172.2, 176.3. MS: *m/z* 321, 306, 263, 236, 219, 220, 192, 163, 150, 144, 135 (base peak), 107, 103, 93, 85, 79, 67, 59, 57, 41.

4.2.8. Passerini reaction between benzoic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-benzoyloxy-2-methylpropanamide (4h). To a solution of 0.460 g (0.00377 mol) benzoic acid in an excess of acetone (3 mL), 0.600 g (0.00372 mol) of adamantyl isonitrile dissolved in 2 mL of acetone was added dropwise at room temperature. The reaction mixture was stirred for 4 days. The excess acetone was removed under reduced pressure and the residue was dissolved in 30 mL of ethyl acetate, washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×20 mL), dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford 0.87 g (68.5%) of a white solid. It was flash chromatographed (90% *n*-hexane/10% ethyl acetate) to give 0.41 g (32.3%) of a white solid (**4h**), mp 101–103 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.24. IR (CCl_4): ν=3441, 2910, 2852, 1730, 1686. ^1H NMR ($CDCl_3$): δ 1.68 (s, 6H), 1.73 (s, 6H), 2.02 (s, 6H), 2.08 (s, 3H), 5.78 (bs, 1H, exchangeable in D_2O), 7.47 (t, 2H, J=7.0 Hz, 8.0 Hz), 7.59 (t, 1H, J=7.0 Hz), 8.00 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 24.6, 29.5, 36.4, 41.5, 51.7, 82.3, 128.5, 129.5, 130.7, 133.2, 164.8, 171.9. MS: *m/z* 341, 283, 240, 219, 193, 192, 191, 164, 135 (base peak), 105, 77, 59.

4.2.9. Passerini reaction between *trans*-cinnamic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4i). To a solution of *trans*-cinnamic acid (0.919 g, 0.0062 mol) in an excess amount of acetone (25 mL), adamantyl isonitrile (1.00 g, 0.0062 mol) in 25 mL of acetone was added dropwise over a period of 10 min at room temperature. A catalytic amount of *p*-toluenesulfonic acid was added and the reaction mixture was stirred for 7 days. The excess acetone was removed under reduced pressure and the residue was dissolved in 90 mL of methylene chloride, washed with 3×40 mL of 5% $NaHCO_3$, 2×30 mL of distilled water. The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to yield 1.36 g of crude **4i**. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.52 g (22.8%) of a white solid (**4i**) with mp 124–125 °C was obtained. 0.30 g of pure unreacted adamantyl isonitrile was also recovered. TLC (85% *n*-hexane/15% ethyl acetate) R_f=0.39. IR (CCl_4) ν: 3438, 3064, 3029, 2910, 2851, 1722, 1686, 1637 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.68 (s, 12H), 2.03 (s, 6H), 2.08 (s, 3H), 5.74 (bs, 1H, exchangeable in D_2O), 6.42 (d, 1H, J=16.0 Hz), 7.40 (s, 3H), 7.53 (s, 2H), 7.68 (d, 1H, J=16.0 Hz). ^{13}C NMR ($CDCl_3$): δ 25.0, 29.8, 36.7, 41.8, 52.0, 82.2, 118.7, 128.5, 129.3, 130.9, 134.6, 145.7, 165.5, 172.3. MS: *m/z* 367, 309, 238, 219, 190, 175, 150, 145, 135 (base peak), 131, 107, 103, 93, 91, 79, 77, 59, 41.

4.2.10. Passerini reaction between trifluoroacetic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-methyl-2-trifluoroacetoxypropanamide (4j). Dropwise, a solution of adamantyl isonitrile (1.61 g, 0.01 mL) in 20 mL of methylene chloride was added to a solution of trifluoroacetic acid (1.14 g, 0.01 mol) in 5 mL of acetone. The solution was stirred overnight. Methylene chloride and excess acetone was removed under reduced pressure. The residue was taken up in methylene chloride, washed with 5% $NaHCO_3$ (40 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4, and the methylene chloride was removed under reduced pressure to afford **4j** (2.51 g, 75.4%). An analytical sample was obtained by vacuum sublimation (50–60 °C at 0.5 mm), mp 98–99 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.42. IR (CCl_4) ν: 3445, 2911, 2852, 1792, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.67 (t, 6H, J=2.7 Hz), 1.70 (s, 6H), 1.97 (d, 6H, J=2.7 Hz), 2.08 (s, 3H), 5.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 29.6,

36.4, 41.5, 52.2, 87.0, 114.4 (q, J=287.0 Hz), 155.4 (q, J=42.4 Hz) 169.7. MS: m/z 333, 219, 192, 176, 155, 135 (base peak), 107, 93, 69, 41. Anal. Calcd for $C_{16}H_{22}F_3NO_3$: C, 57.65; H, 6.65; N, 4.20. Found: C, 57.43; H, 6.67; N, 4.28.

4.2.11. Passerini reaction between acetic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-acetoxy-3,3-dimethylbutanamide (4k). Dropwise, at 0 °C, a solution of adamantyl isonitrile (1.61 g, 0.01 mol) in 15 mL of THF was added to a solution of acetic acid (0.600 g, 0.01 mol) and pivalaldehyde (0.861 g, 0.01 mol) in 20 mL of THF. After the addition of the isonitrile, the ice bath was removed and the solution was stirred for 5 days at rt. THF was removed under reduced pressure and the resulting residue was dissolved in 35 mL of ethyl acetate. The solution was washed with 5% $NaHCO_3$ (15 mL) and distilled water (15 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford crude **4k** (2.74 g, 89.3%). Purification by flash chromatography (90% *n*-hexane/10% ethyl acetate) yielded pure **4k** (1.76 g, 57.3%), mp 140–141 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.25. IR (CCl_4) ν: 3437, 2911, 2852, 1752, 1691, 1513 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (s, 9H), 1.64 (m, 6H), 1.97 (m, 6H), 2.04 (s, 3H), 2.11 (s, 3H), 4.63 (s, 1H), and 5.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.7, 29.8, 32.0, 34.4, 36.7, 42.0, 52.3, 81.5, 167.6, 170.1. MS: m/z 307, 251, 232, 207, 178, 150, 135 (base peak), 120, 93, 79, 57, 43. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.39; H, 9.55; N, 4.51.

4.2.12. Passerini reaction between pivalic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4l). Dropwise, at 0 °C, a solution of adamantyl isonitrile (0.806 g, 0.005 mol) in 10 mL of THF was added to a solution of pivalic acid (0.511 g, 0.005 mol) and pivalaldehyde (0.431 g, 0.005 mol) in 10 mL of THF. After the addition of the isonitrile, the ice bath was removed and the solution was stirred for 6 days at rt. THF was removed under reduced pressure and the resulting residue was dissolved in 15 mL of methylene chloride. The solution was washed with 5% $NaHCO_3$ (15 mL) and distilled water (2×10 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4l** (1.30 g, 74.3%). After recrystallization from 8 mL of *n*-hexane, 0.95 g (54.4%) of a white solid with mp 88–89 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.63. IR (CCl_4) ν: 3437, 2910, 1743, 1689, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.02 (s, 9H), 1.26 (s, 9H), 1.67 (s, 6H), 1.98 (s, 6H), 2.07 (s, 3H), 4.68 (s, 1H), 5.48 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 27.2, 29.4, 34.2, 36.3, 38.9, 41.6, 51.8, 80.6, 167.6, 176.5. MS: m/z 349, 293, 249, 232, 208, 172, 163, 135 (base peak), 117, 85, 70, 57. Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.28; H, 10.15; N, 3.93.

4.2.13. Passerini reaction between benzoic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-benzoyloxy-3,3-dimethylbutanamide (4m). Adamantyl isonitrile (1.61 g, 0.01 mol) was added to a solution of benzoic acid (1.22 g, 0.01 mol) and pivalaldehyde (0.861 g, 0.01 mol) in 20 mL of CH_2Cl_2 at rt and stirred for 2 days. The solution was washed with 5% $NaHCO_3$ (25 mL) and distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and the CH_2Cl_2 was removed under reduced pressure to afford crude **4m** (2.80 g, 75.7%). Recrystallization from *n*-heptane/ethyl acetate (20 mL/3 mL) yielded 2.50 g (67.6%) of pure **4m**, mp 166–168 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.67. IR (CCl_4) ν: 3436, 2911, 2852, 1734, 1688, 1513 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.14 (s, 9H), 1.66 (s, 6H), 1.99 (s, 6H), 2.06 (s, 3H), 4.93 (s, 1H), 5.55 (s, 1H), 7.48 (m, 2H), 7.63 (m, 1H), 8.10 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.4, 34.4, 36.3, 41.6, 52.0, 81.5, 128.7, 133.4, 165.2, 167.2. MS: m/z 369, 313, 283, 269, 240, 208, 192, 177, 135 (base peak), 105, 79, 77, 70. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.66; H, 8.49; N, 3.77.

4.2.14. Passerini reaction between *trans*-cinnamic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4n). Dropwise, at 0 °C, a solution of adamantyl isonitrile (1.61 g, 0.01 mol) in 20 mL of THF was added to a solution of *trans*-cinnamic acid (1.48 g, 0.01 mol) and pivalaldehyde (0.861 g, 0.01 mol) in 20 mL of THF. After the addition of the isonitrile, the ice bath was removed and the solution was stirred for 6 days. THF was removed under reduced pressure and the resulting residue was dissolved in 25 mL of methylene chloride. The solution was washed with 5% $NaHCO_3$ (15 mL) and distilled water (2×10 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4n** (3.54 g, 89.4%). After recrystallization from 22 mL of *n*-hexane, 2.97 g (75%) of a white solid with mp 122–123 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3429, 3060, 2910, 1732, 1687, 1638, 1549, 1512 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.67 (s, 6H), 2.00 (s, 6H), 2.07 (s, 3H), 4.82 (s, 1H), 5.54 (bs, 1H), 6.50 (d, J=16.0 Hz, 1H), 7.44 (m, 3H), 7.55 (dd, J=3.7 Hz, 2H), 7.76 (d, J=16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 29.4, 34.2, 36.3, 41.6, 52.0, 81.1, 117.2, 128.3, 129.1, 130.7, 134.1, 146.0, 165.7, 167.3. MS (ES): m/z 417.9 (M+23), 395.8, 380.9, 313.1, 245.0. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.75; H, 8.40; N, 3.52.

4.2.15. Passerini reaction between trifluoroacetic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-3,3-dimethyl-2-trifluoroacetoxybutanamide (4o). A solution of pivaldehyde (0.43 g, 0.005 mol) in 2 mL of methylene chloride was added to a solution of trifuoroacetic acid (0.57 g, 0.005 mol) in 10 mL of methylene chloride dropwise. A solution of adamantyl isonitrile (0.805 g, 0.005 mol) was added dropwise, to the mixture at −10 °C. The solution stirred for 4 days and the mixture was filtered. It was washed with 30 mL of 5% $NaHCO_3$, 2×20 mL H_2O, dried with Na_2SO_4, and evaporated under reduced pressure to give an oil (1.42 g, 79%) which solidified upon standing. Crude **4o** was recrystallized from 2 mL *n*-heptane to give 1.26 g (69.6%) of pure **4o**, mp 108–111 °C. TLC (90% *n*-hexane/10% ethyl acetate): R_f=0.78. IR (CCl_4) ν: 3437, 2912, 1796, 1693 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.96 and 1.04 (s, 9H), 1.66 (s, 12H), 1.99 (s, 3H), 4.82 (s, 1H), 5.46 (s, 1H, exchanges in TFD). ^{13}C NMR ($CDCl_3$) δ 26.1, 29.5, 34.5,

36.4, 41.6, 52.8, 84.5, 115.0 (q, J=287.0 Hz), 156.4 (q, J=43.0 Hz), 165.4. MS: m/z 361, 343, 305, 292, 268, 232, 208, 193, 176, 135 (base peak), 107, 79, 69, 41. Anal. Calcd for $C_{18}H_{26}F_3NO_3$: C, 59.82; H, 7.25; N, 3.88. Found: C, 59.58; H, 7.30; N, 3.90.

4.2.16. Passerini reaction between acetic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-acetoxy-3,3-dimethylbutanamide (4p). Dropwise, at −15 °C, a solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 10 mL of methylene chloride was added dropwise to a solution of acetic acid (1.20 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 25 mL of methylene chloride over a period of 5 min. After the addition, the ice-bath was removed and the solution stirred overnight at rt. The reaction mixture was washed with 5% $NaHCO_3$ (2×20 mL) and distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4p** (2.75 g, 60.0%). After recrystallization from 3 mL of *n*-hexane, a white solid (1.92 g, 41.9%) with mp 62–63 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.44. IR (CCl_4) ν: 3440, 2965, 1738, 1683, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (s, 9H), 2.11 (s, 3H), 4.64 (s, 1H), 5.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 26.4, 28.8, 34.2, 51.4, 81.2, 167.7, 169.9. MS: m/z 229, 214, 186, 173, 157, 131, 129, 87, 75, 57 (base peak), 43. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.88; H, 10.04; N, 6.11. Found: C, 62.78; H, 10.02; N, 6.21.

4.2.17. Passerini reaction between pivalic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4q). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 5 mL of methylene chloride was added dropwise to a solution of pivalic acid (2.04 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 20 mL of methylene chloride. The solution stirred overnight. The reaction mixture was washed with 5% $NaHCO_3$ (2×25 mL) and distilled water (25 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford 4.39 g (81%) of pure **4q**, mp 87–88 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.48. IR (CCl_4) ν: 3427, 3370, 2955, 2860, 1735, 1667, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.99 (s, 9H), 1.24 (s, 9H), 1.30 (s, 9H), 4.66 (s, 1H), and 5.59 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.5, 27.3, 28.8, 34.4, 39.0, 51.3, 80.8, 167.8, and 176.7. MS: m/z 271, 256, 215, 199, 172, 157, 143, 130, 102, 85, 71, 57 (base peak), 41. Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found: C, 66.26; H, 10.67; N, 5.24.

4.2.18. Passerini reaction between benzoic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-benzoyloxy-3,3-dimethylbutanamide (4r). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 10 mL of methylene chloride was added to a solution of benzoic acid (2.44 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 25 mL of methylene chloride dropwise at −15 °C. After the addition, the ice-bath was removed and the solution stirred overnight at rt. The reaction mixture was washed with 5% $NaHCO_3$ (2×15 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4r** (2.86 g, 49.1%). After recrystallization from 15 mL of carbon tetrachloride, a white solid (1.88 g, 32.3%) with mp 128–129 °C was obtained. The mother liquor was evaporated to yield an additional 0.742 g (12.7%) of a solid with mp 126–127 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.68. IR (CCl_4) ν: 3440, 3380, 3060, 2965, 2870, 1720, 1685, 1598, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.32 (s, 9H), 4.91 (s, 1H), 5.70 (s, 1H), 7.47 (m, 2H), 7.59 (m, 1H), 8.09 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.6, 51.4, 81.7, 128.8, 129.8, 133.6, 165.4, 167.6. MS: m/z 291, 276, 253, 235, 219, 192, 177, 143, 130, 105 (base peak), 87, 77, 70, 57, 41. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.27; H, 8.64; N, 4.74.

4.2.19. Passerini reaction between *trans*-cinnamic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4s). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 10 mL of methylene chloride was added dropwise to a solution of *trans*-cinnamic acid (2.96 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 30 mL of methylene chloride at −15 °C over a period of 10 min. The ice-bath was then removed and the solution stirred overnight at rt. The reaction mixture was washed with 5% $NaHCO_3$ (2×20 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to yield crude **4s** (4.89 g, 77.1%). After recrystallization from *n*-heptane/methylene chloride (10 mL/2 mL), a white solid (2.08 g, 32.8%) with mp 97–98 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.46. IR (CCl_4) ν: 3440, 2960, 2868, 1715, 1680, 1633, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.33 (s, 9H), 4.81 (s, 1H), 5.70 (s, 1H), 6.50 (d, 1H, J=16.0 Hz), 7.38 (m, 3H), 7.54 (m, 2H), 7.74 (d, 1H, J=16.0 Hz). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.4, 51.4, 81.2, 117.3, 128.4, 129.1, 130.8, 134.2, 146.2, 165.8, 167.7. MS: m/z 317, 261, 245, 231, 218, 175, 162, 149, 131 (base peak), 103, 77, 70, 57, 41. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.92; H, 8.52; N, 4.42. Found: C, 71.77; H, 8.47; N, 4.38.

4.2.20. Passerini reaction between trifluoroacetic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-3,3-dimethyl-2-trifluoroacetoxybutanamide (4t). A solution of *tert*-butyl isonitrile (1.25 g, 0.015 mol) in 15 mL of CH_2Cl_2 was added dropwise to a solution of pivaladehyde (1.29 g, 0.015 mol) and trifluoroacetic acid (1.71 g, 0.015 mol) in 30 mL of CH_2Cl_2 at 0 °C over a period of 15 min. The ice-bath was then removed and the solution stirred at rt for 4 days. The solvents were evaporated under reduced pressure to yield 3.92 g of a white solid which was recrystallized from 20 mL of hot *n*-heptane to give 3.06 g (72%) of a white solid (**4t**), mp 120–121 °C. IR (CCl_4) ν: 3446, 2968, 1796, 1693 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.37 (s, 9H), 4.86 (s, 1H), 5.56 (bs, 1H, exchangeable in TFD). ^{13}C NMR ($CDCl_3$): δ 26.4, 29.0, 34.7, 52.2, 84.9, 114.9 (q, J=285.7 Hz), 156.6 (q, J=42.7 Hz), 165.6. MS: m/z 283, 268, 227, 214, 183, 171, 154, 130, 114, 84, 74, 69, 58, 57, 41. Anal. Calcd for $C_{12}H_{20}F_3NO_3$: C, 50.88; H, 7.12; N, 4.94. Found: C, 51.16; H, 7.18; N, 4.97.

4.2.21. Passerini reaction between maleic acid, acetone, and *tert*-butyl isonitrile. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (12a). To a solution of maleic acid (4.06 g, 0.035 mol) in acetone (70 mL), *tert*-butyl isonitrile (5.82 g, 0.07 mol) was added in one portion at rt. The

solution was seeded with a few crystals of *p*-toluene sulfonic acid and stirred for 3 days. It was then evaporated to dryness under reduced pressure and the residue taken up into 75 mL of CH_2Cl_2 and washed with 3×50 mL of 5% $NaHCO_3$ and 70 mL of H_2O, dried with Na_2SO_4, filtered and evaporated under reduced pressure to give 5.20 g of a brown solid. It was recrystallized from 40 mL of hot *n*-heptane and 1 mL of acetonitrile (to which 0.3 g of activated charcoal was added) to give 3.70 g of a yellow solid, mp 100–120 °C. After flash chromatography (60% *n*-hexane/40% ethyl acetate), 3.23 g (23%) of a white solid, pure **12a** with mp 148–149 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.41. IR (CCl_4) ν: 3448, 3401, 2973, 1731, 1687, 1642 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (s, 18H), 1.61 (s, 12H), 6.26 (s, 2H), 6.30 (bs, 2H, exchangeable in TFD). ^{13}C NMR ($CDCl_3$): δ 24.6, 28.6, 51.2, 83.2, 130.2, 163.4, 171.3. MS: *m/z* 398, 383, 343, 326, 299, 256, 228, 160, 143 (base peak), 114, 87, 58, 57, 41. Anal. Calcd for $C_{20}H_{34}N_2O_6$: C, 60.27; H, 8.60; N, 7.03. Found: C, 60.28; H, 8.87; N, 7.08.

4.2.22. Passerini reaction between maleic acid, acetone, and adamantyl isonitrile. Di[2-methyl-*N*-(1-adamantyl)-propanamido-2-]maleate (12b). To a solution of maleic acid (0.360 g, 0.0031 mol) in acetone (20 mL), adamantyl isonitrile (1.00 g, 0.0062 mol) in 10 mL of acetone was added dropwise over a period of 10 min at rt. The solution was seeded with a few crystals of *p*-toluene sulfonic acid and stirred for 5 days. It was then evaporated to dryness under reduced pressure and the residue taken up into 60 mL of CH_2Cl_2 and washed with 3×25 mL of 5% $NaHCO_3$ and 2×25 mL of H_2O, dried with Na_2SO_4, filtered and evaporated under reduced pressure to give a yellow oil that was flash chromatographed (75% *n*-hexane/25% ethyl acetate) to give 0.40 g (23.3%) of a white solid (**12b**) with mp 205–206 °C was obtained. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.36. IR (CCl_4) ν: 3439, 3394, 2910, 2852, 1732, 1684, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.61 (s, 12H), 1.68 (s, 12H), 2.02 (s, 12H), 2.07 (s, 6H), 6.16 (s, 2H, exchangeable in D_2O), 6.24 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.7, 29.5, 36.4, 41.3, 52.0, 83.1, 130.2, 163.3, 171.1.

4.2.23. Passerini reaction between succinic acid, acetone, and *tert*-butyl isonitrile. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)succinate (13a). To a solution of succinic acid (2.84 g, 0.002 mol) in acetone (100 mL), *tert*-butyl isonitrile (4.00 g, 0.004 mol) was added in one portion at rt. The solution was seeded with a few crystals of *p*-toluene sulfonic acid and stirred for 3 days. It was then evaporated to dryness under reduced pressure and the residue taken up into 75 mL of CH_2Cl_2 and washed with 3×50 mL of 5% $NaHCO_3$ and 70 mL of H_2O, dried with Na_2SO_4, filtered and evaporated under reduced pressure to give 1.60 g of a white solid mp 88–97 °C. After flash chromatography (60% *n*-hexane/40% ethyl acetate), 1.35 g (14%) of a white solid (**13a**) mp 106–108 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.46. ^1H NMR ($CDCl_3$): δ 1.35 (s, 18H), 1.59 (s, 12H), 2.62 (s, 4H), 5.94 (bs, 2H). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.6, 29.7, 51.1, 82.2, 170.6, 171.9. MS: *m/z* 401, 385, 345, 328, 301, 260, 242, 228, 215, 187, 160, 142, 114, 101, 86, 69, 59, 58, 57, 41. Anal. Calcd for $C_{20}H_{36}N_2O_6$: C, 59.98; H, 9.06; N, 6.99. Found: C, 60.14; H, 9.10; N, 6.97.

4.2.24. Passerini reaction between succinic acid, acetone, and adamantyl isonitrile. Di[2-methyl-1-(1-adamantyl)-propanamido-2-]succinate (13b). To a solution of succinic acid (1.18 g, 0.01 mol) in acetone (20 mL) and 5 mL of THF, adamantylisonitrile (3.23 g, 0.02 mol) was added at rt. The solution was seeded with *p*-toluene sulfonic acid and stirred for 5 days. The excess acetone and THF were removed under reduced pressure. The residue was dissolved in methylene chloride (50 mL) and washed with 5% $NaHCO_3$ (20 mL) and distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and methylene chloride removed under reduced pressure to afford crude product **13b** (5.22 g, 93.7%). It was recrystallized twice, first from hot carbon tetrachloride/ acetonitrile (20 mL/ 10 mL) and then from hot *n*-heptane/acetonitrile (18 mL/ 27 mL) to give 1.28 g (23.0%) of a solid with mp 218–221 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3420, 2900, 2838, 1737, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.55 (s, 12H), 1.64 (s, 12H), 1.97 (s, 12H), 2.04 (s, 6H), 2.58 (s, 4H), 5.76 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 24.7, 29.6, 29.8, 36.5, 41.4, 51.9, 82.2, 170.7, 171.8.

4.2.25. Passerini reaction between succinic acid, pivalaldehyde, and adamantyl isonitrile. Di[3,3-dimethyl-1-(1-adamantyl)butanamido-2-]succinate (13c). To a solution of succinic acid (0.59 g, 0.005 mol) and pivalaldehyde (0.86 g, 0.01 mol) in methylene chloride (40 mL) and 10 mL of THF, adamantyl isonitrile (1.61 g, 0.01 mol) was added. The solution was stirred for 5 days. It was then evaporated to dryness under reduced pressure to give a residue which was taken up into 40 mL of methylene chloride. It was washed with 25 mL of 5% $NaHCO_3$, 2×25 mL of H_2O dried with Na_2SO_4 and evaporated under reduced pressure to afford 2.46 g (80.4%) of a dark oil which slowly crystallized. It was flash chromatographed (70% *n*-hexane/30% ethyl acetate) to yield 1.26 g (41.2%) of a solid (**13c**) with mp 243–245 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.58. IR (CCl_4) ν: 3420, 2900, 2840, 1735, 1670 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.7 and 2.0 (s, 30H), 2.65 (s, 4H), and 4.65 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.1, 29.6, 34.1, 36.5, 41.6, 52.2, 81.8, 167.0, 171.3. High resolution MS: *m/z* 612, 556, 500, 435, 379, 347, 321, 264, 209, 135 (base peak), 107, 79, 57. Anal. Calcd for $C_{36}H_{56}N_2O_6$: C, 70.55; H, 9.21; N, 4.57. Found: C, 70.73; H, 9.27; N, 4.60.

4.2.26. Passerini reaction between succinic acid, pivalaldehyde, and *tert*-butyl isonitrile. Di(3,3-dimethyl-*N*-*tert*-butylbutanamido-2-]succinate (13d). To a solution of succinic acid (2.36 g, 0.02 mol) and pivalaldehyde (3.44 g, 0.04 mol) in methylene chloride (55 mL), *tert*-butyl isonitrile (3.32 g, 0.04 mol) was added at 0 °C. It was seeded with a crystal of *p*-toluene sulfonic acid and stirred for 4 days at rt. It was washed with 40 mL of 5% $NaHCO_3$, 2×25 mL of H_2O, dried with Na_2SO_4 and evaporated under reduced pressure to afford 7.77 g (85.1%) of an oil which slowly crystallized. It was recrystallized twice from *n*-heptane/ethyl acetate to give 2.3 g (25.2%) of a solid (**13d**) with mp 161–162 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3443, 2967, 2872, 1744, 1687 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.32 (s,18H), 2.7 (s, 4H), 4.6 (s, 2H), and 5.65 (s, 2H). Anal. Calcd for $C_{24}H_{44}N_2O_6$: C, 63.13; H, 9.71; N, 6.13. Found: C, 63.22; H, 9.68; N, 6.27.

4.3. Reactions of α-lactams with maleic anhydride

4.3.1. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with maleic anhydride. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (12a). 1-*tert*-Butyl-3,3-dimethylaziridinone (**5a**) (1.41 g, 0.010 mol) was dissolved in 10 mL of chloroform, a solution of freshly sublimed, powdered maleic anhydride (0.98 g, 0.010 mol) in 10 mL of chloroform was added at 0 °C, and the reaction mixture was stirred at 0 °C for 20 h. After evaporation of the solvent on a rotary evaporator, the solid residue was chromatographed on neutral alumina, Woelm, activity grade one, further deactivated by the addition of water (3 mL of water/100 g of alumina) with benzene–methylene chloride as eluent, to afford 1.07 g (53%) of di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (**12a**), mp 150–151 °C. IR (CCl_4) ν: 3425, 3370, 1730, 1678, 1525 cm^{-1}. UV: λ_{max} (ethanol)= 200 nm, log ε=4.37. λ_{max} (ethanol) of dimethyl maleate= 192.5 nm, log ε=4.34.[37] ^1H NMR ($CDCl_3$) δ 1.39 (s, 18H), 1.65s, (12H), 4.80 (s, 1H), 6.39 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.6, 28.6, 51.2, 83.2, 130.2, 163.4, 171.3. MS: *m/z* 398, 383, 343, 326, 299, 256, 228, 160, 143 (base peak), 114, 87, 58, 57, 41. Anal. Calcd for $C_{20}H_{34}N_2O_6$: C, 60.27; H, 8.60; N, 7.03. Found: C, 60.18; H, 8.41; N, 7.16.

Using a relative ratio of 4 equiv. of α-lactam to 1 equiv. of maleic anhydride, and a reaction time of 48 h at room temperature, increased the isolated yield of **12a**, after chromatography, to 87%.

4.3.2. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with maleic anhydride. Di[2-methyl-*N*-(1-adamantyl)propanamido-2-]maleate (12b). A solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**) (1.15 g, 5.25 mmol) and freshly sublimed maleic anhydride (0.515 g, 5.25 mmol) in 25 mL of carbon tetrachloride was heated to 70 °C for 10 min. It was then washed with 2×25 mL of 2 N HCl, 2×25 mL of H_2O, dried with Na_2SO_4, filtered over Celite, and rotary evaporated to give 1.28 g of a purple solid, which was flash chromatographed (75% *n*-hexane/25% ethyl acetate) to give 0.25 g (17.1%) of di[2-methyl-*N*-(1-adamantyl)propanamido-2-]maleate (**12b**), mp 204–206 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.36. IR (CCl_4) ν: 3439, 3394, 2910, 2852, 1732, 1684, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.61 (s, 12H), 1.68 (s, 12H), 2.02 (s, 12H), 2.07 (s, 6H), 6.16 (s, 2H, exchangeable in D_2O), 6.24 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.7, 29.5, 36.4, 41.3, 52.0, 83.1, 130.2, 163.3, 171.1.

0.22 g (26%) of pure adamantyl isonitrile was also isolated from the reaction and approximately 51% of a purple dye remained on the column.

4.4. Reactions of α-lactams with mineral acids

4.4.1. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with hydrofluoric acid. *N*-(1-Adamantyl)-2-fluoro-2-methylpropanamide (4u). To a solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (0.737 g, 0.0034 mol) in 45 mL of benzene at 7 °C, 5 mL (0.175 mol) of HF/pyridine complex was added. The solution was stirred for 1.5 h, then washed with distilled water (2×25 mL), 2 N HCl (10 mL), and again with distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude *N*-(1-adamantyl)-2-fluoro-2-methylpropanamide (**4u**) (0.55 g, 67.6%). After column chromatography, pure **4u** was obtained (0.42 g, 51.6%), mp 42–44 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.65. IR (CCl_4) ν: 3420, 2960, 2900, 2840, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.51 (s, 6H), 1.65 (s, 6H), 1.98 (d, *J*=2.7 Hz, 6H), 2.05 (s, 3H), 6.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.1 (d, *J*=23.8 Hz), 29.6, 36.5, 41.6, 51.7, 96.3 (d, *J*=181.6 Hz), 172.3 (d, *J*=19.2 Hz). MS: *m/z* 239, 196, 182, 162, 135 (base peak), 120, 107, 93, 79, 61, 41. Anal. Calcd for $C_{14}H_{22}NOF$: C, 70.26; H, 9.27; N, 5.85. Found: C, 70.26; H, 9.29; N, 5.94.

4.4.2. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with aqueous hydrogenbromide. A solution of 9.3 mL (0.093 mol) of 48% (aq) HBr with 20 mL of distilled water was added to 1.21 g (0.0055 mol) of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**). The reaction mixture was stirred for 1 h at room temperature, then approximately 20 mL of liquid over a period of 1 h was distilled over into a receiving flask containing 0.736 g (0.0066 mol) of semicarbazide hydrochloride, 0.591 g (0.0072 mol) of sodium acetate, and 5 mL of distilled water, immersed in an ice/water bath. The receiving flask was then removed from the ice bath and stirred for an additional 45 min at room temperature. The reaction mixture was filtered on Büchner funnel and the solid washed with ice–cold water to afford 0.46 g (65.3%) of pure pivalaldehyde semicarbazone[38] with mp 188–191 °C (rep.[38] mp 191 °C). TLC (100% ethyl acetate) R_f=0.50. MS: *m/z* 143, 128, 111, 100, 86 (base peak), 84, 68, 57, 41.

The residue remaining in the distilling flask was washed with 15% Na_2CO_3 until the solution was basic. A solid precipitated and was collected on a Büchner funnel. It was dried and washed with 10 mL of ice cold ether and again filtered on a Büchner funnel to afford 0.69 g (95.0%) crude 1-adamantanamine. After recrystallization from acetone/methanol pure adamantanamine was obtained (mp 203–205 °C). TLC, IR, and MS were identical to an authentic sample (Aldrich) [TLC (100% ethanol) R_f=0.18. MS: *m/z* 151, 136, 108, 94 (base peak), 77, 57, 41].

4.4.3. Preparation of authentic pivalaldehyde semicarbazide. To a solution of pivalaldehyde (Lancaster, 0.86 g, 0.01 mol) in 35 mL of distilled water was added 1.22 g (0.011 mol) of semicarbazide hydrochloride and 0.984 g (0.012 mol) of sodium acetate. The solution was stirred for 1 h. The precipitate was collected on a Büchner funnel and washed with ice–cold water to afford 1.18 g (82.5%) of pure pivalaldehyde semicarbazone,[38] mp 191 °C (rep.[38] mp 191 °C). TLC (100% ethyl acetate) R_f=0.50. IR (CCl_4) ν: 3460, 3030, 2970, 1683 cm^{-1} (KBr) ν: 3460, 3300, 3180, 3040, 2940, 1690, 1645, 1625, 1600, 1500 cm^{-1}. MS: *m/z* 143, 128, 111, 100, 86 (base peak), 84, 68, 57, 41.

References and notes

1. Part of this work was presented at the 226th National Meeting of the American Chemical Society: New York, NY, 7–11

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2. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126–129.
3. Passerini, M. *Gazz. Chim. Ital.* **1924**, *54*, 529–540.
4. Passerini, M. *Gazz. Chim. Ital.* **1923**, *53*, 410–417.
5. (a) Ugi, I. *Angew. Chem.* **1962**, *74*, 9–22. also, (b) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 8–21.
6. Marquarding, D.; Gokel, G.; Hoffmann, P.; Ugi, I. The Passerini reaction and related reactions. In *Isonitrile chemistry*; Ugi, I., Ed.; Academic: New York, 1971; pp 133–143.
7. Ugi, I.; Lohberger, S.; Karl, R. In *The Passerini reaction and related reactions*; *Comprehensive organic synthesis*, Trost, B. M., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1084–1087.
8. Ugi, I.; Dömling, A.; Hörl, W. Multicomponent reactions in organic chemistry. *Endeavour* **1994**, *18*, 115–122.
9. Lengyel, I.; Sheehan, J. C. *Angew. Chem.* **1968**, *80*, 27–37, also *Angew. Chem., Int. Ed*. **1968**, *7*, 25–36.
10. Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 1356–1359.
11. Lengyel, I.; Mark, R. V.; Troise, C. A. *Synth. Commun.* **1971**, *1*, 153–160.
12. Sheehan, J. C.; Lengyel, I. *J. Org. Chem.* **1966**, *31*, 4244–4246.
13. Talaty, E. R.; Dupuy, A. E., Jr.; Utermohlen, C. M. *Chem. Commun.* **1971**, 16–17.
14. Yusoff, M. M.; Talaty, E. R. *Tetrahedron Lett.* **1996**, *48*, 8695–8696.
15. Shimadzu, M.; Endo, Y.; Shudo, K. *Heterocycles* **1997**, *45*, 735–744.
16. Talaty, E. R.; Yusoff, M. M. *Chem. Commun.* **1998**, 985–986.
17. Lengyel, I.; Cesare, V.; Chen, S.; Taldone, T. *Heterocycles* **2002**, *57*, 677–695.
18. Cesare, V.; Taldone, T.; Lengyel, I. *Heterocycles* **2002**, *57*, 1851–1868.
19. Sheehan, J. C.; Lengyel, I. *J. Am. Chem. Soc.* **1964**, *86*, 746.
20. Lengyel, I.; Uliss, D. B. *Chem. Commun.* **1968**, 1621–1622.
21. Lengyel, I.; Uliss, D. B.; Nafissi-V, M. M.; Sheehan, J. C. *Org. Mass Spectrom.* **1969**, *2*, 1239–1255.
22. Lengyel, I.; Uliss, D. B.; Mark, R. V. *J. Org. Chem.* **1970**, *35*, 4077–4084.
23. Sheehan, J. C.; Nafissi-V, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 1176–1178.
24. (a) Bott, K. *Angew. Chem.* **1968**, *80*, 970–971, also *Angew. Chem., Int. Ed*. **1968**, *7*, 894–895. (b) Bott, K. *Tetrahedron Lett.* **1968**, 3323–3326. (c) Bott, K. *Liebigs Ann. Chem.* **1972**, *755*, 58–66.
25. Kagen, H.; Lillien, I. *J. Org. Chem.* **1966**, *31*, 3728–3731.
26. Crandall, J. K.; Crawley, L. C. *J. Org. Chem.* **1974**, *39*, 489–491.
27. Although both an imino-oxirane (**8**) and an α-lactam (**5**) intermediate have been postulated in a Passerini-like reaction, no firm evidence has been provided: Saegusa, T.; Taka-ishi, N.; Fujii, H. *Tetrahedron* **1968**, *24*, 3795–3798.
28. (a) Stetter, H.; Mayska, P.; Wießner, U. *Neue Synthesen und Reaktionen in der Adamantan-Reihe, Forschungsbericht des Landes Nordrhein-Westfalen Nr. 3095*, Westdeutscher: Opladen, West Germany, 1982. (b) Quast, H.; Seiferling, B. *Tetrahedron Lett.* **1982**, *23*, 4681–4684.
29. Sheehan, J. C.; Beeson, J. H. *J. Am. Chem. Soc.* **1967**, *81*, 362–366.
30. Lengyel, I.; Mark, R. V. *Acta Chim. Acad. Sci. Hung.* **1974**, *81*, 475–479.
31. *CRC handbook of chemistry and physics*; 78th ed. Lide, D. R., Ed.; CRC: Boca Raton, New York, 19971998; pp 8-45–8-55.
32. (a) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604–637, see also pp 741–754; also, *Angew. Chem., Int. Ed*. **1963**, *2*, 565–598 and 633–645. (b) Huisgen, R. *Angew. Chem.* **1968**, *80*, 329–336, also, *Angew. Chem., Int. Ed.* **1968**, *7*, 321–328. (c) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291–2297, **1976**, *41*, 403–419.
33. Kakimoto, M.; Kajigaeski, S.; Kanemasa, S. *Chem. Lett.* **1976**, 47–48.
34. L'abbe, G.; Van Asch, A.; Toppet, S. *Bull. Soc. Chim. Belg.* **1978**, *87*, 11–12.
35. Scrimin, P.; D'Angeli, F.; Veronese, A. C.; Baioni, V. *Tetrahedron Lett.* **1983**, *24*, 4473–4476.
36. Scrimin, P.; D'Angeli, F.; Veronese, A. C. *Synthesis* **1982**, 586–587.
37. Sörensen, N. A. *Ann.* **1941**, *546*, 57–98.
38. Daniloff, S.; Venus-Danilova, E. *Ber. dtsch. chem. ges.* **1926**, *59*, 377–386.

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Synthesis of labelled dihydroartemisinic acid

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Abstract—[15-$^{13}C^{2}H_3$]-Dihydroartemisinic acid (**2a**), [15-$C^{2}H_3$]-dihydroartemisinic acid (**2b**) and [15-$^{13}CH_3$]-dihydroartemisinic acid (**2c**) have been obtained in good yield and high isotopic enrichment by a reconstructive synthesis from artemisinin. These labelled compounds were designed to be used in biosynthetic experiments to determine the origins of artemisinin and other sesquiterpene natural products from *Artemisia annua*.
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1. Introduction

The Chinese medicinal plant *Artemisia annua* L has been the subject of intensive phytochemical investigations over the past two decades, following the discovery of the anti-malarial amorphane sesquiterpene artemisinin (qinghaosu) (**1**).[1] Although the biosynthesis of the amorphane carbocycle from which **1** is almost certainly derived seems to proceed by the normal pathways of terpenoid biosynthesis,[2–7] there is considerable uncertainty regarding the latter steps in the biogenesis of artemisinin, which must involve carbon–carbon cleavage at C-4/C-5 in order to produce a compound based on the *seco*-amorphane skeleton which would be the immediate precursor to the 1,2,4-trioxane ring of **1**.[8] All investigators seem to concur that the amorphane sesquiterpene dihydroartemisinic acid (**2**)[9,10] and/or its 11,13-dehydro analogue, artemisinic acid (arteannuic acid),[4,5,10–16] are advanced precursors en route to artemisinin. However, there are several differing, and sometimes directly conflicting, views as to exactly how the transformation of artemisinic acid/dihydroartemisinic acid into **1** occurs in vivo.[8,10,17–20]

We now report a synthetic route to compound **2** which achieves the incorporation of a stable isotopic label at the 15-position with very high isotopic enrichment and in a good overall yield. Three isotopomers were prepared by this procedure: [15-$^{13}C^{2}H_3$]-dihydroartemisinic acid (**2a**); [15-$C^{2}H_3$]-dihydroartemisinic acid (**2b**); and [15-$^{13}CH_3$]-dihydroartemisinic acid (**2c**).[†] These labelled precursors were designed to be used in feeding experiments with *A. annua* in order to determine the biogenesis of artemisinin and other sesquiterpene natural products from this species. The use of stable-isotope labelled precursors such as **2a**–**2c** has the advantage over all previous biosynthetic studies (which have exclusively used radio-isotopically labelled precursors,[2–5,10,12,15,16,19,20] if labelled substrates were used at all[9,17,18]) that one-dimensional (1D) ^{2}H NMR and/or ^{13}C NMR spectroscopy can be used to directly study their transformations in vivo, providing chemical shift information[‡] from the isotopic label at the 15-position by which metabolites can be identified directly in crude plant extracts; since there is no absolute requirement for a prior

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[†] For all compounds in this paper with the suffix '**a**', the isotopically-normal [15-CH_3] group has been replaced by [15-$^{13}C^{2}H_3$]; for compounds labelled with the suffix '**b**', the [15-CH_3] group has been replaced by [15-$C^{2}H_3$]; for compounds labelled with the suffix '**c**', the [15-CH_3] group has been replaced by [15-$^{13}CH_3$]. The suffix '*' indicates an unspecified isotopic enrichment at the 15-position.

[‡] When ^{13}C is isotopically enriched from the natural abundance level of 1.1% to ca. 100%, there is no effect on carbon chemical shift (δ_C). Deuterium chemical shifts (δ_D) are also essentially identical to proton chemical shifts (δ_H) for nuclei in the same chemical environment, but the substitution of ^{1}H by ^{2}H causes an approximately 0.3 ppm upfield shift in δ_C of the directly-bound carbon (and also results in a 1:1:1 triplet splitting). Thus, a CD group appears as a triplet 0.3 ppm upfield of the corresponding CH resonance in ^{13}C NMR spectroscopy; a CD_2 group appears as a 1:2:3:2:1 quintet situated 0.6 ppm upfield of the corresponding CH_2 resonance; and a CD_3 group appears as a 1:3:6:7:6:3:1 septet lying 0.9 ppm upfield of the corresponding CH_3 resonance. Hence, deuterium and carbon chemical shifts can be used to infer the identity of a labelled metabolite, provided that the resonances in the ^{1}H and ^{13}C NMR spectra of that metabolite, in particular the resonances at the 15-position, have been previously assigned.

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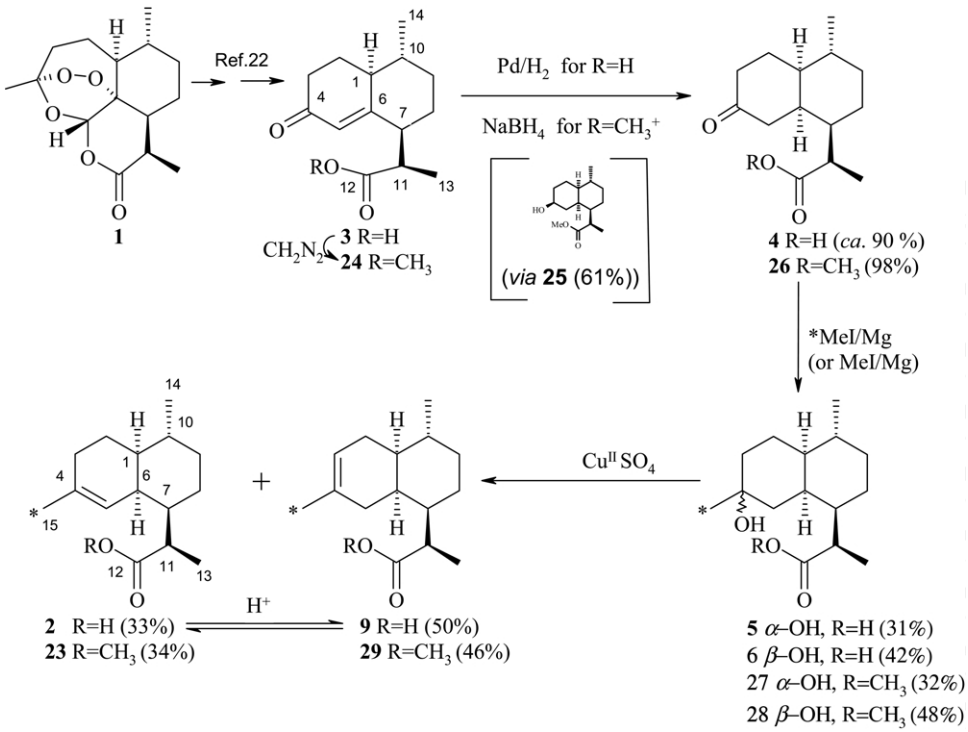


Scheme 1. Synthesis of **2** and its isotopically-labelled forms **2a**–**2c** from **1** via the keto-acid intermediate **4** (∗ =isotopic label at the 15-position). + The methyl ester of **4**, compound **26**, was obtained by Jones oxidation of the immediate reduction product from compound **24**, saturated alcohol **25**.

chromatographic separation of metabolites when using NMR to analyse the metabolism of stable-isotope labelled precursors, the possibility for the introduction of artifacts during extensive sample handling is consequently minimized.[21] The use of stable isotopes also gives more detailed information as to the nature of metabolism than would be possible for studies of the transformations of **2** when conducted using a radio-isotopically labelled precursor, as will be demonstrated in the companion paper, in which experiments involving the feeding of all three labelled precursors **2a**–**2c** to intact plants of *A. annua* are described. In particular, the newly developed two-dimensional (2D) NMR technique of $^{13}C-^{2}H$ correlation spectroscopy ($^{13}C-^{2}H$ COSY)[21] provides a powerful tool by which to analyse the metabolism of the doubly-labelled precursor **2a**.

2. Results and discussion

We have recently reported the preparation of both [15-$^{13}C^{2}H_3$]-dihydroartemisinic acid and [15-$^{13}CH_3$]-dihydro-*epi*-deoxyarteanuin B in moderate yield via a reconstructive synthesis from artemisinin.[22] One disadvantage of this strategy was that there was always an unavoidable and quite extensive depletion of the deuterium label at the 15-position, which made this procedure less than ideal for synthesizing ^{2}H-labelled dihydroartemisinic acid (**2a/2b**) for use in feeding experiments with *A. annua* plants. We have therefore now developed an improved procedure as is shown in Scheme 1, which involves introduction of the isotopic label via Grignard reaction of labelled methyl iodide with the keto-acid **4**, rather than with its synthetic precursor the α,β-unsaturated keto-acid **3** (in our previous synthesis,[22] it was the reduction of the product from Grignard addition with **3** which was responsible for the depletion of the ^{2}H label). The key intermediate, *cis*-decalone **4**, was obtained with quite high stereospecificity from hydrogenation of **3** (less than 10% of the alternative *trans*-decalone stereoisomer was observed in the crude product from this reaction and, in order to keep the overall yield of the synthesis high, the undesired *trans*-decalin isomer was not normally separated at this stage). Although the *trans*-decalones **7** and **8** (Fig. 1) obtained from the Grignard addition of methyl iodide to this crude hydrogenation product were separable from the major reaction products, epimeric *cis*-decalones **5** and **6** (Scheme 1), these minor components were also normally carried through to the next step. Compounds **10** and **11**, the *trans*-decalin analogues of artemisinic acid (**2**) and its Δ^3 regio-isomer (**9**), respectively, were therefore also present as contaminants, following the dehydration of the mixture of tertiary alcohol intermediates **5**–**8** in the last step, and these compounds were most conveniently removed at the very end of the synthesis when the desired product, compound **2**, was separated by HPLC from its regio-isomer **9**.

The synthesis of both of the labelled precursors **2a** and **2b** by this method was superior to our previous procedure[22] in that the retention of the deuterium label in the 15-[$^{13}C^{2}H_3$] and 15-[$C^{2}H_3$] groups of **2a** and **2b** was close to 100%, as shown by the NMR spectra of these compounds (Figs. 2 and 3).[§] We have also been able to enhance the overall yield for this synthesis of **2**, as compared with previously published

[§] However, note that it is important to carefully control the conditions for the Cu(II)-catalysed dehydration step, as use of excess Cu(II) can also lead to an almost complete depletion of ^{2}H label from the 15-position (we were unable to achieve this dehydration by the use of acid catalysis, although this procedure has been reported by others).[23,24]

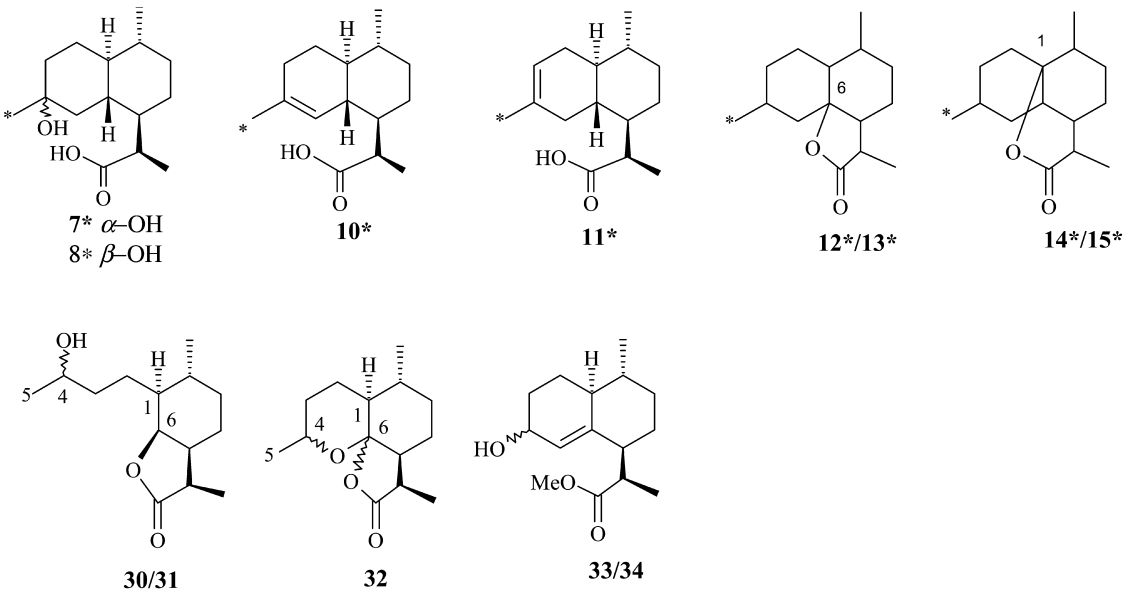


Figure 1. Minor products from the syntheses described in Scheme 1 (* =unspecified isotopic enrichment).

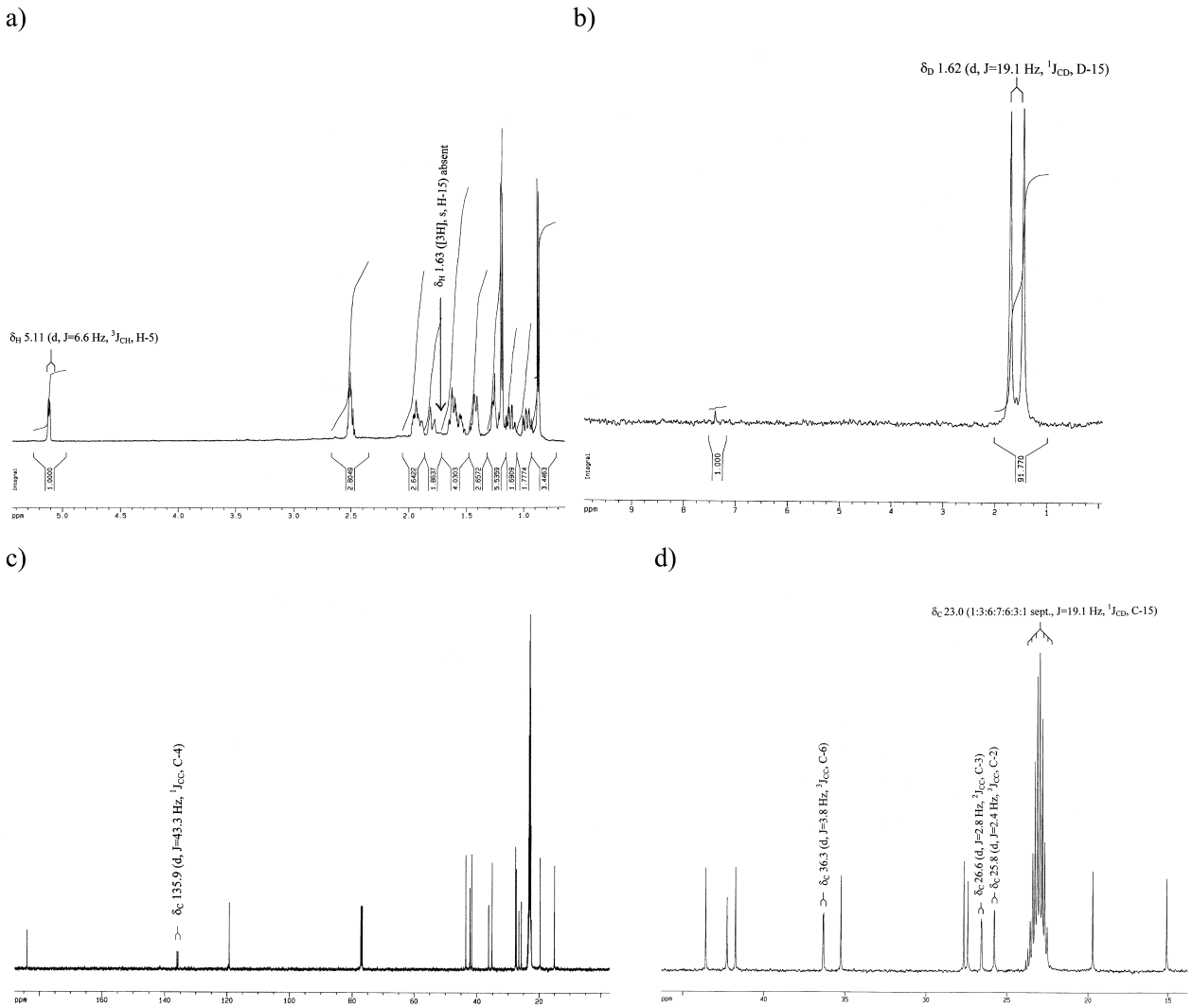


Figure 2. (a) ^{1}H NMR, (b) ^{2}H NMR and (c) ^{13}C NMR (and expansion d) spectra of [15-$^{13}C^{2}H_3$]-dihydroartemisinic acid (**2a**) prepared from artemisinin (**1**), following introduction of the isotopic label to intermediate **4**, showing ca. 100% labelling of both ^{13}C and ^{2}H at the 15-position.

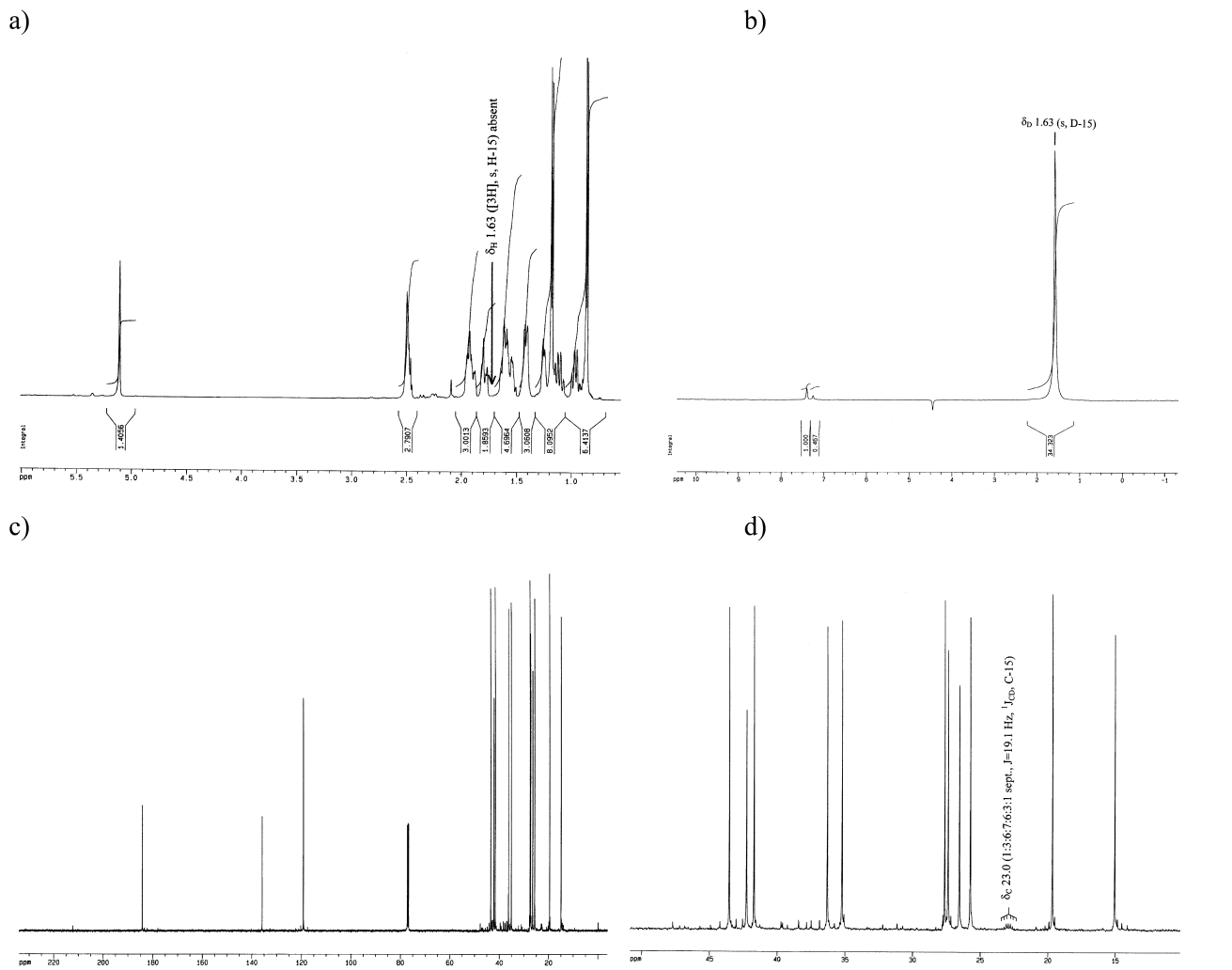
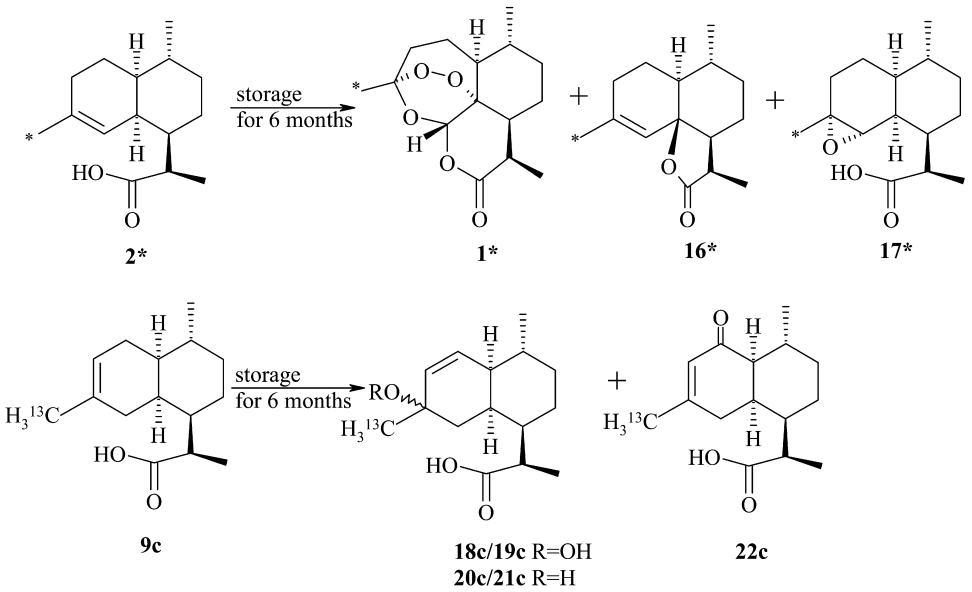


Figure 3. (a) ^{1}H NMR, (b) ^{2}H NMR and (c) ^{13}C NMR (and expansion d) of spectra of [15-$C^{2}H_{3}$]-dihydroartemisinic acid (**2b**) prepared from artemisinin (**1**), following the introduction of isotopic label to intermediate **4**, showing ca. 100% enrichment of ^{2}H label at the 15-position.

procedures which have involved a similar dehydration of a tertiary alcohol to Δ^{3}/Δ^{4} amorphene products,[23–25] by introducing an additional step after the dehydration, in which the (unwanted) Δ^{3} regio-isomer, compound **9**, is equilibrated with its Δ^{4}-isomer, compound **2**. Thus, following the HPLC separation of the two double bond regio-isomers, dihydroartemisinic acid (**2**) and compound **9** (produced in an approximately 5:7 ratio by the dehydration of **5/6**), the purified Δ^{3}-isomer (**9**) was converted back into this same equilibrating mixture with the desired Δ^{4}-isomer, compound **2**, by treatment with acid; and the two isomers were then separated again by HPLC. By applying two such cycles of equilibration and purification, the yield of labelled dihydroartemisinic acid (**2**) was raised from 33% (as had been the case in the (now) penultimate step of the reaction for dehydration of epimeric alcohols **5/6**) to almost 60%, with no associated loss of label from the 15-position. This procedure required careful optimization in order to avoid contamination by other products of double bond rearrangement (such as the five-membered lactones **12** and **13**; and the six-membered lactones **14** and **15** (Fig. 1), which were presumably formed by more extensive acid-catalysed migrations of the Δ^{3} double bond, allowing for the formation of carbocations at C-6 and then C-1, which became ‘trapped’ by the carboxylic acid group).

As reported in our previous communication,[22] dihydroartemisinic acid which had been labelled with a stable isotope at the 15-position was found to be susceptible to autoxidation after prolonged storage for several months, even when kept in the dark at −20 °C in the freezer. This was a significant observation in connection with the proposed use of this compound as a labelled precursor for feeding studies which were designed to establish biosynthetic routes in *A. annua*, because all three of the compounds which were obtained following such storage[22] (compounds **1**, **16** and **17** in Scheme 2), have also been reported as natural products from this species.[26,27] Hence, failure to pay attention to the susceptibility of **2** towards spontaneous autoxidation during storage could lead to an erroneous interpretation when analyzing the results of feeding experiments. Interestingly, the Δ^{3}-isomer of dihydroartemisinic acid (**9**) was also found to be susceptible to spontaneous autoxidation on storage, although, in this case, the isolable oxidation products were simply either allylic hydroperoxides (**18** and **19**), which are expected from the ‘ene-type’ reaction of $^{1}O_{2}$ with the Δ^{3} double bond in **9**, or hydroxides (**20** and **21**) which are probably formed by the homolysis of such hydroperoxides (see the companion paper for a discussion of these processes). The unusual α,β-unsaturated ketone **22**, which was a very minor product of



Scheme 2. Autoxidation of both the desired biosynthetic precursor, labelled dihydroartemisinic acid (**2***) (see Ref. 22), and of its Δ^3-isomer, compound **9c**, after storage for several months (* =unspecified isotopic enrichment).

autoxidation, may be formed by 3,2-allylic rearrangement of either one of the tertiary allylic hydroperoxides **18** or **19** and a subsequent dehydration reaction (cf. similar reactions of closely related compounds which are proposed in Refs. 22,26). There was no sign of any alternative products from the further reactions of such hydroperoxides; and, in particular, the complex rearrangement reactions, which are responsible for the appearance of **1** and **17** during the autoxidation of dihydroartemisinic acid (**2**) on storage, appear not to be occurring in the case of its Δ^3 isomer, compound **9**.

In view of the instability of dihydroartemisinic acid towards prolonged storage, it was clearly preferable that the synthesis of each of the labelled precursors **2a**–**2c** should be performed immediately prior to their use as biogenetic precursors in feeding experiments, so as to avoid the possibility of confusing the products of spontaneous in vitro autoxidation with any products arising from the metabolism of dihydroartemisinic acid in vivo. However, on some occasions this was found to be impractical, and an alternative procedure was therefore developed which parallels the approach already described in Scheme 1. The rationale for this alternative strategy was that the methyl ester of dihydroartemisinic acid, compound **23**, is known to be more stable towards autoxidation than dihydroartemisinic acid (**2**) itself,[28,29] and that it can readily be converted back to **2**, by hydrolysis of the ester group, as and when required for use in feeding experiments.

The synthesis of this alternative product, the methyl ester of dihydroartemisinic acid (**23**), was a straightforward procedure. It is reported that the unsaturated keto-acid **3** from the acid degradation of artemisinin (**1**) can be readily converted into its methyl ester,[30] compound **24**, by treatment with diazomethane,[22] and it was found that **24** could then be subjected to a similar series of transformations as for **3** (Scheme 1). The reduction of the $\Delta^{5,6}$ double bond in compound **24** by sodium borohydride was significantly more stereoselective[¶] than had been the case for the reduction of this same double bond in its free acid analogue compound **3** by hydrogen over a palladium catalyst such that, under optimized conditions, only the *cis*-decalin methyl ester, compound **25**, was observed in the crude reaction product (and no *trans*-decalin isomer was 'carried through' to the key intermediate, compound **26**, as a result); and this is one reason why it was found preferable to esterify the carboxylic acid group early on in the synthesis of **23**, rather than in the final step. In addition, only 1 equiv. of labelled Grignard reagent was then required in the preparation of epimeric tertiary allylic alcohols **27/28** from **26**:[31] by contrast, 2 equiv. had been required for the formation of the free acid analogues of these products, compounds **5/6** in the direct synthesis of dihydroartemisinic acid (**2**) (in this case, 1 equiv. of labelled Grignard reagent was lost in deprotonating the carboxylic acid group). The final step in this alternative synthesis, the dehydration of the mixture of epimeric alcohols **27/28**, yielded the methyl ester of dihydroartemisinic acid (**23**) as a mixture with its Δ^3 regio-isomer (**29**), as expected.

The full ^{13}C and ^{1}H NMR assignments which are reported for the synthetic intermediates and products **4**–**15**, **23** and **25**–**34** in Tables 1–4 were made by the 2D NMR techniques HSQC, HMBC, and ^{1}H–^{1}H COSY; these unambiguous assignments were necessary in order to make an independent verification of issues of stereo- and regio-isomerism at each step of the synthesis described in Scheme 1 based on the analysis of the NOESY spectrum of

[¶] However, note that several alternative reduction products, such as compounds **30**–**34**, which are shown in Figure 1, were obtained from the treatment of **24** with $NaBH_4$ under non-optimized reaction conditions (compounds **30**–**32** probably arise from an initial retro-aldol reaction of the αβ-unsaturated ketone group in **24** under the basic conditions of this reaction).

Table 1. ^{13}C NMR data for isotopically-normal compounds described in Scheme 1 (see Section 4 for the effects of isotopic enrichment on the appearance of the NMR spectra of labelled compounds with suffix '**a**', '**b**' and '**c**')

Position[a]	**4**	**5**	**6**	**9**	**23**	**25**	**26**	**27**	**28**	**29**
1 (CH)	42.6	43.2	43.4	42.2	41.7	42.9	42.6	43.1	43.4	42.2
2 (CH_2)	27.8	23.6	25.7	27.8	25.8	26.3	27.8	23.6	25.8	27.9
3 (CH_2)	36.9	33.6	35.0	119.1 (CH)	26.6	30.4	36.9	33.5	35.2	119.2 (CH)
4 (C)	212.6	70.0	72.1	131.8	135.9	71.8 (CH)	212.2	69.9	71.9	131.8
5 (CH_2)	37.5	33.3	34.9	26.3	119.5 (CH)	30.1	37.5	33.2	34.9	26.3
6 (CH)	42.2	32.2	35.1	33.4	36.4	36.0	38.5	32.2	35.1	33.5
7 (CH)	43.1	43.5	43.2	43.7	44.0	43.7	43.4	43.7	43.6	44.1
8 (CH_2)	25.7	26.4	26.3	25.8	27.5	26.5	25.7	26.4	26.3	25.9
9 (CH_2)	35.1	35.6	35.6	35.6	35.3	35.6	35.1	35.6	35.5	35.6
10 (CH)	27.2	26.5	26.7	27.8	27.7	27.4	27.2	26.5	26.7	27.9
11 (CH)	42.2	42.0	42.3	42.5	42.2	42.3	42.1	42.2	42.2	42.4
12 (C)	182.6	183.0	182.6	183.9	178.0	177.7	177.2	177.8	177.8	177.8
13 (CH_3)	14.9	15.0	14.8	15.1	15.1	15.0	14.9	15.0	14.8	15.2
14 (CH_3)	19.5	19.7	19.6	20.1	19.7	19.6	19.5	19.8	19.6	20.1
15 (CH_3)	—	32.1	26.1	23.6	23.8	—	—	32.1	26.2	23.6
12-OMe	—	—	—	—	51.4	51.4	51.5	51.4	51.4	51.3

[a] Multiplicity determined from DEPT.

each of these compounds. Complete isotopic labelling by three ^2H atoms at the 15-position (as in the case of all of the compounds with the suffix '**a**' and '**b**') generally caused an upfield shift in the ^{13}C NMR spectrum of ca. 0.9 ppm at C-15 and resulted in the splitting of this resonance into a 1:3:6:7:6:3:1 septet[22] due to the 19–20 Hz single-bond carbon–deuterium coupling constant ($^1J_{CD}$), as well as resulting in an absence of the H-15 resonance from the ^1H NMR spectrum. The ca. 100% isotopic enrichment of ^{13}C at the 15-position (as in all of the compounds with the suffix '**a**' and '**c**') resulted in the appearance of doublet splittings in the ^{13}C NMR spectrum due to single-bond ($^1J_{CC}$) and long-range carbon–carbon couplings ($^2J_{CC}$ and $^3J_{CC}$) at some or all of C-3, C-4, C-5 and C-6; as well as a doublet splitting for H-5 in the ^1H NMR spectrum, due to a long-range carbon–proton coupling ($^3J_{CH}$). These effects are described in greater detail in Section 4.

3. Conclusion

Two methods for the preparation of dihydroartemisinic acid, which is labelled at the 15-position by either ^{13}C or $^2H_3$ (or both), have been developed and optimized such that the appropriate labelled precursor can be synthesized in good yield and with close to 100% isotopic enrichment. The first method involved the direct preparation of labelled dihydroartemisinic acid (**2**) from artemisinin (**1**). In view of the tendency of this compound to undergo spontaneous autoxidation on prolonged storage, such labelled versions of dihydroartemisinic acid should be used immediately in feeding experiments with *A. annua* plants. The second synthesis resulted in the methyl ester of dihydroartemisinic acid (**23**), which can be prepared in advance of any biological experiments, as it is more stable to storage than dihydroartemisinic acid itself; it is then a simple

Table 2. ^1H NMR data for isotopically-normal compounds described in Scheme 1 (see Section 4 for the effects of isotopic enrichment in the NMR spectra of labelled compounds with suffix '**a**', '**b**' and '**c**')

Position	**4**	**5**	**6**	**9**	**23**	**25**	**26**	**27**	**28**	**29**
1	1.40	1.20	1.17	1.23	1.25	1.14	1.38	1.19	1.17	1.21
2α	1.69	1.68	1.40	2.05	1.55	1.31	1.70	1.67	1.39	2.04
2β	2.23	1.76	1.88	2.15	1.94	1.95	2.21	1.75	1.89	2.15
3α	2.25	1.43[a]	1.53[a]	5.29	1.91	1.72	2.22	1.67	1.53[a]	5.28
3β	2.35	1.40[a]	1.46[a]	—	1.80	1.34	2.32	1.45	1.45[a]	—
4	—	—	—	—	—	3.59	—	—	—	—
5α	2.07	1.45	1.57	1.92	5.12	1.53	2.05	1.40	1.53	1.88
5β	2.38	1.19	1.24	1.57	—	1.30	2.35	1.19	1.24	1.57
6	2.18	2.17	1.86	2.09	2.50	1.82	2.24	2.16	1.84	2.07
7	1.81	1.68	1.68	1.70	1.62	1.68	1.80	1.66	1.68	1.69
8α	1.56	1.45	1.68	1.49[a]	1.25	1.30	1.36	1.27	1.71	1.38[a]
8β	1.34	1.25	1.44	1.42[a]	1.08	1.24	1.30	1.20	1.23	1.31[a]
9α	1.11	1.00	0.99	1.00	0.94	0.99	1.10	0.98	0.97	0.97
9β	1.82	1.69	1.70	1.69	1.59	1.68	1.79	1.66	1.68	1.65
10	1.82	1.59	1.71	1.39	1.41	1.66	1.80	1.57	1.71	1.37
11	2.18	2.29	2.28	2.29	2.50	2.30	2.19	2.26	2.29	2.31
13	1.15	1.17	1.13	1.18	1.13	1.10	1.10	1.12	1.09	1.13
14	0.96	0.84	0.83	0.82	0.86	0.83	0.96	0.83	0.83	0.81
15	—	1.23	1.28	1.63	1.63	—	—	1.22	1.27	1.63
12-OMe	—	—	—	—	3.68	3.66	3.67	3.66	3.66	3.66

[a] Assignments as α and β interchangeable.

Table 3. ^{13}C NMR data for compounds reported in Figure 1 (see Section 4 for the effects of isotopic enrichment in the NMR spectra of labelled compounds with suffix '**a**', '**b**' and '**c**')

Position[a]	7	8	10	11	12c	13c	14c	15c	30	31	32	33/34
1 (CH)	48.7	48.5	46.8	44.3	49.3	44.4	84.0 (C)	84.6 (C)	45.1	45.1	47.5	45.10/44.93
2 (CH_2)	28.3	25.8	26.6	31.2	24.9	22.8	28.1	34.5	24.9	25.4	22.0	22.92/22.94
3 (CH_2)	39.8	38.1	30.8	120.4 (CH)	34.7	28.3	26.6	30.9	36.2	36.3	33.5	30.11/29.09
4 (C)	71.6	70.4	135.1	132.8	28.0 (CH)	28.6 (CH)	26.4 (CH)	32.6 (CH)	68.2 (CH)	68.6 (CH)	68.3 (CH)	66.53/66.47 (CH)
5 (CH_2)	44.0	42.5	122.4 (CH)	35.5	43.9	42.2	31.6	36.0	23.4 (CH_3)	23.7 (CH_3)	21.0 (CH_3)	120.63/121.69 (CH)
6 (CH)	41.8	39.3	43.4	39.8	85.2 (C)	87.7 (C)	36.4	44.9	79.2	79.1	106.9 (C)	144.76/144.29 (C)
7 (CH)	45.8	46.4	45.7	47.7	43.1	43.7	37.1	37.3	40.4	40.4	44.1	47.31/47.19
8 (CH_2)	29.0	27.6	28.2	27.3	24.3	21.1	27.5	20.9	22.7	22.7	25.1	32.59/32.40
9 (CH_2)	35.5	35.6	35.8	35.3	32.8	31.7	26.5	25.9	33.1	33.0	33.0	35.47
10 (CH)	36.9	36.8	36.2	37.9	30.7	28.4	41.8	30.7	31.3	31.4	31.6	39.59/39.52
11 (CH)	40.3	39.3	39.4	39.3	39.3	38.7	33.6	41.1	42.2	42.2	39.2	41.01/41.05
12 (C)	181.2	179.8	183.4	180.4	179.7	180.1	180.4	176.2	179.7	179.8	179.8	176.86
13 (CH_3)	13.0	14.4	14.3	14.6	9.4	13.1	13.6	14.0	9.1	9.1	8.7	16.19
14 (CH_3)	20.1	20.0	19.8	19.9	19.9	19.5	14.4	14.2	20.0	20.0	18.8	20.19/20.24
15 (CH_3)	25.7	31.5	23.8	23.5	22.3	22.4	16.7	22.0	—	—	—	—
12-OMe	—	—	—	—	—	—	—	—	—	—	—	51.4

[a] Multiplicity determined from DEPT.

procedure to convert this derivative back to labelled dihydroartemisinic acid, just prior to performing a feeding experiment.

4. Experimental

4.1. General

All ^1H and ^{13}C NMR experiments were recorded on either a Bruker DRX 500 or an AV 600 instrument. Chemical shifts are expressed in ppm (δ) relative to TMS as internal standard. Proton chemical shifts, multiplicities, coupling constants and integrals reported in this section are those which were clearly resolved in 1D ^1H NMR spectra without recourse to 2D NMR analysis (see Tables 1–4 in the main text for full ^{13}C and ^1H NMR assignments, which were made by 2D NMR in all cases). ^2H NMR spectra were recorded at 76.7 MHz in $CHCl_3$ solution containing C_6D_6 (10 μl/100 ml), as an internal reference (δ_D 7.43 ppm). HSQC, HMBC, ^1H–^1H COSY and NOESY spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. High-resolution MS were recorded in EI mode at 70 eV on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in $CHCl_3$ on a Shimadzu FT-IR-8201 PC instrument. Column chromatography (CC) was performed using silica gel 60–200 μm (Merck). HPLC separations were performed using a Varian chromatograph equipped with RI star 9040 and UV 9050 detectors and either a normal phase Intersil PREP-SIL or a YMC diol 20 mm×25 cm column, flow rate 8 ml/min. Melting points were recorded by a Perkin–Elmer differential scanning calorimeter 7 (DSC 7). Optical rotations were measured by a Perkin–Elmer 343 polarimeter (Na 589 nm). $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and $CHCl_3$ was used as solvent.

4.2. Acid degradation of artemisinin (1) to 2-(4-methyl-7-oxo-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7-octahydro-naphthalen-1-yl)-propionic acid (3)

See Ref. 22 for the procedure for converting **1** into **3** (see Ref. 30 for other physical properties of **3**).

4.3. Hydrogenation of decalenone 3

To a solution of decalenone **3** (2 g) in EtOAc (100 ml) was added a catalytic amount of Pd/charcoal. The reaction mixture was connected to an atmospheric pressure hydrogenation apparatus and was left stirring overnight. The mixture was filtered and the solvent was removed under reduced pressure to yield a crude product (1.98 g, 98%) consisting predominantly of compound **4**, together with a little of its *trans*-decalone isomer (less than 10% by ^1H NMR spectroscopic analysis of the crude product), which could not be separated chromatographically.

4.3.1. 2-(4-Methyl-7-oxo-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aα-*H*)-decahydro-naphthalen-1-yl)-propionic acid (4). Solid. Mp 160–162 °C; $[\alpha]_D$ −4.7 (*c* 1.3, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3400–2600 (br), 3024, 2961, 2928, 2878, 1717, 1705, 1458 cm^{-1}; ^1H NMR (δ, $CDCl_3$) ppm: 1.15 (3H, d, *J*=6.8 Hz), 0.96 (3H, d, *J*=6.1 Hz)—see

Table 4. ^{1}H NMR data for compounds described in Figure 1 (see Section 4 for the effects of isotopic enrichment observed in the NMR spectra of labelled compounds with suffix '**a**', '**b**' and '**c**')

Position	7	8	10	11	12c	13c	14c	15c	30	31	32	33/34
1	0.63	0.55	0.76	0.86	0.99	1.35	—	—	1.17	1.19	1.26	1.50
2α	1.94	1.78	1.98	2.27	1.81[a]	1.76[a]	1.92[a]	1.45[a]	1.65	1.82	1.83[a]	1.70, 1.70[a]
2β	0.93	1.25	1.78	1.56	1.43[a]	0.91[a]	1.38[a]	2.17[a]	1.55	1.42	1.55[a]	1.70/1.70[a]
3α	1.39	1.29	1.98[a]	5.36	0.98[a]	0.91[a]	1.78[a]	1.66[a]	1.64	1.64	1.76[a]	1.92/1.70[a]
3β	1.73	1.71	1.94[a]	—	1.78[a]	1.46[a]	1.38[a]	1.03[a]	1.41	1.42	1.35[a]	1.35/1.55[a]
4	—	—	—	—	1.82	1.80	2.08	1.61	3.81	3.78	3.98	4.24/4.14
5α	1.05	0.94	5.54	1.57	0.96[a]	1.64[a]	1.78[a]	1.57[a]	1.21	1.20	1.11	5.38/5.41
5β	1.96	2.06	—	2.27	2.02[a]	1.45[a]	1.21[a]	1.44[a]	—	—	—	—
6	1.13	1.43	1.80	1.38	—	—	1.83	1.88	4.40	4.42	—	—
7	1.50	1.27	1.37	1.33	2.02	2.16	1.74	1.78	2.25	2.27	2.16	2.04
8α	1.72	1.77	1.72	1.79	1.66[a]	1.63[a]	1.52	1.67	1.62	1.64	1.78	1.69
8β	1.26	1.25	1.31	1.25	1.13[a]	1.23[a]	1.08	1.03	1.06	1.06	1.04	1.22
9α	1.06	1.01	1.12	1.05	1.13[a]	1.20[a]	1.50	1.06	0.97	1.01	1.07	1.73
9β	1.72	1.71	1.65	1.72	1.63[a]	1.67[a]	1.91	1.50	1.66	1.67	1.66	1.20
10	1.06	1.10	1.31	1.07	1.31	1.57	1.54	2.11	1.35	1.36	1.29	1.19
11	2.69	2.77	2.95	2.83	3.11	2.80	2.74	2.65	2.78	2.78	3.28	2.76
13	1.11	1.12	1.16	1.16	1.12	1.27	1.25	1.27	1.14	1.14	1.09	1.24
14	0.88	0.87	0.89	0.88	0.89	0.90	0.92	0.89	0.95	0.95	0.88	0.92
15	1.22	1.23	1.65	1.63	0.87	0.87	1.02	0.95	—	—	—	—
12-OMe	—	—	—	—	—	—		—	—	—	—	3.67

[a] Assignments as α and β interchangeable.

Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m/z* (rel. int.): 238.1572 [M^+, $C_{14}H_{22}O_3$ requires 238.1569, Δ=−0.3 mmu] (2), 220 (4), 192 (4), 165 (37), 164 (100).

4.4. Grignard reaction of keto-acid 4 with methyl iodide

To small Mg chips (0.40 g) in anhyd. Et_2O (200 ml) was added a solution of isotopically-normal MeI (1.2 ml) in anhyd. Et_2O (50 ml) and the mixture was refluxed for 2 h. A solution of **4** (1.58 g, containing a small amount of its *trans* isomer—see above) in anhyd. Et_2O (200 ml) was added to the Grignard reagent and the reaction was allowed to reflux for a further 3.5 h until completion, as determined by TLC. The mixture was cooled in an ice bath and HCl (10%) was added to pH 1–2, then the reaction mixture was extracted with Et_2O (3×200 ml) and the combined organic layers were washed with brine (3×50 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield a crude product (1.52 g, 96%), consisting predominantly of the *cis*-decalin 4-hydroxy epimers **5** and **6** (in an approximately 3:4 ratio) which could be separated by HPLC (40% EtOAc/*n*-hexane/5% AcOH) for individual characterization, although a crude mixture of the two epimers was generally used in the final step of this synthesis (Section 4.6). Much smaller amounts of the corresponding *trans*-decalin isomers **7** and **8** (Fig. 1) were also isolated by HPLC.

4.4.1. 2-(7α-Hydroxy-4,7-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aα-*H*)-decahydro-naphthalen-1-yl)-propionic acid (5). Oil (490 mg, 31%, R_t 13.6 min). $[\alpha]_D$ −66.2 (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3400–2600 (br), 2937, 2858, 1709, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$)[‖] ppm: 2.29 (1H, dq, *J*=7.0, 6.8 Hz), 2.17 (1H, dd, *J*=13.5, 3.7 Hz), 1.23 (3H, s), 1.17 (3H, d, *J*=6.8 Hz), 0.84 (3H, d, *J*=6.4 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m/z* (rel. int.): 254.1879 [M^+, $C_{15}H_{26}O_3$ requires 254.1882, Δ=0.3 mmu] (4), 236 (10), 221 (6), 208 (7), 193 (19), 163 (45), 162 (100).

4.4.2. 2-(7β-Hydroxy-4,7-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aα-*H*)-decahydro-naphthalen-1-yl)-propionic acid (6). Oil (664 mg, 42%, R_t 16.8 min). $[\alpha]_D$ +9.8 (*c* 0.9, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3599, 3480 (br), 3400–2600, 2930, 2870, 1705, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) ppm: 5.60 (2H, br s, –OH), 2.28 (1H, dq, *J*=7.0, 6.6 Hz), 1.28 (3H, s), 1.13 (3H, d, *J*=6.6 Hz), 0.83 (3H, d, *J*=6.1 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m/z* (rel. int.): 254.1880 [M^+, $C_{15}H_{26}O_3$ requires 254.1882, Δ=0.2 mmu] (9), 236 (24), 221 (10), 208 (22), 193 (44), 163 (90), 162 (100).

4.4.3. 2-(7α-Hydroxy-4,7-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aβ-*H*)-decahydro-naphthalen-1-yl)-propionic acid (7). Oil (25 mg, 2%, R_t 18.8 min). $[\alpha]_D$ −56.7 (*c* 2.5, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3429 (br), 3400–2600, 2974, 2928, 2858, 1703, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) ppm: 5.34 (2H, br s, –OH), 2.69 (1H, dq, *J*=2.5, 7.1 Hz), 1.22 (3H, s), 1.11 (3H, d, *J*=7.1 Hz), 0.88 (3H, d, *J*=5.6 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3; HREIMS *m/z* (rel. int.): 254.1880 [M^+, $C_{15}H_{26}O_3$ requires 254.1882, Δ=0.2 mmu] (2), 236 (20), 221 (18), 208 (28), 193 (35), 163 (100), 162 (98).

4.4.4. 2-(7β-Hydroxy-4,7-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aβ-*H*)-decahydro-naphthalen-1-yl)-propionic acid (8). Oil (30 mg, 2%, R_t 15.1 min). $[\alpha]_D$ −90.3 (*c* 3.0, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3418 (br), 3400–2600 (br), 2970, 2926, 2860, 1705, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) ppm: 6.26 (2H, br s, –OH), 2.77 (1H, dq, *J*=2.5, 7.0 Hz), 2.06 (1H, d, *J*=10.6 Hz), 1.23 (3H, s), 1.12 (3H, d, *J*=7.0 Hz), 0.87 (3H, d, *J*=6.4 Hz), 0.55 (1H, dddd, *J*=10.5, 10.5, 10.5, 3.4 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3; HREIMS *m/z* (rel. int.): 254.1882 [M^+, $C_{15}H_{26}O_3$ requires 254.1882, Δ=0.0 mmu] (6), 236 (23), 221 (12), 208 (30), 193 (32), 163 (60), 162 (100).

[‖] The sample was poorly soluble in this solvent.

4.5. Preparation of isotopically-labelled hydroxy-acids 5 and 6 from 4

4.5.1. [15-$^{13}C^{2}H_3$]-Labelled 5a and 6a. When $^{13}C^{2}H_3I$ (Cambridge Isotope Laboratories, Inc.) was used in place of isotopically-normal MeI, labelled compounds **5a** and **6a** were isolated from Grignard reaction with **4**. Physical properties for **5a** were as for **5** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.23 (H-15) absent from spectrum; ^{2}H NMR (ppm): 1.23 (d, J=19.2 Hz, $^{1}J_{CD}$, D-15); ^{13}C NMR (ppm): 31.2 (1:3:6:7:6:3:1 septet, J=19.2 Hz, $^{1}J_{CD}$, C-15). Physical properties for **6a** were as for **6** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.28 (H-15) absent from spectrum; ^{2}H NMR (ppm): 1.28 (d, J=19.2 Hz, $^{1}J_{CD}$, D-15); ^{13}C NMR (ppm): 25.2 (1:3:6:7:6:3:1 septet, J=19.2 Hz, $^{1}J_{CD}$, C-15). HREIMS of the mixture of **5a** and **6a** *m/z* (rel. int.): 258.2103 [M^+, $C_{14}{}^{13}C_1H_{23}{}^{2}H_3O_3$ requires 258.2103, Δ=0.0 mmu] (3), 240 (10), 221 (5), 212 (7), 193 (12), 167 (38), 166 (100), 165 (21).

4.5.2. [15-$C^{2}H_3$]-Labelled 5b and 6b. When $C^{2}H_3I$ (Cambridge Isotope Laboratories, Inc.) was used in place of isotopically-normal MeI, labelled compounds **5b** and **6b** were isolated from Grignard reaction with **4**. Physical properties for **5b** were as for **5** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.23 (H-15) absent from spectrum; ^{2}H NMR (ppm): 1.23 (s, D-15); ^{13}C NMR (ppm): 31.2 (C-15) not seen, presumably due to splitting into a 1:3:6:7:6:3:1 septet by the three deuterium atoms, and the reduced NOE effect from deuterium as compared to hydrogen. Physical properties for **6b** were as for **6** with the following differences: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.28 (H-15) absent from spectrum; ^{2}H NMR (ppm): 1.28 (s, D-15); ^{13}C NMR (ppm): 25.2 (C-15) not seen, presumably due to splitting into a 1:3:6:7:6:3:1 septet by the three deuterium atoms, and the reduced NOE effect from deuterium as compared to hydrogen. HREIMS of the mixture of **5b** and **6b** *m/z* (rel. int.): 257.2077 [M^+, $C_{15}H_{23}{}^{2}H_3O_3$ requires 257.2070, Δ=−0.7 mmu] (8), 239 (11), 221 (4), 211 (7), 193 (9), 166 (45), 165 (100), 164 (22).

4.5.3. [15-$^{13}CH_3$]-Labelled 5c and 6c. When $^{13}CH_3I$ (Cambridge Isotope Laboratories, Inc.) was used in place of isotopically-normal MeI, labelled compounds **5c** and **6c** were isolated from Grignard reaction with **4**. Physical properties for **5c** were as for **5** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.23 (3H, d, J=126.3 Hz, $^{1}J_{CH}$, H-15); ^{13}C NMR (ppm): 32.1 (ca. 90× normal intensity, C-15). Physical properties for **6c** were as for **6** with the following differences: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.28 (3H, d, J=126.3 Hz, $^{1}J_{CH}$, H-15); ^{13}C NMR (ppm): 26.1 (ca. 90× normal intensity, C-15).

4.6. Dehydration of the mixture of epimeric alcohols 5 and 6

To a mixture of the epimeric alcohols **5** and **6** (1.5 g, containing a little of the *trans*-decalin isomers **7** and **8**) in C_2Cl_4 (50 ml) was added $CuSO_4$ absorbed onto silica gel[32] (6.35 g; prepared by dissolving 1 equiv. by weight of $CuSO_4{\cdot}5H_2O$ (1.6 g) in a minimum volume of water and then adding 3 equiv. by weight of silica gel (4.8 g), stirring the mixture under vacuum until homogeneous, and then drying in an oven).** The reaction mixture was refluxed overnight and completion was determined by TLC, then the mixture was filtered and the silica gel was washed several times by $CHCl_3$. The combined organic solvents were removed under reduced pressure to yield a crude product (1.46 g, 97%) consisting predominantly of compounds **2** and **9**, in an approximately 5:7 ratio, which could be separated by HPLC (2.5% EtOAc/*n*-hexane/0.7% AcOH). Minor amounts of the *trans*-decalin analogues of **2** and **9**, compounds **10** and **11** respectively, were also isolated by using alternative HPLC conditions, but it was generally the crude mixture of the four compounds that was used in this last step (see also Section 4.7).

4.6.1. 2-(4,7-Dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid [dihydroartemisinic acid] (2). 490 mg, 33%, R_t 18.7 min—see Refs. 26,29 for physical properties.

4.6.2. 2-(4,7-Dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid [Δ^3-isomer of dihydroartemisinic acid] (9). Solid. Mp 113–116 °C. (730 mg, 50%, R_t 20.3 min). $[\alpha]_D$ +32.8 (*c* 4.6, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3400–2600 (br), 2968, 2928, 2853, 1705, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) (ppm): 5.29 (1H, br), 2.29 (1H, dq, J=11.2, 6.8 Hz), 1.63 (3H, s), 1.18 (3H, d, J=6.8 Hz), 0.82 (3H, d, J=6.4 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m/z* (rel. int.): 236.1774 [M^+, $C_{15}H_{24}O_2$ requires 236.1776, Δ=0.2 mmu] (3), 218 (1), 180 (1), 163 (28), 162 (100).

4.6.3. 2-(4,7-Dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,(8aβ-*H*)-octahydro-naphthalen-1-yl)-propionic acid (10). ^{1}H NMR (δ, $CDCl_3$) (ppm): 5.54 (1H, s), 2.95 (1H, dq, J=2.9, 6.8 Hz), 1.65 (3H, s), 1.16 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.7 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3. HREIMS *m/z* (rel. int.): 236.1776 [M^+, $C_{15}H_{24}O_2$ requires 236.1776, Δ=0.0 mmu] (15), 218 (12), 163 (51), 162 (100).

4.6.4. 2-(4,7-Dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,8,(8aβ-*H*)-octahydro-naphthalen-1-yl)-propionic acid (11). Oil (41 mg, 3%, R_t 24.5 min, 1.5% EtOAc/*n*-hexane/0.25% AcOH). $[\alpha]_D$ −195.5 (*c* 0.6, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3400–2600, 3034, 2926, 2872, 1705, 1460 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) (ppm): 5.36 (1H, s), 2.83 (1H, dq, J=6.8, 7.1 Hz), 1.63 (3H, s), 1.16 (3H, d, J=7.1 Hz), 0.88 (3H, d, J=5.9 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3; HREIMS *m/z* (rel. int.): 236.1779 [M^+, $C_{15}H_{24}O_2$ requires 236.1776, Δ=−0.2 mmu] (9), 218 (6), 163 (57), 162 (100).

** N.B. It is important not to use more than 1 equiv. of $CuSO_4$ per mole of starting material, otherwise there is appreciable depletion of the ^{2}H-label at the 15-position.

4.7. Preparation of isotopically-labelled dihydroartemisinic acid (2) and its Δ^3 isomer (9) from the dehydration of isotopically-labelled compounds 5 and 6

4.7.1. [15-$^{13}C^2H_3$]-Labelled 2a and 9a. When a mixture of **5a/6a** was used in place of the isotopically-normal starting material, compounds **2a** and **9a** were isolated. Physical properties for **2a** were as for **2** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 5.11 (1H, d, J=6.4 Hz, $^3J_{CH}$, H-5), 1.63 (H-15) absent from spectrum; ^{2}H NMR (ppm): 1.63 (d, J=19.1 Hz, $^1J_{CD}$, D-15); ^{13}C NMR (ppm): 135.9 (d, J=43.1 Hz, $^1J_{CC}$, C-4), 36.3 (d, J=3.9 Hz, $^3J_{CC}$, C-6), 26.6 (d, J=3.1 Hz, $^2J_{CC}$, C-3), 25.8 (d, J=2.4 Hz, $^3J_{CC}$, C-2), 23.9 (s, 1% of 15-$^{13}CH_3$), 23.6 (1:1:1 t, J=19.1 Hz, $^1J_{CD}$, 4% of 15-$^{13}CH_2{}^2H$), 23.3 (1:2:3:2:1 quin, J=19.1 Hz, $^1J_{CD}$, 14% of 15-$^{13}CH_2{}^2H$), 23.0 (1:3:6:7:6:3:1 septet, J=19.1 Hz, $^1J_{CD}$, 81% of 15-$^{13}C^2H_3$); HREIMS: *m/z* (rel. int.) 240.1996 [M^+, $C_{14}{}^{13}C_1H_{21}{}^2H_3O_2$ requires 240.1998, Δ=0.2 mmu] (3), 211 (2), 193 (2), 167 (30), 166 (100), 165 (16). Physical properties for **9a** were as for **9** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 5.29 (1H, dd, J=5.3 Hz, $^3J_{CH}$, 5.3 Hz, H-3), 1.63 (H-15) absent from spectrum; ^{2}H NMR (ppm): 1.63 (d, J=18.9 Hz, $^1J_{CD}$, D-15); ^{13}C NMR (ppm): 131.7 (d, J=43.4 Hz, $^1J_{CC}$, C-4), 33.4 (d, J=2.4 Hz, $^3J_{CC}$, C-6), 26.3 (d, J=2.0 Hz, $^2J_{CC}$, C-5), 22.8 (1:3:6:7:6:3:1 septet, J=18.9 Hz, $^1J_{CD}$, C-15); HREIMS *m/z* (rel. int.): 240.1995 [M^+, $C_{14}{}^{13}C_1H_{21}{}^2H_3O_2$ requires 240.1998, Δ=0.3 mmu] (3), 194 (2), 167 (32), 166 (100), 165 (15).

4.7.2. [15-C^2H_3]-Labelled 2b and 9b. Compounds **2b** and **9b** were isolated when a mixture of **5b/6b** was used in place of the isotopically-normal starting material. Physical properties for **2b** were as for **2** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.63 (H-15) absent from spectrum; ^{2}H NMR (ppm): 1.63 (s, D-15); ^{13}C NMR (ppm): 23.0 (1:3:6:7:6:3:1 septet, J=19.1 Hz, $^1J_{CD}$, C-15) ca. 1% of the height of the other ^{13}C peaks, presumably the very low intensity is due to the effects of both splitting and the reduced NOE effect from deuterium as compared to hydrogen; HREIMS: *m/z* (rel. int.): 239.1959 [M^+, $C_{15}H_{21}{}^2H_3O_2$ requires 239.1964, Δ=0.6 mmu] (4), 221 (1), 193 (1), 166 (30), 165 (100), 164 (8). Physical properties for **9b** were as for **9** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.63 (H-15) absent from spectrum; ^{2}H NMR: 1.63 (s, D-15); ^{13}C NMR (ppm): 22.8 (C-15) not seen, presumably due to splitting into a 1:3:6:7:6:3:1 septet by the three deuterium atoms, and the reduced NOE effect from deuterium as compared to hydrogen; HREIMS *m/z* (rel. int.): 239.1959 [M^+, $C_{15}H_{21}{}^2H_3O_2$ requires 239.1964, Δ=0.5 mmu] (4), 193 (1), 166 (30), 165 (100), 164 (30).

4.7.3. [15-$^{13}CH_3$]-Labelled 2c and 9c. When a mixture of **5c/6c** was used in place of the isotopically-normal starting material, compounds **2c** and **9c** were isolated. Physical properties for **2c** were as for **2** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 5.11 (1H, d, J=6.4 Hz, $^3J_{CH}$, H-5), 1.63 (3H, d, J=125.1 Hz, $^1J_{CH}$, H-15); ^{13}C NMR (ppm): 135.9 (d, J=43.3 Hz, $^1J_{CC}$, C-4), 36.3 (d, J=3.8 Hz, $^3J_{CC}$, C-6), 26.6 (d, J=3.1 Hz, $^2J_{CC}$, C-3), 25.7 (d, J=2.6 Hz, $^3J_{CC}$, C-2), 23.8 (ca. 85× the intensity of the peak in the isotopically-normal spectrum, C-15). HREIMS *m/z* (rel. int.): 237.1799 [M^+, $C_{14}{}^{13}C_1H_{24}O_2$ requires 237.1810, Δ=1.1 mmu] (3), 179 (3), 164 (78), 163 (100). Physical properties for **9c** were as for **9** with the following differences due to isotopic enrichment: ^{1}H NMR (δ, $CDCl_3$) (ppm): 1.63 (3H, d, J=125.2 Hz, $^1J_{CH}$, H-15); ^{13}C NMR (ppm): 131.8 (d, J=43.6 Hz, $^1J_{CC}$, C-4), 33.4 (d, J=2.5 Hz, $^3J_{CC}$, C-6), 27.8 (br, $^3J_{CC}$, C-2), 26.3 (br, $^2J_{CC}$, C-5) 23.6 (ca. 75× the intensity of the corresponding peak in the isotopically-normal spectrum); HREIMS *m/z* (rel. int.): 237.1794 [M^+, $C_{14}{}^{13}C_1H_{24}O_2$ requires 237.1810, Δ=1.6 mmu] (3), 180 (2), 164 (80), 163 (100).

4.8. Conversion of purified 2-(4,[7-$^{13}CH_3$]-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,8,(8aα-*H*)-octahydronaphthalen-1-yl)-propionic acid [the Δ^3-isomer of dihydroartemisinic acid] (9c) to an equilibrating mixture of 9c and dihydroartemisinic acid (2c)

To a solution of **9c** (46 mg) in $CHCl_3$ (50 ml) was added H_2SO_4 (70%, 4.6 ml). The reaction was stirred at room temperature for 2 h, then extracted by $CHCl_3$ (3×100 ml), washed with brine (3×30 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a crude product (42 mg, 91%) consisting predominantly of **2c** and **9c** in an approximately 5:7 ratio, which could be separated by HPLC as described in Section 4.6. These conditions were found to be optimal in that they allowed the mixture of **2c** and **9c** to attain their equilibrium ratio, while minimizing the extent of further double bond isomerization, resulting in unwanted products. Thus, the use of longer reaction times led to the formation of significant amounts of the lactones **12c**–**15c** in addition to the desired compound **2c**. Compounds **12c**–**15c** were separated by HPLC (8% EtOAc/*n*-hexane/0.5% AcOH).

4.8.1. 3,6,[9-$^{13}CH_3$]-Trimethyl-decahydro-1-oxa-cyclopentane[*d*]naphthalene-2-one (12c). Oil (major 'unwanted' rearrangement product—ca. 80% of the total of compounds **12c**–**15c**, R_t 17.1 min). $[\alpha]_D$ +50.6 (*c* 3.0, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3026, 2943, 2866, 2851, 1755, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) (ppm): 3.11 (1H, dq, J=6.9, 7.3 Hz), 1.12 (3H, d, J=7.3 Hz), 0.89 (3H, d, J=6.4 Hz), 0.87 (3H, dd, J=124.5 Hz, $^1J_{CH}$, 6.4 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3—splittings observed for isotopically-labelled compound: 85.2 (d, J=4.2 Hz, $^3J_{CC}$, C-6), 28.0 (d, J=35.5 Hz, $^1J_{CC}$, C-4), 24.9 (d, J=4.8 Hz, $^3J_{CC}$, C-2), 22.3 (C-15, ca. 90× the intensity of other ^{13}C peaks, C-15); HREIMS *m/z* (rel. int.): 237.1807 [M^+, $C_{14}{}^{13}C_1H_{24}O_2$ requires 237.1810, Δ=0.3 mmu] (28), 222 (8), 193 (20), 179 (52), 165 (100), 164 (60), 151 (15), 136 (20), 125 (29).

4.8.2. 3,6,[9-$^{13}CH_3$]-Trimethyl-decahydro-1-oxa-cyclopentane[d]naphthalene-2-one (13c). Oil (2nd major 'unwanted' rearrangement product—ca. 15% of the total of compounds **12c**–**15c**, R_t 27.4 min). $[\alpha]_D$ +71.0 (*c* 0.5, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3015, 2943, 2866, 1751, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) (ppm): 2.80 (1H, dq, J=10.4, 7.8 Hz), 2.16 (1H, ddd, J=10.4, 5.8, 5.8 Hz), 1.27 (3H, d, J=7.8 Hz), 0.90 (3H, d, J=6.5 Hz), 0.87 (3H, dd,

J=124.6 Hz, $^1J_{CH}$, 6.6 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3—splittings observed for isotopically-labelled compound: 87.7 (d, J=4.0 Hz, $^3J_{CC}$, C-6), 28.6 (d, J=35.7 Hz, $^1J_{CC}$, C-4), 22.8 (d, J=4.2 Hz, $^3J_{CC}$, C-2), 22.4 (C-15, ca. 90× the intensity of other ^{13}C peaks, C-15); HREIMS m/z (rel. int.): 237.1809 [M^+, $C_{14}{}^{13}C_1H_{24}O_2$ requires 237.1810, Δ=0.1 mmu] (31), 222 (12), 193 (54), 179 (57), 165 (100), 164 (79), 140 (33), 125 (97).

4.8.3. [4-^{13}CH$_3$],8,11-Trimethyl-10-oxa-tricyclo-[5.3.3.0*1,6*]tridecan-9-one (14c). Oil (very minor rearrangement product—ca. 1% of the total of compounds **12c**–**15c**, R_t 26.1 min). $[\alpha]_D$ −32 (c 0.05, $CHCl_3$); IR ν_{max} ($CHCl_3$): 2926, 2864, 1705, 1460 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) (ppm): 2.74 (1H, dq, J=6.6, 7.2 Hz), 2.08 (1H, m), 1.25 (3H, d, J=7.2 Hz), 1.02 (3H, dd, J=124.3 Hz, $^1J_{CH}$=7.3 Hz), 0.92 (3H, d, J=6.5 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3—splittings observed for labelled compound: 26.4 (d, J=32.5 Hz, $^1J_{CC}$, C-4), 16.7 (C-15, ca. 90× the intensity of other ^{13}C peaks, C-15); HREIMS m/z (rel. int.): 237.1805 [M^+, $C_{14}{}^{13}C_1H_{24}O_2$ requires 237.1810, Δ=0.5 mmu] (56), 193 (6), 180 (100), 152 (79), 125 (72), 124 (43).

4.8.4. [4-^{13}CH$_3$],8,11-Trimethyl-10-oxa-tricyclo-[5.3.3.0*1,6*]tridecan-9-one (15c). Oil (minor rearrangement product—ca. 4% of the total of compounds **12c**–**15c**, R_t 35.1 min). $[\alpha]_D$ −14.3 (c 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3018, 2939, 2866, 1705, 1456 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) (ppm): 2.65 (1H, dq, J=5.7, 7.2 Hz), 2.17 (1H, ddd, J=12.7, 3.0, 3.0 Hz), 2.11 (1H, m), 1.88 (1H, ddd, J=12.7, 2.7, 2.7 Hz), 1.27 (3H, d, J=7.2 Hz), 0.95 (3H, dd, J=124.7 Hz, $^1J_{CH}$=6.2 Hz), 0.89 (3H, d, J=6.7 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3—splittings observed for labelled compound: 44.9 (d, J=4.2 Hz, $^3J_{CC}$, C-6), 34.5 (d, J=4.2 Hz, $^3J_{CC}$, C-2), 32.6 (d, J=35.5 Hz, $^1J_{CC}$, C-4), 22.0 (C-15, ca. 90× intensity of other ^{13}C peaks, C-15); HREIMS m/z (rel. int.): 237.1806 [M^+, $C_{14}{}^{13}C_1H_{24}O_2$ requires 237.1810, Δ=0.4 mmu] (1), 193 (15), 164 (15), 125 (100), 124 (49), 113 (25).

4.9. Autoxidation of labelled dihydroartemisinic acid (2a/2b) on storage

Conditions and results were similar to those described in Ref. 22.

4.10. Autoxidation of 2-(4,7-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid [Δ^3-isomer of dihydroartemisinic acid] (9c) on storage

After storage at −20 °C for 6 months, compound **9c** was found to have undergone autoxidation to a complex mixture of products, which were difficult to separate chromatographically. Compounds **18c**–**22c** were isolated from the mixture in varying degrees of purity by HPLC (30% EtOAc/*n*-hexane/0.7% AcOH).

4.10.1. 2-(7ξ-Hydroperoxy-4,[7-^{13}CH$_3$]-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),7,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid (18c). Oil (major component: ca. 30% of compounds **18c**–**22c**, R_t 25.2 min); IR ν_{max} ($CHCl_3$): 3400–2600, 3020, 2930, 1705, 1653, 1456 cm^{-1}; ^{1}H NMR (characterized by 2D NMR as a mixture with **22c**) (δ, $CDCl_3$) (ppm): 7.30 (1H, br s, −OOH), 6.23 (1H, dd, J=9.8, 5.4 Hz, H-2), 5.54 (1H, d, J=9.8 Hz, H-3), 2.45 (1H, dq, J=10.1, 6.9 Hz, H-11), 1.35 (3H, d, J=127.6 Hz, $^1J_{CH}$, H-15), 1.24 (3H, d, J=6.9 Hz, H-13), 0.95 (3H, d, J=6.5 Hz, H-14); HREIMS m/z (rel. int.): 251.1603 [M^+-H_2O, $C_{14}{}^{13}C_1H_{22}O_3$ requires 251.1602, Δ=−0.1 mmu] (25), 236 (32), 178 (38), 162 (100), 161 (78).

4.10.2. 2-(7ξ-Hydroperoxy-4,[7-^{13}CH$_3$]-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),7,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid (19c). Oil (major component: ca. 40% of compounds **18c**–**22c**, R_t 27.5 min). IR ν_{max} ($CHCl_3$): 3400–2600 (br), 2928, 2853, 1707, 1458 cm^{-1}; ^{1}H NMR (characterized by 2D NMR as a mixture with **21c**) (δ, $CDCl_3$) (ppm): 7.33 (1H, br s, −OOH), 6.12 (1H, dd, J=10.1, 5.0 Hz, H-2), 5.55 (1H, d, J=10.1 Hz, H-3), 2.41 (1H, dq, J=7.1, 6.7 Hz, H-11), 1.30 (3H, d, J=128.5 Hz, $^1J_{CH}$, H-15), 1.18 (3H, d, J=6.7 Hz, H-13), 0.93 (3H, d, J=6.1 Hz, H-14); HREIMS m/z (rel. int.): 235.1648 [$M^+-H_2O_2$, $C_{14}{}^{13}C_1H_{22}O_2$ requires 251.1653, Δ=0.5 mmu] (3), 162 (100), 161 (70).

4.10.3. 2-(7ξ-Hydroxy-4,[7-^{13}CH$_3$]-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),7,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid (20c). Oil (minor component: ca. 10% of compounds **18c**–**22c**). R_t 32.7 min). $[\alpha]_D$ −5.9 (c 0.2, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3400–2600, 2937, 2855, 1717, 1603, 1458 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$) (ppm): 5.91 (1H, dd, J=10.1, 5.2 Hz, H-2), 5.53 (1H, d, J=10.1 Hz, H-3), 2.40 (1H, dq, J=11.2, 7.0 Hz, H-11), 1.32 (3H, d, J=126.1 Hz, $^1J_{CH}$, H-15), 1.17 (3H, d, J=6.9 Hz, H-13), 0.94 (3H, d, J=6.3 Hz, H-14); HREIMS m/z (rel. int.): 235.1646 [M^+-H_2O, $C_{14}{}^{13}C_1H_{22}O_2$ requires 235.1653, Δ=0.8 mmu] (20), 217 (20), 191 (41), 163 (70), 162 (100).

4.10.4. 2-(7ξ-Hydroxy-4,[7-^{13}CH$_3$]-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),7,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid (21c). Oil (minor component: ca. 15% of compounds **18c**–**22c**). ^{1}H NMR (characterized by 2D NMR as a mixture with **19c**) (δ, $CDCl_3$) (ppm): 6.02 (1H, dd, J=9.9, 5.3 Hz, H-2), 5.61 (1H, d, J=9.9 Hz, H-3), 2.40 (1H, dq, J=6.6, 6.9 Hz, H-11), 1.30 (3H, d, J=128.5 Hz, $^1J_{CH}$, H-15), 1.21 (3H, d, J=6.9 Hz, H-13), 0.94 (3H, d, J=6.1 Hz, H-14).

4.10.5. 2-(4,[7-^{13}CH$_3$]-dimethyl-5-oxo-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid (22c). Oil (very minor component: ca. 5% of compounds **18c**–**22c**). ^{1}H NMR (characterized by 2D NMR as a mixture with **18c**) (δ, $CDCl_3$) (ppm): 5.82 (1H, d, J=5.5 Hz, $^3J_{CH}$, H-3,), 1.95 (3H, d, J=126.9 Hz, $^1J_{CH}$, H-15), 1.20 (3H, d, J=6.8 Hz, H-13), 0.84 (3H, d, J=6.5 Hz, H-14).

4.11. Preparation of 2-(4-methyl-7-oxo-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7-octahydro-naphthalen-1-yl)-propionic acid methyl ester (24) from decalenone keto-acid (3)

See Ref. 22 for the procedure used for converting **3** into **24** in the presence of diazomethane and Ref. 30 for the physical properties of **24**.

4.12. Reduction of α,β-unsaturated ketone 24 to secondary alcohol 25 by $NaBH_4$ in pyridine

To a solution of the methyl ester **24** (902 mg) in pyridine (5 ml) was added a solution of $NaBH_4$ (650 mg) in pyridine (4 ml). The reaction mixture was stirred for 3 h at room temperature then diluted with Et_2O (50 ml). HCl (10%) was added to neutralize the solution while cooling in an ice bath. The mixture was extracted by Et_2O (3×100 ml), washed with brine (3×50 ml) and dried ($MgSO_4$). Solvent was removed by a rotary evaporator to yield a crude product (686 mg, 76%) which was purified by CC (50% EtOAc/*n*-hexane) to obtain the alcohol **25**.

4.12.1. 2-(7β-Hydroxy-4-methyl-(1α-H),2,3,(4β-H),(4aα-H),5,6, 7,8,(8aα-H)-decahydro-naphthalen-1-yl)-propionic acid (25). Oil (605 mg, 61%, R_f 0.48). $[\alpha]_D$ −10.4 (*c* 1.5, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3421 (br), 3028, 2936, 2868, 1728, 1448, 1437 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 3.66 (3H, s), 3.59 (1H, dddd, *J*=11.7, 11.7, 4.9, 4.9 Hz), 2.30 (1H, dq, *J*=11.1, 6.9 Hz), 1.10 (3H, d, *J*=6.9 Hz), 0.87 (3H, d, *J*=6.2 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m/z* (rel. int.): 254.1874 [M^+, $C_{15}H_{26}O_3$ requires 254.1882, Δ=0.8 mmu] (1), 236 (3), 205 (2), 149 (100).

4.13. 'Non-optimized' procedures for the reduction of 24 yielding the alternative products 30–32. Reduction by alkaline sodium borohydride

To a solution of **24** (1.0 g) in MeOH (10 ml) cooled in an ice bath, was added dropwise a solution of $NaBH_4$ (0.76 g) in NaOH solution (1 ml, 30%) over a period of 10 min. The mixture was acidified with HCl (2 ml, 3 M), diluted with water (30 ml), extracted with Et_2O (2×30 ml) and the combined organic layers were washed with brine (2×5 ml), dried ($MgSO_4$) and solvent removed under reduced pressure to yield a crude product (611 mg, 61%) consisting of compounds **30**, **31** and **32** which were separated by CC (50% EtOAc/*n*-hexane).

4.13.1. 7-(3ξ-Hydroxy-butyl)-3,6,dimethyl-hexahydro-benzofuran-2-one (30). Oil (R_f 0.26). IR ν_{max} ($CHCl_3$): 2934, 1763, 1462, 1383 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 4.40 (1H, dd, *J*=3.4, 3.4 Hz), 3.81 (1H, quin, *J*=6.2 Hz), 2.78 (1H, dq, *J*= 7.2, 7.2 Hz), 2.25 (1H, m), 1.21 (3H, d, *J*=6.2 Hz), 1.14 (3H, d, *J*=7.2 Hz), 0.95 (3H, d, *J*=6.4 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3; HREIMS *m/z* (rel. int.): 222.1620 [M^+-H_2O, $C_{14}H_{22}O_2$ requires 222.1620, Δ= 0.0 mmu] (4), 207 (18), 196 (21), 165 (15), 122 (80), 94 (100).

4.13.2. 7-(3ξ-Hydroxy-butyl)-3,6,dimethyl-hexahydro-benzofuran-2-one (31). Oil (R_f 0.28). IR ν_{max} ($CHCl_3$): 2934, 1763, 1462, 1383 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 4.42 (1H, dd, *J*=3.4, 3.4 Hz), 3.78 (1H, quin, *J*=6.2 Hz), 2.78 (1H, dq, *J*=7.2, 7.2 Hz), 2.27 (1H, m), 1.20 (3H, d, *J*=6.2 Hz), 1.14 (3H, d, *J*=7.2 Hz), 0.95 (3H, d, *J*=6.4 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3; HREIMS *m/z* (rel. int.): 222.1620 [M^+-H_2O, $C_{14}H_{22}O_2$ requires 222.1620, Δ=0.0 mmu] (13), 207 (21), 196 (29), 165 (19), 122 (92), 94 (100).

4.13.3. 3,6,9-Trimethyl-octahydro-1,10-dioxa-cyclopenta[d]napthalen-2-one (32). Oil (R_f 0.74). ^1H NMR (δ, $CDCl_3$) (ppm): 3.98 (1H, m), 3.28 (1H, dq, *J*=6.3, 7.3 Hz), 1.11 (3H, d, *J*=6.4 Hz), 1.09 (3H, d, *J*=7.3 Hz), 0.88 (3H, d, *J*=6.3 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3.

4.14. Non-optimized procedures for the reduction of 24 yielding the alternative products 33 and 34. Reduction by methanolic sodium borohydride

To a solution of **24** (1.23 g) in MeOH (10 ml) cooled in an ice bath was added $NaBH_4$ (0.92 g) in portions, over a period of 5 min. After a further 10 min, HCl (5 ml, 3 M) was added to pH 4 and the mixture was diluted with water (50 ml) and extracted with Et_2O (2×50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a colourless oil (0.61 g, 50%) consisting of a mixture of the two epimeric alcohols **33** and **34**, which could not be separated chromatographically.

4.14.1. 2-(7ξ-Hydroxy-4-methyl-(1α-H),2,3,(4β-H),(4aα-H),5,6,7octahydro-naphthalen-1-yl)-propionic acid methyl ester (33/34). Oil. ^1H NMR (δ, $CDCl_3$) (ppm): 5.41/5.38 (1H, d, *J*=1.6 Hz), 4.24/4.14 (1H, br s), 3.67 (3H, s), 2.76 (1H, m), 1.24 (3H, d, *J*=6.9 Hz), 0.92 (3H, d, *J*=6.6 Hz)—see Table 4 for full assignments; ^{13}C NMR: see Table 3.

4.15. Jones oxidation of alcohol 25

To a solution of **25** (600 mg) in acetone (5 ml), cooled in an ice bath, was added Jones reagent (freshly prepared by mixing CrO_3 (180 mg), H_2O (0.4 ml) and conc. H_2SO_4 (0.16 ml) and washing the resulting precipitate with water). The reaction mixture was stirred for 30 min, until the starting material had disappeared, as judged by TLC. Then MeOH (10 ml) was added and the mixture was taken up in H_2O (50 ml) and extracted by Et_2O (2×50 ml). The combined organic layers were washed with H_2O (10 ml) and brine (10 ml), dried ($MgSO_4$) and solvent removed under reduced pressure to yield compound **26** (588 mg, 98%) without the need for further purification.

4.15.1. 2-(4-Methyl-7-oxo-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aα-*H*)-decahydro-naphthalen-1-yl)-propionic acid methyl ester (26). Solid. Mp 158–161 °C. $[\alpha]_D$ −18.1 (*c* 2.6, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3013, 2955, 2928, 1713, 1456 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 3.67 (3H, s), 1.10 (3H, d, *J*=6.9 Hz), 0.96 (3H, d, *J*=6.2 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m/z* (rel. int.): 252.1732 [M^+, $C_{15}H_{24}O_3$ requires 252.1725, Δ=−0.7 mmu] (2), 221 (1), 175 (5), 165 (38), 164 (100).

4.16. Grignard reaction of methyl ester 26 with methyl iodide

To a Grignard reagent freshly prepared from Mg (13 mg) and MeI (88 mg) was added a solution of compound **26** (124 mg) in Et_2O (30 ml). The reaction mixture was refluxed for 3 h, then cooled to 0 °C and H_2O (50 ml) was added. The mixture was extracted by Et_2O (2×50 ml), and the combined organic extracts washed with H_2O (10 ml) and

brine (50 ml), dried ($MgSO_4$) and solvent removed on a rotary evaporator to yield a crude product (116 mg, 94%) consisting of a mixture of the 4-hydroxy epimers **27** and **28**, which could be separated by HPLC (30% EtOAc/*n*-hexane) for purposes of characterization, but which were normally used as a mixture for the last step in the synthesis (Section 4.17).

4.16.1. 2-(7α-Hydroxy-4,7-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aα-*H*)-decahydro-naphthalen-1-yl)-propionic acid methyl ester (27). Oil (41 mg, 32%, R_t 22.1 min). $[\alpha]_D$ −11.1 (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3546, 2928, 2856, 1717, 1458 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 3.66 (3H, s), 2.26 (1H, dq, *J*=11.1, 6.8 Hz), 2.16 (1H, ddd, *J*=16.9, 3.8, 3.8 Hz), 1.22 (3H, s), 1.12 (3H, d, *J*=6.8 Hz), 0.83 (3H, d, *J*=6.4 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1. HREIMS: *m*/*z* (rel. int.): 250.1935 [M^+-H_2O, $C_{16}H_{26}O_2$ requires 250.1933, Δ=−0.2 mmu] (3), 236 (1), 218 (2), 201 (1), 191 (4), 175 (4), 163 (81), 162 (100).

4.16.2. 2-(7β-Hydroxy-4,7-dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,7,8,(8aα-*H*)-decahydro-naphthalen-1-yl)-propionic acid methyl ester (28). Oil (60 mg, 48%, R_t 24.2 min). $[\alpha]_D$ +2.3 (*c* 1.3, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3599, 3447 (br), 3007, 2932, 2870, 1728, 1456 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 3.66 (3H, s), 2.29 (1H, dq, *J*=11.1, 6.9 Hz), 1.27 (3H, s), 1.09 (3H, d, *J*=6.9 Hz), 0.83 (3H, d, *J*=6.2 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m*/*z* (rel. int.): 268.2039 [M^+, $C_{16}H_{28}O_3$ requires 268.2038, Δ=−0.1 mmu] (2), 250 (3), 236 (2), 218 (3), 191 (4), 175 (4), 163 (75), 162 (100).

4.17. Dehydration of tertiary alcohols 27/28

The dehydration of the mixture of epimeric alcohols **27/28** (50 mg) was effected in the same way as for the alcohols **5/6** (see Section 4.6) resulting in a crude mixture (45 mg, 90%) containing the double bond regio-isomers, compounds **23** and **29**, which were separated by HPLC (2.5% EtOAc/*n*-hexane/0.7% AcOH).

4.17.1. 2-(4,7-Dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,6,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid methyl ester [dihydroartemisinic acid methyl ester] (23). Oil (16 mg, 34%, R_t 13.7 min). $[\alpha]_D$ −9.6 (*c* 2.4, $CHCl_3$); IR ν_{max} ($CHCl_3$): 2924, 2872, 2851, 1728, 1456, 1437 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 5.12 (1H, s), 3.68 (3H, s), 2.50 (2H, m), 1.63 (3H, d, *J*=0.7 Hz), 1.13 (3H, d, *J*=6.9 Hz), 0.86 (3H, d, *J*=6.5 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m*/*z* (rel. int.): 250.1939 [M^+, $C_{16}H_{26}O_2$ requires 250.1933, Δ=−0.6 mmu] (4), 219 (3), 201 (3), 163 (55), 162 (100).

4.17.2. 2-(4,7-Dimethyl-(1α-*H*),2,3,(4β-*H*),(4aα-*H*),5,8,(8aα-*H*)-octahydro-naphthalen-1-yl)-propionic acid methyl ester [Δ^3-isomer of dihydroartemisinic acid methyl ester] (29). Oil (21 mg; 46%, R_t 15.0 min). $[\alpha]_D$ +34.0 (*c* 10.6, $CHCl_3$); IR ν_{max} ($CHCl_3$): 2970, 2930, 2849, 1728, 1456 cm^{-1}; ^1H NMR (δ, $CDCl_3$) (ppm): 5.28 (1H, d, *J*=3.6 Hz), 3.66 (3H, s), 2.31 (1H, dq, *J*=11.1, 6.8 Hz), 1.63 (3H, s), 1.13 (3H, d, *J*=6.8 Hz), 0.81 (3H, d, *J*=6.4 Hz)—see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS *m*/*z* (rel. int.): 250.1937 [M^+, $C_{16}H_{26}O_2$ requires 250.1933, Δ=−0.4 mmu] (2), 219 (4), 191 (5), 163 (65), 162 (100).

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References and notes

1. Liu, J.-M.; Ni, M.-Y.; Fan, Y.-Y.; Tu, Y.-Y.; Wu, Z.-H.; Wu, Y.-L.; Zhou, W.-S. *Acta Chim. Sin.* **1979**, *37*, 129–143.
2. Kudakasseril, G. J.; Lam, L.; Staba, E. J. *Planta Med.* **1987**, 280–284.
3. Akhila, A.; Thakur, R. S.; Popli, S. P. *Phytochemistry* **1987**, *26*, 1927–1930.
4. Akhila, A.; Rani, K.; Thakur, R. S. *Phytochemistry* **1990**, *29*, 2129–2132.
5. Huang, J.-J.; Zhou, F.-Y.; Wu, L.-F.; Zhen, G.-H. *Acta Chim. Sin.* **1990**, *48*, 275–277.
6. Bouwmeester, H. J.; Wallaart, T. E.; Janssen, M. H. A.; van Loo, B.; Jansen, B. J. M.; Posthumus, M. A.; Schmidt, C. O.; de Kraker, J.-W.; Konig, W. A.; Franssen, M. C. R. *Phytochemistry* **1999**, *52*, 843–854.
7. Chen, D.-H.; Ye, H.-C.; Li, G.-F. *Plant Sci.* **2000**, *155*, 179–185.
8. Bharel, S.; Gulati, A.; Abdin, M. Z.; Srivastava, P. S.; Jain, S. K. *Fitoterapia* **1996**, *LXVII*, 387–402.
9. Kim, N.-C.; Kim, S.-O. *J. Korean Agric. Chem. Soc.* **1992**, *35*, 106–109, CA **117**: 147253c.
10. Wang, Y.; Xia, Z.-Q.; Zhou, F.-Y.; Wu, Y.-L.; Huang, J.-J.; Wang, Z.-Z. *Chin. J. Chem.* **1993**, *11*, 457–463.
11. El-Feraly, F. S.; Al-Meshal, I. A.; Al-Yahya, M. A.; Hifnawy, M. S. *Phytochemistry* **1986**, *25*, 2777–2778.
12. Wang, Y.; Xia, Z.-Q.; Zhou, F.-Y.; Wu, Y.-L.; Huang, J.-J.; Wang, Z.-Z. *Acta Chim. Sin.* **1988**, *46*, 1152–1153.
13. Chen, P. K.; Lukonis, C.; Go, L.; Leather, G. R. *Proc. Plant Growth Regul. Soc. Am. (18th)* **1991**, 2–8, CA **119**: 269078m.
14. Misra, L. N.; Ahmad, A.; Thakur, R. S.; Lotter, H.; Wagner, H. *J. Nat. Prod.* **1993**, *56*, 215–219.
15. Sangwan, R. S.; Agarwal, K.; Luthra, R.; Thakur, R. S.; Singh-Sangwan, N. *Phytochemistry* **1993**, *34*, 1301–1302.
16. Li, Y.; Yang, Z.-X.; Chen, Y.-X.; Zhang, X. *Yaoxue Xuebao* **1994**, *29*, 713–716, CA **122**: 156352q.
17. Nair, M. S. R.; Basile, D. V. *Ind. J. Chem.* **1992**, *31B*, 880–882.
18. Nair, M. S. R.; Basile, D. V. *J. Nat. Prod.* **1993**, *56*, 1559–1566.
19. Wang, Y.; Shen, Z.-W.; Xia, Z.-Q.; Zhou, F.-Y. *Chin. J. Chem.* **1993**, *11*, 476–478.
20. Bharel, S.; Gulati, A.; Abdin, M. Z.; Srivastava, P. S.; Vishwakarma, R. A.; Jain, S. K. *J. Nat. Prod.* **1998**, *61*, 633–636.
21. Brown, G. D. *Phytochem. Rev.* **2003**, *2*, 45–59.

22. Sy, L.-K.; Zhu, N.-Y.; Brown, G. D. *Tetrahedron* **2001**, *57*, 8495–8510.
23. Xu, X.-X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron* **1986**, *42*, 819–828.
24. Constantino, M. G.; Beltrame, M.; da Silva, G. V. J. *Synth. Commun.* **1996**, *26*, 321–329.
25. Ngo, K.-S.; Brown, G. D. *Tetrahedron* **1999**, *55*, 15099–15108.
26. Sy, L.-K.; Brown, G. D.; Haynes, R. *Tetrahedron* **1998**, *54*, 4345–4356.
27. Sy, L.-K.; Liang, G.-Y.; Brown, G. D. *Phytochemistry* **2003**, *64*, 303–323.
28. Sy, L.-K.; Brown, G. D. *Tetrahedron* **2002**, *58*, 897–908.
29. Sy, L.-K.; Brown, G. D. *Tetrahedron* **2002**, *58*, 909–923.
30. Hui, S.-M.; Ngo, K.-S.; Brown, G. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3435–3442.
31. Wu, Y.-L.; Li, Y. *Med. Chem. Res.* **1995**, *5*, 569–586.
32. Nishiguchi, T.; Machida, N.; Yamamoto, E. *Tetrahedron Lett.* **1987**, *28*, 4565–4568.

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In vivo transformations of dihydroartemisinic acid in *Artemisia annua* plants

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Abstract—[15-$^{13}C^{2}H_3$]-dihydroartemisinic acid (**2a**) and [15-$C^{2}H_3$]-dihydroartemisinic acid (**2b**) have been fed via the root to intact *Artemisia annua* plants and their transformations studied in vivo by one-dimensional ^{2}H NMR spectroscopy and two-dimensional $^{13}C-^{2}H$ correlation NMR spectroscopy ($^{13}C-^{2}H$ COSY). Labelled dihydroartemisinic acid was transformed into 16 12-carboxy-amorphane and cadinane sesquiterpenes within a few days in the aerial parts of *A. annua*, although transformations in the root were much slower and more limited. Fifteen of these 16 metabolites have been reported previously as natural products from *A. annua*. Evidence is presented that the first step in the transformation of dihydroartemisinic acid in vivo is the formation of allylic hydroperoxides by the reaction of molecular oxygen with the $\Delta^{4,5}$-double bond in this compound. The origin of all 16 secondary metabolites might then be explained by the known further reactions of such hydroperoxides. The qualitative pattern for the transformations of dihydroartemisinic acid in vivo was essentially unaltered when a comparison was made between plants, which had been kept alive and plants which were allowed to die after feeding of the labelled precursor. This, coupled with the observation that the pattern of transformations of **2** in vivo demonstrated very close parallels with the spontaneous autoxidation chemistry for **2**, which we have recently demonstrated in vitro, has lead us to conclude that the main 'metabolic route' for dihydroartemisinic acid in *A. annua* involves its spontaneous autoxidation and the subsequent spontaneous reactions of allylic hydroperoxides which are derived from **2**. There may be no need to invoke the participation of enzymes in any of the later biogenetic steps leading to all 16 of the labelled 11,13-dihydro-amorphane sesquiterpenes which are found in *A. annua* as natural products.
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1. Introduction

The Chinese plant *Artemisia annua* L. has been the subject of intensive phytochemical investigation over the past two decades following the discovery of the anti-malarial amorphane sesquiterpene artemisinin (qinghaosu) (**1**).[1] Some 47 amorphane and cadinane sesquiterpenes are currently reported from this species in the literature,[2–6] 35 of which contain a 12-carboxy group—the majority of these amorphane and cadinane sesquiterpenes are currently known in both their 11,13-dihydro and 11,13-dehydro forms (see compounds **1**–**28** in Figure 1, for examples). Although the biosynthesis of the amorphane/cadinane skeleton undoubtedly proceeds from mevalonic acid in *A. annua*,[7–10] and requires the participation of those enzymes which are normally associated with sesquiterpene biosynthesis (some of which have now been characterized from this species),[11,12] there is much more uncertainty regarding the manner of the subsequent skeletal rearrangement (involving carbon–carbon cleavage at C-4/C-5) which ultimately gives rise to the 1,2,4-trioxane system of artemisinin (**1**).[13]

A number of previous attempts have been made to delineate the biosynthetic pathway to the unique 1,2,4-trioxane ring in **1**, and experimental evidence has been presented that several of the natural products shown in Figure 1 may be late biosynthetic intermediates *en route* to artemisinin in either their 11,13-dihydro or 11,13-dehydro forms. However, it is clear that only some of these proposals can be correct. Thus, although all investigators seem to concur that either dihydroartemisinic acid (**2**)[14,15] or its 11,13-dehydro analogue artemisinic acid (arteannuic acid) (**3**)[15,17–22] are advanced precursors *en route* to artemisinin, there are several differing, and sometimes directly conflicting, views as to exactly how their transformation into **1** occurs. (It should be noted that compound **3** is also hydroxylated and derivatized as glycosides by plant tissue cultures of *A. annua*, in what appears to be a degradative pathway.)[16] For example, while both Nair and Basile[23,24] and Jain et al.[25] have found experimental evidence that arteannuin B (**4**), or its 11,13-dihydro analogue, dihydroarteannuin B (**5**), can be

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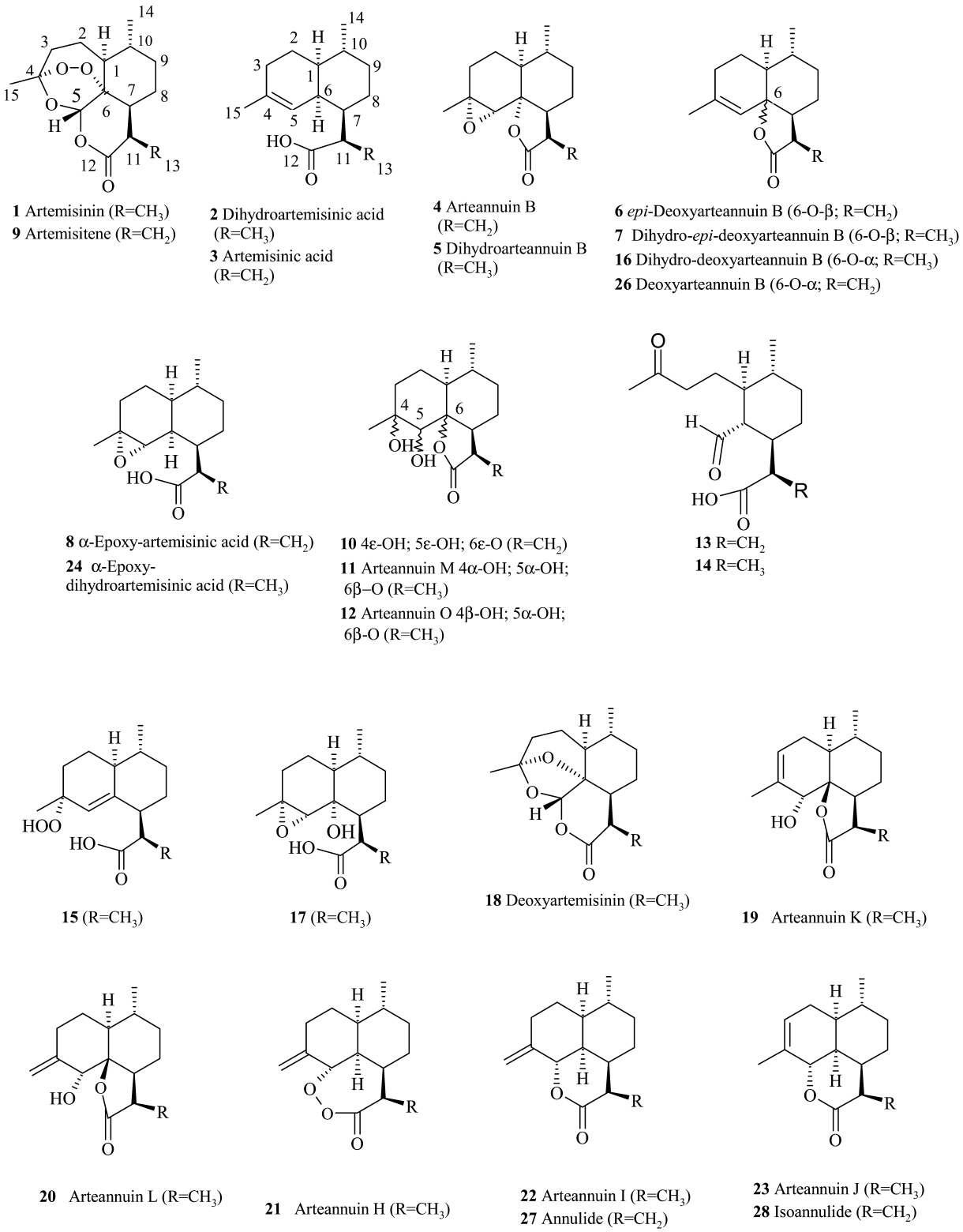


Figure 1. 12-Carboxy-amorphanes and cadinanes discussed in the text which have been reported as natural products from *A. annua*. Note that the majority of these compounds are known in both their 11,13-dihydro and 11,13-dehydro forms.

converted into artemisinin (**1**) by cell-free extracts, Wang et al. have noted that compound **4** was not a precursor of **1**,[15] but suggested rather that *epi*-deoxyarteannuin B (**6**) and dihydro-*epi*-deoxyarteannuin B (**7**) are the true intermediates in the conversion of **2/3** to **1**.[26] They also rejected the 11,13-dehydro natural product, α-epoxy-artemisinic acid (**8**),[27] as a biogenetic precursor of **1**,[15] and it has been proposed by these (and other) authors that the 11,13-dehydro-amorphane artemistene (**9**) may, in fact, be the immediate precursor of **1**.[15,23,28] Dihydroxy-amorphanes, such as compound **10**[29] (and by logical extension its 11,13-dihydro analogues, arteannuins M (**11**)[2,5] and O (**12**)),[5] have

also been implicated as possible biogenetic precursors, which might be converted to **1** via Grob fragmentation to an enolic intermediate which is tautomeric with the *seco*-amorphane **13**[29] (or its 11,13-dihydro analogue **14**),[6] but there is as yet no experimental evidence to support this.

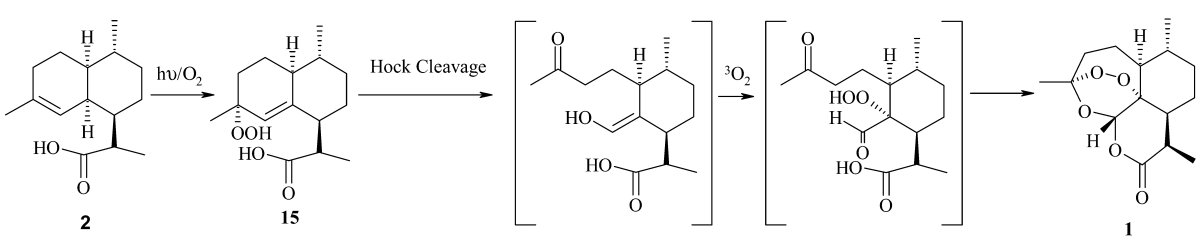
On the other hand, there are now quite a large number of studies which have shown that dihydroartemisinic acid (**2**)/artemisinic acid (**3**) can be transformed into artemisinin (**1**)/artemisitene (**9**) in the chemistry laboratory by photosensitized oxygenation. The initial product of this reaction has been identified as the tertiary allylic hydroperoxide **15**[2] (or its 11,13-dehydro equivalent), which is in turn readily converted to artemisinin (or its 11,13-dehydro equivalent, compound **9**) by reagents such as acid and/or copper (II) in the presence of atmospheric oxygen.[30–38] It has been proposed by Haynes et al. that the mechanism for this chemical conversion involves an enolic intermediate,[33–35] such as that shown in Scheme 1, and we have recently provided convincing evidence from detailed low temperature 2D NMR studies[39] for both the structure and participation of this same intermediate in the mechanism of the spontaneous autoxidation of **2**, which occurs at a much slower rate. The possible relevance to the biogenesis of artemisinin (**1**) in vivo of this 'preparative' pathway for the chemical synthesis of **1** from **2** has been highlighted within the past few years by the isolation of the tertiary allylic hydroperoxide **15** as a natural product from *A. annua*.[40,41] We have since shown that the spontaneous autoxidation of **2** also proceeds via compound **15**, in precisely the same manner which had previously been proposed for the 'chemical' transformation of **2** to **1** by photosensitized oxygenation and treatment with acid/Cu(II) (Scheme 1), but that, in actuality, it requires nothing more[†] than the presence of light and molecular oxygen.[39,43] We have, in addition, shown that compound **15** can also be spontaneously transformed in vitro into dihydroarteannuin B (**5**),[2,39,43] dihydro-*epi*-deoxyarteannuin B (**7**),[2,39] the *seco*-cadinane **14**[6,39] and several other natural products which have previously been obtained as natural products from *A. annua* (Fig. 1).

2. Results and discussion

We set out first to confirm that dihydroartemisinic acid (**2**) is a late biogenetic precursor of artemisinin (**1**) in *A. annua*, as seems to be generally accepted, and secondly to clarify the pathway by which the remarkable transformation of **2** into **1** occurs in vivo. In order to achieve this, we have fed isotopically-labelled dihydroartemisinic acid (either [15-$^{13}C^{2}H_3$]-dihydroartemisinic acid (**2a**), [15-$C^{2}H_3$]-dihydroartemisinic acid (**2b**) or [15-$^{13}CH_3$]-dihydroartemisinic acid (**2c**))[‡] to intact *A. annua* plants via the root. This is one of the most realistic scenarios for studying transformations of **2** in vivo that can be envisaged and we believe it to be an improvement on all previous biosynthetic experiments with *A. annua*, which have routinely employed cell-free extracts. Feeding the labelled precursor to the plant by the intact root is especially favourable when it is considered important to avoid any possibility for the introduction of artifacts which might be created by the spontaneous oxygenation of **2** through exposure to the atmosphere, such as might easily occur during the extensive manipulations of the biological source material which are required when preparing and studying cell-free extracts (see Refs. 39 and 43 and the companion paper for a discussion of the unexpected readiness with which the precursor **2** undergoes such spontaneous autoxidation reactions both in organic solution and on storage).

2.1. Determination of the optimum method for feeding of [15-$^{13}C^{2}H_3$]-dihydroartemisinic acid (2a) to *A. annua* plants

The solubility of dihydroartemisinic acid in deionized water was quite poor, and in order to standardize the conditions for feeding aqueous solutions of either compounds **2a**, **2b** or **2c** to *A. annua* plants, solutions of these labelled precursors were routinely prepared in TRIS buffer (at pH 8.2), which effectively fixed the carboxylate group at the 12-position of **2** in the more soluble conjugate base form, thereby enhancing its aqueous solubility. TRIS was found to be non-injurious to plants (by visual inspection, at least) at the concentrations which were required to provide an effective buffering capacity and for the quantities of dihydroartemisinic acid which were fed to individual plants in each of the experiments described in Sections 2.2–2.4. The ability of *A. annua* plants to assimilate the labelled precursor, either when cut just above the root and immersed by the cut stem in a buffered feeding solution



Scheme 1. Mechanism for the spontaneous conversion of dihydroartemisinic acid (**2**) to artemisinin (**1**) in vitro via the tertiary allylic hydroperoxide (**15**) in the presence of molecular oxygen, as established experimentally in Ref. 39.

[†] The rather unexpected spontaneity of this apparently complex transformation shown in Scheme 1 has been demonstrated to be the result of the proximity of the 12-carboxylic acid group[42] to the $\Delta^{4,5}$-double bond in **2**, which assisted/catalysed both of the autoxidation reactions and the Hock cleavage reaction of the tertiary allylic hydroperoxide intermediate **15**.

[‡] For all compounds with the suffix 'a' in this paper, the [15-CH_3] group has been replaced by [15-$^{13}C^{2}H_3$]; for compounds labelled with the suffix 'b', the [15-CH_3] group has been replaced by [15-$C^{2}H_3$]; for compounds labelled with the suffix 'c', the [15-CH_3] group has been replaced by [15-$^{13}CH_3$]. The suffix '*' indicates an unspecified isotopic enrichment at the 15-position.

of **2a**, or as intact plants, which had been washed clean of soil and immersed by the root, was assayed by immediately extracting these plants with CH_2Cl_2, following the complete uptake of the feeding solution. (The feeding solution was taken up by the plants over a period of a few hours, when administered at a level of roughly 1 ml (containing ca. 2 mg of **2a**) to every 5 g of fresh plant material.)

The resulting crude extracts were analysed directly by ^2H NMR spectroscopy which consistently demonstrated that both intact (root-fed) and 'cut' (stem-fed) *A. annua* plants assimilated between 50–80% of the labelled dihydroartemisinic acid (**2a**) under these conditions. A single doublet peak (δ_D 1.63 ppm, $^1J_{CD}$=19.1 Hz), corresponding to the labelled dihydroartemisinic acid precursor, was observed in all the ^2H NMR spectra of the CH_2Cl_2 extracts which were made in this preliminary study, indicating that no discernible metabolism had occurred over the relatively short period of time used for feeding. By extracting root compartments, stem compartments and leaf/flower compartments separately, it was then possible to estimate the distribution of this labelled precursor within the plant. For plants fed via the cut stem, it was found that there was more or less equal recovery of label between the leaf/flower compartments and the stem compartment (25–40% of the labelled precursor was recovered from each). A parallel distribution was observed between the various aerial parts of the intact plants, with 5–20% remaining in the root. The evident similarities between the two feeding methods ('cut' plants fed via the stem and intact plants fed via the root) appeared to demonstrate that the root of *A. anuua* offered no physiological barrier to the uptake of dihydroartemisinic acid and that the labelled precursor could then be efficiently redistributed throughout the various plant tissues, following its uptake by the root. This was a remarkable result, as it suggested that the most 'natural' feeding method which we could devise ('natural' in the sense that this technique involves the minimum possible disturbance to, and manipulation of, the biological system; and is, therefore, more likely to produce results which most closely mimic the metabolic fate for dihydroartemisinic acid that is naturally present in *A. annua* plants) also resulted in an exceptionally high incorporation of the labelled dihydrortemisinic acid precursor into the tissues of *A. annua* (up to 80% recovery). In consequence, all the feeding experiments which are described in Sections 2.2–2.4 were performed using intact *A. annua* plants which were fed with one of the labelled precursors **2a**, **2b** or **2c** via the root.

2.2. Time-course study of the in vivo transformations of [15-$^{13}C^2H_3$]-dihydroartemisinic acid (2a) which was fed to intact *A. annua* plants via the root

The experimental design for the study of the metabolism of dihydroartemisinic acid in *A. annua* plants which is described in this section involved feeding 21 intact plants with 5 mg each of compound **2a** via the root, using the optimized procedure which was developed in Section 2.1. The plants were kept alive hydroponically by periodic replacement of water in their feeding vials, and CH_2Cl_2 extracts were made at approximately daily intervals until the experiment had been completed after six days. Each extraction event involved groups of three plants which were separated into a root compartment and 'aerial parts',[§] then extracted individually (triplicate replication) by dichloromethane and analysed immediately by ^2H NMR spectroscopy, as described in Section 2.1. ^2H NMR spectroscopic analysis of the crude extracts of the aerial parts made at 10, 24, 33, 48, 72, 96 and 144 h after the commencement of feeding indicated substantial changes, as is shown in Figure 2 (in which one representative ^2H NMR spectrum is shown from each of the triplicate extracts made at these times after feeding **2a**). In these spectra, the doublet at δ_D 1.63 ppm, ($^1J_{CD}$=19.1 Hz), corresponding to the [15-$^{13}C^2H_3$] label in compound **2a**, can clearly be seen to decline in abundance over the course of the experiment relative to the other peaks in the ^2H NMR spectrum and to be replaced, most obviously, by a doublet at δ_D 1.68 ppm. Inspite of the complexity of these spectra, one can also appreciate the appearance of several other doublets, in particular at δ_D 1.27, 1.34 and 2.14 ppm.

Although the largish one-bond $^{13}C-^2H$ coupling constant ($^1J_{CD}$=19.1 Hz) of all the metabolites which were doubly-labelled at the 15-position made a detailed visual analysis of the one-dimensional ^2H NMR spectra from the crude extracts of the aerial parts difficult, it did allow for the direct analysis of these crude extracts by two-dimensional $^{13}C-^2H$ correlation NMR spectroscopy.[44] $^{13}C-^2H$ COSY[44,45] is an unusual NMR technique which has apparently found little application in the literature, perhaps due both to the need for special hardware to provide ^2H excitation and decoupling (although modern NMR spectrometers do now routinely incorporate the necessary hardware) and the requirement for doubly-labelled sample molecules. It is, however, an excellent tool for the analysis of the crude plant extracts which were obtained in this experiment, since it allows the ^{13}C chemical shift at the 15-position of metabolites to be also established, for ^{13}C nuclei which are connected by a single bond to ^2H nuclei at the same position—thereby enabling metabolites to be identified with greater confidence from characteristic chemical shifts in both the ^{13}C and ^2H dimensions (see Ref. 45 for a detailed discussion of the preliminary application of this technique to a biosynthetic experiment). $^{13}C-^2H$ COSY analysis of the crude plant extracts indicated that the most abundant deuterium resonances at δ_D 1.68, 1.27, 1.34 and 2.14 ppm were connected by a single bond to carbon resonances at δ_C 22.6, 23.6, 22.2 and 29.1 ppm, respectively (a two-dimensional peak was also observed in most samples at δ_D 1.63/δ_C 22.9 ppm, corresponding to the labelled precursor **2a**).

When allowance was made for the effects of ^2H isotopic enrichment on ^{13}C chemical shift (resulting in a ca. 0.3 ppm upfield shift in the position of ^{13}C resonance for each directly attached deuterium atom),[43,44] the isotopically-normal values for each of these four metabolites could then

[§] Since preliminary experiments (not discussed) had indicated that there was little difference between the leaf/flower compartment and the stem compartment, as regards the incorporation and subsequent transformations of labelled **2**, these two compartments were combined together and treated as the 'aerial parts' in this experiment.

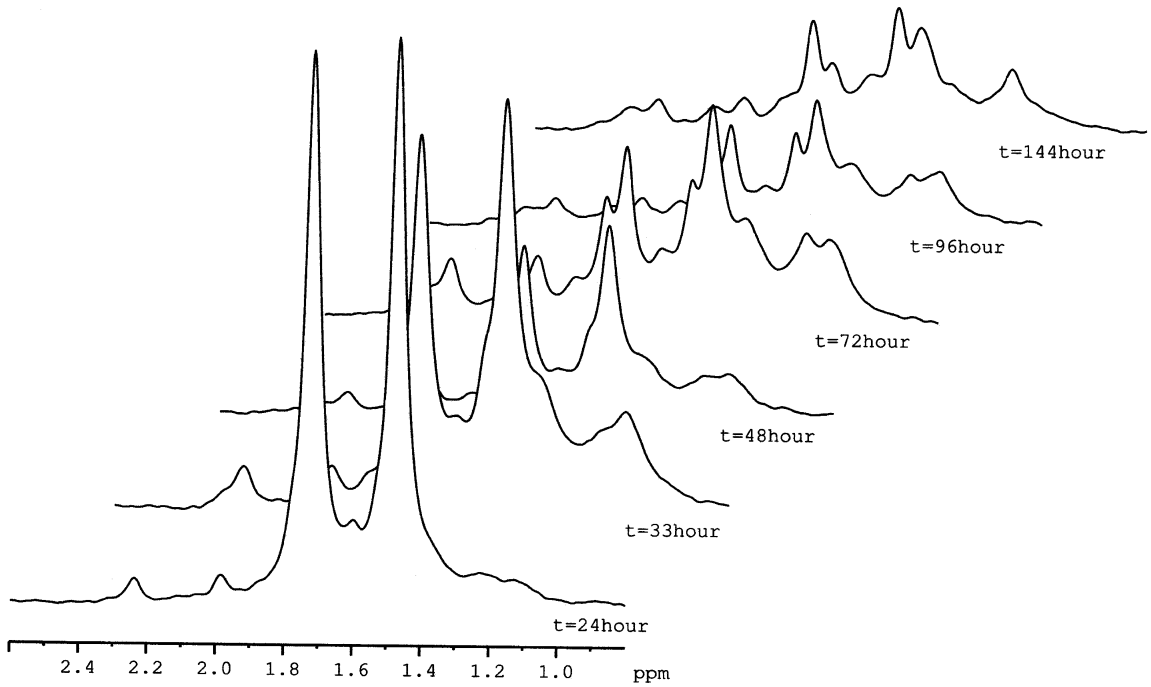


Figure 2. Expansion of the aliphatic region for representative ^{2}H NMR spectra from the aerial parts of *A. annua* plants which were fed with compound **2a** and then extracted in triplicate by CH_2Cl_2 after 24, 33, 48, 72, 96 and 144 h.

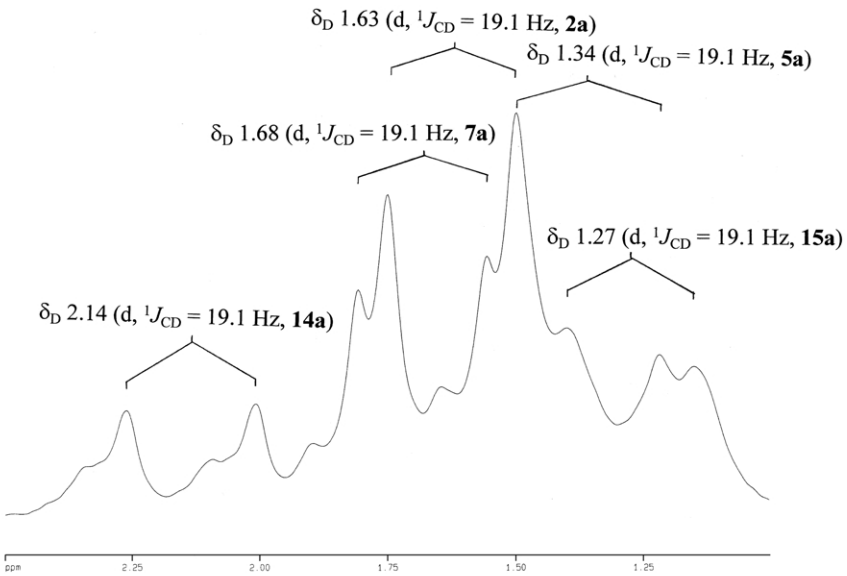
be inferred as δ_C 23.5, 24.5, 23.1 and 30.0 ppm, respectively, assuming that there has been complete retention of the ^{2}H label in the 15-methyl group (note that the 15-position of isotopically-normal dihydroartemisinic acid resonates at δ_C 23.8 ppm which is in good agreement with the carbon chemical shift observed at δ_C 22.9 ppm for labelled **2a** in this $^{13}C-^{2}H$ COSY experiment, according to such an analysis). The deuterium and carbon chemical shifts at the 15-position for the four metabolites which are most clearly resolved in Figure 2 would then be entirely consistent with their assignments as compounds **7a**,[2,43,45] **15a**,[2,45] **5a**[2,45] and **14a**[39,45] respectively, based on the fully-assigned NMR data which has been reported in the literature for each of these compounds. The ^{13}C and ^{1}H chemical shifts at the at the 15-position for the various secondary metabolites that have subsequently been isolated in this study (which constitute a large percentage of all of the 11,13-dihydro-amorphane/cadinane sesquiterpenes known from *A. annua*) are presented in Table 1 in order to illustrate that these two chemical shift parameters can indeed be used with some confidence in assigning the structures of compounds **5**, **7**, **14** and **15** (references are given to the fully assigned ^{13}C and ^{1}H NMR data, as originally reported, in each case).

Returning to the analysis of the one-dimensional ^{2}H NMR spectra, such as those shown in Figure 2, we next attempted to estimate the relative percentage amount for each of the labelled compounds **2a**, **5a**, **7a**, **14a** and **15a** that was present in all of the 21 crude extracts of the aerial parts of *A. annua* which had been fed with **2a**. In the event, computational simulation of each spectrum proved to be the only realistic way to achieve a semi-quantitative analysis: each deuteriated component of the extract was modelled as a doublet of Lorentzian lines ($^{1}J_{CD}$=19.1 Hz; line width at half height approximately 2.5–5.5 Hz) centred at δ_D 1.63, 1.34, 1.68, 2.14 and 1.27 ppm, respectively. Allowing for the presence of a large number of additional minor metabolites in these spectra, it can be seen from the examples given in Figure 3 that a good correspondence could be achieved between the ^{2}H NMR spectra and their simulations using this approach (several minor doublet peaks at δ_D 2.19, 1.78, 1.51 and 1.44 were also included in

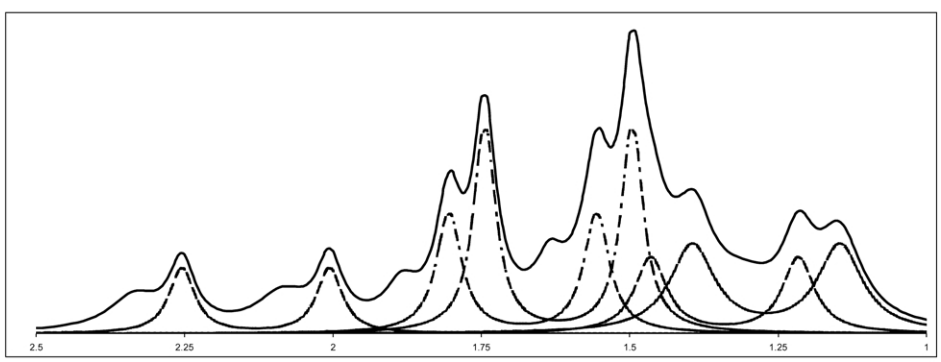
Table 1. ^{1}H and ^{13}C chemical shifts at the 15-position for all of the metabolites **1**, **2**, **5**, **7**, **11** and **14**–**25** which have been reported in the literature.

11,13-Dihydro amorphane/cadinane sesquiterpenes from *A. annua*	δ_H	δ_C	Ref.	11,13-Dihydro amorphane/cadinane sesquiterpenes from *A. annua*	δ_H	δ_C	Ref.
1	1.44	25.2	47	**17**	1.36	23.6	6
2	1.63	23.8	2	**18**	1.53	23.9	48
5	1.35	23.1	2,45	**19**	1.78	21.2	2, 5
7	1.68	23.5	2,43,45	**20**	4.93, 4.91	114.5	2, 5
11	1.39	26.6	2,5	**21**	4.91, 4.84	106.6	2, 49
14	2.14	30.0	6,39,45	**22**	5.05, 4.81	105.1	2
15	1.29	24.5	2,45	**23**	1.78	18.8	2
16	1.70	24.1	4	**24**	1.31	23.6	6,43
				25	1.33	24.2	5

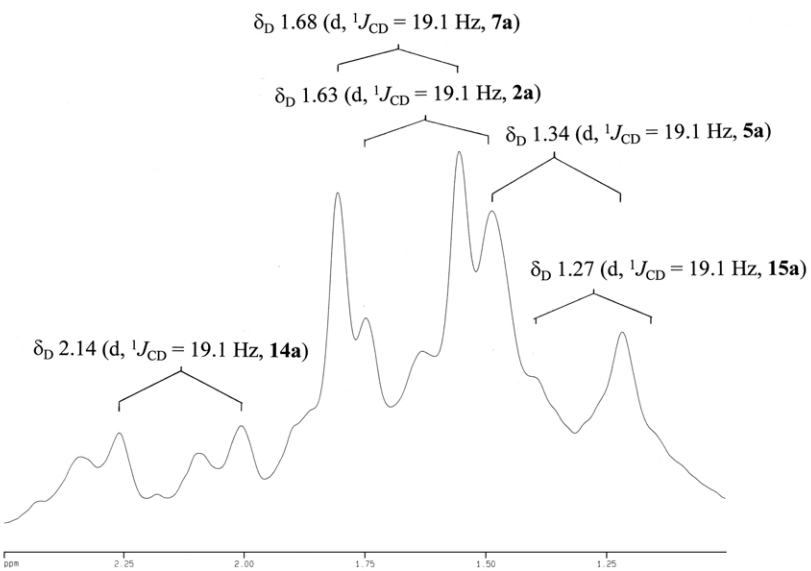
(a)


δD 1.63 (d, 1JCD = 19.1 Hz, 2a)
δD 1.34 (d, 1JCD = 19.1 Hz, 5a)
δD 1.68 (d, 1JCD = 19.1 Hz, 7a)
δD 1.27 (d, 1JCD = 19.1 Hz, 15a)
δD 2.14 (d, 1JCD = 19.1 Hz, 14a)
ppm
2.25
2.00
1.75
1.50
1.25

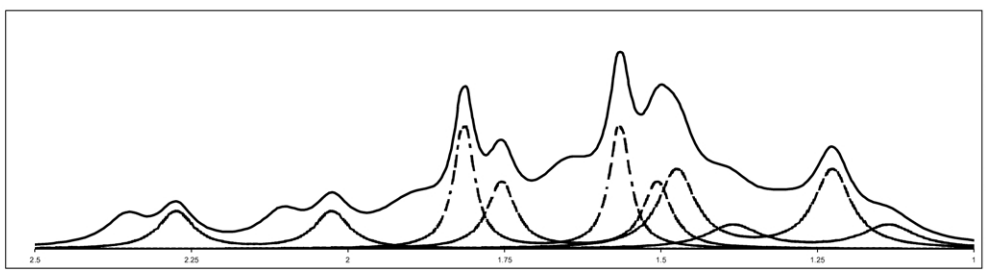
(b)


2.5
2.25
2
1.75
1.5
1.25
1

(c)


δD 1.68 (d, 1JCD = 19.1 Hz, 7a)
δD 1.63 (d, 1JCD = 19.1 Hz, 2a)
δD 1.34 (d, 1JCD = 19.1 Hz, 5a)
δD 1.27 (d, 1JCD = 19.1 Hz, 15a)
δD 2.14 (d, 1JCD = 19.1 Hz, 14a)
ppm
2.25
2.00
1.75
1.50
1.25

(d)


2.5
2.25
2
1.75
1.5
1.25
1

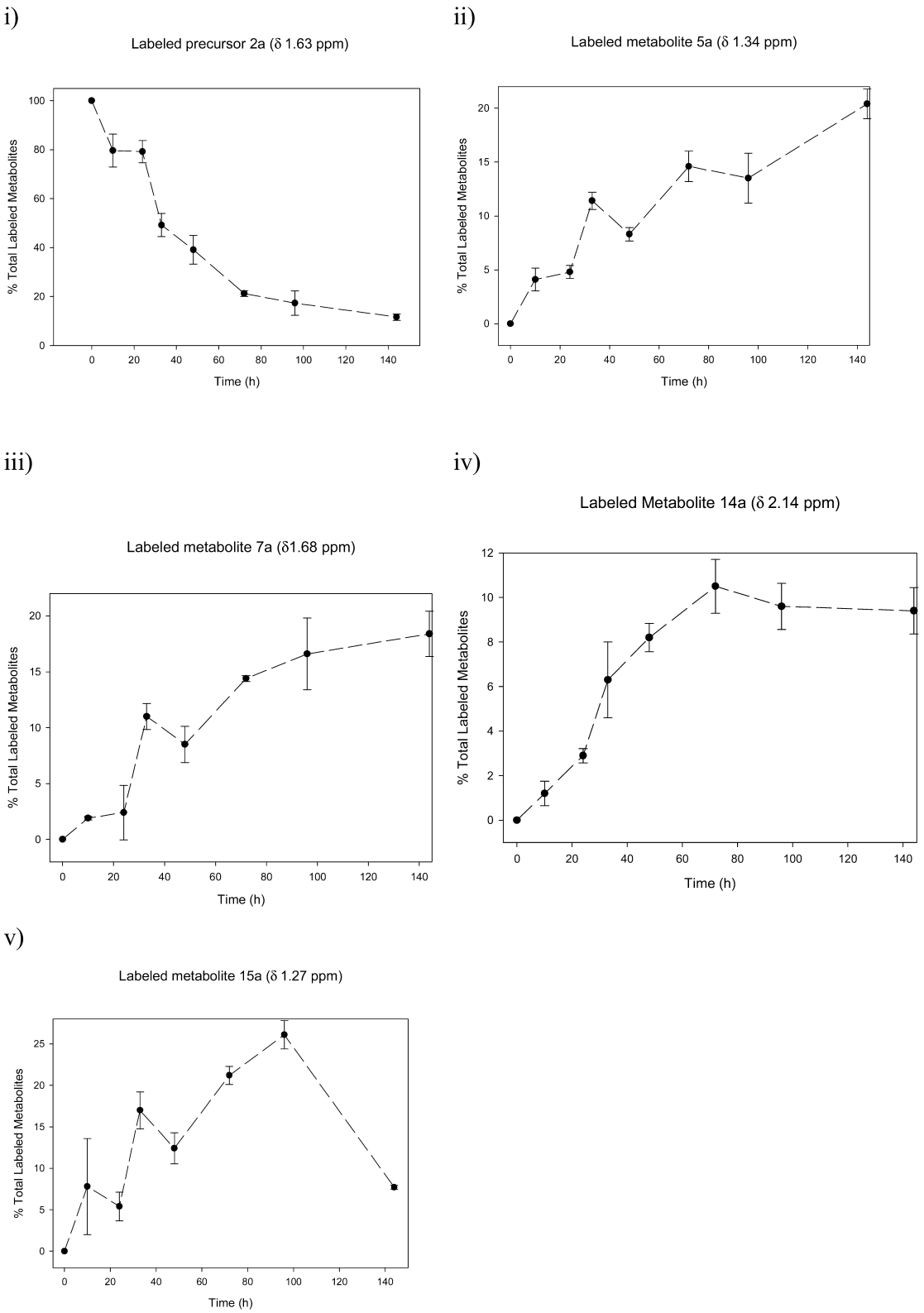
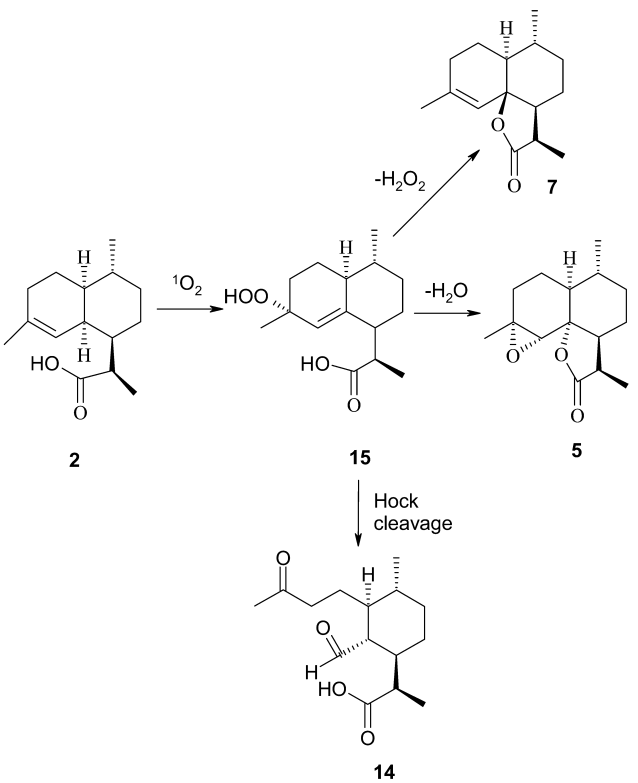


Figure 4. Variation with time in the percentage amounts of (i) **2a**, (ii) **5a**, (iii) **7a**, (iv) **14a** and (v) **15a** in the crude aerial extracts of *A. annua* plants fed with **2a**. Each data point is the average of the percentage metabolite amount from three replicates, each of which was estimated by computational simulation (Fig. 3). The corresponding standard deviations are indicated by error bars.

Figure 3. Two examples of the ^{2}H NMR spectra of the extracts of the aerial parts made at (a) 72 h and (c) 144 h after feeding *A. annua* with **2a**; and the corresponding computer simulations (b) and (d) which were used to estimate the percentage amounts of compounds **14a**, **7a**, **2a**, **5a** and **15a** (in order of decreasing deuterium chemical shift at the 15-position) in these crude extracts (the contribution of the doublets from the major components of the extract to the overall spectral simulation are shown explicitly by dotted lines).

these modeling simulations in order to obtain accurate fits to experimental data, but are not explicitly shown as 'dotted' lines in Figure 3 for overall ease of visualization—the origins of these minor peaks are discussed in the next section).

We then proceeded to make an approximate quantification of the extent of the in vivo transformations of **2a** with time, based on such simulations. The result is shown in Figure 4 as a plot of the estimated percentage amounts of each of compounds **2a**, **5a**, **7a**, **14a** and **15a** against time. This figure confirms a general trend in which the amount of the labelled precursor **2a** has declined with time at approximately the same rate at which all of metabolites **5a**, **7a** and **14a** have increased. However, the behavior of metabolite **15a**, which increased at the start of the experiment, reached a maximum after around 96 h, and then declined in abundance was more consistent with its role as an intermediate[46] in the conversion of **2a** to each of **5a**, **7a** and **14a**. Our conclusion from this analysis was therefore, that the most dominant pathway for the transformation of dihydroartemisinic acid in the aerial parts of *A. annua* is: **2→15→(5+7+14)** as is shown in Scheme 2. A similar analysis of the root extracts (not shown) suggested a comparable metabolic profile to that described for the aerial parts, but with reactions occurring at a very much slower rate (ca. 80% of the labelled precursor remained unchanged at the end of the experiment).



Scheme 2. The most dominant pathways for the transformation of dihydroartemisinic acid (**2**) in vivo, as established by 1D and 2D NMR studies of crude *A. annua* plant extracts (Figs. 2–4 and 6–8). Note that these pathways were all also observed from in vitro studies of the spontaneous autoxidation of **2** (Ref. 39).

2.3. Time-course study of the in vivo transformations of [15-C^2H_3]-dihydroartemisinic acid (2b) in both living and dead *A. annua* plants which were fed by the root

In a second experiment, 45 *A. annua* plants were individually fed via the root with 4.4 mg each of [15-C^2H_3]-dihydroartemisinic acid (**2b**). Three plants were extracted in the morning, soon after feeding had been completed, and these extracts, for which no metabolism was observed, were designated as the 'zero-time' point (0 h). The remaining plants were divided into two groups of 21 plants each: one group was kept alive hydroponically, as previously, and the second group was deprived of water and allowed to die naturally by desiccation. Leaf/flower, stem and root compartments for each plant were extracted separately at intervals over a four-day period (employing triplicate replication as before). As might be expected, the weight of the group of plants which was deprived of water after feeding (expressed as a percentage of the total weight of the plant at the time of feeding) decreased drastically over the course of the experiment (Fig. 5) and we believe that these plants were dead roughly one day after commencement of the extraction regime (or, at least, that the intracellular environment had become sufficiently dehydrated that enzymatic processes could no longer occur, which is equivalent for the purposes of the discussion which follows). By contrast, the extraction weight of the 'live' group of plants remained relatively constant (at around 60–70% of the initial weight—data not shown) and these plants were visually quite healthy over the entire course of the experiment.

Extracts were made from both live and dead groups of plants on an evening/morning schedule at 8, 24, 32, 48, 56, 72 and 80 h after the zero-time point and were immediately analysed by ^2H NMR spectroscopy. The absence of $^{13}C-^2H$ coupling at the 15-position of **2b** and its metabolites made interpretation of the one-dimensional ^2H NMR spectra from this experiment much simpler than was the case when feeding compound **2a** in Section 2.2 (Fig. 2). The most dominant peaks seen in these spectra for both the 'live' and 'dead' groups of plants appeared as singlets at the same chemical shifts as previously (δ_D 1.68, 1.27, 1.34 and 2.14 ppm). In addition, several minor singlet peaks were now clearly resolved at δ_D 2.20, 1.78, 1.51 and 1.44 ppm, becoming more obvious for the later extracts in particular (Figure 6—only examples from the 'dead' group of plants are shown, but the 'live' group gave very similar results).

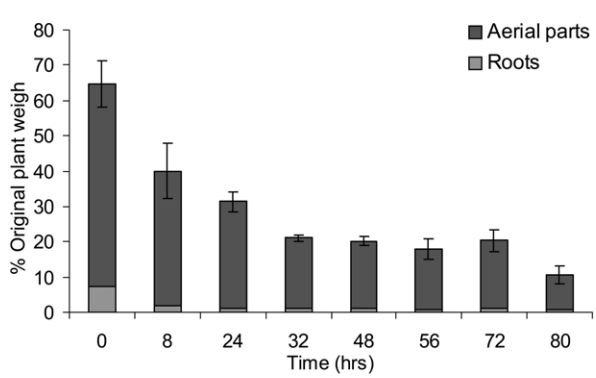


Figure 5. Weight at extraction of *A. annua* plants which were allowed to die by desiccation after feeding of compound **2b** via the root, expressed as a percentage of their weight at the time of feeding (each entry is an average of three replicates).

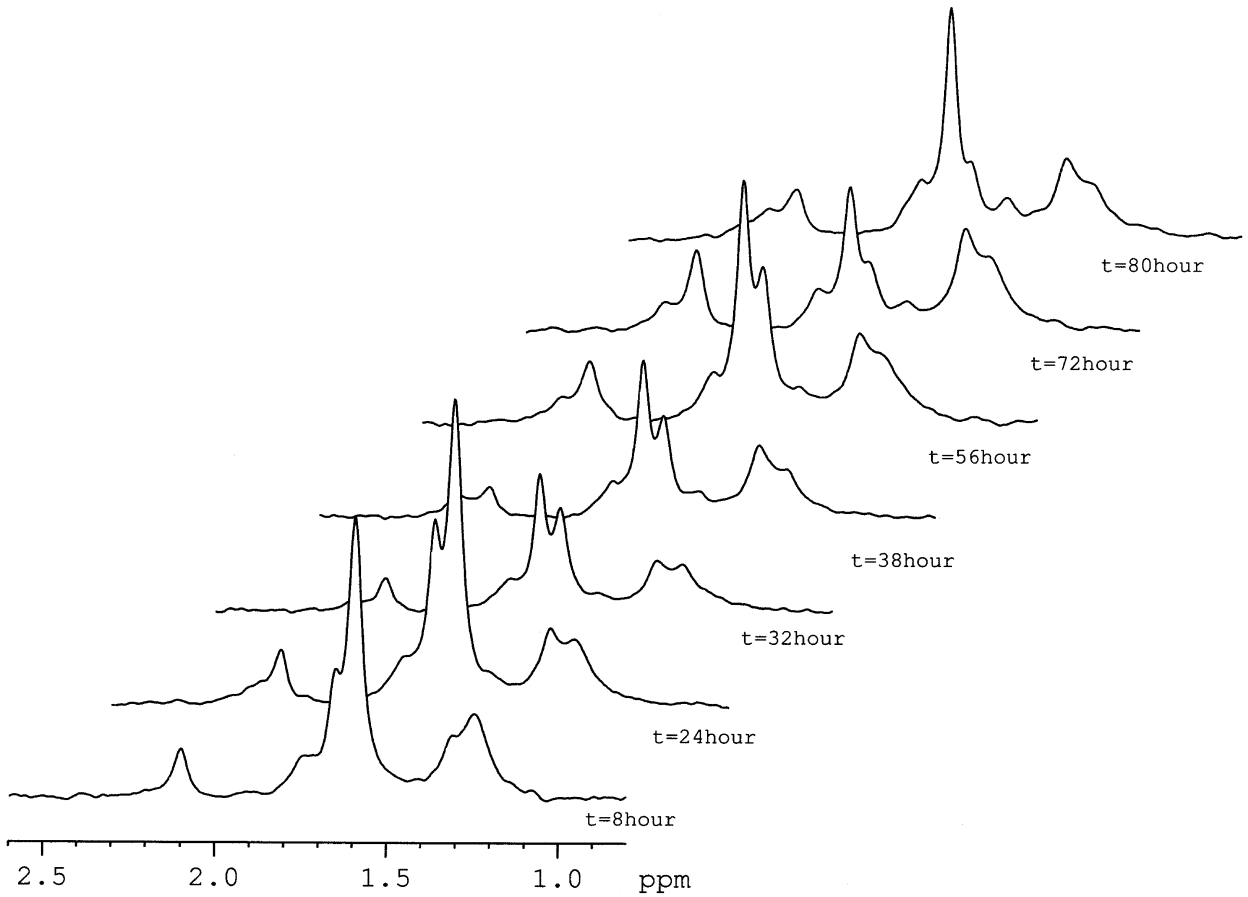


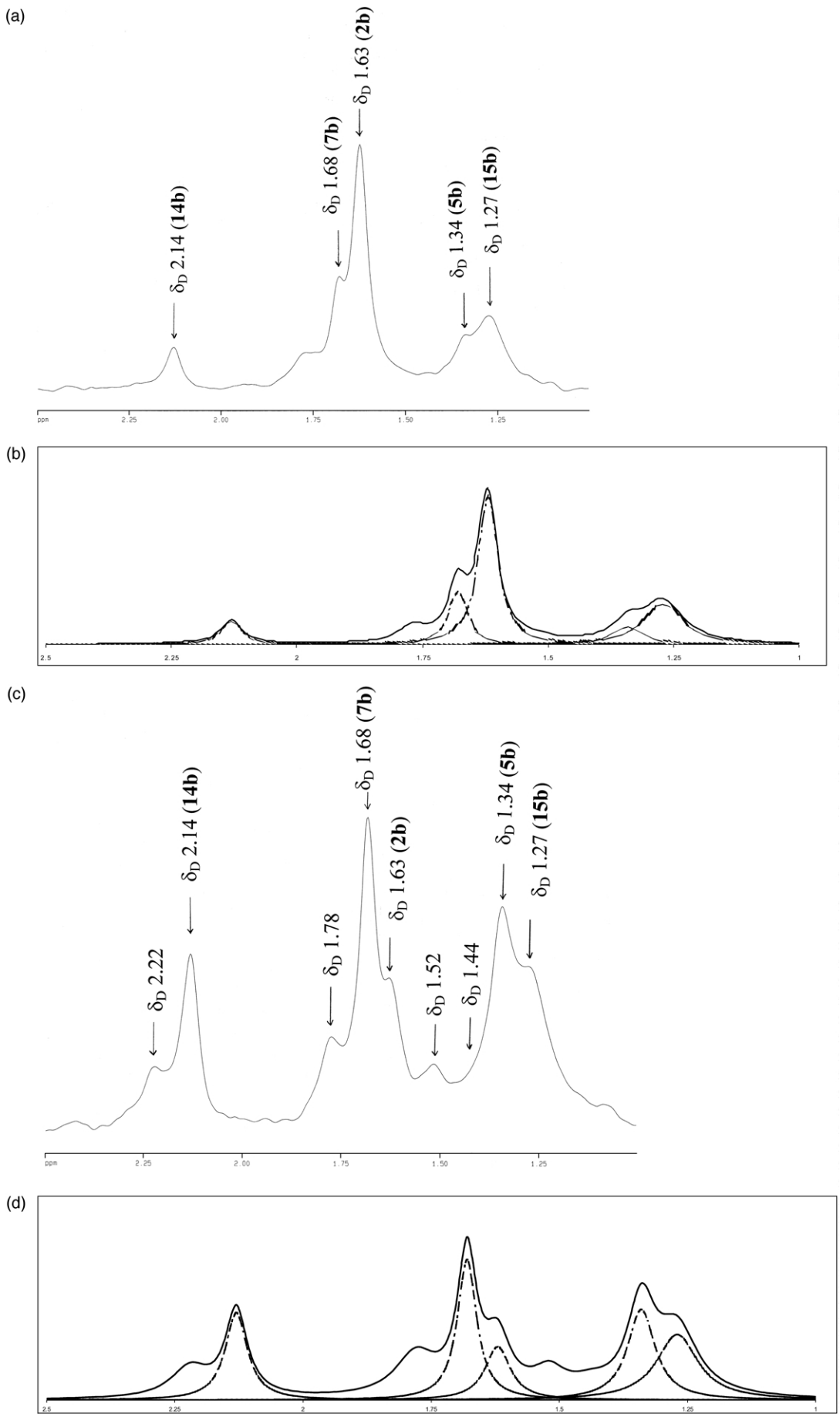
Figure 6. Expansion of the aliphatic region for representative ^{2}H NMR spectra from the aerial parts of *A. annua* which were allowed to die by desiccation after feeding with **2b** and then extracted in triplicate by CH_2Cl_2 after 8, 24, 32, 48, 56, 72 and 80 h.

Furthermore, a broad poorly resolved resonance was also noted in the alkene region of the spectrum between δ_D 4.7 and 5.1 ppm (not shown in Figure 6) in several of the spectra taken towards the end of the experiment.

Based on the results of the previous section, the more intense deuterium resonances at δ_D 1.63, 1.68, 1.34, 1.27 and 2.14 ppm were proposed to correspond to the labelled [15-C^{2}H$_3$] group in compounds **2b**, **7b**, **5b**, **15b** and **14b** respectively, and the percentage amounts of each of these compounds in all of the extracts made in this experiment could then be estimated reasonably accurately by computational simulation (fitting a single Lorentzian line at each chemical shift), as is shown in Figure 7.

The variation over time in the percentage amounts of the precursor **2b** and each of the four most abundant metabolites, for the group of plants which was allowed to die by desiccation immediately after feeding of **2b**, is depicted in Figure 8. These results were almost identical with those obtained for the 'live' group of plants in this same experiment (results not shown) and also with the results for plants which had been kept alive in the previous section, as summarized in Figure 4. In particular, compound **15b** again appeared to be an intermediate, which reached its peak at around 32 h. It is worth noting that the rates of decline in the precursor and its transformation into products **5b**, **7b** and **14b** in this second experiment (Fig. 8) were also somewhat faster than for the first (Fig. 4), which may be the result of a warmer average temperature and continuous sunshine during the hours of daylight (see Section 4.1.4). One can perhaps discern a diurnal fluctuation in the amounts of the precursor **2b**, which tends to be more abundant in those extracts made in the morning (24, 48 and 72 h) and to have undergone an increased rate of conversion to its metabolites **5b**, **7b** and **14b** in the extracts which were made in the late afternoon (8, 32, 56 and 80 h), superimposed on the general trend. This would be consistent with a continuous replenishment from the root of **2** in the aerial parts during both day and night time and with an increased rate of autoxidation of **2** during the hours of daylight. We therefore, suggest that **2b** undergoes chemical transformations in the 'dead' group of plants in exactly the same way as for the 'live' group (i.e. via the pathway **2b**→**15b**→(**5b**+**7b**+**14b**)). Analysis of the root extracts from both the live and dead groups of plants showed only very limited transformations of **2b**, as had been observed previously for the precursor **2a** in Section 2.2.

Finally, we turn to the minor peaks which were observed in some of the ^{2}H NMR spectra from this experiment at δ_D 2.19, 1.78, 1.51 and 1.44 ppm and which were most clearly resolved for the later extracts in Figure 6 (there was also a broad poorly-resolved resonance at δ_D 1.30–1.40 ppm in some of these spectra). In order to determine the identities of the minor metabolites of **2b** which were responsible for these peaks, we combined together all the crude plant extracts from this experiment and subjected them to


(a)
δD 2.14 (14b)
δD 1.68 (7b)
δD 1.63 (2b)
δD 1.34 (5b)
δD 1.27 (15b)
ppm
2.25
2.00
1.75
1.50
1.25
(b)
2.5
2.25
2
1.75
1.5
1.25
1
(c)
δD 2.22
δD 2.14 (14b)
δD 1.78
δD 1.68 (7b)
δD 1.63 (2b)
δD 1.52
δD 1.44
δD 1.34 (5b)
δD 1.27 (15b)
ppm
2.25
2.00
1.75
1.50
1.25
(d)
2.5
2.25
2
1.75
1.5
1.25
1

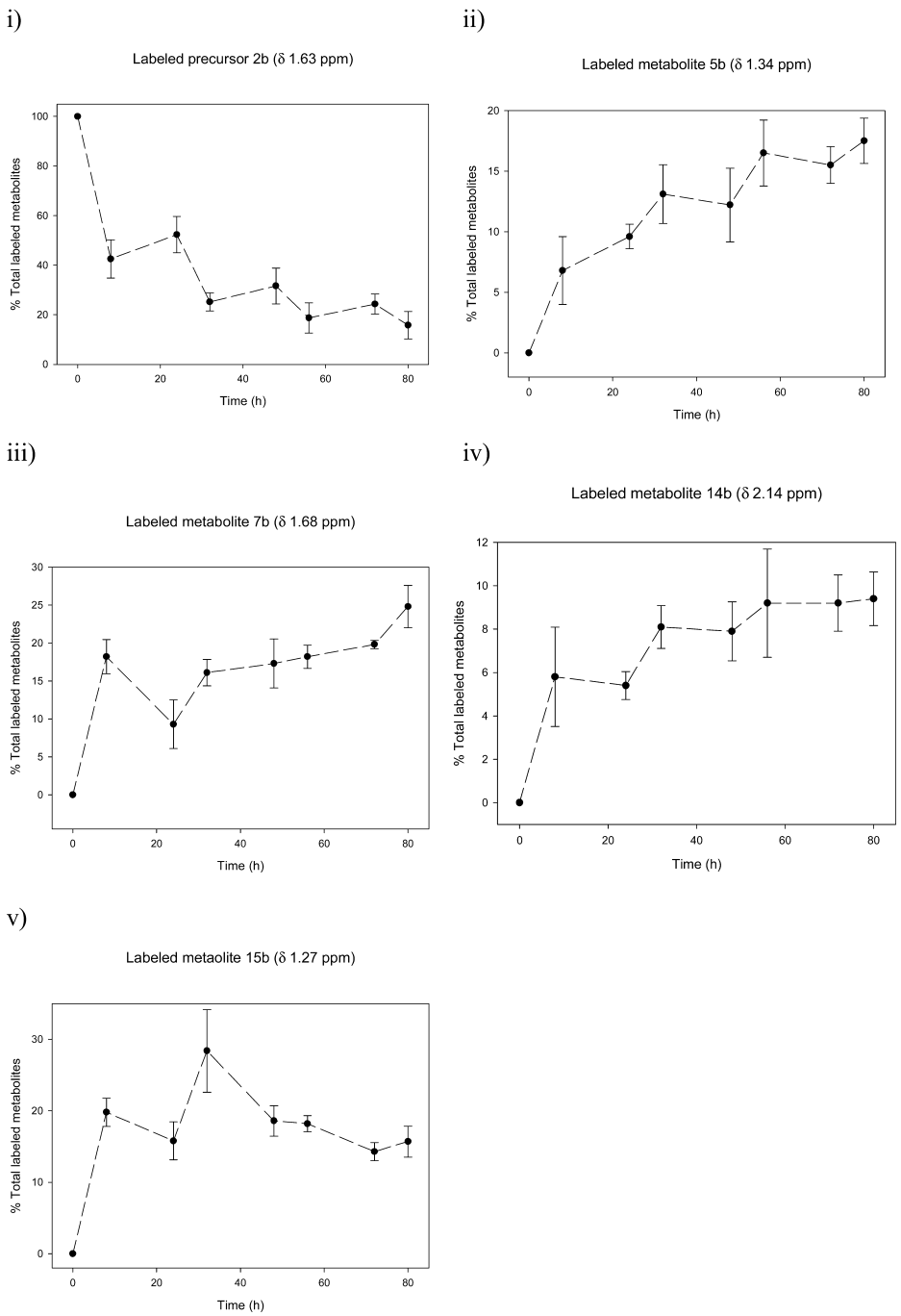
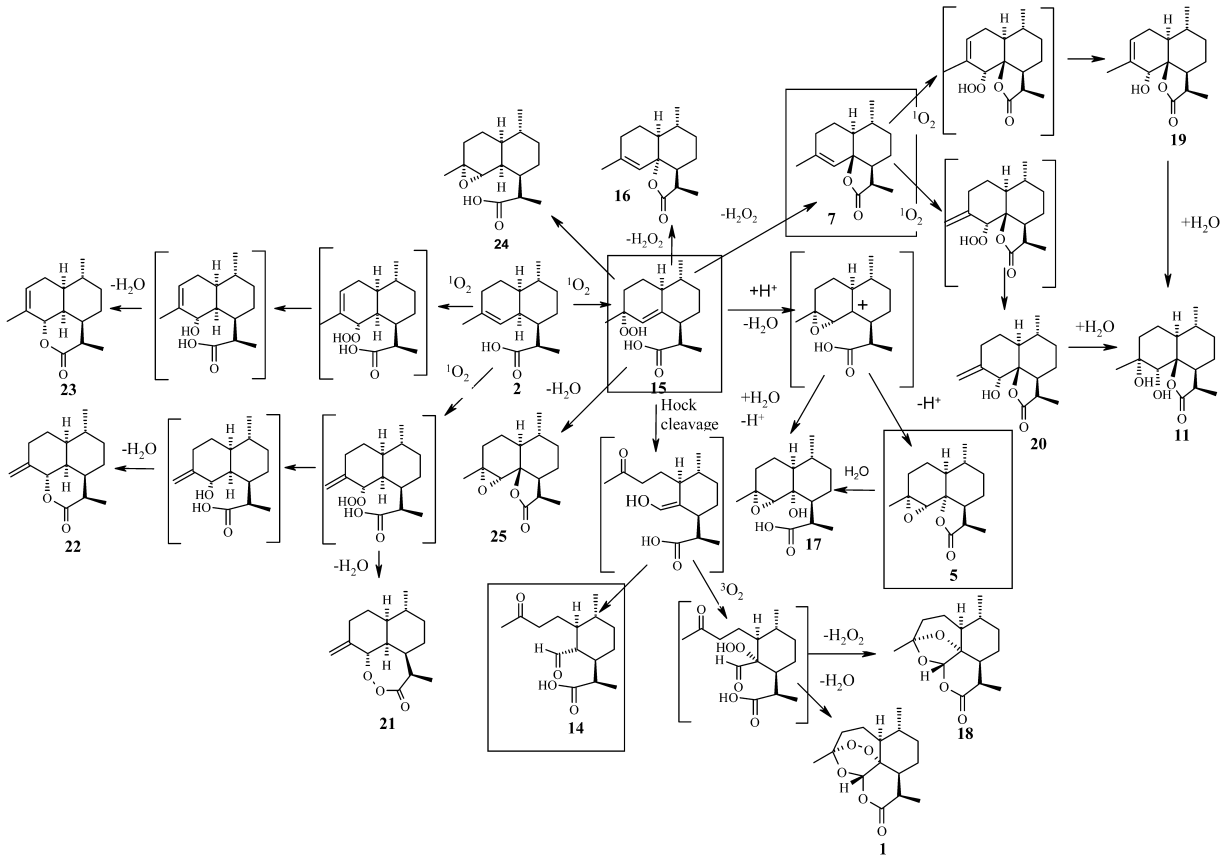


Figure 8. Variation in the percentage amounts of (i) **2b**, (ii) **5b**, (iii) **7b**, (iv) **14b** and (v) **15b** with time in the crude aerial extracts of *A. annua* plants which were fed with **2b** and allowed to die by desiccation. Each point is the average of the percentage amount from three replicates, each of which was estimated by computational simulation (Fig. 7). The corresponding standard variations are indicated by an error bar.

chromatographic separation, as is described in the next section.

2.3.1. Chromatographic separation of the combined extracts of the aerial compartment of *A. annua* plants which had been fed with 2b. Extensive HPLC separations of the combined crude extracts obtained from the feeding of [15-C^2H_3]-dihydroartemisinic acid (**2b**) to both the 'live' and 'dead' groups of plants described in the previous section resulted in the isolation of 16 deuterium-labelled 12-carboxy-11,13-dihydro-amorphane and cadinane sesquiterpenes (Scheme 3 and Table 2) As expected, compounds **5b**,

Figure 7. Two examples of the ^2H NMR spectra of extracts of the aerial parts of *A. annua* made at (a) 8 and (c) 72 h after feeding with **2b** (the plants were allowed to die by desiccation after feeding); and (b) and (d) the corresponding computer simulations which were used to estimate the percentage amounts of compounds **14b**, **7b**, **2b**, **5b** and **15b** (in order of decreasing chemical shift at the 15-position) in these crude extracts (the contribution of the singlets—due to the major components of the extract—to the overall spectral simulation are shown by dotted lines; contributions from minor components are not explicitly shown for overall ease of visualization).



Scheme 3. Proposed routes for the in vivo transformations of dihydroartemisinic acid (**2**) (mechanisms are based largely on previous in vitro studies) leading to the 16 amorphane and cadinane metabolites which were isolated in feeding experiments with *A. annua* in Section 2.3. Boxed structures represent the most abundant metabolites to be isolated (as shown in Scheme 2).

7b and **14b**, which are the products of the most dominant pathways shown in Scheme 2, were obtained in large quantities. The amounts of all 16 metabolites obtained by chromatographic separation are indicated in Table 2, together with the ratio of the [15-C^2H_3]/[15-CH_3] isotopomers for each metabolite, as determined by ^1H, ^{13}C NMR and mass spectrometry. (Note that since several HPLC purification steps were involved in obtaining each metabolite and, because

Table 2. Amounts and isotopic composition, as determined by various spectroscopic techniques, of [15-C^2H_3]-labelled metabolites which were isolated chromatographically after feeding **2b** to *A. annua* plants.

Compound (δ_D (ppm) at the 15-position)[a]	Amount isolated (mg)	Percentage of the [15-C^2H_3]-isotopomer as a total of both the labelled [15-C^2H_3]- and unlabelled [15-CH_3]-isotopomers recovered from the plant extracts, as estimated by three spectroscopic techniques (%)		
		From ^1H NMR	From ^{13}C NMR[b]	From MS
1b (1.44)	9.0	<5	<5	7
2b (1.63)	1.0	>40	>90	83
5b (1.35)	0.6	ca. 70	ca. *70*	—
7b (1.68)	3.8	>70	ca. 60	75
11b (1.39)	0.1	>50	ca. 50	70
14b (2.13)	0.3	ca. 70	ca. 70	75
15b (1.29)	0.8	>70	75	—
16b (1.68)	0.1	>70	>80	83
17b (1.35)	0.3	>70	ca. 70	74
18b (1.52)	1.5	>50	ca. 70	63
19b (1.78)	0.1	>60	—	73
20b (4.94 (br))	0.1	67	>80	73
21b (4.93, 4.85)	0.3	16	<5	17
22b (5.07, 4.86)	1.1	73	ca. 80	75
23b (1.78)	0.1	>50	—	—
24b (1.31)	0.1	>70	—	77
25b (1.32)	0.1	>70	>80	88

[a] This deuterium chemical shift was used for identifying metabolites in the crude plant extracts.
[b] Feeding experiments with [15-$^{13}CH_3$] labelled dihydroartemisinic acid (**2c**) in Section 2.4, generally confirmed the results shown in this column.

the recoveries at each step were unknown and likely to be quite variable, the amounts shown in Table 2 should be treated as underestimates and as only being semi-quantitative). Although a large number of other natural products were, of course, also isolated from this chromatographic separation (see Ref. 6 for an indication of the non-sesquiterpenoid metabolites that are typically also found in *A. annua*), none contained any detectable amount of ^{2}H label.

Of the 16 labelled metabolites of **2**, 15 have already been reported as natural products from *A. annua*, including:¶ artemisinin (**1**),[47] dihydroarteannuin B (**5**),[2,45] dihydro-*epi*-deoxyarteannuin B (**7**),[2,45] arteannuin M (**11**),[2,5] the keto-aldehyde **14**,[6,39] the tertiary hydroperoxide of dihydroartemisinic acid (**15**),[2,45] dihydro-deoxyarteannuin B (**16**),[4] the β-epoxy alcohol **17**,[6] deoxyartemisinin (**18**),[48] arteannuin K (**19**),[2,5] arteannuin L (**20**),[2,5] arteannuin H (**21**),[2,49] arteannuin I (**22**),[2] arteannuin J (**23**)[2] and α-epoxy-dihydroartemisinic acid (**24**).[6,43] The only metabolite not to have been obtained previously as a natural product was dihydro-*epi*-arteannuin B (**25**), although this compound has recently been reported as an intermediate in the chemical synthesis of the natural product, arteannuin O (**12**).[5] Based on this chromatographic separation, it can be concluded that the minor peaks seen in the ^{2}H NMR spectra in Figures 6 and 7 at δ_D 1.78, 1.51 and 1.44 ppm were probably due to arteannuins K and J (**19b/23b**), deoxyartemisinin (**18b**) and artemisinin (**1b**), respectively. The poorly defined resonances between 4.7 and 5.1 ppm which were observed in some of the crude extracts might have been due to some or all of arteannuin L (**20b**), arteannuin H (**21b**) and arteannuin I (**22b**). The broad 'hump' of poorly resolved resonances in the range δ_D 1.30–1.40 ppm, commonly encountered in the later extracts, were perhaps due to some or all of the metabolites **11b**, **17b**, **24b** and **25b**. Deuterium signals were not directly observed in the ^{2}H NMR spectra of the crude plant extracts from dihydro-deoxyarteannuin B (**16b**) as the weak resonance for the 15-position in this compound (δ_D 1.68 ppm) would have been completely obscured by the much stronger peaks from the principal metabolite **7b** (also at δ_D 1.68 ppm). The identity of the peak at δ_D 2.19 ppm, which was quite significant in many crude ^{2}H NMR spectra (particularly the later ones), remains uncertain, as no metabolite exhibiting this deuterium resonance was obtained after chromatographic separation. However, we suspect that it may be the 5-carboxylic acid analogue of the natural product **14b**; as the aldehyde group in this compound is known to undergo facile spontaneous oxidation[39] to yield a dicarboxylic acid product which may have been too polar to be isolated by the normal phase chromatographic separation procedures employed in this study.

A careful analysis of the ^{1}H NMR, ^{13}C NMR and mass spectra for all of the metabolites from the chromatographic separation (Table 2) indicated that the [15-C^{2}H$_3$]-isotopomer (i.e. '**b**' suffix) accounted for roughly 70% of the total metabolite recovered (comprising both the labelled and the isotopically-normal [15-CH$_3$] form), with only two exceptions. These were artemisinin (**1**) and arteannuin H (**21**), both of which were isolated as a mixture of approximately 5–15% of the deuterium-labelled isotopomer with the unlabelled (isotopically-normal) form. In no case was there any evidence whatsoever for the presence of 'partially' labelled forms of any of these metabolites, which would have been easily detectable by the presence of molecular ions for the [15-C^{2}H$_2$H]- and [15-C^{2}HH$_2$]-isotopomers in mass spectrometry. Since there was therefore, no reason to propose the existence of metabolic processes which would cause the deuterium label to be progressively 'lost' from the 15-position in vivo, we believe that the isotopically-normal forms of all of these metabolites must represent *bona fide* natural products, which would have been present in *A. annua* in any case, even if labelled dihydroartemisinic acid had not been administered to the plants. The percentage ratio of the [15-C^{2}H$_3$]-isotopomer to the [15-CH$_3$]-isotopomer should therefore, give an indication of the extent, relative to the unperturbed system, by which artificially administered **2b** is being converted into the various secondary metabolites that are typical of *A. annua*, when fed to the plant via the root. If this is so, then the conclusion must be that when dihydroartemisinic acid was fed to *A. annua* plants via the root, two of the 16 metabolites into which it was converted, compounds **1** and **21**, were accumulated to a significantly lesser extent than all of the other fourteen (**5b**, **7b**, **11b**, **14b**–**20b** and **22b**–**25b**), as compared with the 'natural' situation.

2.4. Time-course study of the transformations of [15-^{13}CH$_3$]-dihydroartemisinic acid (2c) which was fed to *A. annua* plants via the root

Several experiments were also performed involving the feeding of [15-^{13}CH$_3$]-dihydroartemisinic acid (**2c**) to *A. annua* plants via the root. However, these experiments were, in general, found to be much more difficult to analyse than for the feeding of either **2a** or **2b**, as the option for an initial screening of crude plant extracts for labelled compounds by ^{2}H NMR spectroscopy, which in Sections 2.2 and 2.3 had clearly and rapidly indicated the presence of—and transformations undergone by—the ^{2}H label without any interference from the (much more abundant) non-labelled components of the plant matrix, no longer existed. The crude extracts of plants which had been fed with compound **2c** always had to be subjected first to chromatographic separation in order to establish the presence of a ^{13}C-isotopically-enriched metabolite, and this was a tedious and time-consuming task without the benefit of the ^{2}H label, which had enabled the most promising chromatographic fractions to be rapidly targeted in Section 2.3.1. However, those ^{13}C-labelled metabolites which were chromatographically isolated from these experiments fully confirmed the results established from feeding experiments with both **2a** and **2b** in the previous sections. In particular, the intensity of the ^{13}C resonance at the 15-position, relative to other ^{13}C resonances in each of the purified metabolites could be used to estimate the percentages of the 15-[^{13}CH$_3$]-labelled forms of metabolites which were derived from **2c** vs. the 'natural' level of each metabolite. This data generally corroborated the isotopomeric ratios that are shown in Table 2 (which had been estimated from the reduced intensity of the isotopically-normal 15-[CH$_3$] peak relative to other peaks

¶ References are given to the most complete or reliable NMR data that is currently available for these compounds; this data was used in confirming the identities of these metabolites.

in the ^{13}C NMR spectrum—due to both labelled and unlabelled forms of each metabolite in Section 2.3). Hence, this experiment provided independent confirmation of the conclusion that the extent of isotopic-labelling in both artemisinin (**1**) and arteannuin H (**21**) was significantly less than that for all the other fourteen metabolites of **2**.

3. Conclusion

Based on several precedents from the chemical literature, and from our recent detailed experimental investigations (and speculations) on the in vitro transformations of dihydroartemisinic acid,[2,4,6,42–44] it is proposed that the 16 compounds which have been isolated from feeding *A. annua* with compound **2** are biogenetically related by the series of spontaneous reactions occurring in vivo, which are shown in Scheme 3. This series of transformations is also consistent with all of the time-course studies discussed above (see in particular Figures 4 and 8).

The first chemical reaction in the in vivo transformations of dihydroartemisinic acid is the 'ene-type' addition of singlet molecular oxygen to the $\Delta^{4,5}$-double bond of **2**, which is known to yield the tertiary allylic hydroperoxide **15**, as well as to two alternative secondary allylic hydroperoxides, as minor products.[49] Most of the metabolites encountered in this study can then be derived from **15** by the established reactions of such hydroperoxides.[50] In particular, S_N2' attack of the 12-carboxylate at the allylic hydroperoxide group would result in either dihydro-*epi*-deoxyarteannuin B (**7**) or its epimer, dihydro-deoxyarteannuin B (**16**), while both dihydroartennuin B (**5**) and its lactone ring-opened analogue **17** may arise by protonation of the hydroperoxide and rearrangement to an epoxy carbocation, which accompanies the elimination of water. Spontaneous Hock cleavage[39,50] of the tertiary allylic hydroperoxide group in **15** would produce the enolic intermediate shown in both Schemes 1 and 3, which can then either tautomerize to the aldehyde metabolite **14**, or react with $^3O_2$ to yield artemisinin (**1**) and/or deoxyartemisinin (**18**).

If the metabolite **7** were to undergo an 'ene-type' reaction between its $\Delta^{4,5}$-double bond and $^1O_2$, in the same manner as that which has already been demonstrated experimentally for **2**,[39] then homolysis[50] of the resulting hydroperoxides would also account for the minor metabolites arteannuin K (**19**), arteannuin L (**20**) and arteannuin M (**11**) (there is in vitro evidence to support such a mechanism for at least one of these metabolites).[43] Known spontaneous reactions of one of the alternative secondary allylic hydroperoxides[2,4,49] from reaction of $^1O_2$ with **2** would also simply account for the biogenesis of arteannuin H (**21**) and arteannuin I (**22**), while, by analogy, the other secondary hydroperoxide might reasonably be expected to undergo a similar spontaneous conversion[2,4] to arteannuin J (**23**), although there is as yet no direct evidence for this in the literature.

As noted above, the predominant transformation pathway observed for **2** in vivo (**2**→**15**→(**5**+**7**+**14**) in Scheme 2) was qualitatively exactly the same as that which has been shown to occur for the spontaneous autoxidation of **2** in vitro.[39] Quantitatively, however, there was a significant difference in that, such transformations of dihydroartemisinic acid in organic solution were completed only after several weeks in vitro, whereas they occurred within just a few days in vivo in the aerial parts of *A. annua*. In this regard, it is interesting to note that analyses of the ^2H NMR spectra of the roots invariably showed very much more limited transformations of **2** (although the pattern was probably qualitatively quite similar). These observations are consistent with the proposal that that the primary route for transformation of **2** in vivo is by an autoxidative reaction of the $\Delta^{4,5}$-double bond with singlet oxygen ($^1O_2$), which is generally considered to be the reactive species in such processes. $^1O_2$ may be relatively abundant in the aerial parts due to the presence of plant pigments which can act as photosensitizers, but rather scarce in the roots which lack pigmentation. The suggestion that, in vivo, compound **2** undergoes rapid plant pigment-photosensitized oxidation to the tertiary allylic hydroperoxide **15**, followed by subsequent spontaneous reactions of this hydroperoxide, rather than transformations mediated by enzymes, is also consistent with the observation that the same pattern of transformations was noted in plants which were allowed to die after having being fed with the labelled precursor, as for plants which were kept alive hydroponically for several days.

All of the preceding findings have led us to the conclusion that dihydroartemisinic acid is the late biogenetic precursor to almost all of the 11,13-dihydro-amorphanes and cadinane sesquiterpenes which have been described from *A. annua* in the past, and that dihydroartemisinic acid is rapidly transformed into these metabolites in vivo by spontaneously-occurring chemical reactions rather than by enzymically-catalysed processes. The least satisfactory aspect of this unifying hypothesis, which neatly accounts for the biogenesis of many of the large number of 11,13-dihydro-amorphane and cadinane sesquiterpenes which are now known from *A. annua*, relates to artemisinin (**1**) itself. Although artemisinin has sometimes been reported to be the most abundant sesquiterpene from *A. annua* (accounting for more than 1% of the total plant weight, in some studies), the appearance of the labelled form of this compound was only ever noted at the end of the various feeding experiments which are described in Sections 2.2–2.4, and the percentage of the labelled metabolite, relative to the isotopically-normal compound (which, as discussed earlier, is believed to represent the natural product that would have been present in any case), was always much lower than that found for all the other metabolites, with the exception of arteannuin H.

In this regard, it is intriguing to note that artemisinin and arteannuin H were the only two labelled metabolites to be isolated in this study which contained intact peroxy groups (effectively the hydroperoxide precursor has been 'trapped' by a second functional group in the molecule, in both cases), whereas all the other labelled metabolites are presumed to be derived from the further reactions of such hydroperoxides (see Scheme 3). The apparent correlation between chemical structure and the extent of transformation which is undergone by the labelled precursor **2** has led us to undertake a preliminary investigation of the behaviour of the tertiary allylic hydroperoxide of dihydroartemisinic acid

(**15**) in aqueous medium rather than organic solution (although published in vitro studies[39] have conclusively shown that artemisinin (**1**) is the major product from the slow transformations of **15** in $CDCl_3$ solution, there is apparently no data concerning the reactions of **15** in water). These studies turned out to be difficult to perform on account of the poor aqueous solubility of **15** and we have found that it was only possible to characterize the products from this reaction by making a comparison with the ^1H NMR spectra of 'authentic standards' which were acquired in the same aqueous medium. However, we consistently failed to observe any conversion of **15** into **1** in water in our preliminary experiments; rather, compound **15** appears to undergo transformation within a few days into **14** in alkaline solution (in which it is more soluble) and into **7** in acidic solution; although this is somewhat of an over-simpification as these aqueous transformations of **15** were quite complex in all cases. Based on these observations, we propose that the accumulation of artemisinin (**1**) and arteannuin H (**21**) in *A. annua* might only be occurring when compound **2** undergoes autoxidation in a predominantly lipophilic environment, in which the hydroperoxide intermediates are comparatively stable. Such an environment is found in the glandular trichomes[51] on the surface of the leaves and stems. Special proteins are required to transport terpenoids[52] into the glandular trichomes, which would perhaps be the last cellular compartment to be accessed when the labelled precursor is fed via the root, thereby explaining the late appearance and low yield of the labelled forms of **1** and **21**. By contrast, the biogenesis of all the other fourteen metabolites may be occurring via homolytic cleavage and other rearrangement mechanisms, which are more characteristic of allylic hydroperoxides in an aqueous environment, i.e. predominantly in the cytoplasm of those cells which constitute the bulk plant tissues. More detailed studies of the autoxidation of **2** in aqueous solution, as well as biosynthetic experiments involving isolated glandular hairs (which it should be possible to obtain by abrasion of the leaf surface) are clearly needed in order to substantiate this hypothesis.

Although we currently favour the above explanation for the apparent anomalies in the biogeneses of **1** and **21** from **2**, as compared to most of the other 11,13-dihydro-amorphane sesquiterpenes found in *A. annua*, one could, of course, put forward several other alternatives. One possibility is that although the 14 metabolites, compounds **5**, **7**, **11**, **14**–**20** and **22**–**25** are indeed all products of spontaneous autoxidation reactions of **2** in an aqueous environment, the main biosynthetic route from **2** to **1** in vivo requires the participation of an enzyme. This enzyme might perhaps be related to the dioxygenases[53] which oxidatively cleave double bonds that have been described in the literature on diapocarotenoid biosynthesis, and, for some reason, this enzyme would not have been efficiently accessed by **2** when fed via the root in this experiment (see comments on the glandular hairs above). If this were true, then the limited accumulation of **1** observed in this paper would merely be the result of a minor (alternative) autoxidative pathway, and future experiments should reveal a 'dioxygenase-like' enzyme in *A. annua* with the appropriate activity for synthesizing the 1,2,4-trioxane ring, localized in a compartment which is relatively inaccessible to **2** when fed by the root.

A second possibility is that one of the more abundant metabolites, compounds **5**, **7** or **14** which are shown as 'products' in Scheme 2 is, in fact, an intermediate in the later stages of the biogenesis of artemisinin, and that the in vitro route for the transformation of **2** into **1** via **15** is again of only minor (or even no) importance in vivo. If this were the case, then, over the course of a much more extended experiment, one might expect to see the level of whichever of these metabolites was the true intermediate in the conversion of **2** to **1** decline at a similar rate to that of the long-term accumulation of artemisinin. Given the contradictory results reported in the literature for the biosynthetic status of **5** and **7** (see Section 1), it might be worth performing future root-feeding experiments in which the labelled forms of each of one of either **5**, **7** or **14** were administered to intact plants of *A. annua* in order to resolve this question. In addition, if any of compounds **5**, **7** or **14** were truly late intermediates of **1**, then it ought to be possible to find enzymes which catalyse the conversion of one of these natural products to artemisinin.

A third possibility, also raised in Section 1, is that the 11,13-dehydro form of dihydroartemisinic acid, artemisinic acid (**3**) is of much more significance than dihydroartemisinic acid (**2**) as an advanced precursor of artemisinin (**1**). If this were the case, then the conversion of dihydroartemisinic acid (**2**) to artemisinin (**1**) observed in this paper would again represent only a minor biosynthetic pathway, and one would hope that a future feeding experiment, in which labelled artemisinic acid (**3**) was administered to intact *A. annua* plants via the roots, would result in a much more substantial recovery of labelled artemisinin (**1**). In this regard, it is interesting to note that the 11,13-dehydro analogues[‖] of several of the labelled compounds recorded in Scheme 3, including artemisinic acid (**3**),[54] arteannuin B (**4**),[55] *epi*-deoxyarteannuin B (**6**),[4,56] the keto-aldehyde **13**,[29] deoxyarteannuin B (**26**),[4] annulide (**27**)[4,57] and isoannulide (**28**)[4,57] (Fig. 1) were all also isolated from the experiments in which *A. annua* plants had been fed with **2b**, but in no case was there any evidence for detectable deuterium labelling in these natural products. It therefore, appears that there is no significant biosynthetic pathway for desaturation of **2** at the 11,13-position to yield **3** and, by implication, its metabolites **4**, **6**, **13** and **26**–**28**. However, the presence or absence of a biosynthetic pathway for the reverse reaction in *A. annua*, i.e. the reduction of artemisinic acid (**3**) at the 11,13-dehydro position to yield dihydroartemisinic acid (**2**) (and, by implication, the 16 metabolites described herein), still remains to be determined.

4. Experimental

4.1. General

All ^1H and ^{13}C NMR experiments were recorded on either a Bruker DRX 500 or an AV 600 instrument. Chemical shifts are expressed in ppm (δ) relative to TMS as internal standard. ^2H NMR spectra were recorded at 76.77 MHz in

[‖] Again, references are given to the most complete or reliable NMR data which is currently available for these natural products, which was used in establishing their identities.

$CHCl_3$ solution containing C_6D_6 (10 μl/100 ml) which acted as both an internal ^2H reference (δ_D 7.43 ppm; spectra also showed a small peak for natural abundance ^2H in the $CHCl_3$ solvent at δ_D 7.28 ppm) and as an internal standard for calibrating the amount of ^2H label present in the crude plant extracts (the deuterium integral for the d_6-benzene resonance at δ_D 7.43 ppm had the same value as that for the 15-position (δ_D 1.63 ppm) of **2a** when 0.53 mg was dissolved in 0.6 ml $CHCl_3/C_6D_6$ solution; for **2b**, 0.38 mg in 0.6 ml $CHCl_3/C_6D_6$ solution gave the same result). The chemical shift of the reference compound was considered unlikely to interfere with the products of metabolism of dihydroartemisinic acid, for which the ^2H signal was observed either in the aliphatic region (δ_D 1–2.5 ppm) or in the alkene region (δ_D 4.5–5.5 ppm) of the spectrum—see Sections 2.2 and 2.3). The ratio of the ^2H integral for all the metabolites present in the crude plant extract to the ^2H integral for the d_6-benzene internal standard was routinely used to estimate the amount of ^2H label which was present in such extracts, based on prior experiments using known amounts of the labelled precursors **2a** or **2b** (see above). In order to acquire ^2H NMR spectra, the broadband nucleus was set to the ^2H frequency and the lock cable was physically disconnected from the probe of the NMR spectrometer, so as to prevent the leakage of the lock signal into the acquisition channel. Since it then became impossible to shim the sample, our normal practice was to have first shimmed an NMR tube of the same manufacture and containing exactly the same volume of $CDCl_3$ solution (0.6 ml) immediately prior to the acquisition of each ^2H NMR spectrum. Using this technique, the linewidth at half height for most ^2H spectra was found to be fairly constant (between 2.5–3.5 Hz); we believe that the major contribution to line broadening in ^2H NMR spectra was then from the unavoidable effects of quadrupolar relaxation in ^2H NMR spectroscopy,[58,59] rather than from magnetic inhomogeneities associated with poor shimming. $^{13}C-^2H$ COSY NMR spectra were acquired in this same solvent and according to the procedures described in Refs. 44 and 45. High-resolution MS were recorded in EI mode at 70 eV on a Finnigan-MAT 95 MS spectrometer. Column chromatography (CC) was performed using silica gel 60–200 μm (Merck). HPLC separations were performed using a Varian chromatograph equipped with RI star 9040 and UV 9050 detectors and a normal phase semi-preparative YMC diol column (20 mm×25 cm), flow rate 8 ml/min.

4.1.1. *A. annua* plants. Several batches of *A. annua* plants were grown in individual pots outdoors in Hong Kong, from seed which had been sown between October and February (seeds were supplied by the NCCPG *Artemisia* collection, Cambridge, UK, and taxonomically verified specimens are held by the collection). These plants were generally used in feeding experiments when mature and beginning to come into flower (3–4 months after germination).

4.1.2. Determination of the optimum method for feeding [15-$^{13}C^2H_3$]-dihydroartemisinic acid (2a) to *A. annua* plants

4.1.2.1. Preparation of the feeding solution of 2a. The maximum solubility of compound **2a** in TRIS buffer (50 mM, pH 8.2) was determined as ca. 2.3 mg/ml after ultrasonification for 1 h (^1H NMR analysis showed no changes in the chemical composition of **2a** as a result of ultrasonification). In consequence, feeding solutions were prepared containing 2.0–2.2 mg **2a**/1 ml of buffer.

4.1.2.2. Procedure for 'stem-feeding' cut plants. Individual plants (3–5 g) were cut just above the level of the soil and were fed with the labelled precursor at a rate of approximately 1 mg **2a**/2 g fresh plant material, by immersing the cut stem in a vial containing the feeding solution. The plants were exposed to a strong light source (500 W bulb) and a constant flow of air (from a nearby fan) in order to promote the uptake of the feeding solution via the transpiration stream. Under these conditions, plants were normally able to take up all the feeding solution over a period of 2–6 h. A small amount of TRIS buffer was then added to the feeding vial in order to rinse any remaining labelled precursor from the walls of the vial, and the plants were left for a short while longer to take up this additional small volume.

4.1.2.3. Procedure for feeding intact plants via the root. Individual plants (3–5 g) were carefully removed from the excess soil in their pots and their roots were washed free of remaining soil. The cleaned root was immersed in a vial containing the feeding solution (approximately 1 mg of **2a**/2 mg fresh weight plant material) and exposed to strong light and air flow, as above, in order to increase the rate of transpiration. All the feeding solution was normally assimilated by intact plants within 4–6 h under these conditions.

4.1.2.4. Extraction procedure. For both cut (stem-fed) and intact (root-fed) plants, it was found that the total plant weight after complete assimilation of the feeding solution was between 60–80% of the original weight just before feeding; this loss in weight was probably due to some dehydration occurring as a result of the forcing conditions which were employed to stimulate transpiration. Cut plants were separated into stems and leaf/flower compartments and these two compartments were extracted separately; intact plants were separated into stem, leaf/flower and root compartments. Each portion was ground to a fine powder under liquid N_2, then immersed in CH_2Cl_2 (ca. 250 ml/10 g plant material) in a container wrapped in aluminium foil (to exclude light and thereby minimize the formation of autoxidation products from **2**) and left overnight on a shaker. The solvent was dried ($MgSO_4$) and removed by rotary evaporation to yield the crude plant extract as an aromatic green gum; this procedure was repeated three times and the dichloromethane extracts (stems 1–3% w/w; leaf/flower 2–5% w/w; root <0.5% w/w) were combined and analysed immediately by NMR. A second methanolic extract of the residual plant material was then made in the same way, using MeOH in place of CH_2Cl_2.

4.1.2.5. Analysis of the CH_2Cl_2 extracts. The initial analysis of the CH_2Cl_2 extracts of *A. annua* plants which had been fed with **2a** was made by ^2H NMR spectroscopy and samples were dissolved in $CHCl_3$ (0.6 ml) containing C_6D_6 (10 μl/100 ml), as in Section 4.1. Samples were also sometimes analysed by ^1H and ^{13}C NMR spectroscopies in $CDCl_3$ solution in order to confirm the results of ^2H NMR analysis. However, these analyses were in general much less informative, as signals from the plant matrix obscured most of the resonances from the labelled precursor (by contrast, there was negligible signal from the plant matrix in the ^2H NMR spectra of the crude extracts and the analyses of these

spectra for the presence of the labelled precursor and/or its metabolites was a straightforward matter).

4.1.2.6. Analysis of the MeOH extracts. The MeOH extracts from plants fed with **2a** were dissolved in MeOH and analysed by ^{2}H NMR sectroscopy. Generally, such analyses consistently indicated a much lower incorporation of ^{2}H-label (<15% of that present in the CH_2Cl_2 extracts) and the methanolic extracts were not investigated further in this experiment or any of the experiments described in subsequent sections.

4.1.3. Time-course study of the transformation of 2a which was fed to intact *A. annua* plants via the root. Twenty one plants (typical weight 5–10 g per plant) were fed individually via the root with 2.5 ml of a stock solution of **2a** in TRIS buffer (105 mg/52.5 ml), as described in Section 4.1.2. Uptake of the labelled precursor was completed within 6 h of the commencement of feeding and plants were kept alive under hydroponic conditions for several days by continual replenishment of deionized water into the feeding vials. The ambient temperature was 22–28 °C over the course of the experiment with mostly overcast weather. Groups of three plants were separated into aerial (stem/leaf/flower) and root compartments and extracted individually by CH_2Cl_2 (see previous section) at 10, 24, 33, 48, 72, 96 and 144 h after the commencement of feeding. Immediate analysis was made, as previously, by ^{2}H NMR spectroscopy following preparation of each of the 21 crude aerial CH_2Cl_2 extracts and 21 root extracts. The incorporation of ^{2}H label into the CH_2Cl_2 extract of the aerial parts remained at 1.5–3 mg (30–60%) over the course of the experiment, while the incorporation into the roots dropped from 15% at the beginning to almost 0% at the end. The percentage amount of each metabolite in each extract which was present in the aliphatic region of the spectrum was then computationally modeled by a programme written in Microsoft Excel. This simulation calculated the intensity of 151 discrete points, at intervals of 0.01 ppm over the range δ_D 1.0–2.5 ppm, as a summation of each component doublet in the spectrum, for which a discrete Lorentzian line was calculated according to the formula:[60]

$$\mathrm{Int}_i = A\ (1/T_2)/[(1/T_2)^2 + 4\pi^2(\nu_i - \nu_a)^2]$$

where: Int_i=intensity of discrete frequency point i; A=weighting factor (equivalent to the percentage amount of a metabolite in the crude extract); $1/T_2$=line broadening factor (in fact, the reciprocal of the transverse relaxation rate—for clearly resolved peaks such as δ_D 7.43 [d_6-benzene] it could be obtained by measuring the line width at half height in the real spectrum and multiplying by π); ν_i=chemical shift in Hz of discrete point at frequency i, which is being simulated; ν_a=two frequencies calculated per metabolite, corresponding to both lines of a doublet, centred at the appropriate resonant frequency for the chemical shift at the 15-position of that metabolite, expressed in Hz (B_0=76.77 MHz) and separated by 19.1 Hz.

This spectral simulation programme allowed the operator to enter parameters for the line width; the precise value for the center of each of the doublet resonances; and the estimated percentage composition of the major doublet resonances, for metabolites which were centred at δ_D 1.27 (**15a**), 1.34 (**5a** and possibly **17a**), 1.63 (**2a**), 1.68 (**7a** and possibly **16a**) and 2.14 (**14a**) ppm (as well as minor doublet resonances at 1.31 (**24a**), 1.32 (**25a**), 1.39 (**11a**), 1.44 (**1a**), 1.51 (**18a**), 1.78 (**19a** and **23a**) and 2.19 (unidentified) ppm. These parameters could then be repetitively re-adjusted in order to obtain optimum agreement between the simulated spectrum and the ^{2}H NMR experiment.

4.1.3.1. Analysis of extracts from feeding of 2a by ^{13}C–^{2}H COSY. See Refs. 44 and 45 for a description of the ^{13}C–^{2}H COSY experiment. Several samples which appeared to be similar by one-dimensional ^{2}H NMR were generally combined together, giving extracts totalling 100–150 mg in weight—the maximum amount which could be dissolved in 0.2 ml of $CHCl_3$ in a 'capillary' NMR tube and then analysed using a 'dual' microprobe.

4.1.4. Time-course study of the transformation of 2b which was fed to intact *A. annua* plants via the root. Forty five plants (5–10 g fresh weight for each plant) were fed individually via the root with 2.2 ml of a stock solution of **2b** in TRIS buffer (200 mg/100 ml) as described in the preceding sections. Uptake of the labelled precursor was completed within 4–10 h of the commencement of feeding. Three plants were then extracted immediately to serve as a 'zero-time' point and the remaining plants were divided into two groups of 21 plants each.[**] One group was kept alive hydroponically for several days by periodically replenishing deionized water in the feeding vials, while the other was allowed to die by dessication. Ambient temperature over the course of the experiment was 30–32 °C, with strong sunlight throughout.

Three plants from each group were then separated into aerial (stem/leaf/flower) and root compartments and extracted individually by CH_2Cl_2 (as previously) on an evening/morning schedule at 8/24, 32/48, 56/72 and 80 h after the 'zero-time' point. The residual plant material was subsequently re-extracted by MeOH: as previously, the MeOH extracts contained comparatively little ^{2}H-label relative to the CH_2Cl_2 extracts and were not analysed further. Immediate ^{2}H NMR analysis of each of the 45 CH_2Cl_2 aerial extracts revealed that the recovery of ^{2}H label remained constant at between 1–2 mg from the aerial parts (20–40%) over the course of the experiment. The percentage amount for each of the most dominant labelled components of the mixture (resonances at δ_D 1.29 (**15b**), 1.34 (**5b** and **17b**), 1.63 (**2b**), 1.68 (**17b** and **16b**) and 2.14 (**14b**) ppm) was then computationally simulated by a programme written in Microsoft Excel which was similar to that described in Section 4.1.3, but in which each metabolite resonance was represented by a singlet rather than a doublet. Minor metabolites, represented by singlets at 1.31 (**24b**), 1.32 (**25b**), 1.39 (**11b**), 1.44 (**1b**), 1.52 (**18b**), 1.78 (**19b** and **23b**) and 2.19 (unidentified) ppm, were also included in these simulations in order to obtain better fits to the experimental data. Strongly overlapped and poorly resolved ^{2}H-resonances were also observed between δ_D 4.7

[**] In a control experiment, vials containing **2b** in TRIS buffer (but without *A. annua* plants) were subjected to these same conditions over the duration of the feeding period. No changes were noted in the composition of **2b**.

and 5.1 ppm, but generally accounted for less than 5% of the total ^{2}H-incoroporation by a comparison of the ^{2}H integral for this region with that of the aliphatic region. No attempt was made to include these resonances, which are probably due to metabolites **20b**, **21b** and **22b**, in the quantification.

4.2. Separation of labelled metabolites from the CH_2Cl_2 extracts of the aerial parts of *A. annua* plants which were fed with 2b

All 45 CH_2Cl_2 extracts from the aerial parts of *A. annua* plants which had been fed with **2b** were combined together (total weight 1.7 g) and subjected to a preliminary HPLC separation (18% EtOAc/*n*-hexane) from which 26 fractions were collected over a 45 min period. The column was 'washed' with 50% EtOAc/*n*-hexane/1% AcOH between each injection in order to obtain a 'polar residue'. Individual fractions from the preliminary HPLC separation, which showed significant signal in ^{2}H NMR spectroscopy, were then subjected to further HPLC separations, with the composition of the mobile phase being varied according to the degree of polarity of each fraction under study, in order to obtain labelled metabolites of sufficient purity for spectroscopic characterization. The compounds 'washed' from the preliminary HPLC and collected as the 'polar residue' were also re-subjected to HPLC separation (50% EtOAc/*n*-hexane/1% AcOH) and 24 fractions were collected. Those fractions which contained resonances in their ^{2}H NMR spectra, corresponding to a more polar series of metabolites, were subjected to yet more rounds of HPLC separation until pure compounds were obtained. The 16 labelled metabolites which were isolated from all these extensive HPLC procedures are listed below.

4.2.1. [15-C^{2}H$_3$]-Artemisinin (1b)/artemisinin (1). Oil (9.0 mg; R_t 19.2 min in the preliminary HPLC; R_t 29.2 min, 10% EtOAc/*n*-hexane). ^{1}H NMR (δ, $CDCl_3$) ppm: 5.86 (1H, s, H-5), 3.40 (1H, dq, J=5.5, 7.3 Hz, H-11), 2.44 (1H, ddd, J=14.6, 13.0, 3.9 Hz, H-3), 2.05 (1H, ddd, J=14.6, 4.6, 2.7 Hz, H-2), 2.00 (1H, ddddd, J=13.9, 2.9, 2.9, 2.9, 2.7 Hz, H-2), 1.88 (1H, dddd, J=10.5, 3.4, 3.4, 3.4 Hz, H-8), 1.77 (2H, m, H-7, H-9) 1.49 (1H, m, H-10) 1.45 (>95% of [3H], s, H-15), 1.38 (1H, m, H-1), 1.21 (3H, d, J=7.3 Hz, H-13), 1.08 (1H, dddd, J=12.8, 12.8, 12.8, 2.5 Hz, H-8), 1.00 (3H, d, J=5.9 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 172.1 (C-12), 105.4 (C-4), 93.7 (C-5), 79.5 (C-6), 50.1 (C-1), 45.0 (C-7), 37.5 (C-10), 35.9 (C-3), 33.6 (C-9), 32.9 (C-11), 25.2 (C-15, >95% intensity of isotopically-normal peak), 24.9 (C-2), 23.4 (C-8), 19.8 (C-14), 12.6 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.44 (s); CIMS *m*/*z* (rel. int.): 253 [M^+-O_2, $C_{15}H_{19}{}^2H_3O_3$] (2)/250 [M^+-O_2, $C_{15}H_{22}O_3$] (26), 235 (15), 232 (17), 209 (32), 192 (100), 180 (34), 152 (72).

4.2.2. [15-C^{2}H$_3$]-Dihydroartemisinic acid (2a)/dihydroartemisinic acid (2). Oil (1.0 mg; R_t 25.2 min in the preliminary HPLC; R_t 15.6 min, 12% EtOAc/*n*-hexane/0.5% AcOH). ^{1}H NMR (δ, $CDCl_3$) ppm: 5.11 (1H, s, H-5), 2.51 (2H, m, H-6, H-11), 1.98–1.87 (2H, m, H-2, H-3), 1.80 (1H, dd, J=17.1, 6.9 Hz, H-3), 1.63 (<60% of [3H], s, H-15), 1.19 (3H, d, J=6.9 Hz, H-13), 1.11 (1H, dddd, J=12.8, 12.8, 12.3, 3.2 Hz, H-8), 0.96 (1H, dddd, J=12.3, 12.3, 12.3, 2.7 Hz, H-9), 0.87 (3H, d, J=6.4 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 182.0 (C-12), 135.9 (C-4), 119.3 (C-5) 43.6 (C-7), 42.3 (C-11), 41.7 (C-1), 36.3 (C-7), 35.3 (C-9), 27.7 (C-10), 27.4 (C-8), 26.6 (C-3), 25.8 (C-2), 23.8 (C-15, <10% intensity of the isotopically-normal peak), 19.7 (C-14), 15.1 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.63 (s); HREIMS *m*/*z* (rel. int.): 239.1966 [M^+, $C_{15}H_{21}{}^2H_3O_2$ requires 239.1964] (10)/236.1767 [M^+, $C_{15}H_{24}O_2$ requires 236.1776] (2), 211 (2), 166 (27), 165 (100), 162 (16).

4.2.3. [15-C^{2}H$_3$]-Dihydroarteannuin B (5b)/dihydroarteannuin B (5). Oil (0.6 mg; R_t 25.2 min in the preliminary HPLC; R_t 33.0 min, 12% EtOAc/*n*-hexane/0.5% AcOH). ^{1}H NMR (δ, $CDCl_3$) ppm: 3.02 (1H, s, H-5), 2.77 (1H, dq, J=8.5, 8.0 Hz, H-11), 2.25 (1H, ddd, J=13.0, 8.5, 2.5 Hz, H-7), 1.93 (1H, dd, J=14.4, 4.8 Hz, H-3), 1.88 (1H, m, H-9), 1.82 (1H, dddd, J=12.8, 2.8, 2.8, 2.8 Hz, H-8), 1.54–1.45 (3H, m, H-2, H-8, H-10), 1.38 (3H, d, J=8.0 Hz, H-13), 1.35 (ca. 30% of [3H], s, H-15), 1.23 (1H, dddd, J=12.3, 12.3, 12.3, 4.1 Hz, H-9), 0.96 (3H, d, J=6.6 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 179.5 (C-12), 83.0 (C-6), 59.5 (C-5), 58.1 (C-4), 50.2 (C-7), 45.6 (C-1), 38.6 (C-11), 34.8 (C-9), 30.5 (C-10), 24.1 (C-3), 23.1 (C-15, ca. 30% intensity of the isotopically-normal peak), 21.6 (C-8), 18.5 (C-14), 16.2 (C-2), 12.6 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.35 (s).

4.2.4. [15-C^{2}H$_3$]-Dihydro-*epi*-deoxyarteannuin B (7b)/dihydro-*epi*-deoxyarteannuin B (7). Oil. (3.8 mg; R_t 12.5 min in the preliminary HPLC; R_t 17.6 min, 7% EtOAc/*n*-hexane). ^{1}H NMR (δ, $CDCl_3$) ppm: 5.64 (1H, s, H-5), 3.14 (1H, dq, J=7.3, 7.1 Hz, H-11), 2.15–2.06 (2H, m, H-3, H-7), 2.04 (1H, dddd, J=18.1, 11.2, 6.6, 2.3 Hz, H-3), 1.89 (1H, dddd, J=13.0, 6.6, 2.7, 1.4 Hz, H-2), 1.75–1.63 (3H, m, H-2, H-8, H-9), 1.69 (<30% of [3H], s, H-15), 1.43 (1H, dddq, J=10.5, 10.5, 6.9, 6.4 Hz, H-10), 1.19 (1H, m, H-8), 1.15 (3H, d, J=7.1 Hz, H-13), 1.05 (1H, dddd, J=12.6, 10.5, 9.8, 2.5 Hz, H-9), 0.94 (3H, d, J=6.4 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 179.4 (C-12), 142.2 (C-4), 121.8 (C-5), 83.2 (C-6), 46.6 (C-1), 42.8 (C-7), 39.7 (C-11), 32.5 (C-9), 30.8 (C-3), 29.7 (C-10), 23.5 (C-15; ca. 40% intensity of the the isotopically-normal peak), 23.4 (C-8), 21.0 (C-2), 19.6 (C-14), 9.5 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.68 (s); HREIMS *m*/*z* (rel. int.): 237.1812 [M^+, $C_{15}H_{19}{}^2H_3O_2$ requires 237.1808] (38)/234.1623 [M^+, $C_{15}H_{22}O_2$ requires 234.1620] (13), 219 (12), 193 (75), 190 (23), 164 (100), 161 (37).

4.2.5. [15-C^{2}H$_3$]-Arteannuin M (11b)/arteannuin M (11). Oil (0.1 mg; R_t 17.0 min for the 'polar residue' from preliminary HPLC; R_t 40.0 min, 40% EtOAc/*n*-hexane/0.7% AcOH). ^{1}H NMR (δ, $CDCl_3$) ppm: 3.46 (1H, s, H-5), 3.09 (1H, dq, J=7.1, 7.2 Hz, H-11), 2.65 (1H, ddd, J=12.8, 7.1, 5.5 Hz, H-7), 1.39 (<50% of [3H], s, H-15), 1.13 (3H, d, J=7.2 Hz, H-13), 0.93 (3H, d, J=6.4 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 179.1 (C-12, not seen due to low intensity), 86.3 (C-6, not seen due to low intensity), 74.2 (C-5), 72.6 (C-4, not seen due to low intensity), 41.7 (C-1), 39.1 (C-7), 38.8 (C-11), 34.2 (C-3), 32.3 (C-9), 29.9 (C-10), 26.6 (C-15, ca. 50% intensity of the other peaks), 23.9 (C-8), 22.1 (C-2), 20.1 (C-14), 9.4 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.39 (s); HREIMS *m*/*z* (rel. int.): 253.1751 [M^+-H_2O, $C_{15}H_{19}{}^2H_3O_3$ requires 253.1757] (3)/250.1553 [M^+-H_2O, $C_{15}H_{22}O_3$ requires 250.1569] (1), 235 (4), 232 (1), 225 (10), 222 (6), 195 (12), 179 (100).

4.2.6. [15-C^2H_3]-1α-Formyl-2β-[3-butanone]-3α-methyl-6β-(2-propanoic acid)-cyclohexane (14b)/1α-formyl-2β-[3-butanone]-3α-methyl-6β-(2-propanoic acid)-cyclohexane (14). Oil (0.3 mg). ^1H NMR (δ, $CDCl_3$) ppm: 9.58 (1H, d, *J*=4.9 Hz, H-5), 2.45–2.32 (3H, m, H-3, H-6), 2.14 (ca. 30% of [3H], s, H-15), 1.18 (3H, d, *J*=6.9 Hz, H-13), 0.94 (3H, d, *J*=6.4 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 208.3 (C-4), 205.9 (C-5), 177.4 (C-12), 56.1 (C-6), 42.3 (C-1), 41.2 (C-11), 41.0 (C-7), 38.1 (C-3), 34.7 (C-9), 33.4 (C-10), 30.0 (C-15, ca. 30% intensity of the isotopically-normal peak), 26.7 (C-2), 23.5 (C-8) 19.6 (C-14), 14.4 (C-13); ^2H NMR (δ, $CHCl_3$) ppm: 2.13 (s); HREIMS *m/z* (rel. int.): 253.1749 [M^+-H_2O, $C_{15}H_{19}{}^2H_3O_3$ requires 253.1757] (3)/250.1564 [M^+-H_2O, $C_{15}H_{22}O_3$ requires 250.1569] (1), 235 (76), 232 (31), 222 (6), 179 (100).

4.2.7. [15-C^2H_3]-Dihydroartemisinic acid tertiary hydroperoxide (15b)/dihydroartemisinic acid tertiary hydroperoxide (15). Oil (0.8 mg; R_t 9.8 for the 'polar residue' from preliminary HPLC; R_t 26.6 min, 22% EtOAc/*n*-hexane/0.5% AcOH). ^1H NMR (δ, $CDCl_3$) ppm: 5.25 (1H, s, H-5), 2.75 (1H, dq, *J*=6.9, 6.9 Hz, H-11), 1.29 (<30% of [3H], s, H-15), 1.27 (3H, d, *J*=6.9 Hz, H-13), 0.94 (3H, d, *J*=6.2 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 178.4 (C-12), 146.4 (C-6), 120.2 (C-5), 80.8 (C-4), 47.2 (C-7), 45.0 (C-1), 40.6 (C-11), 38.6 (C-10), 35.5 (C-9), 32.7 (C-8), 28.8 (C-3), 24.5 (C-15, ca. 25% intensity of the isotopically-normal peak), 22.5 (C-2), 20.0 (C-14), 15.8 (C-13); ^2H NMR (δ, $CHCl_3$) ppm: 1.28 (s).

4.2.8. [15-C^2H_3]-Dihydro-deoxyarteannuin B (16b)/dihydro-deoxyarteannuin B (16). Oil (0.1 mg; R_t 13.8 min in the preliminary HPLC; R_t 26.6 min, 5% EtOAc/*n*-hexane). ^1H NMR (δ, $CDCl_3$) ppm: 5.53 (1H, s, H-5), 2.74 (1H, dq, *J*=8.2, 8.0 Hz, H-11), 2.19 (1H, ddd, *J*=12.3, 8.2, 2.3 Hz, H-7), 2.03 (1H, m, H-3), 1.92 (1H, m, H-3) 1.80 (1H, m, H-9) 1.70 (<30% of [3H], s, H-15), 1.67 (1H, m, H-8), 1.44 (1H, dddd, *J*=12.3, 12.3, 12.3, 3.4 Hz, H-8), 1.34 (3H, d, *J*=8.0 Hz, H-13), 1.17 (1H, dddd, *J*=12.3, 12.1, 12.1, 3.7 Hz, H-9), 0.97 (3H, d, *J*=6.2 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 180.6 (C-12, not seen due to low intensity), 142.3 (C-4), 120.5 (C-5), 86.7 (not seen due to low intensity), 49.8 (C-7), 46.6 (C-1), 39.0 (C-11), 35.3 (C-9), 30.7 (C-10), 26.0 (C-3), 24.1 (C-15, <20% intensity of the other peaks), 22.0 (C-8), 20.1 (C-2), 19.9 (C-14), 13.1 (C-13); ^2H NMR (δ, $CHCl_3$) ppm: 1.68 (s); HREIMS *m/z* (rel. int.): 237.1811 [M^+, $C_{15}H_{19}{}^2H_3O_2$ requires 237.1808] (47)/234.1623 [M^+, $C_{15}H_{22}O_2$ requires 234.1620] (10), 193 (50), 191 (52), 164 (100), 161 (28).

4.2.9. [15-C^2H_3]-4α,5α-Epoxy-6α-hydroxy-amorphan-12-oic acid (17b)/4α,5α-epoxy-6α-hydroxy-amorphan-12-oic acid (17). Oil (0.3 mg; R_t 10.6 min for the 'polar residue' from preliminary HPLC; R_t 22.1 min, 22% EtOAc/*n*-hexane/0.6% AcOH). ^1H NMR (δ, $CDCl_3$) ppm: 3.24 (1H, s, H-5), 3.06 (1H, dq, *J*=4.0, 7.1 Hz, H-11), 1.36 (<30% of [3H], s, H-15), 1.33 (3H, d, *J*=7.1 Hz, H-13), 0.87 (3H, d, *J*=6.8 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 181.1 (C-12), 70.6 (C-6), 60.9 (C-4, C-5), 50.1 (C-7), 48.6 (C-1), 39.5 (C-11), 34.6 (C-9), 30.7 (C-10), 26.2 (C-8), 24.4 (C-3), 23.5 (C-15, ca. 30% intensity of the isotopically-normal peak), 19.0 (C-14), 18.9 (C-13), 15.1 (C-2); ^2H NMR (δ, $CHCl_3$) ppm: 1.35 (s); HREIMS *m/z* (rel. int.): 253.1750 [M^+-H_2O, $C_{15}H_{19}{}^2H_3O_3$ requires 253.1757] (4)/250.1565 [M^+-H_2O, $C_{15}H_{22}O_3$ requires 250.1569] (1), 235 (4), 232 (1), 179 (100).

4.2.10. [15-C^2H_3]-Deoxyartemisinin (18b)/deoxyartemisinin (18). Oil (1.5 mg; R_t 15.8 min in the preliminary HPLC; R_t 23.4 min, 10% EtOAc/*n*-hexane). ^1H NMR (δ, $CDCl_3$) ppm: 5.70 (1H, s, H-5), 3.19 (1H, dq, *J*=4.6, 7.1 Hz, H-11), 2.01 (1H, ddd, *J*=13.1, 4.6, 4.6 Hz, H-7), 1.94–1.88 (2H, m, H-2, H-8), 1.63 (1H, m, H-3), 1.53 (<50% of [3H], s, H-15), 1.20 (3H, d, *J*=7.1 Hz, H-13), 0.94 (3H, d, *J*=5.7 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 173.5 (C-12), 109.2 (C-4), 99.7 (C-5), 82.4 (C-6), 44.6 (C-1), 42.4 (C-7), 35.4 (C-10), 33.9 (C-3), 33.5 (C-9), 32.8 (C-11), 24.0 (C-15, ca. 30% intensity of the isotopically-normal peak), 23.5 (C-8), 22.0 (C-2), 18.6 (C-14), 12.6 (C-13); ^2H NMR (δ, $CHCl_3$) ppm: 1.52 (s); HREIMS *m/z* (rel. int.): 269.1699 [M^+, $C_{15}H_{19}{}^2H_3O_4$ requires 269.1707] (10)/266.1509 [M^+, $C_{15}H_{22}O_4$ requires 266.1518] (6), 225 (35), 222 (10), 168 (63), 165 (52), 164 (100), 151 (77).

4.2.11. [15-C^2H_3]-Arteannuin K (19b)/arteannuin K (19). Oil (0.1 mg; R_t 35–39 min in the preliminary HPLC; R_t 35.1 min, 20% EtOAc/*n*-hexane). ^1H NMR (δ, $CDCl_3$) ppm: 5.67 (1H, d, *J*=3.2 Hz, H-3), 3.69 (1H, d, *J*=3.2 Hz, H-5), 3.11 (1H, dq, *J*=6.8, 7.1 Hz, H-11), 2.72 (1H, ddd, *J*=10.7, 6.8, 5.8 Hz, H-7), 2.29 (1H, ddd, *J*=18.5, 11.5, 3.2 Hz, H-2), 1.98 (1H, m, H-2), 1.78 (<40% of [3H], s, H-15), 1.15 (3H, d, *J*=7.1 Hz, H-13), 0.94 (3H, d, *J*=5.8 Hz, H-14); ^2H NMR (δ, $CHCl_3$) ppm: 1.78 (s); HREIMS *m/z* (rel. int.): 253.1756 [M^+, $C_{15}H_{19}{}^2H_3O_3$ requires 253.1757] (3)/250.1557 [M^+, $C_{15}H_{22}O_3$ requires 250.1569] (1), 208 (30), 180 (27), 167 (100).

4.2.12. [15-C^2H_2]-Arteannuin L (20b)/arteannuin L (20). Oil (0.1 mg; R_t 35–39 min in the preliminary HPLC; R_t 32.8 min, 20% EtOAc/*n*-hexane). ^1H NMR (δ, $CDCl_3$) ppm: 4.94 (33% of [1H], dd, *J*=1.6, 1.6 Hz, H-15), 4.91 (33% of [1H], dd, *J*=1.6, 1.6 Hz, H-15), 4.11 (1H, s, H-5), 3.11 (1H, dq, *J*=5.9, 7.1 Hz, H-11), 2.60 (1H, ddd, *J*=11.4, 5.9, 5.9 Hz, H-7), 2.38 (1H, ddd, *J*=14.6, 13.5, 5.1 Hz, H-3), 2.26 (1H, dd, *J*=14.6, 4.1 Hz, H-3), 1.86 (1H, d, *J*=12.6 Hz, H-2), 1.75 (1H, m, H-8), 1.72 (1H, ddd, *J*=11.2, 11.2, 3.5 Hz, H-1), 1.63 (1H, m, H-9), 1.45 (1H, dddd, *J*=13.5, 12.6, 11.2, 4.1 Hz, H-2), 1.14 (3H, d, *J*=7.1 Hz, H-13), 1.09 (1H, ddd, *J*=12.8, 12.8, 12.8 Hz, H-9) 0.95 (3H, d, *J*=6.6 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 179.2 (C-12, not seen due to low intensity), 146.6 (C-4, not seen due to low intensity), 114.9 (C-15, <20% intensity of the isotopically-normal peak); 86.2 (C-6, not seen due to low intensity), 73.5 (C-5), 41.8 (C-1), 38.8 (C-11), 38.4 (C-7), 32.4 (C-9), 30.7 (C-10), 29.1 (C-3), 25.2 (C-2), 24.3 (C-8), 20.1 (C-14), 9.3 (C-13); ^2H NMR (δ, $CHCl_3$) ppm: 4.94 (br s); HREIMS *m/z* (rel. int.): 252.1687 [M^+, $C_{15}H_{20}{}^2H_2O_3$ requires 252.1695] (4)/250.1564 [M^+, $C_{15}H_{22}O_3$ requires 250.1569] (1), 234 (8), 232 (3), 179 (100), 178 (48), 177 (32).

4.2.13. [15-C^2H_2]-Arteannuin H (21b)/arteannuin H (21). Oil (0.3 mg; R_t 9.2–11.2 min in the preliminary HPLC; R_t 14.3 min, 2% EtOAc/*n*-hexane). ^1H NMR (δ, $CDCl_3$) ppm: 5.03 (1H, d, *J*=12.3 Hz, H-5), 4.91 (84% of

[1H], q, J=1.8 Hz, H-15), 4.84 (85% of [1H], q, J=1.8 Hz, H-15), 3.52 (1H, q, J=7.1 Hz, H-11), 2.24 (1H, ddd, J=13.9, 4.5, 2.9 Hz, H-3), 2.18 (1H, dd, J=13.9, 13.9 Hz, H-3), 2.08 (1H, ddd, J=12.3, 4.2, 3.9 Hz, H-6), 1.95 (1H, dddd, J=13.7, 4.1, 2.1, 2.1 Hz, H-2), 1.87 (1H, dddd, J=13.2, 3.5, 3.5, 3.5 Hz, H-9), 1.77 (1H, ddd, J=14.0, 3.7, 3.1 Hz, H-8), 1.74 (1H, dddd, J=12.0, 3.9, 3.7, 1.0 Hz, H-7), 1.64 (1H, m, H-10), 1.38 (1H, dddd, J=13.9, 13.7, 4.7, 4.5 Hz, H-2), 1.26 (1H, m, H-8), 1.21 (3H, d, J=7.1 Hz, H-13), 1.05 (1H, dddd, J=13.2, 12.3, 12.3, 3.0 Hz, H-9), 0.88 (3H, d, J=6.2 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 180.1 (C-12), 145.3 (C-4), 106.6 (C-15; no clear change in peak intensity relative to the isotopically-normal spectrum), 84.8 (C-5), 50.9 (C-6), 45.2 (C-1), 43.3 (C-7), 40.3 (C-11), 35.5 (C-9), 30.7 (C-3), 28.6 (C-2 and C-10), 22.7 (C-8), 19.7 (C-14), 15.6 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 4.93 (br s), 4.85 (br s) HREIMS m/z (rel. int.): 252.1690 [M^+, $C_{15}H_{20}{}^2H_2O_3$ requires 252.1695] (16)/250.1575 [M^+, $C_{15}H_{22}O_3$ requires 250.1569] (80), 234 (48), 232 (32), 206 (77), 204 (33), 191 (25), 179 (60), 177 (100).

4.2.14. [15-C^{2}H$_2$]-Arteannuin I (22b)/arteannuin I (22). Oil (1.1 mg; R_t 13.1 min in the preliminary HPLC; R_t 21.3 min, 6% EtOAc/*n*-hexane). ^{1}H NMR (δ, $CDCl_3$) ppm: 5.05 (27% of [1H], s, H-15), 4.96 (1H, d, J=11.9 Hz, H-5), 4.82 (27% of [1H], s, H-15), 2.69 (1H, dq, J=7.1, 7.3 Hz, H-11), 2.25 (1H, d, J=13.9 Hz, H-3), 2.15 (1H, ddd, J=13.9, 13.9, 4.6 Hz, H-3), 2.04–1.95 (2H, m, H-2, H-6) 1.94–1.86 (2H, m, H-7, H-9) 1.81–1.73 (2H, m, H-1, H-8), 1.47 (1H, dddd, J=13.9, 13.9, 4.5, 4.5 Hz, H-2), 1.29 (1H, dddd, J=13.1, 13.1, 13.1, 3.7 Hz, H-8), 1.23 (3H, d, J=7.3 Hz, H-13), 1.05 (1H, dddd, J=13.2, 13.2, 13.1, 3.9 Hz, H-9) 0.91 (3H, d, J=6.4 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 174.4 (C-12), 146.0 (C-4), 105.1 (C-15; ca. 20% intensity of the isotopically-normal peak); 76.8 (C-5), 45.5 (C-6), 43.7 (C-1), 40.5 (C-11), 40.0 (C-7), 35.0 (C-9), 29.4 (C-3), 28.7 (C-2), 28.1 (C-10), 22.7 (C-8), 20.1 (C-14), 13.3 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 5.07 (s), 4.86 (s); HREIMS m/z (rel. int.): 236.1739 [M^+, $C_{15}H_{20}{}^2H_2O_2$ requires 236.1746] (100)/234.1614 [M^+, $C_{15}H_{22}O_2$ requires 234.1619] (33), 208 (73), 206 (22), 191 (24), 124 (100).

4.2.15. [15-C^{2}H$_3$]-Arteannuin J (23b)/arteannuin J (23). Oil (0.1 mg—only ca. 50% pure; R_t 13.1 min in the preliminary HPLC; R_t 20.4 min, 6% EtOAc/*n*-hexane). ^{1}H NMR (δ, $CDCl_3$) ppm: 5.37 (1H, s, H-3), 4.93 (1H, d, J=12.1 Hz, H-5), 2.75 (1H, dq, J=7.1, 7.3 Hz, H-11), 1.79 (<50% of [3H], s, H-15), 1.24 (3H, d, J=7.3 Hz, H-13), 0.88 (3H, d, J=6.3 Hz, H-14); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.78 (s).

4.2.16. [15-C^{2}H$_3$]-α-epoxy-dihydroartemisinic acid (24b)/α-epoxy-dihydroartemisinic acid (24). Oil (0.1 mg; R_t 39–43 min in the preliminary HPLC; R_t 23.3 min, 20% EtOAc/*n*-hexane). ^{1}H NMR (δ, $CDCl_3$) ppm: 2.63 (1H, s, H-5), 2.61 (1H, dq, J=10.5, 6.9 Hz, H-11), 2.04 (1H, br m, H-6), 1.84 (1H, d, J=14.4 Hz, H-3), 1.32 (<30% of [3H], s, H-15), 1.29 (3H, d, J=6.9 Hz, H-13), 0.86 (3H, d, J=6.6 Hz, H-14); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.31 (s); HREIMS m/z (rel. int.): 237.1812 [M^+-H_2O, $C_{15}H_{19}{}^2H_3O_2$ requires 237.1808] (40)/234.1602 [M^+-H_2O, $C_{15}H_{22}O_2$ requires 234.1620] (12), 182 (100).

4.2.17. [15-C^{2}H$_3$]-Dihydro-*epi*-arteannuin B (25b)/dihydro-*epi*-arteannuin B (25). Oil (0.1 mg; R_t 13.8 min in the preliminary HPLC; R_t 27.6 min, 5% EtOAc/*n*-hexane). ^{1}H NMR (δ, $CDCl_3$) ppm: 3.24 (1H, dq, J=7.0, 7.1 Hz, H-11), 3.01 (1H, s, H-5), 2.42 (1H, ddd, J=10.2, 7.0, 6.6 Hz, H-7), 1.91 (1H, m, H-3), 1.88 (1H, m, H-3) 1.86–1.72 (1H, m, H-8) 1.33 (<30% of [3H], s, H-15), 1.18 (3H, d, J=7.1 Hz, H-13), 1.06 (1H, dddd, J=12.8, 12.8, 9.8, 2.0 Hz, H-9) 0.89 (3H, d, J=6.2 Hz, H-14); ^{13}C NMR (δ, $CDCl_3$) ppm: 179.3 (C-12, not seen due to low intensity), 84.6 (C-6, not seen due to low intensity), 63.1 (C-4, not seen due to low intensity), 60.5 (C-5), 40.7 (C-7), 39.7 (C-1), 39.1 (C-11), 31.8 (C-9), 29.5 (C-10), 27.2 (C-3), 24.2 (C-15, not seen, <20% intensity of the other peaks), 23.5 (C-8), 20.1 (C-2 and C-14), 9.4 (C-13); ^{2}H NMR (δ, $CHCl_3$) ppm: 1.32 (s); HREIMS m/z (rel. int.): 253.1578 [M^+, $C_{15}H_{19}{}^2H_3O_3$ requires 253.1757] (4)/250.1562 [M^+, $C_{15}H_{22}O_3$ requires 250.1569] (1), 235 (4), 232 (1), 179 (100).

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References and notes

1. Liu, J.-M.; Ni;, M.-Y.; Fan, Y.-Y.; Tu, Y.-Y.; Wu, Z.-H.; Wu, Y.-L.; Zhou, W.-S. *Acta Chim. Sin.* **1979**, *37*, 129–143.
2. Sy, L.-K.; Brown, G. D.; Haynes, R. *Tetrahedron* **1998**, *54*, 4345–4356.
3. Sy, L.-K.; Brown, G. D. *Phytochemistry* **1998**, *48*, 1207–1211.
4. Sy, L.-K.; Brown, G. D. *Phytochemistry* **2001**, *58*, 1159–1166.
5. Sy, L.-K.; Cheung, K.-K.; Zhu, N.-Y.; Brown, G. D. *Tetrahedron* **2001**, *57*, 8481–8493.
6. Brown, G. D.; Liang, G.-Y.; Sy, L.-K. *Phytochemistry* **2003**, *64*, 303–323.
7. Akhila, A.; Rani, K.; Thakur, R. S. *Phytochemistry* **1990**, *29*, 2129–2132.
8. Huang, J.-J.; Zhou, F.-Y.; Wu, L.-F.; Zhen, G.-H. *Acta Chim. Sin.* **1990**, *48*, 275–277.
9. Akhila, A.; Thakur, R. S.; Popli, S. P. *Phytochemistry* **1987**, *26*, 1927–1930.
10. Kudakasseril, G. J.; Lam, L.; Staba, E. J. *Planta Med.* **1987**, 280–284.
11. Chen, D.-H.; Ye, H.-C.; Li, G.-F. *Plant Sci.* **2000**, *155*, 179–185.
12. Bouwmeester, H. J.; Wallaart, T. E.; Janssen, M. H. A.; van Loo, B.; Jansen, B. J. M.; Posthumus, M. A.; Schmidt, C. O.; de Kraker, J.-W.; Konig, W. A.; Franssen, M. C. R. *Phytochemistry* **1999**, *52*, 843–854.
13. Bharel, S.; Gulati, A.; Abdin, M. Z.; Srivastava, P. S.; Jain, S. K. *Fitoterapia* **1996**, *LXVII*, 387–402.

14. Kim, N.-C.; Kim, S. O. *J. Korean Agric. Chem. Soc.* **1992**, *35*, 106–109.
15. Wang, Y.; Xia, Z.-Q.; Zhou, F.-Y.; Wu, Y.-L.; Huang, J.-J.; Wang, Z.-Z. *Chin. J. Chem.* **1993**, *11*, 457–463.
16. Kawamoto, H.; Asada, Y.; Sekine, H.; Furuya, T. *Phytochemistry* **1998**, *48*, 1329–1333.
17. Sangwan, R. S.; Agarwal, K.; Luthra, R.; Thakur, R. S.; Singh-Sangwan, N. *Phytochemistry* **1993**, *34*, 1301–1302.
18. Wang, Y.; Xia, Z.-Q.; Zhou, F.-Y.; Wu, Y.-L.; Huang, J.-J.; Wang, Z.-Z. *Acta Chim. Sin.* **1988**, *46*, 1152–1153.
19. Chen, P. K.; Lukonis, C.; Go, L.; Leather, G. R. *Proc. Plant Growth Regul. Soc. Am. (18th)* **1991**, 2–8.
20. El-Feraly, F. S.; Al-Meshal, I. A.; Al-Yahya, M. A.; Hifnawy, M. S. *Phytochemistry* **1986**, *25*, 2777–2778.
21. Misra, L. N.; Ahmad, A.; Thakur, R. S.; Lotter, H.; Wagner, H. *J. Nat. Prod.* **1993**, *56*, 215–219.
22. Li, Y.; Yang, Z.-X.; Chen, Y.-X.; Zhang, X. *Yaoxue Xuebao* **1994**, *29*, 713–716.
23. Nair, M. S. R.; Basile, D. V. J. *Nat. Prod.* **1993**, *56*, 1559–1566.
24. Nair, M. S. R.; Basile, D. V. *Ind. J. Chem.* **1992**, *31B*, 880–882.
25. Bharel, S.; Gulati, A.; Abdin, M. Z.; Srivastava, P. S.; Vishwakarma, R. A.; Jain, S. K. *J. Nat. Prod.* **1998**, *61*, 633–636.
26. Wang, Y.; Shen, Z.-W.; Xia, Z.-Q.; Zhou, F.-Y. *Chin. J. Chem.* **1993**, *11*, 476–478.
27. Wu, Z.-H.; Wang, Y.-Y. *Acta Chim. Sin.* **1984**, *42*, 596–598.
28. Vandenberghe, D. R.; Vergauwe, A. N.; van Montagu, M.; van den Eeckhout, E. G. *J. Nat. Prod.* **1995**, *58*, 798–803.
29. Brown, G. D. *Phytochemistry* **1994**, *36*, 637–641.
30. Zhou, W.-S. *Pure Appl. Chem.* **1986**, *58*, 817–824.
31. Roth, R. J.; Acton, N. *J. Chem. Ed.* **1991**, *68*, 612–613.
32. Acton, N.; Roth, *J. Org. Chem.* **1992**, *57*, 3610–3614.
33. Vonwiller, S. C.; Warner, J. A.; Mann, S. T.; Haynes, R. K. *J. Am. Chem. Soc.* **1995**, *117*, 11098–11105.
34. Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 451–453.
35. Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73–79.
36. Jung, M.; ElSohly, H. N.; Croom, E. M.; McPhail, A. T.; McPhail, D. R. *J. Org. Chem.* **1986**, *51*, 5417–5419.
37. Ye, B.; Wu, Y.-L. *J. Chem. Soc., Chem. Commun.* **1990**, 726–727.
38. Nowak, D. M.; Lansbury, P. T. *Tetrahedron* **1998**, *54*, 319–336.
39. Sy, L.-K.; Brown, G. D. *Tetrahedron* **2002**, *58*, 897–908.
40. Wallaart, T. E.; van Uden, W.; Lubberink, H. G. M.; Woerdenbag, H. J.; Pras, N.; Quax, W. J. *J. Nat. Prod.* **1999**, *62*, 430–433.
41. Wallaart, T. E.; Pras, N.; Quax, W. J. *J. Nat. Prod.* **1999**, *62*, 1160–1162.
42. Sy, L.-K.; Brown, G. D. *Tetrahedron* **2002**, *58*, 909–923.
43. Sy, L.-K.; Zhu, N.-Y.; Brown, G. D. *Tetrahedron* **2001**, *57*, 8495–8510.
44. Brown, G. D. *^{13}C–^{2}H correlation spectroscopy, development and applications to chemical and biological problems,* 15th International Meeting on NMR Spectroscopy, 8th–12th July, Durham, UK, 2001.
45. Brown, G. D. *Phytochem. Rev.* **2003**, *2*, 45–59.
46. Atkins, P. W. Physical chemistry. 5th ed. Oxford University Press: New York, 1994; Chapter 25.7.
47. Huang, J.-J.; Nicholls, K. M.; Cheng, C.-H.; Wang, Y. *Acta Chim. Sin.* **1987**, *45*, 305–308.
48. Sy, L.-K.; Brown, G. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2421–2429.
49. Sy, L.-K.; Ngo, K.-S.; Brown, G. D. *Tetrahedron* **1999**, *55*, 15127–15140.
50. Frimer, A. *Chem. Rev.* **1979**, *79*, 359–385.
51. Rodriguez, E.; Healey, P. L.; Mehta, I. Biology and chemistry of plant trichomes. Plenum: New York, 1984.
52. Lange, B. M.; Wildung, M. R.; Staubar, E. J.; Sánchez, C.; Pouchnik, D.; Croteau, R. *Proc. Nat. Acad. Sci.* **2000**, *97*, 2934–2939.
53. Jako, C.; Coutu, C.; Roewer, I.; Reed, D. W.; Pelcher, E.; Covello, P. S. *Plant Sci.* **2002**, *163*, 141–145.
54. Kim, S.-U.; Han, J.; Lim, Y.-H. *Planta Med.* **1996**, *62*, 480–481.
55. Marsaiolo, A. J.; Fuijiwara, F. Y.; Foglio, M. A.; Sharapin, N.; Zhang, J.-S. *Mag. Res. Chem.* **1994**, *32*, 583–590. Agrawal, P. K.; Vishwakarma, R. A.; Jain, D. C.; Roy, R. *Phytochemistry* **1991**, *30*, 3469–3471.
56. Brown, G. D. *J. Nat. Prod.* **1992**, *55*, 1756–1760.
57. Brown, G. D. *Phytochemistry* **1993**, *32*, 391–393.
58. Smith, I. C. P. In *Deuterium NMR. NMR of newly accessible nuclei*; Laszlo, P., Ed.; Academic: New York, 1983; Vol. 2, pp 1–24.
59. Braun, S.; Kalinowski, H.-O.; Berger, S. 100 and more basic NMR experiments. VCH: Weinheim, 1996; p 264.
60. van de Ven, F. J. M. Multidimensional NMR in liquids. VCH: Weinheim, 1995; p 25.

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A facile synthesis of pyrrolo[1,2-*a*]benzimidazoles and pyrazolo[3,4:4′,3′]pyrrolo[1,2-*a*]benzimidazole derivatives

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Abstract—Reaction of 2-cyanomethylbenzimidazole **1** with hydrazonoyl halides **2** led to formation of pyrrolo[1,2-*a*]benzimidazole derivatives **7**. Similar reaction of **1** with halides **3** afforded 5-amino-4-(benzimidazol-2-yl)pyrazole derivatives **11** or 1-amino-2-arylpyrazolo[3,4:4′,3′]pyrrolo[1,2-*a*]benzimidazol-4-one **14** depending on the reaction conditions. The mechanisms of the studied reactions are discussed.
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1. Introduction

Hydrazonoyl halides are highly versatile intermediates for the synthesis of a variety of heterocyclic compounds.[1] Also, benzimidazoles represent an important heterocyclic system due to their pharmacological activity.[2] In addition many efforts have been made to develop methods for preparation of pyrrolo[1,2-*a*]benzimidazole.[3–5] This is because derivatives of this ring system proved to have many applications, for example, pyrrolo[1,2-*a*]benzimidazole based antitumor agent system,[6] cytotoxicity against melanoma and renal cancers;[7] cytotoxicity against leukemia and gasteric cancer cell lines,[8] cytotoxicity of various PBI and APBI derivatives,[9] as novel chlain esterase inhibitors,[10] as photochromic compound.[11] Also some pyrrolo[1,2-*a*]benzimidazole derivatives are useful in treating central nervous system disorder,[12] and as topoisomerase inhibitor.[13] In addition, they are used in the synthesis of basic dyes[14] and polymethine dyes.[15]

2. Results and discussion

In continuation of our interest in the synthesis of novel polyfunctionalized heterocycles of biological importance,[16] we report here a facile one-pot synthesis of the title compounds via reaction of hydrazonoyl halides **2** and **3** with 2-cyanomethylbenzimidazole **1**. Thus treatment of hydrazonoyl halides **2a-f** with 2-cyanomethylbenzimidazole **1** in chloroform in the presence of triethylamine under reflux, afforded products identified as 2-arylazo-3-cyano-1-substituted pyrrolo[1,2-*a*]benzimidazoles **7** (Scheme 1). All of the isolated products **7a-f** gave satisfactory elemental analyses and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS, UV) consistent with their assigned structures. For example, the IR spectra of the products showed conjugated nitrile absorption band near 2200 cm^{-1}, absence of carbonyl absorption and the appearance of NH absorption band in the region 3450–3200 cm^{-1}. Furthermore, the electronic absorption spectra of **7a-f** in dioxane revealed in each case, three intense maxima at λ near 410, 330 and 250 nm assignable to arylazochromophore. The formation of **7a-f** from the reaction of **1** with **2** seems to follow the sequence outlined in Scheme 1 (route a). It is suggested that the reaction starts with nucleophilic substitution of the halogen group in **2** by the carbanion of **1** namely **4** to give **5** which cyclizes via elimination of the elements of water to give **7a-f** as end products.

On the other hand, treatment of hydrazonoyl chlorides **3a-f** with 2-cyanomethylbenzimidazole **1** in ethanolic sodium ethoxide solution at room temperature, afforded a single product in each case, as evidenced by TLC and ^{1}H NMR spectroscopic analyses. The structure of the isolated products was established by analytical and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS) and identified as alkyl 5-amino-1-aryl-4-(benzimidazol-2-yl)pyrazole-3-carboxylate **11** (Scheme 2). For example, the IR spectra showed the presence of characteristic NH and NH_2 absorption bands in the region 3450–3200 cm^{-1} and the absence of conjugated nitrile absorption band near 2200 cm^{-1} for each product. In addition they revealed the ester carbonyl near 1705 cm^{-1}.

Keywords: 2-Cyanomethylbenzimidazole; Hydrazonoyl halides; Pyrrolo[1,2-*a*]benzimidazole; 5-Amino-4-(benzimidazol-2-yl)pyrazole; 1-Amino-2-arylpyrazolo[3,4:4′,3′]pyrrolo[1,2-*a*]benzimidazol-4-one.
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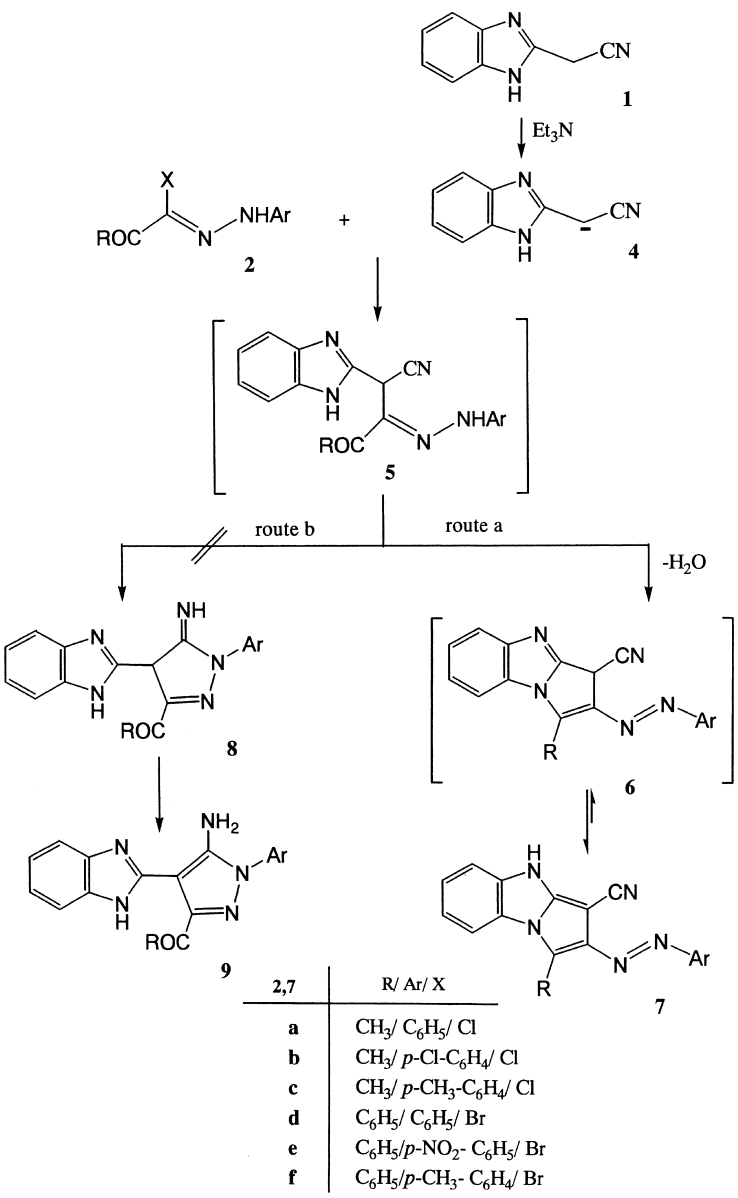
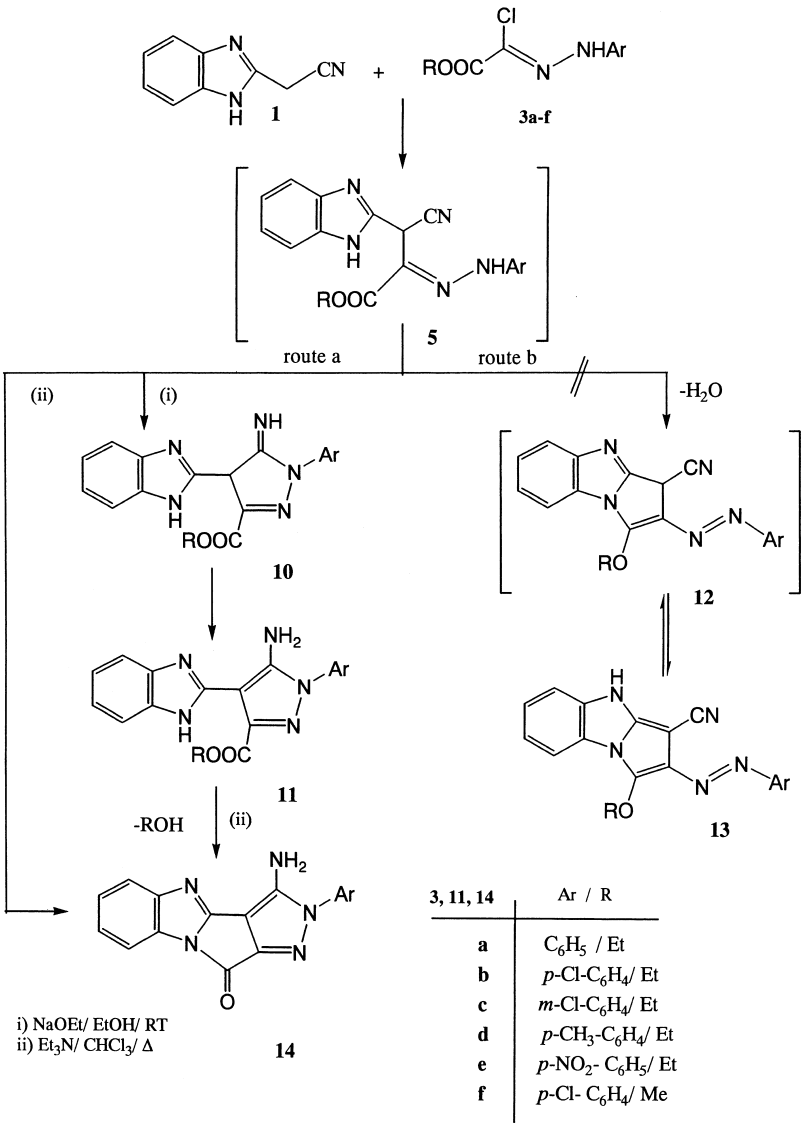


Scheme 1.

The assigned structures were further supported by their chemical reactions. Thus heating **11b** or **11f** in chloroform in the presence of triethylamine yielded the same product **14b**. Also, treatment of 2-cyanomethylbenzimidazole **1** with hydrazonoyl chlorides **3a-d** in chloroform in the presence of triethylamine under reflux, afforded, in each case, one single product **14a-d** as evidenced by TLC and ^{1}H NMR spectroscopy of the reaction products (Scheme 2). The mass spectra of the products exhibited in each case a molecular ion peak with high intensity. ^{1}H NMR spectra were devoid of signals characteristic of an ethyl group. The latter structure was firmly established for the reaction products by alternate synthesis of the product **14b** via reaction of methyl *N*-(*p*-chlorophenyl)hydrazonochloroacetate **3f** with **1** in chloroform in the presence of triethylamine under reflux to afford a product, which proved to be identical in all respects (mp, mixed mp, spectral data) with **14b**. An attempt to cycle **11e** to get **14e** by the same method was not successful. However, **14e** was obtained in small yield (30%) by heating **11e** in refluxing xylene for 48 h.

3. Experimental

Melting points were recorded on Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Pye Unicam SP-3000 infrared spectrophotometer. ^{1}H NMR and ^{13}C spectra were determined on a Varian Gemini 200 spectrometer (200 MHz) in DMSO-d_6 with TMS as an internal standard. Mass spectra were recorded on a GCMS-QP 1000EX Schimadzu spectrometer. The electronic spectra were recorded using Perkin–Elmer Lambda 4B UV–VIS spectrophotometer. Elemental analyses were carried out at the microanalytical center, University of Cairo, Giza, Egypt. The starting 2-cyanomethybenzimidazole **1**[17] and hydrazonoyl halides **2** and **3**[18–21] were



Scheme 2.

prepared as previously described. Due to the limited solubility of products **7**, **11** and **14** in common ^{13}C NMR solvents, the ^{13}C NMR spectra were recoded for **7a-c**, **7e**, **11d**, **e**, **14a-c** and **14e** only as representative examples of the series prepared.

3.1. Synthesis of pyrrolo[1,2-*a*]benzimidazoles 7a-f

General method. To a solution of 2-cyanomethylbenzimidazole **1** (0.79 g, 5 mmol) and the appropriate hydrazonoyl halide **2** (5 mmol) in chloroform (40 mL) was added triethylamine (0.7 mL, 5 mmol) at room temperature. The reaction mixture was refluxed for 8 h and the solvent was then evaporated and the residue was treated with methanol. The solid that formed was collected and crystallized from dimethylformamide to give **7a-f** in needle form.

3.1.1. 3-Cyano-1-methyl-2-phenylazo-4*H*-pyrrolo[1,2-*a*]-benzimidazole 7a. The compound was obtained in 80% yield, orange, mp 264 °C; IR (KBr) ν 3394 (NH), 2200 (CN) cm^{-1}; ^1H NMR (DMSO) δ 2.7 (s, 3H), 7.2–7.5 (m, 5H), 7.6–7.9 (m, 2H), 8.0–8.2 (m, 1H), 8.6–8.8 (m, 1H), 13.2 (s, 1H); ^{13}C NMR (DMSO) δ 13.6, 113.8, 117.2, 118.4, 122.5, 126.2, 126.4, 128.5, 129.6, 130.4, 134.2, 137.1, 145.6, 155.4, 164.1, 177.7 ppm; MS, *m/z* (%): 300 (21.9), 299 (100), 207 (25.4), 194 (26.6), 92 (64.6), 77 (48.4), 65 (72.1); UV (dioxane), λ_{max} (nm): 438, 354, 256. Anal. Calcd for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 72.45; H, 4.23; N, 23.75%.

3.1.2. 3-Cyano-1-methyl-2-(*p*-chlorophenylazo)-4*H*-pyrrolo[1,2-*a*]benzimidazole 7b. The compound was obtained in 82% yield, red, mp 280 °C; IR (KBr) ν 3170 (NH), 2206 (CN) cm^{-1}; ^1H NMR (DMSO) δ 2.7 (s, 3H), 7.2–7.7 (m, 5H), 7.8–8.0 (m, 2H), 8.6–8.7 (m, 1H), 13.2 (s, 1H); ^{13}C NMR (DMSO) δ 13.5, 110.0, 112.6, 115.4, 116.9, 117.8, 121.8, 123.1, 125.3, 127.6, 129.9, 132.9, 143.4, 146.3, 153.1, 162.9 ppm; MS, *m/z* (%): 335 (35.4), 334 (27.7), 333 (100), 207 (45.4), 126 (53.8), 90 (39.9), 75 (26.0), 64 (32), 63 (43.5); UV (dioxane), λ_{max} (nm): 447, 359, 256. Anal. Calcd for $C_{18}H_{12}ClN_5$: C, 64.77; H, 3.63; N, 20.98. Found: C, 64.91; H, 3.85; N, 20.86%.

3.1.3. 3-Cyano-1-methyl-2-(*p*-methylphenylazo)-4*H*-pyrrolo[1,2-*a*]benzimidazole 7c. The compound was obtained in 78% yield, orange, mp 274 °C; IR (KBr) ν 3163 (NH), 2206 (CN) cm^{-1}; ^1H NMR (DMSO) δ 2.3 (s, 3H), 2.5 (s, 3H), 7.2–7.5 (m, 5H), 7.6–7.7 (m, 2H), 8.5–8.6 (m, 1H), 13.2 (s, 1H); ^{13}C NMR (DMSO) δ 13.6, 23.2, 113.4, 117.1, 118.5 122.2, 126.1, 126.3, 128.2, 131.6 134.0, 136.9, 139.8, 145.1, 153.1, 163.5, 177.6; MS, *m/z* (%): 314 (20.1), 313 (100), 207 (26.1), 106 (70.2); UV (dioxane), λ_{max} (nm): 440, 350, 255. Anal. Calcd for $C_{19}H_{15}N_5$: C, 72.82; H, 4.83; N, 22.35. Found: C, 73.01; H, 4.55; N, 22.60%.

3.1.4. 3-Cyano-1-phenyl-2-phenylazo-4*H*-pyrrolo[1,2-*a*]-benzimidazole 7d. The compound was obtained in 77% yield, orange, mp 254 °C; IR (KBr) ν 3340 (NH), 2129 (CN) cm^{-1}; ^1H NMR (DMSO) δ 7.3–8.0 (m,14H), 8.7–8.8 (m,1H); MS, *m/z* (%): 361 (75.8), 360 (100), 333 (22.1), 257 (44.7), 127 (15.2), 92 (48.1), 77 (72.6), 65 (60.3); UV (dioxane), λ_{max} (nm): 451, 324, 276. Anal. Calcd for $C_{23}H_{15}N_5$: C, 76.44; H, 4.18; N, 19.38. Found: C, 76.24; H, 4.50; N, 19.62%.

3.1.5. 3-Cyano-1-phenyl-2-(*p*-nitrophenylazo)-4*H*-pyrrolo[1,2-*a*]benzimidazole 7e. The compound was obtained in 80% yield, reddish brown, mp 170 °C; IR (KBr) ν 3425 (NH), 2183 (CN) cm^{-1}; ^1H NMR (DMSO) δ 7.2–7.5 (m, 12H), 8.0 (d, *J*=9.1 Hz, 1H), 8.8 (d, *J*=9.1 Hz, 1H); ^{13}C NMR (DMSO) δ 108.2, 115.3, 117.6, 119.5, 126.2, 126.3, 126.9, 127.2, 127.6, 127.9, 128.2, 129.0, 129.2, 130.3, 130.5, 131.0, 132.3, 134.8, 138.6, 140.3, 177.3 ppm; MS, *m/z* (%): 407 (5.3), 406 (17.7), 105 (100), 77 (78.4); UV (dioxane), λ_{max} (nm): 400, 320, 268. Anal. Calcd for $C_{23}H_{14}N_6O_2$: C, 67.97; H, 3.47; N, 20.68. Found: C, 68.10; H, 3.52; N, 21.01%.

3.1.6. 3-Cyano-1-phenyl-2-(*p*-methylphenylazo)-4*H*-pyrrolo[1,2-*a*]benzimidazole 7f. The compound was obtained in 78% yield, reddish brown, mp 185 °C; IR (KBr) ν 3425 (NH), 2175 (CN) cm^{-1}; ^1H NMR (DMSO) δ 2.3 (s, 3H); 6.8–7.8 (m, 11H), 8.0–8.2 (m, 2H), 9.9 (s, 1H); MS, *m/z* (%): 376 (10.2), 375 (51.4), 374 (100), 268 (11.5), 77 (54.8), 64 (19.3); UV (dioxane), λ_{max} (nm): 416, 328, 258. Anal. Calcd for $C_{24}H_{17}N_5$: C, 76.78; H, 4.57; N, 18.66. Found: C, 76.80; H, 4.23; N, 18.76%.

3.2. Synthesis of alkyl 5-amino-1-aryl-4-(benzimidazol-2-yl)pyrazole-3-carboxylate derivatives 11a-f

General method. To an ethanolic sodium ethoxide solution, prepared from sodium metal (0.1 g, 5 mmol) and absolute ethanol (30 mL), was added 2-cyanomethylbenzimidazole **1** (0.79 g, 5 mmol) with stirring. To the resulting solution, the appropriate hydrazonoyl chloride **3** (5 mmol) was added at room temperature. The mixture was stirred for 12 h at room temperature. During this time the hydrazonoyl chloride dissolved and the crude product precipitated. The latter was filtered, washed with water, dried and finally crystallized from the proper solvent to give the respective product **11a-f** as polycrystalline materials.

3.2.1. Ethyl 5-amino-1-phenyl-4-(benzimidazol-2-yl)pyrazole-3-carboxylate 11a. The compound was obtained in 70% yield, yellow, mp 203 °C (methanol); IR (KBr) ν 3440, 3178, 3062 (NH_2, NH), 1705 (CO) cm^{-1}; ^1H NMR (DMSO) δ 1.3 (t, *J*=7 Hz, 3H); 4.2 (q, *J*=7 Hz, 2H), 4.3 (s, 2H), 7.0–7.3 (m, 8H), 8.0–8.1 (m, 1H), 11.0 (s, 1H); MS, *m/z* (%): 348 (5.9), 347 (25.7), 273 (10.1), 156 (13.9), 92 (69.3), 91 (100).Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.74; H, 5.22; N, 20.00%.

3.2.2. Ethyl 5-amino-1-(*p*-chlorophenyl)-4-(benzimidazol-2-yl)pyrazole-3-carboxylate 11b. The compound was obtained in 80% yield, yellow, mp 390 °C (ethanol); IR (KBr) ν 3417, 3240, 3200 (NH_2, NH), 1710 (CO) cm^{-1}; ^1H NMR (DMSO) δ 1.2 (t, *J*=7 Hz, 3H); 4.2 (q, *J*=7 Hz, 2H), 4.3 (s, 2H), 7.1–7.5 (m, 7H), 7.6–7.8 (m, 1H), 11.1 (s, 1H); MS, *m/z* (%): 383 (12.0), 382 (7.7), 381 (29.9), 307 (10.1), 157 (12.7), 156 (23.3), 127 (51.4), 125 (100), 99 (41.5), 90 (33.4). Anal. Calcd for $C_{19}H_{16}ClN_5O_2$: C, 59.76; H, 4.22; N, 18.34. Found: C, 59.55; H, 4.34; N, 18.60%.

3.2.3. Ethyl 5-amino-1-(*m*-chlorophenyl)-4-(benzimidazol-2-yl)pyrazole-3-carboxylate 11c. The compound was obtained in 78% yield, yellow, mp 200 °C (ethanol); IR (KBr) ν 3417, 3155, 3070 (NH_2, NH), 1705 (CO) cm^{-1}; ^1H NMR (DMSO) δ 1.2 (t, *J*=7 Hz, 3H); 4.3 (q, *J*=7 Hz, 2H), 4.5 (s, 2H), 7.0–7.4 (m, 7H), 7.6–7.8 (m, 1H), 11.0 (s, 1H); MS, *m/z* (%): 383 (10.8), 382 (8.1), 381 (37.4), 307 (12.2),242 (15.5), 157 (24.2), 156 (27.8), 127 (17.7), 125 (100), 99 (61.3). Anal. Calcd for $C_{19}H_{16}ClN_5O_2$: C, 59.76; H, 4.22; N, 18.34. Found: C, 59.87; H, 4.26; N, 18.58%.

3.2.4. Ethyl 5-amino-1-(*p*-methylphenyl)-4-(benzimidazol-2-yl)pyrazole-3-carboxylate 11d. The compound was obtained in 73% yield, yellow, mp 200 °C (methanol); IR (KBr) ν 3447, 3170, 3100 (NH_2, NH), 1705 (CO) cm^{-1}; ^1H NMR (DMSO) δ 1.3 (t, *J*=7 Hz, 3H); 2.3 (s, 3H), 4.2 (q, *J*=7 Hz, 2H), 4.4 (s, 2H), 7.1–7.5 (m, 8H); 9.9 (s, 1H); ^{13}C NMR (DMSO) δ 15.8, 22.1, 63.1, 112.0, 116.7, 116.9, 117.3, 118.4, 121.3, 124.7, 125.5, 131.4, 131.6, 133.9, 136.4, 144.3, 147.6, 162.6 ppm; MS, *m/z* (%): 362 (7.4), 361 (30.2), 156 (11.1), 107 (23.0), 106 (63.1), 105 (100), 77 (46.3). Anal. Calcd for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.65; H, 5.43; N, 19.24%.

3.2.5. Ethyl 5-amino-1-(*p*-nitrophenyl)-4-(benzimidazol-2-yl)pyrazole-3-carboxylate 11e. The compound was obtained in 71% yield, yellow, mp 243 °C (DMF–ethanol); IR (KBr) ν 3394, 3170, 3055 (NH_2, NH), 1705 (CO) cm^{-1}; ^1H NMR (DMSO) δ 1.3 (t, *J*=7 Hz, 3H); 4.2 (q, *J*=7 Hz, 2H), 4.3 (s, 2H), 7.0–7.6 (m, 8H), 11.0 (s, 1H); ^{13}C NMR (DMSO) δ 16.0, 63.9, 112.1, 116.6, 116.9, 117.3, 121.3, 122.7, 124.9, 125.8, 127.2, 127.3, 143.8, 144.1, 147.3, 150.1, 162.1 ppm; MS, *m/z* (%): 393 (22.5), 392 (100), 352 (48.5), 346 (25.7), 242 (23.3), 168 (20.7), 157 (53.5), 136 (45.6), 122 (17.9), 91 (22.2), 90 (70.9). Anal. Calcd for $C_{19}H_{16}N_6O_4$: C, 58.16; H, 4.11; N, 21.42. Found: C, 58.32; H, 4.05; N, 21.68%.

3.2.6. Methyl 5-amino-1-(*p*-chlorophenyl)-4-(benzimidazol-2-yl)pyrazole-3-carboxylate 11f. The compound was obtained in 83% yield, yellow, mp 232 °C (DMF–ethanol); IR (KBr) ν 3394, 3170, 3055 (NH_2, NH), 1710 (CO) cm^{-1}; ^1H NMR (DMSO) δ 3.4 (s, 3H), 4.7 (s, 2H), 7.1–7.6 (m, 7H), 8.2–8.3 (m, 1H), 12.0 (s, 1H); MS, *m/z* (%): 369 (25.1), 368 (20.3), 367 (10.0), 168 (28.1), 125 (100). Anal. Calcd

for $C_{18}H_{14}ClN_5O_2$: C, 58.78; H, 3.84; N, 19.04. Found: C, 59.01; H, 3.65; N, 19.33%.

3.3. Synthesis of 1-amino-2-arylpyrazolo[3,4:4′,3′]-pyrrolo[1,2-*a*]benzimidazole-4-ones 14a-d

Method A. To a solution of 2-cyanomethylbenzimidazole **1** (0.79 g, 5 mmol) and the appropriate hydrazonoyl chloride **3a-d** (5 mmol) in chloroform (40 mL) was added triethylamine (0.7 mL, 5 mmol) at room temperature. The reaction mixture heat at reflux for (12 h). The solvent was evaporated and the residue was treated with methanol. The solid that formed was collected and crystallized from DMF–ethanol to give **14** as polycrystalline materials.

Method B. Compound **14b** was prepared by the same method described for the synthesis of **14** using methyl *N*-(*p*-chlorophenyl)hydrazonochloroacetate **3f** instead of **3b**. The solid that formed was collected and crystallized from ethanol. The product was identical in all respects (mp, mixed mp, IR, MS, ^{1}H and ^{13}C NMR) with that obtained by method A.

Method C. Compound **14b** was prepared by heating of **11b** or **11f** (5 mmol) in chloroform (40 mL) at reflux in the presence of triethylamine (0.7 mL, 5 mmol) for (8 h). The solid that formed was collected and crystallized from ethanol. The product is identical in all respects (mp, mixed mp, IR, MS, ^{1}H and ^{13}C NMR) with that obtained by methods A and B.

3.3.1. 1-Amino-2-phenylpyrazolo[3,4:4′,3′]pyrrolo[1,2-*a*]-benzimidazol-4-one 14a. The compound was obtained in 72% yield, yellow, mp 261 °C; IR (KBr) ν 3390, 3184 (NH_2), 1710 (CO) cm^{-1}; ^{1}H NMR (DMSO) δ 4.3 (s, 2H), 6.9–7.0 (m, 1H), 7.2–7.4 (m, 3H), 7.5–7.8 (m, 4H), 8.1–8.2 (m,1H); ^{13}C NMR (DMSO) δ 116.3, 117.0, 117.8, 119.3, 124.3, 124.9, 128.9, 129.0, 131.0, 131.2, 138.6, 139.6, 144.2, 151.6, 162.2 ppm; MS, *m*/*z* (%): 301 (25.8), 300 (22.5), 142 (11.3), 77 (100). Anal. Calcd for $C_{17}H_{11}N_5O$: C, 67.76; H, 3.68; N, 23.25. Found: C, 67.89; H, 3.57; N, 23.47%.

3.3.2. 1-Amino-2-(*p*-chlorophenyl)pyrazolo[3,4:4′,3′]-pyrrolo[1,2-*a*]benzimidazol-4-one 14b. The compound was obtained in 75% yield, yellow, mp 348 °C; IR (KBr) ν 3402, 3147 (NH_2), 1710 (CO) cm^{-1}; ^{1}H NMR (DMSO) δ 4.6 (s, 2H), 7.2–7.6 (m, 7H), 7.9–8.0 (m, 1H); ^{13}C NMR (DMSO) δ 116.7, 120.5, 120.7, 122.1, 127.1, 129.3, 129.7, 131.7, 133.9, 134.2, 134.5, 134.6, 136.3, 155.4, 156.1; MS, *m*/*z* (%): 337 (31.4), 336 (48.5), 335 (100), 309 (35.4), 150 (13.3), 131 (22.2), 111 (37,2), 77 (16.1), 75 (53.2). Anal. Calcd for $C_{17}H_{10}ClN_5O$: C, 60.81; H, 3.00; N, 20.86. Found: C, 60.9; H, 3.12; N, 21.01%.

3.3.3. 1-Amino-2-(*m*-chlorophenyl)pyrazolo[3,4:4′,3′]-pyrrolo[1,2-*a*]benzimidazole-4-one 14c. The compound was obtained in 71% yield, yellow, mp 363 °C; IR (KBr) ν 3449, 3237 (NH_2), 1710 (CO) cm^{-1}; ^{1}H NMR (DMSO) δ 4.6 (s, 2H), 6.9–7.0 (m, 1H), 7.2–7.5 (m, 6H), 7.7–7.8 (m, 1H); ^{13}C NMR (DMSO) δ 113.5, 114.0, 114.6, 115.0, 115.9, 123.6, 125.8, 126.1, 127.9, 130.3, 132.4, 135.7, 136.0, 146.1, 156.6; MS, *m*/*z* (%): 337 (24.0), 336 (17.0), 335 (58.9), 183 (100), 102 (44.0), 63 (37.2). Anal. Calcd for $C_{17}H_{10}ClN_5O$: C, 60.81; H, 3.00; N, 20.86. Found: C, 61.11; H, 2.92; N, 20.90%.

3.3.4. 1-Amino-2-(*p*-methylphenyl)pyrazolo[3,4:4′,3′]-pyrrolo[1,2-*a*]benzimidazol-4-one 14d. The compound was obtained in 70% yield, yellow, mp 280 °C; IR (KBr) ν 3401, 3209 (NH_2), 1712 (CO) cm^{-1}; ^{1}H NMR (DMSO) δ 1.2 (s, 3H), 4.5 (s, 2H), 7.1–8.0 (m, 7H), 8.1–8.2 (m, 1H); MS, *m*/*z* (%): 316 (25.0), 315 (28.3), 132 (18.0), 91 (100), 77 (33.6). Anal. Calcd for $C_{18}H_{13}N_5O$: C, 68.56; H, 4.15; N, 22.21. Found: C, 68.46; H, 4.34; N, 22.41%.

3.3.5. Synthesis of 14e. A solution of **11e** (3 mmol) in xylene (15 mL) was refluxed for 48 h. The reaction mixture was cooled. The crude product was collected and crystallized from DMF to give **14e**. The compound was obtained in 30% yield, yellow, mp 298 °C; IR (KBr) ν 3407, 3235 (NH_2), 1710 (CO) cm^{-1}; ^{1}H NMR (DMSO) δ 4.6 (s, 2H), 7.2–7.6 (m, 6H), 7.8–8.1 (m, 2H); MS, *m*/*z* (%): 346 (13.2), 242 (23.3), 207 (10.6), 168 (26.4), 157 (64.6), 136 (62.7), 131 (33.1), 103 (38.9), 90 (100), 76 (34.7), 64 (59.8), 52 (28.3). Anal. Calcd for $C_{17}H_{10}N_6O_3$: C, 58.96; H, 2.91; N, 24.27. Found: C, 59.01; H, 2.74; N, 24.36%.

References and notes

1. Shawali, A. S. *Chem. Rev.* **1993**, *93*, 2731.
2. Charlson, A. J.; Harrington, J. S. *Carbohydr. Res.* **1972**, *43*, 383.
3. Adabbagh, F.; Bowman, W. R. *Tetrahedron Lett.* **1997**, *38*, 3793.
4. Anastasiou, D.; Campi, E. M.; Chaouk, H.; Jackson, W. R. *Tetrahedron* **1992**, *48*, 7467.
5. Langer, P.; Doring, M.; Schreiner, P. R.; Gorls, H. *Eur. J. Org. Chem.* **2001**, *12*, 2245.
6. (a) Xing, C.; Wu, P.; Sibo, E. B.; Dorr, T. *J. Med. Chem.* **2000**, *43*, 457. (b) Japan Kokai Tokkyo Koho JP 05,112,570, 1993; *Chem. Abstr.* **1993**, *119*, 180786t. (c) Craigo, W. A.; Lesureur, B. W.; Skibo, E. B. *J. Med. Chem.* **1999**, *42*, 3324.
7. Schulz, W. G.; Islam, I.; Skibo, E. B. *J. Med. Chem.* **1995**, *38*, 109.
8. Ahn, C. A.; Kim, S. K. *Arch. Pharm. Res.* **1996**, *19*, 535.
9. Skibo, E. B.; Gordon, S.; Bess, L.; Boruah, R.; Heileman, M. J. *J. Med. Chem.* **1997**, *40*, 1327.
10. Chen, Y. L. U.S. US 5,428,043, 1995; *Chem. Abstr.* **1996**, *124*, 8613b.
11. Kawase, I.; Tanaka, M. Jpn. Kohai Tokkyo Koho JP 08 12, 677, 1996; *Chem. Abstr.* **1996**, *124*, 31760j.
12. Ho, W.; Maryanoff, B. E.; McComsey, D. F.; Nortey. USA. US. 5,521,200, 1996; *Chem. Abstr.* **1996**, *125*, 114628r.
13. Schulz, W. G.; Skibo, E. B. *J. Med. Chem.* **2000**, *43*, 629.
14. Hanas, H. J.; Grycchtol, K. Ger. Offen. 2,902,763, 1980; *Chem. Abstr.* **1980**, *93*, 206156j.
15. Uchida, T.; Masukawa, T.; Nakayama, N. Jpn. Kohai Tokkyo Koho JP 04 25,567, 1992; *Chem. Abstr.* **1992**, *117*, 9823n.
16. (a) Awad, E. M.; Elwan, N. M.; Hassaneen, H. M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2001**, *84*, 1172. (b) Hassaneen, H. M.; Elwan, N. M.; Hassaneen, H. M. *Synth. Commun.* **2002**, *32*, 3047. (c) Elwan, N. M.; Abdelhadi,

H. A.; Abdallah, T. A.; Hassaneen, H. M. *Tetrahedron* **1996**, *52*, 3451.
17. Copeland, R. A. B.; Day, A. R. *J. Am. Chem. Soc.* **1943**, *65*, 1074.
18. Eweiss, N. F.; Osman, A. *J. Heterocycl. Chem.* **1980**, *17*, 1713.
19. Shawali, A. S.; Abdelhamid, A. O. *Bull. Chem. Soc. Jpn* **1976**, *49*, 321.
20. Shawali, A. S.; Eweiss, N. F.; Hassaneen, H. M. *Bull. Chem. Soc. Jpn* **1975**, *48*, 365.
21. Baker, J. W. *J. Chem. Soc.* **1932**, 1148.

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Design and synthesis of new ethylenediamine or propylenediamine diacetic acid derivatives for Re(I) organometallic chemistry

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Abstract—A general synthetic approach for a novel range of bifunctional chelating agent (BCA) for the '*fac*-$[M(CO)_3]^+$' core (M=^{99m}Tc, ^{99}Tc or Re) has been developed. The strategy includes the facile preparation of these tridentate ligands possessing a tertiary amine bearing two carboxylic acid functions as coordinating site and an aromatic amino group for coupling to a biovector. First complexation study has shown that these compounds act exclusively as tridentate ligands (via the two acids and the tertiary amine functions). The convenient synthesis of these new ligands coupled with their high affinity for Re(I) make them quite promising for biomedical applications.
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1. Introduction

The technetium-99m is the most important radionuclide in diagnostic nuclear medicine. This preferential use of ^{99m}Tc-radiopharmaceuticals reflects the ideal nuclear properties of the isotope ($T_{1/2}$=6 h, 140 keV gamma emitter), as well as its low cost and its convenient availability from commercial generators. Consequently, it is of high priority to develop efficient molecules with a chelating group specific for this radionuclide.[1] Efforts to design new chelate systems for this nuclide and rhenium for subsequent use, respectively, in diagnostic and therapy have led to the development of new Tc or Re-specific ligands.

Whereas in the past, the Tc or Re compounds bore preferentially N,S tetradentate ligands[2] which form stable technetium(V) or rhenium(V) complexes,[3] over the last 20 years, organometallic technetium and rhenium complexes in low oxidation states have gained considerable attention in the development of novel target-specific radiopharmaceuticals.[4–9] Because of the high kinetic inertness and their ease of preparation, Tc(I)/Re(I)-tricarbonyl complexes are attractive for use in labelling site-specific biomolecules.[10]

Previous in vitro studies on the macroscopic and n.c.a (non carrier added) level suggested that ideal chelating systems for the '*fac*-$[M(CO)_3]^+$' core, in respect of a potential radiopharmaceutical application, should contain one or more amine functionalities (preferentially aromatic *N*-heterocycles) in combination with a carboxylic acid function.[11] Recently, Schibli and co-workers[12] have compared the in vivo and in vitro behaviours of different ^{99m}Tc(I)-tricarbonyl complexes with various bi- and tridentate ligand systems. They have concluded that for the radiolabelling with *fac*-$[^{99m}Tc(CO)_3]^+$or *fac*-$[^{186/188}Re(CO)_3]^+$, tridentate chelating systems were preferable since they formed organometallic compounds with more favourable pharmacokinetics.

We here provide a facile and convenient synthetic approach for the tridentate bifunctional chelating agent (BCA) which incorporates the design features illustrated in Figure 1; these include: (i) a tridentate coordinating site for low oxidation state metal carbonyls, (ii) a linking site to a biomolecule via the amino functionality (iii) a tethering moiety (an ethylene or propylene bridge) between the linking and coordinating sites. The enhancement of bridge size should limit the possible interaction between the secondary aromatic amine

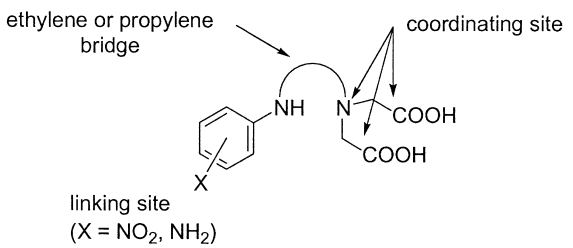

Figure 1. Design features of novel Re(I) ligands.

Keywords: Bifunctional chelating agent; Imino diacetic acid; Rhenium(I).
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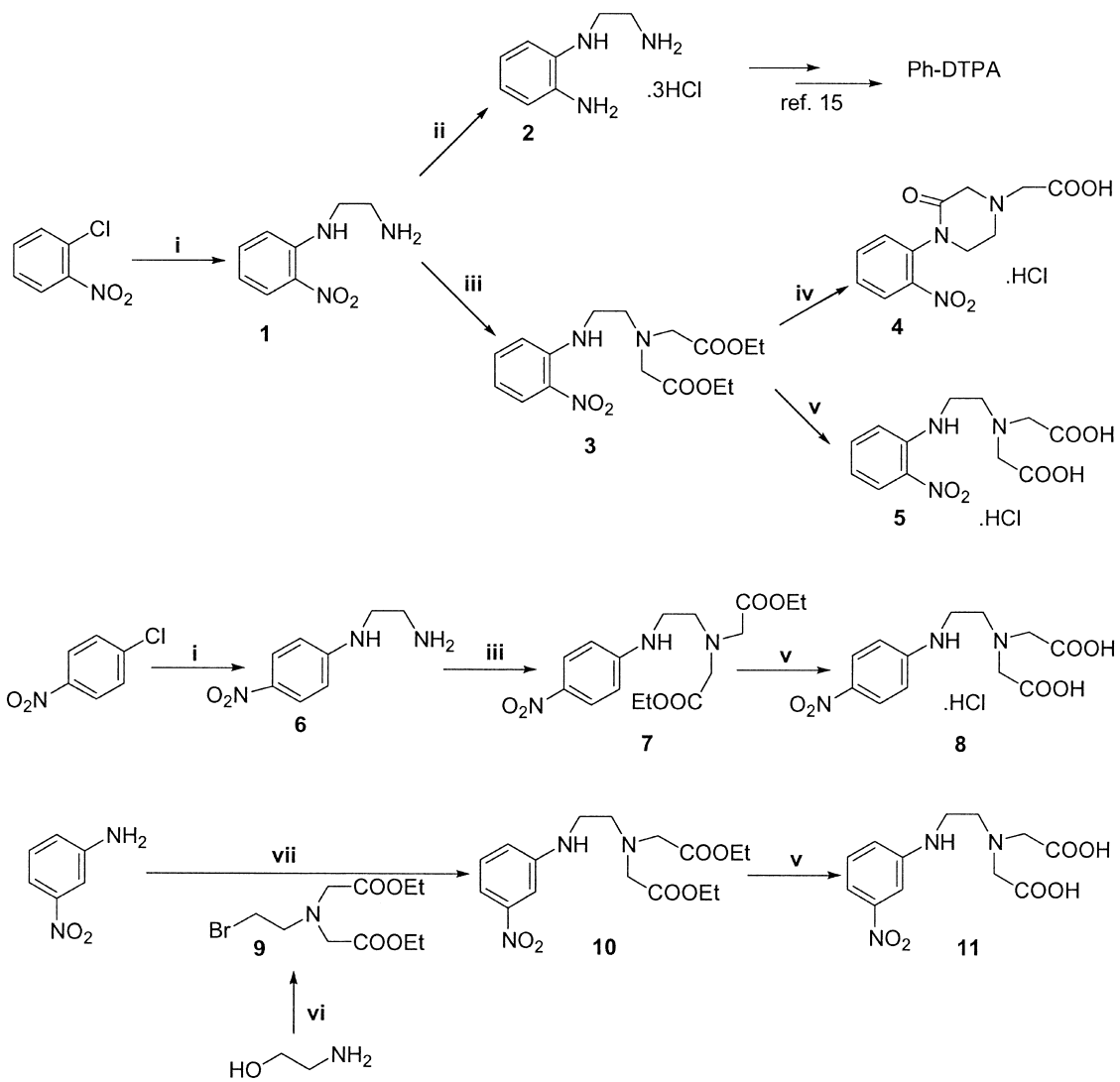
and the iminodiacetic acid group during the complexation reaction. In this paper, we describe the synthesis of a range of new ethylenediamine diacetic acid derivatives (EDDA) and propylenediamine diacetic acid derivatives (PDDA) which, on preliminary examination, exhibits significant Re(I)-specificity.

2. Results and discussion

Amino polycarboxylic acid based ligand systems like iminodiacetic acid react readily with the *fac*-$[M(CO)_3]^+$ core to form complexes which have a stable octahedral coordination sphere, where substitution reaction via a dissociative or an associative mechanism is unlikely.[12,13] Our synthetic strategy offers a simple method for generating aminodiacetic acid derivatives bearing an aromatic amino group for coupling to biomolecules.

The syntheses of nitrophenylethylenediaminediacetic acid derivatives (NO_2Ph-EDDA) were performed in three steps as described in Scheme 1. The key step was the introduction of the nitro group (future linking site) during the synthesis of the chelating moiety.

For *ortho* and *para*-NO_2Ph-EDDA ligands, we used an elegant and rapid route to synthesise nitrophenyldiamine intermediates.[14] By refluxing *o*- or *p*-chloronitrobenzene with an excess of ethylenediamine, we obtained **1** and **6** respectively in 93 and 85% yield. This one-step substitution reaction gave better yields than the Gabriel two-steps synthesis using 2-bromoethylphtalimide as starting material. Another advantage of this first step was the rapid access to the triamine **2** by reduction of the nitro group using $SnCl_2$ as reducing agent in acidic conditions. This compound **2** obtained in two steps with an overall yield of 86% was a versatile intermediate in the synthesis of Ph-DTPA, (phenyleneetylenetriamine pentaacetic acid) a potent ligand for radioimmunotherapy. This method proved more suitable than that described by Gouin et al.[15]



Scheme 1. *o,m,p*-NO_2Ph-EDDA ligand synthesis *Reagents and conditions:* (i) ethylenediamine, 100 °C, 1 h–1 h 30 min 85–93% (ii) (a) $SnCl_2$, HCl, 100 °C, 1 h (b) H_2S 92% (iii) $BrCH_2COOEt$, K_2CO_3, KI, ACN, 60 °C, 12 h, 83–90% (iv) 6 N HCl, 110 °C, 1 day, 70% (v) 2 N NaOH/EtOH, 70 °C, 3 h then 2 N HCl 78–90% (vi) Ref. 19, 62% (vii) **9**, K_2CO_3, KI, ACN, 60 °C, 3 h, 60%.

which uses a classical three-step sequence (peptidic coupling–amine deprotection–amide reduction) providing an overall yield of no more than 73%.

The second step was the dialkylation of the primary amine function of **1** and **6**. According to the classical alkylation method,[16] diethyl esters **3** and **7** were obtained with good yields through the action of two equivalents of ethylbromoacetate in the presence of a catalytic amount of KI and a slight excess of K_2CO_3 in acetonitrile. Even with a large excess of ethylbromoacetate, the desactivating nitro group did not allowed the alkylation of the aromatic amine function. Recently, a report has been published on *N*,*N*-dialkylation of *p*-nitroaniline using CsF-Celite/alkyl halides/acetonitrile combination[17] but in our case, these conditions afforded mainly the dialkylated ester and the trialkylated ester only in minor proportion (>5%).

Attempts to prepare and obtain pure *ortho*-NO_2Ph-EDDA by the direct acid hydrolysis of **3** failed and resulted in the formation of the six-membered azalactam **4** in 70% yield. Genik–Sas–Berezowsky et al.[18] have already noticed that cyclization of the non-fully substituted EDDA derivatives took place quite readily under acid conditions. To circumvent this lactamisation, compounds **3** and **7** were hydrolysed in smooth basic conditions followed by acidification step providing easily the corresponding pure hydrochloride salts of diacids **5** and **8** in 80% yield.

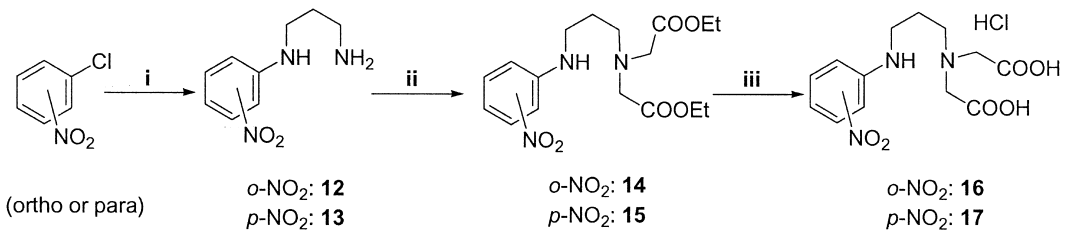
An alternative pathway was investigated to obtain the *meta*-NO_2Ph-EDDA **11**. *m*-nitroaniline was converted to the dialkylated ester **10** after alkylation reaction with compound **9**. This intermediate was first prepared by a well-known two-steps synthesis using ethanolamine as starting material.[19] Basic hydrolysis of the ester followed by acidification step afforded the ligand **11** in 90% yield.

The three *o*-, *p*-, *m*-NO_2Ph-EDDA derivatives were achieved respectively in 67, 55 and 33% yield and the yields of each step, especially the amine alkylation step, were not affected by the position of the nitro group on the aromatic ring.

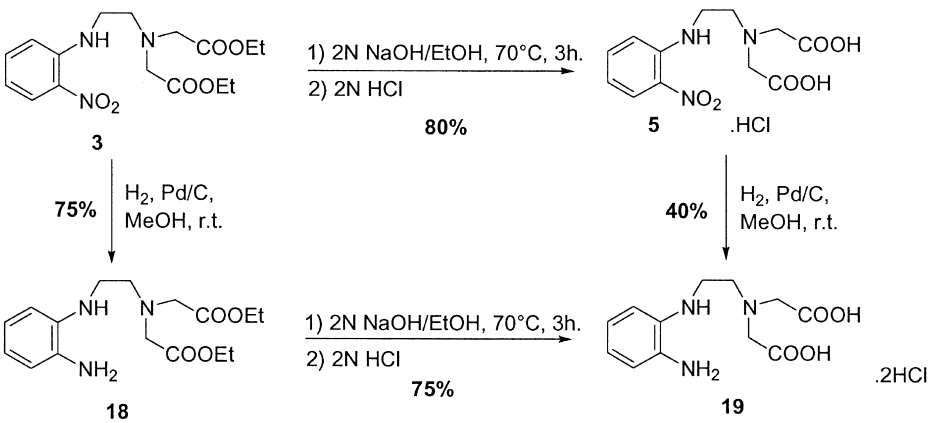
Using the same versatile route than for the ligands **5** and **8**, we also synthesized the *o*- and *p*-NO_2Ph-PDDA substituting ethylenediamine by 1,3-diaminopropane as starting material in the first step (Scheme 2). These two ligands **16** and **17**, having one carbon more between the linking and chelating moieties, have been obtained respectively in 67 and 60% yield.

For rapid functionalization of a biomolecule, the introduction of the nitro group is a decisive advantage of the presented synthetic strategy. For example, as shown in Scheme 3, bifunctional chelating agent **19** was achieved in 40% yield by catalytic hydrogenation of the nitro group of **5**. Nevertheless, **19** was obtained with a better overall yield in two steps, starting from **3** (56%). We found that it was easier to purify intermediates using reduction then basic hydrolysis sequence than the opposite. The aromatic amine function allows e.g. in the case of **19**, the coupling to a carboxylic acid of a biomolecule. The same synthetic procedure of functionalization could be applied to all our ligands.

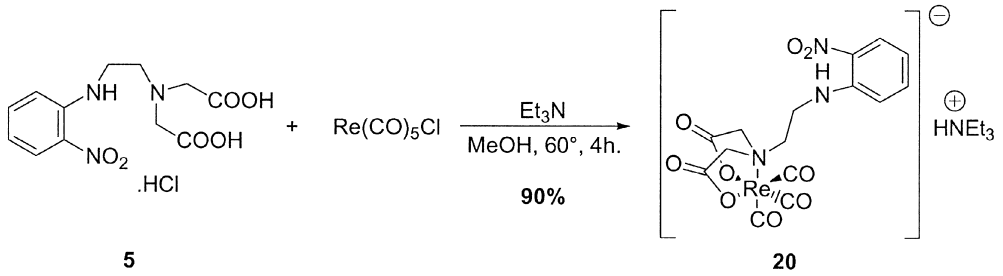
The coordination chemistry behaviour of one of our ligands has also been investigated. When reacted with the $Re(CO)_5Cl$ precursor in methanol and in the presence of



Scheme 2. *o*,*p*-NO_2Ph-PDDA derivatives *Reagents and conditions*: (i) (a) 1,3-diaminopropane, 100 °C, 1 h 92% (ii) $BrCH_2COOEt$, K_2CO_3, KI, ACN, 60 °C, 12 h, 83–90% (iii) 2 N NaOH/EtOH, 70 °C, 3 h then 2 N HCl, 80%.



Scheme 3. BCA synthesis.



5 20

Scheme 4. Re(I) complex formation.

triethylamine, the ligand **5** formed almost quantitatively a well-defined species with a metal-to-ligand ratio of 1:1 as evident by proton NMR spectroscopy and mass spectra (Scheme 4).

In the free ligand, the two methylene groups appear as an unique singlet (3.59 ppm). After complexation with $Re(CO)_5Cl$, the singlet splits into two doublets forming the pattern of two AB-spin systems at 3.48 and 3.65 ppm (J=16 Hz). This feature is in accordance with the proposed tridentate coordination via the tertiary amine and the two carboxylic acids. The complex was a $NHEt_3^+$ salt as evident by elemental analysis. This is confirmed by the negative Electrospray spectrum that presents two prominent ion peaks with an isotope distribution pattern consistent with the monomeric anion $[Re(CO)_3(NO_2Ph\text{-}EDDA)]^-$. The IR spectrum revealed firstly the presence of N–H stretching band of secondary aromatic amine and secondly three bands in the carbonyl stretching region (2029–1887 cm^{-1}) which is characteristic of a *fac*-octahedral tricarbonyl metal moiety.[20] This proved the tridentate coordination of the metal-tricarbonyl core via the EDDA ligand. The complex is soluble in all polar organic solvents and is stable to aerial oxidation.

3. Conclusion

A versatile way to produce tridentate chelating systems for low oxidation state metal carbonyls like $M(CO)_3$ fragment (M=Tc or Re) was presented. While still maintaining a simplicity of synthesis and high overall yield, we have developed a new range of amino diacetic acid derivatives. A decisive advantage of the presented synthetic strategy is that this kind of molecules already possesses a linking site for future coupling to biomolecule. First complexation study has shown that these compounds act exclusively as tridentate ligands (via the two acids functions and the tertiary amine). The convenient synthesis of this new range of molecules coupled with their high affinity for Re(I) make them promising candidates for radiopharmaceuticals. Rhenium(I) and technetium(I) chemistry of all our ligands are currently in progress.

4. Experimental

All chemicals were of the highest purity commercially available. Solvents were purified by standard methods before use and stored over 0.3 nm molecular sieves. Silica gel (0.060–0.200 nm) was purchased from Acros. TLC was performed using precoated Kieselgel 60 plates F_{254} (TLC plates, Merck) and was visualized by UV or iodine.

NMR spectra were recorded on a Bruker AC 200 (50.323 MHz for ^{13}C and 200.133 MHz for ^1H), 250 (62.896 MHz for ^{13}C and 250.133 MHz for ^1H) or 300 apparatus (75.467 MHz for ^{13}C and 300.13 MHz for ^1H). Chemical shifts are indicated in δ values (ppm) downfield from internal TMS, and coupling constants (J) are given in Hertz (Hz). Multiplicities were recorded as s (singlet), d (doublet), t (triplet) q (quadruplet), qt (quintuplet) and m (multiplet). For aromatic ring NMR assignments, the protons (or carbons) were numbered from 1 to 6 starting from carbon bearing the secondary aromatic amine and turning clockwise. Infrared spectrum was recorded as KBr pellets on a BRUKER Vector 22 spectrophotometer in the range 4000–400 cm^{-1}. Electrospray or DCI-Mass spectra were obtained on a NERMAG R 10–10 mass spectrometer. Microanalysis was performed by the microanalytical department of the Ecole Nationale Supérieure de Chimie de Toulouse. Melting points were determinated on a stuart melting point SMP3 apparatus and are uncorrected.

4.1. Synthesis of EDDA derivatives

4.1.1. *N*-(2-Nitrophenyl)ethylenediamine (1). 2-Nitrochlorobenzene (10 g, 0.063 mol) and ethylenediamine (40 g, 0.67 mol) were stirred 1 h under reflux. After distillation of the excess of ethylenediamine, the crude was acidified at pH 6 with 2 N HCl, then heated and filtrated. After cooling, 13.02 g of *N*-(2-nitrophenyl)ethylenediamine hydrochloride were collected as yellow needles.

The product was dissolved in water (10 mL). The solution was basified at pH 12 and extracted twice with chloroform (15 mL). The organic layer was dried with sodium sulfate, filtered and concentrated to dryness under reduce pressure to give **1** as an orange oil (10.60 g, 93%)

^1H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.32 (bs, 2H, NH_2); 3.04 (m, 2H, CH_2); 3.35 (m, 2H, CH_2); 6.62 (m, 1H, H-5); 6.85 (m, 1H, H-3); 7.41 (m, 1H, H-4); 8.13 (m, 1H, H-6); 8.24 (s, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 40.8 (CH_2); 45.7 (CH_2); 113.6 (C-3); 115.3 (C-5); 127.0 (C-6); 133.0 (C-2); 136.3 (C-4); 145.6 (C-1); MS (DCI/NH_3): 182 ($M+H^+$); 199 ($M+NH_4^+$); mp=261 °C; Anal.: found (as hydrochloride salt): C, 44.2; H, 5.6; N, 19.7%; $C_8H_{12}N_3O_2Cl$ requires: C, 44.2; H, 5.6; N, 19.3%.

4.1.2. *N*-(2-Aminophenyl)ethylenediamine trihydrochloride (2). 3.00 g (16.6 mmol) of **1** and 13.5 g

(59.8 mmol) of $SnCl_2.2H_2O$ were heated at 100 °C in concentrated chlorhydric acid (30 mL). After 1 h, the mixture was cooled and filtrated. The residue was dissolved in water and H_2S gas was bubbled into the solution to precipitate tin salt. After filtration, the filtrate was concentrated to dryness under reduce pressure to give **2** as pale yellow crystals (3.97 g, 92%).

^{1}H NMR (200 MHz, D_2O) δ_H (ppm): 3.13 (m, 2H, CH_2); 3.44 (m, 2H, CH_2); 6.77–6.87 (m, 2H, ArH); 7.17–7.33 (m, 2H, ArH); ^{13}C NMR (50.3 MHz, D_2O) δ_C (ppm): 40.7 (CH_2); 42.4 (CH_2); 116.8 (C-5); 120.4 (C-3); 122.0 (C-6); 126.7 (C-4); 134.0 (C-1); 143.0 (C-2); MS (DCI/NH_3): 152 [(M−3HCl)+H$^+$]; mp=214 °C; Anal.: found (as trihydrochloride salt): C, 37.0; H, 6.3; N, 15.8%; $C_8H_{16}N_3Cl_3$ requires: C, 36.9; H, 6.1; N, 16.1%.

4.1.3. *N*-(2-Nitrophenyl)ethylenediamine-*N′*,*N′*-diethyldiacetate (3). A mixture of **1** (785 mg, 4.34 mmol), potassium iodide (1.44 g, 0.87 mmol), potassium carbonate (9.00 g, 6.51 mmol) and ethyl bromoacetate (1.00 mL, 9.02 mmol) in acetonitrile (100 mL), over an atmosphere of nitrogen, was boiled one night at 60 °C. The insoluble materials were filtered off and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (eluent: CH_2Cl_2 then CH_2Cl_2/AcOEt: 4/6) to give **3** as an orange oil (1.38 g, 90%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.24 (t, 6H, *J*=7.1 Hz, $2CH_3$); 3.13 (m, 2H, NCH_2); 3.37 (m, 2H, NCH_2); 3.60 (s, 4H, $2NCH_2$); 4.15 (q, 4H, *J*=7.1 Hz, $2OCH_2$); 6.63 (m, 1H, H-5); 6.82 (m, 1H, H-3); 7.40 (m, 1H, H-4); 8.15 (m, H, H-6); 8.35 (bs, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 14.2 (CH_3); 41.0 (NCH_2); 52.1 (NCH_2); 55.5 ($2NCH_2$); 60.8 (2 OCH_2); 113.9 (C-3); 115.1 (C-5); 126.8 (C-6); 136.1 (C-2); 139.0 (C-4); 145.2 (C-1); 171.0 (2CO); MS (DCI/NH_3): 354 (M+H$^+$).

4.1.4. 4-(2-Nitrophenyl)-3-oxopiperazin-1-yl acetic acid (4). 1.12 g (3.17 mmol) of compound **3** into 10 mL of 6 N HCl were refluxed during 24 h. After cooling, the solvent was removed under reduced pressure. The crude product was taken in 10 mL of ethyl acetate and the organic layer was washed twice with water (30 mL), dried with sodium sulfate and concentrated under vacuum to give **4** as a yellow solid (620 mg, 70%).

^{1}H NMR (200 MHz, D_2O) δ_H (ppm): 3.70 (m, 2H, NCH_2); 4.16 (m, 4H, $2NCH_2$); 4.26 (m, 2H, NCH_2); 7.50 (m, 1H, H-6); 7.70 (m, 1H, H-4); 7.84 (m, 1H, H-5); 8.16 (m, 1H, H-3); ^{13}C NMR (50.3 MHz, D_2O) δ_C (ppm): 46.3 (NCH_2); 51.4 (NCH_2); 55.5 (NCH_2); 58.5 (NCH_2); 126.5 (C-3); 131.6 (C-5); 133.7 (C-6); 134.7 (C-2); 136.5 (C-4); 147.3 (C-1); 165.7 (CO); 169.8 (COOH); MS (DCI/NH_3): 280 (M+H$^+$); 297 (M+NH_4^+). Anal.: found (as hydrochloride salt): C, 41.0; H, 4.7; N, 11.4%; mp=204 °C; $C_{12}H_{15}N_3O_5Cl_2$ requires: C, 40.9; H, 4.3; N, 11.9%.

4.1.5. *N*-(2-Nitrophenyl)ethylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (5). 353 mg (1 mmol) of diester **3** in 10 mL of a 2 N NaOH/ethanol (1/1) solution were heated at 70 °C for 3 h. After cooling, the solution was acidified with 2 N HCl until pH was 1 and left a few hours at 4 °C. The obtained precipitate was filtered and dried under vacuum to give **5** as yellow powdery product (267 mg, 80%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 3.02 (m, 2H, NCH_2); 3.43 (m, 2H, NCH_2); 3.59 (s, 4H, $2NCH_2$); 6.67 (m, 1H, H-5); 7.06 (m, 1H, H-3); 7.52 (m, 1H, H-4); 8.03 (m, 1H, H-6); 8.33 (bs, 1H, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 40.6 (NCH_2); 51.8 (NCH_2); 54.3 (NCH_2); 114.5 (C-3); 115.0 (C-5); 126.0 (C-6); 130.9 (C-2); 136.4 (C-4); 144.9 (C-1); 171.8 (2CO); MS (DCI/NH_3): 298 (M+H$^+$). Anal.: found (as hydrochloride salt): C, 43.4; H, 4.8; N, 12.2%; mp=219 °C; $C_{12}H_{16}N_3O_6Cl$ requires: C, 43.2; H, 4.8; N, 12.6%.

4.1.6. *N*-(4-Nitrophenyl)ethylenediamine (6). 4-nitrochlorobenzene (10 g, 0.063 mol) and ethylenediamine (40 g, 0.67 mol) were stirred 1 h and half under reflux. After distillation of the excess of ethylenediamine, the crude was taken in hot distillated water (150 mL) and filtrated. After cooling, **6** was collected as an orange solide (9.70 g, 85%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.36 (s, 2H, NH_2); 3.01 (m, 2H, CH_2); 3.25 (m, 2H, CH_2); 5.29 (s, 1H, NH); 6.66 (d, 2H, *J*=9.4 Hz, H-2, H-6); 8.05 (d, 2H, *J*=9.4 Hz, H-3, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 40.5 (CH_2); 45.2 (CH_2); 111.1 (C-2, C-6); 126.5 (C-3, C-5); 137.8 (C-4); 154.4 (C-1); MS (DCI/NH_3): 182 (M+H$^+$), 199 (M+NH_4^+); mp=142 °C, Anal.: found: C, 52.8; H, 6.0; N, 22.7%; $C_8H_{11}N_3O_2$ requires: C, 52.7; H, 6.0; N, 23.1%.

4.1.7. *N*-(4-Nitrophenyl)ethylenediamine-*N′*,*N′*-diethyldiacetate (7). Using the same procedure than **3**, 786 mg of **6** gave **7** as an orange oil (1.27 g, 83%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.28 (t, 6H, *J*=7.1 Hz, $2CH_3$); 3.00 (m, 2H, NCH_2); 3.13 (m, 2H, NCH_2); 3.52 (s, 4H, $2NCH_2$); 4.12 (q, 4H, *J*=7.1 Hz, $2OCH_2$); 6.41 (bs, 1H, NH); 6.82 (d, 2H, *J*=9.2 Hz, H-2, H-6); 8.01 (d, 2H, *J*=9.2 Hz, H-3, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 13.9 (CH_3); 40.5 (NCH_2); 51.9 (NCH_2); 54.9 ($2NCH_2$); 60.9 (2 OCH_2); 110.7 (C-2, C-6); 126.5 (C-3, C-5); 137.2 (C-4); 153.8 (C-1); 171.7 (2CO); MS (DCI/NH_3): 354 (M+H$^+$).

4.1.8. *N*-(4-Nitrophenyl)ethylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (8). Using the same procedure than **5**, 353 mg of compound **7** gave **8** as orange powdery product (260 mg, 78%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 2.93 (~t, 2H, *J*=6.2 Hz, NCH_2); 3.23 (~t, 2H, *J*=6.2 Hz, NCH_2); 3.50 (s, 4H, $2NCH_2$); 6.65 (d, 2H, *J*=9.3 Hz, H-2, H-6); 7.30 (bs, 1H, NH); 8.03 (d, 2H, *J*=9.3 Hz, H-3, H-5); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 40.4 (NCH_2); 52.1 (NCH_2); 54.6 (NCH_2); 110.7 (C-2, C-6); 126.1 (C-3, C-5); 135.5 (C-4); 154.2 (C-1); 172.3 (2CO); MS (DCI/NH_3): 298 (M+H$^+$). Anal.: found (as hydrochloride salt): C, 43.3; H, 4.6; N, 12.7%; mp=186 °C; $C_{12}H_{16}N_3O_6Cl$ requires: C, 43.2; H, 4.8; N, 12.6%.

4.1.9. *N*-(3-Nitrophenyl)ethylenediamine-*N′*,*N′*-diethyldiacetate (10). In an atmosphere of nitrogen, a mixture of

3-nitroaniline (310 mg, 2.24 mmol), potassium iodide (310 mg, 1.87 mmol), potassium carbonate (514 mg, 3.73 mmol) and compound **9** (663 mg, 2.24 mmol) in acetonitrile (100 mL) was boiled under reflux for 3 h. The insoluble materials were filtered off and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with CH_2Cl_2 to give **10** as a brown oil (474 mg, 60%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.27 (m, 6H, $2CH_3$); 3.15 (m, 4H, $2NCH_2$); 3.57 (s, 4H, NCH_2); 4.19 (s, 4H, $2OCH_2$); 5.60 (bs, 1H, NH); 6.90 (m, 1H, H-6); 7.35 (m, 3H, H-2, H-4, H-5); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 13.9 (CH_3); 42.2 (NCH_2); 52.7 (NCH_2); 55.2 ($2NCH_2$); 60.8 (2 OCH_2); 105.4 (C-2); 110.6 (C-6); 118.4 (C-4); 129.5 (C-5); 148.2 (C-3); 149.2 (C-1); 171.7 (2CO); MS (DCI/NH_3): 354 ($M+H^+$).

4.1.10. *N*-(3-Nitrophenyl)ethylenediamine-*N′*,*N′*-diacetic acid (11). Using the same procedure than **5**, 353 mg of compound **10** gave **11** as brown crystals (267 mg, 90%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 2.88 (~t, 2H, J=6.3 Hz, NCH_2); 3.15 (~t, 2H, J=6.3 Hz, NCH_2); 3.51 (s, 4H, $2NCH_2$); 6.35 (bs, 1H, NH); 6.98 (m, 1H, H-6); 7.33 (m, 3H, H-2, H-4, H-5); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ_C (ppm): 41.0 (NCH_2); 52.3 (NCH_2); 54.7 (NCH_2); 105.1 (C-2); 109.6 (C-6); 118.2 (C-4); 129.9 (C-5); 148.7 (C-3); 149.7 (C-1); 172.7 (2CO); MS (DCI/NH_3): 298 ($M+H^+$); mp=150 °C; Anal.: found: C, 48.0; H, 5.2; N, 13.9%; $C_{12}H_{15}N_3O_6$ requires: C, 48.5; H, 5.0; N, 14.1%.

4.2. Synthesis of PDDA derivatives

4.2.1. *N*-(2-Nitrophenyl)propylenediamine (12). Using the same procedure than **1** and substituting ethylenediamine by 1,3-diaminopropane (46.62 g, 0.63 mol), we obtained after purification **12** as an orange-red oil (11.42 g, 93%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.20 (bs, 2H, NH_2); 1.82 (q, 2H, J=7.0 Hz, CH_2); 2.82 (t, J=7.0 Hz, 2H, NCH_2); 3.33 (m, 2H, NCH_2); 6.56 (m, 1H, H-5); 6.80 (m, 1H, H-3); 7.35 (m, 1H, H-4); 8.04 (m, 1H, H-6); 8.11 (bs, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 32.3 (CH_2); 39.8 (NCH_2); 41.0 (NCH_2); 113.9 (C-3); 115.7 (C-5); 126.9 (C-6); 131.8 (C-2); 136.4 (C-4); 145.7 (C-1); MS (DCI/NH_3): 196 ($M+H^+$); 213 ($M+NH_4^+$); mp=174 °C; Anal.: found (as hydrochloride salt): C, 46.8; H, 6.2; N, 18.2%; $C_9H_{14}N_3O_2Cl$ requires: C, 46.7; H, 6.1; N, 18.2%.

4.2.2. *N*-(4-Nitrophenyl)propylenediamine (13). Using the same procedure than **6** and substituting ethylenediamine by 1,3-diaminopropane (46.62 g, 0.63 mol), we obtained after purification **13** as an orange solide (11.30 g, 92%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H (ppm): 1.40 (s, 2H, NH_2); 1.75 (m, 2H, CH_2); 2.89 (m, 2H, CH_2); 3.30 (m, 2H, CH_2); 5.76 (bs, 1H, NH); 6.92 (d, 2H, J=9.4 Hz, H-2, H-6); 7.21 (d, 2H, J=9.4 Hz, H-3, H-5); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 31.3 (CH_2); 40.5 (CH_2); 42.5 (CH_2); 110.8 (C-2, C-6); 126.5 (C-3, C-5); 140.8 (C-6); 153.7 (C-1); MS (DCI/NH_3): 196 ($M+H^+$); 213 ($M+NH_4^+$); Anal.: found: C, 55.1; H, 6.7; N, 21.3%; mp=94 °C; $C_9H_{13}N_3O_2$ requires: C, 55.1; H, 6.6; N, 21.4%.

4.2.3. *N*-(2-Nitrophenyl)propylenediamine-*N′*,*N′*-diethyl-diacetate (14). Using the same procedure than **3**, 846 mg of compound **12** gave **14** as an orange oil (1.44 g, 90%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.19 (t, 6H, J=7.0 Hz, $2CH_3$); 1.81 (qt, J=6.7 Hz, 2H, CH_2); 2.81 (m, 2H, NCH_2); 3.45 (m, 2H, NCH_2); 3.55 (s, 4H, $2NCH_2$); 4.15 (q, 4H, J=7.0 Hz, $2OCH_2$); 6.55 (m, 1H, H-5); 6.86 (m, 1H, H-3); 7.35 (m, 1H, H-4); 8.09 (m, 1H, H-6); 8.19 (bs, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C (ppm): 13.9 (CH_3); 27.0 (CH_2); 40.8 (NCH_2); 51.5 (NCH_2); 55.1 ($2NCH_2$); 60.5 (2 OCH_2); 113.7 (C-3); 115.1 (C-5); 126.7 (C-6); 131.7 (C-2); 136.2 (C-4); 145.6 (C-1); 171.1 (2CO); MS (DCI/NH_3): 368 ($M+H^+$).

4.2.4. *N*-(4-Nitrophenyl)propylenediamine-*N′*,*N′*-diethyl-diacetate (15). Using the same procedure than **3**, 846 mg of compound **13** gave **15** as an orange oil (1.33 g, 83%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.23 (t, 6H, J=7.0 Hz, $2CH_3$); 1.69 (m, 2H, CH_2); 2.78 (m, 2H, NCH_2); 3.35 (m, 2H, NCH_2); 3.49 (s, 4H, $2NCH_2$); 4.17 (q, 4H, J=7.0 Hz, $2OCH_2$); 6.51 (d, 2H, J=9.4 Hz, H-2, H-6); 7.72 (bs, 1H, NH); 8.00 (d, 2H, J=9.4 Hz, H-3, H-5); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 14.4 (CH_3); 25.3 (CH_2); 41.9 (NCH_2); 52.4 (NCH_2); 54.9 ($2NCH_2$); 60.8 (2 OCH_2); 110.6 (C-2, C-6); 126.5 (C-3, C-5); 136.4 (C-4); 154.2 (C-1); 171.3 (2CO); MS (DCI/NH_3): 368 ($M+H^+$).

4.2.5. *N*-(2-Nitrophenyl)propylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (16). Using the same procedure than **5**, 367 mg of compound **14** gave **16** as a yellow powder (278 mg, 80%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 1.47 (m, 2H, CH_2); 2.77 (m, 2H, NCH_2); 3.48 (m, 6H, $3NCH_2$); 6.70 (m, 1H, H-5); 7.09 (m, 1H, H-3); 7.56 (m, 1H, H-4); 8.02 (m, H, H-6); 8.30 (bs, 1H, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 26.2 (CH_2); 40.6 (NCH_2); 51.0 (NCH_2); 54.5 (NCH_2); 114.3 (C-3); 114.8 (C-5); 126.1 (C-6); 130.7 (C-2); 136.4 (C-4); 145.1 (C-1); 172.2 (2CO); MS (DCI/NH_3): 312 ($M+H^+$). Anal.: found (as hydrochloride salt): C, 44.6; H, 5.1; N, 12.4%; mp=158 °C; $C_{13}H_{18}N_3O_6Cl$ requires: C, 44.9; H, 5.2; N, 12.1%.

4.2.6. *N*-(4-Nitrophenyl)propylenediamine-*N′*,*N′*-diacetic acid hydrochloride salt (17). Using the same procedure than **5**, 367 mg of compound **15** gave **17** as an hydroscopic orange powder (274 mg, 79%).

^{1}H NMR (250 MHz, DMSO-d_6) δ_H (ppm): 1.67 (q, J=6.6 Hz, 2H, CH_2); 2.77 (t, 2H, J=6.6 Hz, NCH_2); 3.20 (m, 2H, NCH_2); 3.44 (s, 4H, $2NCH_2$); 6.64 (d, 2H, J=9.5 Hz, H-2, H-6); 7.50 (bs, 1H, NH); 7.56 (d, 2H, J=9.5 Hz, H-3, H-5); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ_C (ppm): 26.2 (CH_2); 40.6 (NCH_2); 51.4 (NCH_2); 54.6 (NCH_2); 110.6 (C-2, C-6); 126.2 (C-3, C-5); 135.2 (C-4); 154.5 (C-1); 172.4 (2CO); MS (DCI/NH_3): 312 ($M+H^+$); mp=130 °C; Anal.: found (as hydrochloride salt): C, 40.7;

H, 4.9; N, 11.2% $C_{13}H_{18}N_3O_6Cl.2H_2O$ requires: C, 40.7; H, 5.7; N, 11.0%.

4.3. Synthesis of bifunctional chelating agent

4.3.1. *N*-(2-Aminophenyl)ethylenediamine-*N*′,*N*′-diethyldiacetate (18). Catalytic hydrogenation of **3** (0.54 g, 1.53 mmol) in methanol (25 mL) over 10% Pd/C (20% w/w) was carried out at atmospheric pressure. After 30 min, the catalyst was filtered off (Celite), and the solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with methanol to give **18** as a brown oil (0.37 g, 75%).

^{1}H NMR (250 MHz, $CDCl_3$) δ_H (ppm): 1.24 (t, 6H, J=7.1 Hz, $2CH_3$); 3.07 (m, 4H, $2NCH_2$); 3.55 (s, 4H, $2NCH_2$); 4.13 (q, 4H, J=7.1 Hz, $2OCH_2$); 6.57–6.67 (m, 4H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C (ppm): 14.2 (CH_3); 41.6 (NCH_2); 53.0 (NCH_2); 55.1 ($2NCH_2$); 60.7 (2 OCH_2); 111.2 (C-3); 115.6 (C-5); 118.0 (C-6); 119.8 (C-2); 134.6 (C-4); 137.3 (C-1); 171.7 (2CO); MS (DCI/NH_3): 324 ($M+H^+$).

4.3.2. *N*-(2-Aminophenyl)ethylenediamine-*N*′,*N*′-diacetic acid dihydrochloride salt (19). *Method A*: 200 mg (0.62 mmol) of diester **18** in 10 mL of a 2 N NaOH/ethanol (1/1) solution was heated at reflux for 3 h. After cooling, the solution was acidified until pH was 1 with 2 N HCl. The solution was concentrated and the residue was taken twice with acetone (20 mL). After filtration, the filtrate was evaporated, dried under vacuum to afford a brown solid (168 mg, 75%).

Method B: Catalytic hydrogenation of **5** (510 mg, 1.53 mmol) in methanol (25 mL) over 10% Pd/C (20% w/w) was carried out at atmospheric pressure. After 30 min, the catalyst was filtered off (Celite), and the solvent was removed under reduced pressure. The residue was taken in water and the solution was acidified until pH was 1. After filtration, the filtrate was concentrated and dried under vacuum. The crude material was purified by a short column chromatography on silica gel, eluting with methanol to give **19** as a brown solid (221 mg, 40%).

^{1}H NMR (200 MHz, D_2O) δ_H (ppm): 2.74 (m, 2H, NCH_2); 3.04 (m, 2H, NCH_2); 3.14 (s, 4H, NCH_2); 6.72 (m, 4H, ArH); ^{13}C NMR (62.9 MHz, D_2O) δ_C (ppm): 44.8 (NCH_2); 55.9 (NCH_2); 61.5 ($2NCH_2$); 116.2 (C-6); 118.9 (C-4); 122.4 (C-3); 123.3 (C-2); 137.2 (C-5); 139.3 (C-1); 182.4 (2CO); MS (DCI/NH_3): 268 ($M+H^+$); mp=221 °C; Anal.: found (as dihydrochloride salt): C, 43.0; H, 5.6; N, 12.7% $C_{12}H_{19}N_3O_4Cl_2$ requires: C, 43.4; H, 6.1; N, 12.4%.

4.4. Synthesis of Re(I) tricarbonyl complex

4.4.1. Re(I) tricarbonyl *o*-NO_2Ph-PDDA complex (20). 100 mg (0.3 mmol) of the ligand **5**, 250 mg (0.3 mmol) of commercial $Re(CO)_5Cl$ and 1.26 ml (0.9 mmol) of Et_3N were solved in MeOH (20 mL) and stirred at 60 °C for 4 h. The solution was evaporated to dryness and the residue was washed with ether (3×30 mL) then was dissolved in a minimum of MeOH (5 mL). Addition of ether (30 mL) afforded a yellow precipitate which was filtered and concentrated to dryness under reduce pressure. The crystallisation step was repeated twice. In these conditions, produced Et_3NHCl staid in the filtrate and **20** was obtained as a yellow powder (triethylamine hydrochloride salt, 180 mg, 90%).

NMR ^{1}H (300 MHz, DMSO-d_6) δ_H (ppm): 1.07 (t, 9H, J=7.1 Hz, CH_3); 3.01 (q, 6H, J=7.1 Hz, NCH_2); 3.39 (m, 2H, NCH_2); 3.48 (AB system, 2H, J=16.0 Hz, CH_2CO); 3.59 (m, 2H, NCH_2); 3.65 (AB system, 2H, J=16.0 Hz, CH_2CO); 6.63 (m, 1H, H-6); 7.17 (d, 1H, J=8.5 Hz, H-4); 7.50 (m, 1H, H-5); 8.00 (dd, 1H, J=8.5 and 1.5 Hz, H-3); 8.13 (t, J=6,0 Hz, 1H, NH).^{13}C NMR (75.5 MHz, DMSO-d_6) δ_C (ppm): 9.17 (CH_3); 38.5 (NCH_2); 46.2 (NCH_2); 63.2 (CH_2CO); 67.2 (NCH_2); 114.9 (C-6); 116.0 (C-4); 126.8 (C-3); 131.8 (C-2); 137.2 (C-5); 145.0 (C-1); 178.8 (2CO); 199.1, 199.4 (3CO), IR (KBr): 3369 br, 2029 s, 1917 s, 1887 s, 1666 s cm^{-1}; MS (ES^-): 564 (60), 566 (100) [M^-]; mp=217 °C; Anal.: found: C, 38.1; H, 4.3; N, 8.4%; $C_{21}H_{29}N_4O_9Re$ requires: C, 37.8; H, 4.3; N, 8.4%.

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References and notes

1. (a) Dilworth, J. R.; Parrot, S. J. *Chem. Soc. Rev.* **1998**, *27*, 43–55. (b) Jurisson, S.; Lydon, J. D. *Chem. Rev.* **1999**, *99*, 2205–2218.
2. Johannsen, B.; Spiess, H. *Top. Curr. Chem.* **1996**, *176*, 77–122.
3. (a) Benoist, E.; Fourteau, L.; Coulais, Y.; Dartiguenave, M. *J. labelled cpd. Radiopharm.* **2001**, *44*, S521–S523. (b) Le Gal, J.; Benoist, E.; Gressier, M.; Coulais, Y.; Dartiguenave, M. *Tetrahedron Lett.* **2002**, *43*, 9295–9297.
4. (a) Alberto, R.; Schibli, R.; Schubiger, P. A.; Abram, U.; Kaden, T. A. *Polyhedron* **1996**, *15*, 1079–1089. (b) Alberto, R.; Schibli, R.; Abram, U.; Egli, A.; Knapp, F. F.; Schubiger, P. A. *Radiochim. Acta* **1997**, *79*, 99–103. (c) Alberto, R.; Schibli, R.; Schubiger, P. A.; Abram, U.; Kaden, T. A. *J. Am. Chem. Soc.* **1998**, *120*, 7987–7988.
5. Banerjee, S. R.; Levadala, M. K.; Lazarova, N.; Wei, L.; Valliant, J. F.; Stephenson, K. A.; Babich, J. W.; Maresca, K. P.; Zubieta, J. *Inorg. Chem.* **2002**, *41*, 6417–6425.
6. Kramer, D. J.; Davison, A.; Davis, W. M.; Jones, A. G. *Inorg. Chem.* **2002**, *41*, 6181–6183.
7. Pietzsch, H. J.; Gupta, A.; Reisgys, M.; Drews, A.; Seifert, S.; Syhre, R.; Spies, H.; Alberto, R.; Abram, U.; Schubiger, P. A.; Johannsen, B. *Bioconjugate Chem.* **2000**, *11*, 414–424.
8. Kothari, K. K.; Raghuraman, K.; Pillarsetty, N. K.; Hoffman, T. J.; Owen, N. K.; Katti, K. V.; Volkert, W. A. *Appl. Radiat. Isotopes* **2003**, *58*, 543–549.
9. Minutolo, F.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4514–4515.
10. Alberto, R.; Ortner, K.; Wheatley, N.; Schibli, R.; Schubiger, P. A. *J. Am. Chem. Soc.* **2001**, *123*, 3135–3136.
11. (a) Schibli, R.; Schwarzbach, R.; Alberto, R.; Ortner, K.;

Schmalle, H.; Dumas, C.; Egli, A.; Schubiger, P. A. *Bioconjugate Chem.* **2002**, *13*, 750–756. (b) Schibli, R.; Netter, M.; Scapozza, L.; Birringer, M.; Schelling, P.; Dumas, C.; Schoch, J.; Schubiger, P. A. *J. Organomet. Chem.* **2003**, *668*, 67–74.

12. Schibli, R.; La Bella, R.; Alberto, R.; Garcia-garayoa, E.; Ortner, K.; Abram, U.; Schubiger, P. A. *Bioconjugate Chem.* **2000**, *11*, 345–351.
13. Petrig, J.; Schibli, R.; Dumas, C.; Alberto, R.; Schubiger, P. A. *Chem. Eur. J.* **2001**, *7*, 1868–1873.
14. Fourneau, J. P.; de Lestrange, Y. *Bull. Soc. Chim. Fr.* **1947**, 827–838.
15. Gouin, S. G.; Gestin, J.-F.; Reliquet, A.; Meslin, J. C.; Deniaud, D. *Tetrahedron Lett.* **2002**, *43*, 3003–3005.
16. Loussouarn, A.; Duflos, M.; Benoist, E.; Chatal, J.-F.; Le Baut, G.; Gestin, J-F. *J. Chem. Soc., Perkin Trans. 1* **1998**, 237.
17. Hayat, S.; Rahman, A.; Choudhary, M. I.; Khan, K. M.; Schumann, W.; Bayer, E. *Tetrahedron* **2001**, *57*, 9951–9957.
18. Genik-Sas-Berezowsky, R. M.; Spinner, I. H. *Can. J. Chem.* **1970**, *48*, 163–175.
19. Williams, M. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1151–1158.
20. Heard, P. J.; Sroisuwan, P.; Tocher, D. A. *Polyhedron* **2003**, *22*, 1321–1327.

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Stereoselective synthesis of heterosubstituted aziridines and their functionalization

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Abstract—Lithiated (α-chloroalkyl)heterocycles, generated by deprotonation with LDA at −78 °C in THF, add to various enantiopure imines affording 'one pot' chiral heterosubstituted aziridines in a diastereoselective manner. Lithiated heterosubstituted aziridines, obtained by deprotonation of the corresponding aziridines with *n*-BuLi at −78 °C in THF, were trapped by electrophiles (D_2O or CH_3I) with high stereoselectivity.
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1. Introduction

Aziridines are useful chiral building blocks for the synthesis of modified amino acids[1] and nitrogen-containing functional compounds via ring opening and ring expansion reactions.[2–4] Chiral aziridines form an attractive class of compounds, since they are available in highly enantioenriched form by a variety of procedures and can be used for asymmetric synthesis in a number of different ways.[5]

Studies on the chemistry of aziridinyl anions, which are a particular kind of carbanions, have previously appeared.[6] For example, the alkylation of 2-phenylsulfonylaziridines, via aziridinyllithium formation and trapping with alkyl halides, was reported.[7] Generation of aziridinyllithiums of phenyl aziridine thioesters and trapping with electrophiles seemed to proceed with retention of configuration or moderate diastereoselectivities according to the starting isomer.[8]

We reported, some time ago, a simple diastereoselective synthesis of various heterosubstituted aziridines based on a Darzens reaction of lithiated (α-chloroalkyl)heterocycles with imines.[9] The option of freeing the masked acyl group of some heteroaryl moieties,[10] makes these aziridine derivatives susceptible to further functionalization.[11] Concerning the generation of aziridinyl anions as synthetic intermediates, we found recently, in our laboratories, that some *N*-sulfonyloxazolinylaziridines can easily be lithiated and then captured by electrophiles in a configurationally stable manner.[12]

In this paper we describe the synthesis of chiral heterosubstituted aziridines by the coupling reaction of lithiated (α-chloroalkyl)heterocycles with various enantiopure imines. Some of the chiral aziridines obtained were then lithiated and captured by electrophiles; the stereochemistry of these reactions has been also investigated.

2. Results and discussion

The required (α-chloroalkyl)heterocycles **1a**–**h**, prepared as described in Section 4, and stoichiometric amount of the enantiopure (*R*)-imine **2a** were added to a stirred solution of lithium diisopropylamide (LDA) in THF at −78 °C to produce diastereoselectively the chiral aziridines **3a**–**h**, in satisfactory yields (30–90%), as reported in Table 1.

The substituted aziridines, containing new stereocentres, were isolated as the only reaction products. A *cis* arrangement (the heterocycle and the phenyl group both on the same side) was noticed for compounds (+)-**3a**, (+)-**3b**, (−)-**3c**, (+)-**3e**, (+)-**3g** and (+)-**3h** while the aziridines (−)-**3d**, and (−)-**3f** showed a *trans* arrangement (the heterocycle and the phenyl group on opposite sides).

Keywords: Heterosubstituted aziridines; Aziridinyl anion; Nucleophilic addition.
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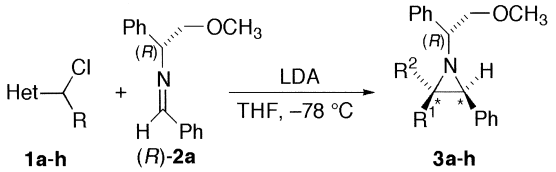
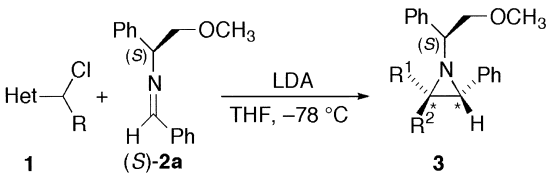
Table 1. Synthesis of chiral nonracemic heterosubstituted aziridines from (α-chloroalkyl)heterocycles and the enantiopure (*R*)-imine **2a**



Compound	R^1	R^2	Product **3** (yield %)[a]	dr[b]	Relative configuration[c]	$[\alpha]_D^{22}$[d]
1a	4-Methylthiazol-2-yl	H	(+)-**3a** (48)	>98:2	$2'R^*,3'R^*$	+12.9
1b	4-Methylthiazol-2-yl	CH_3	(+)-**3b** (90)	>98:2	$1'R,2'S,3'S$[e,f]	+23.1
1c	2-Benzothiazolyl	H	(−)-**3c** (90)	>98:2	$2'R^*,3'R^*$	−61.7
1d	CH_3	2-Benzothiazolyl	(−)-**3d** (60)	>98:2	$2'R^*,3'S^*$	−199.4
1e	4,4-Dimethyl-2-oxazolin-2-yl	H	(+)-**3e** (45)	>98:2	$1'S,2'S,3'S$[e]	+28.1
1f	CH_3	4,4-Dimethyl-2-oxazolin-2-yl	(−)-**3f** (35)	>98:2	$1'S,2'R,3'S$[e,f]	−43.6
1g	2-Pyridyl	H	(+)-**3g** (60)	>98:2	$2'R^*,3'R^*$	+22.4
1h	4-Pyridyl	H	(+)-**3h** (30)	>98:2	$2'R^*,3'R^*$	+40.0

[a] Isolated yield.
[b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; only one diastereomer in the ^{1}H NMR spectrum of the crude product.
[c] Denoted by configurational descriptors R^*,R^* and R^*,S^*; by convention, when the absolute configuration is not known the first center is always assigned to be R^*.
[d] *c* 0.01–0.07, $CHCl_3$ (see Section 4 for details).
[e] Absolute configuration ascertained as described (see text).
[f] See also Ref. 18.

Table 2. Synthesis of chiral nonracemic heterosubstituted aziridines from (α-chloroalkyl)heterocycles and the enantiopure (*S*)-imine **2a**



Compound	R^1	R^2	Product **3** (yield %)[a]	dr[b]	Relative configuration	$[\alpha]_D^{22}$[c]
1a	4-Methylthiazol-2-yl	H	(−)-**3a** (45)	>98:2	$2'R^*,3'R^*$	−12.6
1e	4,4-Dimethyl-2-oxazolin-2-yl	H	(−)-**3e** (52)	>98:2	$1'R,2'R,3'R$[d]	−29.3
1f	CH_3	4,4-Dimethyl-2-oxazolin-2-yl	(+)-**3f** (31)	>98:2	$1'R,2'S,3'R$[d]	+43.1

[a] Isolated yield.
[b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; only one diastereomer in the ^{1}H NMR spectrum of the crude product.
[c] *c* 0.01–0.07, $CHCl_3$ (see Section 4 for details).
[d] Presumed absolute configuration on the basis of data of Table 1.

Analogous reactions were performed using the substrates **1a**, **1e**, and **1f** and the enantiopure (*S*)-imine **2a**. The obtained results are reported in Table 2. The chiral heterosubstituted aziridines (−)-**3a**, (−)-**3e**, and (+)-**3f** were isolated in satisfactory yields (31–52%). As expected, these products showed similar optical rotation values of those measured for compounds (+)-**3a**, (+)-**3e**, and (−)-**3f** (Table 1) but with opposite sign.

An attempt was made to react the substrates **1a** and **1f** with different enantiopure imines (*S*)-**2b** and (*R*)-**2b** (Chart 1), following the same reaction procedure reported above.

The reactions proceed in a highly stereoselective manner,

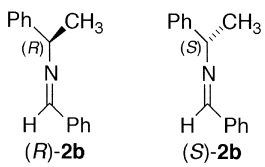


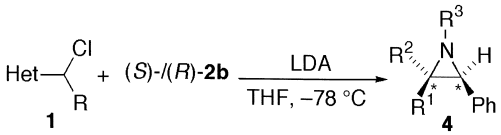
Chart 1.

affording (+)-**4a**, (+)-**4f**, and (−)-**4a**, (−)-**4f**, respectively, in satisfactory yields (50–55%). The results are reported in Table 3. (+)- and (−)-**4a** were isolated as an inseparable mixture of two diastereomers of $(2'R^*,3'R^*)$ configuration in a ratio of 4:1. (+)- and (−)-**4f** were instead a mixture of two separable diastereomers (petroleum ether/Et_2O 7/3) obtained in a 2:1 ratio both having a $(2'R^*,3'S^*)$ configuration. The ratios were evaluated from the ^{1}H NMR spectra of the crude products.

The higher diastereoselectivity observed using the chiral imines (*R*)- and (*S*)-**2a**, rather than the chiral imines (*R*)- and (*S*)-**2b** could be due to the different steric hindrance of the alkyl group linked to the nitrogen atom. Moreover, we suppose that the oxygen atom of 2-methoxy-1-phenylethyl substituent of **2a** can participate to the internal coordination[6d] during the process that leads to the aziridinic ring closure, affording the products in a more stereoselective manner.

The lithiation of aziridines (+)-**3a**, and (+)-**4a** with *n*-butillithium (*n*-BuLi) at −78 °C in THF, followed by the

Table 3. Synthesis of chiral nonracemic heterosubstituted aziridines from (α-chloroalkyl)heterocycles and the enantiopure (*S*)- and (*R*)-imines **2b**



Compound	Imine	R^1	R^2	R^3	Product (yield %)[a]	dr[b]
1a	(*S*)-**2b**	4-Methylthiazol-2-yl	H	(*S*)-PhCHCH$_3$	(+)-**4a** (50)	$2'R^*,3'R^*/2'R^*,3'R^*$=4/1[c,d]
1a	(*R*)-**2b**	4-Methylthiazol-2-yl	H	(*R*)-PhCHCH$_3$	(−)-**4a** (53)	$2'R^*,3'R^*/2'R^*,3'R^*$=4/1[c,d]
1f	(*S*)-**2b**	CH_3	4,4-Dimethyl-2-oxazolin-2-yl	(*S*)-PhCHCH$_3$	(+)-**4f** (55)	$2'R^*,3'S^*/2'R^*,3'S^*$=2/1[d,e]
1f	(*R*)-**2b**	CH_3	4,4-Dimethyl-2-oxazolin-2-yl	(*R*)-PhCHCH$_3$	(−)-**4f** (52)	$2'R^*,3'S^*/2'R^*,3'S^*$=2/1[d,e]

[a] Overall isolated yields in both diastereomers.
[b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy on the crude product; relative configuration.
[c] An inseparable mixture of two *cis*-configurated diastereomeric aziridines formed. (+)-**4a**: $[\alpha]_D^{22}$=+14.1; (−)-**4a**: $[\alpha]_D^{22}$=−13.5.
[d] *c* 0.03–0.08, $CHCl_3$ (see Section 4 for details).
[e] A diastereomeric mixture of two ($2'R^*,3'S^*$)-configurated aziridines separable by column chromatography (silica gel, petroleum ether/Et_2O 7/3) formed. (+)-**4f**: (major diastereomer) $[\alpha]_D^{22}$=+36.0; (minor diastereomer) $[\alpha]_D^{22}$=+24.3; (−)-**4f**: (major diastereomer) $[\alpha]_D^{22}$=−35.3; (minor diastereomer) $[\alpha]_D^{22}$=−25.9.

addition of deuterium oxide (D_2O) or methyl iodide (CH_3I) after 1 h gave the 2-deuterated thiazolylaziridines **5** (90%D) and **6** (95%D) and the 2-methylated thiazolylaziridine (+)-**3b**, retaining the configuration of the starting aziridines (Chart 2).

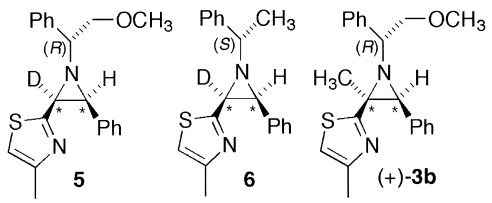


Chart 2.

The structures of the 2-deuterated aziridines **5** and **6** were established by ^{1}H NMR data: the doublet of the aziridinic α-hydrogen, substituted by a deuterium atom, almost disappears, while the doublet of the aziridine β-hydrogen becomes a singlet. No chemical shift displacements were observed for the deuterated compounds **5** and **6** which then retain the configurations of the starting aziridines (+)-**3a**, and (+)-**4a**.

The stereochemistry of aziridines (+)- and (−)-**3a**, (−)-**3c**, (+)- and (−)-**3e**, (+)-**3g**, (+)-**3h**, (+)- and (−)-**4a** was assigned on the basis of the ^{1}H NMR coupling constants between the two aziridinyl hydrogens ($J_{cis}>J_{trans}$);[13] the configurations of aziridines (+)-**3b**, (−)-**3d**, (+)- and (−)-**3f**, (+)- and (−)-**4f** were established on the basis of an upfield shift of the CH_3 group in the case of a *cis* relationship with the Ph group. Indeed, it has been reported that an high field displacement occurs when a CH_3 group is on the same side of a Ph group, while a smaller upfield shift is observed when the Me group and H are on the same side.[14] The configuration assignment was also confirmed, for these latter aziridines by ^{13}C NMR spectroscopy on the basis of the very small long-range $^3J_{CH}$ coupling constant ($^3J_{CH3-H}\approx$0 Hz) between the aziridine β-hydrogen and the carbon of the α-methyl group when these groups are on opposite sides, as reported.[15] The good crystalline form of compound (+)-**3b** allowed us to perform X-ray measurements (Fig. 1) and to assign in this case the absolute configuration.[16] The aziridine asymmetric carbons have 2′*S* and 3′*S* configuration; while the nitrogen has 1′*R* configuration. These latter results also confirm the assigned *cis* relative configuration (the heterocycle and the CH_3 group both on the same side).

Moreover, it was possible to assign the absolute configuration to oxazolinylaziridines (+)-**3e** and (−)-**3f** by NMR spectroscopy, as follows. Oxazolinylaziridine (+)-**3e** was assigned the *cis* relative configuration with the nitrogen lone pair *trans* to the vicinal aziridine ring protons (H_a and H_b) on the basis of the value ($^3J_{H-H}$=6.9 Hz) of their coupling constant.[17] After complete attribution of all the protons (^{1}H, ^{13}C, selective homonuclear decoupling experiments, HETCOR and HMBC) the absolute configuration was deduced from 2D-NOESY correlations. Between the two possible diastereomers **3e**-**A** and **3e**-**B** (Fig. 2), both having the same relative configuration, strong NOE interactions between H_c and H_a/H_b together with a weak one between CH_3O and H_b (at δ=2.90) were diagnostic of a 1′*S*,2′*S*,3′*S* absolute configuration for the aziridine ring. Relative[18] and absolute configuration (1′*S*,2′*R*,3′*S*) of the oxazolinylaziridine (−)-**3f** was similarly established using 2D-NOESY Phase-Sensitive experiments showing in this case, in particular, significant NOEs interactions either between

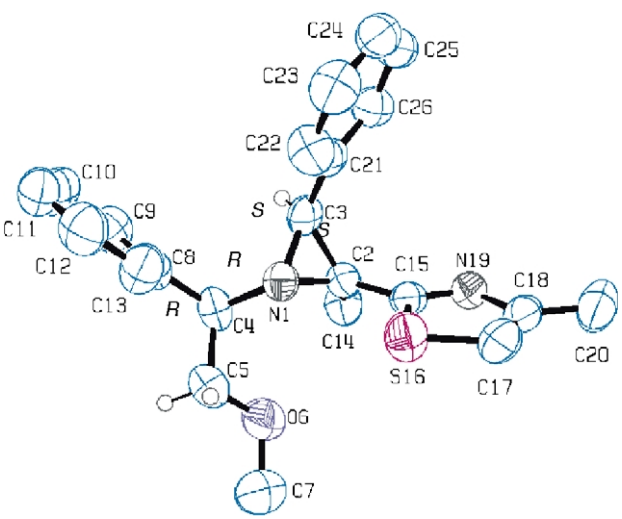


Figure 1. ORTEP view of compound (+)-**3b**.

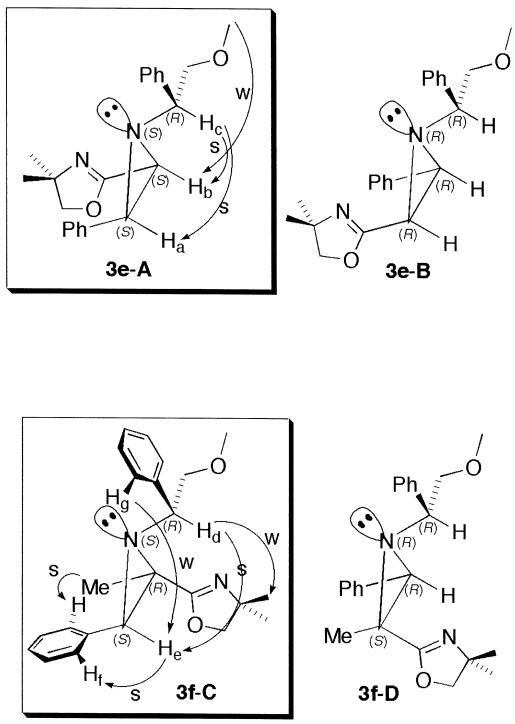


Figure 2. Oxazolinylaziridines **3e** (diastereomers **3e**-**A** and **3e**-**B**) and **3f** (diastereomers **3f**-**C** and **3f**-**D**). Selected NOEs interactions; s=strong, w=weak.

the benzylic proton H_d and the aziridine proton H_e or the latter with both the *ortho* aromatic ring protons H_f and H_g, as depicted in Figure 2 in the case of diastereomer **3f**-**C** compared to diastereomer **3f**-**D** having the same relative configuration. These close proximity relationships between the above-cited protons for the two diastereomers **3e**-**A** and **3f**-**C**, and consequently, the relative conformations of the two side chains linked at the nitrogen atoms, were also confirmed by means of calculations. To this end, preliminarily, equilibrium geometries were calculated for each diastereomer having the same relative and absolute configuration of **3e**-**A**,**B** and **3f**-**C**,**D** starting with a systematic conformer distribution analysis. Conformers were grouped into families on the basis of relevant torsion angle values. The best representative of each family was submitted to a PM3 semi-empirical geometry optimization and, in order to introduce electron correlation in the computation of the energetics, we performed, on the best conformer of each analogue, single-point calculations using the density functional theory (DFT) at the B3LYP/6-31+G*//PM3 level of theory.[19] The resulting diastereomers, the best representatives in terms of energy and geometry of **3e**-**A**,**B** and **3f**-**C**,**D** (Fig. 3), were found to have the same local conformations of those depicted in Figure 2, so supporting the NOESY conclusions.

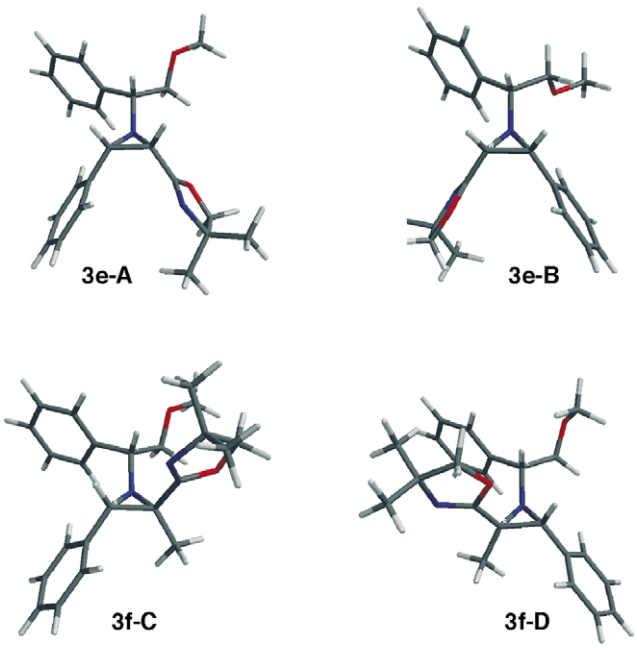


Figure 3. PM3-optimized geometries of the four diastereomers (1′*S*,2′*S*,3′*S*)-**3e**-**A**, (1′*R*,2′*R*,3′*R*)-**3e**-**B**, (1′*S*,2′*R*,3′*S*)-**3f**-**C**, (1′*R*,2′*S*,3′*R*)-**3f**-**D**.

3. Conclusion

In conclusion, chiral heterosubstituted aziridines can be prepared in a diastereoselective manner, by the 'one pot' addition of lithiated (α-chloroalkyl)heterocycles to various enantiopure imines. The different steric hindrance and coordination power of the alkyl group, linked to the iminic nitrogen atom, could influence the aziridine ring closure process and, consequently, the diastereoselectivity. Aziridines synthesized from chiral imines (*R*)- and (*S*)-**2a** form in a higher diastereoselectivity than those from the chiral imines (*R*)- and (*S*)-**2b**. Moreover, aziridines (+)-**3a** and (+)-**4a** can be lithiated and trapped by deuterium oxide or methyl iodide to give more functionalized aziridines with retention of configuration.

4. Experimental

n-BuLi was a commercial solution in hexanes (Aldrich) and was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[20] THF, lithium diisopropylamide (LDA), deuterium oxide, methyl iodide, (*R*)-(−)-2-amino-2-phenylethanol, (*S*)-(+)-2-amino-2-phenylethanol, (*R*)-(+)-1-phenylethylamine, (*S*)-(−)-1-phenylethylamine, 4-methylthiazole, 2-aminothiophenol, glycolic acid, lactic acid, 2,4,4-trimethyl-2-oxazoline, 2-ethyl-4,4-dimethyl-2-oxazoline, 2-(chloromethyl)pyridine hydrochloride, 4-(chloromethyl)pyridine hydrochloride, were of commercial grade (Aldrich), and were used without further purification. Acetaldehyde and benzaldehyde of commercial grade (Aldrich), were purified by distillation prior to use. Petroleum ether refers to the 40–60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as solvent and TMS as internal standard (δ_H=7.24 for ^{1}H spectra; δ_H=77.0 for ^{13}C spectra). The IR spectra were recorded on a Perkin–Elmer spectrometer Model 283. GC–MS analyses were performed with Hewlett–Packard HP-5890 series II gas chromatograph (5% diphenyl/95% dimethylpolysiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with an HP 5971 mass-selective detector operating at 70 eV (EI). The electrospray ionization (HR-ESI-MS) experiments were

carried out in a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionization source. MS(+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL), dissolved in solution 0.1% acetic acid, methanol/water 50/50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50, and 25 V relative to ground, respectively. Polarimetric measurements were performed by a Jasco P-1020 polarimeter. Melting points were determined using an electrothermal melting point apparatus and are uncorrected. TLC were performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63–200 μm) using petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen, in oven-dried glassware using syringe/septum cap techniques.

4.1. General procedures for the preparation of the substrates (1a–h) and imines (2a–b)

Compound **1a** was prepared by formylation of 4-methylthiazole, reduction of the so obtained 2-thiazolylaldehyde and subsequent halogenation, following reported synthetic protocols.[9d] Compound **1b** was obtained by the coupling reaction of 2-(4-methyl)thiazolyllithium with acetaldehyde and subsequent halogenation.[9d] Substrates **1c**, **1d** were obtained by reaction of 2-aminothiophenol with glycolic or lactic acid and subsequent halogenation.[21] 2-(α-Chloroalkyl)oxazolines **1e**, **1f** were prepared by halogenation of the commercially available 2-methyl and 2-ethyl derivatives according to reported procedures.[22] 2-(α-Choroalkyl)-piridines **1g**, **1h** were obtained by treatment of the commercially available hydrochlorides with a 5% NaOH solution.[22] Chiral imines **2a**,**2b** were prepared by the coupling of chiral 2-methoxy-1-phenylethylamine (*R* or *S*) or chiral 1-phenylethylamine (*R* or *S*) with benzaldehyde according to the reported protocols.[23] 2-Methoxy-1-phenylethylamine (*R* or *S*) was prepared by methylation[24] of the commercial enantiopure 2-amino-2-phenylethanol (*R* or *S*).

4.2. General procedure for the preparation of heterosubstituted aziridines (3a–h)

To a stirred solution of LDA (2.0 M in hexanes, 1 mL, 2.0 mmol), in THF (30 mL) at −78 °C under nitrogen, a mixture of 1 mmol of **1a–h**, and 1 mmol of imine **2a** in 10 mL of THF was added dropwise. After 20 min the resulting mixture was slowly allowed to warm to room temperature and then, after 3 h, quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography [silica gel, petroleum ether/Et_2O, 1:1 for (+)-**3a**, (+)-**3b**, (−)-**3c**, (+)-**3e**, (+)-**3g**, 7:3 for (+)-**3h**, 9:1 for (−)-**3f** and (−)-**3d**] to afford the pure heterosubstituted aziridines, yields: 30–90%. The substituted aziridines (−)-**3a**, (−)-**3e**, (+)-**3f**, (+)- and (−)-**4a**, (+)- and (−)-**4f** were prepared with this same procedure.

4.2.1. 2-[1-(2-Methoxy-1-phenylethyl)-3-phenylaziridin-2-yl]-4-methylthiazole (+)-3a. Yield: 168 mg, (48%), yellow solid, mp 95–97 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 2.31 (s, 3H), 3.12 (d, 1H, *J*=6.4 Hz), 3.21 (dd, 1H, *J*=5.0, 7.2 Hz), 3.28 (s, 3H), 3.62 (d, 1H, *J*=6.4 Hz), 3.70 (dd, 1H, *J*=5.0, 9.7 Hz), 3.85 (dd, 1H, *J*=7.2, 9.7 Hz), 6.58 (s, 1H), 7.05–7.27 (m, 6H), 7.33 (t, 2H, *J*=7.6 Hz), 7.50 (d, 2H, *J*=7.2 Hz). ^{13}C NMR (100.62 MHz): δ 16.8, 47.4, 47.7, 50.9, 73.4, 77.7, 113.0, 126.7, 127.4, 127.6, 127.7, 127.9, 128.2, 134.8, 139.5, 152.1, 167.6. GC–MS (70 eV) *m*/*z* (rel. int.): 350 (7, M^+), 305 (5), 347 (7), 215 (100), 188 (53). IR (film): 3080, 3020, 2910, 2860, 1600, 1590, 1450, 1300, 1230, 1100, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=+12.9 ($CHCl_3$, *c* 0.07). HR-ESI-MS: *m*/*z* calcd for $C_{21}H_{23}N_2OS$: 351.1531, $[M+H]^+$; found 351.1528.

4.2.2. 2-[1-(2-Methoxy-1-phenylethyl)-2-methyl-3-phenylaziridin-2-yl]-4-methylthiazole (+)-3b. Yield: 327.6 mg (90%), yellow solid, mp 82–84 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 2.06 (s, 3H), 2.31 (d, 3H, *J*=0.8 Hz), 3.01 (s, 1H), 3.35 (s, 3H), 3.76–3.87 (m, 3H), 6.60 (q, 1H, *J*=0.8 Hz), 7.05–7.55 (m, 10H). ^{13}C NMR (100.62 MHz): δ 17.7, 17.8, 50.9, 54.1, 59.6, 65.3, 78.5, 113.6, 126.9, 127.7, 128.1, 128.2, 128.6, 128.8, 136.4, 140.5, 142.9, 173.5. GC–MS (70 eV) *m*/*z* (rel. int.): 364 (1, M^+), 238 (61), 229 (100), 207 (28), 91 (44). IR (film): 3030, 2920, 2860, 1450, 1300, 1120, 750, 700 cm^{-1}. $[\alpha]_D^{22}$=+23.1 ($CHCl_3$, *c* 0.06). HR-ESI-MS: *m*/*z* calcd for $C_{22}H_{25}N_2OS$: 365.5126, $[M+H]^+$; found 365.5120.

4.2.3. 2-[1-(2-Methoxy-1-phenylethyl)-3-phenylaziridin-2-yl]benzothiazole (−)-3c. Yield: 347.4 mg (90%), yellow solid, mp 60–62 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 3.23 (d, 1H, *J*=6.2 Hz), 3.27–3.29 (m, 4H), 3.72 (dd, 1H, *J*=4.6, 9.0 Hz), 3.77 (d, 1H, *J*=6.2 Hz), 3.91 (t, 1H, *J*=9.0 Hz), 7.05–7.50 (m, 12H), 7.74 (d, 1H, *J*=8.0 Hz), 7.90 (d, 1H, *J*=8.0 Hz). ^{13}C NMR (100.62 MHz): δ 43.1, 44.2, 59.0, 60.7, 78.7, 126.6, 126.8, 127.3, 127.4, 127.5, 127.6, 127.9, 128.0, 128.2, 128.3, 135.3, 139.3, 151.5, 166.2. GC–MS (70 eV) *m*/*z* (rel. int.): 386 (5, M^+), 355 (8), 327 (10), 251 (100). IR ($CHCl_3$): 3060, 3020, 2950, 1600, 1590, 1490, 1440, 1375, 1100, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=−61.7 ($CHCl_3$, *c* 0.01). HR-ESI-MS: *m*/*z* calcd for $C_{24}H_{23}N_2OS$: 387.1531, $[M+H]^+$; found 387.1530.

4.2.4. 2-[1-(2-Methoxy-1-phenylethyl)-2-methyl-3-phenylaziridin-2-yl]benzothiazole (−)-3d. Yield: 240 mg (60%), yellow solid, mp 131–133 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 1.53 (s, 3H), 2.99 (s, 3H), 3.48–3.63 (m, 2H), 3.93 (t, 1H, *J*=6.4 Hz), 4.10 (s, 1H), 7.15–7.50 (m, 12H), 7.87 (d, 1H, *J*=7.8 Hz), 8.10 (d, 1H, *J*=8.0 Hz). ^{13}C NMR (100.62 MHz): δ 19.9, 48.9, 50.8, 58.7, 62.8, 77.1, 121.4, 123.3, 125.0, 126.1, 126.8, 127.5, 127.7, 127.8, 128.2, 128.3, 135.2, 136.8, 140.5, 152.7, 170.3. IR (film): 3060, 3020, 2950, 1600, 1490, 1440, 1375, 1100, 750, 690 cm^{-1}. $[\alpha]_D^{22}$=−199.4 ($CHCl_3$, *c* 0.02). HR-ESI-MS: *m*/*z* calcd for $C_{25}H_{25}N_2OS$: 401.1690, $[M+H]^+$; found 401.1703.

4.2.5. 2-[1-(2-Methoxy-1-phenylethyl)-3-phenylaziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (+)-3e. Yield:

157.5 mg (45%), white solid, mp 71–72 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 1.00 (s, 3H), 1.08 (s, 3H), 2.86 (d, 1H, J=6.8 Hz), 2.90 (d, 1H, J=6.8 Hz), 3.03 (t, 1H, J=5.5 Hz), 3.37 (s, 3H), 3.58 (d, 1H, J=8.0 Hz), 3.66–3.75 (m, 2H), 3.90 (dd, 1H, J=8.0, 9.7 Hz), 7.13–7.30 (m, 9H), 7.48 (d, 1H, J=7.2 Hz). ^{13}C NMR (100.62 MHz): δ 27.9, 28.0, 43.4, 44.2, 59.1, 66.9, 73.9, 76.6, 78.7, 126.8, 127.4, 127.5, 127.6, 127.7, 128.2, 132.0, 139.4, 162.0. GC–MS (70 eV) *m*/*z* (rel. int.): 350 (8, M^+), 319 (7), 238 (20), 215 (100), 91 (60). IR (film): 3050, 2910, 1650, 1450, 1370, 1100 cm^{-1}. $[\alpha]_D^{22}$=+28.1 ($CHCl_3$, *c* 0.01). HR-ESI-MS: *m*/*z* calcd for $C_{22}H_{27}N_2O_2$: 351.2072, $[M+H]^+$; found 351.2073.

4.2.6. 2-[1-(2-Methoxy-1-phenylethyl)-2-methyl-3-phenylaziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (−)-3f. Yield: 127.4 mg (35%), white solid, mp 66–68 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 1.20 (s, 3H), 1.38 (s, 6H), 3.27 (s, 3H), 3.55 (s, 1H), 3.67–3.78 (m, 3H), 4.04 (s, 2H), 7.14–7.31 (m, 8H), 7.45–7.50 (m, 2H). ^{13}C NMR (100.62 MHz): δ 17.0, 28.0, 28.3, 43.9, 48.6, 58.9, 64.8, 67.2, 77.0, 78.6, 126.4, 127.2, 127.4, 127.5, 127.9, 128.2, 136.4, 140.6, 163.4. GC–MS (70 eV) *m*/*z* (rel. int.): 364 (4, M^+), 332 (6), 317 (8), 238 (43), 91 (100). IR (film): 3030, 2960, 2910, 2880, 1645, 1450, 1310, 1130, 750, 700 cm^{-1}. $[\alpha]_D^{22}$=−43.6 ($CHCl_3$, *c* 0.05). HR-ESI-MS: *m*/*z* calcd for $C_{23}H_{29}N_2O_2$: 365.2229, $[M+H]^+$; found 365.2221.

4.2.7. 2-[1-(2-Methoxy-1-phenylethyl)-3-phenylaziridin-2-yl]pyridine (+)-3g. Yield: mg 198.0 (60%), white solid, mp 110–111 °C (petroleum ether). ^{1}H NMR (400.13 MHz): δ 3.07 (d, 1H, J=6.8 Hz), 3.22 (dd, 1H, J=5.5, 6.9 Hz), 3.28 (s, 3H), 3.46 (d, 1H, J=6.8 Hz), 3.73 (dd, 1H, J=5.5, 9.7 Hz), 3.86 (dd, 1H, J=6.9, 9.7 Hz), 6.97–7.54 (m, 13H), 8.39 (d, 1H, J=4.8 Hz). ^{13}C NMR (100.62 MHz): δ 46.9, 51.3, 59.2, 73.7, 78.0, 121.5, 122.3, 126.4, 127.5, 127.7, 127.9, 128.0, 128.4, 135.5, 135.9, 140.3, 148.7, 157.0. GC–MS (70 eV) *m*/*z* (rel. int.): 330 (1, M^+), 285 (9), 207 (26), 195 (100), 182 (24), 180 (20), 92 (53). IR ($CHCl_3$): 3060, 2950, 1590, 1460, 1100 cm^{-1}. $[\alpha]_D^{22}$=+22.4 ($CHCl_3$, *c* 0.02). HR-ESI-MS: *m*/*z* calcd for $C_{22}H_{23}N_2O$: 331.1810, $[M+H]^+$; found 331.1805.

4.2.8. 4-[1-(2-Methoxy-1-phenylethyl)-3-phenylaziridin-2-yl]pyridine (+)-3h. Yield: 99 mg (30%), white solid, mp 72–74 °C (*n*-hexane). ^{1}H NMR (400.13 MHz): δ 3.01 (d, 1H, J=6.7 Hz), 3.20 (dd, 1H, J=4.7, 7.7 Hz), 3.26 (d, 1H, J=6.7 Hz), 3.29 (s, 3H), 3.70 (dd, 1H, J=4.7, 9.5 Hz), 3.83 (dd, 1H, J=7.7, 9.5 Hz), 7.05 (s, 5H), 7.16 (d, 2H, J=3.8 Hz), 7.26 (d, 1H, J=8.0 Hz), 7.32 (t, 2H, J=7.3 Hz), 7.50 (d, 2H, J=7.3 Hz), 8.37 (s, 2H). ^{13}C NMR (100.62 MHz): δ 46.7 49.0, 59.2, 73.9, 78.3, 123.2, 126.7, 127.5, 127.6, 127.7, 127.8, 128.4, 129.8, 135.4, 139.8, 148.9. GC–MS (70 eV) *m*/*z* (rel. int.): 330 (1, M^+), 195 (100), 167 (10), 91 (7). IR ($CHCl_3$): 3060, 3020, 2910, 2880, 1600, 1490, 1450, 1420, 1190, 1120, 900, 730, 700 cm^{-1}. $[\alpha]_D^{22}$=+40.0 ($CHCl_3$, *c* 0.07). HR-ESI-MS: *m*/*z* calcd for $C_{22}H_{23}N_2O$: 331.1810, $[M+H]^+$; found 331.1806.

4.2.9. 2-[1-(2-Methoxy-1-phenylethyl)-3-phenylaziridin-2-yl]-4-methyl-thiazole (−)-3a. Yield: 157.5 mg (45%), yellow solid, mp, spectroscopic data, GC–MS and HR-ESI-MS data are the same of those reported for the enantiomer (+)-**3a**. $[\alpha]_D^{22}$=−12.6 ($CHCl_3$, *c* 0.06).

4.2.10. 2-[1-(2-Methoxy-1-phenylethyl)-3-phenylaziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (−)-3e. Yield: 182 mg (52%), white solid, mp, spectroscopic data, GC–MS and HR-ESI-MS data are the same of those reported for the enantiomer (+)-**3e**. $[\alpha]_D^{22}$=−29.3 ($CHCl_3$, *c* 0.01).

4.2.11. 2-[1-(2-Methoxy-1-phenylethyl)-2-methyl-3-phenylaziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (+)-3f. Yield: 112.84 mg (31%), white solid, mp, spectroscopic data, GC–MS and HR-ESI-MS data are the same of those reported for the enantiomer (−)-**3f**. $[\alpha]_D^{22}$=+43.1 ($CHCl_3$, *c* 0.04).

4.2.12. 2-[3-Phenyl-1-(1-phenylethyl)-aziridin-2-yl]-4-methylthiazole (+)-4a. Overall yield: 160 mg (50%), yellow oil. Inseparable mixture of two *cis*-configurated diastereomeric aziridines (dr=4/1 by ^{1}H NMR of the crude product). $[\alpha]_D^{22}$=+14.1 ($CHCl_3$, *c* 0.07).

Major diastereomer. ^{1}H NMR (400.13 MHz): δ 1.55 (d, 3H, J=6.5 Hz), 2.32 (s, 3H), 3.05 (q, 1H, J=6.5 Hz), 3.19 (d, 1H, J=6.4 Hz), 3.39 (d, 1H, J=6.4 Hz), 6.59 (s, 1H), 7.07–7.25 (m, 6H), 7.34 (t, 2H, J=7.6 Hz), 7.50 (d, 2H, J=7.3 Hz). ^{13}C NMR (100.62 MHz): δ 16.9, 23.0, 46.6, 50.0, 70.0, 113.3, 126.9, 127.0, 127.3, 127.6, 128.3, 128.4, 135.0, 143.6, 152.3, 168.0. GC–MS (70 eV) *m*/*z* (rel. int.): 320 (1, M^+), 215 (100), 200 (4), 188 (9), 112 (25). HR-ESI-MS: *m*/*z* calcd for $C_{20}H_{21}N_2S$: 321.1425, $[M+H]^+$; found 321.1428. IR (film): 3060, 3020, 2910, 2840, 1720, 1600, 1440, 740, 700 cm^{-1}.

Minor diastereomer. ^{1}H NMR (400.13 MHz): δ 1.55 (d, 3H, J=6.5 Hz), 2.32 (s, 3H), 3.05 (q, 1H, J=6.5 Hz), 3.26 (d, 1H, J=6.4 Hz), 3.31 (d, 1H, J=6.4 Hz), 6.46 (s, 1H), 7.07–7.25 (m, 6H), 7.34 (t, 2H, J=7.6 Hz), 7.44 (d, 2H, J=7.3 Hz). ^{13}C NMR (100.62 MHz): δ 17.0, 22.7, 46.6, 50.0, 70.0, 113.2, 126.9, 127.1, 127.3, 127.5, 128.2, 128.4, 135.1, 143.6, 152.2, 167.9. For IR, GC–MS and HR-ESI-MS see Major diastereomer.

4.2.13. 2-[2-Methyl-3-phenyl-1-(1-phenylethyl)-aziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (+)-4f. Overall yield: 183.7 mg (55%), colorless oil. A diastereomeric mixture of two (2′*R* *,3′*S* *)-configurated aziridines separable by column chromatography (silica gel, petroleum ether/Et_2O 7/3) formed; dr 2/1.

Major diastereomer. 119.0 mg, oil. ^{1}H NMR (400.13 MHz): δ 0.95 (s, 3H), 1.05 (s, 3H), 1.55 (d, 3H, J=6.4 Hz), 1.80 (s, 3H), 2.71 (s, 1H), 3.49 (q, 1H, J=6.4 Hz), 3.54 (d, 1H, J=7.0 Hz), 3.63 (d, 1H, J=7.0 Hz), 7.1–7.5 (m, 10H). ^{13}C NMR (100.62 MHz): δ 14.3, 24.2, 28.0, 28.1, 45.4, 51.9, 61.8, 66.9, 78.7, 126.6, 127.0, 127.2, 127.3, 127.4, 128.2, 136.8, 144.4, 164.5. GC–MS (70 eV) *m*/*z* (rel. int.): 334 (1, M^+), 229 (100), 174 (40), 104 (54). IR ($CHCl_3$): 3060, 2940, 2850, 1640, 1450, 1360 cm^{-1}. $[\alpha]_D^{22}$=+36.0 ($CHCl_3$, *c* 0.03). HR-ESI-MS: *m*/*z* calcd for $C_{22}H_{27}N_2O$: 335.2123, $[M+H]^+$; found 335.2119.

Minor diastereomer. 64.3 mg, oil. ^{1}H NMR (400.13 MHz):

δ 0.91 (s, 3H), 0.94 (s, 3H), 1.44 (s, 3H), 1.52 (d, 3H, J=6.4 Hz), 2.88 (s, 1H), 3.46 (d, 1H, J=7.9 Hz), 3.51 (q, 1H, J=6.4 Hz), 3.63 (d, 1H, J=7.9 Hz), 7.2–7.3 (m, 8H), 7.45 (d, 1H, J=7.5 Hz), 7.57 (d, 1H, J=7.5 Hz). ^{13}C NMR (100.62 MHz): δ 14.3, 25.0, 27.9, 28.0, 29.7, 45.0, 52.8, 66.9, 78.6, 126.4, 126.5, 126.7, 126.9, 127.7, 128.2, 137.0, 145.2, 164.4. $[\alpha]_D^{22}$=+24.3 ($CHCl_3$, c 0.02). For IR, GC–MS and HR-ESI-MS see Major diastereomer.

4.2.14. 2-[3-Phenyl-1-(1-phenylethyl)-aziridin-2-yl]-4-methylthiazole (−)-4a. Inseparable mixture of two *cis*-configurated diastereomeric aziridines (dr=4/1 by ^{1}H NMR of the crude product). Overall yield: 169.6 mg (53%), yellow oil. $[\alpha]_D^{22}$=−13.5 ($CHCl_3$, c 0.08). Spectroscopic data, GC–MS and HR-ESI-MS data are the same of those reported for the mixture of the corresponding enantiomers (+)-**4a**.

4.2.15. 2-[2-Methyl-3-phenyl-1-(1-phenylethyl)-aziridin-2-yl]-4,4-dimethyl-4,5-dihydrooxazole (−)-4f. A diastereomeric mixture of two ($2'R^*$,$3'S^*$)-configurated aziridines separable by column chromatography (silica gel, petroleum ether/Et_2O 7/3) formed; dr 2/1. Overall yield: 173.7 mg (52%), colorless oil. Spectroscopic data, GC–MS and HR-ESI-MS data are the same of those reported for the two corresponding enantiomers (+)-**4f**.

Major diastereomer. $[\alpha]_D^{22}$=−35.3 ($CHCl_3$, c 0.03).

Minor diastereomer. $[\alpha]_D^{22}$=−25.9 ($CHCl_3$, c 0.02).

4.3. General procedure for the preparation of deuterated and methylated thiazolyl aziridines [5, 6, and (+)-3b]

To a stirred solution of 1 mmol of (+)-**3a**, or (+)-**4a** in THF (30 mL) at −78 °C, *n*-BuLi (2.5 M in hexanes, 1 mL, 2.5 mmol) was added dropwise under nitrogen. The resulting mixture was stirred at −78 °C for 1 h, and then 1.5 mmol of D_2O or CH_3I was added and the reaction was warmed up to room temperature and quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 1:1) to afford the pure deuterated or methylated aziridines **5**, **6**, and (+)-**3b**; yields: 50–90%.

4.3.1. 2-[2-Deutero-1-(2-methoxy-1-phenylethyl)-3-phenyl-aziridin-2-yl]-4-methylthiazole (5). Yield: 315.9 mg (90%), (90%D), yellow oil. The IR and ^{13}C NMR data are the same of compound (+)-**3a**. In the ^{1}H NMR spectrum the doublet at 3.12 ppm becomes a singlet, while the doublet at 3.62 ppm almost disappears. GC–MS (70 eV) m/z (rel. int.): 351 (1, M^+), 216 (100), 189 (7), 113 (17). HR-ESI-MS: m/z calcd for $C_{21}H_{22}DN_2OS$: 352.1594, $[M+H]^+$; found 352.1589. $[\alpha]_D^{22}$=+13.3 ($CHCl_3$, c 0.07).

4.3.2. 2-[2-Deutero-3-phenyl-1-(1-phenylethyl)-aziridin-2-yl]-4-methylthiazole (6). Inseparable mixture of two *cis*-configurated diastereomeric aziridines (dr=4/1) both 95%D. Overall yield: mg 288.9 (90%), yellow oil. IR and ^{13}C NMR data are the same of compound (+)-**4a**.

Major diastereomer. In the ^{1}H NMR spectrum the doublet at 3.19 ppm becomes a singlet, while the doublet at 3.39 ppm disappears. GC–MS (70 eV) m/z (rel. int.): 321 (0, M^+), 216 (100), 201 (11), 113 (15). HR-ESI-MS: m/z calcd for $C_{20}H_{20}DN_2S$: 322.1488, $[M+H]^+$; found 322.1481.

Minor diastereomer. In the ^{1}H NMR spectrum the doublet at 3.26 ppm becomes a singlet, while the doublet at 3.31 ppm disappears. For GC–MS and HR-ESI-MS see Major diastereomer.

4.3.3. 2-[1-(2-Methoxy-1-phenylethyl)-2-methyl-3-phenylaziridin-2-yl]-4-methylthiazole (+)-3b. Yield: 182 mg (50%), yellow solid, mp, spectroscopic data, GC–MS and HR-ESI-MS data are the same of those above-reported for this compound. $[\alpha]_D^{22}$=+23.9 ($CHCl_3$, c 0.06).

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References and notes

1. Baldwin, J. E.; Farthing, C. N.; Russel, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761–3764.
2. Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron* **1994**, *35*, 1653–1656.
3. (a) Deyrup, J. A. *The chemistry of heterocyclic compounds*; Hassner, A., Ed.; Wiley: New York, 1983; Vol. 42, pp 1–124. (b) Pearson, W. H.; Lion, B. W.; Bergmeier, S. C. *Comprehensive heterocyclic chemistry II*; Padwa, A., Ed.; Pergamon: Oxford, 1996; Vol. 1A, pp 1–60. (c) Rai, K. M. L.; Hassner, A. *Comprehensive heterocyclic chemistry II*; Padwa, A., Ed.; Pergamon: Oxford, 1996; Vol. 1A, pp 61–96.
4. Contrill, A. A.; Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron* **1998**, *54*, 2181–2208.
5. (a) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599–619. (b) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*(11), 1693–1715. (c) Mc Coull, W.; Davis, F. A. *Synthesis* **2000**(10), 1347–1365.
6. (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. (b) Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607–1608. (c) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941–6942. (d) Alezra, V.; Bonin, M.; Micouin, L.; Policar, C.; Husson, H.-P. *Eur. J. Org. Chem.* **2001**, 2589–2594.
7. Reutrakul, V.; Prapansiri, V.; Panyachotipun, C. *Tetrahedron Lett.* **1984**, *25*, 1949.

8. (a) Seebach, D.; Haner, R. *Chem. Lett.* **1987**, 49. (b) Haner, R.; Olano, B.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1676.
9. (a) Florio, S.; Troisi, L.; Capriati, V. *J. Org. Chem.* **1995**, *60*, 2279–2282. (b) Florio, S.; Troisi, L.; Capriati, V. *Tetrahedron Lett.* **1998**, *39*, 7951–7954. (c) Florio, S.; Troisi, L.; Capriati, V.; Ingrosso, G. *Tetrahedron Lett.* **1999**, *40*, 6101–6104. (d) Bona, F.; De Vitis, L.; Florio, S.; Ronzini, L.; Troisi, L. *Tetrahedron* **2003**, *59*, 1381–1387, and ref. therein.
10. (a) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, *1*, 13–16. (b) Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781–4784. (c) Dondoni, A. In *Modern synthetic methods*; Scheffold, R., Ed.; Helvetica Chimica Acta: Basel, Switzerland, 1992; pp 377–473.
11. Dondoni, A.; Perrone, D. *Aldrichim. Acta* **1997**, *30*, 35–46.
12. Luisi, R.; Capriati, V.; Florio, S.; Ranaldo, R. *Tetrahedron Lett.* **2003**, *44*, 2677–2681.
13. Wartski, L. *Bull. Soc. Chim. Fr.* **1975**, 1663.
14. Alvernhe, G.; Laurent, A. *Bull. Soc. Chim. Fr.* **1970**, *8-9*, 3003–3010.
15. Kingsbury, C. A.; Durham, D. L.; Hutton, R. *J. Org. Chem.* **1978**, *43*, 4696–4700.
16. CCDC 212745 contain the supplementary crystallographic data (excluding structure factors) for compound (+)-**3b**. These data can be obtained free of charge via www.ccdc.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336-033; or deposit@ccdc.cam.ac.uk).
17. Yonezawa, T.; Morishima, I. *J. Mol. Spectry* **1968**, *27*, 210.
18. The observed $^{1}J_{CH}$ value of 167.2 Hz found for the aziridine C–H bond also testified a trans relationship between this bond and the nitrogen lone pair as described in Ref. 17. This same orientation of the nitrogen lone pair was also spectroscopically confirmed ($^{1}J_{CH}$=162.7 Hz) in the case of compound (+)-**3b**.
19. All calculations and graphical representations were performed by SPARTAN, Version 02, Wavefunction, Inc., Irvine, CA, USA, 2002.
20. Suffert, J. *J. Org. Chem.* **1989**, *54*, 509–512.
21. (a) Chikashita, H.; Ikegami, S.; Okumura, T.; Itoh, K. *Synthesis* **1986**, *5*, 375–377. (b) Zubarovskii, V. M. *Zhr. Obsch. Khim.* **1954**, *24*, 1664. *Chem Abstr.* **1955**, *49*, 13223. (c) Altamura, M.; Perrotta, E. *J. Org. Chem.* **1993**, *58*, 272–274. (d) Florio, S.; Granito, C.; Ingrosso, G.; Troisi, L. *Eur. J. Org. Chem.* **2000**, 3465–3472, and ref. therein.
22. Capriati, V.; Florio, S.; Ingrosso, G.; Granito, C.; Troisi, L. *Eur. J. Org. Chem.* **2000**, 478–484, and references therein cited.
23. (a) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570–1572. (b) De Kimpe, N.; De Cock, W.; Stevens, C. *Tetrahedron* **1992**, *48*, 2739–2760.
24. Smith, A. B.; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879–10888.

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Asymmetric transformation of chiral auxiliary-substituted *N*-acyl-α-dehydro(1-naphthyl)alanines into 3,4-dihydrobenzo[*f*]quinolinone derivatives via photoinduced electron transfer

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Abstract—Electron transfer-initiated photocyclizations of the title compounds [(*Z*)-**1**] with an (*S*)-alanine methyl ester auxiliary in methanol containing a tertiary amine were found to give (*S*,*S*)- and (*R*,*S*)-3,4-dihydrobenzo[*f*]quinolinones (**2**) as major products. The magnitude of diastereomeric excess (de) for (*S*,*S*)-**2** was varied from 0 to 55%, depending on the properties of the amine and solvent employed. The mechanism of asymmetric induction in the photocyclization process eventually affording **2** was discussed based on solvent, tertiary amine and temperature effects on the de value.
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1. Introduction

Organic photochemistry has continued to contribute to the development of efficient and selective transformations for the preparation of complicated molecules which could not have been synthesized by conventional methods.[1] There are many cases where the products derived from photocyclization and photoaddition reactions of organic compounds are formed via prochiral intermediates. Thus far, much attention has been given to developing novel asymmetric reactions utilizing these photoreactions in liquid and solid phases.[2–4] Many asymmetric photoreactions giving chiral products in high enantio- and diastereoselectivities have been reported in recent years.[4] However, there are only a few asymmetric photoreactions of synthetic utility, especially in liquid phase. In the course of our systematic study regarding photoinduced electron transfer (ET) reactions of α-dehydroamino acid derivatives, we found that ET-initiated photocyclizations of *N*-acyl-α-dehydro(1-naphthyl)alanines in methanol containing triethylamine (TEA) give racemic 3,4-dihydrobenzo[*f*]quinolinones.[5] The fact that many heterocyclic compounds having the dihydroquinolinone ring exhibit pharmacological and physiological activities allows us to expect such an activity also for chiral dihydrobenzoquinolinones.[6] Thus, the incorporation of a chiral auxiliary into the starting α-dehydro(1-naphthyl)-alanine derivative makes it possible to develop novel asymmetric photoreactions enabling the construction of chiral dihydrobenzoquinolinone ring in liquid phase and then to shed some light on the mechanism of ET-initiated photocyclizations found by us. For these ends we synthesized (*Z*)-*N*-acyl-α-dehydro(1-naphthyl)alanines [(*Z*)-**1a–c**] having an (*S*)- or (*R*)-alanine methyl ester auxiliary and investigated the effects of chiral auxiliary, tertiary amine, solvent and temperature on the magnitude of diastereomeric excess (de).

2. Results and discussion

The starting (*Z*)-**1a–c** were prepared in good yields by the ring-opening reactions of (*Z*)-1-naphthyl-substituted oxazolones with (*S*)-alanine (**1a**,**b**) or (*R*)-alanine (**1c**) methyl ester.[7] After a nitrogen-purged methanol solution of (*Z*)-**1a** (3.75×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 400 W high-pressure Hg lamp for 70 min at room temperature, the product mixture obtained was subjected to column chromatography over silica gel, which allowed us to isolate the starting (*Z*)-**1a** (yield, 8.1%), (*E*)-**1a** (4.0%), a mixture of (*S*,*S*)-**2a** and (*R*,*S*)-**2a** (32.9%), and benzo[*f*]isoquinoline derivative (**3a**) (21.8%) (Scheme 1). The structures of isolated products were determined based on their spectroscopic and physical properties and were confirmed by the $^{1}H-^{1}H$ and $^{13}C-^{1}H$ COSY spectra of these products. The same product distribution was obtained

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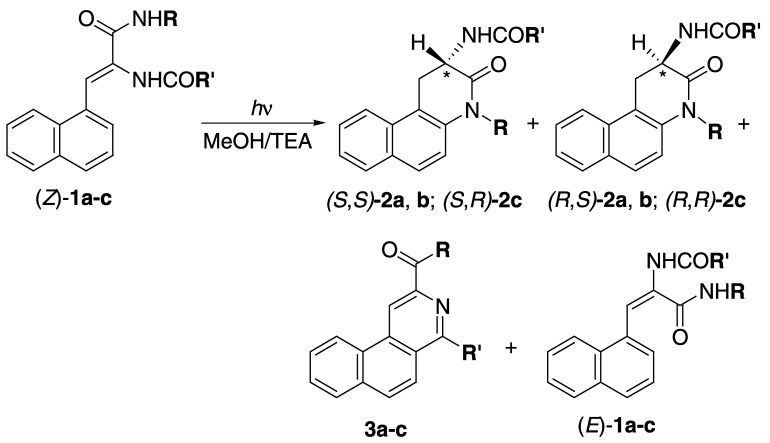


1a (**R**= (*S*)-*CH(Me)CO_2Me, **R'**= Me), **1b** (**R**= (*S*)-*CH(Me)CO_2Me, **R'**= Ph), **1c** (**R**= (*R*)-*CH(Me)CO_2Me, **R'**= Me)

Scheme 1.

also by the 150 min irradiation of (*Z*)-**1b** (3.75×10^{-3} mol dm^{-3}), and (*Z*)-**1b** (yield, 4.5%), (*E*)-**1b** (4.0%) and diastereomeric mixtures of **2b** (34.4%) were isolated by usual workup of the **1b**-derived reaction mixture. The very low ^{1}H NMR yield of **3b** (1.5%) made its isolation virtually impossible. The diastereomeric mixture of (*S*,*S*)-**2a**,**b** and (*R*,*S*)-**2a**,**b** could be separated by repeated preparative TLC (silica gel). From a ^{1}H NMR spectral analysis of each diastereomer of **2a**,**b** we see that the methine proton signals in the chiral auxiliary of each diastereomer are detected at different positions (5.26 and 5.04 ppm for **2a**; 5.35 and 5.16 ppm for **2b**). An X-ray structural analysis of single crystal derived from the diastereomer of **2b** (showing its methine proton signal at 5.16 ppm) revealed that the asymmetric carbon in the dihydroquinolinone ring has the (*R*)-configuration (Fig. 1). Furthermore, a comparison of circular dichroism (CD) spectra of the (*R*,*S*)-**2b** and (*S*,*S*)-**2b** confirmed that the dihydroquinolinone ring having (*R*)- and (*S*)-configurations gives CD bands of positive and negative signs at 250 nm, respectively (Fig. 2). Thus, the absolute configuration of the asymmetric carbon in the ring can be definitely determined by ^{1}H NMR and CD spectral analyses of a given diastereomer and, additionally, the area ratio of the methine proton signals (detected at 5.26 [(*S*,*S*)-**2a**], 5.35 [(*S*,*S*)-**2b**], 5.04 [(*R*,*S*)-**2a**], and 5.16 ppm [(*R*,*S*)-**2b**]) allows us to estimate the magnitude of de.

In Table 1 are summarized conversion of (*Z*)-**1**, selectivity for **2**, and % de obtained after the 5 h irradiation in methanol at room temperature. Although steric bulkiness of the chiral auxiliary R lowers the selectivity for **2** as compared to R=Me (88→49%),[5] the presence of the (*S*)-alanine auxiliary resulted in a preferential formation of (*S*,*S*)-**2a** (de=9%). The observation that the irradiation of (*Z*)-**1c** possessing the (*R*)-alanyl group under the same conditions

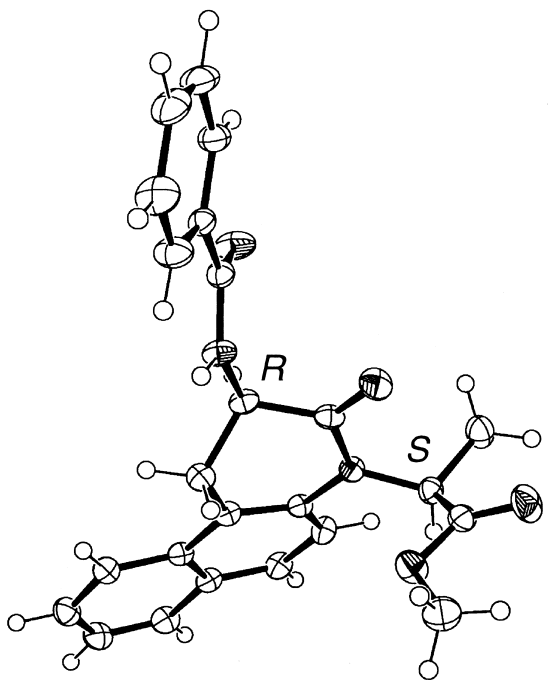


Figure 1. ORTEP drawing of (*R*,*S*)-**2b**.

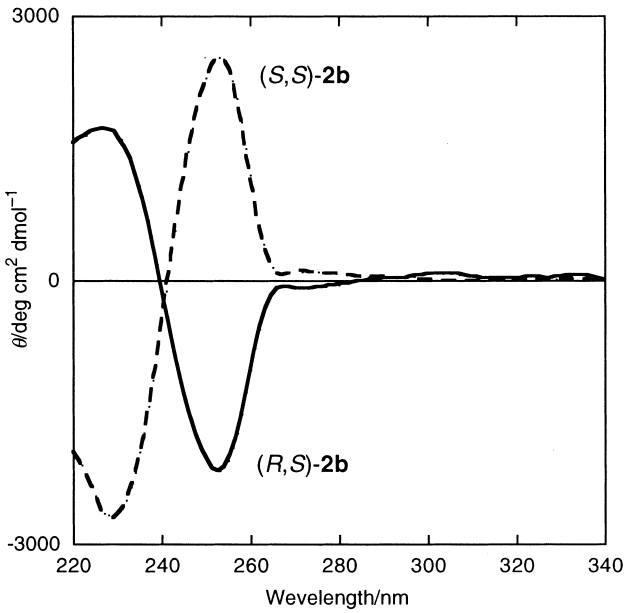


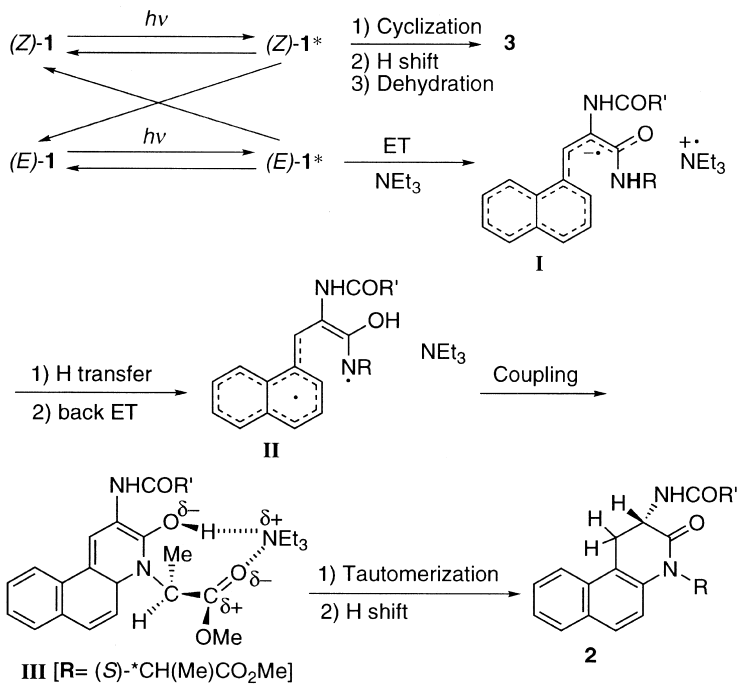
Figure 2. Circular dichroism spectra of (*S*,*S*)-**2b** and (*R*,*S*)-**2b** (4.0×10^{-5} mol dm^{-3}) in MeOH at room temperature.

Table 1. Chiral auxiliary, tertiary amine, temperature and solvent effects on the conversion of (*Z*)-**1**, selectivity or **2**, and diasterermeric excess for (*S*,*S*)-**2** or (*R*,*R*)-**2** obtained by the 5 h irradiation of (*Z*)-**1** (3.75×10^{-3} mol dm^{-3})

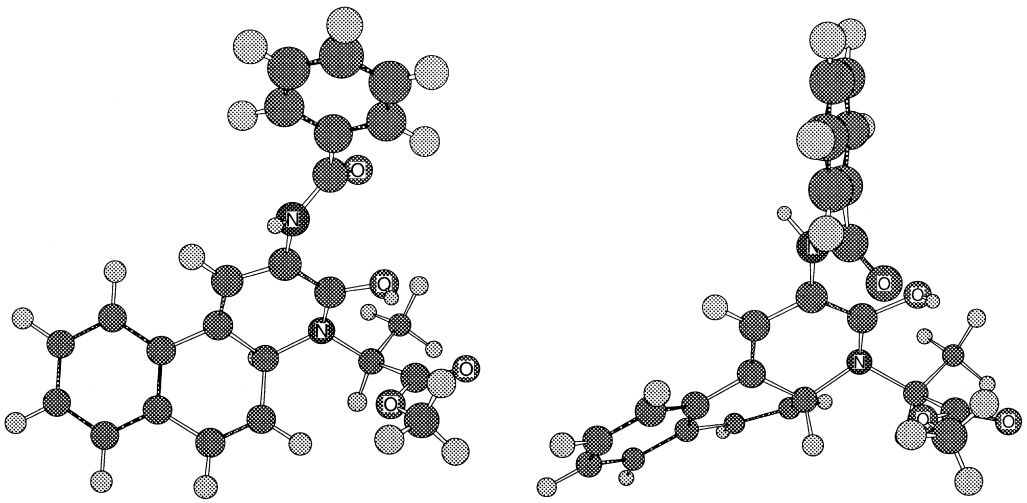
(*Z*)-**1**	Tertiary amine	Solvent	Temperature (°C)	Conversion (%)[a]	Selectivity (%)[b]	(*S*,*S*)-**2** (%)[c]	(*R*,*S*)-**2** (%)[c]	de (%)
1a	TEA	MeOH	25	79	49	54.5	45.5	9
1b	TEA	MeOH	25	46	45	56.5	43.5	13
1c	TEA	MeOH	25	79	39	54.5[d]	45.5[e]	9
1a	TMA[f]	MeOH	25	72	48	59.0	41.0	18
1a	MP[g]	MeOH	25	74	52	65.5	34.5	31
1a	PEP[h]	MeOH	25	65	55	50.0	50.0	0
1b	MP	MeOH	25	70	20	67.5	32.5	35
1a	TEA	MeOH	−30	63	64	57.0	43.0	14
1a	TEA	MeOH	−78	65	90	55.5	44.5	11
1a	TEA	MeOH–MeCN (1:1 v/v)	25	82	30	63.0	37.0	26
1a	TEA	MeOH–MeCN (1:9 v/v)	25	63	9	77.5	22.5	55
1a	MP	MeOH–MeCN (1:9 v/v)	25	67	13	72.0	28.0	44

[a] Conversion was estimated by subtracting the sum of composition of (*Z*)-**1** and (*E*)-**1** from 100.
[b] Selectivity for **2** was evaluated by dividing the composition of **2** by the sum of the composition of each photoproduct, where the composition of (*E*)-**1** was excluded from the calculation of this selectivity.
[c] Composition in a mixture of both diastereomers.
[d] (*R*,*R*)-**2c**.
[e] (*S*,*R*)-**2c**.
[f] Timethylamine.
[g] l-Methylpiperidine.
[h] *N*-Isopropyl-*N*-ethylisopropylamine.

gives preferentially (*R*,*R*)-**2c** in the same de demonstrates the occurrence of asymmetric induction in the cyclization process eventually yielding **2**. It was suggested in the previous study that the asymmetric carbon at the 3-position in the dihydrobenzoquinolinone ring is generated by tautomerization of the enol intermediate **III** (formed via the biradical intermediate **II**), as shown in Scheme 2.[5] Evidence in support of this suggestion comes from the fact that deuterium attached to the alanine auxiliary-substituted amide nitrogen is transferred to the 3-position in the quinolinone ring on irradiation in MeOD as well as in acetonitrile.[5] Furthermore, a ^{1}H NMR spectral analysis of a CD_3OD solution of (*S*,*S*)- or (*R*,*S*)-**2** containing TEA (0.10 mol dm^{-3}), which was permitted to stand for 12 h at room temperature, showed no occurrence of the racemization of each diastereomer. This result confirms that the asymmetric protonation takes place on forming the dihydroquinolinone ring. An inspection of the ORTEP drawing for (*R*,*S*)-**2b** indicates the methoxycarbonyl group in the (*S*)-alanyl moiety to be directed preferentially to one of the two diastereofaces and, hence, allows us to expect that there are differences in the extent of hydrogen-bonding and electronic interactions of TEA with **III** between two diastereofaces. Taking into account that the cyclization of **II** forms two stereoisomers **IIIA** and **IIIB** (Fig. 3), conformations of (*S*)-alanine auxiliary in these two stereoisomers are optimized through MM2 and PM5 calculations. Figure 3 shows that the conformation of each (*S*)-alanine auxiliary is



Scheme 2.



IIIA **IIIB**

Figure 3. Energy-minimized conformation of **IIIA** and **IIIB**.

very similar to that for (*R*,*S*)-**2b** in the solid state, strongly suggesting that the enol intermediate **III** adopts a similar conformation in solution. Accordingly, we are able to provide a good explanation for factors that control the observed asymmetric induction by invoking more favorable hydrogen-bonding and electronic interactions (shown in Scheme 2) in one diastereoface than in the other. The nitrogen atom in a TEA molecule is positively charged by forming a hydrogen bond to the hydroxy hydrogen of the enol intermediate **III** and its nitrogen is stabilized through an electrostatic interaction with the methoxy and/or carbonyl oxygen in the alanine auxiliary. As evident from Figure 3, the hydroxy proton adds to the olefinic carbon preferentially from one diastereoface to give (*S*,*S*)-diastereomer in excess. Asymmetric transformation of (*Z*)-**1b** into (*S*,*S*)-**2b** was achieved in a similar de (Table 1).

Since TEA as an electron donor is considered to exist in the very vicinity of a given substrate during the photocyclization process, Scheme 2 allows us to predict that the magnitude of de for (*S*,*S*)-**2a** strongly depends on the steric bulkiness about the tertiary amino nitrogen, namely, a decrease in this bulkiness results in an enhanced de by strengthening hydrogen-bonding and electrostatic interactions described above and an increase in the bulkiness gives the reverse result. The finding that the de value is increased in the following order: PEP$\ll$TEA$<$TMA$<$MP is consistent with our prediction (Table 1) and, hence, substantiates the mechanism for the observed asymmetric induction. If we consider that reaction temperature exerts a great effect on the extent of hydrogen-bonding interaction, an examination of temperature effects on the de value may shed some light on the mechanism of the asymmetric photocyclization of (*Z*)-**1**. Although this value was not much influenced by temperature, pronounced temperature effects on the selectivity for **2** was observed (49$\rightarrow$90%). It is very likely that an increase in the polarity and hydrogen-bonding solvation ability of methanol contributes to an increase in the selectivity. Because a decrease in temperature may enhance the ability of TEA to form hydrogen bonds with the enol intermediate **III** and methanol to almost the same extent, it is reasonable to conclude that hydrogen-bonding interaction between TEA and methanol lowers the magnitude of de for (*S*,*S*)-**2**. If we accept these considerations, the use of acetonitrile as a co-solvent is predicted to strengthen hydrogen-bonding and electrostatic interactions between the tertiary amino nitrogen and the enol **III** and, hence, to result in a net increase in de for (*S*,*S*)-**2**. In Table 1 are collected the results obtained for the (*Z*)-**1a**-TEA and (*Z*)-**1a**-MP systems. As predicted, the de value increases with an increase in concentration of the aprotic polar solvent, providing additional proof of the mechanism for asymmetric induction in our systems.

3. Conclusions

It was found that the irradiation of α-dehydronaphthylalanines having (*S*)-alanine auxiliary in methanol containing a tertiary amine preferentially gives (*S*,*S*)-dihydrobenzoquinolinones. The use of a mixture of acetonitrile and methanol as a solvent increased de for these quinolinones up to 55%. Analyses of tertiary amine and solvent effects on the magnitude of de strongly suggested that hydrogen-bonding and electrostatic interactions between a given tertiary amine and the enol intermediate play an important role in bringing about the asymmetric photocyclization of (*S*)-alanine methyl ester-substituted α-dehydro(1-naphthyl)alanine derivatives.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR and IR spectra were taken with a JEOL JNM-A500 spectrometer and a Hitachi 270-30 infrared spectrometer, respectively. Chemical shifts were determined using tetramethylsilane as an internal standard. UV absorption spectra were recorded on a Shimadzu UV-2200 spectrophotometer. A cell with a 10 mm pathlength was used. Circular dichroism spectra were recorded on a Nihonbunko J-600 spectropolarimeter. The optical rotations were measured on a Nihonbunko DIP-370 polarimeter.

Elemental analyses were performed on a Perkin–Elmer PE2400 series II CHNS/O analyzer. MeOH and MeCN were purified according to the standard procedures and freshly distilled prior to use. TEA was fractionally distilled from sodium hydroxide. All other reagents used were obtained from commercial sources and were of the highest grade available. MM2 and PM5 calculations were accomplished by using CAChe 5.0 for Windows available from Fujitsu Ltd, 2002.

4.2. General procedure for the synthesis of (*Z*)-2-methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone and (*Z*)-4-(1-naphthylmethylene)-2-phenyl-5(4*H*)-oxazolone

N-Acetylglycine or *N*-benzoylglycine (0.087 mol), 1-naphthaldehyde (16.1 g, 0.103 mol), and sodium aceate (5.3 g, 0.067 mol) were added to acetic anhydride (100 mL) and the resulting mixture was heated at 75–85 °C for 6 h (*N*-acetylglycine) or 1 h (*N*-benzoylglycine) with stirring. The mixture was cooled with ice and the solid separated out was collected by filtration with suction and washed with water, small amounts of cold EtOH and then with dry hexane. After the crude product had been air-dryed at room temperature, it was recrystallized from hexane–$CHCl_3$ to give yellow crystals (40–50%).

4.2.1. (*Z*)-2-Methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 159.0–160.0 °C. IR (KBr): 1760, 1650, 1260 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.43 (3H, s), 7.54 (1H, dd, *J*=7.3, 7.9 Hz), 7.58 (1H, dd, *J*=7.3, 8.6 Hz), 7.61 (1H, dd, *J*=7.3, 8.6 Hz), 7.88 (1H, d, *J*=7.9 Hz), 7.93 (1H, d, *J*=8.6 Hz), 8.02 (1H, s), 8.24 (1H, d, *J*=8.6 Hz), 8.75 (1H, d, *J*=7.3 Hz).

4.2.2. (*Z*)-2-Phenyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 166.0–167.0 °C. IR (KBr): 1797, 1647, 1167 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (2H, dd, *J*=7.3, 7.6 Hz), 7.55 (1H, dd, *J*=8.6, 8.6 Hz), 7.62 (1H, dd, *J*=7.3, 7.3 Hz), 7.63 (1H, dd, *J*=8.6, 8.6 Hz), 7.64 (1H, dd, *J*=6.7, 8.6 Hz), 7.90 (1H, d, *J*=8.6 Hz), 7.97 (1H, d, *J*=8.6 Hz), 8.13 (1H, s), 8.21 (2H, d, *J*=7.6 Hz), 8.31 (1H, d, *J*=8.6 Hz), 9.03 (1H, d, *J*=6.7 Hz).

4.3. General procedure for the synthesis of (*Z*)-2-acetylamino-*N*-[(*S*)-1-(methoxycarbonyl)ethyl]-3-(1-naphthyl)-2-propenamide [(*Z*)-1a], (*Z*)-2-benzoylamino-*N*-[(*S*)-1-(methoxycarbonyl)ethyl]-3-(1-naphthyl)-2-propenamide [(*Z*)-1b] and (*Z*)-2-acetylamino-*N*-[(*R*)-1-(methoxycarbonyl)ethyl]-3-(1-naphthyl)-2-propenamide [(*Z*)-1c]

(*Z*)-2-Methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone (for **1a**,**c**, 0.010 mol) or (*Z*)-4-(1-naphthylmethylene)-2-phenyl-5(4*H*)-oxazolone (for **1b**, 0.010 mol) was added to dry $CHCl_3$ (30 mL) containing triethylamine (0.012 mol) and (*S*)-alanine methyl ester hydrochloride (for **1a**,**b**, 0.010 mol) or (*R*)-alanine methyl ester hydrochloride (for **1c**, 0.010 mol) and the resulting solution was refluxed for 1–2 h. The reaction mixture was washed with water (50 mL) and then $CHCl_3$ layer was dried over $MgSO_4$. After removal of the solvent under reduced pressure, the solid obtained was recrystallized twice from EtOAc affording colorless crystals (40–60%).

4.3.1. (*Z*)-2-Acetylamino-*N*-[(*S*)-1-(methoxycarbonyl)-ethyl]-3-(1-naphthyl)-2-propenamide [(*Z*)-1a]. Mp 149.0–150.0 °C. IR (KBr): 3220, 3052, 2986, 2950, 1746, 1650, 1632 cm^{-1}. $[\alpha]_D^{25}$=+47.3 (*c*=0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.37 (3H, d, *J*=6.7 Hz), 1.83 (3H, s), 3.66 (3H, s), 4.44 (1H, dq, *J*=6.7, 6.7 Hz), 7.51–7.60 (5H, m), 7.90 (1H, d, *J*=7.9 Hz), 7.94–7.96 (2H, m), 8.47 (1H, d, *J*=6.7 Hz), 9.25 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.9, 22.7, 48.2, 51.9, 124.2, 124.6, 125.5, 126.1, 126.3, 126.4, 128.5 (2C), 131.0, 131.3, 132.0, 133.2, 164.9, 169.4, 173.1. Anal. calcd (found) for $C_{19}H_{20}N_2O_4$: C, 67.05 (67.10); H, 5.92 (6.04); N, 8.23% (8.12%).

4.3.2. (*Z*)-2-Benzoylamino-*N*-[(*S*)-1-(methoxycarbonyl)-ethyl]-3-(1-naphthyl)-2-propenamide [(*Z*)-1b]. Mp 168.5–169.0 °C. IR (KBr): 3256, 3040, 1752, 1632, 1620 cm^{-1}. $[\alpha]_D^{25}$=+55.7 (*c*=0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.39 (3H, d, *J*=7.3 Hz), 3.68 (3H, s), 4.48 (1H, dq, *J*=7.3, 7.3 Hz), 7.43 (2H, dd, *J*=7.3, 7.3 Hz), 7.45 (1H, dd, *J*=7.3, 7.9 Hz), 7.52 (1H, dd, *J*=7.3, 7.3 Hz), 7.55 (1H, dd, *J*=6.7, 7.9 Hz), 7.59 (1H, dd, *J*=6.7, 8.6 Hz), 7.66 (1H, d, *J*=7.3 Hz), 7.77 (1H, s), 7.83 (2H, d, *J*=7.3 Hz), 7.87 (1H, d, *J*=7.9 Hz), 7.94 (1H, d, *J*=7.9 Hz), 8.04 (1H, d, *J*=8.6 Hz), 8.62 (1H, d, *J*=7.3 Hz), 9.74 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.9, 48.2, 51.9, 124.2, 125.4, 126.0, 126.1, 126.4, 126.5, 127.8 (2C), 128.1 (2C), 128.4, 128.5, 131.0, 131.3, 131.5, 131.8, 133.2, 133.8, 164.8, 166.1, 173.0. Anal. calcd (found) for $C_{24}H_{22}N_2O_4$: C, 71.63 (71.47); H, 5.51 (5.30); N, 6.96% (6.80%).

4.3.3. (*Z*)-2-Acetylamino-*N*-[(*R*)-1-(methoxycarbonyl)-ethyl]-3-(1-naphthyl)-2-propenamide [(*Z*)-1c]. Mp 149.0–150.0 °C. IR (KBr): 3220, 3052, 2986, 2950, 1746, 1650, 1632 cm^{-1}. $[\alpha]_D^{25}$=−42.4 (*c*=0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.37 (3H, d, *J*=6.7 Hz), 1.83 (3H, s), 3.66 (3H, s), 4.44 (1H, dq, *J*=6.7, 6.7 Hz), 7.51–7.60 (5H, m), 7.90 (1H, d, *J*=7.9 Hz), 7.94–7.96 (2H, m), 8.47 (1H, d, *J*=6.7 Hz), 9.25 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.9, 22.7, 48.2, 51.9, 124.2, 124.6, 125.5, 126.1, 126.3, 126.4, 128.5 (2C), 131.0, 131.3, 132.0, 133.2, 164.9, 169.4, 173.1. Anal. calcd (found) for $C_{19}H_{20}N_2O_4$: C, 67.05 (66.62); H, 5.92 (5.97); N, 8.23% (7.85%).

4.4. General procedure for the irradiation of (*Z*)-1a–c

For the purpose of analyzing the effects of chiral auxiliary, tertiary amine, and solvent on the magnitude of de, a MeOH or MeOH–MeCN solution (10 mL) of (*Z*)-**1** (3.75×10^{-3} mol dm^{-3}) containing tertiary amine (0.10 mol dm^{-3}) was irradiated under nitrogen at room temperature with Pyrex-filtered light from a 450 W high-pressure Hg lamp for 5.0 h (MeOH solution) or 10 h (MeOH–MeCN solution). After removal of the solvent under reduced pressure, the mixture obtained was dissolved in $CHCl_3$ and washed twice with 0.1 mol dm^{-3} HCl (20 mL). $CHCl_3$ layer was concentrated to dryness in vacuo. The resulting residue was dissolved in DMSO-d_6 and subjected to ^1H NMR spectral analysis. The composition was estimated from the area ratio of a given ^1H NMR signal for each compound. In order to analyze the temperature effect on the magnitude of de, a MeOH solution (100 mL) of (*Z*)-**1a** (3.75×10^{-3} mol dm^{-3}) in the presence of TEA (0.10^{-3} mol dm^{-3}) was irradiated under nitrogen with

Pyrex-filtered light from a 400 W high-pressure Hg lamp at −30 or −78 °C. After 2.0 h irradiation, an appropriate amount of the solution (10 mL) being irradiated was pipetted off and concentrated to dryness in vacuo. The resulting residue was dissolved in DMSO-d_6 and subjected to ^{1}H NMR spectral analysis. For the ^{2}H (D) tracer experiment a MeOD solution (10 mL) of (*Z*)-**1a** (3.75×10^{-3} mol dm^{-3}) was allowed to stand for 12 h in the presence of TEA (0.10 mol dm^{-3}) and then irradiated for 5.0 h. After the solution had been concentrated to dryness, the resulting residue was dissolved in DMSO-d_6 and subjected to ^{1}H NMR spectral analysis.

On the other hand, a solution (500 mL) of (*Z*)-**1a**,**b** (3.75×10^{-3} mol dm^{-3}) in MeOH containing TEA (0.10 mol dm^{-3}), placed in a Pyrex vessel, was irradiated for a given period of time under nitrogen with Pyrex-filtered light from a 400 W high-pressure Hg lamp at room temperature. After 70 min (**1a**) or 150 min (**1b**) irradiation, an appropriate amount of the solution (5 mL) being irradiated was pipetted off and concentrated to dryness in vacuo giving the residue which was subjected to ^{1}H NMR spectral analysis in DMSO-d_6. The remaining solutions of **1a**,**b** were concentrated to dryness under reduced pressure and the resulting residues were subjected to column chromatography over silica gel (230 mesh, Merck) eluting with EtOAc–hexane. For the purpose of isolating each diastereomer of **2a** and **2b**, preparative TLC plate (silica gel) was also used. Physical and spectroscopic properties of (*E*)-**1a**,**b**, (*S*,*S*)-**2a**,**b**, (*R*,*S*)-**2a**,**b** and **3a** are as follows.

4.4.1. (*E*)-1a. Mp 102.0–103.0 °C. IR (KBr): 3276, 3048, 2952, 1740, 1678, 1626 cm^{-1}. $[\alpha]_D^{25}=-46.4$ (c=0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.05 (3H, d, J=6.7 Hz), 2.03 (3H, s), 3.51 (3H, s), 4.26 (1H, dq, J=6.7, 7.3 Hz), 7.40 (1H, dd, J=7.3, 8.6 Hz), 7.44 (1H, d, J=7.3 Hz), 7.46 (1H, s), 7.52 (1H, dd, J=6.7, 7.9 Hz), 7.55 (1H, dd, J=6.7, 7.3 Hz), 7.80 (1H, d, J=8.6 Hz), 7.91 (1H, d, J=7.9 Hz), 8.00 (1H, d, J=7.3 Hz), 8.30 (1H, d, J=7.3 Hz), 9.74 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.4, 23.4, 47.4, 51.7, 114.0, 124.4, 125.4, 125.7, 125.9, 126.0, 127.1, 128.2, 131.2, 132.0, 133.0, 133.8, 164.1, 168.5, 172.3. Anal. calcd (found) for $C_{19}H_{20}N_2O_4$: C, 67.05 (67.04); H, 5.92 (6.06); N, 8.23% (8.48%).

4.4.2. (*E*)-1b. Mp 128.5–130.0 °C. IR (KBr): 3274, 3058, 2950, 1743, 1644 cm^{-1}. $[\alpha]_D^{25}=-45.2$ (c=0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.12 (3H, d, J=6.7 Hz), 3.53 (3H, s), 4.31 (1H, dq, J=6.7, 7.3 Hz), 7.36 (1H, s), 7.44 (1H, dd, J=7.3, 7.9 Hz), 7.53–7.56 (2H, m), 7.54 (2H, dd, J=7.3, 7.3 Hz), 7.57 (1H, dd, J=6.7, 7.9 Hz), 7.61 (1H, d, J=7.3, 7.3 Hz), 7.84 (1H, d, J=7.9 Hz), 7.94 (1H, d, J=7.9 Hz), 7.98 (2H, d, J=7.3 Hz), 8.06 (1H, d, J=7.9 Hz), 8.37 (1H, d, J=7.3 Hz), 10.26 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.5, 47.4, 51.6, 116.9, 124.4, 125.4, 125.7, 126.0, 126.2, 127.3, 127.7 (2C), 128.2, 128.3 (2C), 131.2, 131.5, 131.6, 133.0, 133.8, 133.9, 163.8, 165.0, 172.4. Anal. calcd (found) for $C_{24}H_{22}N_2O_4$: C, 71.63 (71.78); H, 5.51 (5.26); N, 6.96% (6.78%).

4.4.3. (3*S*)-2-Acetylamino-3,4-dihydro-1-[(*S*)-1-(methoxycarbonyl)ethyl]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2a]. Mp 86.0–89.0 °C. IR (KBr): 3316, 3064, 2986, 2950, 1746, 1659, 1635 cm^{-1}. $[\alpha]_D^{25}=+35.2$ (c=0.5, MeOH). CD (MeOH) $[\theta]_{250}=-1488$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.49 (3H, d, J=6.7 Hz), 1.92 (3H, s), 3.01 (1H, dd, J=15.9, 15.3 Hz), 3.60 (1H, dd, J=15.3, 5.5 Hz), 3.60 (3H, s), 4.51 (1H, ddd, J=15.9, 7.9, 5.5 Hz), 5.26 (1H, q, J=6.7 Hz), 7.45 (1H, dd, J=8.3, 7.3 Hz), 7.53 (1H, d, J=9.2 Hz), 7.56 (1H, dd, J=8.6, 7.3 Hz), 7.90 (1H, d, J=9.2 Hz), 7.90 (1H, d, J=8.3 Hz), 8.01 (1H, d, J=8.6 Hz), 8.37 (1H, d, J=7.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.1, 22.6, 27.1, 48.2, 52.1, 53.6, 116.2, 119.1, 123.3, 124.9, 127.2, 128.2, 128.3, 129.9, 130.7, 136.3, 168.3, 169.4, 171.0. Anal. calcd (found) for $C_{19}H_{20}N_2O_4$: C, 67.05 (66.75); H, 5.92 (5.71); N, 8.23% (8.18%).

4.4.4. (3*S*)-2-Benzoylamino-3,4-dihydro-1-[(*S*)-1-(methoxycarbonyl)ethyl]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2b]. Mp 184.0–186.0 °C. IR (KBr): 3404, 2944, 1746, 1680, 1650 cm^{-1}. $[\alpha]_D^{25}=+7.6$ (c=0.5, MeOH). CD (MeOH) $[\theta]_{250}=-2036$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.54 (3H, d, J=6.7 Hz), 3.29 (1H, dd, J=15.2, 14.6 Hz), 3.62 (3H, s), 3.70 (1H, dd, J=15.2, 6.1 Hz), 4.80 (1H, ddd, J=14.6, 8.6, 6.1 Hz), 5.35 (1H, q, J=6.7 Hz), 7.48 (1H, dd, J=7.9, 7.9 Hz), 7.52 (2H, dd, J=7.3, 7.9 Hz), 7.58 (1H, d, J=9.2 Hz), 7.58–7.60 (2H, m), 7.94 (1H, d, J=9.2 Hz), 7.94 (1H, d, J=7.9 Hz), 7.95 (2H, d, J=7.3 Hz), 8.09 (1H, d, J=8.5 Hz), 8.90 (1H, d, J=8.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.1, 26.8, 48.6, 52.1, 53.5, 116.1, 119.1, 123.3, 124.8, 127.2, 127.4 (2C), 128.2, 128.3 (3C), 129.9, 130.6, 131.5, 134.0, 136.3, 166.1, 168.3, 171.0. Anal. calcd (found) for $C_{24}H_{22}N_2O_4$: C, 71.63 (71.80); H, 5.51 (5.34); N, 6.96% (6.59%).

4.4.5. (3*R*)-2-Acetylamino-3,4-dihydro-1-[(*S*)-1-(methoxycarbonyl)ethyl]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2a]. Mp 111.0–113.0 °C. IR (KBr): 3304, 3052, 2992, 2950, 1743, 1656, 1640 cm^{-1}. $[\alpha]_D^{25}=-60.0$ (c=0.5, MeOH). CD (MeOH) $[\theta]_{250}=+1803$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.57 (3H, d, J=6.7 Hz), 1.94 (3H, s), 2.96 (1H, dd, J=15.3, 15.3 Hz), 3.62 (3H, s), 3.64 (1H, dd, J=15.3, 6.1 Hz), 4.55 (1H, ddd, J=15.3, 7.9, 6.1 Hz), 5.04 (1H, q, J=6.7 Hz), 7.34 (1H, d, J=8.5 Hz), 7.46 (1H, dd, J=8.5, 6.7 Hz), 7.56 (1H, dd, J=8.5, 6.7 Hz), 7.91 (1H, d, J=8.5 Hz), 7.91 (1H, d, J=8.5 Hz), 8.02 (1H, d, J=8.5 Hz), 8.39 (1H, d, J=7.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.6, 22.6, 26.2, 48.1, 52.2, 54.0, 116.3, 119.2, 123.3, 124.9, 127.2, 128.3, 128.4, 129.9, 130.6, 136.5, 168.5, 169.5, 170.9. Anal. calcd (found) for $C_{19}H_{20}N_2O_4\cdot H_2O$: C, 63.68 (63.95); H, 6.19 (5.86); N, 7.82% (7.44%).

4.4.6. (3*R*)-2-Benzoylamino-3,4-dihydro-1-[(*S*)-1-(methoxycarbonyl)ethyl]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2b]. Mp 110.5–111.0 °C. IR (KBr): 3416, 2948, 1746, 1682, 1664 cm^{-1}. $[\alpha]_D^{25}=-10.0$ (c=0.02, MeOH). CD (MeOH) $[\theta]_{250}=+2306$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.59 (3H, d, J=6.7 Hz), 3.29 (1H, dd, J=15.9, 14.6 Hz), 3.65 (3H, s), 3.72 (1H, dd, J=15.9, 6.1 Hz), 4.84 (1H, ddd, J=14.6, 8.2, 6.1 Hz), 5.16 (1H, q, J=6.7 Hz), 7.36 (1H, d, J=9.2 Hz), 7.48 (1H, dd, J=7.3, 7.9 Hz), 7.53 (2H, dd, J=6.7, 7.9 Hz), 7.59 (1H, dd, J=7.9, 8.5 Hz), 7.59 (1H, dd, J=7.9, 7.9 Hz), 7.95 (1H, d, J=7.3 Hz), 7.95 (1H, d, J=9.2 Hz), 7.96 (2H, d, J=6.7 Hz), 8.09 (1H, d, J=8.5 Hz), 8.88 (1H, d, J=8.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.5, 26.5, 48.6, 52.2, 53.6, 116.3, 119.3, 123.3, 124.9, 127.2, 127.5

(2C), 128.28, 128.30 (3C), 129.8, 130.6, 131.5, 134.0, 136.3, 166.4, 168.4, 170.9. Anal. calcd (found) for $C_{24}H_{22}N_2O_4$: C, 71.63 (71.58); H, 5.51 (5.42); N, 6.96% (6.69%).

4.4.7. 2-[(*S*)-1-(Methoxycarbonyl)ethylaminocarbonyl]-4-methylbenzo[*f*]isoquinoline (3a). Mp 117.0–118.0 °C. IR (KBr): 3340, 3040, 2986, 2944, 1743, 1668, 1623 cm^{-1}. $[\alpha]_D^{25}=-38.4$ (c=0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.54 (3H, d, J=7.3 Hz), 3.04 (3H, s), 3.72 (3H, s), 4.70 (1H, dq, J=7.3, 7.3 Hz), 7.78–7.86 (2H, m), 8.07–8.18 (3H, m), 8.85–8.93 (1H, m), 9.06–9.13 (2H, m). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.3, 22.5, 47.9, 52.1, 113.4, 122.7, 123.7, 126.4, 127.9, 128.6, 128.7, 129.1, 129.7, 132.8, 134.4, 143.5, 157.2, 164.0, 172.8. Anal. calcd (found) for $C_{19}H_{18}N_2O_3$: C, 70.79 (70.62); H, 5.86 (5.86); N, 8.64% (8.64%).

4.5. X-ray crystallographic analysis of (*R*,*S*)-2b

A colorless crystal (of the molecular formula $C_{24}H_{22}N_2O_4$) having approximate dimensions of 0.23×0.20×0.20 mm^3 was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed with Mo K_α radiation (λ=0.71069 Å) on a Rigaku RAXIS-RAPID equipped with an imaging plate. Data collection and cell refinement: MSC/AFC diffractometer control. Data reduction: *teXsan for windows version 1.06*.[8] Structure solution: *SIR92*.[9] Refinement: *SHELXL97*.[10]

4.6. Crystal data for (*R*,*S*)-2b

$C_{24}H_{22}N_2O_4$, f_w=402.45; monoclinic, space group $P2_1$; a=6.0757(7), b=19.3406(2), c=8.5842(1) Å, α=90, β=102.961(4), V=90°, V=983.0(2) $Å^3$; Z=2; D_{calc}=1.360 g cm^{-3}; R=0.0414, $wR(F^2)$=0.1164. Crystallographic data (excluding these structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 220636. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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References and notes

1. *Synthetic Organic Photochemistry*. Horspool, W. M., Ed.; Plenum: New York, 1984.
2. (a) Rau, H. *Chem. Rev.* **1983**, *83*, 535–547. (b) Koch, H.; Runsink, J.; Scharf, H.-D. *Tetrahedron Lett.* **1983**, *24*, 3217–3220. (c) Naito, T.; Toda, Y.; Ninomiya, I. *Heterocycles* **1984**, *22*, 237–240. (d) Lange, G. L.; Decicco, C.; Lee, M. *Tetrahedron Lett.* **1987**, *28*, 2833–2836. (e) Rao, V. P.; Turro, N. J. *Tetrahedron Lett.* **1989**, *30*, 4641–4644. (f) Piva, O.; Mortezaei, R.; Henin, F.; Muzart, J.; Pete, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 9263–9284. (g) Piva, O.; Pete, J.-P. *Tetrahedron Lett.* **1990**, *31*, 5157–5160. (h) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741–770. (i) Christoph, H.; Xuechao, X.; Warzecha, K.-D.; Peter, R.; Helmunt, G.; Martin, D. *Pure Appl. Chem.* **1998**, *70*, 2167–2176. (j) Jayaraman, S.; Uppili, S.; Natarajan, A.; Joy, A.; Chong, K. C. W.; Netherton, M. R.; Zenova, A.; Scheffer, J. R.; Ramamurthy, V. *Tetrahedron Lett.* **2000**, *41*, 8231–8235. (k) Kohmoto, S.; Miyaji, Y.; Tsuruoka, M.; Kishikawa, K.; Yamamoto, M.; Yamada, K. *J. Chem. Soc. Perkin Trans. 1* **2001**, 2082–2088. (l) Formentin, P.; Sabater, M. J.; Chretien, M. N.; Garcia, H.; Scaiano, J. C. J. *J. Chem. Soc. Perkin Trans. 2* **2002**, 164–167. (m) Shim, S. C.; Kim, D. S.; Yoo, D. J.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2002**, *67*, 5718–5726.
3. (a) Leibovitch, M.; Olovsson, G.; Sundarababu, G.; Ramamurthy, V.; Scheffer, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 1219–1220. (b) Gamlin, J. N.; Jones, R.; Lelbovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203–209. (c) Mordechai, L.; Gunnar, O.; John, R. S.; James, T. *J. Am. Chem. Soc.* **1998**, *120*, 12755–12769. (d) Joy, A.; Scheffer, J. R.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 119–121. (e) Scheffer, J. R. *Can. J. Chem.* **2001**, *79*, 349–357. (f) Shailaja, J.; Sundararajan, U.; Joy, A.; Ramamurthy, V. *Microporous Mesoporous Mater.* **2001**, *48*, 319–328. (g) Kaanumalle, L. S.; Sivaguru, J.; Arunkumar, N.; Karthikeyan, S.; Ramamurthy, V. *Chem. Commun.* **2003**, 116–117.
4. (a) Bertrand, S.; Hoffmann, N.; Humbel, S.; Pete, J. *J. Org. Chem.* **2000**, *65*, 8690–8703. (b) Griesbeck, A. G.; Kramer, W.; Lex, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 577–579. (c) Jones, S.; Atherton, J. C. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1117–1119. (d) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982–7990. (e) Chong, K. C. W.; Sivaguru, J.; Shichi, T.; Yoshimi, Y.; Ramamurthy, V.; Scheffer, J. R. *J. Am. Chem. Soc.* **2002**, *124*, 2858–2859.
5. (a) Sakurai, T.; Morioka, Y.; Maekawa, K.; Kubo, K. *Heterocycles* **2000**, *53*, 271–276. (b) Maekawa, K.; Igarashi, T.; Kubo, K.; Sakurai, T. *Tetrahedron* **2001**, *57*, 5515–5526.
6. (a) Martinez, G. R.; Walker, K. A. M.; Hirschfeld, D. R.; Bruno, J. J.; Yang, D. S. *J. Med. Chem.* **1992**, *35*, 620–628. (b) Jones, C. D.; Audia, J. E.; Lawhorn, D. E.; McQuaid, L. A.; Neubauer, B. L.; Pike, A. J.; Pennington, P. A.; Stamm, N. B.; Toomey, R. E.; Hirsch, K. S. *J. Med. Chem.* **1993**, *36*, 421–423. (c) Nishikawa, T.; Omura, M.; Iizuka, T.; Saito, I.; Yoshida, S. *Arzneim.-Forsch./Drug Res.* **1996**, *46*, 875–878. (d) Oshiro, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Nishi, T. *J. Med. Chem.* **1998**, *41*, 658–667. (e) Oshiro, Y.; Sakurai, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottorii, K.; Uwahodo, Y.; Miwa, T.; Nishi, T. *J. Med. Chem.* **2000**, *43*, 177–189. (f) Butenschön, I.; Möller, K.; Hönsel, W. *J. Med. Chem.* **2001**, *44*, 1249–1256.
7. (a) Rao, Y. S.; Filler, R. *Synthesis* **1975**, 749–764. (b) Rzeszotarska, B.; Karolak-Wojciechowska, J.; Broda, M. A.; Galdecki, Z.; Trzezwinska, B.; Koziol, A. E.; Int, J. *Int. J. Pept. Protein Res.* **1994**, *44*, 313–319.
8. Molecular Structure Corporation, *teXan for Windows. Single Crystal Structure Analysis Software. Ver. 1.06*; The Woodlands: Texas, 1999.
9. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Cryst.* **1994**, *27*, 1045–1050.
10. Sheldrick, G. M. Program for the refinement of crystal structure. *SHELXL 97*. University of Gottingen: Gottingen, 1997.

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Computational studies of vinyl-stabilized halonium ions

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Abstract—Conformational studies of 1-halo-2-butenylcations have been carried out by means of density functional and ab initio calculations. The presence of an adjacent vinyl group reduced the importance of bridging by halogen atoms as evidenced by geometric and energetic analyses. Eclipsed forms were found to be minima in several cases.
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1. Introduction

Halonium ions are well-documented species formed as intermediates in a variety of chemical processes, particularly in the electrophilic addition of halogens and similar reagents to alkenes.[1] The extent of halogen bridging to cationic centers that is the formation of halonium ions, is reasonably expected to depend on structural factors stabilizing the cationic center. For example, for bromonium ions formed from ethene, propene, and 2-methylpropene, less stabilization by contribution of electron density is required as alkyl substitution increases at the cationic center. This is illustrated by a comparison of calculated electrostatic potential maps and geometric features.[2] For example, cationic center: C–Br distance increases with weaker bridging in unsymmetrical bromonium ions.[2,3] It is of interest to ascertain the effect of vinylic stabilization on bridging by halogen substituents adjacent to a carbocationic center. It may be anticipated that allylic stabilization of a cationic center would reduce the degree of bridging by neighboring halogen, and that the effect might be greater for fluorine and chlorine than with the more effective bromine bridging atom. Viewed another way, the results of these calculations speak to the nature of the intermediates derived from addition of halogens and analogous reagents to dienes.

The simplest systems incorporating these features are the 4-chloro-1-buten-3-yl cation **1**, the corresponding bromine analog and the fluorine analogs **2** and **3**, respectively (Fig. 1).

Density functional theory studies of these systems were carried out at the B3LYP/6-311+G(d) computational level

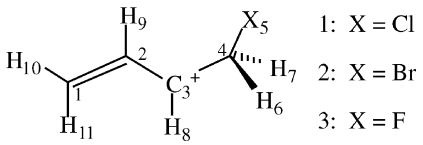

Figure 1. 4-Halo-1-buten-3-yl cations.

(additional computation methods were also used and are noted accordingly). In addition, conformational energy searches were conducted by monitoring the energy changes resulting from 360° rotation about the 3–4 bond. Structural parameters and thermally corrected enthalpies were determined for each stationary point located.[†]

2. Computational methods

All structures were fully optimized by analytical gradient using the Gaussian 98[4] suites. Density functional (DFT) calculations used the exchange potentials of Becke[5a] and the correlation functional of Lee, Yang and Parr.[5b] Electron correlation was included via optimizations utilizing second order Møller–Plesset Perturbation Theory methods (MP2).[6] Frequencies were computed by analytical methods. Reported enthalpies were corrected for zero-point energy differences (ZPVE) (unscaled[‡]) and thermal effects at 298.150 K. Full conformational searches were carried out by systematic changes (15–20° increments) in the 2–3–4–5 dihedral angles followed by full optimizations of the maxima and minima. All stationary points gave rise to the correct number of imaginary frequencies.

Keywords: Carbonium ions; Halogen compounds; Theoretical studies; Olefins.
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[†] The calculated structures are not necessarily identical with intermediates formed in particular reactions. The calculations do not include the presence of counterions as ion pairs and apply to free cations in vacuum.
[‡] Scaling factors for these DFT and MP2 methods are small, 1–3%.[7]

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Table 1. Relative enthalpies and structural parameters for **1**: B3LYP/6-311+G(d)

Conformation	$C_2-C_3-C_4-Cl$[a] (°)	ΔH[b]	C_3-C_4-Cl[c] (°)	$Cl-C_4$[d]	$Cl-C_3$[e]
4	0.0	0	118	177	277
5	54.8	13.2	108	180	266
6	99.5	1.79	92.7	183	240
7	180.0	7.04	115	177	274

[a] Dihedral angle.
[b] kJ mol^{-1} at 298.15 K.
[c] Bond angle.
[d] Bond length (pm).
[e] Interatomic distance (pm).

3. Results and discussion

3.1. 4-Chloro-1-buten-3-yl cation (1)

Enthalpy and important structural parameters are shown in Table 1. Relative enthalpies as a function of torsional angle $D(2-3-4-5)$ in **1** are shown in Figure 2. In the 0–180° region two minimum energy structures **4** and **6** are observed, at dihedral angles of 0 and 99.5°, respectively. The minimum energy structure **4** at 0° corresponds to an eclipsed conformation with C_s symmetry (C_2,Cl eclipsed), cf. Figure 2 in which a dashed line or p-orbital depicts the terminus of the attached π-system of the molecular framework. Structure **4** lies 1.79 kJ mol^{-1} lower in enthalpy than the local minimum structure **6** at 99.5°. Dihedral angles of 54.8 and 180° represent transition state conformations **5** and **7**, respectively. Structure **5** lies 13.2 kJ mol^{-1} higher in enthalpy than **4** and corresponds to a conformation in which H_6 and H_8 are nearly eclipsed (separated by a dihedral angle of 5.86°). Structure **7** (C_s symmetry) lies 7.0 kJ mol^{-1} above **4** and corresponds to a conformation in which Cl and H_8 are eclipsed. Figure 3 represents the entire conformational energy curve and includes points at 260.5 and 305.2° representing the mirror image forms of **5** and **6**, respectively.

The conformer **6** corresponding to torsion angle 99.5° shows a lengthening of the 4,5 bond and decrease of the 3,4,5 bond angle, as well as a decrease of the 3,5 internuclear distance. These structural features are consistent with bridging of the cationic center C_3 by chlorine. The chlorine in **6** makes a dihedral angle of 9.5° with the p-orbital axis on C_3 and this near eclipsing is also compatible with weak bridging by chlorine. Bridged structures computed in this study are shown as halonium ions (σ-complexes), and no distinction is made here with formulation of the structures as π-complexes.[8,9]

Evidence for the existence of chloronium ions as intermediates in the addition of chlorine to alkenes includes

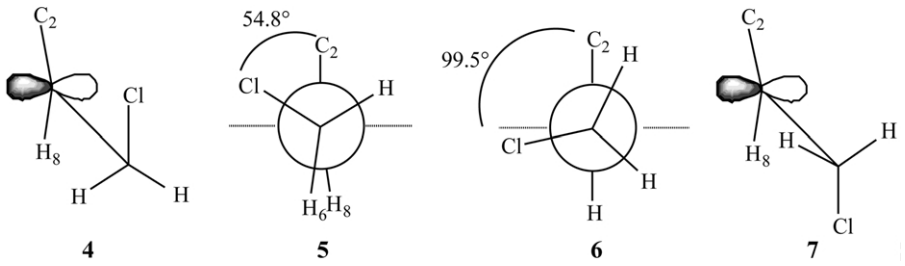

Figure 2. Representations of stationary points for **1**.

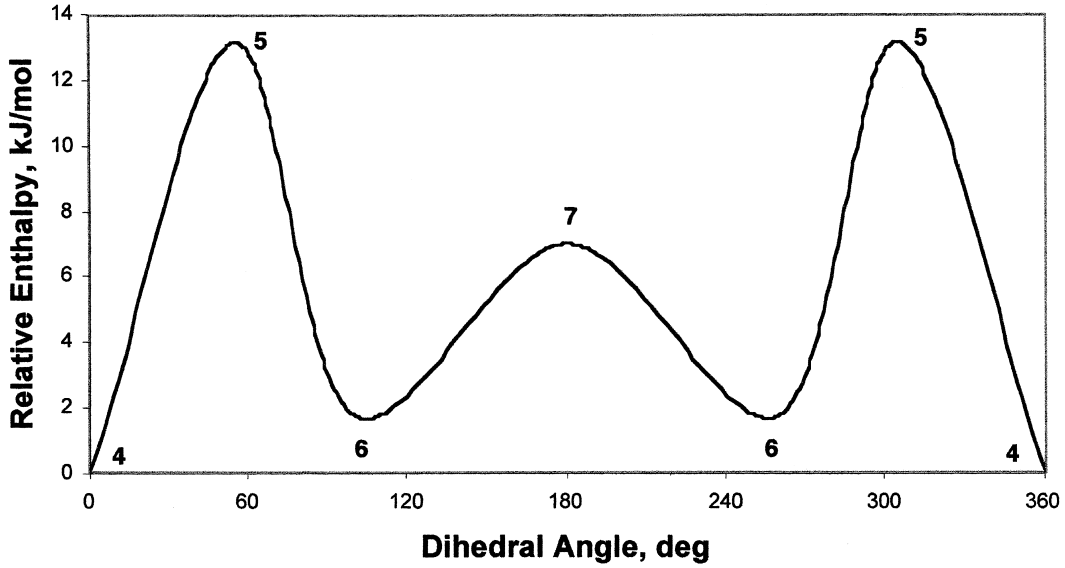

Figure 3. Relative enthalpies vs dihedral angle for **1**: B3LYP/6-311+G(d).

Table 2. Relative enthalpies and structural parameters of **1**

	B3LYP/6-311+G(d)		B3LYP/6-311+G(2d,p)		B3LYP/AUG-cc-pVDZ		MP2/6-311+G(d)	
	4	**6**	**4**	**6**	**4**	**6**	**4**	**6**
ΔH[a]	0	1.8	0	1.3	0	2.2	0	0.084
$D(2-3-4-5)$[b]	0	99.5°	0	99.0°	0	99.1°	0	99.1°
$A(3-4-5)$[c]	117.7°	92.7°	117.6°	92.0°	117.3°	91.9°	116.1°	86.0°
$R(4-5)$[d]	177	183	177	183	178	—	175	181

[a] Enthalpies are in kJ mol^{-1} at 298.15 K.
[b] *D*, dihedral angle.
[c] *A*, bond angle.
[d] *R*, interatomic distance (pm).

stereoselective *anti* addition. For example, *trans*-2-butene reacts with chlorine in a nonpolar solvent with oxygen present to give 98% *meso*-2,3-dichlorobutane (2% of substitution product was obtained).[10] NMR evidence for a stable chloronium ion has been reported.[11]

In structure **6** the geometry about the cationic center C_3 is planar and this also suggests weak bridging in the chloronium ion **6**. Conformation **4** clearly represents a nonbridged structure since the chlorine is perpendicular to the p-orbital axis. The 3–4–5 bond angle of 117.7° is relatively large, and the C_4–Cl bond length of 177 pm is normal.[12] The nonbonded C_3–Cl distance of 277 pm in **4** is identical to the nonbonded C–Cl distance in chloroethane calculated using B3LYP/6-311+G(d) model chemistry. In both structures 4 and 6 the carbon framework 1–2–3–4 is planar.[§]

The finding that the eclipsed conformation **4** is a stable conformer, slightly more stable than the chloronium ion **6** prompted us to carry out further optimizations with B3LYP using larger basis sets, as well as optimizations with alternative model chemistries. The results are shown in Table 2.

All of the methods in Table 2 show the eclipsed conformer **4** slightly more stable than the weakly bridged chloronium ion **6**. The MP2 calculation shows a significantly smaller Cl–C_4–C_3 bond angle than the B3LYP methods, and also shows very little energy difference between **4** and **6**. A single point calculation at the QCISD(T)/6-31+G(d)//MP2/6-311+G(d) level showed **4** to be 3.9 kJ mol^{-1} more stable than **6**.

In contrast to the vinyl-substituted chloronium ion **6**, the butyl chloronium ion **8** (Fig. 4) shows a strikingly different enthalpy-conformation dependence, the main feature of which is the presence of one dominant stable conformation. Full optimizations of 1-chloro-2-butyl cation show that the most stable conformation is the chloronium ion **8** corresponding to a torsion angle $D(5-1-2-3)$ of 102°. The following structural parameters were found for chloronium ion **8**: bond angle Cl–C_1–C_2=75.9° (considerably smaller than the corresponding angle in **6**), C_2–Cl distance=207 pm (considerably shorter than the corresponding distance $R3-5$ in **6**; note that the numbering differs for **6** and **8**). The Cl–C_1 bond length in **8** is 186 pm, which is essentially unchanged from **6**. The dihedral angle in **8** Cl–C_1–C_2, p-orbital axis is approximately 12°, and the cationic center C_2 in **8** is close to planar.

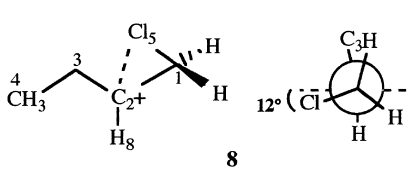

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Figure 4. Representations of the 1-butylchloronium ion.

Based on the comparison of structural parameters, chloronium ion **8** is more strongly bridged than the vinylchloronium ion **6**. The butyl chloronium ion **8** is approximately 23 kJ mol^{-1} more stable than the nearest minimum energy conformation. Consequently, vinyl stabilization of a cationic center lessens the need for bridging by an adjacent chlorine.

A second instructive comparison is that with the isomeric *trans*-2-butylchloronium ion **9** (Fig. 5). In this more highly symmetrical bridged structure the C–C–Cl angle is 67.3° and the C–Cl–C angle is 45.4° based on B3LYP/6-311+G(d) optimization. Halonium ions derived from symmetrical methyl-substituted ethenes are more strongly bridged than those from unsymmetrical alkenes.[3] The conclusion is that bridging is weaker in the unsymmetrical chloronium ion **8** than in symmetrical structure **9** and still weaker in the vinylchloronium ion **6**. This is attributed to delocalization of positive charge by resonance in the vinyl group in **6**.

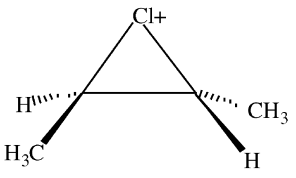

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Figure 5. *trans*-2-Butylchloronium.

3.2. 4-Bromo-1-buten-3-yl cation (2)

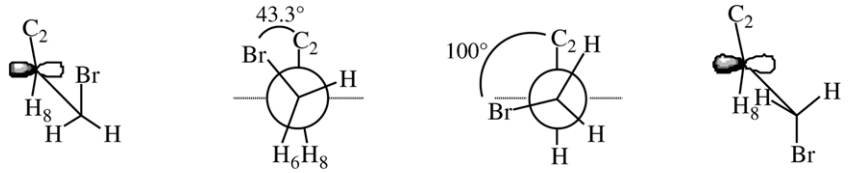
Optimized enthalpies and structural parameters were determined as a function of torsion angle for **2** and the results are shown in Table 3 and in Figures 6 and 7.

[§] The AIM[4b] (Atoms in Molecules) calculated covalent bond orders are 0.36 for the Cl–C3 bond compared with 1.02 for the Cl–C4 bond in **1**. For comparison, the bond order for the C–Cl in *trans*-2-butylchloronium ion vide infra is 0.80.

Table 3. Relative enthalpies[a] and structural parameters for **2**:B3LYP/6-311+G(d)

$C_2-C_3-C_4-Br$[b]	ΔH	C_3-C_4-Br[c] (°)	$Br-C_4$[d]	$Br-C_3$[e]
0.0° (**2a**)	18.0	119	193	293
43.3° (**2b**)	22.2	112	196	286
100° (**2c**)	0.0	90.0	200	247
180° (**2d**)	24.3	116	193	289

[a] Enthalpies in kJ mol^{-1} at 298.15 K.
[b] Dihedral angle.
[c] Bond angle.
[d] Bond length.
[e] Interatomic distance (pm).



2a **2b** **2c** **2d**

Figure 6. Representations of stationary points for **2**.

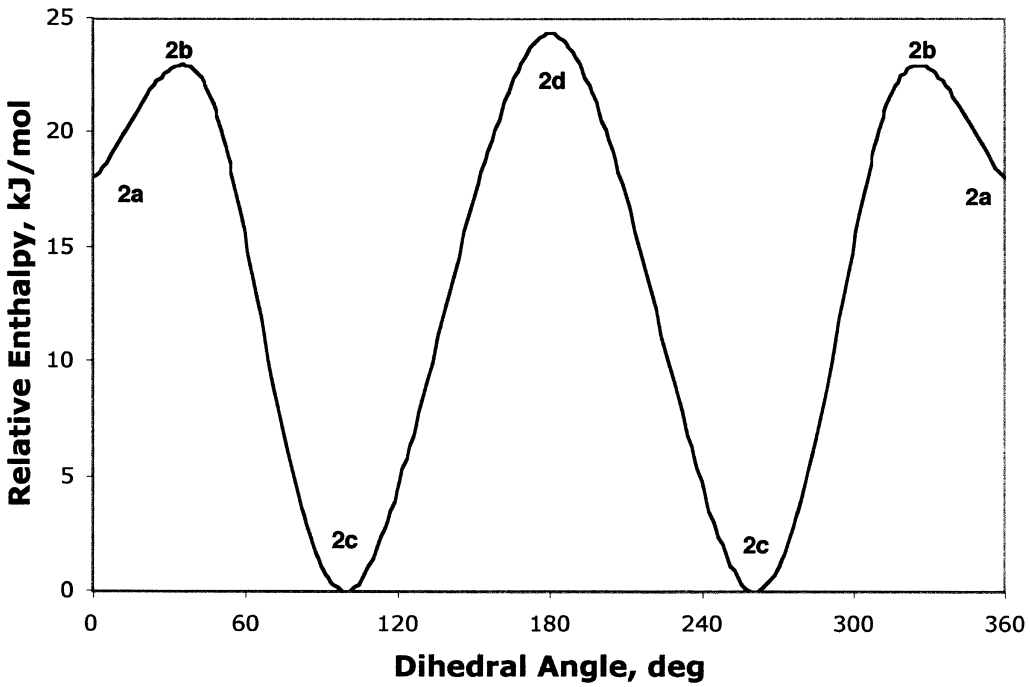
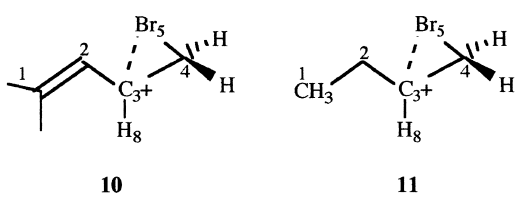


Figure 7. Relative enthalpies vs. dihedral angles for **2**: B3LYP/6-311+G(d).

In contrast to the chlorine analog, the most stable conformer for **2** occurs at a torsion angle of 100°, corresponding to the bromonium ion **10** (Fig. 8). The bromonium ion is characterized by a longer C_4-Br bond length, a shorter C_3-Br internuclear distance, and a smaller C_3-C_4-Br bond angle relative to other conformations.

The bromonium ion is lower in energy by 18 kJ mol^{-1} than the local minimum energy conformer at a torsion angle of 0° as a consequence of bromine bridging. The geometry about the cationic center C_3 in **10** is planar, as with the analogous chloronium ion, with angles $C_2-C_3-H_8$, $C_4-C_3-H_8$, and $C_2-C_3-C_4$ adding to 360.0°.

The butyl bromonium ion **11**¶ (Fig. 8) is more strongly bridged than the vinylbromonium ion **10**, with a $Br-C_4-C_3$ bond angle of 75.1°, a C_4-Br bond length of 203 pm, and a $Br-C_3$ interatomic distance of 217 pm. This again demonstrates the stabilizing effect of the vinyl group on the cationic center in **10**, leading to less effective bridging in **10** relative to **11**.



10 **11**

Figure 8. Bromonium ions **10** and **11**.

We also found that the structure of the bromonium ion **10** is unaffected by the polarity of the medium. A full optimization in a dielectric continuum corresponding to that of water (78.39 D) led to a structure that was only slightly

¶ The structure for **11** was optimized using B3LYP/6-31+G(d) model chemistry.

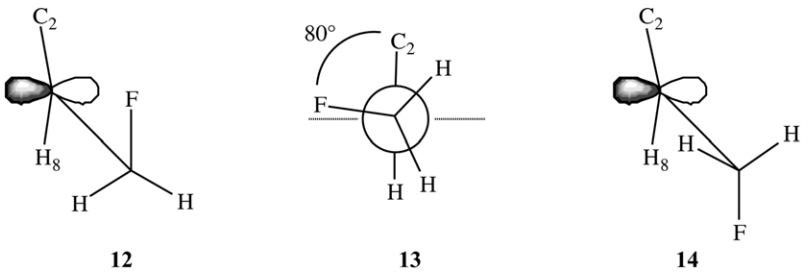


Figure 9. Representations of stationary points of **3**: B3LYP/6-311+G(d).

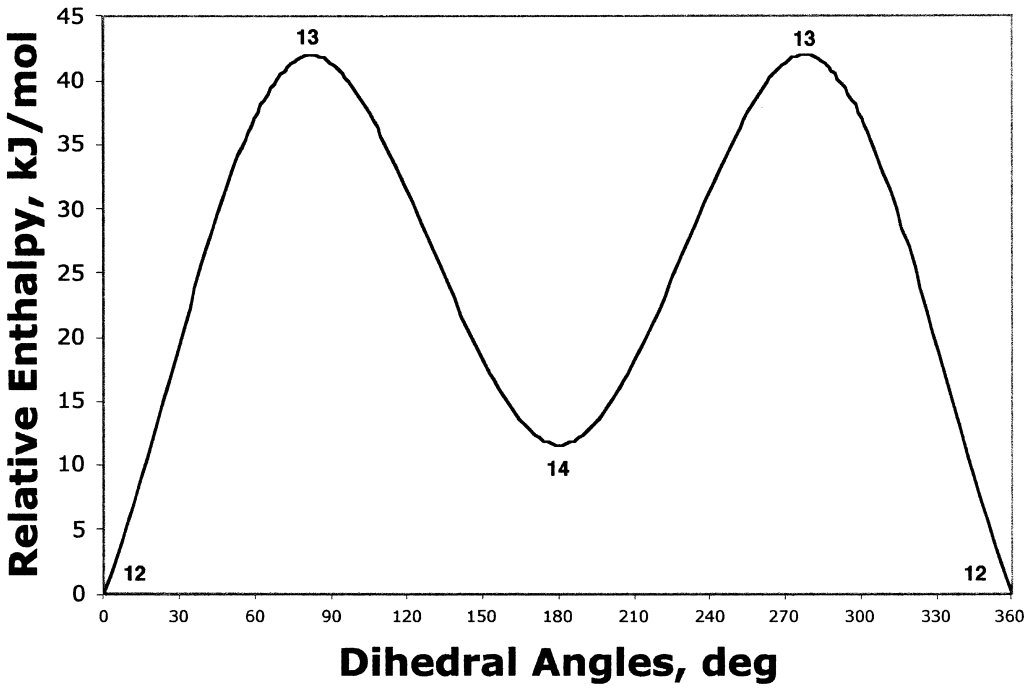


Figure 10. Relative enthalpy vs dihedral angle for **3**: B3LYP/6-311+G(d).

different from the structure obtained under vacuum conditions. The major difference was the C_3-C_4-Br angle, which expanded from 92.0 to 94.7°.

3.3. 4-Fluoro-1-buten-3-yl cation 3

A preliminary conformational search showed minimum energy conformations at 0 and 180° dihedral angles, and energy maxima in the vicinity of 90 and 270°. Full optimizations of **3** were carried out at the B3LYP/6-311+G(d) and MP2/6-311+G(d) levels. Stationary points were obtained at dihedral angles $D(2-3-4-5)$ of 0 and 180° (conformations **12** and **14** respectively, Figure 9), both minima, and formula **13** at about 80°, a transition state conformation. Figure 10 shows the change of relative enthalpy with dihedral angle $D(2-3-4-5)$ for **3**. In this case, the putative fluoronium ion **13** is a first-order saddle point in contrast to the chloronium and bromonium ions and eclipsed forms are energy minima.

Enthalpy data and structural parameters for these structures optimized by both the B3LYP and MP2 methods are given in Table 4.

Table 4. Relative enthalpies and structural parameters for **3**

Conformations	B3LYP/6-311+G(d)			MP2/6-311+G(d)		
	12	**13**	**14**	**12**	**13**	**14**
ΔH^a	0	41.9	11.6	0	37.6	12.6
$D(2-3-4-5)^b$	0°	79.9	180°	0°	81.6°	180°
$A(3-4-5)^c$	113.2°	101.5°	111.8°	111.9°	102.3°	110.7°
$R(4-5)^d$	136	140	136	136	139	136

[a] Enthalpies are in kJ mol^{-1} at 298.15 K.
[b] *D*, Dihedral angle.
[c] *A*, Bond angle.
[d] *R*, Interatomic distance (pm).

4. Summary

A comparison of the three 4-halo-1-buten-3-yl cations **1**-**3** shows a clear trend. With the bromine analog in which bridging with the cationic center is strongest, the bridged conformer is lower in enthalpy by 18.0 kJ mol^{-1} than the local minimum enthalpy conformer (the eclipsed structure with dihedral angle=0°). In the chlorine analog with weaker bridging, the chloronium ion **6** is approximately equal (and in most calculations slightly higher) in enthalpy than the eclipsed conformer **4**. Experimental studies both in the gas-phase and in solution are consistent with these findings and

show the greater tendency of bromine to form bridged halonium ions.[13–16] Computational studies of bromo- and chlorocations derived from several cycloalkenes have also shown that bromonium ions are more stable than the analogous chloronium ions in those systems.[17]

The fluorine analog is particularly interesting. In this case conformation **13** with a dihedral angle of about 80° is not a stabilized bridged form, and in fact proved to be a saddle point with enthalpy about 38–42 kJ mol^{-1} above the eclipsed form **12**. An AIM (Atoms in Molecules) calculation[4b] revealed that the covalent bond order between F and C_3 was only 0.15. Saturated fluoronium ions have been represented as transition structures by others.[18–21] In contrast to the results with bromine, calculations have shown that the 0° conformer in which the fluorine is eclipsed with the adjacent carbon atom 2 is the most stable conformer for the 3-fluorobut-2-yl cation.[18]

Clearly, there is a delicate balance among the competing factors that are involved in stabilizing the cationic centers. What is not clear are the factors that favor eclipsed forms over more conventional staggered conformations.

References and notes

1. (a) De la Mare, P. B. D.; Bolton, R. *Electrophilic addition to unsaturated systems*; Elsevier: Amsterdam, 1966. (b) In *The chemistry of double-bonded functional groups*; Patai, S., Ed.; Wiley: London, 1989. (c) Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, *28*, 207.
2. (a) Solomons, G.; Fryhle, C. *Organic chemistry*; 7th ed. Wiley: New York, 2000; pp 340, 341. (b) Shellhamer, D. F.; Allen, J. L.; Allen, R. D.; Gleason, D. C.; Schlosser, C. O.; Powers, B. J.; Probst, J. W.; Rhodes, M. C.; Ryan, A. J.; Titterington, P. K.; Vaughan, G.; Heasley, V. L. *J. Org. Chem.* **2003**, *68*, 3932–3937. (c) Damrauer, R.; Leavell, M. D.; Hadad, C. M. *J. Org. Chem.* **1998**, *63*, 9476–9485.
3. (a) Galland, B.; Evleth, E. M.; Ruasse, M.-F. *J. Chem. Soc., Chem. Commun.* **1990**, 898–900. (b) Klobukowski, M.; Brown, R. S. *J. Org. Chem.* **1994**, *59*, 7156–7160. For a discussion of the bromination of unsymmetrical alkenes, see: (c) Carroll, F. A. *Perspectives on structure and mechanism in organic chemistry*; Brooks/Cole: Pacific Grove, CA, 1998; p 563 ff.
4. (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A. Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nahayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision A.9. (b) Stefanov, B. B.; Cioslowski, J. R. *J. Comp. Chem.* **1995**, *16*, 1394–1404, and earlier papers.
5. (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.
6. Møller, C.; Plesset, M. S. *Phys. Rev. B* **1934**, *46*, 618–622.
7. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502–16513.
8. Hamilton, T. P.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1990**, *112*, 8260–8265.
9. Cossi, M.; Persico, M.; Tomasi, J. *J. Am. Chem. Soc.* **1994**, *116*, 5373–5378.
10. Poutsma, M. L. *J. Am. Chem. Soc.* **1965**, *87*, 2172–2183.
11. Olah, G. A.; Bollinger, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 4744–4752.
12. Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. Introduction to organic chemistry; 4th ed. Macmillan: New York, 1992; p 152.
13. Olah, G. A.; Mo, Y. K. *Carbonium ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley Interscience: New York, 1976; Vol. V. Chapter 36.
14. Olah, G. A. Halonium ions; Wiley Interscience: New York, 1975.
15. Berman, D. W.; Anicich, V.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1239–1248.
16. Holmes, J. L.; Lossing, F. P.; McFarlane, R. A. *Int. J. Mass Spectrom. Ion Proc.* **1988**, *86*, 209.
17. Teberekidis, V. I.; Sigalas, M. P. *Tetrahedron* **2003**, *59*, 4749–4756.
18. Reynolds, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 8676–8682.
19. Shaler, T. A.; Morton, T. H. *J. Am. Chem. Soc.* **1989**, *111*, 6868–6870.
20. Shaler, T. A.; Morton, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9222–9226.
21. (a) Hehre, W. J.; Hiberty, P. C. *J. Am. Chem. Soc.* **1974**, *96*, 2665–2677. (b) Olah, G. A.; Prakash, G. K. S.; Krishnamurthy, V. V. *J. Org. Chem.* **1983**, *48*, 5116–5117.

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Practical ex-chiral-pool methodology for the synthesis of dopaminergic tetrahydroindoles

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Abstract—Chemo- and regioselective transformations of asparagine gave access to optically active 5- and 6-amino tetrahydroindolizines when the 3-aminobutyrolactone (*S*)-**2** was employed as a key intermediate. The target compounds were approached by a sequential and regiocontrolled bis-electrophilic attack in the positions 2 and 3 of the pyrrole ring system. Receptor binding experiments showed stereocontrolled receptor recognition leading to the D3 selective agonist (*S*)-**8** with D3 binding that is comparable to the natural neurotransmitter dopamine.
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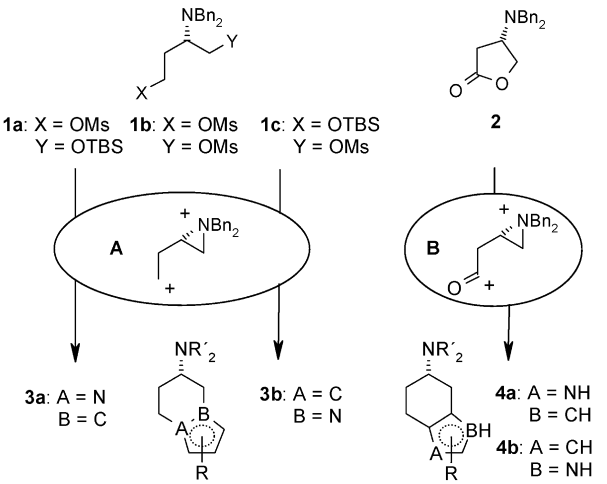
1. Introduction

Chemo- and regioselective functionalization of asparagine and aspartic acid has become an attractive method for the construction of bioactive compounds including natural products and non-proteinogenic amino acids.[1] We recently presented efficient methodology for a regioselective preparation of the aspartate derivatives **1a**–**c** disclosing a straightforward access to a variety of amino alcohols, β-amino acids and lactam-bridged peptide mimetics.[2] Depending on the chemical necessities, the introduction of nucleophiles can be realized in the positions 1, 2 and 4. Thus, the building blocks **1** can serve as equivalents for the chiral synthon **A**. Exploiting the 1,4-bis-electrophilic properties, valuable applications in the field of medicinal chemistry could be disclosed when the attack of pyrrole derived nucleophiles in the positions 1 and 2 of the heterocyclic unit led to slaframine derivatives and dopaminergic bicyclic ergoline analogs (**3a**,**b**).[3] As an extension of our very recent efforts,[4] target driven SAR studies required the access to regioisomeric azabicyclo[4.3.0]-nonanes of type **4** that should be approached by a sequential and regiocontrolled bis-electrophilic attack in the positions 2 and 3 of the pyrrole ring system. We envisioned realizing this plan by *C*-acylation and aziridinium promoted 6-*endo*-tet cyclization[5] when the dibenzyl-protected asparagine derivative (*S*)-**2**[6] should be employed as a synthetic equivalent for the synthon **B**. In this paper, we describe an enantiospecific approach of the 5- and 6-aminotetrahydroindoles **4a** and **4b**, and the regio- and stereoselective dopamine receptor binding of the test compounds in both enantiomeric configurations (Scheme 1).



Scheme 1.

Our initial investigations were directed towards the synthesis of the 5-aminotetrahydroindoles of type **4a**. For the preparation of the dibenzylamino substituted lactone (*S*)-**2**, natural asparagine was converted into the *N*,*N*-dibenzyl protected aparagine benzyl ester. Subsequent chemoselective reduction of the ester group and lactonization afforded the chiral building block (*S*)-**2** in 36% overall yield, according to our previously described protocol.[6] To attach (*S*)-**2** to the pyrrole moiety, we tried to exploit a nucleophilic ring-opening reaction with pyrrole lithiated in 2-position (Scheme 2).

To prevent problems with the acidic NH-function, we

Keywords: Ex-chiral pool synthesis; Asparagine; Receptor binding; Aminobutyrolactone.
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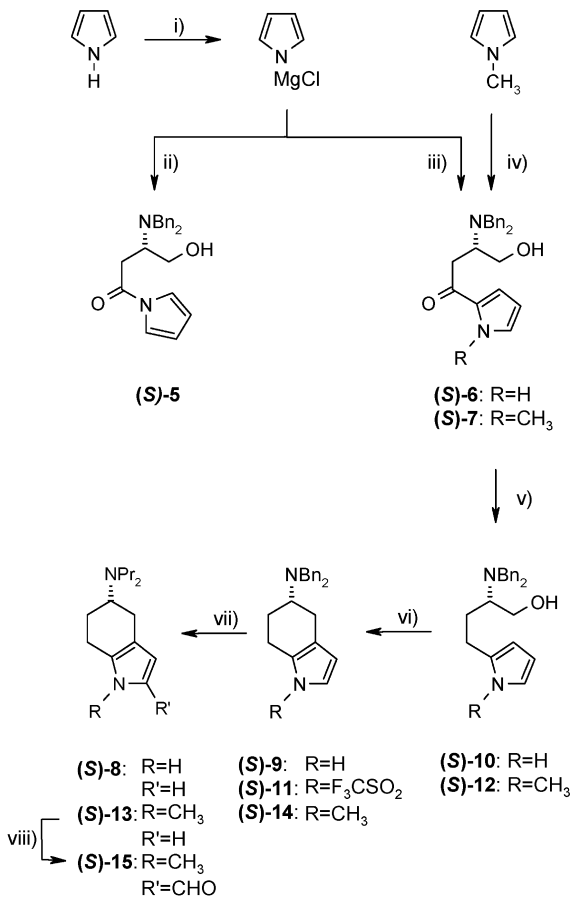


Scheme 2. (i) MeMgCl, toluene, 0 °C; (ii) (*S*)-**2** (1.0 equiv.), 0 °C, 30 min (59%); (iii) (*S*)-**2** (0.5 equiv.), 100 °C, 75 min (87%); (iv) (1) *n*-BuLi, TMEDA, THF, room temperature, 15 min, (2) (*S*)-**2**, THF, −78 °C (62%); (v) $AlCl_3$, *t*-$BuNH_2{\times}BH_3$, CH_2Cl_2, 0 °C, 1 h ((*S*)-**10**: 44%; (*S*)-**12**: 73%); (vi) $(F_3CSO_2)_2O$, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C to room temperature, 1 h ((*S*)-**9**: 48% and (*S*)-**11**: 18%; (*S*)-**14**: 67%); (vii) (1) $Pd(OH)_2$/C, 1 atm H_2, MeOH–EtOAc (1:1), room temperature, 4 h; (2) $NaBH(OAc)_3$, propionaldehyde, 1,2-DCE, room temperature, 1.75 h ((*S*)-**8**: 78%; (*S*)-**13**: 58%); (viii) $POCl_3$, DMF, 0 °C, 1 h (85%).

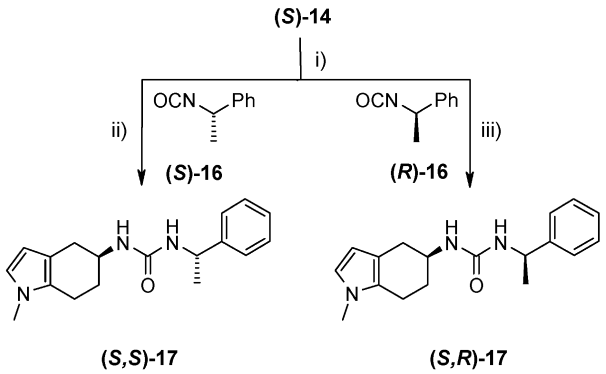
started with *N*-methylpyrrole which was lithiated with *n*-BuLi/TMEDA and subsequently reacted with the lactone (*S*)-**2**.[7] In fact, the reaction proceeded smoothly furnishing the ketone (*S*)-**7** in 62% yield. Employing a mixture of borane–*tert*-butylamine complex and $AlCl_3$ as an effective reducing system,[8] the carbonyl function could be degraded to the methylene unit resulting in formation of the cyclization precursor (*S*)-**12** (73%). Activation of the primary alcohol function with trifluoromethanesulfonic anhydride resulted in a cationic ring closure[9] to afford the *N*-methyltetrahydroindole (*S*)-**14** in 67% yield. It was important to conduct the reaction in presence of 4-methyl-2,6-di-*tert*-butylpyridine as a sterically demanding and effective proton scavenger. By contrast, the use of triethylamine, being previously described for similar aziridinium promoted reactions, gave only 23% yield in this case. 4-Methyl-2,6-di-*tert*-butylpyridine could be easily separated by flash chromatography and recycled for further experiments. The exchange of the benzyl protecting groups with the pharmacophoric propyl substituents was done by catalytic debenzylation followed by a reductive alkylation of the resulting primary amine with propionaldehyde and sodium triacetoxyborohydride to give the test compound (*S*)-**13** in 58% yield.

Starting from dipropylaminotetrahydroindolizines,[4] we recently found that the introduction of a carbaldehyde function into the 2-position of the pyrrole partial structure increased the dopaminergic activity, especially the affinity to the D3 subtype. Therefore, it was interesting for us to see if we could also improve the receptor binding properties by a C-formylation of the tetrahydroindole (*S*)-**13**. We subjected (*S*)-**13** to Vilsmeier conditions and obtained the 2-formyl derivative (*S*)-**15** in 85% yield.

To perform systematic structure–activity-relationship studies, it was also interesting for us to work out a synthesis for the 5-aminotetrahydroindole (*S*)-**8** with a pyrrole NH moiety being putatively involved in hydrogen bonding interaction with the receptor. We first tried the use of N-protected pyrroles including *N*-Ts, *N*-Boc, *N*-SEM and NMe_2 derivatives when activation for a nucleophilic attack should be facilitated by *o*-directed metallation.[10–12] However, lithiation and subsequent treatment with the amino lactone (*S*)-**2** resulted in hardly separable educt/product mixtures and the formation of side products. Thus we turned our attention to a method of Nicolaou et al.[13] when a reagent derived from MeMgCl and pyrrole[14] was used to react with γ-butyrolactone. Depending on the reaction temperature and the stoichiometry, regioselective C–N or C–C bond formation was detected. We observed that pyrrolemagnesium chloride reacted as a *N*-nucleophile with 1.0 equiv. of the lactone (*S*)-**2** at 0 °C to afford the hydroxyamide (*S*)-**5** (59%). On the other hand, employing an excess of the organometallic reagent (2 equiv.) at 100 °C resulted in formation of the ketopyrrole (*S*)-**6** in 87% yield. Obviously, (*S*)-**6** is produced by subsequent N-acylation, *o*-directed metallation and *N*,*C*-acyl migration. Reduction of the carbonyl group afforded the cyclization precursor (*S*)-**10**. Activation of the alcohol function with trifluoromethanesulfonic anhydride led to exclusive *C*-alkylation resulting in formation of the tetrahydroindole (*S*)-**9** as well as the *N*-Tf substituted compound (*S*)-**11** as a side product. The dipropyl derivative (*S*)-**8** was obtained from (*S*)-**9** by hydrogenolytic debenzylation and reductive alkylation in 78% yield. Employing the identical procedures, we synthesized the optical antipodes (*R*)-**8**, (*R*)-**13** and (*R*)-**15** starting from unnatural (*R*)-asparagine.

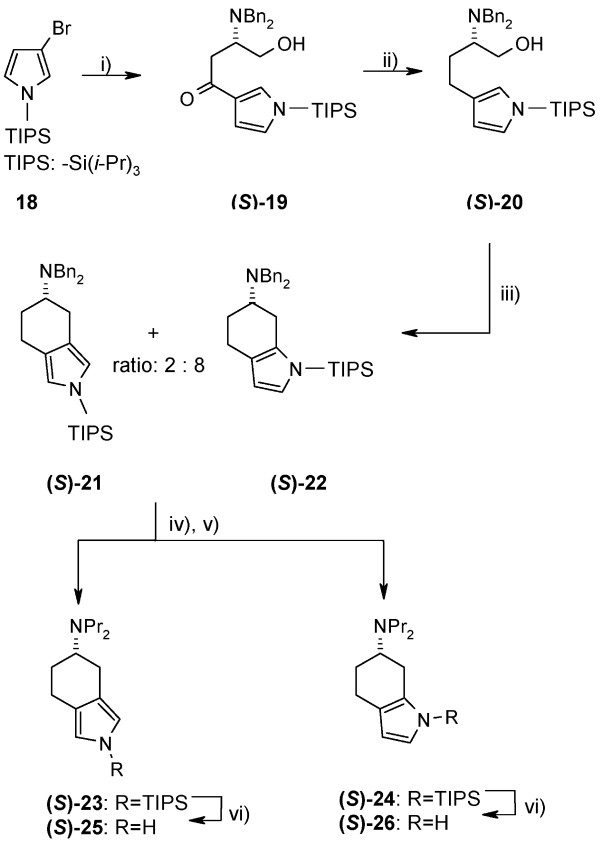
To prove the optical integrity of the reaction pathway by diastereomer formation, coupling with the chiral isocyanates (*S*)-**16** and (*R*)-**16** was done and subsequent HPLC analysis should be performed. Choosing (*S*)-**14** as a representative final product, hydrogenolysis and coupling of the resulting primary amine with the enantiomers (*S*)-**16** and (*R*)-**16** gave the diastereomeric ureas (*S*;*S*)-**17** and (*S*;*R*)-**17**, respectively. Subsequent HPLC analysis including doping experiments indicated a diastereomeric excess >95% (Scheme 3).

For the synthesis of the 6-amino substituted regioisomers of type **4b**, we had to alter the attachment point for the acylation of the pyrrole moiety with the chiral C4 equivalent (*S*)-**2** when metallation in position 3 should be facilitated by halogen metal exchange of the readily available *N*-TIPS



Scheme 3. (i) $Pd(OH)_2/C$, 1 atm H_2, EtOAc–MeOH (1:1), room temperature, 24 h; (ii) (*S*)-**16**, CH_2Cl_2, room temperature, 6 h (66%); (iii) (*R*)-**16**, CH_2Cl_2, room temperature, 6 h (73%).

substituted 3-bromopyrrole **18**.[15] In detail, treatment of **18** with *n*-BuLi at room temperature followed by addition of the amino lactone (*S*)-**2** resulted in formation of the amino alcohol (*S*)-**19** in 47% yield. After reduction of the carbonyl group with borane–*tert*-butylamine in presence of $AlCl_3$, cationic cyclization was induced by activation of the alcohol function with trifluoromethanesulfonic anhydride. Actually, electrophilic attack into the positions 2 and 4 of the aromatic system was observed leading to formation of the tetrahydroindole (*S*)-**22** and the tetrahydroisoindole (*S*)-**21**, respectively, as a 4:1 mixture of nearly separable regioisomers. Exchange of the benzyl groups with propyl substituents via hydrogenolysis and reductive alkylation gave pure (*S*)-**23** (9%) and (*S*)-**24** (62%) after flash chromatography. Finally, fluoride promoted desilylation furnished the final products (*S*)-**25**[16] and (*S*)-**26** in 82 and 69% yield, respectively. Employing the identical procedures, the preparation of the optical antipodes (*R*)-**25** and (*R*)-**26** was performed starting from unnatural (*R*)-asparagine (Scheme 4).



Scheme 4. (i) (1) *n*-BuLi, pentane, room temperature, 15 min; (2) (*S*)-**2**, THF, 0 °C (47%); (ii) $AlCl_3$, *t*-$BuNH_2{\times}BH_3$, CH_2Cl_2, 0 °C, 30 min, (51%); (iii) $(F_3CSO_2)_2O$, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C to room temperature, 60 min (79%; (*S*)-**21**–(*S*)-**22**=2:8); (iv) $Pd(OH)_2/C$, 1 atm H_2, MeOH–EtOAc (1:1), room temperature, 2 h; (v) $Na(OAc)_3BH$, propionaldehyde, 1,2-DCE, room temperature, 45 min ((*S*)-**23**: 9%; (*S*)-**24**: 62%); (vi) Bu_4NF, THF, room temperature, 30 min ((*S*)-**25**: 82%; (*S*)-**26**: 69%).

The final products (*S*)-**8**, (*S*)-**13**, (*S*)-**15**, (*S*)-**25**, (*S*)-**26** and their enantiomers we evaluated in vitro for their abilities to displace [^{3}H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[17] D3[18] and D4.4[19] being stably expressed in CHO cells (Table 1). D1 affinities were determined by employing porcine striatal membrane preparations and the D1 selective antagonist [^{3}H]SCH23390.[20] As a reference drug, the neurotransmitter dopamine was utilized. All the test compounds investigated

Table 1. Receptor binding data of the tetrahydroindoles **8**, **13**, **15**, **26** and the tetrahydroisoindoles **25** in comparison to the reference compound dopamine at the human dopamine receptor subtypes $D2_{long}$, $D2_{short}$, D3, D4.4 and the porcine D1 receptor (K_i values in nM)

Compound	K_i values (nM)[a]				
	[^{3}H]SCH23390, porcine D1	[^{3}H]spiperone			
		Human $D2_{long}$	Human $D2_{short}$	Human D3	Human D4.4
(*S*)-**8**	35,000[b]	12,000	9700	38+1900[c]	1700
(*R*)-**8**	28,000	28,000	17,000	2000	3000
(*S*)-**13**	16,000	13,000	62+9900	34+1800	610
(*R*)-**13**	16,000	20,000	190+15,000	16,000	3100
(*S*)-**15**	45,000	72,000	56,000	12,000	17,000
(*R*)-**15**	80,000	45,000	65,000	1000	29,000
(*S*)-**25**	24,000	94+11,000	92+6900	33+1100	28+2500
(*R*)-**25**	43,000	28,000	28,000	3700	5400
(*S*)-**26**	21,000	27,000	27,000	7600	20,000
(*R*)-**26**	42,000	36,000	21,000	9400	14,000
Dopamine	7.0+6500	20+1900	17+1100	50+1600	1.2+62

[a] K_i values are the means of 2 to 6 experiments each done in triplicate.
[b] $K_{0.5}$ values derived from the competition curves calculated in a one-site binding mode.
[c] $K_{i\ high}$ and $K_{i\ low}$ values for the high and low affinity binding sites, when the analysis of the dose response curve clearly indicated a biphasic competition.

displayed only weak D1 binding. For all the subtypes investigated, the (*R*)-enantiomers gave K_i values in the micromolar range indicating only moderate affinity. On the other hand, the 5-aminotetrahydroindole (*S*)-**8** showed a biphasic curve for the D3 receptor with a $K_{i\ high}$ of 38 nM indicating high D3 affinity and selectivity as well as agonist properties. While alkylation of the indole-*N* of (*S*)-**8** by a methyl group leading to (*S*)-**13** resulted in a combination of D3 and $D2_{short}$ activity ($K_{i\ high}$=62 nM for $D2_{short}$, $K_{i\ high}$=34 nM for D3), additional formyl substitution in position 2 decreased receptor binding and showed only micromolar affinities as indicated for (*S*)-**15**. This result is in contrast to our recent observations for aminoindolizines when the introduction of a carbaldehyde function gave a beneficial effect.[4] Shifting the propylamino substituent from position 5 to 6 of the tetrahydroindole scaffold as realized in (*S*)-**26**, the receptor recognition was strongly reduced. Interestingly, the tetrahydroisoindole regioisomer (*S*)-**25** revealed substantial receptor affinities to all subtypes of the D2 family with $K_{i\ high}$ values of 94, 92, 33 and 28 nM for $D2_{long}$, $D2_{short}$, D3 and D4, respectively. Considering the absolute configuration of the active enantiomer, this result corroborates previous observations that the pyrroleethylamine moiety, which is part of the BCD tricyclic partial structure of the ergolines, is the active portion of this class of dopamine agonists.[16] To confirm the binding property of the most promising, D3 selective compound (*S*)-**8**, we determined its agonist activity in a mitogenesis assay utilizing D3 expressing CHO dhfr$^-$ cells measuring the increase of [^{3}H]thymidine uptake stimulated by the test compound. The data (EC_{50}=28 nM, agonist effect=55% compared to the effect of the full agonist quinpirol (100%)) clearly indicate agonist properties and, thus, are in agreement with the binding experiments.

In conclusion, chemo- and regioselective transformations of asparagine gave access to optically active 5- and 6-amino tetrahydroindolizines. Additionally, tetrahydroisoindoles were obtained as side products. Receptor binding experiments showed stereocontrolled receptor recognition leading to the D3 selective agonist (*S*)-**8** with D3 binding that is comparable to dopamine. Compounds of this type might be of interest for the treatment of Parkinson's disease.

2. Experimental

2.1. General

Solvents and reagents were purified and dried by standard procedures. Unless otherwise noted reactions were conducted under dry N_2. Evaporations of final product solutions were done under vacuo with a rotatory evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. If not otherwise stated MS were run by EI ionization (70 eV) with solid inlet, HRMS were obtained employing peak matching $M/\Delta M$=10,000. ^{1}H NMR spectra were recorded at 360 MHz spectrometers, if not otherwise stated in $CDCl_3$ relative to TMS; ^{13}C NMR spectra were recorded at 90 MHz in $CDCl_3$. Elemental analyses were performed by Beetz Microanalysis Laboratory and by the Institute of Organic Chemistry (Analytical Departments) of the Friedrich-Alexander University Erlangen-Nürnberg.

2.1.1. (*S*)-3-Dibenzylamino-4-hydroxypyrrol-1-ylbutane-1-one ((*S*)-5). To a solution of methylmagnesium chloride (0.33 mL, 1.0 mmol, 3.0 M in THF) in toluene (5 mL) pyrrole (69 μL, 1.0 mmol) was added dropwise at 0 °C and stirred for 15 min. Then a solution of lactone (*S*)-**2** (281 mg, 1.0 mmol) in toluene (3 mL) was added dropwise and stirred for further 30 min at 0 °C. Then water and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**5** (205 mg, 59%) as a colorless oil: $[\alpha]_D^{20}$=+56.6° (*c*=3.0 $CHCl_3$); IR 3445, 1713 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.65 (s, 1H), 2.79 (dd, *J*=15.0, 8.0 Hz, 1H), 3.14 (dd, *J*=15.0, 5.0 Hz, 1H,), 3.5–3.7 (m, 3H), 3.55 (d, *J*=13.0 Hz, 2H), 3.85 (d, *J*=13.0 Hz, 2H), 6.30 (d, *J*=2.4 Hz, 2H), 7.2–7.3 (m, 2H), 7.2–7.4 (m, 10H); ^{13}C NMR (90 MHz) δ 31.9, 53.5, 56.4, 61.5, 113.3, 118.9, 127.2, 128.1, 128.3, 138.4, 170.9; APCI-MS: 349 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.45): C, 75.83; H, 6.94; N, 8.04. Found: C, 75.89; H, 6.90; N, 8.07.

2.1.2. (*S*)-3-Dibenzylamino-4-hydroxy-1-(1*H*-pyrrol-2-yl)-butane-1-one ((*S*)-6). To a solution of methylmagnesium chloride (3.33 mL, 10.0 mmol, 3.0 M in THF) in toluene (10 mL) pyrrole (0.83 mL, 12.0 mmol) was added dropwise at 0 °C. The mixture was stirred at 50 °C for 1 h. Then a solution of lactone (*S*)-**2** (1.41 g, 5 mmol) in toluene (10 mL) was added. After stirring for a further 75 min at 100 °C the mixture was allowed to cool to room temperature. Then saturated NH_4Cl and Et_2O were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**6** (1.51 g, 87%) as a colorless oil: $[\alpha]_D^{20}$=+46.3° (*c*=2.0, $CHCl_3$); IR 3403, 3027, 1634 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.70 (dd, *J*=14.0, 4.0 Hz, 1H), 2.96 (s, 1H), 3.16 (dd, *J*=14.0, 8.0 Hz, 1H), 3.4–3.6 (m, 3H), 3.50 (d, *J*=13.0 Hz, 2H), 3.87 (d, *J*=13.0 Hz, 2H), 6.28 (ddd, *J*=4.0, 2.5, 2.5 Hz, 1H), 6.90 (ddd, *J*=4.0, 2.5, 1.5 Hz, 1H), 7.04 (ddd, *J*=2.5, 2.5, 1.5 Hz, 1H), 7.3–7.5 (m, 10H), 9.56 (s, 1H); ^{13}C NMR (90 MHz) δ 34.8, 53.6, 57.1, 61.8, 110.9, 116.5, 125.00, 127.3, 128.5, 129.0, 131.9, 138.9, 188.8. CIMS 349 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.45): C, 75.83; H, 6.94; N, 8.04. Found: C, 75.47; H, 7.04; N, 7.69. The enantiomer (*R*)-**6** was prepared as described for (*S*)-**6** using (*R*)-**2**: $[\alpha]_D^{20}$=−47.7° (*c*=1.0, $CHCl_3$).

2.1.3. (*S*)-3-Dibenzylamino-4-hydroxy-1-(1-methyl-pyrrol-2-yl)-butan-1-one ((*S*)-7). TMEDA (4.86 mL, 32.3 mmol) and *N*-methylpyrrole (3.75 mL, 42.1 mmol) were added to *n*-BuLi (20.2 mL, 32.3 mmol, 1.6 M in hexane) and allowed to stir 15 min at room temperature. This mixture was then added dropwise to a solution of (*S*)-**2** (3.04 g, 10.8 mmol) in THF (80 mL) at −78 °C until no more (*S*)-**2** could be detected via TLC (petroleum ether–EtOAc 7:3). Saturated $NaHCO_3$ (20 mL) was added and the reaction mixture was warmed to room temperature. Et_2O and water were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**7** (2.43 g, 62%) as a colorless oil: $[\alpha]_D^{20}$=+39.6° (*c*=0.5, $CHCl_3$); IR 3447, 1639 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.70 (dd, *J*=14.0, 8.5 Hz, 1H), 2.98 (s, 1H), 3.16 (dd, *J*=14.0,

4.0 Hz, 1H), 3.40–3.60 (m, 1H), 3.40–3.60 (m, 2H), 3.50 (d, J=13.5 Hz, 2H), 3.86 (d, J=13.5 Hz, 2H), 3.93 (s, 3H), 6.13 (dd, J=4.0, 2.5 Hz, 1H), 6.83 (dd, J=2.5, 1.5 Hz, 1H), 6.93 (dd, J=4.0, 1.5 Hz, 1H), 7.20–7.35 (m, 10H); ^{13}C NMR (90 MHz) δ 36.0, 37.7, 53.6, 57.2, 61.8, 108.1, 119.6, 127.3, 128.5, 129.0, 130.6, 131.6, 139.0, 189.4; CIMS 362 (M^+). Anal. Calcd for $C_{23}H_{26}N_2O_2$ (362.48): C, 76.21; H, 7.23; N, 7.73. Found: C, 76.34; H, 7.34; N, 7.74. The enantiomer (*R*)-**7** was prepared as described for (*S*)-**7** using (*R*)-**2**: $[\alpha]_D^{20}=-41.5°$ (c=0.5, $CHCl_3$).

2.1.4. (*S*)-5-Dipropylamino-4,5,6,7-tetrahydroindole ((*S*)-8). Compound (*S*)-**8** was prepared as described for (*S*)-**13** using (*S*)-**9** (45 mg, 0.142 mmol). The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**8** (24 mg, 78%) as a colorless oil: $[\alpha]_D^{20}=-49.5°$ (c=1.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 0.89 (t, J=7.4 Hz, 6H, $CH_2CH_2CH_3$), 1.5–1.6 (m, 4H, $CH_2CH_2CH_3$), 1.7 (m, 1H, H-6_{ax}), 2.1 (m, 1H, H-6_{eq}), 2.5–2.6 (m, 4H, CH_2CH_2-CH_3), 2.6–2.7 (m, 4H, H-$4_{eq,ax}$, H-$7_{eq,ax}$), 3.0–3.1 (m, 1H, H-5_{ax}), 5.97 (dd, J=2.7, 2.7 Hz, 1H, H-3), 6.63 (dd, J=2.7, 2.7 Hz, 1H, H-2), 7.80 (s, 1H, NH); ^{13}C NMR (90 MHz) δ 11.85 ($NCH_2CH_2CH_3$), 21.68 ($NCH_2CH_2CH_3$), 22.82, 24.53 (C-4, C-7), 26.09 (C-6), 52.83 ($NCH_2CH_2CH_3$), 58.26 (C-5), 107.66 (C-3), 116.00 (C-3a), 116.52 (C-2), 126.13 (C-7a); EIMS 220 (M^+). Anal. Calcd for $C_{14}H_{24}N_2$ (220.36): C, 76.31; H, 10.98; N, 12.71. Found: C, 76.25; H, 10.99; N, 12.66. The enantiomer (*R*)-**8** was prepared as described for (*S*)-**13** using (*R*)-**9**: $[\alpha]_D^{20}=+50.0°$ (c=0.5, $CHCl_3$).

2.1.5. (*S*)-5-Dibenzylamino-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-9) and (*S*)-1-trifluoromethylsulfonyl-5-dibenzylamino-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-11). Trifluoromethanesulfonic anhydride (0.59 mL, 3.60 mmol) was added dropwise to an ice cooled solution of (*S*)-**10** (926 mg, 2.77 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.48 g, 7.20 mmol). The mixture was stirred for 1 h at room temperature. Then saturated $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to give (*S*)-**9** (423 mg, 48%) and (*S*)-**11** (220 mg, 18%) as colorless oils: (*S*)-**9**: $[\alpha]_D^{20}=-58.9°$ (c=2.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 1.81 (dddd, J=12.5, 12.0, 12.0, 6.0 Hz, 1H), 2.14 (ddd, J=12.5, 2.5, 2.2 Hz, 1H), 2.5–2.7 (m, 4H), 3.01 (dddd, J=12.0, 10.0, 6.0, 2.2 Hz, 1H), 3.66 (d, J=14.0 Hz, 2H), 3.75 (d, J=14.0 Hz, 2H), 5.96 (dd, J=2.6, 2.6 Hz, 1H), 6.59 (dd, J=2.6, 2.6 Hz, 1H), 7.3–7.5 (m, 10H), 7.64 (s, 1H); ^{13}C NMR (90 MHz) δ 22.9, 24.4, 25.4, 54.0, 54.3, 115.0, 122.4, 125.2, 126.8, 128.3, 128.4, 130.4, 140.4. EIMS 316 (M^+). Anal. Calcd for $C_{22}H_{24}N_2$ (316.45): C, 83.50; H, 7.64; N, 8.85. Found: C, 83.49; H, 7.65; N, 8.87. (*S*)-**11**: $[\alpha]_D^{20}=-11.5°$ (c=2.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 1.76 (dddd, J=12.5, 12.0, 12.0, 5.3 Hz, 1H), 2.20 (ddd, J=12.5, 5.3, 2.4 Hz, 1H), 2.5–2.7 (m, 4H), 2.9–3.0 (m, 1H), 3.65 (d, J=14.0 Hz, 2H), 3.74 (d, J=14.0 Hz, 2H), 6.16 (d, J=3.5 Hz, 1H), 6.94 (d, J=3.5 Hz, 1H), 7.2–7.5 (m, 10H); ^{13}C NMR (90 MHz) δ 22.9, 24.4, 25.4, 53.9, 54.3, 115.0, 119.3 (q, J=323 Hz), 122.4, 125.2, 126.8, 128.2, 128.4, 130.4, 140.3;. EIMS 448 (M^+). Anal. Calcd for $C_{23}H_{23}F_3N_2O_2S$ (448.51): C, 61.59; H, 5.17; N, 6.25. Found: C, 61.55; H, 5.18; N, 6.20. The enantiomers (*R*)-**9** and (*R*)-**11** were prepared as described for (*S*)-**9** and (*S*)-**11** using (*R*)-**10**: (*R*)-**9**: $[\alpha]_D^{20}=+57.2°$ (c=3.0, $CHCl_3$); (*R*)-**11**: $[\alpha]_D^{20}=+13.4°$ (c=3.0, $CHCl_3$).

2.1.6. (*S*)-2-Dibenzylamino-4-(1*H*-pyrrol-2-yl)-butan-1-ol ((*S*)-10). $AlCl_3$ (2.62 g, 19.70 mmol) was suspended in CH_2Cl_2 (90 mL) and cooled to 0 °C. Borane–*tert*butylamine complex (3.43 g, 39.40 mmol) was slowly added. The mixture was allowed to stir for 10 min giving a clear colorless solution. A solution of (*S*)-**6** (2.29 g; 6.57 mmol) in as little CH_2Cl_2 as can be was added dropwise to the ice-cooled solution and stirred for a further 60 min. Then water was carefully added at 0 °C. The solution was warmed up to room temperature and 0.1 M HCl was added until the gas evolution stopped. Then CH_2Cl_2 was added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**10** (959 mg, 44%) as a colorless oil: $[\alpha]_D^{20}=+70.0°$ (c=1.0, $CHCl_3$); IR 3427, 3376 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.54 (dddd, J=13.5, 9.0, 8.0, 6.0 Hz, 1H), 2.04 (dddd, J=13.5, 9.0, 7.0, 4.0 Hz, 1H), 2.52 (ddd, J=15.0, 8.0, 7.0 Hz, 1H), 2.63 (ddd, J=15.0, 9.0, 6.0 Hz, 1H), 2.83 (dddd, J=9.0, 9.0, 5.5, 4.0 Hz, 1H), 2.92 (s, 1H), 3.4–3.6 (m, 2H), 3.43 (d, J=14.0 Hz, 2H), 3.79 (d, J=14.0 Hz, 2H), 5.93 (ddd, J=3.5, 2.5, 1.5 Hz, 1H), 6.14 (ddd, J=3.5, 3.0, 1.5 Hz, 1H), 6.63 (ddd, J=3.0, 2.5, 1.5 Hz, 1H), 7.3–7.5 (m, 10H), 7.80 (s, 1H); ^{13}C NMR (90 MHz) δ 25.1, 25.9, 53.3, 58.4, 60.9, 105.2, 108.5, 116.3, 127.2, 128.5, 129.1, 131.6, 139.3; EIMS 334 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O$ (334.37): C, 79.01; H, 7.84; N, 8.38. Found: C, 78.98; H, 7.82; N, 8.07. The enantiomer (*R*)-**10** was prepared as described for (*S*)-**10** using (*R*)-**6**: $[\alpha]_D^{20}$-69.0° (c=1.0, $CHCl_3$).

2.1.7. (*S*)-2-Dibenzylamino-4-(1-methyl-1*H*-pyrrol-2-yl)-butan-1-ol ((*S*)-12). $AlCl_3$ (1.16 g, 8.70 mmol) was suspended in CH_2Cl_2 (30 mL) and cooled to 0 °C. Borane–*tert*butylamine complex (1.51 g, 17.4 mmol) was added slowly. The mixture was allowed to stir for 10 min giving a clear colorless solution. A solution of (*S*)-**7** (1.05 g; 2.90 mmol) in as little CH_2Cl_2 as can be was added dropwise to the ice-cooled solution and stirred for a further 60 min. Then water was carefully added at 0 °C. The solution was warmed up to room temperature and 0.1 M HCl was added until the gas evolution stopped. Then CH_2Cl_2 was added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography ($CHCl_3$–EtOAc, 95:5) to give (*S*)-**12** (734 mg, 73%) as a colorless oil: $[\alpha]_D^{20}=+92.0°$ (c=1.0, $CHCl_3$); IR 3439 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.55 (dddd, J=13.5, 9.5, 9.0, 5.5 Hz, 1H), 2.07 (dddd, J=13.5, 10.0, 6.5, 4.0 Hz, 1H), 2.45 (ddd, J=15.5, 9.0, 6.5 Hz, 1H) 2.52 (ddd, J=15.5, 10.0, 5.5 Hz, 1H), 2.87 (dddd, J=9.5, 9.5, 5.5, 4.0 Hz, 1H), 3.04 (s, 1H), 3.43 (d, J=13.0 Hz, 2H), 3.50 (s, 3H), 3.5–3.6 (m, 2H), 3.83 (d, J=13.0 Hz, 2H), 5.91 (dd, J=3.0, 2.0 Hz, 1H), 6.07 (dd, J=3.0, 2.5 Hz, 1H), 6.56 (dd, J=2.5, 2.0 Hz, 1H), 7.2–7.4 (m, 10H); ^{13}C NMR (90 MHz) δ 23.9, 24.6, 33.5, 53.2, 58.8, 60.8, 105.6, 106.8, 121.3, 127.2, 128.5, 129.1, 132.5, 139.2; EIMS 348 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O$ (348.49): C, 79.27; H, 8.10; N, 8.04. Found: C, 79.01; H, 7.95; N, 7.89. The enantiomer (*R*)-**12** was prepared as

described for (*S*)-**12** using (*R*)-**7**: $[\alpha]_D^{20}=-91.5°$ (c=1.0, $CHCl_3$).

2.1.8. (*S*)-5-Dipropylamino-1-methyl-4,5,6,7-tetrahydroindole ((*S*)-13). A solution of (*S*)-**14** (386 mg, 1.17 mmol) and $Pd(OH)_2$/C (333 mg) in EtOAc and MeOH (1:1) (20 mL) was stirred under hydrogen atmosphere (1 atm) at room temperature for 24 h. The solution was filtered and evaporated to give the crude amine (176 mg). The crude product was dissolved in 1,2-dichloroethane (20 mL), propionaldehyde (0.17 mL, 2.34 mmol) and sodium triacetoxyborohydride (595 mg, 2.81 mmol) were added. After stirring for 1 h at room temperature, $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**13** (160 mg, 58%) as a colorless oil: $[\alpha]_D^{20}=-48.4°$ (c=0.25, $CHCl_3$); ^{1}H NMR (360 MHz) δ 0.87 (t, J=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.45 (tq, J=7.5, 7.5 Hz, 4H, $NCH_2CH_2CH_3$), 1.69 (dddd, J=12.0, 12.0, 12.0, 6.0 Hz, 1H, H-6_{ax}), 2.02 (dddd, J=12.0, 6.0, 4.0, 2.0 Hz, 1H, H-6_{eq}), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.4–2.7 (m, 4H, H-4, H-7), 2.95 (dddd, J=12.0, 11.5, 5.0, 2.0 Hz, H-5_{ax}), 3.46 (s, 3H, NCH_3), 5.89 (d, J=2.5 Hz, 1H, pyrrole-H-3), 6.48 (d, J=2.5 Hz, 1H, pyrrole-H-2); ^{13}C NMR (90 MHz) δ 11.84 ($NCH_2CH_2CH_3$), 21.82, 24.71 ($NCH_2CH_2CH_3$, C-4, C-7), 26.02 (C-6), 33.03 (NCH_3), 52.81 ($NCH_2CH_2CH_3$), 57.93 (C-5), 106.11 (C-3), 116.34 (C-3a), 120.39 (C-2), 127.43 (C-7a); EIMS 234 (M^+); combustion analysis from the dibenzoyl-L-tartaric acid salt (mp 107 °C). Anal. Calcd for $C_{33}H_{40}N_2O_2$ (592.69): C, 72.47; H, 11.77; N, 7.35. Found: C, 72.53; H, 11.69; N, 7.29; HRMS calcd for $C_{15}H_{26}N_2$ (M^+): 234.20997. Found: 234.20959. The enantiomer (*R*)-**13** was prepared as described for (*S*)-**13** using (*R*)-**14**: $[\alpha]_D^{20}=+49.4°$ (c=1.0, $CHCl_3$).

2.1.9. (*S*)-5-Dibenzylamino-1-methyl-4,5,6,7-tetrahydroindole ((*S*)-14). Trifluoromethanesulfonic anhydride (0.48 mL, 2.94 mmol) was added dropwise to an ice cooled solution of (*S*)-**12** (682 mg, 1.96 mmol) and 2,6-di-*tert*-butyl-4-methyl-pyridine (1.21 g, 5.88 mmol). The mixture was stirred for 1 h at room temperature. Then saturated $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to give (*S*)-**14** (433 mg, 67%) as a colorless oil: $[\alpha]_D^{20}=-47.0°$ (c=1.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 1.79 (dddd, J=12.0, 12.0, 12.0, 5.5 Hz, 1H), 2.17 (m, 1H), 2.44 (m, 1H), 2.60–2.76 (m, 3H), 2.98 (dddd, J=12.0, 10.0, 6.0, 2.5 Hz, 1H), 3.40 (s, 3H), 3.66 (d, J=14.0 Hz, 2H), 3.73 (d, J=14.0 Hz, 2H), 5.88 (d, J=2.5 Hz, 1H), 6.44 (d, J=2.5 Hz, 1H), 7.10–7.40 (m, 10H, ArH); ^{13}C NMR (90 MHz) δ 21.6, 24.7, 24.9, 32.8, 53.8, 55.1, 105.9, 116.5, 120.1, 126.4, 127.3, 128.0, 128.3, 140.7; EIMS 330 (M^+). Anal. Calcd for $C_{23}H_{26}N_2$ (330.48): C, 83.59; H, 7.93; N, 8.48. Found: C, 83.56; H, 7.76; N, 8.37. The enantiomer (*R*)-**14** was prepared as described for (*S*)-**14** using (*R*)-**12**: $[\alpha]_D^{20}=+47.5°$ (c=1.0, $CHCl_3$).

2.1.10. (*S*)-5-Dipropylamino-1-methyl-4,5,6,7-tetrahydroindol-2-carbaldehyde ((*S*)-15). $POCl_3$ (36 μL, 0.392 mmol) was added at 0 °C to a solution of (*S*)-**13** (46 mg, 0.196 mmol) in DMF (5 mL). The reaction mixture was stirred for a further 60 min. After that the reaction solution was added to ice cooled 1 N NaOH and the product was extracted with Et_2O. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**15** (44 mg, 85%) as a colorless oil: $[\alpha]_D^{20}=-65.5°$ (c=0.4, $CHCl_3$); IR 1654 cm^{-1}; ^{1}H NMR (360 MHz) δ 0.89 (t, J=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.3–1.5 (m, 4H, $NCH_2CH_2CH_3$), 1.6–1.7 (m, 1H, H-6_{ax}), 2.0–2.1 (m, 1H, H-6_{eq}), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.4–2.8 (m, 4H, H-4, H-7), 2.8–3.0 (m, 1H, H-5_{ax}), 3.80 (s, 3H, NCH_3), 6.64 (m, 1H, pyrrole-H-3), 9.38 (s, 1H, CHO); ^{13}C NMR (90 MHz) δ 11.84 ($NCH_2CH_2CH_3$), 22.01, 22.19, 24.88 ($NCH_2CH_2CH_3$, C-4,C-7), 25.41 (C-6), 32.18 (NCH_3), 52.78 ($NCH_2CH_2CH_3$), 57.33 (C-5), 119.76 (C-3a), 122.84 (C-3), 131.42 (C-7a), 139.60 (C-2), 178.54 (CHO); EIMS 262 (M^+). Anal. Calcd for $C_{16}H_{26}N_2O$ (262.40): C, 73.24; H, 9.99; N, 10.68. Found: C, 72.91; H, 10.00; N, 10.65. The enantiomer (*R*)-**15** was prepared as described for (*S*)-**15** using (*R*)-**13**: $[\alpha]_D^{20}=+63.5°$ (c=0.5, $CHCl_3$).

2.1.11. 1-[(*S*)-1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-5-yl]-3-[(*S*)-phenylethyl]-urea ((*S*,*S*)-17) and 1-[(*S*)-1-methyl-4,5,6,7-tetrahydro-1*H*-indol-5-yl]-3-[(*R*)-phenylethyl]-urea ((*S*,*R*)-17). Compound (*S*)-**14** (83 mg, 0.251 mmol) and $Pd(OH)_2$/C (83 mg), dissolved in EtOAc–MeOH (9:1, 5 mL), were stirred for 24 h at room temperature under hydrogen atmosphere (1 atm). After removing the catalyst by filtration, the solution was divided in two equal parts and evaporated separately. (*R*)-Phenylethyl isocyanate (*R*)-**16** (17 μL, 0.123 mmol) was added to a solution of one part of the residue (14 mg, 0.092 mmol) in CH_2Cl_2 (3 mL). After stirring for 6 h at room temperature, the solvent was removed and the residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*;*R*)-**17** (20 mg, 73%) as a colorless oil. (*S*)-Phenylethyl isocyanate (17 μL, 0.123 mmol) was added to a solution of the second part of the residue (17 mg, 0.112 mmol) in CH_2Cl_2 (3 mL). After stirring for 6 h at room temperature, the solvent was removed and the residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*,*S*)-**17** (22 mg, 66%) as a colorless oil. An analytical sample was prepared: (*S*,*S*)-**17**: $[\alpha]_D^{20}=-13.1°$ (c=0.7, $CHCl_3$); IR 3332, 1623 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.45 (d, J=6.8 Hz, 3H), 1.82 (m, 1H), 1.97 (m, 1H), 2.25 (m, 1H), 2.45–2.80 (m, 3H), 3.45 (s, 3H), 4.05 (m, 1H), 4.25 (d, J=7.5 Hz, 1H), 4.42 (d, J=7.5 Hz, 1H), 4.79 (m, 1H), 5.84 (d, J=2.7 Hz, 1H), 6.47 (d, J=2.7 Hz, 1H), 7.2–7.4 (m, 5H); EIMS 297 (M^+). Anal. Calcd for $C_{18}H_{23}N_3O$ (297.40): C, 72.70; H, 7.80; N, 14.13. Found: C, 72.44; H, 7.68; N, 14.25. (*S*,*R*)-**17**: IR 3330, 1627 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.42 (d, J=6.8 Hz, 3H), 1.81 (dddd, J=15.0, 13.1, 13.0, 6.7 Hz, 1H), 2.17 (m, 1H), 2.34 (dd, J=15.5, 6.0 Hz, 1H), 2.44 (dd, J=15.5, 12.4 Hz, 1H), 2.3–2.5, 2.7–2.9 (m, 2H), 3.39 (s, 3H), 4.05 (m, 1H), 4.33 (d, J=8.6 Hz, 1H), 4.53 (d, J=5.8 Hz, 1H), 4.67 (ddd, J=13.0, 12.4, 6.0 Hz, 1H), 5.85 (d, J=2.7 Hz, 1H), 6.46 (d, J=2.7 Hz, 1H), 7.2–7.4 (m, 5H, ArH);. EIMS 297 (M^+); HRMS calcd for $C_{18}H_{23}N_3O$ (M^+): 297.18411. Found: 297.18418. HPLC (Lichrosorb Si 60 7μ, CH_2Cl_2–MeOH 99:1, 1.5 mL min^{-1}, detection UV: 256 nm) t_R 13.0 min (97.5%, (*S*,*R*)-**17**), 10.2 min (2.5%, (*S*,*S*)-**17**).

2.1.12. (*S*)-3-Dibenzylamino-4-hydroxy-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)-butan-1-one ((*S*)-19). To a solution of 3-bromo-1-triisopropylsilyl pyrrole (605 mg, 2.0 mmol) in pentane (5 mL), *n*-BuLi (1.25 mL, 2.0 mmol, 1.6 M in hexane) was added dropwise. The mixture was stirred for 15 min at room temperature. The solution was then slowly added to (*S*)-**2** (281 mg, 1.0 mmol) dissolved in THF (5 mL) at 0 °C. The addition was stopped, when no more lactone (*S*)-**2** could be detected via TLC (petroleum ether–Et_2O 1:1). Then water and Et_2O were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether -Et_2O 1:1) to give (*S*)-**19** (234 mg, 47%) as a colorless oil: $[\alpha]_D^{20}$+50.0° (*c*=0.5, $CHCl_3$); IR 3445, 1652 cm^{-1}; ^1H NMR (360 MHz) δ 1.11 (d, *J*=7.5 Hz, 18H), 1.47 (qq, *J*=7.5, 7.5 Hz, 3H), 2.70 (dd, *J*=14.5, 7.7 Hz, 1H), 3.05 (s, 1H), 3.14 (dd, *J*=14.5, 4.3 Hz, 1H), 3.53 (d, *J*=13.4 Hz, 2H), 3.5–3.6 (m, 3H), 3.85 (d, *J*=13.4 Hz, 2H), 6.70 (dd, *J*=3.0, 1.5 Hz, 1H), 6.75 (dd, *J*=3.0, 2.0 Hz, 1H), 7.2–7.4 (m, 10H), 7.39 (dd, *J*=2.0, 1.5 Hz, 1H); ^{13}C NMR (90 MHz) δ 11.3, 17.4, 36.6, 53.4, 56.6, 61.7, 110.7, 125.5, 127.0, 127.8, 128.2, 128.8, 129.3, 139.0, 194.6. Anal. Calcd for $C_{31}H_{44}N_2O_2Si$ (504.79): C, 73.76; H, 8.79; N, 5.55. Found: C, 73.83; H, 8.70; N, 5.59. The enantiomer (*R*)-**19** was prepared as described for (*S*)-**19** using (*R*)-**2**: $[\alpha]_D^{20}$=−48.5° (*c*=0.5, $CHCl_3$).

2.1.13. (*S*)-2-Dibenzylamino-4-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)-butan-1-ol ((*S*)-20). Compound (*S*)-**20** was prepared as described for (*S*)-**12** using (*S*)-**19** (1.44 g, 2.86 mmol). The residue was purified by flash chromatography (petroleum ether–Et_2O, 8:2) to give (*S*)-**20** (721 mg, 51%) as a colorless oil: $[\alpha]_D^{20}$=+80.9° (*c*=2.0, $CHCl_3$); IR 3449 cm^{-1}; ^1H NMR (360 MHz) δ 1.09 (d, *J*=7.5 Hz, 18H), 1.44 (qq, *J*=7.5, 7.5 Hz, 3H), 1.4–1.5 (m, 1H), 2.04 (dddd, *J*=13.5, 9.5, 6.5, 4.0 Hz, 1H), 2.45 (ddd, *J*=14.5, 9.0, 6.5 Hz, 1H), 2.52 (ddd, *J*=14.5, 9.5, 5.5 Hz, 1H), 2.86 (dddd, *J*=9.5, 9.5, 4.5, 4.0 Hz, 1H), 3.14 (s, 1H), 3.4–3.6 (m, 2H), 3.44 (d, *J*=13.5 Hz, 2H), 3.81 (d, *J*=13.5 Hz, 2H), 6.17 (dd, *J*=2.5, 1.5 Hz, 1H), 6.52 (dd, *J*=2.0, 1.5 Hz, 1H), 6.72 (dd, *J*=2.5, 2.0 Hz, 1H), 7.2–7.4 (m, 10H); ^{13}C NMR (90 MHz) δ 11.6, 17.7, 24.7, 26.7, 53.2, 59.0, 60.9, 110.4, 121.0, 124.3, 125.3, 127.1, 128.4, 129.1, 139.5; EIMS 490 (M^+). Anal. Calcd for $C_{31}H_{46}N_2OSi$ (490.81): C, 75.86; H, 9.45; N, 5.71. Found: C, 75.60; H, 9.51; N, 5.71. The enantiomer (*R*)-**20** was prepared as described for (*S*)-**12** using (*R*)-**19**: $[\alpha]_D^{20}$=−79.6° (*c*=2.0, $CHCl_3$).

2.1.14. (*S*)-6-Dibenzylamino-1-triisopropylsilyl-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-22), (*S*)-5-dibenzylamino-2-triisopropylsilyl-4,5,6,7-tetrahydro-2*H*-isoindole ((*S*)-21). Compounds (*S*)-**22** and (*S*)-**21** were prepared as described for (*S*)-**14** using (*S*)-**20** (730 mg, 1.49 mmol). The residue was purified by flash chromatography (petroleum ether–Et_2O, 100:0, 98:2, 95:5) to give a 8:2 mixture (estimated by ^1H NMR) of (*S*)-**22** and (*S*)-**21** (556 mg, 79%) as a colorless oil: (*S*)-**22**: ^1H NMR (360 MHz) δ 1.09 (d, *J*=7.5 Hz, 18H), 1.46 (qq, *J*=7.5, 7.5 Hz, 3H), 1.73 (dddd, *J*=12.0, 12.0, 12.0, 5.5 Hz, 1H), 2.0–2.1 (m, 1H), 2.4–2.5 (m, 1H), 2.4–2.5 (m, 1H), 2.6–2.7 (m, 1H), 2.8–2.9 (m, 1H), 3.02 (dddd, *J*=12.0, 11.0, 4.5, 2.0 Hz, 1H), 3.66 (d, *J*=14.0 Hz, 2H), 3.76 (d, *J*=14.0 Hz, 2H), 5.97 (d, *J*=2.5 Hz, 1H), 6.64 (d, *J*=2.5 Hz, 1H), 7.2–7.5 (m, 10H); (*S*)-**21**: ^1H NMR (360 MHz) δ 6.36 (s, 1H), 6.40 (s, 1H). EIMS 472 (M^+); The enantiomers (*R*)-**22** and (*R*)-**21** were prepared as described for (*S*)-**14** using (*R*)-**20**.

2.1.15. (*S*)-6-Dipropylamino-1-triisopropylsilyl-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-24), (*S*)-5-dipropylamino-2-triisopropylsilyl-4,5,6,7-tetrahydro-2*H*-isoindole ((*S*)-23). A solution of (*S*)-**21** and (*S*)-**22** (563 mg, 1.19 mmol) and $Pd(OH)_2/C$ (563 mg) in EtOAc and MeOH (1:1) was stirred under hydrogen atmosphere (1 atm) at room temperature for 2 h. The solution was filtered and evaporated to give the crude amines (307 mg). The crude product was dissolved in 1,2-dichloroethane, propionaldehyde (0.17 mL, 2.38 mmol) and sodium triacetoxyborohydride (605 mg, 2.86 mmol) were added. After stirring for 45 min at room temperature, $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**24** (278 mg, 62%) and (*S*)-**23** (40 mg, 9%) as colorless oils: (*S*)-**24**: $[\alpha]_D^{20}$=−29.8° (*c*=0.5, $CHCl_3$); ^1H NMR (360 MHz) δ 0.89 (t, *J*=7.2 Hz, 6H), 1.11 (d, *J*=7.5 Hz, 18H),1.3–1.7 (m, 8H), 1.9–2.1 (m, 1H), 2.4–2.8 (m, 8H), 3.0 (m, 1H), 6.02 (d, *J*=2.7 Hz, 1H), 6.69 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (90 MHz) δ 11.8, 12.5, 18.2, 22.0, 23.0, 26.2, 27.7, 52.9, 58.2, 108.8, 119.9, 124.6, 131.5; EIMS 376 (M^+). Anal. Calcd for $C_{23}H_{44}N_2Si$ (376.71)×1/4H_2O: C, 72.47; H, 11.77; N, 7.35. Found: C, 72.53; H, 11.69; N, 7.29. (*S*)-**23**: $[\alpha]_D^{20}$=−35.8° (*c*=0.5, $CHCl_3$); ^1H NMR (360 MHz) δ 0.88 (t, *J*=7.2 Hz, 6H), 1.08 (d, *J*=7.5 Hz, 18H),1.39 (q, *J*=7.5 Hz, 3H), 1.4–1.5 (m, 4H), 1.5–1.7 (m, 1H), 1.9–2.0 (m, 1H), 2.5–2.6 (m, 4H), 2.5–2.9 (m, 4H), 3.0–3.1 (m, 1H), 6.40 (s, 1H), 6.42 (s, 1H); EIMS 376 (M^+). Anal. Calcd for $C_{23}H_{44}N_2Si$ (376.71)×1/2H_2O: C, 71.62; H, 11.76; N, 7.26. Found: C, 71.43; H, 11.76; N, 7.29. The enantiomers (*R*)-**23** and (*R*)-**24** were prepared as described for (*S*)-**24** and (*S*)-**23** using (*R*)-**21**/(*R*)-**22**: (*R*)-**24**: $[\alpha]_D^{20}$=+31.3° (*c*=1.5, $CHCl_3$); (*R*)-**23**: $[\alpha]_D^{20}$=+35.5° (*c*=0.5, $CHCl_3$).

2.1.16. (*S*)-5-Dipropylamino-4,5,6,7-tetrahydro-2*H*-isoindole ((*S*)-25). Compound (*S*)-**25** was prepared as described for (*S*)-**26** using (*S*)-**23** (27 mg, 0.072 mmol). The residue was purified by flash chromatography (CH_2Cl_2–MeOH 8:2) to give (*S*)-**25** (13 mg, 82%) as a colorless oil: $[\alpha]_D^{20}$=−52.1° (*c*=0.5, $CHCl_3$); ^1H NMR (360 MHz) δ 0.88 (t, *J*=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.50 (tq, *J*=7.5, 7.5 Hz, 4H, $NCH_2CH_2CH_3$), 1.61 (dddd, *J*=12.0, 12.0, 12.0, 5.0 Hz, 1H, H-6_{ax}), 2.0 (m, 1H, H-6_{eq}), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.5–2.7 (m, 2H, H-$7_{eq,ax}$), 2.7–2.9 (m, 2H, H-$4_{eq,ax}$), 2.99 (dddd, *J*=12.0, 12.0, 5.0, 2.0 Hz, 1H, H-5_{ax}), 6.47, 6.49 (s, 2H, H-1, H-3), 8.03 (s, 1H, NH).; ^{13}C NMR (90 MHz) δ 11.91 ($NCH_2CH_2CH_3$), 22.03, 22.19 ($NCH_2CH_2CH_3$, C-7), 24.38 (C-4), 27.01 (C-6), 52.83 ($NCH_2CH_2CH_3$), 58.59 (C-5), 112.85, 113.53 (C-3a, C-7a), 119.09, 119.46 (C-1, C-3); EIMS 220 (M^+); HRMS calcd for $C_{14}H_{24}N_2$ (M^+): 220.19395. Found: 220.19379. The enantiomer (*R*)-**25** was prepared as described for (*S*)-**26** using (*R*)-**23**: $[\alpha]_D^{20}$=+53.6° (*c*=0.8, $CHCl_3$).

2.1.17. (*S*)-6-Dipropylamino-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-26). A solution of (*S*)-**24** (45 mg, 0.119 mmol) and TBAF (119 μL, 0.119 mmol, 1.0 M in THF) in THF

(5 mL) was stirred at room temperature for 20 min. Then, satd $NaHCO_3$ solution and Et_2O were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 8:2) to give (*S*)-**26** (18 mg, 69%) as a colorless oil: $[\alpha]_D^{20}=-52.0°$ (c=1.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 0.88 (t, J=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.49 (tq, J=7.5, 7.5 Hz, 4H, $NCH_2CH_2CH_3$), 1.63 (dddd, J=12.0, 12.0, 12.0, 5.5 Hz, 1H, H-5$_{ax}$), 2.0 (m, 1H, H-5$_{eq}$), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.5–2.8 (m, 4H, H-4$_{eq,ax}$, H7$_{eq,ax}$), 3.09 (dddd, J=12.0, 11.0, 5.0, 2.0 Hz, 1H, H-6$_{ax}$), 5.96 (dd, J=2.5, 2.5 Hz, 1H, H-2), 6.63 (dd, J=2.5, 2.5 Hz, 1H, H-3), 7.77 (s, 1H, NH); ^{13}C NMR (90 MHz) δ 11.86 ($NCH_2CH_2CH_3$), 22.04 ($NCH_2CH_2CH_3$), 22.62 (C-4), 25.24 (C-7), 26.46 (C-5), 52.82 ($NCH_2CH_2CH_3$), 107.02 (C-3), 116.41 (C-2), 116.55 (C-3a), 126.26 (C-7a); EIMS 220 (M^+). Anal. Calcd for $C_{14}H_{24}N_2$ (220.36): C, 76.31; H, 10.98; N, 12.71. Found: C, 76.25; H, 10.84; N, 12.61. The enantiomer (*R*)-**26** was prepared as described for (*S*)-**26** using (*R*)-**24**: $[\alpha]_D^{20}=+53.9°$ (c=0.1, $CHCl_3$).

2.2. Receptor binding studies and mitogenesis experiments

To determine the binding affinities of the test compounds the human dopamine receptor subtypes D2$_{long}$, D2$_{short}$, D3 and D4.4, which were heterologously expressed in CHO cell lines, were employed in competition experiments together with the radioligand [^{3}H]spiperone (0.5 nM) and a series of 15 different concentrations of test compounds from 0.1 to 100,000 nM as triplicates according to literature.[19] Dopamine D1 affinities were established using porcine striatal membranes and the D1 selective radioligand [^{3}H]SCH23390 (0.3 nM). The resulting competition curves were analyzed by nonlinear regression analysis using the algorithms of PRISM (GraphPad Software, San Diego, CA) and the derived IC_{50} values were transformed into K_i values according to the equation of Cheng and Prusoff.[21] The resulting competition data were adjusted to mono- and biphasic curves. Considering statistic demands, a biphasic curve fitting was accepted when regression analysis coincidently indicated a rate of high affinity binding sites $>$ 20%. Otherwise, a monophasic curve was calculated. A mitogenesis assay with a D3 receptor expressing cell line was used to establish intrinsic activity according to the literature.[22] Stimulation of the receptor by an agonist or partial agonist test compound was measured an increase of [^{3}H]thymidine incorporation and compared to the full agonist quinpirole.

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References and notes

1. (a) Coppola, G. M.; Schuster, H. F. *Asymmetric synthesis*; Wiley: New York, 1987. (b) Gmeiner, P. In *Enantioselective synthesis of β-amino acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp 67–81. (c) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068.
2. (a) Gmeiner, P.; Kärtner, A.; Junge, D. *Tetrahedron Lett.* **1993**, *34*, 4325. (b) Gmeiner, P.; Kärtner, A. *Synthesis* **1995**, 83. (c) Weber, K.; Kuklinkski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647. (d) Weber, K.; Ohnmacht, U.; Gmeiner, P. *J. Org. Chem.* **2000**, *65*, 7406.
3. (a) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766. (b) Gmeiner, P.; Mierau, J.; Höfner, G. *Arch. Pharm. (Weinheim)* **1992**, *325*, 57.
4. Lehmann, T.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2863.
5. Lehmann, T.; Gmeiner, P. *Heterocycles* **2000**, *53*, 1371.
6. Michel, D.; Waibel, R.; Gmeiner, P. *Heterocycles* **1999**, *51*, 365.
7. (a) Andersen, K. E.; Braestrup, C.; Groenwald, F. C.; Joergensen, A. S.; Nielsen, E. B.; Sonnewald, U.; Soerensen, P. O.; Suzdak, P. D.; Knutsen, L. J. S. *J. Med. Chem.* **1993**, *36*, 1716. (b) Harrowven, D. C.; Dainty, R. F. *Tetrahedron Lett.* **1995**, *36*, 6739.
8. Lau, C. K.; Tardif, S.; Dufresne, C.; Scheigetz, J. *J. Org. Chem.* **1989**, *54*, 491.
9. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, *18*, 734.
10. Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3065.
11. (a) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157. (b) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723.
12. Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3760.
13. Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.
14. Hobbs, C. F.; McMillin, C. K.; Papadopoulus, E. P.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 43.
15. Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.
16. (a) Bach, N. J.; Kornfeld, E. D.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481. (b) Bosch, J.; Roca, T.; Perez, C. G.; Montanari, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 563.
17. Hayes, G.; Biden, T. J.; Selbie, L. A.; Shine, J. *Mol. Endocrinol.* **1992**, *6*, 920.
18. Sokoloff, P.; Andrieux, M.; Besançon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. *Eur. J. Pharmacol.* **1992**, *225*, 331.
19. Asghari, V.; Sanyal, S.; Buchwaldt, S.; Paterson, A.; Jovanovic, V.; Van Tol, H. H. M. *J. Neurochem.* **1995**, *65*, 1157.
20. Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.
21. Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
22. Hübner, H.; Kraxner, J.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 4563.

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A new approach to helical primary structures of four-membered rings: (*P*)- and (*M*)-tetraspiro[3.0.0.0.3.2.2.2]hexadecane☆

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Abstract—A new approach to helical primary structures of four-membered rings uses a cycloaddition of a trimethylenketeniminium salt to suitable tailored methylenecyclobutanes to assemble the desired carbon framework. The results are short and effective syntheses of (*M*)-trispiro[3.0.0.3.2.2]tridecane [(*M*)-**5**], and (*P*)- and (*M*)-tetraspiro[3.0.0.0.3.2.2.2]hexadecane [(*P*)- and (*M*)-**24**]. Unlike helices of three-membered rings, the specific rotation decreases, as the length of the helix increases.
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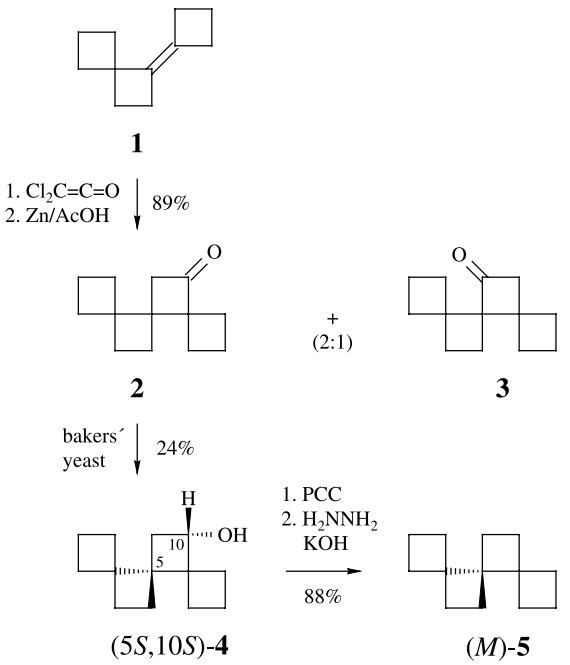
1. Introduction

The interesting quest, whether and to what extent the chiroptical properties of helical hydrocarbons of spiro-annelated rings are governed by static parameters like the identity period and the diameter and length of the helix, and/or by dynamic phenomena like conformational changes may best be answered experimentally in conjunction with an appropriate theoretical treatment. Towards this end, helical structures of rings of different size, and, for five-membered and larger rings, with different location of the spiro-centers should be considered. However, until now only three examples exist,[1,2] and methods with a general applicability for a synthesis of such compounds are rare.[3]

We recently described the synthesis of (*M*)-trispiro-[3.0.0.3.2.2]tridecane [(*M*)-**5**],[1] the first helical hydrocarbon of spiroannelated four-membered rings,[4] via a substance-, diastereo- and enantioselective enzymatic reduction of an inseparable 2:1-mixture of the trispiroketones **2** and **3** [**2**/**3**–(5*S*,10*S*)-**4**], itself obtained from bicyclobutylidene **1** by an addition of dichloroketene and a reductive dehalogenation. Oxidation with pyridinium chlorochromat followed by Wolff–Kishner reduction then yielded (*M*)-**5** (Scheme 1).



Scheme 1.

To improve the synthesis of **5**, and to make it suitable for a synthesis of higher analogues as well, we thought it necessary to prevent the formation of regioisomers and to establish the spiro[3.3]heptan-1-one subunit in **2** regio-specifically in a single step. Towards this end, we envisaged a cycloaddition of a trimethylenketeniminium salt **10**[5] to 1-methylenespiro[3.3]heptane (**8**), readily obtained by methylenation of **6**. As will be shown below, this approach proved successful, and therefore, a synthesis of the next higher analogue via a homologization of **6**, followed by the same set of reactions as used for the synthesis of **2** [**6**–**7**–**9**–**11**(**12**)] seemed feasible (Scheme 2). Stereochemically, a large preference for a formation of (5*R**,6*R**)-**11** with the desired helical carbon framework could be expected, and

☆ Polyspiranes, Part 28. For Part 27, see Ref. 1.

Keywords: Helicenes; Spiro compounds; Keteniminium salts; Cyclobutanones; Resolution.
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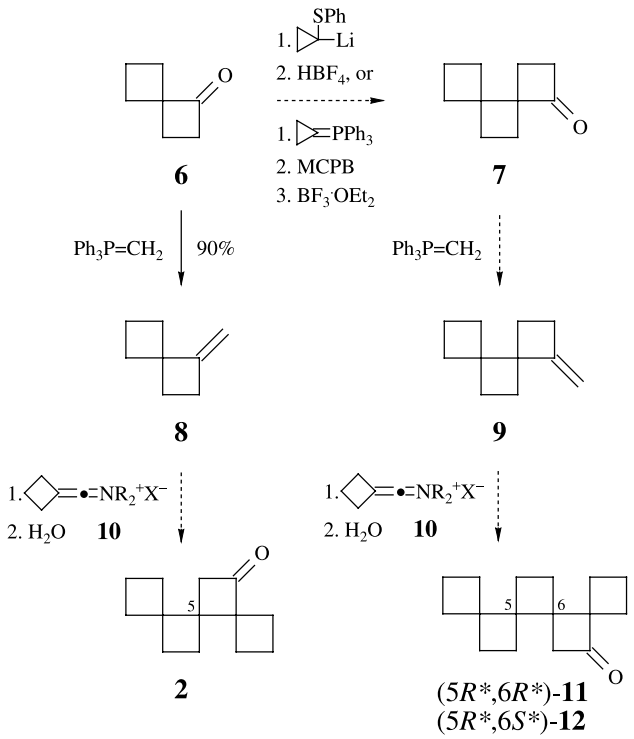
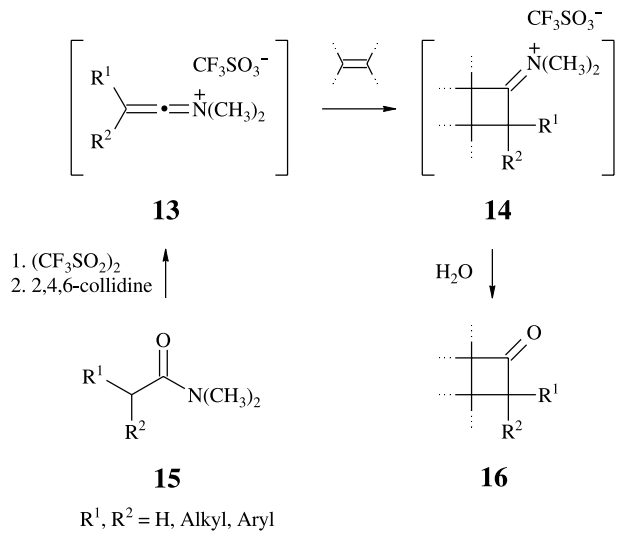


Scheme 2.

concerning its resolution, alternative possibilities to an enzymatic reduction were available. Of these, a use of (−)-diisopinocampheylchloroborane [(−)-DIP-Cl][6] as *S*-selective reducing agent for α-tertiary cycloalkanones and/or a use of (*S*)-(−)-2-hydrazino-2-oxo-*N*-(1-phenylethyl)-acetamide[7] as ketone resolving reagent seemed most promising. Research following these lines not only shortened the synthesis of (*M*)-trispiro[3.0.0.3.2.2]tridecane (**5**), but also enabled the first synthesis of (*P*)- and (*M*)-tetraspiro[3.0.0.0.3.2.2.2]hexadecane **24** as next higher analogues.



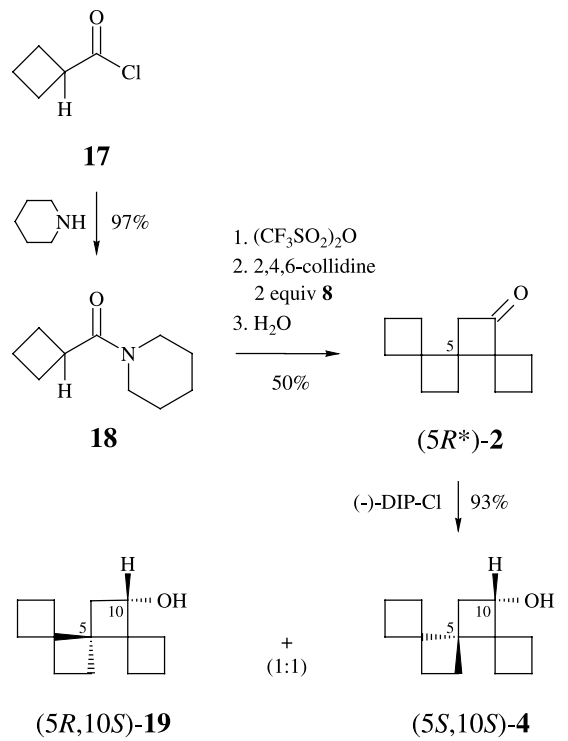
Scheme 3.

2. Results

Due to the pioneering work of Ghosez and co-workers[5] it is well known that keteniminium salts **13** may conveniently be generated by treatment of carboxylic acid amides **15** with trifluromethanesulfonic acid anhydride followed by 2,4,6-collidine, and that these salts effectively add to olefins yielding cyclobutylidene ammonium salts **14**, and, after hydrolysis, cyclobutanones **16** (Scheme 3). However, keteniminium salts derived from cycloalkanecarboxylic acid amides, representing a promising source for a variety of spiranes, have never been explored.

With this knowledge in mind, we reacted cyclobutanecarboxylic acid chloride (**17**) with piperidine and treated a solution of the resulting amide **18**[8] in dichloromethane first with trifluoromethanesulfonic acid anhydride, and then, in the presence of an excess of **8**, with 2,4,6-collidine. After 24 h of reflux and subsequent hydrolysis, the desired trispiroketone **2** was isolated in 50% yield (Scheme 4). This indicates that trimethylenketeniminium salts may offer distinct advantages over trimethylenketene itself,[9] at least in [2+2] cycloadditions with electron-poor olefins.

Having established a short and effective route to **2**, we next investigated its reduction with (−)-DIP-Cl. No reduction of an α-tertiary cyclobutanone had been described before, but spiro[4.4]nonan-1-one as an α-tertiary cyclopentanone had been transformed to the corresponding *S*-configurated alcohol within 12 h in 65% yield and 95% ee.[6] In any case, we were pleased to learn that (−)-DIP-Cl and **2** reacted almost instantaneously, and that the 1:1-mixture of alcohols formed consisted of (5*S*,10*S*)-**4** and a diastereoisomer, tentatively assigned as (5*R*,10*S*)-**19** (Scheme 4). Both alcohols were known from the reduction of **2** with

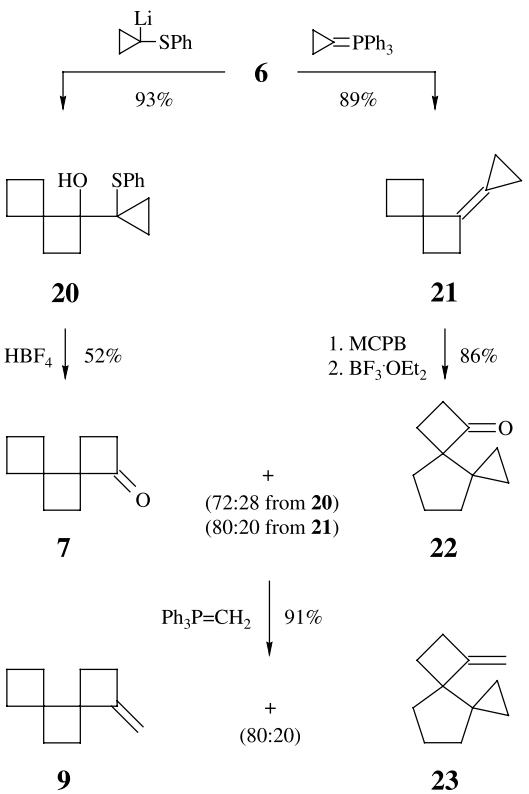


Scheme 4.

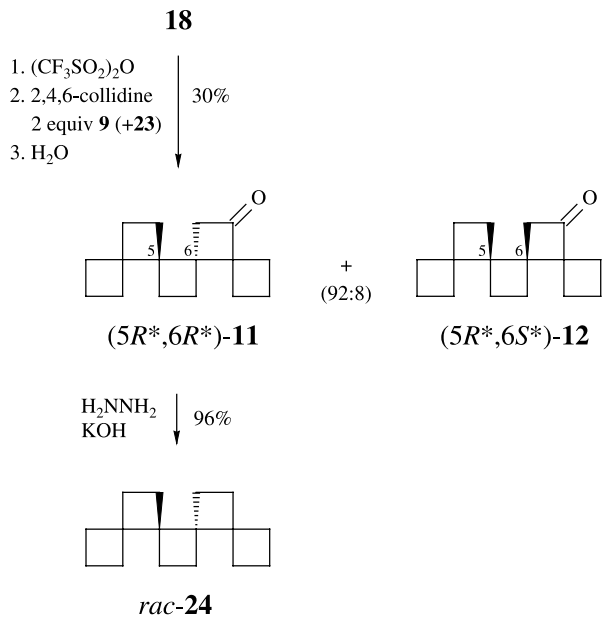
bakers' yeast,[1] and both were enantiomerically pure (>99% ee) according to capillary gas chromatography on a γ-cyclodextrin as chiral phase. As (5*S*,10*S*)-**4** had already been transformed to (*M*)-**5** by oxidation with pyridinium chlorochromate followed by Wolff–Kishner reduction[1] (Scheme 1), no efforts were made to repeat these reactions with (5*R*,10*S*)-**19**.

For the synthesis of tetraspiro[3.0.0.0.3.2.2.2]hexadecane (**24**), we first explored two routes to ketone **7** as precursor of olefin **9**, itself needed for a cycloaddition to the keteniminium salt derived from **18**: (a) an addition of 1-lithiocyclopropylphenyl sulphide to **6**, and a subsequent rearrangement with tetrafluoroboric acid [**6**–**20**–**7**(**22**)],[10] and (b) a cyclopropylidenation of **6**, and a subsequent epoxidation and rearrangement with boron trifluoride etherate [**6**–**21**–**7**(**22**)] (Scheme 5). In both cases, the C_3–C_4 ring enlargement leading to **7** was accompanied by a C_4–C_5 ring enlargement followed by a C_4–C_3 ring contraction and another C_4–C_5 ring enlargement leading to **22**, yielding the two ketones in a ratio of 72:28 from **20**, and 80:20 from **21**. Unfortunately, the two ketones were inseparable on a preparative scale, and the same was true for the two olefins **9** and **23** derived therefrom. However, no complications were met during the next step.

As was to be expected, the cycloaddition of the keteniminium salt derived from **18** to 1-methylene-dispiro[3.0.3.2]-decane (**9**) proceeded regio- and stereoselectively and delivered the desired tetraspiroketone (5*R**,6*R**)-**11** as major product of a 92:8-mixture with (5*R**,6*S**)-**12**, in 30% combined yield. Separation from (5*R**,6*S**)-**12** and products derived from **23** was achieved by column chromatography, and Wolff–Kishner reduction then yielded tetraspiro[3.0.0.0.3.2.2.2]hexadecane [*rac*-**24**] (Scheme 6). As the number and multiplicities of the resonance lines in the ^{13}C NMR spectrum [15.74 (t), 26.43 (t), 26.51 (t), 30.70 (t), 31.31 (t), 32.37 (t), 49.21 (s), 52.34 (s)] could account for both *rac*-**24** (symmetry C_2) and its achiral counterpart derived from (5*R**,6*S**)-**12** (symmetry C_s), a capillary gas chromatographic analysis on a γ-cyclodextrin as chiral phase proved necessary. This analysis revealed that the hydrocarbon in question was a racemic mixture of two enantiomers, and hence *rac*-**24**.

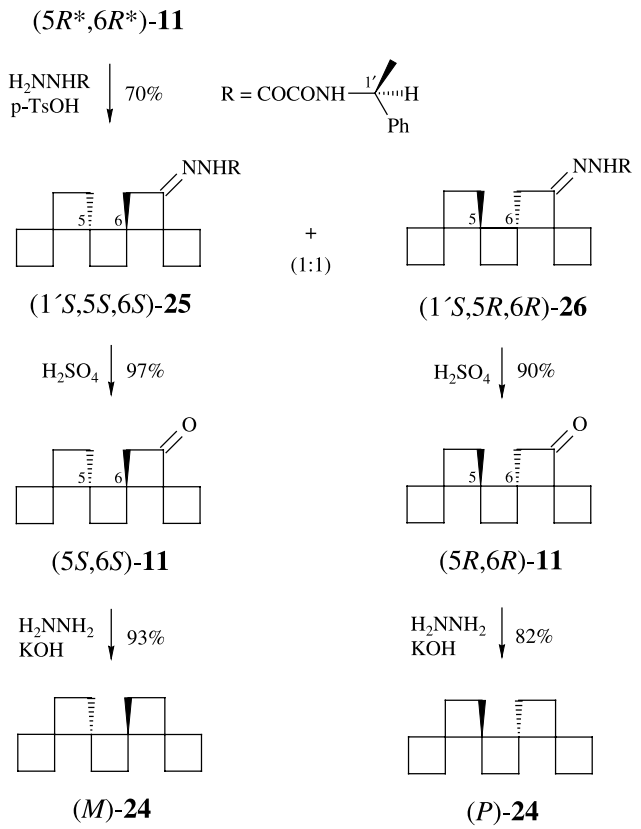


Scheme 5.



Scheme 6.

For the resolution of (5*R**,6*R**)-**11**, we first tried an enantioselective reduction with (−)-DIP-Cl[6] as already applied to the resolution of (5*R**)-**2** (Scheme 4). Unfortunately, this time the two diastereoisomeric alcohols formed were not separable on a preparative scale, neither by column nor by gas chromatography. We therefore investigated the usefulness of (*S*)-(−)-2-hydrazino-2-oxo-*N*-(1-phenylethyl)-acetamide[7] as ketone resolving reagent (Scheme 7). Catalyzed by *p*-toluenesulfonic acid, this reagent yielded a 1:1-mixture of two diastereoisomeric hydrazones, which could be separated by column chromatography on silica gel in pentane/ether (1:1), albeit partial hydrolysis was observed. As a consequence, both the first (R_f=0.33) and the second eluted hydrazone (R_f=0.28) contained ketone (R_f=0.77): the former more (10%) than the latter (3%) (^1H NMR). As the second eluted hydrazone could only contain ketone originating from itself, we hoped that its hydrolysis would deliver an enantiomerically pure ketone. However, due to an incomplete separation from the first eluted hydrazone, the optical purity was slightly diminished (94% ee, $[\alpha]_D^{20}=-46.3°$, c=1.09, acetone), as evidenced by capillary gas chromatography of the corresponding hydrocarbon obtained by Wolff–Kishner reduction (94% ee, $[\alpha]_D^{20}=-24.2°$, c=1.17, $CHCl_3$). The identity of the ketone as (5*S*,6*S*)-**11**, the hydrocarbon as (*M*)-**24** and the hydrazone as (1′*S*,5*S*,6*S*)-**25** followed from the fact, that in the CD



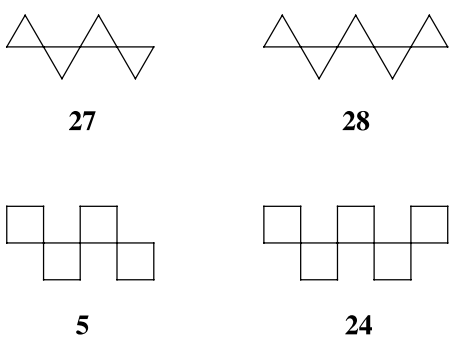
Scheme 7.

spectrum of the ketone ($[\theta]_{302}$=+1967, CH_3OH) a net positive Cotton effect[11] was observed.

For the synthesis of (*P*)-**24**, we used the same set of reactions as for (*M*)-**24**. This time, the starting hydrazone (1′*S*,5*R*,6*R*)-**26** was contaminated with 10% ketone originating from both (1′*S*,5*S*,6*S*)-**25** and (1′*S*,5*R*,6*R*)-**26**. Consequently, its hydrolysis to (5*R*,6*R*)-**11** delivered a product of lower optical purity (92% ee, $[\alpha]_D^{20}$=+45.9°, *c*=1.09, acetone), which translated to (*P*)-**24** (92% ee, $[\alpha]_D^{20}$=+23.9°, *c*=1.18, $CHCl_3$) through Wolff–Kishner reduction.

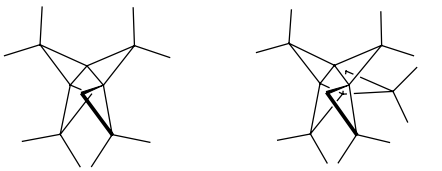
3. Discussion

Until now, only three examples for hydrocarbons with a helical primary structure were known: trispiro[2.0.0.2.1.1]-nonane (**27**),[2a,b] tetraspiro[2.0.0.0.2.1.1.1]undecane (**28**)[2b] and trispiro[3.0.0.3.2.2]tridecane (**5**).[1] The present contribution describes the synthesis of tetraspiro[3.0.0.0.3.2.2.2]-hexadecane (**24**) and thereby allows a first comparison of two pairs of helical primary structures of spiroannelated three and four-membered rings (Scheme 8).

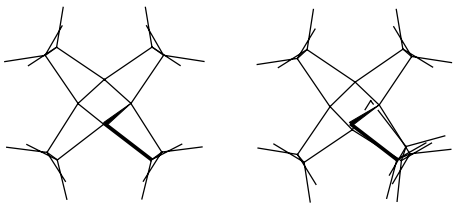


Scheme 8.

As pointed out elsewhere,[1] helical hydrocarbons of spiroannelated three- and four-membered rings form regular helices, but their identity periods differ: that of the former comprises eight three-membered rings within two helical turns, that of the latter five four-membered rings within one helical turn. This means, that in **24** a helical turn is just complete, while in **28** it goes about 50° beyond (Fig. 1). A second difference concerns the fact, that helices of three-membered rings form rigid structures, while those of four-membered rings may adopt different conformations. Thus, within 3 kcal above the global minimum, our conformational search routine HUNTER[12] in connection with MM3[13] located seven additional minima for **5**, and three for **24**. Only the global minimum conformations represent regular helices (Fig. 1), while all other conformations contain non-regular sections. We therefore believe, that the large difference in the specific rotations of (*M*)-**27** ($[\alpha]_D^{20}$=−192.7°, *c*=1.2, $CHCl_3$)[2] and (*M*)-**5** ($[\alpha]_D^{20}$=−63.3°, *c*=1.09, $CHCl_3$)[1] is due to the conformational mobility of



	(*M*)-**27**	(*M*)-**28**
$[\alpha]_D^{20}$ ($CDCl_3$)	- 192.7°	- 381.2°



	(*M*)-**5**		(*M*)-**24**
$[\alpha]_D^{20}$ ($CDCl_3$)	- 63.3°		- 24.2°
ΔH_f^0 (kcal/mol)	**79.3**	81.5	**104.3**
	80.1	81.9	106.1
	80.7	82.0	106.3
	80.7	82.2	106.5

Figure 1. Global minimum structures of (*M*)-**27**, (*M*)-**28**, (*M*)-**5** and (*M*)-**24**: views along the helical axis. The structure of (*M*)-**28** was generated using the crystal structure data of *rac*-**28**.[2b] The remaining structures were determined by molecular mechanics using PC-model[14] [(*M*)-**27**] and the conformational search routine HUNTER[12] in connection with MM3[13] [(*M*)-**5**, (*M*)-**24**], respectively. All carbon–hydrogen bonds within the inner spheres have been omitted for clarity. For (*M*)-**5** and (*M*)-**24**, the heats of formation (in kcal/mol) of all minimum conformations up to 3 kcal/mol above the global minimum (in bold) are given. For views of their structures, see Ref. 1.

(*M*)-**5**, not present in (*M*)-**27**, and to the fact, that (*M*)-**5** describes a distinctly shorter section of a helix than (*M*)-**27**.

As mentioned above, the number of conformations within 3 kcal/mol above the global minimum is reduced from eight in (*M*)-**5** to four in (*M*)-**24**. This indicates that the conformational mobility of a helix of four-membered rings decreases, as the length of the helix increases. It was therefore tempting to speculate,[1] that the large difference between the specific rotations of (*M*)-**27** and (*M*)-**5** for (*M*)-**28** ($[\alpha]_D^{20}=-381.2°$, $c=1.2$, $CHCl_3$)[2] and (*M*)-**24** ($[\alpha]_D^{20}=-24.2°$, $c=1.17$, $CHCl_3$) could diminish. However, the contrary is true: while the specific rotation of (*M*)-**27** doubles, the specific rotation of (*M*)-**5** is cut in three. The reason for this unexpected result is not yet clear, but ab initio calculations on a sufficiently large set of potentially low-lying conformers with subsequent calculation of Boltzmann-averaged CD or ORD spectra should help to clarify the matter.[15]

4. Experimental

4.1. General

IR-spectra were obtained with a Perkin–Elmer 298 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 or a Varian VXR 500 or VXR 600 spectrometer. For standards other than TMS the following chemical shifts were used: δ_H (C_2HDCl_4)=5.99, δ_H ($CHCl_3$)=7.24, δ_H (C_6D_5H)=7.15, δ_C ($C_2D_2Cl_4$)=73.71, δ_C ($CDCl_3$)=77.00, δ_C (C_6D_6)=128.00. ^{13}C multiplicities were studied by APT and/or DEPT measurements. Mass spectra were obtained with a Varian CH 5 (CI) or a Finnegan MAT 95 spectrometer (EI und HR-EI) operated at 70 eV. Optical rotations were measured on a Perkin–Elmer 241 digital polarimeter in a 1 dm cell. UV and CD spectra were obtained with a JASCO J-710/720 spektropolarimeter. Preparative GC was carried out on a Carlo-Erba GC 6000 Vega series 2 instrument employing a thermal conductivity detector, and hydrogen as carrier gas. Analytical GC was performed on a Carlo-Erba GC 6000 Vega series 2 instrument employing a split/splitless injector, a FID 40 detector, and hydrogen (0.6 bar) as carrier gas. The following columns were used: (A): 3 m×1/4″ all-glass system, 15% FFAP on Chromosorb W AW/DMCS 60/80 mesh; (B) 25 m×0.25 mm i.d. deactivated fused-silica capillary column coated with oktakis-(2,6-di-*O*-pentyl-3-*O*-butyryl)-γ-cyclodextrin (Lipodex® E); (C) 25 m×0.25 mm i.d. deactivated fused-silica capillary column coated with oktakis-(2,3-di-*O*-pentyl-6-*O*-methyl)-γ-cyclodextrin (Lipodex® G). Product ratios were not corrected for relative response. R_f values are quoted for Macherey & Nagel Polygram SIL G/UV254 plates. Colorless substances were detected by oxidation with 3.5% alcoholic 12-molybdophosphoric acid and subsequent warming. Melting points were observed on a Reichert microhotstage and are not corrected. Microanalytical determinations were done at the Microanalytical Laboratory of the Institute of Organic Chemistry, Göttingen. (*S*)-(−)-1-phenyl-ethylamine, 98%, used for the preparation of (*S*)-(−)-2-hydrazino-2-oxo-*N*-(1-phenyl-ethyl)-acetamide [(*S*)-(−)-**9**],[7] was purchased from Aldrich Chemical Company, Inc.

4.1.1. 1-Methylene-spiro[3.3]heptane (8). To a suspension of methyltriphenylphosphonium bromide (46.4 g, 130 mmol) in anhydrous ether (250 ml) was added under argon with stirring potassium-*t*-butoxide (14.6 g, 130 mmol) and the mixture heated to reflux. After 15 min, most of the ether was distilled off (bath temperature up to 60 °C), **6** (12.1 g, 110 mmol) was added dropwise, and after additional 30 min at 60 °C the reaction was complete according to GC [column A, 120 °C; retention times (min): 1.03 (**8**), 4.63 (**6**)]. The mixture was diluted with pentane (100 ml) and hydrolyzed with water (11 ml). The organic layer was decanted, the residue was extracted with pentane (2×70 ml), and the combined organic phases were washed with water (3×70 ml) and dried ($MgSO_4$). The solvent was distilled off through a 20 cm vigreux column (bath temperature up to 130 °C) and the remaining material fractionated to yield 10.7 g (90%) of **8** as colorless liquid, bp 116–118 °C (purity 97% GC). IR (neat): 1670 cm^{-1} (C=C); ^1H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.73–1.87 (m, 2H), 1.95 (t, J=8 Hz, 2H), 1.95–2.03 (m, 2H), 2.10–2.17 (m, 2H), 2.51 (tt, J=8, 2 Hz, 2H), 4.67 (t, J=2 Hz, 1H), 4.88 (t, J=2 Hz, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): δ=16.15 (t), 27.30 (t), 32.01 (t), 34.41 (t), 50.80 (s), 101.40 (t), 159.10 (s); MS (EI): m/e=108 (3, M^+), 79 (100); C_8H_{12} requires C, 88.82; H, 11.18. Found: C, 88.96; H, 10.98.

4.1.2. 1-(Cyclobutylcarbonyl)-piperidine (18). To a solution of piperidine (34.0 g, 0.40 mol) in dichloromethane (150 ml) was added under argon with stirring cyclobutyryl chloride (23.6 g, 0.20 mol) such that, the internal temperature did not exceed 25 °C. After the addition was complete, the mixture was stirred for 30 min at room temperature and then washed with water (80 ml), 2 N HCl (80 ml), saturated sodium bicarbonate (80 ml) and dried ($MgSO_4$). The solvent was distilled off and the residue fractionated to yield 32.6 g (97%) of **18** as colorless liquid, bp 147 °C/16 Torr (purity 99% GC) (lit.[8] bp 89–91 °C/1 Torr). IR (neat): 1640 cm^{-1} (C=O); ^1H NMR (600 MHz, symm $C_2D_2Cl_4$, C_2DHCl_4 int, 120 °C): δ=1.47–1.54 (m, 4H), 1.58–1.65 (m, 2H), 1.83–1.98 (m, 2H), 2.09–2.17 (m, 2H), 2.28–2.37 (m, 2H), 3.18–3.26 (m, 1H), 3.37 (br s, 4H); ^{13}C NMR (150.8 MHz, symm $C_2D_2Cl_4$, $C_2D_2Cl_4$ int, 120 °C): δ=17.70 (t), 24.28 (t), 24.92 (t), 25.74 (t), 37.11 (d), 44.10 (br t), 172.38 (s); MS (EI): m/e=167 (42, M^+), 84 (100); $C_{10}H_{17}NO$ requires C, 71.81; H, 10.24; N, 8.55. Found: C, 71.75; H, 10.18; N, 8.60.

4.1.3. (5*R)-Trispiro[3.0.0.3.2.2]tridecan-10-one (2).** To a solution of **18** (1.68 g, 10 mmol) in 1,2-dichloroethane (10 ml) was added at −15 °C under argon with stirring trifluoromethanesulfonic acid anhydride (3.38 g, 12 mmol), and, within 20 min, a solution of 2,4,6-collidine (1.46 g, 12 mmol) and **8** (2.16 g, 20 mmol). The mixture was heated for 24 h to reflux and then concentrated on a rotary evaporator (bath temperature 35 °C/15 Torr). The residual black oil was extracted with anhydrous ether (3×20 ml), and the remaining material hydrolyzed in a two-phase system of dichloromethane (15 ml) and water (15 ml). After 2 h of reflux, GC analysis [column A, 230 °C; retention times (min): 2.58 (**2**), 4.49 (**18**)] indicated the presence of a 76:24-mixture of **2** and **18**. The organic phase was washed with 2 N H_2SO_4 (10 ml), dried ($MgSO_4/K_2CO_3$) and concentrated on a rotary evaporator (bath temperature 35 °C/15 Torr), and the residual brown oil (2.50 g)

chromatographed on silica gel (0.05–0.20 mm) in pentane/ether [8:2, R_f=0.62 (**2**); column 75×5 cm] yielding 950 mg (50%) of **2** as colorless liquid (purity 96% GC). The ^{1}H and ^{13}C NMR data reported[1] are data from spectra of a 2:1-mixture with **3** in C_6D_6. The data for pure **2** in $CDCl_3$ are as follows: ^{1}H NMR (500 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.65–1.82 (m, 5H), 1.82–1.92 (m, 1H), 1.95–2.15 (m, 7H), 2.15–2.30 (m, 4H), 2.60 (d, J=17 Hz, 1H), 2.92 (d, J=17 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=16.29 (t), 16.77 (t), 24.87 (t), 27.23 (t), 27.92 (t), 30.91 (t), 32.01 (t), 32.73 (t), 43.77 (s), 48.85 (s), 49.57 (t), 67.23 (s), 213.22 (s).

4.1.4. (5*S*,10*S*)-(+)-Trispiro[3.0.0.3.2.2]tridecan-10-ol [(5*S*,10*S*)-4] and (5*R*,10*S*)-(−)-trispiro[3.0.0.3.2.2]tridecan-10-ol [(5*R*,10*S*)-19]. To (−)-diisopinocampheylchloroborane [(−)-DIP-Cl] (642 mg, 2.00 mmol) was added under argon with stirring (*R**)-**2** (380 mg, 2.00 mmol) via a syringe. A slightly exothermic reaction was observed, and, within a few minutes, a clear solution had formed. After 45 min at room temperature, the solution was diluted with ether (4 ml), and diethanolamine (210 mg, 2.0 mmol) was added, causing a heavy precipitate. After 1 h the mixture was filtrated and the residue washed with pentane (2×4 ml). The combined organic phases were washed with saturated sodium carbonate (4 ml) and water (4 ml), and dried ($MgSO_4$). The solvents were evaporated and the residue chromatographed on silica gel (0.05–0.20 mm) in pentane/ether[7:3; R_f=0.32 (**4**/**19**); column 60×4.5 cm] to give 356 mg (93%) of a 1:1-mixture of **4** and **19**. According to capillary gas chromatography on a chiral phase [column B, 120 °C, retention times (min): 24.68 (**4**), 28.86 (**19**)] both alcohols were enantiomerically pure (>99% ee). Analytically pure samples were obtained by preparative GC [column A, 210 °C; retention times (min): 9.75 (**4**), 10.65 (**19**)]. Their ^{1}H NMR data were identical with those of racemic samples.[1]

4.1.5. 1-(1-Phenylsulfanyl-cyclopropyl)-spiro[3.3]heptan-1-ol (20). To a stirred solution of cyclopropyl phenyl sulphide (21.6 g, 144 mmol) in anhydrous tetrahydrofuran (300 ml) under argon at 0 °C was added within 45 min a 1.60 M solution of *n*-butyllithium in hexane (90 ml, 144 mmol). After 1.5 h at 0 °C, a solution of **6** (13.2 g, 120 mmol) in tetrahydrofuran (40 ml) was added within 30 min and the temperature maintained for additional 1.5 h at 0 °C. The mixture was hydrolyzed with saturated ammonium chloride (15 ml), the liquid phase was decanted, and the residue was extracted with ether (3×50 ml). The organic phases were concentrated on a rotary evaporator (bath temperature 50 °C/15 Torr), and the residual oil (36 g) was chromatographed on silica gel (0.05–0.20 mm) first using pentane (column 70×3 cm) to yield 5.0 g of unreacted cyclopropyl phenyl sulphide, and then ether to yield 29.0 g (93%) of **20** as slightly yellowish oil. IR (neat): 3600–3300 cm^{-1} (OH_{ass}); ^{1}H NMR (600 MHz, symm $C_2D_2Cl_4$, C_2DHCl_4 int, 120 °C): δ=0.85–0.90 (m, 1H), 1.04–1.09 (m, 1H), 1.13–1.18 (m, 2H), 1.70–1.95 (m, 7H), 2.07–2.14 (m, 1H), 2.26 (br s, 1H), 2.45 (ddd, J=10, 10, 10 Hz, 1H), 2.54 (ddd, J=10, 10, 10 Hz, 1H), 7.21 (tt, J=8, 1 Hz, 1H), 7.30 (dd, J=8, 8 Hz, 2H), 7.56 (dd, J=8, 1 Hz, 2H); ^{13}C NMR (150.8 MHz, symm $C_2D_2Cl_4$, $C_2D_2Cl_4$ int, 120 °C): δ=10.79 (t), 14.67 (t), 14.88 (t), 27.16 (t), 29.87 (t), 29.90 (t), 31.41 (t), 31.54 (s), 51.08 (s), 80.73 (s), 125.92 (d), 128.30 (d), 129.94 (d), 136.79 (s); MS (EI): *m*/*e*=260 (85, M^+), 192 (100); $C_{16}H_{20}SO$ requires C, 73.80; H, 7.74; S, 12.31. Found: C, 73.85; H, 7.87.

4.1.6. 1-Cyclopropylidenspiro[3.3]heptane (21). To a suspension of potassium-*t*-butoxide (44.8 g, 0.40 mol) in dry benzene (700 ml) was added under argon with stirring cyclopropyltriphenylphosphonium bromide (153 g, 0.40 mmol) and the mixture heated for 2 h to 55 °C. **6** (22.0 g, 0.20 mol) was added, and after additional 2 h at 70 °C the reaction was complete according to GC [column A, 140 °C; retention times (min): 1.97 (**21**), 2.37 (**6**)]. The mixture was diluted with pentane (700 ml) and hydrolyzed with water (30 ml). The liquid phase was decanted and the residue extracted with pentane (2×100 ml). The combined organic phases were concentrated through a 40 cm vigreux column (bath temperature up to 130 °C), and the residue was diluted with pentane (600 ml), causing a heavy precipitate. The mixture was filtered and the residue washed with pentane (2×100 ml). The combined filtrates were concentrated through a 40 cm vigreux column (bath temperature up to 135 °C) and the residue was fractionated through a microdistillation apparatus to yield 23.8 g (89%) of **21** as colorless liquid, bp 67–68 °C/15 Torr (purity 97% GC). IR (neat): 1788 cm^{-1} (C=C); ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=0.90–0.95 (m, 2H), 1.09–1.14 (m, 2H), 1.76–1.91 (m, 2H), 1.95–2.02 (m, 2H), 2.03 (t, J=8 Hz, 2H), 2.20–2.27 (m, 2H), 2.58 (ttt, J=8, 2.5, 2.5 Hz, 2H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): δ=0.04 (t), 1.04 (t), 16.51 (t), 26.38 (t), 32.46 (t), 34.03 (t), 50.83 (s), 107.99 (s), 136.37 (s); MS (EI): *m*/*e*=134 (5, M^+), 91 (100); $C_{10}H_{14}$ requires C, 89.49; H, 10.51. Found: C, 89.51; H, 10.53.

4.1.7. Dispiro[3.0.3.2]decan-1-one (7) and dispiro[2.0.3.3]decan-5-one (22). *A. From* **20**. To a stirred solution of **20** (26.0 g, 0.10 mol) in ether (300 ml) was added at 5–7 °C within 30 min 50% aqueous tetrafluoroboric acid (60 ml). The mixture was allowed to warm to room temperature and the reaction progress was monitored by GC [column A, 245 °C; retention time (min): 18.8 (**20**)]. After 6 h, more tetrafluoroboric acid (10 ml) was added, and after 22 h the reaction was complete. Sodium bicarbonate (50 g, 0.60 mol) was added in portions, and the organic phase was separated, washed with 5% aqueous potassium hydroxide (2×150 ml), water (2×150 ml) and dried ($MgSO_4$). The solvent was distilled off and the residue fractionated to yield 7.8 g (52%) of a 72:28-mixture of **7** and **22** as colorless liquid, bp 78–80 °C/13 Torr. Analytically pure samples were obtained by preparative GC [3 m×1/4″ all-glass system, 15% FFAP on Chromosorb W AW/DMCS 60/80 mesh, 180 °C; retention times (min): 3.11 (**7**), 3.44 (**22**)]. **7**: IR (neat): 1770 cm^{-1} (C=O); ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.65–1.74 (m, 1H), 1.74–1.90 (m, 6H), 1.90–1.98 (m, 1H), 1.99–2.06 (m, 1H), 2.13–2.23 (m, 3H), 2.83 (m_c, 2H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): δ=16.05 (t), 19.82 (t), 25.23 (t), 30.87 (t), 31.04 (t), 31.16 (t), 43.28 (t), 48.23 (s), 70.80 (s), 213.42 (s); MS (EI): *m*/*e*=150 (17, M^+), 79 (100); $C_{10}H_{14}O$ requires C, 79.96; H, 9.39. Found: C, 80.10; H, 9.46. **22**: IR (neat): 1765 cm^{-1} (C=O); ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=0.31–0.37 (m, 1H), 0.43–0.56 (m, 3H), 1.52–1.60 (m, 1H),

1.64–1.84 (m, 6H), 2.10–2.16 (m, 1H), 2.61 (m_c, 1H), 2.85 (m_c, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): δ=8.55 (t), 9.14 (t), 20.76 (t), 22.51 (t), 26.98 (s), 35.10 (t), 35.97 (t), 42.59 (t), 72.72 (s), 215.52 (s); MS (EI): *m/e*=150 (6, M^+), 79 (100); $C_{10}H_{14}O$ requires C, 79.96; H, 9.39. Found: C, 80.14; H, 9.55.

B. From **21**. To a vigorously stirred solution of **21** (26.8 g, 200 mol) in dichloromethane (350 ml) was added a 0.7 M aqueous solution of sodium bicarbonate (500 ml), and, within 2.5 h at 5 °C, a solution of 3-chloro-peroxybenzoic acid (54.3 g, 70% w/w, 220 mol) in dichloromethane (500 ml). After 1 h, the reaction was complete according to GC [column A, 160 °C; retention times (min): 1.45 (**21**), 3.00 (epoxide), 4.51 (**7**), 5.08 (**22**)]. The organic layer was washed with 1 N NaOH (200 ml), dried (K_2CO_3/$MgSO_4$), and concentrated to approximately 500 ml by distillation over a 40 cm vigreux column. Solid potassium carbonate (1.0 g) was added to the remaining solution, until it was cooled to 5 °C and borontrifluoride etherate (300 mg, 2.1 mmol) was added drop by drop, causing an exothermic reaction, which with the last drops subsided. After the addition was complete, the mixture was stirred for 30 min at room temperature, until it was washed with 1 N NaOH (50 ml), water (150 ml), and dried (K_2CO_3/$MgSO_4$). The solvent was distilled off over a 40 cm vigreux column and the residue fractionated to yield 25.9 g (86%) of a 80:20-mixture of **7** and **22** as colorless liquid, bp 85–88 °C/13 Torr (purity 97% GC). Analytically pure samples were obtained by preparative GC. Their NMR data were identical with those of authentic samples.

4.1.8. 1-Methylene-dispiro[3.0.3.2]decane (9) and 5-methylene-dispiro[2.0.3.3]decane (23). To a suspension of methyltriphenylphosphonium bromide (78.5 g, 220 mmol) in anhydrous ether (450 ml) was added under argon with stirring potassium-*t*-butoxide (24.6 g, 220 mmol) and the mixture heated to reflux. After 1 h, a 80:20-mixture of **7** and **22** (25.5 g, 170 mmol) was added dropwise, and after additional 1 h of reflux the reaction was complete according to GC [column A, 160 °C; retention times (min): 1.39 (**9**), 1.54 (**23**), 4.51 (**7**), 5.08 (**22**)]. The mixture was hydrolyzed with saturated aqueous ammonium chloride (15 ml), the liquid phase was decanted, the residue was extracted with pentane (3×200 ml), and the combined organic phases were filtrated, washed with water (3×200 ml) and dried ($MgSO_4$). Most of the solvents were distilled off over a 40 cm vigreux column (bath temperature up to 70 °C), the residue was diluted with pentane (200 ml), and, after filtration, first concentrated by distillation over a 20 cm vigreux column (bath temperature up to 135 °C) and then fractionated over a microdistillation apparatus to yield 22.9 g (91%) of a 80:20-mixture of **9** and **23** as colorless liquid, bp 95 °C/55 Torr. Analytically pure samples were obtained by preparative GC. **9**: IR (neat): 1669 cm^{-1} (C=C); ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.61–1.69 (m, 1H), 1.69–1.85 (m, 7H), 1.91–1.97 (m, 1H), 2.05–2.14 (m, 3H), 2.41–2.53 (m, 2H), 4.73 (t, *J*=2.5 Hz, 1H), 4.75 (t, *J*=2.0 Hz, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): δ=15.48 (t), 26.42 (t), 27.92 (t), 29.28 (t), 30.35 (t), 30.36 (t), 31.37 (t), 49.02 (s), 56.02 (s), 103.29 (t), 155.55 (s); MS (EI): *m/e*=148 (14, M^+), 79 (100); $C_{11}H_{16}$ requires C, 89.12; H, 10.88. Found: C, 89.24; H, 10.88. **23**: IR (neat): 1670 cm^{-1} (C=C); ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=0.27–0.34 (m, 2H), 0.40–0.48 (m, 1H), 0.48–0.56 (m, 1H), 1.52–1.60 (m, 1H), 1.62–1.82 (m, 8H), 1.87–1.94 (m, 1H), 2.29 (m_c, 1H), 2.48 (m_c, 1H), 4.67 (t, *J*=2.5 Hz, 1H), 4.70 (t, *J*=2.0 Hz, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): δ=8.29 (t), 10.21 (t), 21.55 (t), 27.17 (t), 28.39 (t), 28.46 (s), 34.68 (t), 39.70 (t), 57.16 (s), 104.42 (t), 156.36 (s); MS (EI): *m/e*=148 (1, M^+), 120 (100); $C_{11}H_{16}$ requires C, 89.12; H, 10.88. Found: C, 89.06; H, 10.86.

4.1.9. (5*R,6*R**)-Tetraspiro[3.0.0.0.3.2.2.2]hexadecan-11-one [(5*R**,6*R**)-11] and (5*R**,6*S**)-tetraspiro-[3.0.0.0.3.2.2.2]hexadecan-11-one [(5*R**,6*S**)-12].** To a solution of **18** (8.40 g, 50 mmol) in dichloromethane (50 ml) was added at −15 °C under argon with stirring trifluoromethanesulfonic acid anhydride (16.9 g, 60 mmol), and, within 20 min, a solution of 2,4,6-collidine (7.26 g, 60 mmol) in a 78:22-mixture of **9** and **23** (14.8 g, 100 mmol). The mixture was heated for 44 to reflux and then concentrated on a rotary evaporator (bath temperature 35 °C/15 Torr). The residual black oil was extracted with anhydrous ether (4×70 ml), and the remaining material hydrolyzed in a two-phase system of dichloromethane (70 ml) and water (70 ml). After 2 h of reflux, GC analysis [column A, 230 °C; retention times (min): 4.48 (**18**), 5.76 (**11/12**)] indicated the presence of a 60:40-mixture of **11/12** and **18**. The organic phase was washed with 2 N H_2SO_4 (60 ml), dried ($MgSO_4$/K_2CO_3) and concentrated on a rotary evaporator (bath temperature 35 °C/15 Torr). The residual brown oil (21.5 g) was extracted with pentane/ether (1:1; 2×100 ml), the combined extracts were concentrated on a rotary evaporator (bath temperature 35 °C/15 Torr), and the remaining oil (10.7 g) was chromatographed first on silica gel (0.05–0.20 mm) in pentane/ether [95:5, column 70×5 cm, R_f=0.36–0.39 (**11/12**)] yielding 3.43 g (30%) of a 92:8-mixture of **11** and **12** (^{1}H NMR), and then on silica gel (0.040–0.063 mm) in pentane/ether [97:3, column 70×5 cm, R_f=0.21 (**11**), 0.19 (**12**)] yielding 2.42 g (21%) of pure **11** and 0.50 g (4%) of a 2:1-mixture of **11** and **12** (^{1}H NMR) as colorless oils. **12** could not be obtained pure. **12**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): only the protons neighboring the carbonyl group could be assigned: δ=2.60 (*J*=17 Hz, 1H), 2.88 (*J*=17 Hz, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): all resonances could be assigned: δ=15.33 (t), 16.28 (t), 25.46 (t), 27.14 (t), 27.80 (t), 28.27 (t), 28.96 (t), 31.21 (t), 31.21 (t), 31.94 (t), 46.60 (s), 47.42 (s), 50.64 (t), 54.28 (s), 66.13 (s) 213.17 (s). **11**: ^{1}H NMR (600 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.55–1.90 (m, 10H), 1.95–2.25 (m, 9H), 2.36–2.43 (m, 1H), 2.71 (d, *J*=17 Hz, 1H), 3.31 (d, *J*=17 Hz, 1H); ^{13}C NMR (150.8 MHz, $CDCl_3$, $CDCl_3$ int): δ=15.46 (t), 16.56 (t), 26.26 (t), 26.60 (t), 26.90 (t), 26.97 (t), 27.09 (t), 30.48 (t), 31.34 (t), 32.08 (t), 43.81 (s), 48.91 (s), 50.61 (t), 52.57 (s), 67.76 (s), 213.17 (s); MS (EI): *m/e*=230 (<1, M^+), 120 (100); $C_{16}H_{22}O$ requires C, 83.43; H, 9.63. Found: C, 83.55; H, 9.67.

4.1.10. *rac*-Tetraspiro[3.0.0.0.3.2.2.2]hexadecane [*rac*-24]. To a solution of hydrazine hydrate (300 mg, 6.0 mmol) and powdered potassium hydroxide (450 mg, 8.0 mmol) in diethylene glycol (4.0 ml) was added under argon with stirring **11** (230 mg, 1.0 mmol). The mixture was heated for 2 h to 160 °C, until it was diluted with water (40 ml) and

extracted with pentane (3×20 ml). The combined extracts were washed with water (30 ml), dried ($MgSO_4$), and concentrated using a 20 cm vigreux column. Last traces of solvent were evaporized under reduced pressure yielding 207 mg (96%) of *rac*-**24** as colorless oil (purity 97% GC). The enantiomers could be resolved by capillary gas chromatography on a chiral phase [column C, 105 °C, retention times (min): 40.32/41.49 (*rac*-**24**)]. An analytically pure sample was obtained by preparative GC [column A, 200 °C; retention time (min): 3.01 (*rac*-**24**)]. ^{1}H NMR (500 MHz, $CDCl_3$, $CHCl_3$ int): δ=1.45 (m_c, 2H), 1.53–1.63 (m, 4H), 1.64–1.72 (m, 2H), 1.75–1.94 (m, 10H), 1.98–2.05 (m, 2H), 2.25 (m_c, 2H), 2.35–2.44 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$, $CDCl_3$ int): δ=15.74 (t), 26.43 (t), 26.51 (t), 30.70 (t), 31.31 (t), 32.37 (t), 49.21 (s), 52.34 (s); MS (EI): *m*/*e*=216 (<1, M^+), 120 (96), 79 (100); $C_{16}H_{24}$ requires C, 88.82; H, 11.18. Found: C, 88.71; H, 10.90.

4.1.11. (1′*S*,5*S*,6*S*)-2-(*N*′-Tetraspiro[3.0.0.0.3.2.2.2]hexadec-11-ylidene-hydrazino)-2-oxo-*N*-(1-phenyl-ethyl)-acetamide [(1′*S*,5*R*,6*S*)-25] and (1′*S*,5*R*,6*R*)-2-(*N*′-tetraspiro[3.0.0.0.3.2.2.2]hexadec-11-ylidene-hydrazino)-2-oxo-*N*-(1-phenyl-ethyl)-acetamide [(1′*S*,5*S*,6*R*)-26]. To a suspension of (*S*)-(−)-2-hydrazino-2-oxo-*N*-(1-phenyl-ethyl)-acetamide[7] (2.59 g, 12.5 mmol) in benzene (200 ml) was added under argon with stirring **11** (1.15 g, 5.0 mmol) and a 0.74 M solution of anhydrous *p*-toluenesulfonic acid in benzene (10 ml, 7.4 mmol). The mixture was heated to reflux and the reaction progress monitored by TLC in pentane/ether [1:1; R_f=0.77 (**11**), 0.33 (**26**), 0.28 (**25**)]. After 2 h more acetamide (0.52 g, 2.5 mmol) was added, and after an additional hour the reaction was complete. The mixture was filtrated, the residue was washed with ether (2×50 ml), and the combined filtrates were washed with saturated sodium carbonate (50 ml), water (100 ml), and dried ($MgSO_4$). The solvents were distilled off (bath temperature 60 °C/15 Torr), and the remaining material (2.70 g) was chromatographed on silica gel (0.05–0.20 mm) in pentane/ether [1:1, column 100×6.5 cm; R_f=0.77 (**11**), 0.33 (**26**), 0.28 (**25**)] yielding 690 mg (33%) of **26** as sticky oil, 290 mg (14%) of a 3:1-mixture of **25** and **26** as waxy solid, and 480 mg (23%) of **25** as amorphous solid, mp 116–117 °C. **25**: ^{1}H NMR (300 MHz, C_6D_6, C_6D_5H int): δ=1.08–1.18 (m, 1H), 1.13 (d, *J*=7 Hz, 3H), 1.32–1.42 (m, 1H), 1.45–1.80 (m, 10H), 1.80–2.00 (m, 3H), 1.90 (d, *J*=16 Hz, 1H), 2.04–2.32 (m, 5H), 2.66 (d, *J*=16 Hz, 1H), 5.10 (dq, *J*=9, 7 Hz, 1H), 6.96–7.14 (m, 5H), 8.10 (d, *J*=9 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (150.8 MHz, C_6D_6, C_6D_6 int): δ=16.02 (t), 16.85 (t), 21.80 (q), 26.87 (t), 26.91 (t), 27.05 (t), 28.67 (t), 29.79 (t), 30.98 (t), 31.73 (t), 32.45 (t), 37.10 (t), 47.37 (s), 48.99 (s), 50.03 (d), 52.86 (s), 58.64 (s), 126.83 (d), 127.63 (d), 128.97 (d), 143.44 (s), 155.75 (s), 159.79 (s), 167.95 (s). **26**: ^{1}H NMR (300 MHz, C_6D_6, C_6D_5H int): δ=1.12–1.20 (m, 1H), 1.20 (d, *J*=7 Hz, 3H), 1.32–1.44 (m, 1H), 1.46–1.82 (m, 10H), 1.82–2.00 (m, 3H), 1.92 (d, *J*=16 Hz, 1H), 2.00–2.30 (m, 5H), 2.69 (d, *J*=16 Hz, 1H), 5.12 (dq, *J*=9, 7 Hz, 1H), 6.98–7.12 (m, 3H), 7.16–7.22 (m, 2H), 8.34 (d, *J*=9 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (150.8 MHz, C_6D_6, C_6D_6 int): δ=15.87 (t), 16.72 (t), 21.57 (q), 26.69 (t), 26.76 (t), 26.89 (t), 28.55 (t), 29.54 (t), 30.81 (t), 31.56 (t), 32.30 (t), 36.90 (t), 47.21 (s), 48.84 (s), 49.83 (d), 52.72 (s), 58.51 (s), 126.62 (d), 127.50 (d), 128.83 (d), 143.22 (s), 155.53 (s), 159.63 (s), 167.79 (s).

4.1.12. (5*S*,6*S*)-(−)-Tetraspiro[3.0.0.0.3.2.2.2]hexadecan-11-one [(5*S*,6*S*)-11]. To a solution of (1′*S*,5*S*,6*S*)-**25** (356 mg, 0.85 mmol) in benzene (25 ml) was added 60% H_2SO_4 (4.0 ml). The resulting two-phase system was vigorously stirred at room temperature. According to TLC [pentane/ether (1:1); R_f=0.77 (**11**), 0.28 (**25**)], after 1 h the hydrolysis was complete. The organic phase was decanted, the heterogeneous residue was extracted with benzene (10 ml), and the combined organic phases were washed with water (10 ml) and dried ($MgSO_4$). Evaporation of the solvent (bath temperature 55 °C/15 Torr) yielded 190 mg (97%) of crude (5*S*,6*S*)-**11** (purity 97% GC). Preparative GC [column A, 230 °C; retention time (min): 5.76 (**11**)] yielded an analytically pure sample as colorless oil (94% ee; $[\alpha]_D^{20}$=−46.3, *c*=1.09, acetone). For the preparation of (*M*)-**24**, the crude material was used. The ^{1}H NMR data were identical with those of racemic **11**. UV (CH_3OH): λ_{max}=292 nm, ε=14; CD (CH_3OH): $[\theta]_{302}$=+1964.

4.1.13. (5*R*,6*R*)-(+)-Tetraspiro[3.0.0.0.3.2.2.2]hexadecan-11-one [(5*R*,6*R*)-11]. (1′*S*,5*R*,6*R*)-**26** (587 mg, 1.40 mmol) was hydrolyzed as described for (1′*S*,5*S*,6*S*)-**25** yielding 292 mg (90%) of crude (5*R*,6*R*)-**11** (purity 97% GC). Preparative GC [column A, 230 °C; retention time (min): 5.76 (**11**)] yielded an analytically pure sample as colorless oil (92% ee; $[\alpha]_D^{20}$=+45.9°, *c*=1.09, acetone). For the preparation of (*P*)-**24**, the crude material was used. The ^{1}H NMR data were identical with those of racemic **11**.

4.1.14. (*M*)-(−)-Tetraspiro[3.0.0.0.3.2.2.2]hexadecane [(*M*)-24]. To a solution of hydrazine hydrate (150 mg, 3.0 mmol) and powdered potassium hydroxide (224 mg, 4.0 mmol) in diethylene glycol (2 ml) was added under argon with stirring (5*S*,6*S*)-**11** (99 mg, 0.43 mmol) and the mixture heated to 160 °C. After 1 h, the mixture was diluted with water (20 ml) and extracted with pentane (3×15 ml). The extracts were washed with water (20 ml), dried ($MgSO_4$) and concentrated on a rotary evaporator (bath temperature 40 °C/15 Torr) to yield 87 mg (93%) of crude (*M*)-**24** (purity 97% GC). Preparative GC [column A, 200 °C; retention time (min): 3.01 (*M*)-**24**)] yielded 40 mg of analytically pure (*M*)-**24** as colorless oil ($[\alpha]_D^{20}$=−24.2°, *c*=1.17, $CHCl_3$). According to capillary chromatography on a chiral phase [column C, 105 °C, retention times (min): 40.68 (*M*)-**24**, 41.13 (*P*)-**24**], the material contained 3% (*P*)-**24** (94% ee). The ^{1}H NMR data were identical with those of racemic **24**.

4.1.15. (*P*)-(+)-Tetraspiro[3.0.0.0.3.2.2.2]hexadecane [(*P*)-24]. (5*R*,6*R*)-**11** (150 mg, 0.65 mmol) was reduced as described for (5*S*,6*S*)-**11** yielding 110 mg (79%) of crude (*P*)-**24** (purity 97% GC). Preparative GC [column A, 200 °C; retention time (min): 3.01 (*M*)-**24**)] yielded 56 mg of analytically pure (*P*)-**24** as colorless oil ($[\alpha]_D^{20}$=+23.9°, *c*=1.18, $CHCl_3$). According to capillary chromatography on a chiral phase [column C, 105 °C, retention times (min): 39.70 (*M*)-**24**, 41.49 (*P*)-**24**], the material contained 4% (*M*)-**24** (92% ee). The ^{1}H NMR data were identical with those of racemic **24**.

References and notes

1. Fitjer, L.; Gerke, R.; Weiser, J.; Bunkoczi, G.; Debreczeni, J. E. *Tetrahedron* **2003**, *59*, 4443–4449.
2. (a) de Meijere, A.; Khlebnikov, A. F.; Kostikov, R. R.; Kozhuskov, S. I.; Schreiner, P. R.; Wittkopp, A.; Yufit, D. S. *Angew. Chem.* **1999**, *111*, 3682–3685, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3474–3477. (b) de Meijere, A.; Khlebnikov, A. F.; Kozhushkov, S. I.; Kostikov, R. R.; Schreiner, P. R.; Wittkopp, A.; Rinderspacher, C.; Menzel, H.; Yufit, D. S.; Howard, J. A. K. *Chem. Eur. J.* **2002**, 828–842.
3. For early reviews, see: (a) Krapcho, A. P. *Synthesis* **1974**, 383–419. (b) Krapcho, A. P. *Synthesis* **1976**, 425–444. (c) Krapcho, A. P. *Synthesis* **1978**, 77–126.
4. For approaches to helical primary structures of 1,2-spiro-annelated cyclopentane rings, see: (a) Kakiuchi, K.; Okada, H.; Kanehisa, N.; Kai, Y.; Kurosawa, H. *J. Org. Chem.* **1996**, *61*, 2972–2979. (b) Gaini-Rahimi, A.; Steeneck, C.; Meyer, I.; Fitjer, L.; Pauer, F.; Noltemeyer, M. *Tetrahedron* **1999**, *55*, 3905–3916.
5. (a) Ghosez, L.; Falmagne, J. B.; Escudero, J.; Taleb-Sahraoui, S. *Angew. Chem.* **1981**, *93*, 926–927, *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879–880. (b) Markó, I.; Ronsmans, B.; Hesbain-Frisque, A. M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192–2194. (c) Schmit, C.; Falmagne, J. B.; Escudero, J.; Vanlierde, H.; Ghosez, L. *Org. Synth.* **1990**, *69*, 199–205.
6. Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Org. Chem.* **1986**, *51*, 3394–3396.
7. Leonard, N. J.; Boyer, J. H. *J. Org. Chem.* **1950**, *15*, 42–45.
8. **18** has first been obtained by Hopkins et al.: Hopkins, T. R.; Neighbors, R. P.; Phillips, L. V. *J. Agric. Food Chem.* **1967**, 501–507. However, no spectroscopic data were given.
9. For a cycloaddition of trimethylenketene to an electron-rich olefin, see: (a) Fitjer, L.; Quabeck, U. *Angew. Chem.* **1987**, *99*, 1054–1056, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1023–1025. (b) Fitjer, L.; Steeneck, C.; Gaini-Rahimi, S.; Schröder, U.; Justus, K.; Puder, P.; Dittmer, M.; Haßler, C.; Weiser, J.; Noltemeyer, M.; Teichert, M. *J. Am. Chem. Soc.* **1998**, *120*, 317–328.
10. (a) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H.; Bogdanowicz, J. *J. Am. Chem. Soc.* **1977**, *99*, 3080–3087. (b) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, J. *J. Am. Chem. Soc.* **1977**, *99*, 3088–3100.
11. For a review on the chiroptical properties of carbonyl compounds, see: Kirk, D. N. *Tetrahedron* **1986**, *42*, 777–818.
12. Weiser, J.; Holthausen, M.; Fitjer, L. *J. Comput. Chem.* **1997**, *18*, 1264–1281.
13. Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551–8556.
14. *PC-Model*, Version 4.0; Serena Software: P.O. Box 3076, Bloomington, IN 47402.
15. For a comparative study of modern quantum chemical methods to predict CD spectra, see: (a) Diedrich, C.; Grimme, S. *J. Phys. Chem. A* **2003**, *107*, 2524–2539. For a treatment of conformationally flexible molecules, see: (b) Grimme, S.; Bahlmann, A.; Haufe, G. *Chirality* **2002**, *14*, 793–797.

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An unusually robust triple bond: synthesis, structure and reactivity of 3-alkynylcyclopropenes

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Abstract—Several 1,2-diphenyl- and 1,2,3-triphenyl-3-alkynylcyclopropenes have been prepared in moderate to very good yields by the reaction of acetylenic nucleophiles with the appropriate cyclopropenylium salt. Single crystal X-ray structures of four of the cyclopropenes were obtained. Stereoselective reduction of the triple bond failed in all cases, whereas model compounds lacking the cyclopropene moiety were reduced successfully. A rational for this lack of reactivity is proposed. The solution-phase thermochemistry of the 3-alkynyl-1,2,3-triphenylcyclopropenes was explored, affording 3-alkynyl-1*H*-indenes in moderate to good yields.
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1. Introduction

Recently we described the syntheses of an iridabenzene[1] and an iridabenzene valence isomer[2] starting from a nucleophilic 3-vinylcyclopropene.[3] Key to this new technique was stereospecific preparation of the requisite organic ligand, a (*Z*)-3-(2-iodoethenyl)cyclopropene (**1**). Although this cyclopropene could be prepared in high yield and excellent stereoselectivity,[1] we sought additional versatile routes for ligand synthesis. As an alternative to the Wittig approach, we presumed that selective reduction of a triple bond (Fig. 1) could be a viable method to access the needed ligands since a number of stereospecific and high yielding reagents have been reported in recent years.[4] This pathway was particularly attractive in our studies because of the ease of preparing the ethynylcyclopropene precursors. Although reports of 3-alkynylcyclopropenes are limited,[5] there are many preparations of cyclopropenes involving cyclopropenylium ions and various nucleophiles.[6] Cyclopropenylium ions are highly electrophilic and their reactions with nucleophiles ordinarily proceed in high yields.[7] We surmised that reaction of an acetylenic Grignard reagent with a cyclopropenylium ion, stereoselective reduction of the triple bond, and halodesilation[8] of the terminal substituent would give the (*Z*)-3-(2-haloethenyl)cyclopropenes needed for metallabenzene and valence isomer formation. We report herein the synthesis of a family of 3-alkynylcyclopropenes, their solid-state structures, and the surprising inertness of the triple bond towards reduction. We also describe the thermal reactivity of several derivatives.

2. Results and discussion

2.1. Cyclopropene synthesis

For our studies we focused on the use of 1,2,3-triphenylcyclopropenylium bromide (**2a**)[9] and 1,2-diphenylcyclopropenylium perchlorate (**2b**)[10] as the synthesis and chemistry of these salts is well delineated.[7] For example, treatment of **2a** with the appropriate acetylenic nucleophile in THF at −78 °C afforded cyclopropenes **3a** and **4a** in very good yields (Scheme 1). The trimethylsilyl group of **3a** was removed readily by K_2CO_3 in MeOH and Et_2O to give the

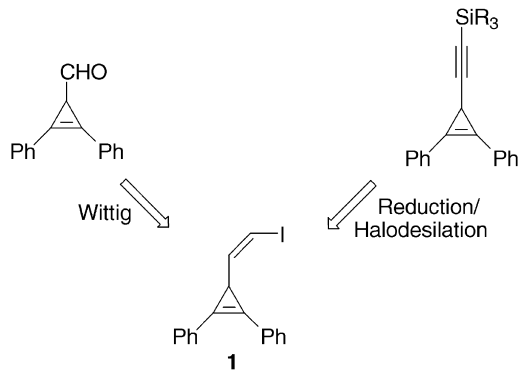

Figure 1. Synthetic approaches to (*Z*)-3-(2-haloethenyl)cyclopropenes.

Keywords: Alkynes; Cyclopropenes; Strained compounds; Thermochemistry.
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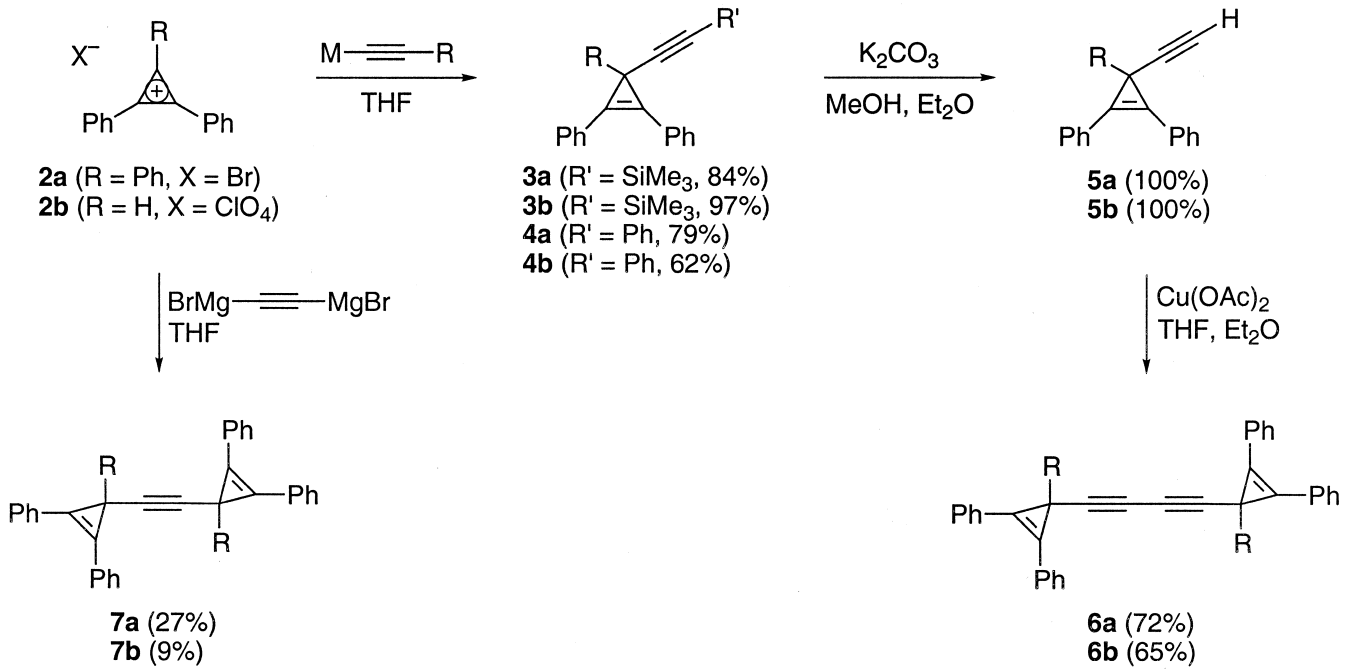


Scheme 1.

terminal acetylene **5a** in quantitative yield. Cyclopropene **5a** was then converted into a 1,4-bis(cyclopropenyl)-1,3-butadiyne system (**6a**) using a modified Eglinton–Glaser reaction.[11] The corresponding ethynyl-linked biscyclopropene **7a** was prepared in modest yield by treating **2a** with 0.5 equiv. of ethynyldimagnesium dibromide. The synthesis of the corresponding diphenylcyclopropenes **3b**–**7b**, which proceeded in an analogous fashion, has been described previously.[12]

2.2. Solid-state structures

Owing to the highly unsaturated and inherently reactive nature of cyclopropenes, we obtained single crystal X-ray structures for several derivatives (**3a**, **4b**, **6b**, **7a**). The molecular structures of **3a** and **4b** are shown in Figure 2.

Table 1. Selected bond lengths (Å) and bond angles (deg) for 3-alkynylcyclopropenes **3a**, **4b**, **6b**, **7a**, and the parent molecule

	Parent[a]	3a	4b	6b	7a[b]
C(1)–C(2)	1.278(2)[c]	1.290(2)	1.297(2)	1.297(3)	1.302(3)
C(1)–C(3)	1.500(2)	1.515(2)	1.517(2)	1.507(3)	1.527(4)
C(2)–C(3)	1.502(2)	1.525(2)	1.514(2)	1.516(3)	1.529(3)
C(3)–C(4)	1.448(2)	1.462(2)	1.444(2)	1.447(3)	1.472(3)
C(4)–C(5)	1.184(2)	1.198(2)	1.200(3)	1.200(3)	1.208(5)[d]
C(5)–R′	[e]	1.827(2)	1.432(2)	1.387(4)	[e]
C(1)–C(2)–C(3)	65.2(1)	64.5(1)	64.8(1)	64.3(2)	64.7(2)
C(1)–C(3)–C(2)	49.1(1)	50.2(1)	50.7(1)	50.8(1)	50.5(2)
C(1)–C(2)–C(Ph)	[e]	154.6(2)	153.1(1)	154.6(2)	151.5(3)
C(2)–C(1)–C(Ph)	[e]	153.8(2)	154.7(1)	155.2(2)	152.2(3)
C(3)–C(4)–C(5)	179.0(1)	178.1(2)	175.9(1)	178.6(2)	177.0(4)[d]
C(4)–C(5)–R′	[e]	177.2(2)	174.8(1)	179.8(2)	[e]

[a] Ref. 5e.
[b] Averages values for two independent molecules.
[c] Libration corrected value; see Ref. 5f.
[d] C(4)–C(4A) in **7a**.
[e] No comparable value.

Selected bond lengths and angles for all four systems, as well as comparison with the analogous values in the C_5 parent 3-ethynylcyclopropene,[5e] are given in Table 1. Typical of cyclopropenes in the solid state,[13] the carbon–carbon double bond lengths in the phenyl substituted derivatives are quite short (1.290–1.302 Å) and the sp^3 bond angles about C3 (50.2–50.8°) are highly constrained. The carbon–carbon triple bond lengths are in the normal range (1.198–1.208 Å). Almost all these values are longer or greater than in 3-ethynylcyclopropene,[5e] (C=C 1.255 Å, C≡C 1.184 Å, C1–C3–C2 49.4°), even if libration corrected values are considered.[5f] These increases are clearly due to the phenyl substituents which not only reduce the libration but also release the electron concentration and thus relieve some of the tension in the highly strained parent molecule.

Interestingly, the packing diagrams for **6b** and **7a** show several close intermolecular C–H···π contacts. For **6b**, the hydrogen on C3 sits 2.69 Å above/below the π-bond of the cyclopropene ring in the next molecule (Fig. 3). The intermolecular H3–C4 distance in **6b** is also quite short (2.78 Å). These contacts result in a packing motif that is reminiscent of one necessary for a topochemical diacetylene polymerization. However, H3 pushes the neighboring diynes apart, thus yielding 1,4-polymerization parameters (d=5.43 Å, γ=53°, and S_1=3.81 Å) that are somewhat outside the range typically observed for such monomers (d≈5 Å, γ≈45°).[14]

The crystal packing in **7a** is considerably more complex (Fig. 4). The individual molecules alternate their orientation and are offset with respect to one another. This arrangement is such that one of the *meta* protons of a cyclopropenyl phenyl group is pointed into the π-bond of a neighboring cyclopropenyl unit with a C–H···π contact of 2.72 Å (center of the double bond). In addition, the *ortho* and *para*

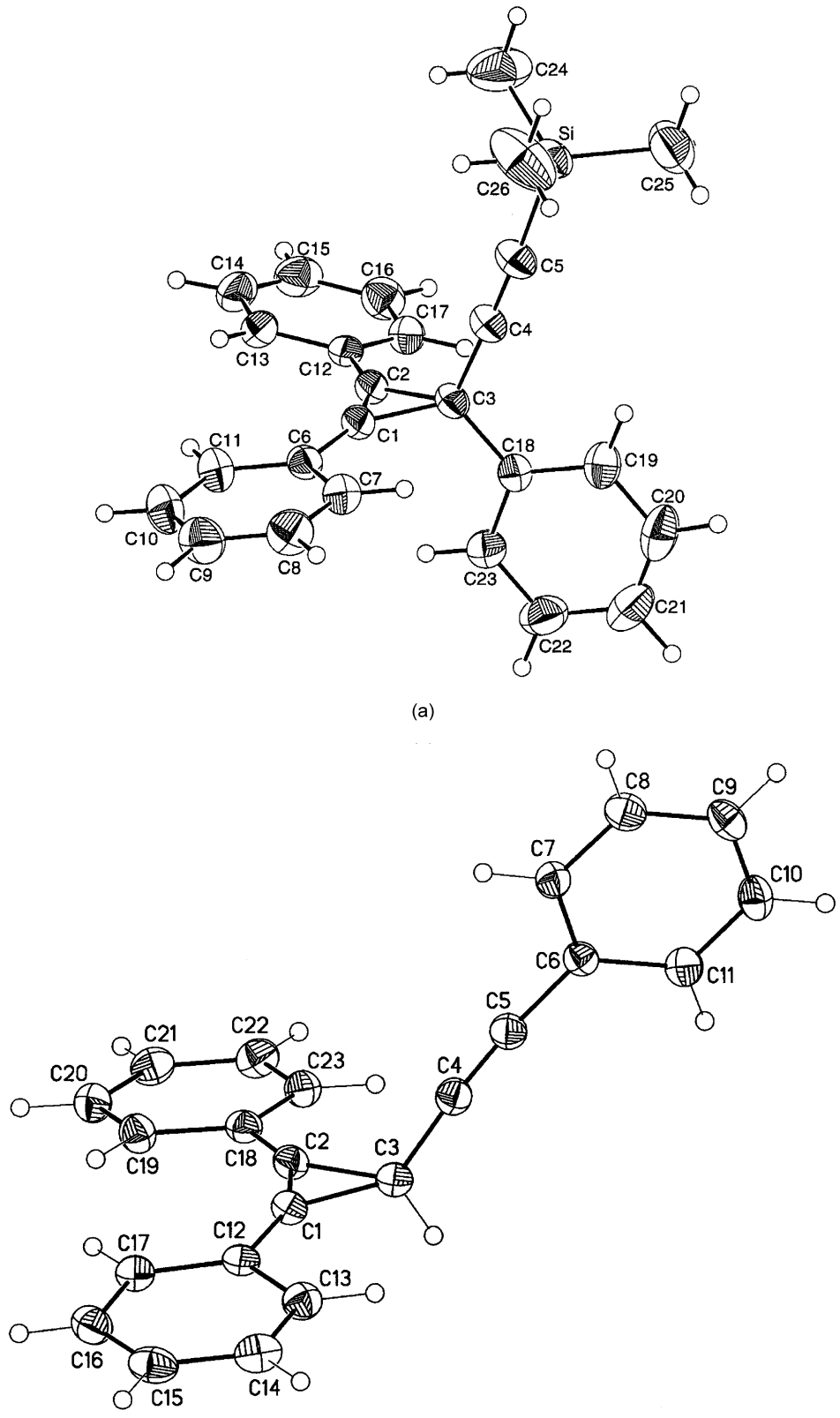


Figure 2. Molecular structures of cyclopropenes **3a** (top) and **4b** (bottom).

protons on the same cyclopropenyl phenyl group possess short C–H···π contacts (3.24 and 3.47 Å) with the two phenyl rings that are attached to the same neighboring cyclopropenyl unit.

2.3. Attempted reduction

With a number of 3-alkynylcyclopropenes now available, we attempted the stereospecific reduction of the triple bond.

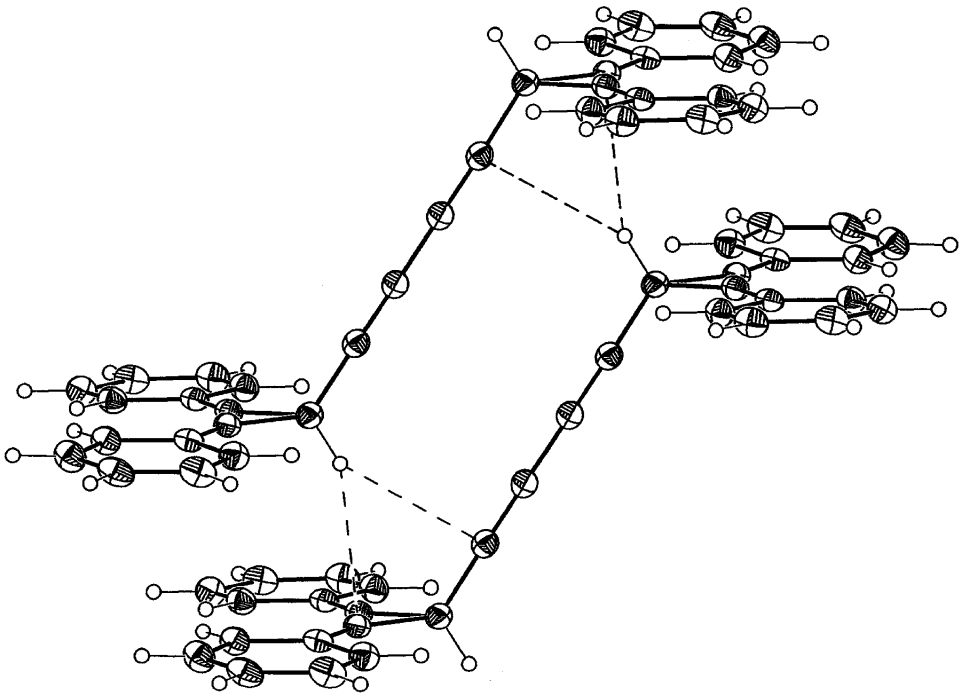


Figure 3. Crystal packing of cyclopropene **6b**.

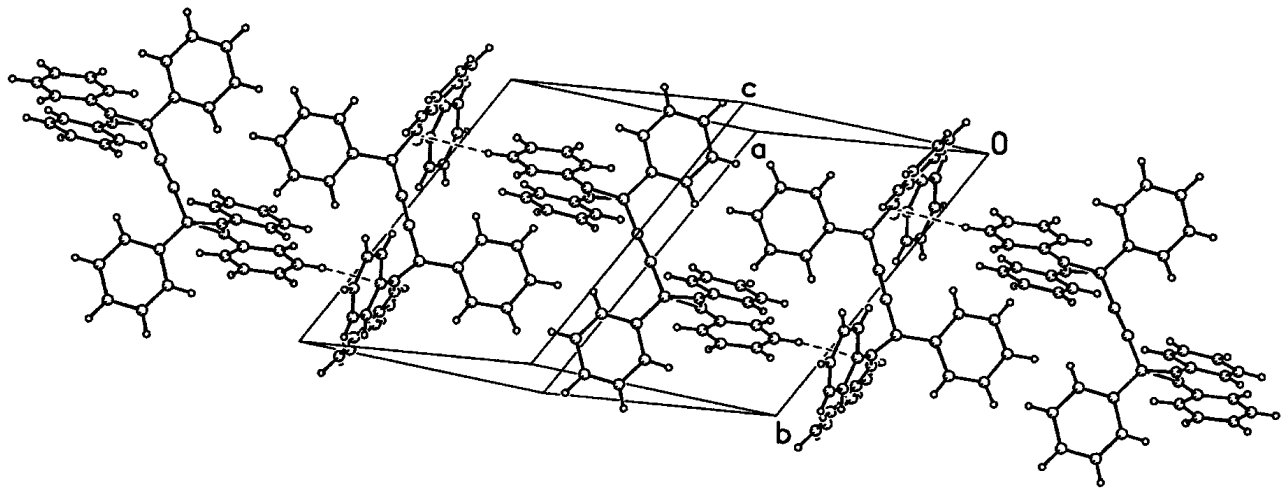
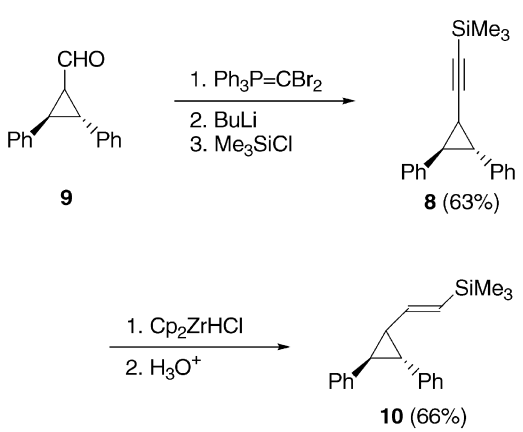


Figure 4. Crystal packing of cyclopropene **7a**.

Reaction of **3a** with Schwartz's reagent (Cp_2ZrHCl)[15] followed by aqueous work-up resulted in complete recovery of starting material. Use of 'Cp_2TiH', generated in situ from Cp_2TiCl_2 and *i*-BuMgBr,[16] also resulted in recovery of **3a**. Careful hydrogenation with Lindlar's catalyst faired no better as the cyclopropene double bond was reduced preferentially. DIBAL-H (in a variety of solvents and temperatures) and $LiAlH_4$, both of which would give the undesired *E*-geometry, either failed to work or reduced the double bond preferentially. Examination of Figure 2(a) suggested that steric bulk might be the culprit for the unreactivity[17] and that use of **3b**, missing the Ph substituent at C3, would be more suitable. Unfortunately, exposure of **3b** to the various reagents and conditions described above also led to recovery of starting material or over-reduced products.



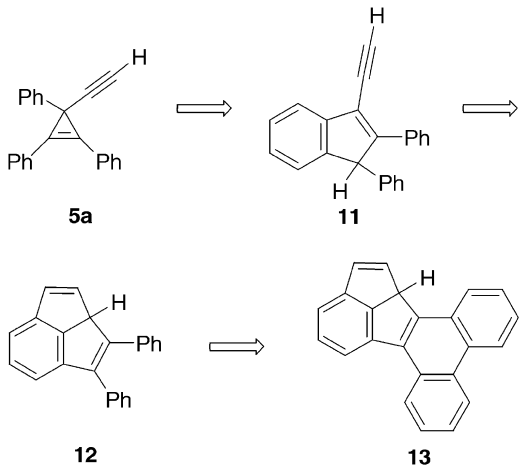
Scheme 2.

To what then can this surprising inertness of the triple bond in **3** be ascribed? Reagents and reaction conditions were ruled out as repetition of the above experiments with both (1-hexynyl)trimethylsilane and (2-phenylethynyl)trimethylsilane gave in every instance the correct product from *cis*-reduction (J=10–11 Hz). This result then suggested that electronics, and not sterics, were the cause of the unreactivity of the triple bond. To confirm this hypothesis, we prepared alkyne **8** (Scheme 2), the cyclopropane analog of **3b**. Exposure of aldehyde **9**[18] to the Corey–Fuchs procedure[19] and quench of the resultant acetylide ion with Me_3SiCl gave **8** in 63% yield. Treatment of **8** with either Cp_2ZrHCl or 'Cp_2TiH' followed by aqueous work-up resulted in complete, stereospecific reduction of the triple bond, furnishing alkene **10** in 66% yield. Surprisingly, the expected *Z*-geometry about the double bond was instead *E*-, based on an alkene coupling constant of 14.2 Hz. Isomerization of *Z*-alkenylsilanes to *E*- is a relatively facile process, and we have encountered this problem before while investigating alternative syntheses of *Z*-2-(cyclopropenyl)ethenylsilanes.[20]

One possible explanation for the lack of reactivity of the triple bond in the alkynylcyclopropenes is due to hyperconjugation. The σ-bond to an sp hybridized carbon might be a reasonably good hyperconjugative electron acceptor for delocalization of the electron pair in the cyclopropenyl π-bond, since a resonance structure that is $(\text{cyclopropenium})^+$ $(\text{alkyne})^-$ seems reasonable. This in turn deactivates the triple bond to attack of the electrophilic reagents. Such hyperconjugation has been shown to occur in both difluorocyclopropanes[21] and fluorocyclopropenes.[22] Unfortunately, high level theoretical calculations on our molecules have not been illuminating.

2.4. Thermochemistry

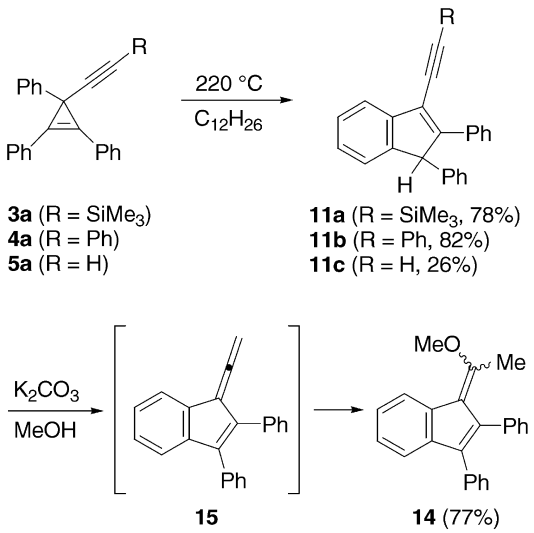
Given the current interest in 'buckybowls' and other related fullerene fragments,[23] we investigated the thermal chemistry of the 3-alkynyl-1,2,3-triphenylcyclopropenes as they might permit access to novel polycyclic aromatic hydrocarbons. After initially opening to the vinylcarbene,[6a,24] the alkynylated systems should undergo C–H insertion on the phenyl at C3 to yield indenes[25] such as **11** (Scheme 3).



Scheme 3.

Unlike the related 3-vinylcyclopropenes, which furnish cyclopentadienes via electrocyclic ring closure (in addition to indenes),[26] the distal alkyne carbon is too remote to undergo analogous reactivity.[5d] Brown rearrangement[23a] (vinylidene formation and subsequent C–H insertion) could lead to the cyclopent[cd]indene skeleton (**12**),[27] or with sufficient energy (pyrolysis or photolysis), to indene/phenanthrene hybrid **13**.[28]

Our initial attempts focused on the thermolysis of **3a**–**5a**. DSC analysis showed that these molecules underwent exothermic reaction around 225 °C. Heating dodecane solutions of the cyclopropenes to 220 °C for 2 h proceeded with complete conversion to indenes **11a**–**11c** (Scheme 4).[28] These compounds result from insertion of the resultant vinylcarbene into one of the *ortho* C–H bonds of the Ph substituent on C3 in **5**. Interestingly, indenes **11** do not undergo sigmatropic rearrangement under the reaction conditions to give the corresponding indenes with the double bond residing between the two Ph substituents, which would be the expected, thermodynamically preferred double bond configuration.[29] In an attempt to prepare a larger quantity of **11c**, desilylation of **11a** with K_2CO_3 in $MeOH/Et_2O$ unexpectedly furnished methoxyfulvene **14** as the sole product, isolated in 77% yield as a 14:1 mixture of regioisomers. This presumably occurs by base-induced isomerization to form unstable vinylidene **15**,[30] which then is attacked by the nucleophilic base and subsequently protonated. This instability/facile isomerization is possibly why **11c** was produced in low yield. Unfortunately, neither **12** nor **13** were observed in our experiments. Formation of these compounds will likely require temperatures greater than 500 °C, attainable only by flash vacuum pyrolysis.



Scheme 4.

3. Conclusions

In summary, we have prepared in very good yield a family of 3-ethynylcyclopropenes by the reaction of cyclopropenylium salts with acetylenic nucleophiles. The X-ray crystal structures of four of these compounds were determined, exhibiting short carbon–carbon double bonds and highly constrained bond angles at C3, both attributable to the

strained nature of the three-membered ring. Attempts to reduce the carbon–carbon triple bond in a stereoselective fashion failed to give the desired products, likely due to electronic effects resulting from hyperconjugation of the cyclopropene with the alkyne moiety. Thermolysis of the cyclopropenes gave alkynylindenes, the product of ring-opening with C–H insertion on the Ph substituent on C3. Treatment of the silyl-protected indene with base afforded an unstable vinylideneindene which reacted further to furnish a benzofulvene. Future studies will be directed toward the high temperature pyrolysis of the alkynylindenes and stereoselective reduction of alkynylstannanes.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in either $CDCl_3$ or CD_2Cl_2 using a Varian Inova 300 NMR (^{1}H: 299.94 MHz, ^{13}C: 75.43 MHz) spectrometer Chemical shifts (δ) are expressed in ppm downfield from $SiMe_4$ using the residual solvent as internal standard ($CDCl_3$–^{1}H: 7.27 ppm, ^{13}C: 77.0 ppm; CD_2Cl_2–^{1}H: 5.32 ppm, ^{13}C: 54.0 ppm). Coupling constants are expressed in Hz. IR spectra were recorded using a Nicolet Magna-FTIR 550 spectrometer. Melting points were determined on a Meltemp II apparatus and are uncorrected. DSC analyses were performed using a TA Instruments DSC 2920. Elemental analyses were performed by Robertson Microlit Laboratories, Inc.

Triphenylcyclopropenylium bromide (**2a**)[9] was prepared according to the literature. All other reagents were purchased from commercial suppliers and used as received. CH_2Cl_2 and pyridine were distilled from CaH_2 under an N_2 atmosphere prior to use. Et_2O and THF were distilled from Na/benzophenone ketyl immediately prior to use. All other chemicals were of reagent quality and used as obtained from the manufacturers. Column chromatography was performed on Whatman reagent grade silica gel (230–400 mesh). Rotary chromatography was performed on a Chromatotron using silica gel (60 PF_{254}) plates (1–4 mm). Baker pre-coated silica gel plates were used for analytical (200×50×0.25 mm^3) thin layer chromatography. Reactions were carried out in an inert atmosphere (dry N_2 or Ar) when necessary.

4.1.1. 3-(Trimethylsilylethynyl)-1,2,3-triphenylcyclopropene (3a). Ethylmagnesium bromide was prepared from magnesium (0.30 g, 12 mmol) and dropwise addition of bromoethane (1.30 g, 12 mmol) in THF (20 mL). Once the addition of bromoethane was complete, the reaction was heated at reflux for 20 min. The suspension was then cooled to 0 °C under an atmosphere of N_2 and ethynyltrimethylsilane (1.38 g, 14 mmol) was added quickly via syringe. The resulting gray suspension was stirred at 0 °C for 15 min with the evolution of ethane gas. The mixture was then warmed to ambient temperature and stirred for an additional 15 min. THF (10 mL) was added to dissolve the solids.

In a separate flask triphenylcyclopropenyl bromide (**2a**, 869 mg, 2.5 mmol) in THF (175 mL) was cooled to −78 °C under N_2. The solution of alkynylmagnesium bromide was added to the cold suspension of **2a** using a double-ended needle under N_2 pressure over a 5 min period. The flask was rinsed with THF (10 mL) and the rinse was added to the suspension of **2a**. After stirring at −78 °C for 1 h, the cooling bath was removed and the mixture was stirred at ambient temperature for 12 h. Excess Grignard reagent was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O, the phases were separated, and the aqueous phase was extracted again with Et_2O. The combined organics were washed with water, saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$), filtered through celite, and concentrated to give a yellow oil. Purification by preparative radial thin-layer chromatography (2 mm rotor, hexanes) furnished **3a** (765 mg, 84%) as a white solid, mp 150.6 °C (DSC). ^{1}H NMR ($CDCl_3$): 7.70 (dd, J=7.6, 1.8 Hz, 4H), 7.52–7.34 (m, 8H), 7.26 (t, J=7.3 Hz, 2H), 7.18 (t, J=7.2 Hz, 1H), 0.18 (s, 9H). ^{13}C NMR ($CDCl_3$): 142.19, 129.92, 129.88, 128.93, 128.03, 126.39, 126.10, 125.72, 111.79, 108.55, 82.84, 23.93, 0.31. IR (KBr): 2153, 1834. Calcd for $C_{26}H_{24}Si$: C, 85.66; H, 6.64. Found: C, 85.46; H, 6.67.

4.1.2. 3-(Phenylethynyl)-1,2,3-triphenylcyclopropene (4a). Use of phenylethyne (1.43 g, 14 mmol) in the procedure described above for **3a** gave after purification compound **4a** (728 mg, 79%) as a white solid, mp 155.5 °C (DSC). ^{1}H NMR ($CDCl_3$): 7.76 (dd, J=7.9, 1.3 Hz, 4H), 7.60 (d, J=7.7 Hz, 2H), 7.51–7.37 (m, 8H), 7.33–7.25 (m, 5H), 7.19 (t, J=7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): 142.52, 131.81, 131.59, 129.91, 129.84, 128.99, 128.10, 127.45, 126.48, 126.16, 125.80, 124.02, 112.16, 92.35, 78.47, 23.77. IR (KBr): 2215, 1829. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.44; H, 5.57.

4.1.3. 3-Ethynyl-1,2,3-triphenylcyclopropene (5a). Cyclopropene **3a** (547 mg, 1.5 mmol) was dissolved in Et_2O (8 mL) and MeOH (20 mL). Anhydrous K_2CO_3 (221 mg, 1.6 mmol) was added and the resulting suspension was stirred at ambient temperature for 8 h. Et_2O and water were added, the layers separated, and the aqueous phase extracted with Et_2O. The combined organics were washed with brine and dried ($MgSO_4$). The suspension was filtered through celite and concentrated to give **5a** (436 mg, 99%) as a pale yellow solid. Recrystallization from hexanes afforded a pure, colorless sample, mp 117.8 °C (DSC). ^{1}H NMR ($CDCl_3$): 7.72 (d, J=8.0 Hz, 4H), 7.56–7.36 (m, 8H), 7.28 (t, J=7.2 Hz, 2H), 7.18 (t, J=7.2 Hz, 1H), 2.18 (s, 1H). ^{13}C NMR ($CDCl_3$): 141.77, 129.86, 129.41, 129.02, 128.12, 126.11, 126.00, 125.88, 111.43, 86.42, 66.16, 22.86. IR (KBr): 3291, 2152, 1834. Calcd for $C_{23}H_{16}$: C, 94.48; H, 5.52. Found: C, 94.41; H, 5.59.

4.1.4. 1,4-Bis(1,2,3-triphenylcycloprop-2-enyl)-1,3-butadiyne (6a). Cyclopropene **5a** (117 mg, 0.4 mmol) and $Cu(OAc)_2$ (250 mg, 1.2 mmol) were suspended in pyridine (2 mL), water (1 mL) and dioxane (1 mL). The suspension was warmed with stirring to 45 °C and all solids dissolved to give a blue solution. A precipitate started to form after 20 min at 45–50 °C. After a total of 2 h of stirring at 45–50 °C, during which the blue color gradually changed to green, the flask was cooled to 0 °C and the precipitate was collected by filtration. The tan solid was washed with 10%

HCl solution and water, then dried in vacuo. Recrystallization from benzene (~3 mL) gave **6a** (84 mg, 72%) as small white cubes, mp 229 °C (melt with decomp.). ^{1}H NMR (CD_2Cl_2): 7.69 (d, J=7.7 Hz, 8H), 7.51–7.38 (m, 16H), 7.26 (t, J=7.5 Hz, 4H), 7.17 (t, J=7.3 Hz, 2H). ^{13}C NMR (CD_2Cl_2): 141.94, 130.39, 130.18, 129.62, 128.86, 126.63, 126.45, 126.32, 111.81, 80.49, 64.11, 24.31. IR (KBr): 2142, 1832. Calcd for $C_{46}H_{30}$: C, 94.81; H, 5.19. Found: C, 94.68; H, 5.41.

4.1.5. Bis(1,2,3-triphenylcycloprop-2-enyl)ethyne (7a). A 0.5 M solution of ethynyldimagnesium dibromide in THF was prepared according to the literature.[31] A portion of the solution (1.3 mL, 0.65 mmol) was diluted with THF (40 mL) and cooled to −78 °C under N_2. Cyclopropenylium salt **2a** (434 mg, 1.25 mmol) was added to the cold Grignard solution and the reaction was stirred for 2 h. The reaction was warmed to ambient temperature and stirred for an additional 12 h. Et_2O and saturated NH_4Cl solution were added. The phases were separated and the organic phase was washed with saturated $NaHCO_3$ solution, water, and brine. The organic phase was dried ($MgSO_4$), filtered through celite, and concentrated. The residual material was chromatographed (preparative radial thin-layer chromatography, 2 mm rotor, 9:1 petroleum ether/EtOAc) affording a pale yellow solid. Recrystallization from boiling hexanes (~10 mL) yielded **7a** (97 mg, 27%) as white needles, mp 190 °C (melt with decomp.). ^{1}H NMR ($CDCl_3$): 7.71 (d, J=7.6 Hz, 8H), 7.45–7.32 (m, 12H), 7.19 (t, J=7.3 Hz, 4H), 7.10 (t, J=7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): 143.37, 129.86, 129.02, 128.86, 127.91, 126.82, 126.23, 125.46, 112.58, 80.94, 23.54. IR (KBr): 1828. Calcd for $C_{44}H_{30}$: C, 94.59; H, 5.41. Found: C, 94.61; H, 5.47.

4.1.6. 2-(*trans*-2,3-Diphenylcyclopropyl)ethynyltrimethylsilane (8). CBr_4 (2.12 g, 6.4 mmol), PPh_3 (3.53 g, 13.4 mmol), and dry CH_2Cl_2 (25 mL) were combined and stirred at room temperature for 20 min, forming a deep orange-red solution. After cooling to 0 °C, aldehyde **9** (1.34 g, 6 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the mixture stirred at 0 °C for 30 min, then room temperature for 3 h. The suspension was diluted with Et_2O (100 mL), filtered through celite, and the solids washed with additional Et_2O (30 mL). After concentration, the residue was passed over a short silica gel column using hexanes (100 mL). Concentration of the solution gave the crude dibromoalkene (1.95 g, 86%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$): 7.41–7.21 (m, 10H), 5.87 (d, J=9.0 Hz, 1H), 2.87 (dd, J=9.0, 6.2 Hz, 1H), 2.63 (t, J=5.7 Hz, 1H), 2.37 (td, J=9.0, 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 140.25, 137.05, 136.66, 128.90, 128.59, 128.54, 126.87, 126.48, 88.07, 33.13, 32.83, 30.43.

To a stirred solution of the above dibromoalkene (1.89 g, 5 mmol) and dry Et_2O (40 mL) at 0 °C was added butyllithium (5 mL, 2.5 M, 12.5 mmol) dropwise. After stirring at 0 °C for 15 additional min, freshly distilled Me_3SiCl (2.17 g, 20 mmol) in Et_2O (3 mL) was added. The mixture was allowed to stir and warm to room temperature over 1 h. The reaction was quenched by addition of saturated NH_4Cl solution (10 mL). The aqueous layer was removed and the organics dried ($MgSO_4$), filtered, and concentrated. Purification by preparative radial thin-layer chromatography (4 mm rotor, hexanes) afforded **8** (1.07 g, 63% from **9**) as a white solid, mp 51.6–52.5 °C. ^{1}H NMR ($CDCl_3$): 7.46–7.22 (m, 10H), 2.87 (t, J=6.0 Hz, 1H), 2.63 (dd, J=8.6, 6.3 Hz, 1H), 2.37 (dd, J=8.6, 5.5 Hz, 1H), 0.11 (s, 9H). ^{13}C NMR ($CDCl_3$): 139.97, 137.15, 128.50, 128.31, 127.75, 126.52, 126.44, 126.23, 104.74, 86.10, 33.47, 33.43, 20.39, −0.14. IR (KBr): 2164, 1598. Calcd for $C_{20}H_{22}Si$: C, 82.70; H, 7.63. Found: C, 82.47; H, 7.67.

4.1.7. (*E*)-2-(*trans*-2,3-Diphenylcyclopropyl)ethenyltrimethylsilane (10). Cyclopropane **8** (49 mg, 0.17 mmol) was placed in a flame-dried round bottom flask and dissolved in dry THF (3 mL). Cp_2ZrHCl (53 mg, 0.20 mmol) was added in three portions and the reaction was stirred at room temperature for 1 h. Wet pentane (3 mL) was added to the mixture, which was then stirred for an additional 2 h. Concentration of the mixture and flash chromatography of the residue over silica (hexanes) gave alkene **10** (33 mg, 66%) as colorless oil. ^{1}H NMR ($CDCl_3$): 7.42–7.21 (m, 10H), 5.76 (dd, J=14.2, 10.1 Hz, 1H), 5.52 (d, J=14.2 Hz, 1H), 2.81 (dd, J=9.1, 6.1 Hz, 1H), 2.59 (t, J=5.6 Hz, 1H), 2.37 (td, J=9.6, 5.1 Hz, 1H), 0.19 (s, 9H). ^{13}C NMR ($CDCl_3$): 146.38, 141.40, 137.84, 129.22, 129.15, 128.49, 128.19, 126.31, 126.22, 125.99, 34.12, 33.07, 31.45, 0.19. HRMS calcd for $C_{20}H_{24}Si$: 292.1647. Found: 292.1653.

4.1.8. 1,2-Diphenyl-3-(trimethylsilylethynyl)-1*H*-indene (11a). A solution of cyclopropene **3a** (50 mg, 0.137 mmol) in dodecane (2 mL) was heated in a ~220 °C sand bath for 2 h. The dodecane was removed under vacuum and the residue purified by column chromatography (hexanes/CH_2Cl_2, 3:1), giving **11a** (39 mg, 78%) as a beige powder, mp 127.0–127.5 °C. ^{1}H NMR ($CDCl_3$): 7.95 (br d, J=7.0 Hz, 2H), 7.57 (d, J=7.3 Hz, 1H), 7.39–7.09 (m, 11H), 5.13 (s, 1H), 0.36 (s, 9H). ^{13}C NMR ($CDCl_3$): 152.20, 146.74, 143.04, 139.94, 133.53, 128.83, 128.28, 128.04, 127.96, 127.94, 127.18, 126.78, 126.33, 123.54, 121.39, 120.49, 103.83, 100.17, 56.78, −0.06. IR (KBr): 2140, 1596. Calcd for $C_{26}H_{24}Si$: C, 85.66; H, 6.64. Found: C, 85.53; H, 6.48.

4.1.9. 1,2-Diphenyl-3-(phenylethynyl)-1*H*-indene (11b). Thermolysis of **4a** (60 mg, 0.163 mmol) as described above gave **11b** (49 mg, 82%) as a light yellow powder, mp 148.5–149.1 °C. ^{1}H NMR ($CDCl_3$): 8.05 (d, J=8 Hz, 2H), 7.76–7.69 (m, 3H), 7.52–7.36 (m, 6H), 7.32–7.20 (m, 8H), 5.25 (s, 1H). ^{13}C NMR ($CDCl_3$): 151.42, 146.87, 143.19, 139.97, 134.77, 131.73, 128.83, 128.46, 128.28, 128.18, 127.95, 127.88, 127.20, 126.77, 126.36, 123.26, 120.48, 97.40, 84.71, 56.91. IR (KBr): 2203, 1597. Calcd for $C_{29}H_{20}$: C, 94.53; H, 5.47. Found: C, 94.26; H, 5.33.

4.1.10. 1,2-Diphenyl-3-ethynyl-1*H*-indene (11c). Thermolysis of **5** (50 mg, 0.171 mmol) as described above gave **11c** (13 mg, 26%) as a pale yellow solid, mp 113–114 °C. ^{1}H NMR ($CDCl_3$): 7.96 (d, J=7.2 Hz, 2H), 7.79 (d, J=7.8 Hz, 1H), 7.40–7.25 (m, 4H), 7.21–7.08 (m, 7H), 5.01 (s, 1H), 2.24 (s, 1H). ^{13}C NMR ($CDCl_3$): 152.23, 146.17, 143.21, 140.79, 134.49, 129.66, 128.01, 128.07, 128.17, 127.70, 127.02, 126.36, 123.37, 121.23, 120.02, 103.03, 101.32, 59.93. IR (KBr): 3297, 2142, 1597. Calcd for $C_{23}H_{16}$: C, 94.48; H, 5.52. Found: C, 94.27; H, 5.41.

4.1.11. 1-(α-Methoxyethylidene)-2,3-diphenylindene (14). Indene **11a** (29 mg, 0.08 mmol) was subjected to the protiodesilylation reaction conditions described for the preparation of **5a**. Purification of the crude material by column chromatography (hexanes/CH_2Cl_2, 1:1) furnished **14** (20 mg, 77%) as a yellow solid, mp 170.5–171.0 °C. ^{1}H NMR ($CDCl_3$): 8.21 (br d, J=7.0 Hz, 1H), 7.39 (br d, J=7.3 Hz, 1H), 7.33–7.16 (m, 12H), 3.97 (s, 3H), 1.91 (s, 3H). ^{13}C NMR ($CDCl_3$): 162.26, 140.17, 138.57, 137.43, 137.27, 135.71, 135.06, 130.60, 129.83, 127.94, 127.72, 126.63, 126.23, 125.29, 124.96, 124.25, 120.85, 119.48, 55.02, 15.97. IR (KBr): 2935, 2840, 1610, 1592. Calcd for $C_{24}H_{20}O$: C, 88.85; H, 6.21. Found: C, 88.61; H, 6.07.

4.2. X-ray crystal structures

Data for **3a** were obtained on an Enraf-Nonius CAD-4 Turbo diffractometer; solution and refinement (C atoms anisotropic, H atoms riding) were accomplished with teXsan (v. 1.7 for SGI workstations). Data for **4b**, **6b**, and **7a** were obtained on a Siemens SMART diffractometer; solution and refinement (C atoms anisotropic, H atoms riding) were performed on F^2 with SHELXTL program suite (v. 5.03). Crystallographic data (excluding structure factors) for the reported structures have been deposited with the Cambridge Crystallographic Data Center as supplementary publications no. CCDC-217174 (**3a**), 216916 (**4b**), 216917 (**6b**), and 216918 (**7a**).

4.2.1. Compound 3a. $C_{26}H_{24}Si$, M_r=364.56, colorless tablet, 0.20×0.05×0.04 mm^3, monoclinic, space group $P2_1/c$, a=3.8508(2), b=21.5422(3), c=21.4937(8) Å, β=91.860(2)°, V=1782.06(9) Å^3, Z=4, ρ_{calc}=1.298 g cm^{-3}, Mo K_α radiation (λ=0.71069 Å), μ=0.74 cm^{-1}, F(000)=720, T=−114 °C, $2\theta_{max}$=45°, 2657 independent reflections scanned, 548 reflections in refinement ($I \geq 3\sigma(I)$), 113 parameters, R=0.085, R_w=0.089.

4.2.2. Compound 4b. $C_{23}H_{16}$, M_r=292.36, colorless plate, 0.28×0.24×0.13 mm^3, monoclinic, space group $P2_1/c$, a=10.3133(1), b=19.7581(1), c=8.1048(1) Å, β=100.070(1)°, V=1626.08(3) Å^3, Z=4, ρ_{calc}=1.194 g cm^{-3}, Mo K_α radiation (λ=0.71073 Å), μ=0.068 mm^{-1}, F(000)=616, T=−115 °C, $2\theta_{max}$=56.7°, 3166 independent reflections scanned, 2276 reflections observed ($I \geq 2\sigma(I)$), 208 parameters, $R1$=0.0509, $wR2$=0.1179.

4.2.3. Compound 6b. $C_{34}H_{22}$, M_r=430.52, colorless plate, 0.27×0.22×0.06 mm^3, monoclinic, space group $P2_1/c$, a=15.3093(12), b=4.1431(3), c=18.9043(15) Å, β=106.678(2)°, V=1148.6(2) Å^3, Z=2, ρ_{calc}=1.245 g cm^{-3}, Mo K_α radiation (λ=0.71073 Å), μ=0.070 mm^{-1}, F(000)=452, T=−115 °C, $2\theta_{max}$=49.4°, 1666 independent reflections scanned, 1223 reflections observed ($I \geq 2\sigma(I)$), 154 parameters, $R1$=0.0523, $wR2$=0.1238.

4.2.4. Compound 7a. $C_{44}H_{30}$, M_r=558.68, colorless plate, 0.21×0.18×0.05 mm^3, triclinic, space group $P1$, a=10.3207(2), b=12.9619(1), c=14.4042(3) Å, α=64.213(1), β=79.148(1), γ=67.475(1)°, V=1602.14(5) Å^3, Z=2, ρ_{calc}=1.158 g cm^{-3}, Mo K_α radiation (λ=0.71073 Å), μ=0.066 mm^{-1}, F(000)=588, T=−115 °C, $2\theta_{max}$=49.9°, 4720 independent reflections scanned, 2880 reflections observed ($I \geq 2\sigma(I)$), 397 parameters, $R1$=0.0627, $wR2$=0.1482.

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References and notes

1. (a) Gilbertson, R. D.; Weakley, T. J. R.; Haley, M. M. *J. Am. Chem. Soc.* **1999**, *121*, 2597–2598. (b) Gilbertson, R. D.; Lau, T. L. S.; Lanza, S.; Wu, H.-P.; Weakley, T. J. R.; Haley, M. M. *Organometallics* **2003**, *22*, 3279–3289.
2. Gilbertson, R. D.; Weakley, T. J. R.; Haley, M. M. *Chem. Eur. J.* **2000**, *6*, 437–441.
3. See also: (a) Wu, H.-P.; Lanza, S.; Weakley, T. J. R.; Haley, M. M. *Organometallics* **2002**, *21*, 2824–2826. (b) Jacob, V.; Weakley, T. J. R.; Haley, M. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3470–3473. (c) Wu, H.-P.; Weakley, T. J. R.; Haley, M. M. *Organometallics* **2002**, *21*, 4320–4322. (d) Jacob, V.; Weakley, T. J. R.; Haley, M. M. *Organometallics* **2002**, *21*, 5394–5400.
4. Larock, R. C. *Comprehensive organic transformations*; 2nd ed. Wiley-VCH: New York, 2000.
5. (a) Domnin, I. N.; Ivanov, A. L.; Fovorskaya, I. A. *Zh. Org. Khim.* **1986**, *22*, 1780–1783. (b) Ivanov, A. L.; Domnin, I. N. *Zh. Org. Khim.* **1988**, *24*, 2547–2552. (c) Maier, G.; Rang, H.; Emrich, R. *Liebigs Ann.* **1995**, 153–160. (d) Haley, M. M.; Biggs, B.; Looney, W. A.; Gilbertson, R. D. *Tetrahedron Lett.* **1995**, *36*, 3457–3460. (e) Baldridge, K. K.; Biggs, B.; Bläser, D.; Boese, R.; Haley, M. M.; Maulitz, A. H.; Siegel, J. S. *Chem. Commun.* **1998**, 1137–1138. (f) Dunitz, J. D. *Chem. Commun.* **1999**, 2547–2548. (g) Maier, G.; Neudert, J.; Wolf, O.; Pappusch, D.; Sekiguchi, A.; Tanaka, M.; Matsuo, T. *J. Am. Chem. Soc.* **2002**, *124*, 13819–13826.
6. (a) Halton, B.; Banwell, M. G. Cyclopropenes. In *The chemistry of the cyclopropyl group*; Rappaport, Z., Ed.; Wiley: New York, 1987; pp 1223–1339. (b) Baird, M. S. In *Cyclopropenes—synthesis by construction of the system. Methods of organic chemistry*; de Meijere, A., Ed.; Thieme: Stuttgart, 1996; Vol. E17d, pp 2695–2744.
7. (a) Komatsu, K.; Yoshida, Z. In *Cyclopropenylium salts. Methods of organic chemistry (Houben-Weyl)*; de Meijere, A., Ed.; Thieme: Stuttgart, 1996; Vol. E17d, pp 3079–3192. (b) Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371–1427.
8. There are a number of possible procedures for dehalosilation with retention of the *Z*-geometry; see Ref. 4, pp 432–434 and 749–750.
9. Xu, R.; Breslow, R. *Organic Syntheses*; Freeman, J. P., Ed.; Wiley: New York, 1998; Coll. Vol. IX, pp 730–732.

10. Donaldson, W. A.; Hughes, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 4846–4859.
11. (a) Glaser, C. *Chem. Ber.* **1869**, *2*, 422–424. (b) Eglinton, G.; McRae, W. *Adv. Org. Chem.* **1963**, *4*, 225–328. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.
12. Gilbertson, R. D.; Weakley, T. J. R.; Haley, M. M. *J. Org. Chem.* **2000**, *65*, 1422–1430.
13. Boese, R. *Advances in strain in organic chemistry*; Halton, B., Ed.; JAI: London, 1992; Vol. 2, pp 191–254.
14. Enkelmann, V. *Adv. Polym. Sci.* **1984**, *63*, 91–136, and references cited therein.
15. (a) Schwartz, J.; Labinger, J. A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333–340. (b) Swanson, D. R.; Nguyen, D.; Noda, Y.; Negishi, E.-I. *J. Org. Chem.* **1991**, *56*, 2590–2591. (c) Lipshutz, B. H.; Keil, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861–5864.
16. Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85–88.
17. We have encountered other systems where substituents at C3 have also impeded subsequent reactivity. For example, see: Gilbertson, R. D.; Weakley, T. J. R.; Haley, M. M.; Weiss, H.-C.; Boese, R. *Organometallics* **1998**, *17*, 3105–3107.
18. (a) Huber, M. K.; Dreiding, A. S. *Helv. Chim. Acta* **1974**, *57*, 748–750. (b) Komendantov, M. I.; Panasyuk, T. B. *Zh. Org. Khim.* **1985**, *21*, 1437–1442.
19. Corey, E. J.; Fuchs, P. W. *Tetrahedron Lett.* **1972**, 3769–3772.
20. (a) For a recent example, see: Mori, A.; Takahisa, E.; Nishihara, Y.; Hiyama, T. *Can. J. Chem.* **2001**, *79*, 1522–1524. (b) Gilbertson, R. D.; Haley, M. M. Unpublished results.
21. Getty, S. J.; Hrovat, D. A.; Xu, J.-D.; Barker, S. A.; Borden, W. T. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1689–1701.
22. Karney, W. L.; Borden, W. T. *J. Am. Chem. Soc.* **1997**, *119*, 3347–3350.
23. (a) Brown, R. F. C. *Eur. J. Org. Chem.* **1999**, 3211–3222. (b) Scott, L. T.; Bronstein, H. E.; Preda, D. V.; Ansems, R. B. M.; Bratcher, M. S.; Hagen, S. *Pure Appl. Chem.* **1999**, *71*, 209–219. (c) Hagen, S.; Hopf, H. *Top. Curr. Chem.* **1998**, *196*, 45–89. (d) Mehta, G.; Rao, H. S. P. *Advances in strain in organic chemistry*; Halton, B., Ed.; JAI: London, 1997; Vol. 6, pp 139–187.
24. Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271–1294.
25. For the only known alkynylindene, see: Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637–2647.
26. (a) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanaka, N.; Loza, R. *J. Org. Chem.* **1978**, *43*, 1481–1492. (b) Zimmerman, H. E.; Aasen, S. M. *J. Org. Chem.* **1978**, *43*, 1493–1506.
27. For a closely related cyclopent[cd]indene, see: Dürr, H.; Fuchs, V. *Tetrahedron Lett.* **1976**, 4049–4052.
28. Structure assignments for **11a–b** were confirmed by COSY, HMBC, and HMQC NMR experiments; **11c** was assigned by analogy.
29. Pettit, W. A.; Wilson, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 6372–6379.
30. Wentrup, C.; Benedikt, J. *J. Org. Chem.* **1980**, *45*, 1407–1409.
31. Brandsma, L. *Preparative acetylenic chemistry*; Elsevier: Amsterdam, 1988; pp 28–29.

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Oxidation of toluenes to benzoic acids by oxygen in non-acidic solvents

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Abstract—Oxidation of substituted toluenes by molecular oxygen at one atmosphere to the corresponding substituted benzoic acids in non-acidic solvents was investigated. Satisfactory oxidation of halo-, methoxy-, and cyano-toluenes were achieved using $Co(C_{18}H_{35}O_2)_2/NH_4Br$ or $Co(OAc)_2$/NaBr/AcOH as catalysts in the presence of a radical initiator.
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1. Introduction

Substituted benzoic acids are very important materials in chemical and pharmaceutical industries and can be prepared by oxidation of the corresponding substituted toluenes.[1–3] In recent years, oxidation processes with environmentally friendly oxidants have received much attention.[4–6] One of the most attractive oxidants is molecular oxygen. Normally, the oxidation with molecular oxygen is carried out in aliphatic acid medium, which causes corrosive and environmentally less-friendly problems.[7] Up to date, oxidation of substituted toluenes to the corresponding aromatic acids in non-acidic solvent has rarely been reported. Ishii and co-workers investigated the catalytic oxidation of alkylbenzenes with molecular oxygen by N-hydroxyphthalimide combined with $Co(OAc)_2$ in acetonitrile.[8] But the reaction conditions were unsatisfactory for substrates with electron-attracting groups. The oxidation of *p*-chlorotoluene gave only 40% yield, and no reaction was observed for *p*-nitrotoluene. Zhang et al. studied the oxidation of substituted toluenes with molecular oxygen in several organic solvents, such as acetonylacetone, 2-heptanone, nitrobenzene, DMF, acetonitrile, and butyl acetate with yield of 2%.[9] In this paper, we reported a new and effective method for oxidation of substituted toluenes with molecular oxygen under atmospheric pressure in non-acidic solvents, such as dichlorobenzene, chlorobenzene, and bromobenzene using $Co(C_{18}H_{35}O_2)_2/NH_4Br$ or $Co(OAc)_2$/NaBr/AcOH as the catalyst in the presence of a radical initiator.

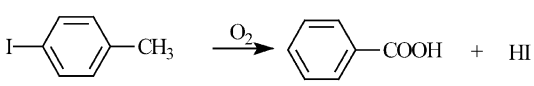
2. Results and discussion

The oxidation of halotoluenes, methoxytoluenes, cyanotoluenes and *p*-xylene with molecular oxygen under atmospheric pressure in halobenzene solvent was investigated, using $Co(C_{18}H_{35}O_2)_2/NH_4Br$ (system A) or $Co(OAc)_2$/NaBr (system B) as the catalyst in the presence of a radical initiator, AIBN. The catalyst $Co(C_{18}H_{35}O_2)_2$ and the co-catalyst NH_4Br (system A) were more soluble in halobenzene. The results are listed in Table 1.

Among the halotoluenes (entries 1, 2, 3 and 4, Table 1) *p*-bromotoluene gave the best yield of 92% while only 32 and 66% were obtained for *p*-fluorotoluene and *p*-chlorotoluene, respectively. However, *p*-iodotoluene gave benzoic acid and stearic acid without any *p*-iodobenzoic acid formed. An explanation was illustrated in Scheme 1.

The oxidation of *p*-methoxytoluene gave good yield (88%, Table 1, entry 7). However, the substrate impurity must be purified to remove small amount of *p*-hydroxytoluene, which serves as the radical inhibitor.

The oxidation of *p*-xylene gave 96% yield of *p*-phthalic acid after 9 h while only *p*-toluic acid was observed in 2 h. These results were consistent with Digurov's result, which showed that the formation of *p*-phthalic acid commenced only after



$$2\,HI + Co(C_{18}H_{35}O_2)_2 \longrightarrow 2\,C_{17}H_{35}COOH + CoI_2$$

Scheme 1.

Keywords: Oxidation; Toluenes; Benzoic acids; Oxygen.
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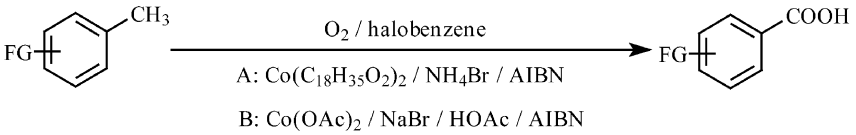
Table 1. Oxidation of substituted toluenes in halobenzene



Entry	Substrate	Solvent	Cat.[a]	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	*p*-FC_6H_4Me	Dichlorobenzene	A	150	8	*p*-FC_6H_4COOH	32
2	*p*-ClC_6H_4Me	Dichlorobenzene	A	150	8	*p*-ClC_6H_4COOH	66
3	*p*-BrC_6H_4Me	Dichlorobenzene	A	150	8	*p*-BrC_6H_4COOH	92
4	*p*-IC_6H_4Me	Dichlorobenzene	A	150	8	*p*-IC_6H_4COOH	—[c]
5	*p*-$NO_2C_6H_4Me$	Dichlorobenzene	A	150	9	*p*-$NO_2C_6H_4COOH$	Trace
6	*o*-$NO_2C_6H_4Me$	Dichlorobenzene	A	150	9	*o*-$NO_2C_6H_4COOH$	Trace
7	*p*-$CH_3OC_6H_4Me$	Dichlorobenzene	A	150	4.5	*p*-$CH_3OC_6H_4COOH$	88
8	4-Cl-2-FC_6H_3Me	Dichlorobenzene	A	150	6	4-Cl-2-FC_6H_3COOH	85
9	*p*-$CH_3C_6H_4Me$	Dichlorobenzene	A	150	9	*p*-$HOOCC_6H_4COOH$	96
10	*p*-BrC_6H_4Me	Chlorobenzene	A	130	9	*p*-BrC_6H_4COOH	83
11	*p*-BrC_6H_4Me	Bromobenzene	A	150	9	*p*-BrC_6H_4COOH	90
12	*p*-FC_6H_4Me	Dichlorobenzene	B	110	8	*p*-FC_6H_4COOH	83
13	*p*-ClC_6H_4Me	Dichlorobenzene	B	110	8	*p*-ClC_6H_4COOH	84
14	*p*-BrC_6H_4Me	Dichlorobenzene	B	110	3	*p*-BrC_6H_4COOH	90
15	*p*-$NO_2C_6H_4Me$	Dichlorobenzene	B	110	9	*p*-$NO_2C_6H_4COOH$	67
16	*o*-$NO_2C_6H_4Me$	Dichlorobenzene	B	110	9	*o*-$NO_2C_6H_4COOH$	Trace
17	*p*-$CH_3OC_6H_4Me$	Dichlorobenzene	B	110	3	*p*-$CH_3OC_6H_4COOH$	94
18	4-Cl-2-FC_6H_3Me	Dichlorobenzene	B	110	5	4-Cl-2-FC_6H_3COOH	87
19	4-Br-2-FC_6H_3Me	Dichlorobenzene	B	110	4.5	4-Br-2-FC_6H_3COOH	91
20	*p*-CNC_6H_4Me	Chlorobenzene	B	110	2.5	*p*-CNC_6H_4COOH	96
21	*m*-CNC_6H_4Me	Chlorobenzene	B	110	3.5	*m*-CNC_6H_4COOH	87
22	*o*-CNC_6H_4Me	Chlorobenzene	B	110	7	*o*-CNC_6H_4COOH	31
23	*p*-$CH_3C_6H_4Me$	Dichlorobenzene	B	110	2	*p*-$CH_3C_6H_4COOH$	51
24	*p*-$CH_3C_6H_4Me$	Dichlorobenzene	B	110	9	*p*-$HOOCC_6H_4COOH$	92

[a] A: $Co(C_{18}H_{35}O_2)_2$ (6 mol%)/NH_4Br (5 mol%), 4 mol% AIBN; B: $Co(OAc)_2$ (5 mol%)/NaBr(3 mol%)/HOAc (50 mol%), 2 mol% AIBN.
[b] Isolated yield.
[c] Benzoic acid as the product.

p-tolualdehyde had been completely converted to *p*-toluic acid.[10]

Chlorobenzene and bromobenzene were also screened as solvents. Satisfactory yields were obtained (Table 1, entries 10 and 11).

The more common catalyst $Co(OAc)_2$ in the presence of catalytic amount of acetic acid (system B) was also examined. The results showed that almost all of the substrates were converted to the corresponding benzoic acids in higher yields at lower temperature (entries 12–24 in Table 1).

Cyano group is compatible with the reaction conditions (Table 1, entries 20, 21 and 22). However, the positions of substitution strongly influenced the yields. Up to 96 and 87% of isolated yields (entries 20 and 21) were obtained for *p*- and *m*-cyanobenzoic acids within about 3 h while only 31% of *o*-cyanobenzoic acid was achieved after 7 h. Meanwhile, *o*-nitrotoluene was not oxidized under these conditions. However, *p*-nitrotoluene led to *p*-nitrobenzoic acid in 67% yield.

The system B proved to be more efficient both in rate and yield. A lower temperature of 110 °C was required in system B compared to 150 °C in system A. The yields of *p*-fluorobenzoic acid and *p*-chlorobenzoic acid were improved greatly from 32 and 66% (Table 1, entries 1 and 2) to 83 and 84% (Table 1, entries 12 and 13), respectively. The possible reason was that hydrophilic acetic acid could promote the decomposing of intermediate $ArCH_2OOH$.[9]

When $Co(C_{18}H_{35}O_2)_2$/NH_4Br or $Co(OAc)_2$/NaBr was used without any added radical initiator, no oxidation occurred. Radical initiators, such as AIBN, NHPI and benzoyl peroxide, were carried out under same conditions using *p*-bromotoluene as the substrate. The all exhibited the same activity at 150 °C while benzoyl peroxide was not effective at all at 110 °C (Table 2).

4-Chloro-2-fluorobenzoic acid and 4-bromo-2-fluorobenzoic acid are important pharmaceutical agents,[11,12] and were obtained in high yields (Table 1, entries 8, 18 and 19).

Table 2. Comparison of the efficiency of NHPI, $(C_6H_5CO_2)_2$ and AIBN[a]

Entry	Initiator	Cat.[b]	Temp (°C)	Time (h)	Yield[c] (%)
1	AIBN	A	150	9	92
2	$(C_6H_5CO_2)_2$	A	150	9	92
3	NHPI	A	150	9	95
4	AIBN	B	110	3	90
5	$(C_6H_5CO_2)_2$	B	110	3	Trace
6	NHPI	B	110	3	92

[a] *p*-Bromotoluene (15 mmol) was used as substrate.
[b] A: $Co(C_{18}H_{35}O_2)_2$ (6 mol%)/NH_4Br (5 mol%), 4 mol% of radical initiator; B: $Co(OAc)_2$ (5 mol%)/NaBr (3 mol%)/HOAc (50 mol%), 2 mol% of radical initiator.
[c] Isolated yield.

The mechanism for the aerobic oxidation of substituted toluenes catalyzed by cobalt(II) compounds has been proposed.[7,10,13,14] It is suggested that Co(II) reacts with dioxygen to generate a liable dioxygen complex of superoxocobalt(III) or μ-peroxocobalt(III) complex. These cobalt-oxygen species, which were reported to be easily formed by the one-electron reduction of dioxygen using cobalt(II),[15,16] assist the generation of the radical from AIBN at high temperature. Bromide, a promoter, may form Br· radical at low catalyst concentration to initiate the reaction.[10]

In conclusion, we have developed a practical procedure for the catalytic oxidation of substituted toluenes to corresponding aromatic acids in non-acidic solvent of halobenzenes under atmospheric pressure in the presence of a radical initiator. It is noteworthy that the reaction systems are applicable for the oxidation of both electron-withdrawing and electron-donating substituted toluenes.

3. Experimental

3.1. General remarks

Melting points were measured with a Yanaco Mp 500 apparatus. ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz spectrometer with tetramethylsilane as the internal standard.

3.2. General procedure

Substituted toluene, catalysts, radical initiator, and halobenzene were added to a three-necked flask with a reflux condenser. The mixture was heated, with oxygen bubbling through the solution for 3–10 h. After the reaction was finished, the mixture was cooled to room temperature, and crystals precipitated. Then crude product was obtained by filtration and further purified by recrystallization with ethanol/water. The yields of acids were 32–96%.

3.3. Typical procedure

3.3.1. Typical procedure for the oxidation of *p*-bromotoluene in catalyst system A. *p*-Bromotoluene (2.56 g, 15 mmol), AIBN (0.098 g, 0.6 mmol), $Co(C_{18}H_{35}O_2)_2$ (0.557 g, 0.9 mmol), and dichlorobenzene (20 mL) were added to a three-necked flask with a reflux condenser, and the mixture was heated at 150 °C, then oxygen was bubbled through the solution for 9 h. After the reaction was finished, the mixture was cooled to room temperature and *p*-bromobenzoic acid was precipitated. The crude product (2.71 g) was purified by recrystallization with ethanol/water, mp 251–252 °C [lit.[17] 251–253 °C]. The yield was 92%.

3.3.2. Typical procedure for the oxidation of *p*-methoxytoluene in catalyst system B. *p*-Methoxytoluene (2 g, 16.4 mmol), AIBN (0.081 g, 0.4 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.204 g, 0.8 mmol), NaBr (0.056 g, 0.54 mmol), HOAc (0.49 g, 8.2 mmol) and dichlorobenzene (10 mL) were added to a three-necked flask fitted with a reflux condenser. The mixture was heated to 110 °C with oxygen bubbling through the solution for 3 h. After the reaction was finished, the mixture was cooled to room temperature and *p*-methoxybenzoic acid was precipitated. The crude product was recrystallized with ethanol/water. Then 2.3 g of *p*-methoxybenzoic acid was obtained and the yield was 94%, mp 183–184 °C [lit.[18] 184 °C].

3.3.3. *p*-Fluorobenzoic acid. 4-Fluorotoluene was oxidized to give 4-fluorobenzoic acid as a white solid, mp 184–186 °C [lit.[19] 185 °C].

3.3.4. *p*-Chlorobenzoic acid. Oxidation of 4-chlorotoluene gave 4-chlorobenzoic acid as a white solid, mp 240–242 °C [lit.[20] 243 °C].

3.3.5. Cyanobenzoic acid (*p*-, *m*-, *o*-). *p*-Cyanotoluene, *m*-cyanotoluene and *o*-cyanotoluene were oxidized with molecular oxygen catalyzed by system B to give *p*-cyanobenzoic acid, *m*-cyanobenzoic acid and *o*-cyanobenzoic acid as white solids, respectively. *p*-Cyanobenzoic acid: mp 217–218 °C [lit.[21] 219 °C]; *m*-cyanobenzoic acid: mp 215–216 °C [lit.[21] 217 °C]; *o*-cyanobenzoic acid: mp 187–188 °C [lit.[22] 187 °C].

3.3.6. *p*-Phthalic aid. Oxidation of *p*-xylene catalyzed by system A gave *p*-phthalic aid as a white solid, 96% yield. Sublimes without melting at ca. 300 °C [lit.[23]].

3.3.7. *p*-Toluic acid. Oxidation of *p*-xylene catalyzed by system B gave *p*-phthalic aid as a white solid, 51% yield, mp 180–181 °C [lit.[24] 181 °C].

3.3.8. 4-Chloro-2-fluorobenzoic acid. White solid, mp 207–210 °C (C_2H_5OH/H_2O); δ_H (300 MHz, CD_3COCD_3) 7.9–8.0 (1H, m, ArH), 7.4–7.6 (2H, m, ArH).

3.3.9. 4-Bromo-2-fluorobenzoic acid. White solid, mp 237–240 °C (C_2H_5OH/H_2O); δ_H (300 MHz, CD_3COCD_3) 8.0–8.1 (1H, m, ArH), 7.6–7.8 (2H, m, ArH).

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References and notes

1. Sheldon, R. A.; Kochi, J. K.; et al. *Metal-catalyzed oxidations of organic compounds*; Academic: New York, 1981.
2. Hudlicky, M. *Oxidation in organic chemistry*. *ACS Monograph 186*; American Chemical Society: Washington, DC, 1990.
3. Trost, B. M. *Comprehensive organic synthesis (oxidation)*; Pergamon: New York, 1991.
4. Sato, K.; Aoki, M.; Tagaki, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386–12387.

5. Varma, R. S.; Saini, R. K. *Tetrahedron Lett.* **1998**, *39*, 1481–1482.
6. Varma, R. S.; Dahiya, R. *Tetrahedron Lett.* **1998**, *39*, 1307–1308.
7. Peeters, M. P. J.; Busio, M.; Leijten, P. *Appl. Catal.* **1994**, *118*, 51–62.
8. Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810–6813.
9. Zhang, X.-F.; Shi, X.-T. *Synth. Chem. (in Chinese)* **1998**, *6*(4), 433–437.
10. Raghavendrachar, P.; Ramachandran, S. *Ind. Engng Chem. Res.* **1992**, *31*, 453–462.
11. Kazuhito, I.; Toru, T.; Norio, N.; Toru, N.; Hiroyuki, N. JP 344 752, 2000.
12. Reinhard, K.; Hans-Ludwig, S.; Eugen, F.; Horst, H. DE 19 941 540, 2001.
13. Morimoto, T.; Ogata, Y. *J. Chem. Soc. (B)* **1967**, *62*, 62–66.
14. Onopchenko, A.; Sohultz, A. J. G. *J. Org. Chem.* **1973**, *38*, 3729–3733.
15. Niederhoffer, E. C.; Timmons, J. H.; Martell, A. E. *Chem. Rev.* **1984**, *84*, 137–203.
16. Bozell, J. J.; Hames, B. R.; Dimmel, D. R. *J. Org. Chem.* **1995**, *60*, 2398–2404.
17. Ohkura, K.; Kashino, S.; Haisa, M. *Bull. Chem. Soc. Jpn* **1972**, *45*, 2651–2652.
18. Gilman, H.; Langham, W.; Willis, H. B. *J. Am. Chem. Soc.* **1940**, *62*, 346–348.
19. Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Andersen, K. K. *J. Am. Chem. Soc.* **1963**, *85*, 3146–3156.
20. Ho, T.-L. *Synthesis* **1972**, 560–562.
21. Weast, R. C.; Astle, M. J. *Handbook of data on organic compounds*; CRC: Boca Raton, FL, 1985; p 218.
22. Weast, R. C.; Astle, M. J. CRC handbook of chemistry and physics. 63rd ed. CRC: Boca Raton, FL, 1982; p C-453.
23. Weast, R. C.; Astle, M. J. *Handbook of data on organic compounds*; CRC: Boca Raton, FL, 1985; p 190.
24. Brunet, J. J.; Sidot, C.; Loubinoux, B.; Caubere, P. *J. Org. Chem.* **1979**, *44*, 2199–2202.

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Furanaphin: a novel naphtho[2,3-*c*]furan-4(1*H*)-one derivative from the aphid *Aphis spiraecola Patch*

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Abstract—A novel naphtho[2,3-*c*]furan-4(1*H*)-one derivative **1**, named furanaphin, was isolated from the aphid *A. spiraecola P*. The structure of the compound was established by a single crystal X-ray analysis of its (*S*)-MTPA ester. Furanaphin was found to have cytotoxicity against HL-60 human tumor cells.
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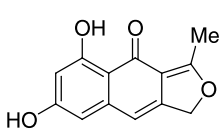
1. Introduction

The extensive investigations of Todd followed by Cameron and their co-workers revealed that a number of aphids produced novel pigments such as xanthoaphins,[1–7] chrysoaphins,[1–9] erythroaphins,[1–5,10–21] protoaphins[1–4,7,9,20,22–31] and so on. Unfortunately, however, their extraordinary work stopped in the early 1980s. Since then hardly any studies of aphid pigments have been reported.[32] Therefore, we started chemical investigations of the pigments found in aphids, having an interest in biological activities and biological meaning for aphids themselves.

We focused at first on *Aphis spiraecola P*. which is a yellowish aphid (max. 1.5 mm long) feeding on *Polygonum cuspidatum* Sieb. et Zucc., since structures of yellowish substances in the aphid had not yet been studied. In our chemical study, a new naphtho[2,3-*c*]furan-4(1*H*)-one derivative, named furanaphin (**1**), together with 6-hydroxymusizin (**2**) was isolated as a yellowish hydrophobic compound. In this paper, we would like to describe the isolation of these compounds, their structure determination, and the cytotoxicity of **1** against HL-60 (leukemia) human tumor cells.



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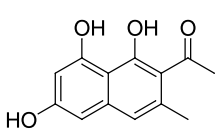

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2. Results and discussion

The aphid *A. spiraecola P*. was collected into a trap by suction with an aspirator in June in Tokushima Prefecture, Japan. The aphid was squashed in ether, and then the ethereal supernatant solution was separated by decantation. The residue was washed with several portions of fresh ether. The combined ethereal solutions were evaporated and subjected to silica-gel column chromatography to afford two yellow pigments **1** and **2**. The less polar compound **2** was identified as 6-hydroxymusizin from chemical and spectroscopic data.[33,34] On the other hand, **1**, isolated as yellow-hued crystals, mp 211–214 °C (dec), is in fact a new natural product, whose infrared spectrum in KBr indicated the presence of hydroxyl (3187 cm^{-1}, br) and intramolecularly-hydrogen-bonded carbonyl (1651 cm^{-1}) groups.

The noise-decoupled ^{13}C NMR spectrum of **1** clearly exhibited 13 carbon resonances, which were classified as one methyl, one methylene, three methines, and eight quaternary carbon atoms using distortionless enhancement by polarization transfer (DEPT) ^{13}C NMR analysis. From these results and the HREIMS (*m*/*z* 230.0570), the molecular formula of **1** was established as $C_{13}H_{10}O_4$. In the ^1H NMR spectrum, two hydroxy protons (14.28 and 9.27 ppm) were observed and the proton resonating at 14.28 ppm was hydrogen-bonded presumably with a carbonyl group. The heteronuclear multiple quantum coherence (HMQC) spectra of **1** (Table 1) revealed the

Keywords: Pigment; Naphtho[2,3-*c*]furan-4(1*H*)-one; Aphid; *A. spiraecola P*.
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Table 1. ^{13}C (150 Hz) and ^{1}H (600 Hz) NMR data of **1** in acetone-d_6

Position	δ_C	δ_H
1	77.5	5.51 (2H, d, *J*=2.6 Hz)
3	184.7	
3a	115.1	
4	184.3	
4a	111.6	
5	167.4	
6	100.5	6.18 (1H, d, *J*=2.2 Hz)
7	164.7	
8	104.7	6.35 (1H, d, *J*=2.2 Hz)
8a	143.9	
9	107.4	6.40 (1H, t, *J*=2.6 Hz)
9a	143.4	
3-CH_3	16.1	2.68 (3H, s)
5-OH		14.28 (1H, s)
7-OH		9.27 (1H, br s)

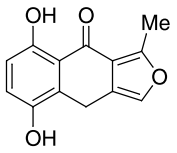
presence of an oxygen-bearing methylene carbon [C 77.5/H 5.51 (2H, d) ppm] and three aromatic and/or olefinic methine carbons [C 100.5/H 6.18 (1H, d) ppm], [C 104.7/H 6.35 (1H, d) ppm], and [C 107.4/H 6.40 (1H, t) ppm]. Furthermore, the carbon signal at 16.1 ppm together with the proton signal at 2.68 (3H, s) ppm hinted at a vinyl methyl group (Table 1), which was located on a particular structure.

The novel structure of **1** was also suggested by the presence of a peculiar olefinic carbon, whose ^{13}C NMR signal was shifted downfield by 184 ppm. That is, although one of the signals at 184.7 or 184.3 ppm can be easily assigned to an ordinary carbonyl carbon, the chemical shift of the other signal must be assigned to an olefinic carbon; this is a highly unusual shift for an olefinic carbon. Moreover, HMBC analysis revealed correlations between the methyl group at 2.68 ppm and carbons at 184.7 and 115.1 ppm. These data implied the existence of a particular α,β-unsaturated carbonyl group. However, it was hard to establish the structure of **1** by spectroscopic means in spite of detailed analyses of 1D and 2D NMR spectra involving $^{1}H-^{1}H$ COSY, NOESY, HMQC, and HMBC measurements.

Hence, **1** was converted to some derivatives (Scheme 1). However, the spectra of the acetate **3** gave very little information on the structure and the generation of **4** puzzled us. Further, no single crystals of **1**, **3** and **4** could be obtained.

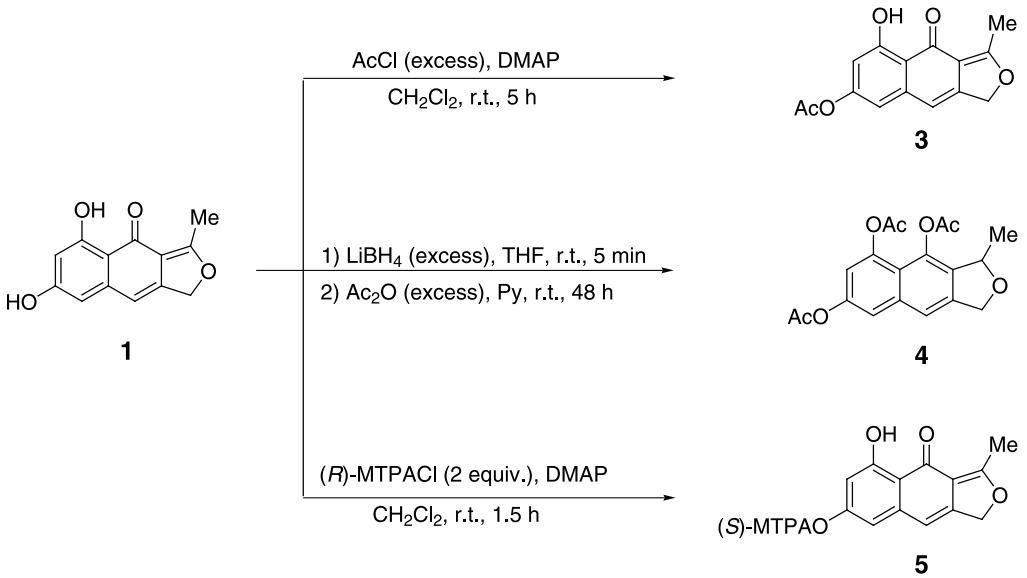
Finally, the structure of **1** could be firmly established when a single crystal of (*S*)-MTPA ester **5** suitable for X-ray analysis was fortuitously obtained by the acylation employing (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) with DMAP in CH_2Cl_2.[35] The IR and ^{1}H NMR spectra of **5** suggested that the skeleton of the compound did not change in the reaction sequence. Figure 1 illustrates the molecular structure of **5** with the atomic numbering. Thus, the structure of furanaphin (**1**) was determined to be 5,7-dihydroxy-3-methylnaphtho[2,3-*c*]furan-4(1*H*)-one. In Figure 2, $^{13}C-^{1}H$ long range correlations in the HMBC spectrum of **1** are shown. The unusual carbon signal at 184.7 ppm can be now assigned to the C-3 olefinic carbon, the β-carbon of the carbonyl, bearing an ethereal oxygen atom.[36]

It was surprising that the aphid product **1** was an analogue of MS-444 (**6**), which was isolated from the culture broth of *Micromonosora* sp. and was found to possess inhibitory activity against myosin light chain kinase (IC_{50}=10 μM).[37,38] On the other hand, **6** at 430 μM showed no antimicrobial activity.[37]



6

So, it was quite interesting to investigate how the difference of the substitution pattern of hydroxyl groups and the position of the olefin between **1** and **6** influenced biological activities. Hence, first of all, **1** was tested for its cytotoxicity against human promyelocytic leukemia HL-60 cells.[39] The



1 **3** **4** **5**

Scheme 1. Acylation of **1**.

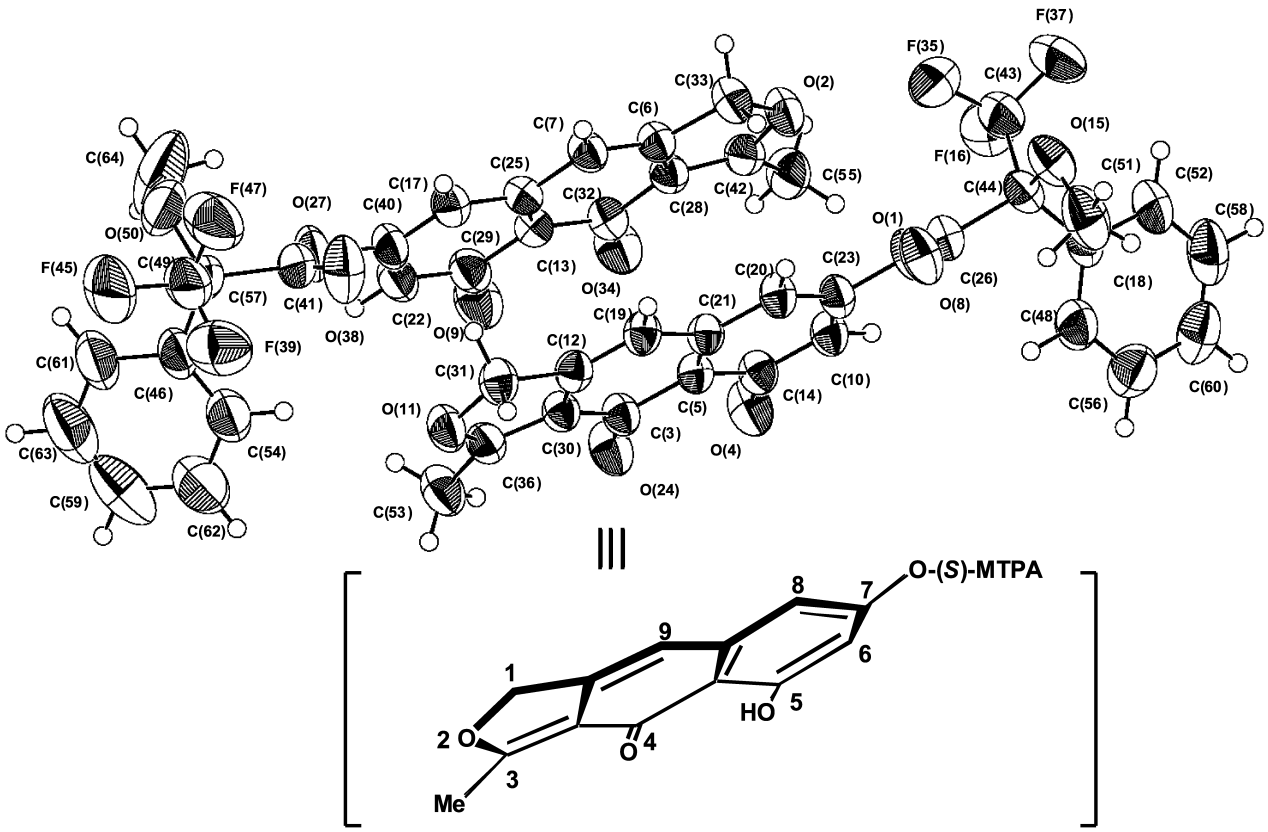


Figure 1. ORTEP structure of **5**.

result was shown in Figure 3, where **1** was found to be active with ED_{50} of 25 μM. This finding encouraged us to continue the investigation of its biological activities including the inhibitory activity against myosin light chain kinase.

3. Conclusion

Thus, **1** is an attractive substance, although we do not know yet the reason why the aphid produces such a novel compound. Further work on the biological activities of **1** and structure determination of other enchanting pigments of aphids is in progress.

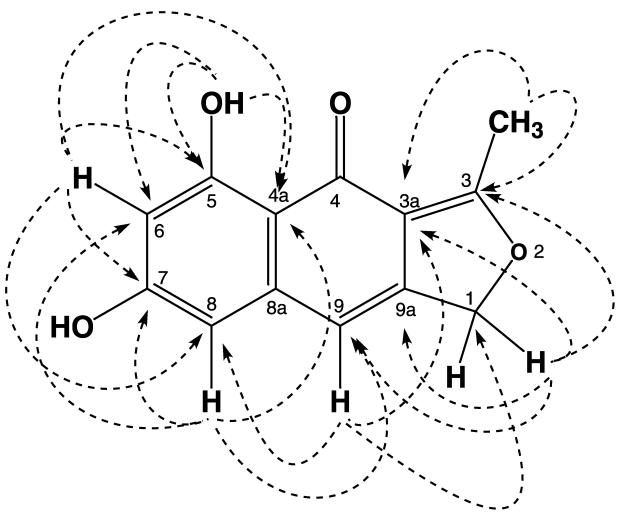
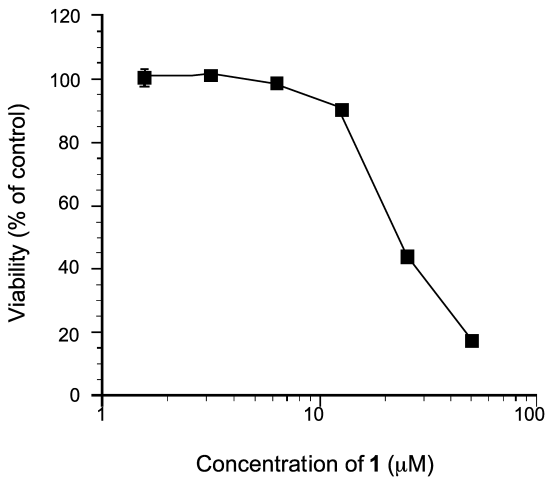


Figure 2. HMBC correlations of **1**.



HL-60 cells were treated with **1** at the indicated concentration for 24 h. Viability of the cells was determined by MTT assay. Data were means ± SD (n= 4).

Figure 3. Cytotoxicity of **1** in HL-60 cells.

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-3

apparatus and were uncorrected. IR spectra were measured on a JASCO FT/IR-410 spectrophotometer. UV–visible spectra were measured on a Shimadzu UV-1650pc spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity-600 (600 MHz) with tetramethylsilane as an internal standard in acetone-d_6. ^{13}C NMR spectra were taken on the Varian Unity-600 (150 MHz); chemical shifts were referenced to the residual solvent signal (acetone-d_6: δ_C 29.8 ppm). Signal multiplicities were established by DEPT experiments. Mass spectra including high-resolution mass spectra were recorded on a JOEL JMX AX-500 spectrophotometer. Column chromatography was carried out with Silica gel 60N (Kanto Chemical Co. Inc., 63–210 μm). Acetyl chloride, acetic anhydride, 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and pyridine were purchased from Nacalai Tesque Inc. $LiBH_4$ and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) were purchased from Aldrich Chemical Co. Inc. They were used without any purification. THF was distilled from sodium/benzophenone ketyl prior to use.

4.2. Material

The aphid *Aphis spiraecola P.* which were feeding on *Polygonum cuspidatum* Sieb. et Zucc., were collected in June in Tokushima Prefecture, Japan in 2001.

4.3. Extraction and isolation

The aphid (12.7 g) was squashed in diethyl ether, and then the ethereal supernatant solution was separated by decantation. The residue was washed with several portions of fresh ether. The combined ethereal solutions were dried over Na_2SO_4 and were evaporated to give a crude extract (0.69 g). The yellowish residue was subjected to silica-gel column chromatography (36 g) using hexane/AcOEt (3:1–1:3) as eluent to afford two yellow pigments **1** (65.4 mg) and **2** (17.2 mg).

4.3.1. Furanaphin (1). Yellow powder, mp 211–214 °C (dec). UV (CH_3CN) λ_{max} 210 (log ε 4.11), 274 (log ε 4.44), 433 (log ε 4.00) nm. IR (KBr): ν_{max} 3187 (–OH), 1651 (C═O), 1623, 1572, 1484, 1432, 1390 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) and ^{13}C NMR (150 MHz, acetone-d_6) see Table 1. MS (EI) *m/z* 230 (M^+), HRMS (EI) calcd for $C_{13}H_{10}O_4$ (M^+) 230.0579, found 230.0570.

4.3.2. 6-Hydroxymusizin (2). Yellow powder, mp 198.4–204 °C (dec). UV (EtOH) λ_{max} 233 (log ε 4.46), 271 (log ε 4.50), 389 (log ε 4.03) nm. IR (neat): ν_{max} 3349 (–OH), 2925, 1634 (C═O), 1588, 1382, 1154 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ 17.31 (1H, br s), 10.46 (1H, br s), 9.17 (1H, br s), 6.83 (1H, d, *J*=0.6 Hz), 6.53 (1H, d, *J*=2.4 Hz), 6.38 (1H, d, *J*=2.4 Hz), 2.74 (3H, s), 2.59 (3H, d, *J*=1.2 Hz). ^{13}C NMR (75 MHz, acetone-d_6): δ 204.8, 169.7, 162.4, 161.0, 141.1, 135.7, 121.0, 113.4, 108.1, 102.5, 101.9, 31.7, 24.7. MS (EI) *m/z* 232 (M^+), HRMS (EI) calcd for $C_{13}H_{12}O_4$ 232.0735, found 232.0737.

4.3.3. Monoacetate 3. A suspension of **1** (5.3 mg) in CH_2Cl_2 (9 mL) was treated with acetyl chloride (33 μL) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (~5.0 mg). The resulting mixture was stirred at ambient temperature for 4 h and then 8 mL of water was added. The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (4 g, hexane/AcOEt=5:1–1:1) to give 3.8 mg of the ester **3** as a yellow powder, mp 164–166 °C. UV (MeOH) λ_{max} 202 (log ε 4.22), 234 (log ε 4.26), 272 (log ε 4.14) nm. IR (neat): ν_{max} 2922, 1770 (C═O), 1650 (C═O), 1590 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 14.02 (1H, br s), 6.59 (1H, d, *J*=2.2 Hz), 6.52 (1H, d, *J*=2.2 Hz), 6.38 (1H, br t), 5.41 (2H, br d, *J*=1.8 Hz), 2.74 (3H, s), 2.31 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.3, 184.2, 168.8, 165.4, 155.7, 141.7, 141.6, 115.1, 114.9, 109.9, 107.0, 106.5, 76.7, 21.2, 16.5. MS (EI) *m/z* 272 (M^+), HRMS (EI) calcd for $C_{15}H_{12}O_5$ 272.0685, found 272.0655.

4.3.4. Triacetate 4. A solution of **1** (4.1 mg) in THF (3 mL) was treated with $LiBH_4$ (~2 mg) at ambient temperature for 0.1 h and then a saturated aqueous NH_4Cl (2 mL) solution was added. The resulting mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in 3 mL of pyridine and 3 mL of acetic anhydride. The mixture was stirred at ambient temperature for 48 h and then 3 mL of water and 3 mL of AcOEt was added. The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by repeated silica-gel column chromatography (3 g, hexane/AcOEt=3:1, 2.5 g, benzene/AcOEt=7:1) to give 1.6 mg of ester **4** as a white powder, mp 61.8–63.4 °C. IR (neat): ν_{max} 2925, 1770 (C═O), 1371 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.54 (1H, s), 7.52 (1H, d, *J*=2.2 Hz), 6.98 (1H, d, *J*=2.2 Hz), 5.37 (1H, q, *J*=6.6 Hz), 5.25 (1H, dt, *J*=12.9, 1.2 Hz), 5.12 (1H, d, *J*=12.9 Hz), 2.40 (3H, s), 2.39 (3H, s), 2.33 (3H, s), 1.51 (3H, d, *J*=6.6 Hz), ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.0, 168.8, 168.5, 147.8, 145.9, 140.8, 138.8, 137.0, 134.8, 118.9, 118.1, 117.3, 116.1, 78.7, 71.4, 21.2, 20.9, 20.3. MS (EI) *m/z* 358 (M^+), HRMS (EI) calcd for $C_{19}H_{18}O_7$ 358.1053, found 358.1034.

4.3.5. (*S*)-MTPA ester 5. To a suspension of **1** (2.0 mg) in CH_2Cl_2 (7 mL) were successively added (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) (3.5 μL) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (~1.0 mg). The resulting mixture was stirred at ambient temperature for 3 h and then was quenched with water (3 mL). The mixture was separated and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by silica-gel column chromatography (3 g, hexane/AcOEt=4:1) to give 2.0 mg of ester **5** as yellow plates (AcOEt/hexane), mp 200–203 °C (dec). IR (neat): ν_{max} 1762 (C═O), 1653 (C═O), 1596, 1464, 1370 cm^{-1}. ^{1}H NMR (600 MHz, acetone-d_6): δ 14.37 (1H, s), 7.71 (1H, dd), 7.55–7.59 (3H, m), 6.80 (1H, d, *J*=2.2 Hz), 6.61 (1H, t, *J*=2.2 Hz), 6.54 (1H, d, *J*=2.2 Hz), 5.65 (2H, d, *J*=2.2 Hz), 3.75 (3H, d, *J*=1.1 Hz), 2.77 (3H, s). ^{13}C NMR (150 MHz, acetone-d_6): δ 188.6, 184.8, 166.4, 165.3, 155.4, 144.5, 143.5, 132.7, 130.9, 129.6, 128.1, 125.3, 123.4, 115.9, 115.7, 109.9, 106.8, 105.8, 78.6, 56.3, 16.7. MS (EI) *m/z* 446 (M^+), HRMS (EI) calcd for $C_{23}H_{17}F_3O_6$ 446.0978, found 446.0974.

Table 2. Crystal data and experimental conditions

Chemical formula/formula weight	$C_{23}H_{17}F_3O_6$/446.377
Crystal system/Space group	Triclinic/*P*1
Z	2
a, *b*, *c* (Å)	7.145(4), 7.308(5), 20.095(2)
α (°)	94.238(2)
β (°)	93.703(3)
γ (°)	106.892(2)
V (Å^3)	997.18(12)
D_x (Mg m^{-3})	1.487
Diffractometer	MXC18
Radiation	Mo Kα
λ (Å)	0.71073
μ (Mo Kα) (mm^{-1})	0.125
Crystal description/crystal dimensions (mm^3)	Cube /0.35×0.3×0.2
T (K)	298
θ_{max} (°)	25.80
Range of *h*, *k*, and *l*	$0\leq h\leq 8$, $-8\leq k\leq 8$, $-24\leq l\leq 24$
Reflections: independent/observed	3320/3048
$R(F)(I>3\sigma(I))/wR(F^2)(I>3\sigma(I))$	0.0534/0.1365
S	1.120
$\Delta\rho$ (e Å^{-3})	−0.346, 0.310

4.4. X-ray analysis of 5

The compound **5**, ($C_{23}H_{17}F_3O_6$), FW=446.377, crystallized from AcOEt/hexane in a triclinic system of the space group *P*1. The crystal data and the experimental details are summarized in Table 2. The structure of **5** was solved by the direct method with the program SHELXL97.[40,41] The structure was refined by the full-matrix least squares method with the program maXus.[42] The weighting scheme was $w=1/(\sigma^2(F_o^2)+0.10000F_o^2)$ for **5**. Positions of several hydrogen atoms were obtained on difference maps and those of the others were calculated geometrically. The anisotropic and isotropic temperature factors were applied to non-hydrogen atoms and hydrogen atoms in the final refinement, respectively. The positional parameters of the hydrogen atoms were constrained to have the C–H distances of 0.96 Å. Atomic scattering factors were taken from the International Tables for Crystallography.[43] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 220660. 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].

4.5. Cytotoxic activity

HL-60 (human promyelocytic leukemia-60) cells were grown in suspension culture and incubated at 37 °C in RPMI-1640 medium supplemented with 10% FBS and glutamine (2 mM). The cytotoxicity of **1** in HL-60 cells was analyzed by colorimetric 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay with some modification.[39] HL-60 (1×10^4 cells) were plated on 96-well plates and allowed to adhere at 37 °C in 5% CO_2/95% air for 1 h. Then 50 μL of serial concentration of test compound **1** was added and the cells incubated for 24 h. After 24 h, 10 μL of MTT (5 mg/mL: stock solution) was added and the cells were incubated for an additional 4 h. Following this time the cells were lysed and the dark blue crystals solubilized with 100 μL of 20% sodium dodecyl sulfate in 0.01 N HCl. The optical density (OD) of each well was measured with a microplate spectrophotometer equipped with a 570 nm filter. The results of cytotoxic activity are expressed as ED_{50} (The concentration of compound that inhibited cell line replication by 50%). The ED_{50} of **1** was 25 μM.

Acknowledgements

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References and notes

1. Duewell, H.; Human, J. P. E.; Johnson, A. W.; MacDonald, S. F.; Todd, A. R. *Nature* **1948**, *162*, 759–761.
2. Human, J. P. E.; Johnson, A. W.; MacDonald, S. F.; Todd, A. R. *J. Chem. Soc.* **1950**, 477–485.
3. Duewell, H.; Johnson, A. W.; MacDonald, S. F.; Todd, A. R. *J. Chem. Soc.* **1950**, 485–490.
4. Duewell, H.; Human, J. P. E.; Johnson, A. W.; MacDonald, S. F.; Todd, A. R. *J. Chem. Soc.* **1950**, 3304–3309.
5. Johnson, A. W.; Quayle, J. R.; Robinson, T. S.; Sheppard, N.; Todd, A. R. *J. Chem. Soc.* **1951**, 2633–2638.
6. Calderbank, A.; Cameron, D. W.; Cromartie, R. I. T.; Hamied, Y. K.; Haslam, E.; Kingston, D. G. I.; Todd, L.; Watkins, J. C. *J. Chem. Soc.* **1964**, 80–89.
7. Banks, H. J.; Cameron, D. W.; Craik, J. C. A. *J. Chem. Soc. C* **1969**, 627–631.
8. Cameron, D. W.; Cromartie, R. I. T.; Hamied, Y. K.; Haslam, E.; Kingston, D. G. I.; Todd, L.; Watkins, J. C. *J. Chem. Soc.* **1965**, 6923–6930.
9. Cameron, D. W.; Chan, H. W.-S. *J. Chem. Soc. C* **1966**, 1825–1832.
10. Brown, B. R.; Johnson, A. W.; MacDonald, S. F.; Quayle, J. R.; Todd, A. R. *J. Chem. Soc.* **1952**, 4928–4935.
11. Brown, B. R.; Johnson, A. W.; Quayle, J. R.; Todd, A. R. *J. Chem. Soc.* **1954**, 107–112.
12. Brown, B. R.; Calderbank, A.; Johnson, A. W.; MacDonald, S. F.; Quayle, J. R.; Todd, A. R. *J. Chem. Soc.* **1955**, 954–958.
13. Brown, B. R.; Calderbank, A.; Johnson, A. W.; Joshi, B. S.; Quayle, J. R.; Todd, A. R. *J. Chem. Soc.* **1955**, 959–965.
14. Brown, B. R.; Calderbank, A.; Johnson, A. W.; Quayle, J. R.; Todd, A. R. *J. Chem. Soc.* **1955**, 1144–1153.
15. Johnson, A. W.; Todd, A. R.; Watkins, J. C. *J. Chem. Soc.* **1956**, 4091–4093.
16. Cameron, D. W.; Cromartie, R. I. T.; Todd, L. *J. Chem. Soc.* **1964**, 48–50.
17. Cameron, D. W.; Cromartie, R. I. T.; Hamied, Y. K.; Scott, P. M.; Todd, L. *J. Chem. Soc.* **1964**, 62–72.
18. Cameron, D. W.; Cromartie, R. I. T.; Hamied, Y. K.; Joshi, B. S.; Scott, P. M.; Todd, L. *J. Chem. Soc.* **1964**, 72–79.
19. Cameron, D. W.; Cromartie, R. I. T.; Hamied, Y. K.; Scott, P. M.; Sheppard, N.; Todd, L. *J. Chem. Soc.* **1964**, 90–97.
20. Cameron, D. W.; Kingston, D. G. I.; Sheppard, N.; Todd, L. *J. Chem. Soc.* **1964**, 98–104.

21. Cameron, D. W.; Chan, H. W.-S.; Thoseby, M. R. *J. Chem. Soc. C* **1969**, 631–637.
22. Brown, B. R.; Ekstrand, T.; Johnson, A. W.; MacDonald, S. F.; Todd, A. R. *J. Chem. Soc.* **1952**, 4925–4928.
23. Cameron, D. W.; Cromartie, R. I. T.; Kingston, D. G. I.; Todd, L. *J. Chem. Soc.* **1964**, 51–61.
24. Calderbank, A.; Cameron, D. W.; Cromartie, R. I. T.; Hamied, Y. K.; Haslam, E.; Kingston, D. G. I.; Todd, L.; Watkins, J. C. *J. Chem. Soc.* **1964**, 80–89.
25. Cameron, D. W.; Chan, H. W.-S.; Kingston, D. G. I. *J. Chem. Soc.* **1965**, 4363–4368.
26. Bowie, J. H.; Cameron, D. W. *J. Chem. Soc.* **1965**, 5651–5657.
27. Cameron, D. W.; Chan, H. W.-S.; Hildyard, E. M. *J. Chem. Soc. C* **1966**, 1832–1836.
28. Blackburn, G. M.; Cameron, D. W.; Chan, H. W.-S. *J. Chem. Soc. C* **1966**, 1836–1842.
29. Cameron, D. W.; Craik, J. C. A. *J. Chem. Soc. C* **1968**, 3068–3072.
30. Banks, H. J.; Cameron, D. W. *Aust. J. Chem.* **1972**, *25*, 2199–2207.
31. Cameron, D. W.; Sawyer, W. H.; Trikojus, V. M. *Aust. J. Biol. Sci.* **1977**, *30*, 173–181.
32. Zhang, G.; He, M.; Xing, Q. *Helv. Chim. Acta* **1997**, *80*, 2502–2506.
33. Brown, K. S., Jr.; Cameron, D. W.; Weiss, U. *Tetrahedron Lett.* **1969**, *6*, 471–476.
34. Brown, K. S., Jr.; Weiss, U. *Tetrahedron Lett.* **1971**, *38*, 3501–3504.
35. Since we could not eliminate the possibility of the presence of a chiral center in compound **1**, (*R*)-MTPACl was employed as an acylating agent.
36. The 7-dehydroxy compound of furanaphin was isolated from Cape aloe and either ^{13}C signal at 184.7 or 185.2 ppm was assigned to the C-3 olefinic carbon. See Koyama, J.; Ogura, T.; Tagahara, K. *Phytochemistry* **1994**, *37*, 1147–1148.
37. Nakanishi, S.; Chiba, S.; Yano, H.; Kawamoto, I.; Matsuda, Y. *J. Antibiot.* **1995**, 948–951.
38. Aotani, Y.; Saitoh, Y. *J. Antibiot.* **1995**, 952–953.
39. Mosmann, T. *J. Immunol. Meth.* **1983**, *65*, 55–63.
40. Sheldrick, G. M. *SHELXL97. Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.
41. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
42. Mackay, S.; Gilmore, C. J.; Edwards, C.; Stewart, N.; Shankland, K. *maXus Computer Program for the Solution and Refinement of Crystal Structures*; Bruker Nonius, The Netherlands, MacScience, Japan and The University of Glasgow, 1999.
43. Maslen, E. N. *International tables for crystallography*; Wilson, A. J. C., Ed.; Munksgaard: Copenhagen, 1992; Vol. C, pp 521–525.

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Asymmetric synthesis of spiro 2-pyrrolidin-5-ones, 2-piperidin-6-ones and 1-isoindolin-3-ones. Part 1: *N*-Acyliminium ion cyclisations with an internal arene nucleophile

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Abstract—A series of chiral non-racemic 5,5- and 5,6-bicyclic lactams is prepared from (*R*)-phenylglycinol. These are isomerised on treatment with aluminium trichloride in 1,2-dichloroethane to give spiro lactams in high yield and >3:1 diastereoselectivity. From four structures determined by X-ray crystallography, it follows that spiro indenes are formed preferentially with retention of configuration at the spiro carbon atom and spiro naphthalenes with inversion.
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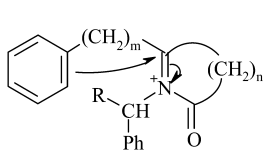
1. Introduction

Spiro lactam structures result from the intramolecular reaction of cyclic *N*-acyliminium ion intermediates with an alkene nucleophile tethered to the iminium carbon atom.[1–6] We have reported similar cyclisations, for example **1→4**, involving an arene nucleophile.[7] Two other examples are known in the context of a thiolium/*N*-acyliminium ion tandem cyclisation sequence.[8] Our first attempts to achieve diastereoselective cyclisation by the same route were unsuccessful, because the chiral *N*-1-phenylethyl group was too easily lost under the acidic conditions required for formation of the iminium ion **2**, and most of the cyclised product was racemic debenzylated spiro lactam **5**.[7] We describe herein[9] how this problem was overcome and diastereoselective spiro cyclisation of **3** achieved by the use of a chiral *N*-substituent derived from (*R*)-phenylglycinol.

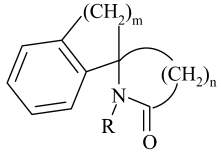
2. Results and discussion

2.1. Bicyclic lactam precursors

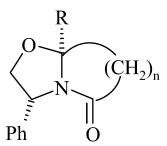
Bicyclic oxylactams based on structures **6** and **7** have been widely employed in asymmetric synthesis of tertiary and quaternary carbon centres;[10] in particular, the synthesis of pyrrolidines from **6** and piperidines from **7**,[11,12] and similarly of 3-substituted isoindolinones from **8**.[13] Similar bicyclic lactams incorporating the requisite ω-arylalkyl substituent at the ring junction position are appropriate precursors for generation of *N*-acyliminium ions **3** and cyclisation to spiro lactams.[14] Indeed, the same methodology has been employed before with alkene nucleophiles (as in Scheme 1),[5] but without any diastereoselection for configuration at the resulting spiro carbon atom. Accordingly, we prepared a series of bicyclic lactams starting from ketoacids **9**–**12** by condensation with (*R*)-phenylglycinol or, for **17**, with (*S*)-valinol.



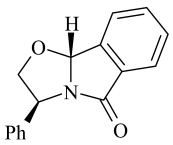
1 R = H
2 R = Me
3 R = CH_2OH



4 R = CH_2Ph
5 R = H



6 *n* = 2
7 *n* = 3



8

Keywords: Diastereoselective; *N*-Acyliminium ions; Spiro lactams.
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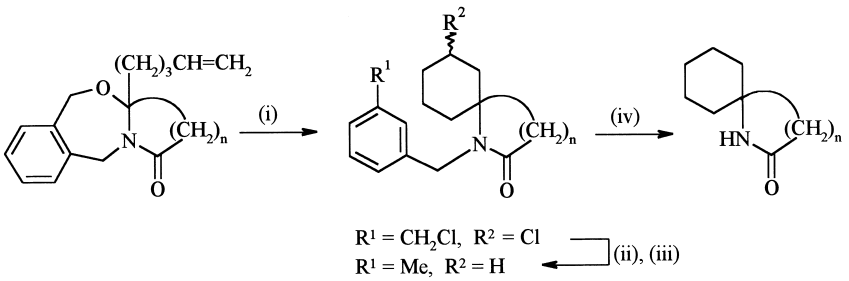
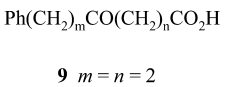
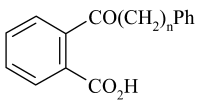
doi:10.1016/j.tet.2003.10.128



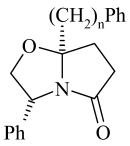
Scheme 1. *Reagents*: (i) $TiCl_4$, DCM, 20 °C (ii) H_2/Pd-C, EtOH; (iii) Bu_3SnH, AIBN; (iv) Na, NH_3, EtOH, −78 °C.



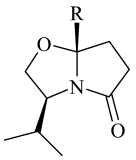
9 $m=n=2$
10 $m=3$, $n=2$
11 $m=2$, $n=3$
12 $m=n=3$



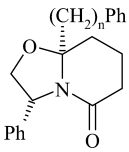
13 $n=2$
14 $n=3$



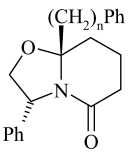
15 $n=2$
16 $n=3$



17 R = $(CH_2)_2Ph$
18 R = Me



19a $n=2$
20a $n=3$



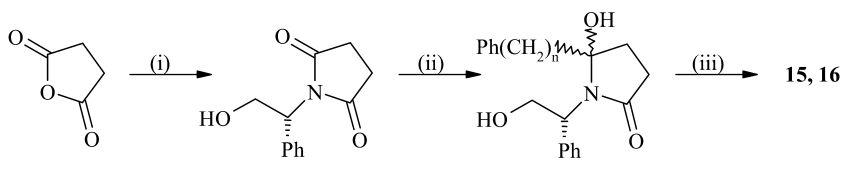
19b $n=2$
20b $n=3$

Bicyclic lactams **15**–**17** were obtained in 52–75% yields, in each case as a single diastereoisomer with the substituent at the ring junction 7a-position *cis* to phenyl (or isopropyl) at the 3-position. This assignment of stereochemistry follows numerous precedents in Meyers's work,[10,11] and the folded shape of the 5,5-fused bicyclic system would be severely strained by a 3-substituent on the inside (*endo*) face. Bicyclic lactams **15** and **16** were also obtained by the alternative route via imide **21** shown in Scheme 2, but in only ca. 21% overall yield from (*R*)-phenylglycinol. The first route from ketoacids represents more efficient use of phenylglycinol.

The 5,6-fused bicyclic lactams **19** and **20** were obtained in 72% yield as inseparable mixtures of two diastereoisomers in ca. 84:16 ratio (from ^{13}C NMR spectra), in accordance with literature precedents.[10,12] The major diastereoisomer is **19a** or **20a**, although the greater conformational flexibility of the 6-membered lactam ring (in comparison with that in **15** and **16**) can accommodate a 3-substituent on the *endo* face of the bicyclic system in the minor isomer **19b** or **20b**. The mixed stereochemistry at the 8a-position is of no consequence because the *N*-acyliminium ion intermediate in the ensuing cyclisation step is planar at this position and the diastereoselectivity of formation of the ultimate spiro lactam products does not depend upon the stereochemistry of the precursor bicyclic lactams.

The corresponding ketoacids **13** and **14** required for the preparation of tricyclic lactams **25** and **26** were made by Grignard addition to phthalic anhydride, but they were imperfectly purified by column chromatography, so the alternative route via the phthalimide **22** was preferable. Grignard addition to **22** afforded the 3-hydroxyisoindolinones **23** and **24** as single diastereoisomers after chromatography (Scheme 3). Our assignment of (*R*)-configuration to C-3 in these products is based on X-ray crystallographic results for the related adduct of 3-butenyl Grignard reagent and **22** described in the accompanying paper.[15] However, the C-3 stereochemistry in **23** and **24** is unimportant, because subsequent acid-catalysed steps involve intermediates in which this position becomes planar and give rise to end-products with either (*R*)- or (*S*)-configuration at this centre.

Treatment of **23** with trifluoroacetic acid (TFA) in dichloromethane (DCM) at 0 °C afforded a mixture of tricyclic lactam **25** and isomeric enamide **27**. Similarly, **24** afforded a mixture of **26** and **28**, which were separated by chromatography. It was noted that decreasing the quantity of TFA resulted in a higher ratio of **26**:**28**, although the highest yield (of both products) was obtained from **24** using a 10-fold excess of TFA (Table 1). Also, partial interconversion of **26** and **28**, and similarly of **25** and **27**, occurred in the presence of TFA in DCM. Tricyclic lactams **25** and **26** were obtained as single diastereoisomers, in which C-9b must have the (*S*)-configuration shown for the



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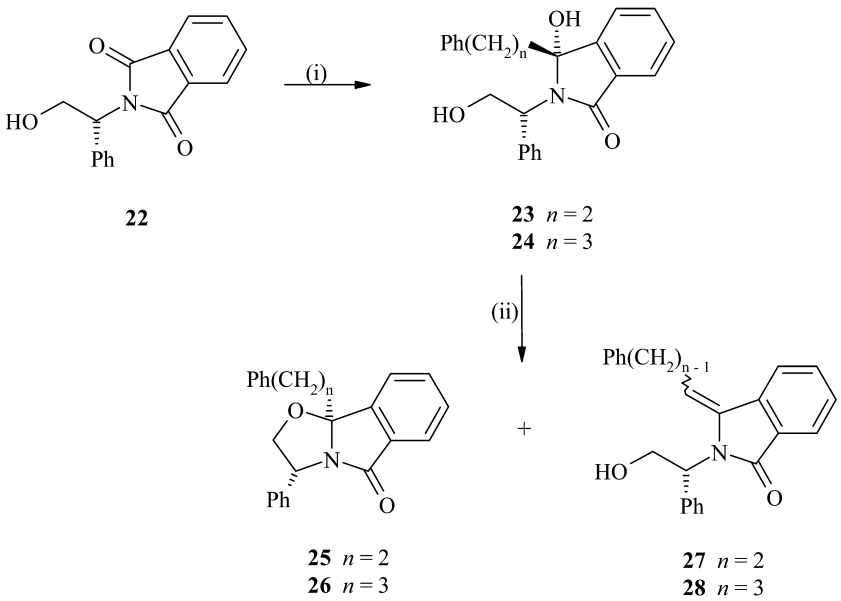
Scheme 2. *Reagents*: (i) (*R*)-$HOCH_2CH(Ph)NH_2$, PhMe, reflux; then Et_3N, reflux; (ii) $Ph(CH_2)_nMgBr$, THF, 0 °C; (iii) TFA, DCM, 0 °C.



Scheme 3. *Reagents*: (i) $Ph(CH_2)_nMgBr$, THF, 0 °C; (ii) TFA, DCM, 0 °C.

Table 1. Effect of TFA on product distribution, **26** and **28**

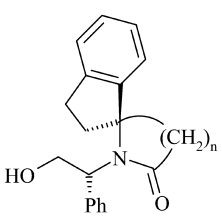
Mole ratio **24**:TFA	Yield **26** (%)	Yield **28** (%)	Total yield (%)	Ratio **26**:**28**
1:30	18.1	53.5	71.6	25:75
1:20	38.4	45.2	83.6	46:54
1:10	48.5	40.7	89.2	53:47
1:2	77.5	3.5	81.0	96:4
1:1	78.5	4.2	82.7	95:5

same reasons discussed previously and following the precedent of **8**.[13] Subsequent conversion into spiro lactams was pursued only with the lactams **25** and **26**, although in principle the enamides could also have been used as precursors for the same *N*-acyliminium ion intermediates and for spiro cyclisation.

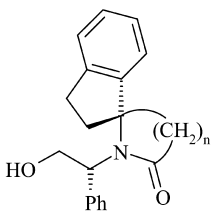
2.2. Cyclisation to spiro lactams

In our previous work, involving the synthesis of spiro lactams,[16] we have used TFA or polyphosphoric acid to achieve the spiro cyclisation step. However, when bicyclic lactam **15** was heated in TFA under reflux for 3 h, it was incompletely converted into a new product, subsequently identified as the spiro lactam **29a**, which was isolated in only 11% yield. On the other hand, treatment of **15** with aluminium trichloride in either dichloromethane or 1,2-dichloroethane (DCE) at room temperature or below resulted in high conversion into two diastereoisomeric spiro products **29a** and **b**, which were cleanly separated by column chromatography. The optimum conditions were found to be a 1:3 mole ratio of **15** to aluminium trichloride in DCE at −5 °C, from which **29a** and **b** were isolated in 93% yield and 78:22 ratio. This ratio appears to be the result of kinetic control, because the minor isomer survived treatment again with $AlCl_3$ in DCE and no interconversion to **29a** occurred. Both spiro products showed IR absorption for OH (absent in **15**) and ^{13}C NMR absorptions for the spiro carbon and for an additional unprotonated aromatic carbon in comparison with the spectra of **15**. The major isomer was more polar, eluting second in chromatography. Its structure was confirmed as **29a** by single crystal X-ray analysis.[9] The minor isomer is therefore **29b**.

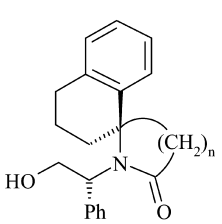
Bicyclic lactam **19** (in this case a mixture of **19a** and **b**) was unreactive under the same reaction conditions used for cyclisation of **15**. 6-Membered lactams such as **7** are also less reactive than 5-membered lactams **6** in metalation and alkylation reactions.[10] However, by using a 1:4 mole ratio of **19** and $AlCl_3$ in DCE at room temperature, cyclisation to the spiro lactams **30a** and **b** was achieved in 88% yield. The major isomer was again the slower running component in chromatography. Single crystal X-ray analysis confirmed the spiro structure with the relative configuration shown in Figure 1. As the side chain chiral centre is derived from (*R*)-phenylglycinol, the spiro carbon is (*S*)-configuration and the structure is as drawn in **30a**. This is entirely consistent with the formation of **29a** as the major product



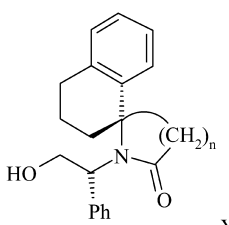
29a $n=2$
30a $n=3$



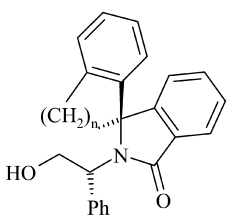
	Yield **a** + **b**	Ratio **a** : **b**
29b $n=2$	92.5%	78:22
30b $n=3$	88.5%	76:24



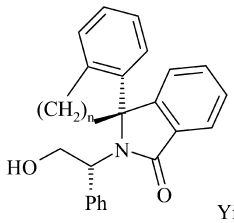
31a $n=2$
32a $n=3$



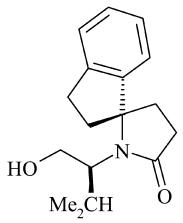
	Yield **a** + **b**	Ratio **a** : **b**
31b $n=2$	90%	20:80
32b $n=3$	99%	25:75



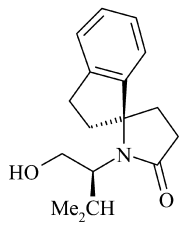
33a $n=2$
34a $n=3$



	Yield **a + b**	Ratio **a : b**
33b $n=2$	75%	57:43
34b $n=3$	75%	45:55



35a



	Yield **a + b**	Ratio **a : b**
35b	87%	74:26

from **15**; in both **29a** and **30a** the new bond to the spiro centre is formed by phenyl from the $Ph(CH_2)_n$ group replacing oxygen of the oxazolidine ring with retention of configuration.

For the corresponding spiro lactam products **31a** and **b** and **32a** and **b** obtained in the same way from bicyclic lactams **16** and **20**, respectively, the diastereoisomer ratio was about the same as before, between 3:1 and 4:1, but the major isomer was now the less polar component in each case. X-Ray diffraction by a single crystal of the major isomer from **20** proved the structure is **32b**.[9] The minor isomer is therefore **32a**, and the minor and major products from **16** are assigned the structures **31a** and **b**, respectively. Formation of the 6-membered carbocyclic ring in **31** and **32** has occurred prefentially with inversion of configuration at the spiro carbon in relation to that in the precursor bicyclic lactams **16** and **20**.

Although conformations in solution are not necessarily the same as those seen in the solid state, it is noteworthy that crystal structures of the less polar products **32b** and **35b** (vide infra) both show intramolecular hydrogen bonding, whereas crystal structures of the more polar products **29a** and **30a** are characterised by intermolecular hydrogen bonding. The chemical shift of the spiro carbon atom varied with the size of rings, in line with previous observations,[2] but the differences between the chemical shift values for diastereoisomeric pairs were always small and did not correlate reliably with the stereochemistry as deduced from comparisons of chromatographic behaviour (Table 2). On the other hand, comparisons of ^{1}H NMR spectra were informative in two respects. The position of the OH resonance differed in most cases by almost 1 ppm between diastereoisomeric pairs, with the resonance for the less polar (intramolecularly hydrogen bonded) compound being always at lower field. In the spectrum of one compound in each pair, which was always the less polar component and the one to which we have assigned stereochemistry involving retention of configuration in forming the spiro centre, signals for two aromatic hydrogens are deshielded, with a complex splitting pattern. These signals are assigned to (one each) *ortho* and *meta* hydrogens of the side chain phenyl group, which is consistent with the absence of corresponding signals in the spectra of either isomeric spiro lactam **35a** and **b** derived from (*S*)-valinol (vide infra).

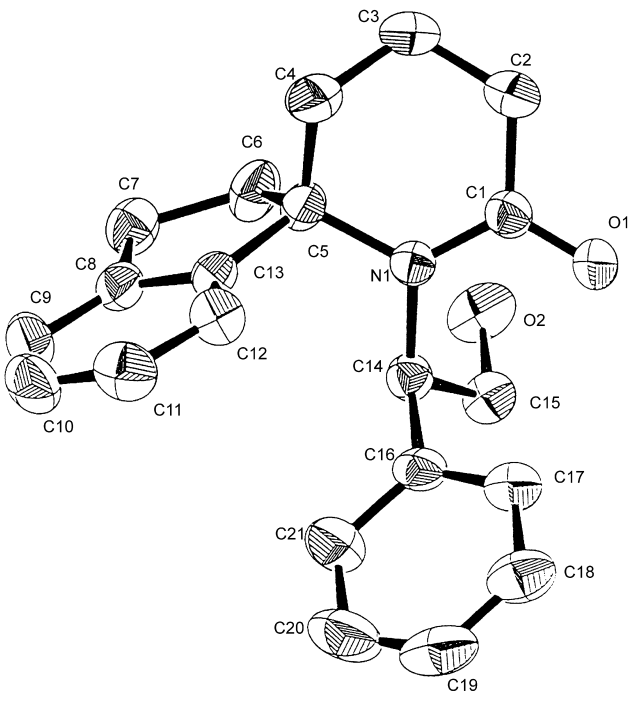


Figure 1. ORTEP drawing of the crystal structure of spiro lactam **30a** with crystallographic numbering scheme (hydrogen atoms omitted).

For spiro cyclisation of the phthalimide-derived tricyclic lactams **24** and **25**, the diastereoselectivity was low. Nevertheless, using comparisons of chromatographic behaviour between diastereoisomeric products, we are able to determine which product has which structure. The major product of the pair **33a** and **b** (with the 5,5-spiro ring system) was the more polar component and its structure is therefore **33a** (formed with retention of configuration at the spiro centre). Conversely, the major product of the pair **34a** and **b** (with the 6,5-spiro ring system) was the less polar component and its structure is therefore, **34b** (formed with inversion of configuration at the spiro carbon). These assignments are also consistent with differences between ^{1}H NMR spectra of diastereoisomeric product pairs in respect of both criteria (OH resonance and deshielded aromatic hydrogen resonances, see Table 2) discussed above.

Bicyclic lactams **6** react with nucleophiles at the 7a-position, with opening of the oxazolidine ring. The stereoselectivity of these reactions depends on several factors. Reduction of **6** (R=Pr, Bu, Ph, $PhCH_2$) by alane or by triethylsilane catalysed by $TiCl_4$ gives pyrrolidines **36** or pyrrolidinones **37** with high diastereoselectivity, the result of retention of configuration.[11] On the other hand, reaction of **6** (R=H) with allyltrimethylsilane in the presence of $TiCl_4$ gives predominantly **37** (R=allyl) by inversion of configuration; allylation of **6** (R=Me) gives a similar result, with inversion preferred over retention by a

Table 2. Comparisons between spiro lactam products

Compound	Ring size[a]	Relative polarity	Yield (%)	δ spiro C	δ OH	δ aryl H
29a	5,5	More	72.6	77.5	4.3	6.5–7.2
29b	5,5	Less	19.9	77.3	4.9	7.1–7.5
30a	6,5	More	67.3	74.7	4.1[b]	6.5–7.3
30b	6,5	Less	21.2	74.3	5.1	7.1–7.3
31a	5,6	More	18.3[c]	69.5	4.3[b]	6.4–7.3
31b	5,6	Less	72.1[c]	69.6	5.2	7.1–7.4
32a	6,6	More	24.9	66.2	4.2[b]	6.4–7.3
32b	6,6	Less	74.3	66.4	5.1	7.0–7.5
33a	5,5	More	43.0	78.4	4.4	6.1–7.8
33b	5,5	Less	32.0	78.4	5.0	6.8–8.0
34a	5,6	More	33.5	68.3	4.1	6.1–7.9
34b	5,6	Less	41.5	70.1	5.3	6.8–8.0
35a	5,5	More	64.2	76.2	4.5	7.3 (s)
35b	5,5	Less	22.4	76.2	5.0	7.3 (s)

[a] Lactam, carbocycle.
[b] OH signal overlapped by signals for C*H*C*H*$_2$OH between δ 3.9–4.4.
[c] Yields 19.8 and 78.4%, respectively, corrected for recovery of 8% unreacted **16**.

factor of 10.[11] However, this stereoselectivity is reversed by a bulkier 3-substituent; for example, for allylation of **18** the diastereoisomer ratio is 1:2 for pyrrolidinones formed by inversion or retention, respectively.

In the light of Meyers's results, we changed the 3-phenyl group in **15** for isopropyl in **17** to see what effect, if any, this might have on the diastereoselectivity of cyclisation to spiro lactams. Rearrangement of **17** catalysed by $AlCl_3$ afforded a 3:1 mixture of diastereoisomeric spiro lactams **35a** and **b**, in which the more polar (slower running) component was the major isomer **35a**. The crystal structure of the minor isomer **35b** was determined by X-ray analysis (Fig. 2), which shows the same intramolecular hydrogen bond and inversion of configuration at the spiro centre as in **32b**. In this system, in contrast to that studied by Meyers,[11] the change of 3-substituent has almost no effect on the diastereoselectivity. This may be attributable to the fact that, for the internal nucleophile involved in spiro cyclisation, the freedom of movement to approach the reaction centre is restricted. We have modelled the cyclisation step, assuming that the oxazolidine ring is opened to give an *N*-acyliminium ion intermediate **38**, in which the conformation of the *N*-substituent is ordered through the C=O group coordinating to aluminium. This confirms that cyclisation with retention of configuration to form a 5-membered ring is preferred, in agreement with our experimental findings, but the model does not indicate a clear preference for inversion vs. retention of configuration for formation of a 6-membered ring.

A further variation in the substitution pattern of the oxazolidine ring of the bicyclic lactam precursors led to an unexpected result. The bicyclic lactam **39** was prepared from (1*R*,2*S*)-norephedrine and keto acid **9**. (^{1}H and ^{13}C

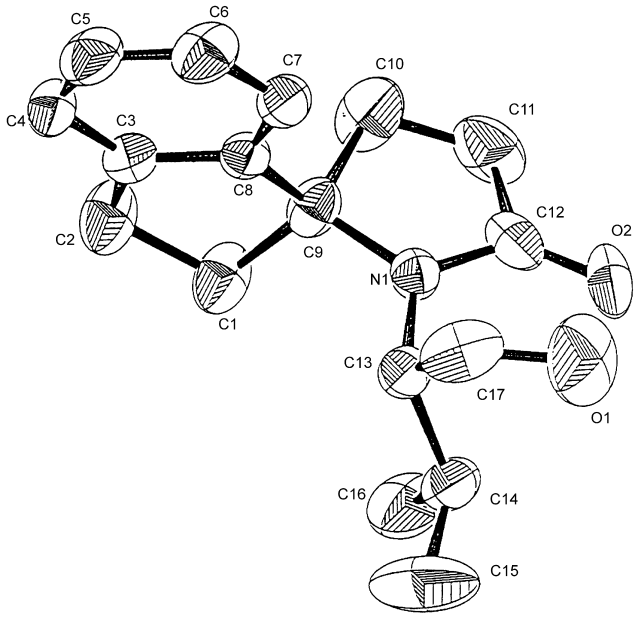
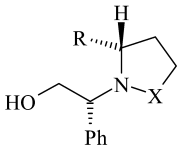
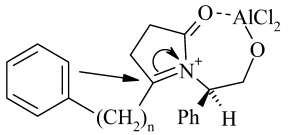


Figure 2. ORTEP drawing of the crystal structure of spiro lactam **35b** with crystallographic numbering scheme (hydrogen atoms omitted).



36 X = CH_2
37 X = C=O



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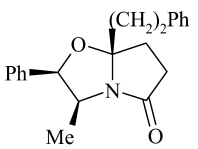

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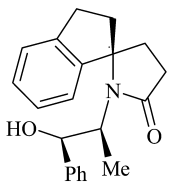

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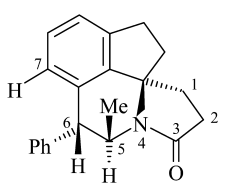

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NMR spectra of **39** indicated the presence of 3% of the 7a-epimer.) We expected **39** to be cyclised to spiro lactam **40**, the major product being the result of retention of configuration as for all the other spiro indenes. However, the product obtained in 44% yield from treatment of **39** with $AlCl_3$ showed no IR or ^1H NMR absorption for an OH group, and the ^{13}C NMR spectrum included signals for four (instead of three) substituted aromatic carbons as well as for the quaternary spiro carbon. The tetracyclic structure **41** for this product is compatible with all the spectroscopic evidence. The spiro carbon must have the (*S*)-configuration (from **40**) and C-5 must have the (*S*)-configuration (from norephedrine), but the configuration at the benzylic position (C-6) is apparently inverted in the process of intramolecular Friedel–Crafts substitution in **40** catalysed by $AlCl_3$. A Dreiding model of structure **41** shows a conformationally rigid piperidine ring with the methyl group in a *pseudo*-axial position. With the phenyl group also *pseudo*-axial, the dihedral angle between bonds to H-5 and H-6 is ca. 60° and the bonds to H-6 and H-7 are nearly coplanar. This accounts for the small coupling constant (J=1.7 Hz) between H-5 and H-6 and for the strong NOE interactions observed between H-5 and H-6 and between H-6 and H-7.

In conclusion, our results demonstrate the efficient formation of a range of spiro lactams by intramolecular reaction of *N*-acyliminium ion intermediates with a tethered arene nucleophile. Stereochemistry, established by X-ray analysis of four spiro lactams, has been correlated with comparisons of chromatographic behaviour and spectroscopic properties between pairs of diastereoisomeric products. Although the diastereoselectivity is only ca. 3:1, diastereoisomeric products are cleanly separable. This paves the way towards the preparation of enantio-pure spiro lactams by removal of the side chain from nitrogen.[17]

3. Experimental

IR Spectra were recorded on Pye-Unicam SP3-200 or Perkin Elmer 1420 spectrophotometers; only those absorptions appropriate to recognise functional groups are reported. NMR Spectra were recorded at 90 MHz for ^1H (22.5 MHz for ^{13}C) on JEOL FX90Q or at 270 MHz for ^1H (67.5 MHz for ^{13}C) on JEOL FX270 or at 300 MHz for ^1H (75 MHz for ^{13}C) on Bruker MSL300 spectrometers for solutions in deuteriochloroform (unless otherwise stated) with tetramethylsilane as internal standard. Assignments of ^{13}C NMR signals were assisted by use of DEPT spectra. In ^{13}C NMR spectra lines enclosed in | | are assigned to the minor diastereoisomer of a pair. Mass spectra were obtained by electron impact at 70 eV on a VG Autospec spectrometer; high resolution spectra were obtained in EI mode or in CI mode using ammonia. Chromatographic separations were performed on MN-silica (230–400 mesh). THF and diethyl ether were dried before use. Light petroleum refers to the fraction bp 40–60 °C (unless otherwise stated). DCM refers to dichloromethane and DCE to 1,2-dichloroethane.

3.1. General procedure for keto acids 9–12

The Grignard reagent freshly prepared in THF was added slowly to the acid anhydride in THF with stirring, which was continued for 3 h. The mixture was poured into dilute sulfuric acid and extracted with ether. The ether extract was extracted with saturated aqueous $NaHCO_3$. The aqueous layer was reacidifed with dilute sulfuric acid and extracted with chloroform. The chloroform extract was dried with $MgSO_4$, filtered, and the solvent evaporated. The residue was purified by chromatography on silica. 6-Phenyl-4-oxohexanoic acid **9** thereby obtained from 2-phenylethyl magnesium bromide and succinic anhydride; mp 88–89 °C (from toluene–light petroleum) (lit.[18] 89 °C). 7-Phenyl-4-oxoheptanoic acid **10** from 3-phenylpropyl magnesium bromide and succinic anhydride, 7-phenyl-5-oxoheptanoic acid **11** from 2-phenylethyl magnesium bromide and glutaric anhydride, and 8-phenyl-5-oxooctanoic acid **12** from 3-phenylpropyl magnesium bromide and glutaric anhydride were all oils, with IR, ^1H NMR and mass spectra consistent with the structures assigned.

3.2. General procedure for bicyclic lactams obtained via keto acids

Equimolar quantities of the appropriate keto acid and (*R*)-(−)-phenylglycinol were dissolved in toluene and heated under reflux for 22–24 h in a Dean–Stark apparatus for azeotropic removal of water. The solution was cooled and toluene removed by evaporation in vacuo. The residue was chromatographed on silica, from which the bicyclic lactam product was eluted with ethyl acetate–chloroform (1:4 v/v).

3.2.1. (3*R*,7a*S*)-3-Phenyl-7a-(2-phenylethyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5-one 15. The title compound was obtained from keto acid **9** (0.38 g) and (*R*)-phenylglycinol (0.25 g), yield 0.433 g (76.5%), mp 113–114 °C (from toluene–light petroleum); HREIMS found M^+ 307.1574. $C_{20}H_{21}NO_2$ requires M 307.1572; IR ν_{max}/cm^{-1} ($CHCl_3$) 1710 (C=O); ^1H NMR (270 MHz) δ 1.83–2.07 (2H, m, CH_2), 2.22 (1H, dt, J=13.5, 10.1 Hz), 2.35–2.47 (1H, m), 2.57–2.73 (3H, m, CH_2 and H-3), 2.87 (1H, dt, J=17.3, 9.9 Hz), 4.12 (1H, dd, J=7.1, 8.7 Hz), 4.66 (1H, t, J=8.5 Hz), 5.22 (1H, t, J=7.6 Hz) and 7.03–7.37 (10H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 30.4 (CH_2), 31.0 (CH_2), 33.2 (CH_2), 38.2 (CH_2), 57.6 (CH), 72.7 (CH_2), 102.3 (C-7a), 125.5 (2×CH), 126.1 (CH), 127.4 (CH), 128.2 (2×CH), 128.5 (2×CH), 128.7 (2×CH), 139.9 (C), 140.9 (C) and 179.2 (C=O); MS m/z 307 (M^+, 2%), 277, (1), 248 (1) and 202 ($M-(CH_2)_2Ph$, 100).

3.2.2. (3*R*,7a*S*)-3-Phenyl-7a-(3-phenylpropyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5-one 16. The title compound was obtained from keto acid **10** (0.50 g) and (*R*)-phenylglycinol (0.25 g), yield 0.312 g (54%), viscous oil; HREIMS found M^+ 321.1729. $C_{21}H_{23}NO_2$ requires M 321.1729; IR ν_{max}/cm^{-1} ($CHCl_3$) 1710 (C=O); ^1H NMR (90 MHz) δ 1.66–1.85 (4H, m, 2×CH_2), 2.00–2.88 (6H, m, 3×CH_2), 3.99 (1H, dd, J=7.1, 8.6 Hz, H-3), 4.55 (1H, t, J=8.4 Hz), 5.15 (1H, apparent t, J=7.7 Hz) and 7.02–7.35 (10H, m aryl H); ^{13}C NMR (22.5 MHz) δ 25.7 (CH_2), 30.8 (CH_2), 33.2 (CH_2), 35.6 (CH_2), 35.8 (CH_2), 57.5 (CH), 72.6 (CH_2), 102.4 (C-7a), 125.5 (2×CH), 125.9 (CH), 127.3 (CH), 128.3 (3×CH), 128.6 (2×CH), 140.0 (C), 141.6 (C) and 179.8 (C=O); MS m/z 321 (M^+, <1%), 264 (1), 230 (1), 217 (7), 202 ($M-(CH_2)_3Ph$, 100) and 91 (47).

3.2.3. (3*R*,7a*S*)-3-(1-Methylethyl)-7a-(2-phenylethyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5-one 17. The title compound was obtained from keto acid **9** (0.51 g) and (*S*)-valinol (0.255 g), yield 0.377 g (56%), viscous oil; HREIMS found M^+ 273.1730. $C_{17}H_{23}NO_2$ requires *M* 273.1729; IR ν_{max}/cm^{-1} ($CHCl_3$) 1710 (C═O); ^1H NMR (270 MHz) δ 0.88 (3H, d, *J*=6.6 Hz, CH_3), 1.08 (3H, d, *J*=6.6 Hz, CH_3), 1.63 (1H, m), 1.90–2.81 (8H, m, 4×CH_2), 3.63 (1H, dt, *J*=7.1, 10.6 Hz, H-3), 3.81 (1H, dd, *J*=6.6, 8.9 Hz), 4.22 (1H, apparent t, *J*=8.6 Hz) and 6.88–7.46 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 18.9 (CH_3), 20.8 (CH_3), 30.6 (CH_2), 30.7 (CH_2), 33.0 (CH_2), 34.0 (CH), 39.0 (CH_2), 61.7 (CH), 70.9 (CH_2), 101.8 (C-7a), 126.1 (CH), 128.1 (2×CH), 128.5 (2×CH), 141.0 (C) and 179.4 (C═O); MS *m*/*z* 273 (M^+, 1%), 230 (1), 217 (1), 188 (2), 174 (24), 168 (M−$(CH_2)_2$Ph 100), 100 (16) and 91 (24).

3.2.4. (3*R*,7a*S*)- and (3*R*,7a*R*)-3-Phenyl-8a-(2-phenylethyl)-2,3,6,7,8,8a-hexahydrooxazolo[3,2-*a*]pyridin-5(5*H*)-one 19a and b. The title compounds were obtained from keto acid **11** (0.82 g) and (*R*)-phenylglycinol (0.50 g), yield 0.84 g (71.5%), viscous oil; diastereoisomer ratio 80:20 of **19a**:**19b** from ^{13}C NMR spectrum; ^1H NMR (90 MHz) δ 1.50–2.80 (10H, m, 5×CH_2), 3.90 (1H, apparent t, *J*=8.4 Hz, H-3), 4.52 (1H, apparent t, *J*=8.6 Hz), 5.37 (1H, apparent t, *J*=8.4 Hz) and 7.09–7.42 (10H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 16.8 (CH_2), |17.0 (CH_2)|, |30.0 (CH_2)|, 30.5 (CH_2), 30.7 (CH_2), 31.1 (CH_2), |36.3 (CH_2)|, 36.5 (CH_2), 58.8 (CH), |59.1 (CH)|, 69.5 (CH_2), |71.4 (CH_2)|, |95.0 (C-8a)|, 95.8 (C-8a), 125.5 (2×CH), 126.1 (CH), 126.3 (CH), 127.2 (CH), 127.4 (CH), 128.2 (2×CH), 128.6 (3×CH), 139.8 (C), 141.1 (C), |141.7 (C)|, |167.5 (C═O)| and 170.0 (C═O); MS *m*/*z* 321 (M^+, <1%), 251 (8), 216 (M−$(CH_2)_2$Ph, 100) and 120 (24).

3.2.5. (3*R*,7a*S*)- and (3*R*,7a*R*)-3-Phenyl-8a-(3-phenylpropyl)-2,3,6,7,8,8a-hexahydrooxazolo[3,2-*a*]pyridin-5(5*H*)-one 20a and b. The title compounds were obtained from keto acid **12** (0.80 g) and (*R*)-phenylglycinol (0.47 g), yield 0.82 g (71.5%), viscous oil; diastereoisomer ratio 83:17 of **20a**:**20b** from ^{13}C NMR spectrum; ^1H NMR (90 MHz) δ 1.36–1.90 (6H, m, 3×CH_2), 2.05–2.73 (6H, m, 3×CH_2), 3.67 (1H, dd, *J*=8.0, 8.9 Hz, H-3), 4.39 (1H, apparent t, *J*=8.6 Hz), 5.30 (1H, apparent t, *J*=7.7 Hz) and 7.10–7.35 (10H, m, aryl H); ^{13}C NMR (22.5 MHz) δ |14.2 (CH_2)|, 16.5 (CH_2), 25.5 (CH_2), |29.7 (CH_2)|, |30.2 (CH_2)|, 30.6 (CH_2), 30.7 (CH_2), |33.4 (CH_2)|, 33.8 (CH_2), 35.3 (CH_2), 58.2 (CH), |58.7 (CH)|, 69.0 (CH_2), |70.9 (CH_2)|, |94.9 (C-8a)|, 95.6 (C-8a), 125.4 (2×CH), 125.6 (CH), |125.8 (CH)|, 126.1 (2×CH), |127.1 (CH)|, 127.9 (CH), 128.1 (3×CH), 128.3 (2×CH), 139.8 (C), 141.4 (C), |167.1 (C═O)| and 169.5 (C═O); MS *m*/*z* 335 (M^+, 1%), 264 (1), 216 (M−$(CH_2)_3$Ph, 100) and 120 (20).

3.2.6. (2*R*,3*S*,7a*R*)-3-Methyl-2-phenyl-7a-(2-phenylethyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 39. The title compound was obtained from keto acid **9** (0.53 g) and (*1R,2S*)-norephedrine (0.39 g), yield 0.42 g (50%), viscous oil; IR ν_{max}/cm^{-1} ($CHCl_3$) 1715 (C═O); ^1H NMR (270 MHz) δ 0.85 (3H, d, *J*=7.3 Hz, CHCH_3), 2.04–3.03 (8H, m, 4×CH_2), 4.50 (1H, m, C*H*CH_3), 5.03 (1H, d, *J*=5.6 Hz, C*H*Ph) and 7.20–7.44 (10H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 15.6 (CH_3), 30.4 (CH_2), 32.6 (CH_2), 33.2 (CH_2), 40.8 (CH_2), 55.2 (CH), 82.0 (CH), 100.6 (C-7a), 126.1 (2×CH), 127.8 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.6 (CH), 136.5 (C), 141.3 (C) and 178.6 (C═O); MS *m*/*z* 321 (M^+, <1%), 303 (<1), 232 (<1), 215 (100), 186 (10), 124 (65), 117 (15) and 91 (30). Additional lines in the ^1H NMR spectrum due to *ca* 4% of the 7a-epimer δ 1.02 (3H, d, *J*=6.9 Hz, CHCH_3), 4.10 (1H, m, C*H*CH_3) and 5.46 (1H, d, *J*=7.6 Hz, C*H*Ph).

3.3. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-succinimide 21 and -phthalimide 22

The succinimide **21** was prepared following the literature procedure for the (*S*)-enantiomer,[19] but using (*R*)-phenylglycinol; yield 59% of a viscous oil, ^1H NMR spectrum in agreement with lit.[19] The phthalimide **22** was prepared from phthalic anhydride (0.27 g) and (*R*)-phenylglycinol (0.25 g), which were mixed and heated at 140–150 °C for 4 h. The mixture was cooled and dissolved in chloroform (40 mL), then extracted successively with dilute sulfuric acid (1 M, 2×20 mL), aqueous sodium bicarbonate (2×20 mL) and water (2×20 mL), dried ($MgSO_4$), and the solvent evaporated in vacuo. The residue was chromatographed on silica from which ethyl acetate–chloroform (1:4 v/v) eluted the phthalimide **22** (0.49 g, 100%), mp 64–66 °C (toluene–light petroleum); HREIMS found MH^+ 268.0980. $C_{16}H_{14}NO_3$ requires 268.0974; ^1H and ^{13}C NMR and mass spectra in agreement with those reported for **22**, which was obtained previously as an oil.[20]

3.4. Bicyclic/tricyclic lactams obtained via imides

An excess of the Grignard reagent freshly prepared from 2-phenylethyl bromide (1.1 g) and magnesium (0.15 g) in THF was added to the succinimide **21** (0.44 g) in THF with stirring. After aqueous work up and extraction of the product into ether, which was dried ($MgSO_4$) and evaporated, the crude hydroxy lactam was redissolved in DCM (10 mL) and added dropwise to TFA (1.6 mL) in DCM (25 mL) cooled at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 1 h before addition of saturated aqueous ammonium chloride (100 mL) and extraction with chloroform (2×20 mL). The extract was dried ($MgSO_4$) and the chloroform evaporated in vacuo. The residue was chromatographed on silica, eluting with ethyl acetate–chloroform (1:4 v/v) to afford the bicyclic lactam **15** (0.24 g, 21% based on (*R*)-phenylglycinol), identical with the sample obtained above. In the same way starting from 3-phenylpropyl bromide and succinimide **21**, the bicyclic lactam **16** was obtained (20% based on (*R*)-phenylglycinol), identical with the sample obtained via keto acid **10**.

3.4.1. 2-(2-Hydroxy-1(*R*)-phenylethyl)-3(*R*)-hydroxy-3-(2-phenylethyl)-2,3-dihydroisoindol-1(1*H*)-one 23. The Grignard reagent was prepared from 2-phenylethyl bromide (1.50 g) and magnesium (0.20 g) in THF and added rapidly with stirring to phthalimide **22** (0.49 g) in THF (20 mL) at 0 °C. After evaporation of the solvent, the crude product was chromatographed on silica, eluting with ethyl acetate–chloroform (1:4 v/v) to give the lactam **23** (0.40, 59%) as a viscous oil; HREIMS found M^+ 373.1678. $C_{24}H_{23}NO_3$ requires *M* 373.1678; ^1H NMR (270 MHz) δ 1.57 (2H,

apparent quint, J=12.6, 5.1 Hz, CH_2), 1.94 (1H, td, J=13.8, 4.8 Hz), 2.14 (1H, td, J=12.6, 7.6 Hz), 3.69 (1H, dd, J=10.5, 3.8 Hz, CHPh), 4.59–4.80 (2H, m, CH_2OH), 5.42 (1H, s, OH), 6.31 (2H, m, aryl H), 7.01 (2H, m, aryl H) and 7.30–7.60 (10H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 29.8 (CH_2), 38.5 (CH_2), 58.8 (CH), 62.8 (CH_2), 91.9 (C-3), 121.7 (CH), 123.2 (CH), 125.7 (CH), 128.0 (5×CH), 128.6 (2×CH), 128.8 (2× CH), 129.5 (CH), 131.5 (C), 132.7 (CH), 138.9 (C), 140.5 (C), 146.4 (C) and 168.9 (C=O); MS m/z 373 (M^+, 10%), 355 (13), 342 (21), 250 (16), 237 (18), 130 (10), 106 (36), 91 (100) and 77 (14).

3.4.2. 2-(2-Hydroxy-1(*R*)-phenylethyl)-3(*R*)-hydroxy-3-(3-phenylpropyl)-2,3-dihydroisoindol-1(1*H*)-one 24. The title compound was obtained in the same way starting from 3-phenylpropyl bromide (1.48 g), magnesium (0.18 g) and phthalimide **22** (0.52 g); yield 0.45 g (65%) of a viscous oil; HREIMS found MH^+ 388.1915. $C_{25}H_{26}NO_3$ requires 388.1913; ^{1}H NMR (270 MHz) δ 0.55–0.72 (2H, m, CH_2), 1.22–2.05 (4H, m, 2×CH_2), 3.75 (1H, dd, J=10.6, 4.0 Hz, CHPh), 4.22 br (1H, s, OH), 4.61 (1H, dd, J=10.2, 4.3 Hz), 4.75 Br (1H, apparent t, J=10.6 Hz) overlapping 4.80 (1H, s, OH), 6.64 (2H, dd, J=5.6, 2.0 Hz, H-4 and H-7), 7.02–7.14 (3H, m, aryl H), 7.27–7.41 (5H, m, aryl H) and 7.46–7.55 (4H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 25.7 (CH_2), 35.4 (CH_2), 36.3 (CH_2), 59.0 (CH), 63.2 (CH_2), 92.3 (C-3), 122.0 (CH), 123.4 (CH), 125.9 (CH), 128.2 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 129.7 (CH), 131.6 (C), 132.8 (CH), 139.0 (C), 141.7 (C), 146.7 (C) and 169.1 (C=O); MS m/z 388 (MH^+, 75%), 370 (9), 340 (100), 278 (10), 250 (25), 106 (27) and 91 (13).

3.4.3. (*R*)-3-Phenyl-(*S*)-9b-(2-phenylethyl)-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 25 and 2-[(*R*)-(2-hydroxy-1-phenylethyl)]-3-(2-phenylethylidene)-2,3-dihydroisoindol-1(1*H*)-one 27. Hydroxy lactam **23** (0.18 g) in dry DCM (5 mL) was added slowly with stirring to TFA (0.11 g) in DCM cooled to 0 °C. The solution was stirred for 1 h as it warmed to room temperature, then poured into saturated aqueous sodium bicarbonate. The organic phase was separated and the aqueous layer reextracted with chloroform (2×10 mL). The extracts were combined, dried ($MgSO_4$), and the solvent evaporated. The residue was chromatographed on silica, eluting with ethyl acetate–chloroform (1:4 v/v). Lactam **25** (135 mg, 74%) was obtained as a viscous oil; HREIMS found M^+ 373.1682. $C_{24}H_{23}NO_3$ requires M 373.1678; ^{1}H NMR (270 MHz) δ 1.53 and 1.62 (each 1H, overlapping dt, J=12.4, 5.3 Hz, CH_2), 1.94 and 2.14 (each 1H, distorted dt, J=12.4, 5.3 Hz, CH_2), 2.53 br (1H, s, OH), 3.69 and 4.62 (each 1H, dd, J=9.0, 4.0 Hz, CH_2OH) overlapping 4.75 br (1H, t, J=9.0 Hz, CHPh), 5.43 (1H, s, OH), 6.28–6.32 (2H, m, aryl H), 7.00–7.03 (3H, m, aryl H), 7.31–7.39 (4H, m, aryl H) and 7.47–7.60 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 29.8 (CH_2), 38.5 (CH_2), 58.8 (CH), 62.8 (CH_2), 91.9 (C-3), 121.0 (CH), 123.2 (CH), 125.7 (CH), 128.0 (5×CH), 128.6 (2×CH), 128.8 (2×CH), 129.5 (CH), 131.5 (C), 132.7 (CH), 138.9 (C), 140.5 (C), 146.4 (C) and 168.9 (C=O); MS m/z 373 (M^+, <1%), 342 (M−CH_2OH, 21), 250 (16), 237 (18), 130 (10), 106 (36), 91 (100) and 77 (13). Later fractions eluted from the column afforded the enamide **27** (9 mg, 5%) as a white solid, mp 158–159 °C (from toluene–light petroleum); HREIMS found M^+ 355.1581. $C_{24}H_{21}NO_2$ requires M 355.1572; ^{1}H NMR (270 MHz) δ 3.86 and 3.94 (each 1H, overlapping dd, J=17.0, 7.8 Hz, CH_2OH), 4.18–4.32 (2H, m, CH_2Ph), 4.48–4.59 (1H, br, OH), 5.25 (1H, dd, J=3.7, 7.8 Hz, alkene CHCH$_2$), 5.60 (t, J=7.8 Hz, alkane CHCH$_2$), 6.99 (1H, dd, J=7.3, 1.6 Hz, aryl H), 7.15–7.35 (7H, m, aryl H), 7.48 (2H, m, aryl H), 7.79 (1H, d, J=7.3 Hz, aryl H) and 7.94 (1H, dd, J=6.6, 1.5 Hz, aryl H); ^{13}C NMR (67.5 MHz) δ 33.2 (CH_2), 61.0 (CH), 64.0 (CH_2), 113.2 (CH), 123.2 (CH), 123.7 (CH), 126.5 (CH), 126.7 (2×CH), 127.6 (CH), 128.0 (2×CH), 128.6 (2×CH), 128.8 (2×CH), 129.0 (CH), 130.1 (C), 132.4 (CH), 135.3 (C), 135.9 (C), 137.7 (C), 139.2 (C) and 168.2 (C=O); MS m/z 355 (M^+, 4%), 324 (M−CH_2OH, 27), 264 (15), 246 (14), 236 (19), 234 (22), 232 (27), 189 (12), 165 (12), 130 (30), 103 (30), 91 (100) and 77 (30).

3.4.4. (*R*)-3-Phenyl-(*S*)-9b-(3-phenylpropyl)-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 26 and 2-[(*R*)-(2-hydroxy-1-phenylethyl)]-3-(3-phenylpropylidene)-2,3-dihydroisoindol-1(1*H*)-one 28. These were prepared in the same way starting from hydroxy lactam **24** (0.36 g) treated with TFA (0.21 g) in DCM, followed by work up and chromatography. Lactam **26** (266 mg, 77%); white solid, mp 107–108 °C (toluene–light petroleum); HREIMS found MH^+ 388.1915. $C_{25}H_{26}NO_3$ requires 388.1913; ^{1}H NMR (270 MHz) δ 0.58–0.75 (2H, m, CH_2), 1.65–2.05 (4H, m, 2×CH_2), 3.75 and 4.61 (each 1H, dd, J=10.6, 4.0 Hz, CH_2OH), 4.22 br (1H, s, OH), 4.75 br (1H, t, J=10.6 Hz, CHPh) overlapping 4.80 (1H, s, OH), 6.63 (2H, dd, J=7.5, 1.8 Hz, H-4 and H-7), 7.02–7.14 (2H, m, aryl H), 7.27–7.40 (5H, m, aryl H) and 7.46–7.54 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 25.7 (CH_2), 35.4 (CH_2), 36.3 (CH_2), 59.0 (CH), 63.2 (CH_2), 92.3 (C-3), 122.0 (CH), 123.4 (CH), 125.9 (CH), 128.2 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 129.7 (CH), 131.6 (C), 132.8 (CH), 139.0 (C), 141.7 (C), 146.7 (C) and 169.1 (C=O); MS m/z 388 (MH^+, 75%), 370 (M−OH, 100), 340 (10), 278 (10), 250 (M−$(CH_2)_3$Ph, 25), 106 (27) and 91 (13). Enamide **28** (12 mg, 7%) obtained from later fractions; white solid, mp 117–121 °C (toluene–light petroleum); HREIMS found M^+ 369.1730. $C_{25}H_{23}NO_2$ requires M 369.1729; ^{1}H NMR (270 MHz) δ 1.25 (1H, m), 1.60 (1H, m), 2.01 (1H, m), 2.79 (2H, m), 4.19–4.48 (2H, m), 5.12–5.48 (2H, m) and 6.65–7.92 (14H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 29.1 (CH_2), 35.7 (CH_2), 61.0 (CH), 64.1 (CH_2), 114.1 (CH), 123.2 (CH), 123.6 (CH), 126.2 (CH), 126.7 (2×CH), 127.6 (CH), 128.4 (CH), 128.5 (CH), 128.7 (3×CH), 130.0 (C), 132.3 (CH), 135.3 (C), 137.7 (C), 140.6 (C) and 168.1 (C=O); MS m/z 369 (M^+, 5%), 338 (7), 278 (6), 250 (10), 158 (100), 103 (12) and 91 (32).

3.5. General procedure for cyclisation to spiro lactams with aluminium trichloride

The hydroxy lactam precursor dissolved in DCE was added dropwise with stirring to aluminium trichloride (typically 3–4 mol eq) in DCE at the temperature stated. An orange–brown colour developed. The mixture was stirred for 3–4 h or until analysis by tlc showed disappearance of the starting material; it was then poured onto ice, acidified by addition of dilute sulfuric acid (1 M) and extracted twice with

chloroform. The combined extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed on silica and the products eluted with ethyl acetate–chloroform (1:4 v/v).

3.5.1. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-2,3-dihydrospiro[indene-1,2′-pyrrolidin]-5′-ones 29a and b. The title compound were obtained from bicyclic lactam **15** (0.31 g) and aluminium trichloride (0.40 g) in DCE at −5 °C. Elution of the column gave first unreacted **15** (3 mg, 1%), followed by the(*R*,*S*)-spiro lactam **29b** (61 mg, 20%), mp 172–173 °C (from toluene–light petroleum); found: C, 77.68; H, 6.64; N, 4.29. $C_{20}H_{21}NO_2$ requires C, 78.14; H, 6.88; N, 4.56%; IR ν_{max}/cm^{-1} ($CHCl_3$) 3340 (O–H) and 1655 (C═O); ^1H NMR (90 MHz) δ 1.86–2.04 (2H, m, CH_2), 2.09–2.37 (2H, m, CH_2), 2.62–2.85 (4H, m, 2×CH_2), 4.04 (3H, m, CH_2CH), 4.88 (1H, br s, OH) and 7.10–7.52 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.2 (CH_2), 30.6 (CH_2), 35.0 (CH_2), 36.7 (CH_2), 61.1 (CH), 65.8 (CH_2), 77.3 (C), 122.9 (CH), 125.4 (CH), 127.3 (2×CH), 127.6 (CH), 128.5 (2×CH), 128.7 (CH), 139.0 (C), 142.9 (C), 144.4 (C) and 177.5 (C═O); MS *m*/*z* M^+ absent, 289 (M−H_2O, 1), 277 (M−CH_2O, 100), 276 (61), 188 (19), 143 (34) and 106 (67). Further elution of the column afforded the (*R*,*R*)-spiro lactam **29a** (223 mg, 73%), mp 195–196 °C (toluene–light petroleum); IR ν_{max}/cm^{-1} ($CHCl_3$) 3350 br (O–H) and 1652 (C═O); ^1H NMR (90 MHz) δ 2.06–2.46 (4H, m, 2×CH_2), 2.53–2.78 (2H, m, CH_2), 2.87–3.12 (2H, m, CH_2), 3.74–4.10 (3H, m, CH_2CH), 4.33 (1H, br t, OH), 6.45 (1H, d, *J*=7.9 Hz, *o*-ArH), 6.71–6.89 (1H, m, *m*-ArH) and 7.02–7.16 (7H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.4 (CH_2), 31.0 (CH_2), 35.0 (CH_2), 35.7 (CH_2), 61.8 (CH), 65.3 (CH_2), 77.5 (C), 124.6 (CH), 124.7 (CH), 126.4 (CH), 127.2 (CH), 127.9 (2×CH), 128.1 (2×CH), 128.5 (CH), 139.1 (C), 142.9 (C), 143.1 (C) and 177.1 (C═O); MS *m*/*z* M^+absent, 289 (M−H_2O, 1), 277 (M−CH_2O, 100), 276 (86), 188 (30), 143 (43), 128 (33) and 106 (97).

3.5.2. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-2,3-dihydrospiro[indene-1,2′-piperidin]-6′-ones 30a and b. The title compound were obtained from the bicyclic lactam **19** (0.33 g) and aluminium trichloride (0.54 g) in DCE at room temperature. Elution of the column gave first the (*R*,*R*)-spiro lactam **30b** (70 mg, 21%), semi-solid; HREIMS found M^+ 321.1721. $C_{21}H_{23}NO_2$ requires *M* 321.1729; ^1H NMR (90 MHz) δ 1.78–2.37 (6H, m, 3×CH_2), 2.62–2.90 (4H, m, 2×CH_2), 3.95–4.30 (3H, m, CH_2CH), 5.11 (1H, br s, OH) and 7.08–7.33 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 17.8 (CH_2), 29.0 (CH_2), 33.9 (CH_2), 35.8 (CH_2), 36.8 (CH_2), 63.7 (CH), 65.8 (CH_2), 74.8 (C), 123.3 (CH), 125.6 (CH), 126.7 (CH), 126.9 (2×CH), 127.3 (CH), 128.2 (2×CH), 128.6 (CH), 137.9 (C), 141.9 (C), 145.7 (C) and 173.4 (C═O). This was followed by the (*R*,*S*)-spiro lactam **30a** (220 mg, 67%), mp 173–174 °C (toluene–light petroleum); found: C, 78.16; H, 7.14; N, 4.19. $C_{21}H_{23}NO_2$ requires C, 78.47; H, 7.21; N, 4.36%; IR ν_{max}/cm^{-1} ($CHCl_3$) 3360 br (O–H) and 1710 (C═O); ^1H NMR (270 MHz) δ 1.23–3.06 (10H, m, 5×CH_2), 3.67 (1H, dd, *J*=7.4, 12.6 Hz, C*H*CH_2), 3.82–3.97 (1H, m,) and 4.06–4.23 (1H, m, CHCH_2), 6.48 (1H, d, *J*=7.2 Hz, *o*-ArH), 6.62 (1H, t, *J*=7.2 Hz, *m*-ArH) and 6.90–7.33 (7H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 17.7 (CH_2), 29.0 (CH_2), 33.9 (CH_2), 35.8 (CH_2), 36.8 (CH_2), 63.7 (CH), 65.8 (CH_2), 74.8 (C), 123.2 (CH), 125.6 (CH), 126.6 (CH), 126.9 (2×CH), 127.3 (CH), 128.2 (2×CH), 128.5 (CH), 137.9 (C), 141.8 (C), 145.6 (C) and 173.4 (C═O); MS *m*/*z* 321 (M^+, <1%), 303 (M−H_2O, 2), 291 (M−CH_2O, 45), 202 (32), 185 (50), 143 (36) and 106 (100).

3.5.3. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-pyrrolidin]-5′-ones 31a and b. The title compound were obtained from the bicyclic lactam **16** (325 mg) and aluminium trichloride (0.40 g) in DCE at −5 °C. Elution of the column gave first unreacted starting material **16** (26 mg, 8%), then the (*R*,*S*)-spiro lactam **31b** (234 mg, 72%), mp 176–177 °C (toluene–light petroleum); found: C, 77.93; H, 7.12; N, 4.20. $C_{21}H_{23}NO_2$ requires C, 78.47; H, 7.21; N, 4.36%; HREIMS found M^+ 321.1733. $C_{21}H_{23}NO_2$ requires *M* 321.1729; IR ν_{max}/cm^{-1} ($CHCl_3$) 3320 br (O–H) and 1655 (C═O); ^1H NMR (90 MHz) δ 1.50–1.87 (4H, m, 2×CH_2), 2.13–2.34 (2H, m, CH_2), 2.58–2.80 (4H, m, 2×CH_2), 3.79–4.25 (3H, m, CH_2CH), 5.12–5.27 (1H, m, exchangeable, OH) and 7.10–7.35 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 20.1 (CH_2), 29.3 (CH_2), 29.9 (CH_2), 35.0 (CH_2), 36.6 (CH_2), 61.7 (CH), 65.8 (CH_2), 69.6 (C), 126.1 (CH), 126.8 (CH), 127.2 (CH), 127.3 (2×CH), 127.6 (CH), 128.4 (2×CH), 129.7 (CH), 138.2 (C), 139.2 (C), 139.6 (C) and 177.9 (C═O); MS *m*/*z* 321 (M^+, <1%), 291 (M−CH_2O, 67), 202 (18), 185 (22), 143 (20), 129 (22) and 106 (100). Later fractions afforded the (*R*,*R*)-spiro lactam **31a** (59 mg, 18%), mp 235–236 °C (toluene–light petroleum); IR ν_{max}/cm^{-1} ($CHCl_3$) 3360 br (O–H) and 1655 (C═O); ^1H NMR (90 MHz) ($CHCl_3$-*d*+MeOH-d_4) δ 1.72–2.92 (10H, m, 5×CH_2), 3.77–3.99 (2H, m, CH_2CH), 4.28 (1H, br, OH) overlapping 4.30 (1H, dd, *J*=8.2, 12.6 Hz, CH_2C*H*), 6.44–6.72 (2H, m, aryl H) and 6.87–7.29 (7H, m, aryl H); ^{13}C NMR (22.5 MHz) ($CHCl_3$-*d*+MeOH-d_4) δ 20.9 (CH_2), 29.8 (CH_2), 30.5 (CH_2), 32.7 (CH_2), 36.6 (CH_2), 62.5 (CH), 65.0 (CH_2), 69.6 (C), 125.6 (CH), 127.3 (2×CH), 128.0 (2×CH), 128.6 (3×CH), 129.2 (CH), 137.3 (C), 138.5 (C), 139.1 (C) and 177.7 (C═O); MS *m*/*z* 321 (M^+, <1%), 303 (M−H_2O, 1), 291 (M−CH_2O, 41), 202 (16), 185 (20) and 106 (100).

3.5.4. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-piperidin]-6′-ones 32a and b. The title compound were obtained from the bicyclic lactam **20** (0.35 g) and aluminium trichloride (0.52 g) in DCE at room temperature. Elution of the column afforded first the (*R*,*S*)-spiro lactam **32b** (260 mg, 74%), mp 113–115 °C (toluene–light petroleum); HREIMS found M^+ 335.1873. $C_{22}H_{25}NO_2$ requires *M* 335.1885; IR ν_{max}/cm^{-1} ($CHCl_3$) 3380 br (O–H) and 1720 (C═O); ^1H NMR (270 MHz) δ 1.67–2.06 (7H, m) and 2.19–2.29 (1H, m, 4×ring CH_2), 2.66–2.82 (4H, m, 2×ring CH_2), 3.80–3.95 (2H, m, CHCH_2OH), 4.17 br (1H, d, *J*=5.1 Hz, C*H*CH_2), 5.08 (1H, dd, *J*=9.8, 2.8 Hz, CH_2O*H*) and 7.09–7.37 (9H, m, aryl H); after shaking the sample with D_2O the OH signal at δ 5.08 disappeared, the signal at δ 4.17 was unchanged, and the signal for CH_2OH simplified to δ 3.84 (1H, dd, *J*=19.0, 5.1 Hz) and 3.91 (1H, dd, *J*=19.0, 1.9 Hz); ^{13}C NMR (22.5 MHz) δ 17.1 (CH_2), 20.5 (CH_2), 29.4 (CH_2), 33.3 (CH_2), 33.8 (CH_2), 38.3 (CH_2), 64.6 (CH), 65.4 (CH_2), 66.4 (C), 126.4 (CH), 126.9 (2×CH), 127.4 (CH), 127.6 (CH), 128.1 (2×CH), 129.4 (CH), 138.1 (C), 138.5 (C), 139.9 (C)

and 173.6 (C═O); MS *m/z* 335 (M^+, <1%), 317 (M−H_2O, 5), 305 (M−CH_2O, 37), 216 (16), 199 (16), 157 (18), 129 (26), 106 (100) and 91 (18). This was followed by the (*R*,*R*)-spiro lactam **32a** (87 mg, 25%), mp 98–100 °C (toluene–light petroleum). Anal. found C, 78.47; H, 7.63; N, 3.84. $C_{22}H_{25}NO_2$ requires C, 78.77; H, 7.51; N, 4.18%; IR ν_{max}/cm^{-1} ($CHCl_3$) 3360 br (O–H) and 1680 (C═O); ^{1}H NMR (90 MHz) δ 1.62–2.38 (8H, m, 4×CH_2), 2.54–2.98 (4H, m, 2×CH_2), 3.86–4.41 (4H, m, CH_2CH and OH) and 6.35–7.30 (8H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 17.4 (CH_2), 20.9 (CH_2), 29.9 (CH_2), 33.3 (CH_2), 33.6 (CH_2), 37.7 (CH_2), 66.1 (C), 66.8 (CH), 125.2 (CH), 126.4 (CH), 126.9 (CH), 127.5 (2×CH), 128.5 (3×CH), 129.2 (CH), 137.5 (C), 138.2 (C), 139.1 (C) and 173.5 (C═O); MS *m/z* 335 (M^+, <1%), 305 (M−CH_2O, 32), 216 (17), 199 (19), 129 (20) and 106 (100).

3.5.5. (*R*,*R*)- and (*R*,*S*)-2′-(2-Hydroxy-1-phenylethyl)-2,3,2′,3′-tetrahydrospiro[indene-1,1′-isoindol]-3′-ones 33a and b. The title compound were obtained from the tricyclic lactam **25** (0.17 g) and aluminium trichloride (0.19 g) in DCE at 0 °C. Elution of the column afforded first the (*R*,*R*)-spiro lactam **33b** (55 mg, 32%) as a viscous oil; HRCIMS found MH^+ 356.1651. $C_{24}H_{22}NO_2$ requires 356.1651; ^{1}H NMR (90 MHz) δ 2.27 (2H, t, *J*=7.2 Hz, CH_2), 2.97–3.18 (2H, m, CH_2), 3.95–4.25 (3H, m, C*H*C*H*$_2$OH), 4.98 br (1H, t, OH), 6.82 (1H, d, *J*=6.8 Hz, *o*-ArH), 7.02–7.13 (1H, m, *m*-ArH), 7.19–7.52 (10H, m, aryl H) and 7.88–7.98 (1H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 30.6 (CH_2), 35.4 (CH_2), 61.0 (CH), 66.0 (CH_2), 78.4 (C), 121.8 (CH), 123.6 (CH), 123.8 (CH), 125.5 (CH), 127.2 (2×CH), 127.4 (CH), 127.8 (CH), 128.4 (CH), 128.6 (2×CH), 129.4 (CH), 130.1 (C), 132.7 (CH), 138.9 (C), 141.4 (C), 144.3 (C), 151.3 (C) and 170.2 (C═O); MS *m/z* 356 (MH^+, <1%), 325 (M−CH_2O, 46), 234 (26), 219 (100), 189 (16), 165 (12) and 106 (13). This was followed by the (*R*,*S*)-spiro lactam **33a** (74 mg, 43%); white solid, mp 143–145 °C (toluene–light petroleum); HRCIMS found MH^+ 356.1653. $C_{24}H_{22}NO_2$ requires 356.1651; ^{1}H NMR (270 MHz) δ 2.67 (1H, ddd, *J*=14.7, 9.4. 6.6 Hz) and 2.87 (1H, ddd, *J*=14.7, 8.9, 4.3 Hz, CH_2-2), 3.20–3.45 (2H, m, CH_2-3), 4.00 (1H, dd, *J*=11.5, 4.3 Hz) and 4.22 (1H, dd, *J*=8.3, 4.3 Hz, C*H*$_2$OH), 4.35 br (1H, s, OH), 4.68 br (1H, t, *J*=10.6 Hz, CHPh), 6.12 (1H, d, *J*=7.6 Hz, *o*-ArH), 6.63 (1H, t, *J*=7.6 Hz, *m*-ArH), 7.01–7.13 (3H, m, aryl H), 7.25–7.44 (7H, m, aryl H) and 7.77 (1H, d, *J*=7.6 Hz, aryl H); ^{13}C NMR (67.5 MHz) δ 31.4 (CH_2), 36.9 (CH_2), 62.4 (CH), 64.7 (CH_2), 78.4 (C), 122.2 (CH), 123.5 (CH), 125.1 (CH), 125.7 (CH), 127.1 (CH), 127.5 (CH), 128.2 (2×CH), 128.3 (2×CH), 128.5 (CH), 129.2 (CH), 131.4 (C), 132.7 (CH), 139.2 (C), 140.9 (C), 144.5 (C), 151.7 (C) and 169.6 (C═O); MS *m/z* 356 (M^+, <1%), 325 (M−CH_2O, 41), 324 (37), 219 (100), 191 (14), 189 (16), 165 (11) and 106 (14).

3.5.6. (*R*,*R*)- and (*R*,*S*)-2′-(2-Hydroxy-1-phenylethyl)-1,2,3,4,2′,3′-hexahydrospiro[naphthalene-1,1′-isoindol]-3′-ones 34a and b. The title compound were obtained from the tricyclic lactam **26** (164 mg) and aluminium trichloride (0.18 g) in DCE at 0 °C for 5 h. Elution of the column afforded first the (*R*,*R*)-spiro lactam **34b** (68 mg, 41.5%); white solid, mp 155–157 °C; HRCIMS found MH^+ 370.1802. $C_{25}H_{24}NO_2$ requires 370.1807; ^{1}H NMR (270 MHz) δ 1.68–2.35 (4H, m, 2×CH_2), 2.84?2.89 (2H, m, CH_2), 4.03–4.12 (2H, m, C*H*$_2$CH), 4.29 (1H, dd, *J*=5.5, 2.2 Hz, CHPh), 5.30 br (1H, s, OH), 6.77 (1H, d, *J*=7.9 Hz, aryl H), 6.99–7.10 (1H, m, aryl H), 7.18–7.33 (2H, m, aryl H), 7.43–7.50 (8H, m, aryl H) and 7.94–7.97 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 20.4 (CH_2), 29.3 (CH_2), 34.6 (CH_2), 61.6 (CH), 66.2 (CH_2), 70.1 (C), 122.8 (CH), 123.9 (CH), 126.1 (CH), 127.2 (CH), 127.3 (2×CH), 127.4 (CH), 128.1 (CH), 128.2 (CH), 128.5 (2×CH), 129.8 (CH and C), 132.4 (CH), 133.7 (C), 139.0 (C), 139.2 (C), 153.3 (C) and 170.8 (C═O); MS *m/z* 369 (M^+, <1%), 339 (M−CH_2O, 100), 338 (M−CH_2OH, 42), 250 (11), 234 (38), 233 (76), 215 (35), 106 (17) and 91 (16). Further elution gave the (*R*,*S*)-spiro lactam **34a** (55 mg, 33.5%) as a viscous oil; HREIMS found MH^+ 370.1804. $C_{25}H_{24}NO_2$ requires 370.1807; ^{1}H NMR (270 MHz) δ 1.95–2.02 (1H, m) and 2.50–2.62 (1H, ddd, *J*=13.5, 10.6, 5.6 Hz, CH_2-2), 2.12–2.28 (2H, m, CH_2), 2.91–3.07 (2H, m, CH_2), 4.06 br (1H, s, OH) overlapping 4.12 (1H, dd, *J*=11.6, 4.6 Hz) and 4.31 (1H, dd, *J*=7.6, 4.6 Hz, C*H*$_2$OH), 4.55–4.62 (1H, m, CHPh), 6.11 (1H, dd, *J*=7.9, 1.0 Hz, *o*-ArH), 6.37 (1H, t, *J*=6.9 Hz, *m*-ArH) and 6.92 (1H, dd, *J*=7.6, 1.3 Hz, aryl H), 7.05–7.17 (7H, m, aryl H), 7.35–7.41 (2H, m, aryl H) and 7.81–7.85 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 20.0 (CH_2), 28.6 (CH_2), 33.9 (CH_2), 61.0 (CH), 63.8 (CH_2), 68.3 (C), 121.2 (CH), 122.5 (CH), 124.6 (CH), 126.2 (CH), 126.5 (CH), 126.8 (2×CH), 126.9 (CH), 127.7 (2×CH), 128.6 (CH), 129.3 (C), 131.0 (CH), 131.3 (C), 137.7 (C), 152.6 (C) and 169.0 (C═O); MS *m/z* 369 (M^+, <1%), 351 (M−H_2O, 2), 339 (M−CH_2O, 100), 338 (M−CH_2OH, 72), 250 (8), 233 (77), 215 (55), 202 (34), 178 (16), 106 (25), 91 (37) and 77 (21).

3.5.7. (*S*,*S*)- and (*S*,*R*)-1′-(1-Hydroxy-3-methylbut-2-yl)-2,3-dihydrospiro[indene-1,2′-pyrrolidin]-5′-ones 35a and b. The title compound were obtained from the bicyclic lactam **17** (0.33 g) and aluminium trichloride (0.50 g) in DCE at −5 °C. Chromatography of the crude product afforded first the (*S*,*R*)-spiro lactam **35b** (74 mg, 22.4%); white solid, mp 142–143 °C; HREIMS found M^+ 273.1731. $C_{17}H_{23}NO_2$ requires *M* 273.1729; ^{1}H NMR (90 MHz) δ 0.98 (6H, d, *J*=6.6 Hz, 2×CH_3), 1.98–3.08 (9H, m, 4×CH_2 and CH), 3.60–3.70 br (2H, m, C*H*$_2$OH), 4.98 br (1H, s, OH) and 7.29 (4H, s, aryl H); ^{13}C NMR (22.5 MHz) δ 20.2 (CH_3), 20.9 (CH_3), 24.9 (CH), 29.5 (CH_2), 29.9 (CH_2), 35.1 (CH), 37.8 (CH_2), 62.4 (CH), 65.1 (CH_2), 76.2 (C), 123.0 (CH), 125.3 (CH), 127.2 (CH), 128.7 (CH), 142.2 (C), 144.8 (C) and 177.9 (C═O); MS *m/z* 273 (M^+, 7%), 255 (M−H_2O, 3), 242 (M−CH_2OH, 68), 188 (23), 171 (47), 143 (55), 128 (100), 115 (41) and 72 (72). Further elution gave the (*S*,*S*)-spiro lactam **35a** (212 mg, 64%); white solid, mp 125–126 °C (toluene–light petroleum). Anal. found C, 74.63; H, 8.62; N, 4.99. $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48; N, 5.13%; ^{1}H NMR (90 MHz) δ 0.59 (3H, d, *J*=6.6 Hz, CH_3), 0.81 (3H, d, *J*=6.6 Hz, CH_3), 2.05–3.02 (9H, m, 4×CH_2 and CH), 3.78–4.10 br (2H, m, C*H*$_2$OH), 4.53 br (1H, s, OH) and 7.30 (4H, s, aryl H); ^{13}C NMR (22.5 MHz) δ 20.1 (CH_3), 20.9 (CH_3), 25.7 (CH), 30.0 (CH_2), 30.7 (CH_2), 35.0 (CH), 38.6 (CH_2), 62.6 (CH), 76.2 (C), 125.0 (CH), 125.2 (CH), 126.8 (CH), 129.2 (CH), 142.5 (C), 144.5 (C) and 176.9 (C═O); MS *m/z* 273 (M^+, 6), 255 (M−H_2O, 6), 242 (M−CH_2OH, 86), 230 (5), 188 (40), 171 (49), 143 (68), 128 (53), 115 (28), 72 (100) and 60 (27).

3.5.8. 5-Methyl-6-phenyl-1,2,5,6,10,11-hexahydrocyclopenta[*kl*]pyrrolo[2,1-*a*]isoquinolin-3(3*H*)-one 41. The title compound was obtained from the bicyclic lactam **39** (0.30 g) and aluminium trichloride (0.40 g) in DCE at 0 °C. Chromatography afforded the tetracyclic lactam **41** (125 mg, 44%) as a viscous oil; HREIMS found M^+ 303.1631. $C_{21}H_{21}NO$ requires *M* 303.1623; IR ν_{max}/cm^{-1} ($CHCl_3$) 1720 (C=O); ^1H NMR (270 MHz) δ 0.97 (3H, d, *J*=7.0 Hz, CH_3), 1.46–1.59 (1H, m), 1.89 (1H, dd) overlapping 1.92–2.00 (1H, m), 2.17 (1H, dd, *J*=11.5, 7.0 Hz), 2.36 (1H, dd, *J*=11.2, 5.6 Hz), 2.49 (1H, ddd, *J*=16.5, 12.8, 7.0 Hz), 2.75 (1H, dd, *J*=15.5, 7.3 Hz), 3.11 (1H, ddd, *J*=15.5, 11.4, 5.6 Hz), 4.02 (1H, s, H-6), 5.20 (1H, dq, *J*=7.0, 1.7 Hz, CH_3CH), 7.04 (1H, d, *J*=6.6 Hz, H-7 or H-9) and 7.16–7.31 (7H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 19.5 (CH_3), 30.0 (CH_2), 31.5 (CH_2), 32.9 (CH_2), 42.3 (CH_2), 50.5 (CH), 51.8 (CH), 68.4 (C-11a), 123.7 (CH), 126.6 (CH), 127.8 (CH), 128.0 (2×CH), 128.2 (CH), 128.5 (2×CH), 132.9 (C), 140.8 (C), 142.3 (C), 142.6 (C) and 177.6 (C=O); MS *m/z* 303 (M^+, 100%), 288 ($M-CH_3$, 7), 260 (13), 232 (11), 203 (18), 128 (16) and 91 (14).

3.6. Crystallographic structure determinations

X-Ray analysis of **30a** and **35b** were carried out on a Rigaku AFC6S four-circle diffractometer with graphite-monochromated Mo Kα radiation, λ=0.710 70 at 20 °C. The structures were solved by direct methods using SHELX-76 and refined on F^2 using SHELXL. Crystal structures of **29a** and **32b** have been reported previously.[9]

3.6.1. Crystal data for 30a.[21] $C_{21}H_{23}NO_2$, *M*=321.40. The crystal size was 0.50×0.50×0.40 mm; orthorhombic, space group $P2_12_12_1$, with unit cell *a*=10.969(3), *b*=15.196(3), *c*=10.266(2) Å, *V*=1711.2(7) Å^3, *Z*=4, D_c=1.248 g cm^{-1}. 2672 reflections were collected in the range $5<2\theta<50°$, of which 2378 were independent (R_{int} 0.0161). Full matrix least squares refinement on F^2 with 219 parameters for 2378 reflections with $I>2\sigma I$ gave final values of R_1=0.0301 and wR_2=0.0721.

3.6.2. Crystal data for 35b.[21] $C_{17}H_{23}NO_2$, *M*=273.36. The crystal size was 0.50×0.30×0.20 mm; orthorhombic, space group $P2_12_12_1$, with unit cell *a*=11.915(1), *b*=18.256(4), *c*=6.915(3) Å, *V*=1504.1(7) Å^3, *Z*=4, D_c=1.207 g cm^{-1}. 3103 reflections were collected in the range $5<2\theta<50°$, of which 2651 were independent (R_{int} 0.0152). Full matrix least squares refinement on F^2 with 182 parameters for 2650 reflections with $I>2\sigma I$ gave final values of R_1=0.0425 and wR_2=0.1041.

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References and notes

1. (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856, and references therein.
2. (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 1515–1518. (b) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951–958.
3. (a) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, 411–414. (b) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695–3700.
4. Inoue, Y.; Tazawa, N.; Watanabe, A.; Aoki, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn* **1992**, *65*, 2866–2868.
5. Ito, T.; Yamazaki, N.; Kibayashi, C. *Synlett* **2001**, 1506–1509.
6. (a) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507–3510. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017–3020.
7. (a) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron Lett.* **1994**, *35*, 7115–7118. (b) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron* **2003**, *59*, 3369–3378.
8. Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S. *J. Org. Chem.* **1998**, *63*, 6778–6779.
9. Preliminary publication of some of these results: Bahajaj, A. A.; Bailey, P. D.; Moore, M. H.; Morgan, K. M.; Vernon, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, *1994*, 2511–2512.
10. (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569, and references therein. (b) Meyers, A. I. In *Stereocontrolled organic synthesis*; Trost, B. M., Ed.; Blackwell Scientific: Oxford, 1994; pp 145–161. (c) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1–8.
11. (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296. (b) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859. (c) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662.
12. (a) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223–2226. (b) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084–7085. (c) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1996**, *37*, 849–852. (d) Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977–980.
13. (a) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3627–3630. (b) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1715–1721.
14. Some other syntheses of spiro lactams via alkylation of the 5-cyano derivative of **7** are unrelated to our present work: cf. (a) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1993**, *58*, 6451–6456. (b) Ribeiro, C. M. R.; de Melo, S. J.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 7227–7230.
15. Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *Tetrahedron*, **2004**, *60*, 1247–1253.
16. (a) Bahajaj, A. A.; Hitchings, G. J.; Moore, M. H.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1211–1214. (b) Bahajaj, A. A.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1041–1046.
17. Fains, O.; Vernon, J. M. *Tetrahedron Lett.* **1997**, *38*, 8265–8266.
18. Staudinger, H.; Schneider, H. *Ber.* **1923**, *56*, 699.
19. Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *4243*, 4246. The (*R*)-enantiomer **21**

has also been reported: Groaning, M. D.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 4639–4642.
20. Aguilar, N.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **1998**, 313–316.
21. Crystallographic data for compounds **30a** and **35b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 213789 and 213790, respectively. 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).

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Asymmetric synthesis of spiro 2-pyrrolidin-5-ones, 2-piperidin-6-ones and 1-isoindolin-3-ones. Part 2: *N*-Acyliminium ion cyclisations with an internal alkene nucleophile

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Abstract—Chiral non-racemic bicyclic and tricyclic oxylactams obtained in two steps from *N*-(2-hydroxy-1(*R*)-phenylethyl)-succinimide and phthalimide are cyclised diastereoselectively in formic acid to give spiro[cyclohexane-1,2′-pyrrolidin]-5-ones and spiro[cyclohexane-1,1′-isoindolin]-3-ones, respectively.
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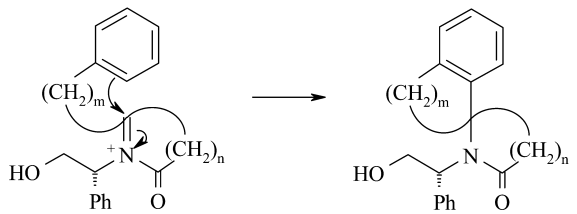
1. Introduction

In the preceding paper,[1] we have shown how Meyers's chiral bicyclic lactam methodology[2] can be used for the diastereoselective cyclisation of *N*-acyliminium ion intermediates **1** to form spiro lactams **2** (Scheme 1). In this paper, we describe similar cyclisations in which the internal nucleophile is an alkene rather than an arene group.



1 **2**

Scheme 1.

Spiro cyclisations of *N*-acyliminium ions with an internal alkene nucleophile were first described by Speckamp and co-workers (Scheme 2).[3] In their spiro lactams **5** the relative stereochemistry of O- and N-substituents *cis*-diequatorial in the cyclohexane ring is a consequence of anti alignment of bonds made and broken in a chair-like transition state **4** in a favoured 6-*endo-exo-trig* cyclisation.[4] The less favoured 5-*exo-exo-trig* process accounts for the formation of 5,5-spiro lactam by-products in some related cases[3] or as the main product in one case.[5] (Note that for spiro cyclisation of an iminium ion the C=N bond must always be *exo*.) There are more recent examples of spiro cyclisations of *N*-acyliminium ions with an internal alkene nucleophile;[6–8] some are based on the use of oxylactams as precursors for the cyclisation step,[9] although there is no control over the configuration at the resulting spiro carbon atom.

2. Results and discussion

Bicyclic oxylactams **9** and **10** were prepared in two steps from the succinimide **6** (Scheme 3). Each of **9** and **10** was obtained as a single diastereoisomer, which is assigned (*S*)-stereochemistry at C-7a from numerous precedents in other work.[2,10] Treatment of **9** with acid under various conditions failed to give spiro lactam products, and this accords with previous failures of attempted 5-*endo-exo-trig* cyclisation via an *N*-acyliminium ion intermediate.[11] However, experiments with **10** were more successful. Treatment of **10** with aluminium trichloride in 1,2-dichloroethane afforded 45% yield of a product oil, which was a ca 3:1 mixture of diastereoisomeric 6,5-spiro lactams **11a** and **b**, containing also a small amount of a 5,5-spiro lactam **12**. The mass spectrum showed the correct molecular ion peaks *m*/*z* 307 and 309, together with other pairs of peaks indicating the presence of one chlorine atom and fragment ions (including loss of 18 and 30 mass units corresponding to H_2O and CH_2O, respectively) which indicate that the oxazolidine ring of **10** has opened to give the $HOCH_2CHPh$ side chain in **11a**,**b**. The ^{13}C NMR spectrum showed resonances for the spiro carbons at δ 65.1 and 64.8 for **11a** and **b** and at δ 77.2 for **12** (cf. ref. 1). The major diastereoisomer is presumably **11a** with (*S*)-configuration at the spiro carbon to accord with our previous results for cyclisation to 6,5-spiro lactams.[1] In

Keywords: Diastereoselective; Spiro lactams; *N*-Acyliminium ions.
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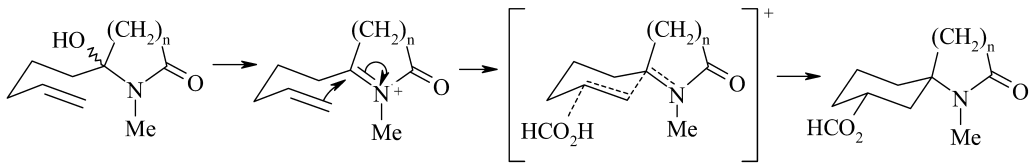
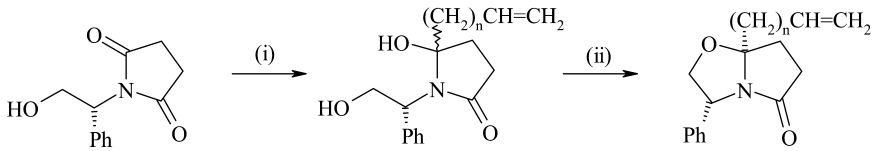


3 **4** **5**

Scheme 2.



6 **7** n = 2, **8** n = 3 **9** n = 2, **10** n = 3

Scheme 3. *Reagents:* (i) $CH_2{=}CH(CH_2)_nMgBr$; (ii) TFA/DCM.

the ^{1}H NMR spectrum the signal assigned to CHCl appeared as a triplet of triplets, J=4.3 and 11.4 Hz; the larger coupling constant is consistent with *trans*-diaxial coupling of CHCl to adjacent ring hydrogens and hence with chlorine being in an equatorial position (cf. ref. 3). Unfortunately, this mixture of **11a**,**b** and **12** was inseparable by chromatography, so we next examined alternative conditions for cyclisation of **10** with a view to obtaining crystalline spiro products.

Treatment of the bicyclic lactam **10** with formic acid at room temperature gave a product mixture which was separated chromatographically into two fractions. The less polar material (7% yield) appeared to be a mixture of diastereoisomeric spiro lactams (^{13}C NMR signals for the spiro carbon at δ 64.8 and 65.4) containing one rather than two formate ester groups. In the mass spectrum a strong fragment ion at m/z 240 corresponds to the loss of CH_2OCHO, suggesting that the formate group is in the side chain. Hence structure **13** is assigned. Although the position of the ring double bond is uncertain, a comparison of ^{13}C chemical shifts for the spiro carbon in **13** with the values for **14a**,**b** suggests that **13** is a cyclohex-3-ene rather than a cyclohex-2-ene. The more polar fraction was the main product (78% yield), which was shown to be a 4:1 mixture of spiro lactams **14a** and **b** (^{13}C NMR spectrum). The mass spectrum showed the correct molecular ion m/z 345, the fragment ion at m/z 286 (loss of CH_2OCHO), and the base peak at m/z 106 (the same as for **11a**,**b**). Also, as for **11a**,**b** the ^{1}H NMR signal for C*H*OCHO (δ 4.9) in the

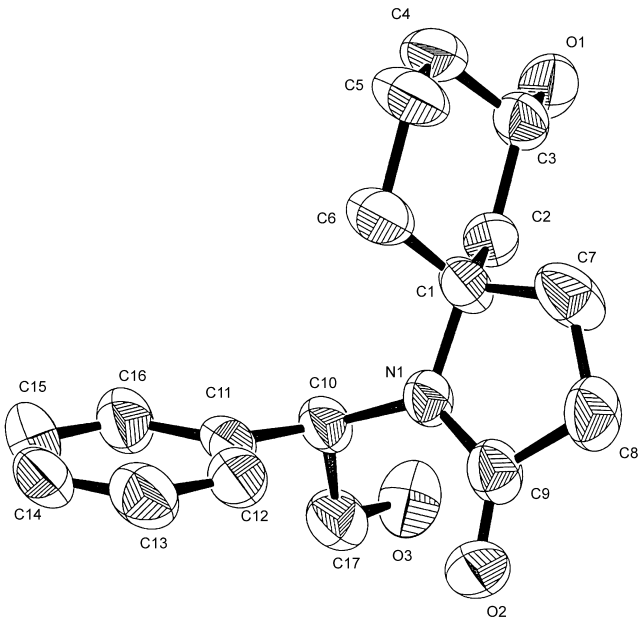
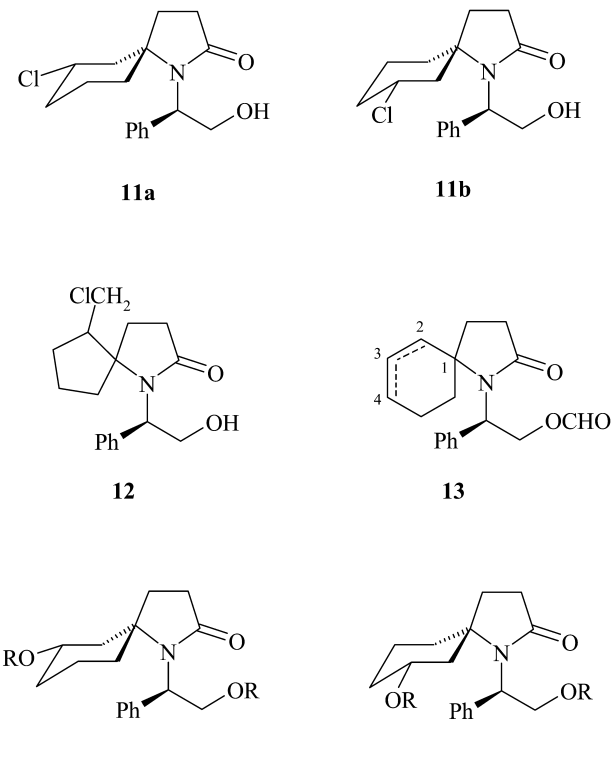


Figure 1. ORTEP drawing of the crystal structure of spiro lactam **15a** with crystallographic numbering scheme (hydrogen atoms omitted).

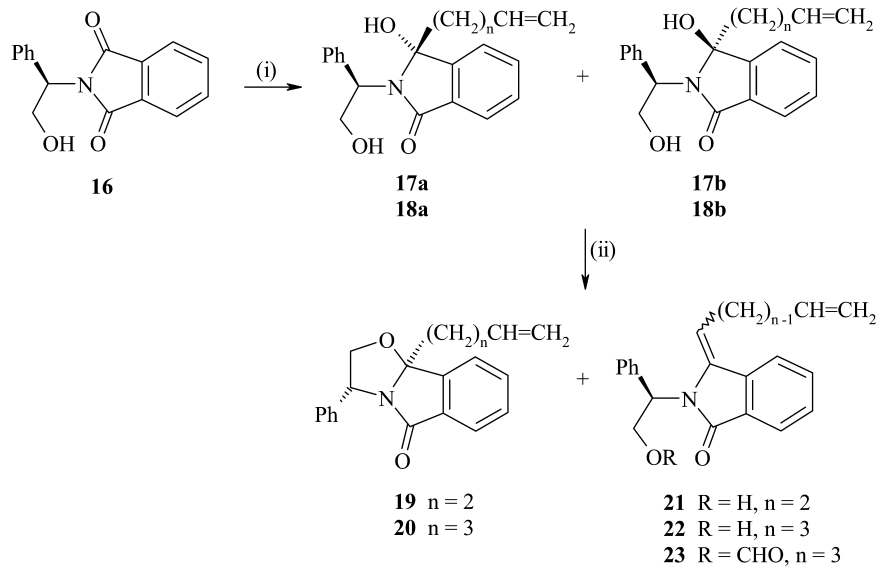


11a **11b**

12 **13**

14a R = CHO
15a R = H

14b R = CHO
15b R = H



Scheme 4. *Reagents:* (i) $CH_2{=}CH(CH_2)_nMgBr$; (ii) TFA/DCM.

cyclohexane ring was a triplet of triplets, J=4.6 and 11.0 Hz, with the larger coupling constant consistent with *trans*-diaxial couplings and hence with the formate group equatorial. Hydrolysis of this mixture of diformates gave the corresponding diols **15a**,**b**, from which the major diastereoisomer was separated by fractional crystallisation. It was shown by X-ray diffraction to have the structure **15a** (Fig. 1) with (*S*)-configuration at the spiro centre. Therefore, the major diformate diastereoisomer is **14a**, and the selectivity of spiro cyclisation from **10** with an alkene nucleophile is the same as that already established for similar cyclisations to 6,5-spiro lactams with an arene nucleophile.[1]

The scope of this approach to spiro lactams was extended to include compounds derived from phthalimide **16**. Addition of ω-alkenyl Grignard reagents to **16** gave, as expected, hydroxy lactams **17** and **18**, in each case as a mixture of diastereoisomers (Scheme 4). These were separable by chromatography, with the major diastereoisomer being the more polar component (eluted second) in each case. The structure **17a** for the major isomer was established by X-ray crystal structure determination (Fig. 2).

Treatment of **17a** with TFA in DCM afforded the tricyclic lactam **19** as the major product (78% yield) as a single diastereoisomer, which has α*R*,9b*S* stereochemistry as in **24**[12] and other related examples.[1] By-products, which were incompletely separated from one another, included probably the enelactam **21**. The same mixture of products was obtained from **17b** with TFA in DCM, consistent with cyclisation via a *N*-acyliminium ion intermediate in which C-3 of **17a**,**b** becomes planar. Consequently, separation of diastereoisomeric hydroxy lactams is unnecessary (where this is possible), and a mixture of **18a** and **b** was treated with TFA in DCM to give the corresponding bicyclic lactam **20** (71% yield), again as a single diastereoisomer, alongside a very small amount of a by-product, probably the enelactam **22** (Scheme 4).

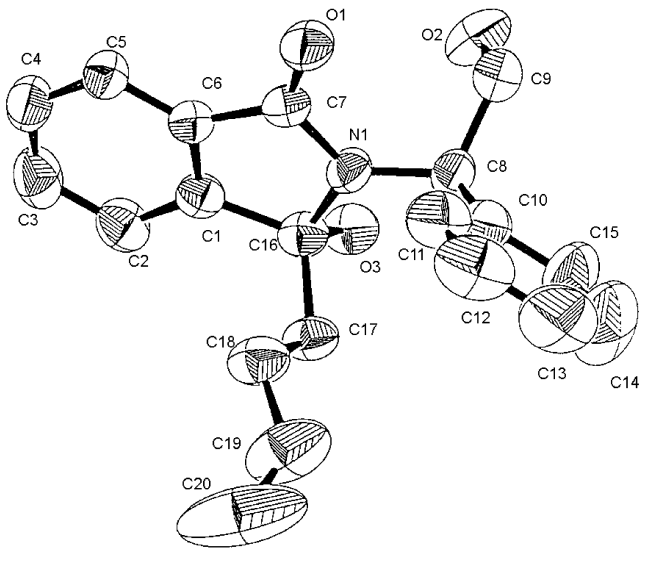
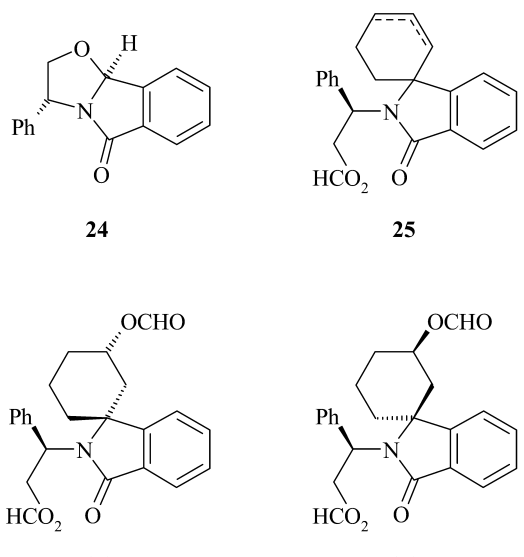


Figure 2. ORTEP drawing of the crystal structure of compound **17a** with crystallographic numbering scheme (hydrogen atoms omitted).



From **19** in formic acid we were unable to obtain a 5,5-spiro lactam, but only very small amounts of unidentified products (cf. **9**). However, from **20** in formic acid we obtained a 4:1 mixture of spiro lactams **26a** and **b** (47% yield), in which **26a** must be the major diastereoisomer. In addition, less polar material eluted in an earlier column fraction was a mixture of at least two by-products, in which the major component was tentatively identified as the enelactam **23** and the minor component as the spirocyclohexene **25** (^{13}C NMR spectra and other evidence).

In conclusion, we have demonstrated several examples of diastereoselective cyclisation of *N*-acyliminium ion intermediates to spirocyclohexane[1,2′]-pyrrolidin-5′-ones and spirocyclohexane[1,1′]isoindolin-3′-ones. The stereochemical preference for formation of the new quaternary carbon centre follows the same pattern as that found for similar *N*-acyliminium ion cyclisations with an internal arene nucleophile.[1] The same approach was not successful for the preparation of corresponding spirocyclopentane derivatives by cyclisations with an internal alkene nucleophile.

3. Experimental

NMR spectra were recorded at 90 MHz for ^{1}H (22.5 MHz for ^{13}C) on JEOL 90Q or at 270 MHz for ^{1}H (67.5 MHz for ^{13}C) on JEOL FX270 spectrometers for solutions in deuteriochloroform (unless otherwise stated) with tetramethylsilane as internal standard. Assignments of ^{13}C NMR signals were assisted by use of DEPT spectra. In ^{13}C NMR spectra lines enclosed in | | are assigned to the minor diastereoisomer of a pair. Mass spectra were obtained by electron impact at 70 eV on a VG Autospec spectrometer; high resolution spectra were obtained in EI mode or in CI mode using ammonia. Chromatographic separations were performed on MN-silica (230–400 mesh). THF and diethyl ether were dried before use. Light petroleum refers to the fraction bp 40–60 °C (unless otherwise stated). DCM refers to dichloromethane.

3.1. Hydroxy lactams 17a,b and 18a,b

3.1.1. (α*R*,3*R*)- and (α*R*,3*S*)-3-(But-3-enyl)-3-hydroxy-2-(2-hydroxy-1-phenylethyl)-2,3-dihydroisoindol-1(1*H*)-ones 17a,b. The Grignard reagent was prepared from magnesium (0.13 g) and 4-bromo-1-butene (0.73 g, 5.4 mmol) in THF (30 mL) and added rapidly to (*R*)-*N*-(2-hydroxy-1-phenylethyl)phthalimide **16**[1] (0.46 g, 1.72 mmol) in THF (20 mL) with stirring at 0 °C. The crude product isolated after aqueous work up was then chromatographed on silica and two products eluted with ethyl acetate/chloroform (1:1 v/v).

(α*R*,3*S*)-*Hydroxy lactam* **17b**: yield 105 mg (19%), viscous oil (HREIMS found M^+ 323.1516. $C_{20}H_{21}NO_3$ requires *M* 323.1521); ^{1}H NMR (270 MHz) δ 1.30 and 1.60 (each 1H, m, H_A and H_B of CH_2 at C-3), 2.07 (2H, m, CH_2), 3.57 (1H, s br, OH), 4.02 (2H, m, C*H*$_2$OH), 4.33 (1H, m, C*H*Ph), 4.67 (1H, s, OH), 4.73 and 4.83 (each 1H, m, H_A and H_B of CH=C*H*$_2$), 5.41 (1H, m, C*H*=CH$_2$) and 7.08–7.72 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 27.6 (CH_2), 35.6 (CH_2), 58.1 (CH), 63.8 (CH_2), 92.7 (C-3), 114.9 (CH_2), 121.6 (CH), 123.5 (CH), 127.6 (CH), 127.9 (2×CH), 128.5 (2×CH), 129.6 (CH), 130.7 (C), 132.7 (CH), 136.7 (C), 138.9 (C), 146.5 (C) and 168.8 (C=O); MS *m*/*z* 324 (MH^+, 2%), 305 (M−H_2O, 4), 292 (M−CH_2OH, 46), 250 (24), 187 (61), 106 (100), 91 (60) and 78 (92).

(α*R*,3*R*)-*Hydroxy lactam* **17a**: yield 420 mg (76%), mp 126–129 °C (from ethyl acetate/hexane) (HREIMS found M^+ 323.1516. $C_{20}H_{21}NO_3$ requires *M* 323.1521); ^{1}H NMR (270 MHz) δ 1.16 (2H, dd, *J*=7.6, 15.7 Hz, CH_2), 1.77–1.88 (1H, m), 2.00–2.19 (1H, m), 3.75–3.84 (1H, m), 4.42 (1H, dd, *J*=1.7, 17.1 Hz), 4.63–4.68 (3H, m), 4.77–4.89 (1H, m), 5.11–5.26 (1H, m), 5.40 (1H, s) and 7.30–7.65 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 28.0 (CH_2), 36.0 (CH_2), 59.0 (CH), 62.9 (CH_2), 92.2 (C-3), 114.9 (CH_2), 122.1 (CH), 123.3 (CH), 128.1 (CH), 128.7 (2×CH), 128.9 (2×CH), 129.8 (C), 131.7 (CH), 132.8 (CH), 136.8 (CH), 138.9 (C), 146.7 (C) and 169.1 (C=O); MS *m*/*z* 324 (MH^+, 2%), 305 (M−H_2O, 2), 292 (M−CH_2OH, 46), 250 (18), 187 (65), 106 (100), 91 (59) and 78 (89).

3.1.2. (α*R*,3*R*)- and (α*R*,3*S*)-3-Hydroxy-2-(2-hydroxy-1-phenylethyl)-3-(pent-4-enyl)-2,3-dihydroisoindol-1(1*H*)-ones 18a,b. The Grignard reagent was prepared from magnesium (165 mg, 6.8 mmol) and 5-bromo-1-pentene (1.02 g, 6.8 mmol) in THF (30 mL). This was added to the phthalimide **21** (454 mg, 1.7 mmol) in THF (20 mL) at 0 °C with stirring. After aqueous work up, the crude product was chromatographed on silica, from which two fractions were eluted with EtOAc/$CHCl_3$ (1:1 v/v).

(α*R*,3*S*)-*Hydroxy lactam* **18b**: 166 mg (29%), mp 90–93 °C (from toluene/light petroleum) (HREIMS found M^+ 337.1667. $C_{21}H_{23}NO_3$ requires *M* 337.1678); ^{1}H NMR (270 MHz) δ 0.68 and 0.95 (each 1H, m, H_A and H_B of CH_2 at C-3), 1.54–2.09 (4H, m, 2×CH_2), 4.09 (1H, m), 4.36 (3H, m), 4.85–5.07 (3H, m), 5.54 (1H, m) and 7.21–7.67 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 22.6 (CH_2), 33.0 (CH_2), 35.8 (CH_2), 57.6 (CH_2), 63.5 (CH_2), 92.9 (C-3), 115.0 (CH_2), 121.5 (CH), 123.4 (CH), 127.5 (CH), 128.0 (2×CH), 128.3 (2×CH), 129.4 (CH), 130.6 (C), 132.5 (CH), 137.7 (CH), 138.7 (C), 146.7 (C) and 168.9 (C=O); MS *m*/*z* 337 (M^+, 1%), 307 (31), 306 (M−CH_2OH, 49), 250 (34), 183 (34), 159 (47), 106 (100) and 77 (30).

(α*R*,3*R*)-*Hydroxy lactam* **18a**: 409 mg (71%), viscous oil (HREIMS found M^+ 337.1667. $C_{21}H_{23}NO_3$ requires *M* 337.1678); ^{1}H NMR (270 MHz) δ 0.41 (2H, quint, *J*=7.0 Hz, CH_2), 1.39–1.47 (1H, m), 1.55–1.66 (1H, m), 1.81–1.94 (1H, m), 3.69 (1H, br d, *J*=10.8 Hz), 4.53–4.70 (5H, m), 5.06–5.21 (1H, m), 5.35 (1H, s) and 7.23–7.55 (9H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 22.8 (CH_2), 33.0 (CH_2), 35.9 (CH_2), 58.9 (CH), 62.9 (CH_2), 92.2 (C), 114.7 (CH_2), 121.8 (CH), 123.2 (CH), 127.9 (CH), 128.3 (2×CH), 128.5 (2×CH), 129.5 (CH), 131.5 (C), 132.5 (CH), 137.9 (CH), 138.9 (C), 146.7 (C) and 168.9 (C=O); MS *m*/*z* 337 (M^+, 1%), 307 (31), 306 (M−CH_2OH, 53), 250 (32), 183 (34), 159 (49), 106 (100), 91 (25) and 77 (32).

3.2. General procedure for bicyclic/tricyclic oxylactams 9, 10, 19 and 20

A two to threefold excess of the Grignard reagent was

freshly prepared from the appropriate ω-alkenyl bromide and magnesium in THF and added rapidly with stirring to the imide **6** or **16** dissolved in THF at 0 °C. This solution was stirred during 1 h and allowed to warm to room temperature before aqueous work up and extraction with ether to give the crude hydroxy lactam. This was redissolved in DCM, cooled in ice, and treated with TFA. After stirring for 1 h at 0 °C, the solution was allowed to warm to room temperature, saturated ammonium chloride solution was added, the organic layer was separated, washed with water, dried ($MgSO_4$), and the solvent evaporated. The crude product was chromatographed on silica using ethyl acetate/chloroform (1:4 v/v) as eluent.

3.2.1. (3*R*,7a*S*)-7a-(But-3-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 9. From 4-bromo-1-butene (0.93 g, 6.9 mmol) and (*R*)-*N*-(2-hydroxy-1-phenylethyl) succinimide **6** (0.50 g, 2.28 mmol); the hydroxy lactam **7** treated with TFA (2.60 g, 22.8 mmol). Bicyclic oxylactam **9** was obtained (183 mg, 31%) as a viscous oil (HREIMS found M^+ 257.1419. $C_{16}H_{19}NO_2$ requires *M* 257.1416); ^{1}H NMR (270 MHz) δ 1.71–1.95 (2H, m, CH_2), 2.21–2.33 (3H, m), 2.42–2.51 (1H, m), 2.68 (1H, ddd, *J*=17.3, 10.2, 2.7 Hz), 2.93 (1H, dt, *J*=17.3, 9.9 Hz), 4.16 (1H, td, *J*=8.5, 1.1 Hz), 4.73 (1H, t, *J*=8.5 Hz), 5.00–5.10 (2H, m, =CH_2), 5.28 (1H, t, *J*=7.8 Hz), 5.83 (1H, ddt, *J*=17.0, 10.2, 6.6 Hz, =CH) and 7.31–7.45 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 28.3 (CH_2), 30.8 (CH_2), 33.1 (CH_2), 35.4 (CH_2), 57.5 (CH), 72.8 (CH_2), 102.3 (C-7a), 115.0 (CH_2), 125.4 (2×CH), 127.4 (CH), 128.6 (2×CH), 137.2 (CH), 140.0 (C) and 179.3 (C=O); MS *m*/*z* 257 (M^+, 4%), 202 ($M-C_4H_7$, 100), 120 (18), 103 (13), 91 (11) and 55 (12).

3.2.2. (3*R*,7a*S*)-7a-(Pent-4-enyl)-3-phenyl-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 10. From 5-bromo-1-pentene (1.09 g, 7.3 mmol) and (*R*)-*N*-(2-hydroxy-1-phenylethyl)succinimide **6** (0.40 g, 1.8 mmol); the hydroxy lactam **8** treated with TFA (2.08 g, 18.3 mmol). Bicyclic oxylactam **10** was obtained (278 mg, 56%) as a viscous oil (HREIMS found M^+ 271.1575. $C_{17}H_{21}NO_2$ requires *M* 271.1572); ^{1}H NMR (270 MHz) δ 1.41–1.75 (4H, m, 2×CH_2), 1.90–2.07 (2H, m, CH_2), 2.17 (1H, dt, *J*=13.5, 10.2 Hz), 2.36 (1H, ddd, *J*=13.2, 9.9, 2.6 Hz), 2.59 (1H, ddd, *J*=17.2, 10.2, 2.6 Hz), 2.83 (1H, dt, *J*=17.2, 10.2 Hz), 4.08 (1H, dd, *J*=8.6, 7.3 Hz), 4.62 (1H, t, *J*=8.6 Hz), 4.90–4.99 (2H, m, CH=CH_2), 5.18 (1H, t, *J*=7.6 Hz), 5.71 (1H, ddt, *J*=17.2, 13.2, 6.6 Hz, C*H*=CH_2) and 7.21–7.38 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 23.6 (CH_2), 31.3 (CH_2), 33.6 (CH_2), 33.8 (CH_2), 36.0 (CH_2), 57.8 (CH), 73.1 (CH_2), 102.9 (C-7a), 115.4 (CH_2), 115.4 (CH), 125.8 (2×CH), 127.7 (CH), 129.0 (2×CH), 138.2 (CH), 140.4 (C) and 179.6 (C=O); MS *m*/*z* 271 (M^+, 2%), 102 ($M-C_5H_9$, 100), 120 (14) and 55 (10).

3.2.3. (3*R*,9b*S*)-9b-(But-3-enyl)-3-phenyl-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 19. TFA (195 mg, 1.7 mmol) was added to hydroxy lactam **17a** (275 mg, 0.85 mmol) in DCM (25 mL) at 0 °C. After the usual work up and chromatography, as above, tricyclic lactam **19** was obtained (200 mg, 74%) as a viscous oil (HREIMS found M^+ 305.1419. $C_{20}H_{19}NO_2$ requires *M* 305.1416); ^{1}H NMR (270 MHz) δ 1.61–1.74 (1H, m), 1.99–2.24 (3H, m), 4.42 (1H, dd, *J*=8.7, 6.8 Hz), 4.78–4.88 (3H, m), 5.33 (1H, dd, *J*=7.7, 7.3 Hz), 5.54–5.69 (1H, m)7.28–7.42 (5H, m, aryl H) and 7.52–7.67 (3H, m, aryl H) and 7.81–7.85 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 28.4 (CH_2), 33.4 (CH_2), 58.2 (CH), 75.7 (CH_2), 101.6 (C-9b), 114.9 (CH_2), 122.3 (CH), 124.5 (CH), 125.6 (2×CH), 127.5 (CH), 128.7 (2×CH), 130.3 (CH), 132.3 (C), 133.3 (CH), 136.8 (CH), 140.1 (C), 145.4 (C) and 174.6 (C=O); MS *m*/*z* 305 (M^+, 8%), 250 ($M-C_4H_7$, 100), 232 (31), 214 (26), 130 (11), 103 (22) and 49 (13). The same product **19** with identical spectra was obtained in similar yield starting from hydroxy lactam **17a** or from a mixture of **17a** and **b**. A later fraction from the column afforded an impure sample of the isomeric enelactam **21** (16 mg).

3.2.4. (3*R*,9b*S*)-9b-(Pent-4-enyl)-3-phenyl-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 20. The mixture of hydroxy lactams **18a**,**b** (523 mg, 1.55 mmol) in DCM (30 mL) was treated with TFA (265 mg, 2.33 mmol) at 0 °C. After aqueous work up and chromatography, as above, tricyclic lactam **20** was obtained (350 mg, 71%) as a viscous oil (HREIMS found M^+ 319.1578. $C_{21}H_{21}NO_2$ requires *M* 319.1572); ^{1}H NMR (270 MHz) δ 0.92–1.08 (1H, m), 1.21–1.42 (1H, m),1.86–2.15 (4H, m, 2×CH_2), 4.41 (1H, dd, *J*=8.7, 6.7 Hz), 4.79 (1H, t, *J*=8.5 Hz), 4.83–4.91 (2H, m, CH=CH_2), 5.59 (1H, ddt, *J*=17.7, 9.6, 6.7 Hz, C*H*=CH_2), 7.25–7.39 (5H, m, aryl H), 7.50–7.57 (2H, m, aryl H), 7.59–7.66 (1H, m, aryl H) and 7.80–7.84 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 23.3 (CH_2), 33.2 (CH_2), 33.5 (CH_2), 58.2 (CH), 75.6 (CH_2), 101.8 (C-9b), 115.1 (CH_2), 122.3 (CH), 124.4 (CH), 125.6 (2×CH), 127.4 (CH), 128.6 (2×CH), 130.2 (CH), 132.2 (C), 133.2 (CH), 137.7 (CH), 140.1 (C), 145.6 (C), and 174.6 (C=O); MS *m*/*z* 319 (M^+, 5%), 250 ($M-C_5H_9$, 100), 232 (22), 130 (12), 103 (23) and 77 (12). A later fraction from the column afforded an impure sample of the isomeric enelactam **22** (7 mg); ^{13}C NMR (67.5 MHz) δ 27.2 (CH_2), 34.3 (CH_2), 61.6 (CH), 64.7 (CH_2), 115.2 (CH), 116.5 (CH_2), 123.9 (CH), 124.3 (CH), 127.4 (2×CH), 128.3 (CH), 129.1 (CH), 129.4 (2×CH), 130.7 (C), 132.9 (CH), 137.6 (CH), 138.4 (C) and 168.8 (C=O); MS *m*/*z* 319 (M^+, 22%), 288 (11), 278 (30), 246 (8), 200 (10), 158 (100), 103 (14), 91 (23) and 77 (10).

3.3. Spiro lactams 11a,b, 14a,b, 15a,b and 26a,b. General procedure for cyclisation in formic acid

The hydroxy lactam in freshly distilled formic acid was allowed to stand at room temperature or heated under reflux until reaction was complete (tlc). The solvent was evaporated in vacuo and the residue redissolved in chloroform, which was washed with aqueous sodium bicarbonate solution, then with water, dried ($MgSO_4$), and evaporated to dryness. The crude product was chromatographed on silica with ethyl acetate/chloroform (1:4 v/v) as eluent.

3.3.1. (α*R*,3*S*,spiro*S*)- and (α*R*,3*R*,spiro*R*)-3-Hydroxy-1′-(2-hydroxy-1-phenylethyl) spiro[cyclohexane-1,2′-pyrrolidin]-5′-ones 15a,b and diformates 14a,b; (α*R*, spiro*S*)- and (α*R*,spiro*R*)-1′-(2-formyloxy-1-phenylethyl)spiro[cyclohex-3-ene-1,2′-pyrrolidin]-5′-ones 13. From bicyclic lactam **10** (223 mg, 0.82 mmol) in formic acid (10 mL) 10 h at room temperature. First material eluted

from the column was a mixture of spirocyclohexene diastereoisomers **13** (17 mg, 7%) as a viscous oil (HREIMS found M^+ 299.1527. $C_{18}H_{21}NO_3$ requires *M* 299.1521); ^{1}H NMR (270 MHz) δ 1.24–2.62 (10H, m), 4.33–4.43 (3H, m), 5.65 (2H, m), 7.23–7.48 (5H, m, aryl H), 8.01 (1H, s, CHO) and |8.09 (1H, s, CHO)|; ^{13}C NMR (67.5 MHz) δ 23.1 (CH_2), |23.2 (CH_2)|, 29.6 (CH_2), |29.7 (CH_2)|, 29.8 (CH_2), |30.1 (CH_2)|, |31.2 (CH_2)|, 32.8 (CH_2), 32.9 (CH_2), |33.0 (CH_2)|, |56.6 (CH)|, 60.5 (CH), |64.0 (CH_2)|, |64.8 (spiro C)|, 65.0 (CH_2), 65.4 (spiro C), 124.5 (CH), 124.6 (CH), 126.6 (CH), 126.7 (CH), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.6 (CH), 128.8 (CH), |138.5 (C)|, 138.9 (C), |160.9 (CHO)|, 163.0 (CHO), |176.7 (lactam C=O)| and 177.7 (lactam C=O); MS *m/z* 299 (M^+, 36%), 253 ($M-HCO_2H$, 10), 245 (64), 240 ($M-CH_2OCHO$, 47), 200 (60), 186 (30), 148 (25), 121 (58), 106 (74), 98 (100), 91 (73) and 77 (60). Later column fractions afforded a mixture of spiro lactams **14a**,**b** (220 mg, 78%, 4:1 ratio) as a viscous oil (HREIMS found M^+ 345.1579. $C_{19}H_{23}NO_5$ requires *M* 345.1576); ^{1}H NMR (270 MHz) δ 1.22–2.19 (10H, m), 2.35–2.60 (2H, m), 4.44 (1H, dd, *J*=9.3, 6.0 Hz), 4.71 (1H, dd, *J*=11.0, 5.8 Hz), 4.92 (1H, tt, *J*=11.0, 4.6 Hz), 5.18 (1H, apparent td, *J*=9.7, 2.8 Hz), 7.28–7.37 (3H, m, aryl H), 7.48 (2H, d *J*=7.7 Hz, aryl H), |7.90 (s, CHO|, 8.03 and 8.07 (each 1H, s, CHO); ^{13}C NMR (67.5 MHz) δ 19.9 (CH_2), |20.5 (CH_2)|, 30.3 (CH_2), |30.5 (CH_2)|, 31.1 (CH_2), |32.9 (CH_2)|, 36.5 (CH_2), 39.5 (CH_2), |42.9 (CH_2)|, |56.7 (CH)|, 56.8 (CH), 64.1 (CH_2), |64.2 (CH_2)|, 65.9 (spiro C), |70.1 (CH)|, 70.7 (CH), 128.3 (2×CH), 128.5 (CH), 129.2 (2×CH), |129.3 (CH)|, |138.5 (C)|, 138.7 (C), |160.8 (CHO)|, 160.9 (CHO), 161.3 (CHO), |161.4 (CH)|, |176.0 (lactam C=O)| and 176.1 (lactam C=O); MS *m/z* 345 (M^+, 7%), 300 (48), 299 ($M-HCO_2H$, 57), 286 ($M-CH_2OCHO$, 73), 198 (28), 152 (40), 121 (62), 106 (100), 103 (51), 91 (47) and 77 (34).

The mixture of diformates **14a**,**b** (178 mg) was added to potassium hydroxide (0.33 g) dissolved in water (3 mL) and ethanol (3 mL) and stirred at room temperature for 8 h. The solution was acidified by addition of dilute hydrochloric acid and extracted several times with chloroform. The combined organic extract was washed, dried ($MgSO_4$), and the solvent evaporated in vacuo. The crude product was a mixture of the spiro lactam diols **15a**,**b** (4:1 ratio from ^{13}C NMR spectrum). The first crop obtained after fractional crystallisation was diol **15a** (85 mg), mp 226–228 °C (from ethanol) (HREIMS found M^+ 289.1672. $C_{17}H_{23}NO_3$ requires *M* 289.1678. Found $M-CH_2O$ 259.1570. $C_{16}H_{21}NO_2$ requires 259.1572); ^{1}H NMR (270 MHz) ($CHCl_3$-*d*/MeOH-d_4) δ 1.06–1.96 (9H, m), 2.10 (1H, ddd, *J*=12.9, 8.9, 4.5 Hz), 2.40–2.60 (2H, m), 3.61–3.71 (1H, m), 3.91–4.00 (1H, m), 4.08 (2H, s, OH, exchanged with MeOH-d_4), 4.34–4.45 (2H, m) and 7.23–7.40 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 19.4 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 33.7 (CH_2), 35.5 (CH_2), 42.0 (CH_2), 59.6 (CH), 63.8 (CH_2), 66.6 (spiro C), 67.2 (CH), 127.0 (2×CH), 127.1 (CH), 128.2 (2×CH), 138.5 (C) and 176.9 (C=O); MS *m/z* 289 (M^+, <1%), 259 ($M-CH_2O$, 75), 258 ($M-CH_2OH$,73), 216 (13), 170 (36), 106 (100) and 91 (32). The sample of diol **15a** submitted to X-ray analysis was further recrystallised from hexane/ethyl acetate. The second crop of crystals (27 mg) from ethanol was relatively enriched in diol **15b**, which showed additional ^{13}C NMR signals δ 20.0 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 45.5 (CH_2), 59.5 (CH), 64.0 (CH_2), 66.6 (CH), 126.9 (CH), 138.3 (C) and 178.0 (C=O).

3.3.2. (α*R*,3*S*,spiro*R*)- and (α*R*,3*R*,spiro*S*)-3-Formyloxy-2′-(2-formyloxy-1-phenylethyl)-2′,3′-dihydrospiro[cyclohexane-1,1′-isoindol]-3′-ones 26a,b. Tricyclic oxylactam **20** (287 mg, 0.90 mmol) was dissolved in formic acid (10 mL) and stirred at room temperature for 32 h. After work up and chromatography, as above, a first fraction was obtained (93 mg, 32%) of viscous oil which was the 3-(pent-4-enylidene)isoindolin-1-one **23** admixed with other component(s) (HREIMS found M^+ 347.1516. $C_{22}H_{21}NO_3$ requires *M* 347.1521); ^{1}H NMR (270 MHz) δ 1.81–2.69 (4H, m, 2×CH_2), 4.77–5.45 (5H, m, 2×C=C*H* and PhC*H*CH_2O), 5.64–5.90 (2H, m, CH=CH_2), 7.28–7.94 (9H, m, aryl H) and 8.03 (1H, s, CHO); ^{13}C NMR (67.5 MHz) δ 26.5 (CH_2), 33.7 (CH_2), 53.5 (CH), 62.5 (CH_2), 113.4 (CH), 115.8 (CH_2), 123.4 (CH), 123.6 (CH), 126.9 (2×CH), 127.9 (CH), 128.7 (CH), 128.8 (2×CH), 132.2 (CH), 137.0 (C), 138.2 (C), 160.6 (CHO) and 167.2 (lactam C=O); MS *m/z* 347 (M^+, 47%), 306 ($M-C_3H_5$, 54), 293 (30), 288 (30), 249 (40), 236 (100), 234 (28),158 (82), 149 (32), 130 (33), 121 (66), 103 (66), 91 (42) and 77 (50). Additional weaker ^{13}C NMR signals attributable to the isomeric spiro enelactam **25**: δ 24.0 (CH_2), 30.6 (CH_2), 32.8 (CH_2), |53.4 (CH)|, 56.4 (CH), |61.7 (CH_2)|, 64.1 (CH_2), 64.7 (C), 122.6 (CH), 123.5 (CH), 125.2 (CH), 127.0 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.6 (CH), 129.7 (CH), 131.8 (CH), 133.9 (C), 134.2 (CH), 135.5 (C), 136.5 (C), 137.0 (CH), 138.0 (C), |138.4 (C)|, 150.3 (C), 160.3 (CHO), |160.9 (CHO)|, |168.1 (lactam C=O)| and 168.9 (lactam C=O).

Further elution afforded the spiro lactams **26a**,**b** (165 mg, 47%, 4:1 ratio) as a viscous oil (HREIMS found M^+ 393.1573. $C_{23}H_{23}NO_5$ requires *M* 393.1576); ^{1}H NMR (270 MHz) δ 1.35–2.33 (8H, m), 4.81–4.91 (2H, m), 5.40–5.56 (2H, m), 7.28–8.09 (9H, m, aryl H), 8.02, 8.05 |and 8.09| (each 1H, s, CHO); ^{13}C NMR (67.5 MHz) δ|18.5 (CH_2)|, 19.9 (CH_2)|, 30.2 (CH_2), |32.7 (CH_2)|, 32.8 (CH_2), |38.6 (CH_2)|, 38.7 (CH_2), |55.9 (CH)|, 56.0 (CH), 63.8 (CH_2), |64.0 (CH_2)|, |66.2 (spiro C)|, 67.0 (spiro C), |69.1 (CH)|, 69.2 (CH), 122.9 (CH), 124.1 (CH), 127.5 (CH), 127.6 (2×CH), 127.9 (CH), 128.4 (CH), 128.6 (2×CH), |130.9 (C)|, 131.1 (C), |131.5 (CH)|,131.7 (CH), |137.4 (C)|, 137.6 (C), 149.1 (C), |150.1 (C)|, |160.0 (CHO)|, 160.1 (CHO), 160.8 (CHO), |160.9 (CHO)|, 168.3 (lactam C=O) and |168.6 (lactam C=O)|; MS *m/z* 393 (M^+, 1%), 347 ($M-HCO_2H$, 36), 334 ($M-CH_2OCHO$, 100), 246 (22), 200 (12), 183 (42), 165 (21), 103 (25), 91 (27) and 77 (18).

3.3.3. (α*R*,3*S*,spiro*S*)- and (α*R*,3*R*,spiro*R*)-3-Chloro-1′-(2-hydroxy-1-phenylethyl)spiro [cyclohexane-1,2′-pyrrolidin]-5′-ones 11a,b. Bicyclic oxylactam **10** (0.19 g, 0.70 mmol) in 1,2-dichloroethane (10 mL) was added with stirring to a cold (−5 °C) solution of aluminium trichloride (0.28 g) in 1,2-dichloroethane (10 mL). Cooling and stirring were maintained for 4 h, after which the mixture was poured onto ice, acidified with dilute sulfuric acid, and extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution and with water, dried

($MgSO_4$), and the solvent evaporated in vacuo. The residue was chromatographed on silica, and products eluted with ethyl acetate/chloroform (1:1 v/v). The 6,5-spiro lactam **11a**,**b** was obtained as an oil (97 mg, 45%, ca 3:1 ratio), containing a small amount of the 5,5-spiro lactam **12**; ^{1}H NMR (270 MHz) δ 1.06–2.31 (10H, m), 2.48–2.57 (2H, m), 3.74 (1H, tt, J=11.4, 4.3 Hz, CHCl), 3.92–4.03 (1H, m, PhC*H*), 4.29–4.46 (2H, m, CH_2OH) overlapping 4.54 (1H, br s, OH), and 7.25–7.36 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 26.9 (CH_2), 29.3 (CH_2), |29.4 (CH_2)|, 29.7 (CH_2), 30.2 (CH_2), 31.0 (CH_2), |32.8 (CH_2)|, |33.1 (CH_2)|, 33.7 (CH_2), |57.1 (CHCl)|, 57.3 (CHCl), |60.0 (CH)|, 60.1 (CH), |64.8 (C)|, 65.1 (CH_2), |65.4 (C)|, 65.5 (CH_2), 127.1 (CH), 127.2 (2×CH), |127.3 (CH)|, 128.4 (2×CH), |128.5 (CH)|, |138.7 (C)|, 139.0 (C), 176.6 C=O) and |176.7 (C=O)|; MS m/z 307 (M^+, <1%), 279, 277 (M−CH_2O, 14, 43), 278, 276 (M−CH_2OH, 24, 56), 242 (33), 200 (18), 188 (29), 120 (16), 106 (100) and 91 (29). Additional, weaker ^{13}C NMR signals attributed to **12** δ 32.3, 32.5, 33.0, 35.8, 42.3, 43.2, 47.2, 55.1, 65.3, 77.2 (spiro C), 126.9, 127.4, 138.6 and 171.2 (C=O).

3.4. Crystallographic structure determinations

X-ray analysis of **15a** and **17a** was carried out on a Rigaku AFC6S four-circle diffractometer with graphite-monochromated Mo Kα radiation, λ=0.710.70 at 20 °C. The structures were solved by direct methods using SHELX-76 and refined on F^2 using SHELXL.

3.4.1. Crystal data for 15a.[13] $C_{17}H_{23}NO_3$, M=289.36 The crystal size was 0.50×0.50×0.40 mm; monoclinic, space group $C2$, with unit cell a=16.402(3), b=8.955(7), c=10.899 4(1) Å, β=103.51°, V=1556.7(12) Å^3, Z=4, D_c=1.269 g cm^{-1} 1521 reflections were collected in the range 5<2θ<50°, of which 1465 were independent (R_{int}=0.0170). Full matrix least squares refinement on F^2 with 192 parameters for 1465 reflections with I>2σI gave final values of R_1=0.0349 and wR_2=0.0892.

3.4.2. Crystal data for 17a.[13] $C_{20}H_{21}NO_3$, M=323.38 The crystal size was 0.30×0.10×0.05 mm; orthorhombic, space group $P2_12_12_1$, with unit cell a=25.502(6), b=8.1085(1), c=8.708(2) Å, V=1800.6(6) Å^3, Z=4, D_c=1.193 g cm^{-1} 2769 reflections were collected in the range 5<2θ<55°, of which 2343 were independent (R_{int}=0.0081). Full matrix least squares refinement on F^2 with 220 parameters for 2337 reflections with I>2σI gave final values of R_1=0.0318 and wR_2=0.0820.

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References and notes

1. Bahajaj, A. A.; Moore, M. H.; Vernon, J. M. *Tetrahedron* **2004**, *60*, 1235–1246.
2. (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569, and references therein. (b) Meyers, A. I. In *Stereocontrolled organic synthesis*; Trost, B. M., Ed.; Blackwell Scientific: Oxford, 1994; pp 145–161. (c) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1–8.
3. (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 1515. (b) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951.
4. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
5. Schoemaker, H. E.; Kruk, C.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, 2437.
6. Inoue, Y.; Tazawa, N.; Watanabe, A.; Aoki, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn* **1992**, *65*, 2866–2868.
7. Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507–3510.
8. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Intl Ed.* **2002**, *41*, 3017–3020.
9. Ito, T.; Yamazaki, N.; Kibayashi, C. *Synlett* **2001**, 1506–1509.
10. (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296. (b) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859. (c) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656–1662.
11. Lochead, A. W.; Proctor, G. R.; Caton, M. P. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2477.
12. Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3627–3630.
13. Crystallographic data for compounds **15a** and **17a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 213792 and 213791, respectively. 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).

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Corrigendum

Corrigendum to "Absolute structure, biosynthesis, and anti-microtubule activity of phomopsidin, isolated from a marine-derived fungus *Phomopsis* sp." [Tetrahedron 59 (2003) 455–459]☆

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In the 'Experimental', pages 458 and 459, section 3.3.1, the solvent of ^{1}H and ^{13}C NMR data for phomopsidin (**1**) was reported incorrectly as $CDCl_3$. The correct solvent is CD_3OD.

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