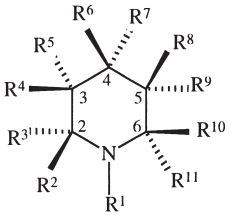
ELSEVIER

Tetrahedron

Tetrahedron Vol. 60, No. 8, 2004

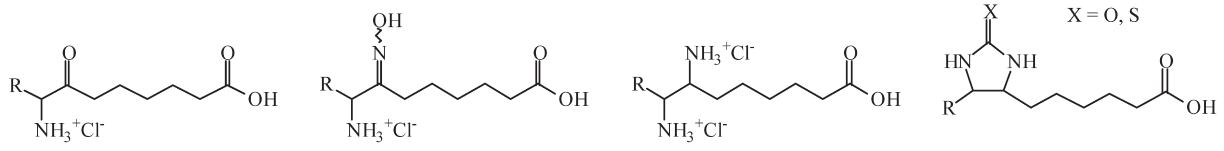
Contents

REPORT

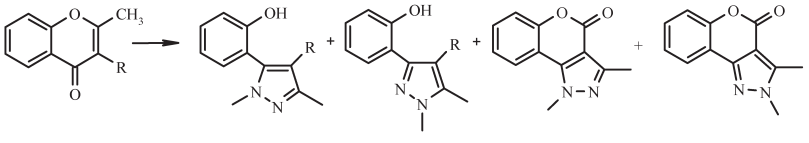


Piperidine scaffolds are widely present in natural products and are commonly used in medicinal chemistry. This report illustrates methods for the preparation of piperidines and in particular the synthesis of 3-, 4- and 5-multisubstituted piperidines.

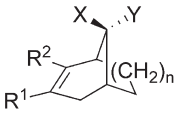
ARTICLES

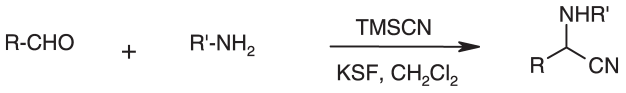


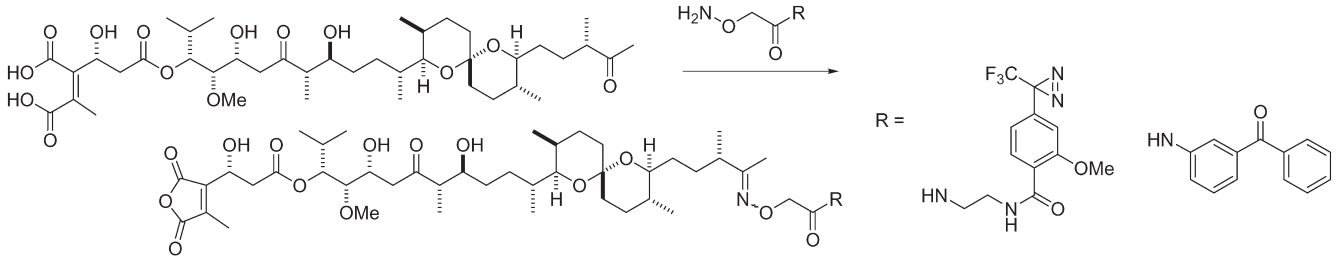
KAPA-derivatives DAPA-derivatives DTB-derivatives

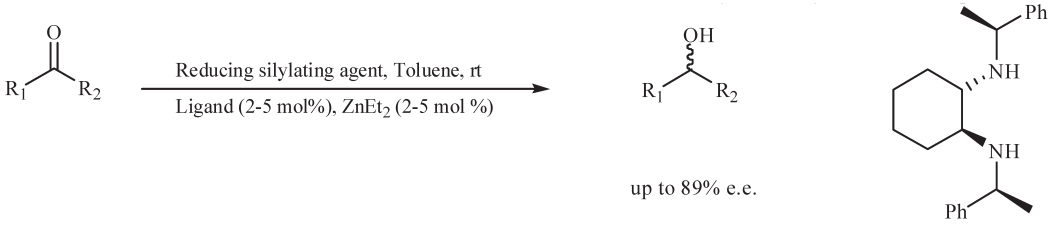


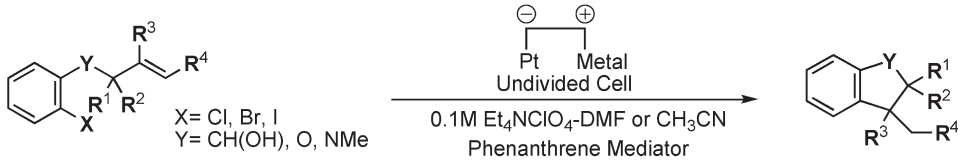
The 3-phosphonic- and 3-carboxylic-chromones react with *N*-methylhydrazine to give substituted pyrazoles, new ligands for formation of Pt(II) and Pd(II) complexes.

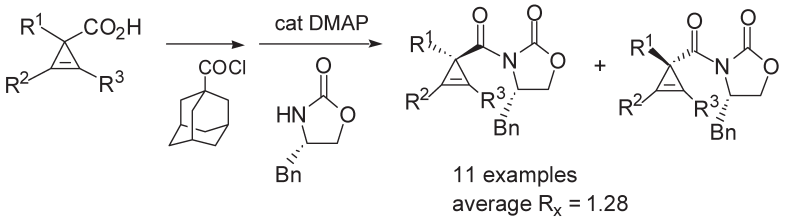


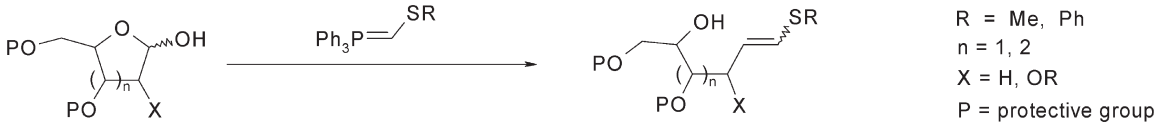


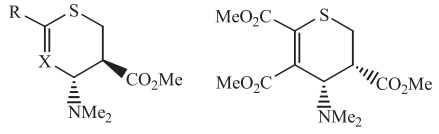






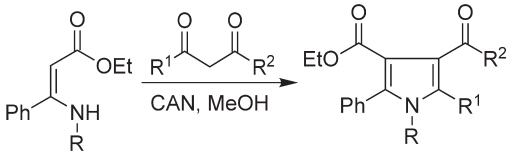


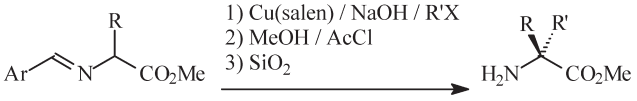




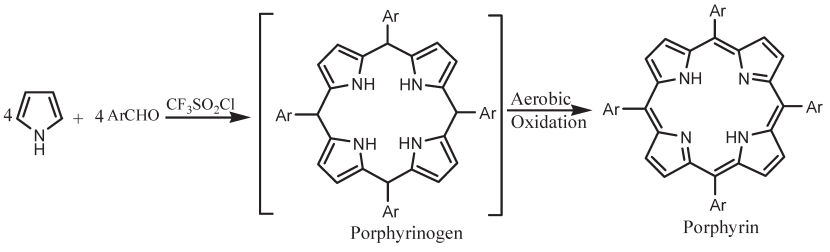
R= Ph, X=N; R=CO_2Me, X=C-CO_2Me.

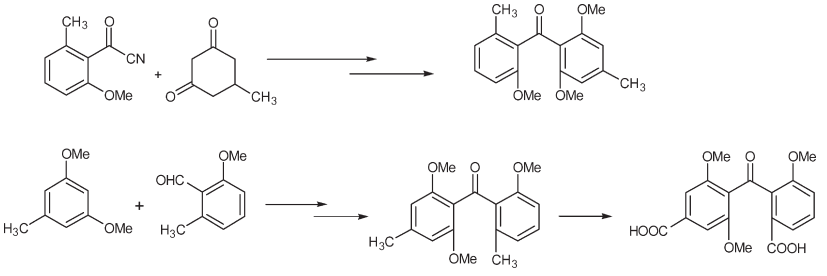
The above chiral non-racemic compounds were among the heterocycles prepared by means of a diastereoselective Diels–Alder reaction.



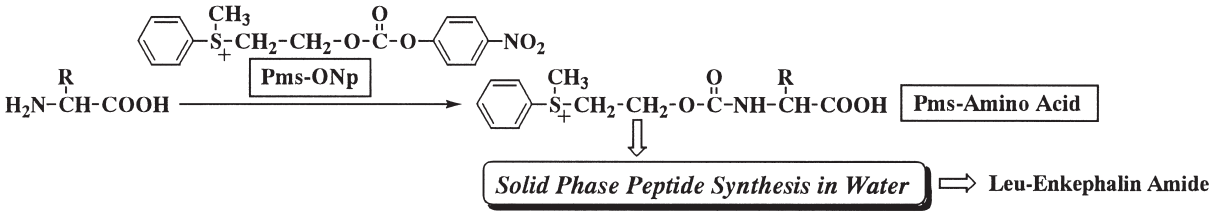


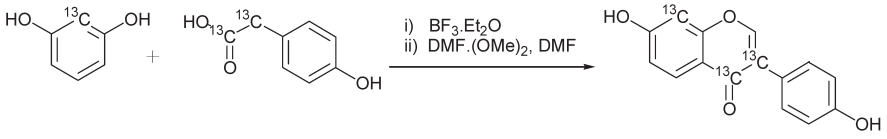
Ar = Ph, 4-ClC_6H_4
R = Et, CH_2CHMe_2, CH_2Ph, $CHMe_2$, Ph, $CH_2CH{=}CH_2$, $CH_2CH_2CO_2Me$, CH_2CO_2Me
R' = CH_2Ph, $CH_2CH{=}CH_2$, 4-$O_2NC_6H_4CH_2$, CH_2CCH, CH_2CCMe

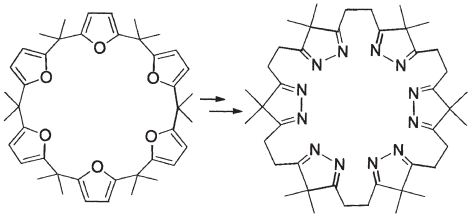


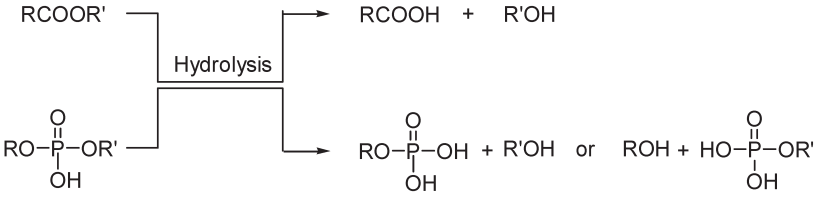


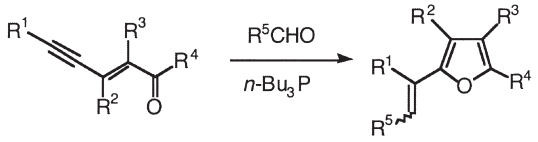
The benzophenone precursor for balanol has been synthesized by a short route.

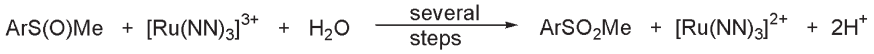


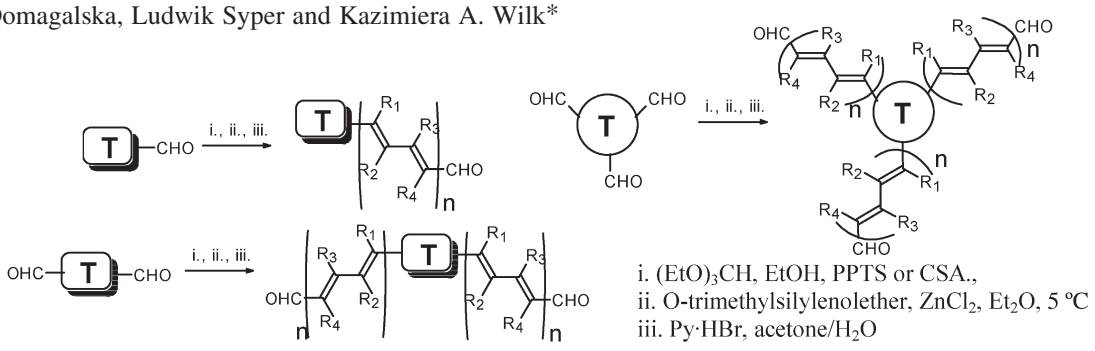


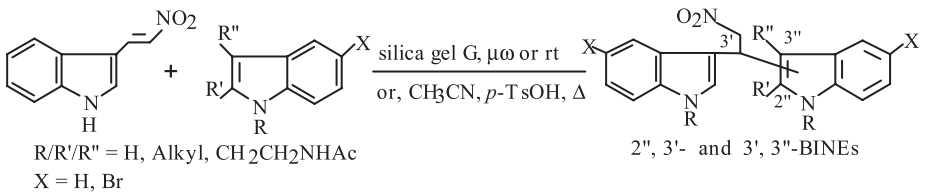












OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1701–1729
Tetrahedron

Tetrahedron report number 670

Synthesis of piperidines

Maxime G. P. Buffat*

Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Received 28 October 2003

Contents

Keywords: Piperidine; Anopterine; Morphine.

* E-mail address: maximebuffat@yahoo.fr

doi:10.1016/j.tet.2003.11.043

1. Introduction

Functionalised piperidines are among the most common building blocks in natural products, and, more interestingly, in many biologically active compounds such as anopterine, pergoline, scopolamine and morphine (Fig. 1). The syntheses of these types of compounds have been studied extensively as the development of new drugs containing six-membered ring heterocycles becomes more and more common.

Previous syntheses of piperidines have been focused on the diastereoselectivity in the formation of 2,6-piperidines. In order that these compounds could be used as drugs, it was necessary to investigate their stereoselective syntheses. Detailed reviews on the syntheses of 2,6-piperidines can be found in the literature.[1,2]

A new aim in the synthesis of piperidines is to make multisubstituted piperidines. The formation of 3-, 4- and/or 5-substituted piperidines and simple piperidines containing quaternary carbon centres is the next challenge. The first step in this long process is to extend the diastereoselective synthesis to tri- or multisubstituted piperidines, followed by the development of new methodology to synthesise them stereoselectively.

This report will try to give a general overview of the synthetic methodology available for the diastereoselective and stereoselective formation of piperidines. The synthesis of 3-, 4- and/or 5-substituted piperidines, as well as the formation of piperidines containing quaternary carbons, will be mainly examined. Their synthesis via cycloaddition is the most common and more reliable method. This strategy is often used as the final step after the construction of a linear chain containing all the functionality of the final compound. The reduction of pyridines is another method usually used in the synthesis of piperidines. This approach becomes limited, however, when a quaternary carbon is present in the piperidine ring. The syntheses of piperidines using rearrangements and ring expansions has also been studied, but this strategy is a less common method and is more often used in particular cases than as a general method.

2. Heterocycle construction

The construction of heterocycles via cycloaddition is

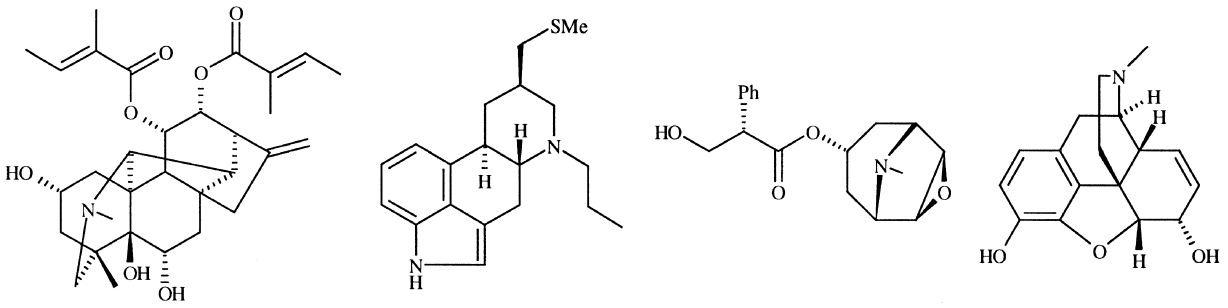
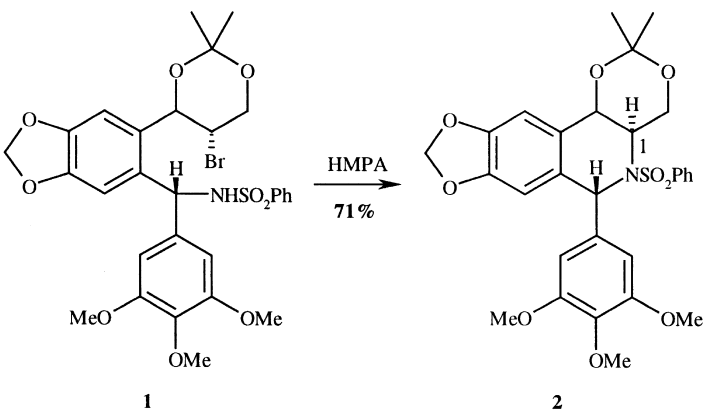
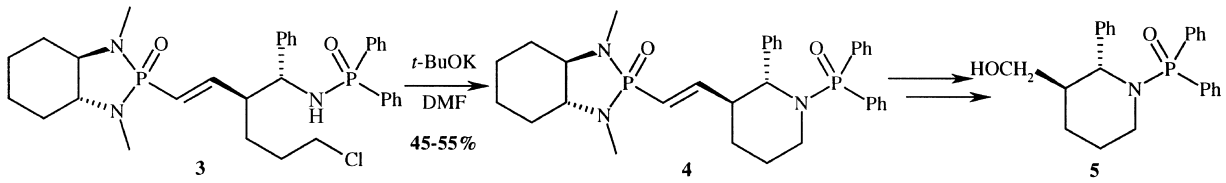


Figure 1.



Scheme 1.



Scheme 2.

probably the most widely used strategy to form piperidines. This approach is diverse and includes simple nucleophilic substitutions, reductive amination, metathesis, aldol reactions, Dieckmann condensations and ene reactions.

2.1. Nucleophilic substitution

2.1.1. Reaction of amines with halides. Nucleophilic substitution is a reliable method of making piperidines and relies on the synthesis of a linear chain which already contains the desired substitution pattern. It is often used as the final step, followed by deprotection of the functional groups, if necessary. Compernolle et al.[3] realised the displacement of a 6-bromide group by a 2-amino group as the main strategy in the formation of polyhydroxylated piperidines using Et_3N as the base. Stronger bases such as sodium hydride can be used for this type of ring closure. Nevertheless, it can be a problem when a tertiary bromide such as **1** is cyclised (Scheme 1). In the synthesis of analogues of podophyllotoxin, Pearce and co-workers[4] observed the formation of two stereoisomers at C-1 when sodium hydride was used as the base. The use of 2 equiv. of HMPA resulted in a longer reaction time, but only the desired stereoisomer **2** was produced in 71% yield.

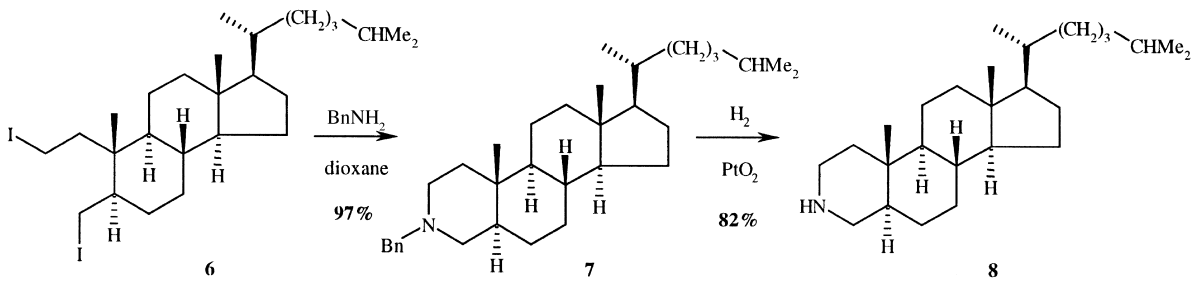
The chloride **3** has been used by Hanessian et al.[5] in the synthesis of enantiomerically pure 2,3-piperidines (Scheme 2). Ring-closure using *tert*-BuOK as the base afforded the piperidine **4** in 45–55% yield. Despite the modest yield, the formation of enantiomerically pure 2,3-piperidines is overall quite effective. Oxidative cleavage, followed by reduction, afforded the target compound **5** in 62% yield.

Cyclisation can also be achieved from a cyano-chloride or -bromide. When Fustero and co-workers[6] added an azaenolate to a cyano-chloride, the resulting iminium anion intermediate cyclised to the corresponding piperidine. Substitution in position 2 and cyclisation occurred in a one-pot procedure.

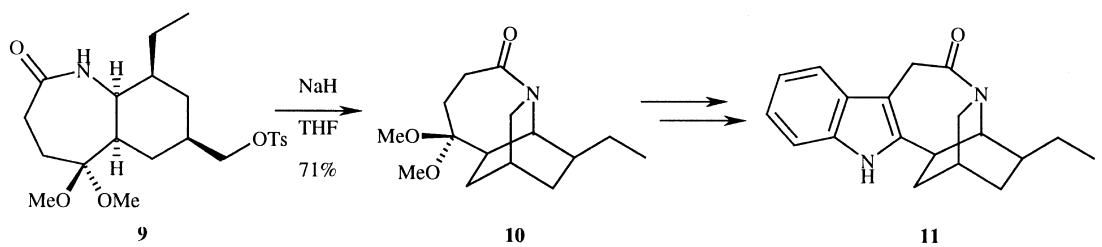
Suginome et al.[7] synthesised 3-aza-5α-cholestane **8** using a bi-molecular reaction rather than an intramolecular cyclisation (Scheme 3). The reaction of benzylamine with the diiodo compound **6** in dioxane afforded the desired piperidine **7** in 97% yield. Deprotection of the amine gave the desired product **8**. The reaction conditions are quite harsh and often require reflux overnight and a large excess of amine. When volatile amines, such as isopropylamine, are used, the reactions are less effective (52% when coupled with **6**) and need to be carried out in a sealed test tube. Mellor and co-workers[8] observed similar yields when starting from a dibromo compound.

The main difficulty of this type of cyclisation compared to the intramolecular nucleophilic substitution is the choice of the correct concentration of reagents. A too dilute reaction mixture gives a slow reaction and, if the reaction mixture is too concentrated or the intramolecular nucleophilic substitution is too slow, polymerisation can occur.

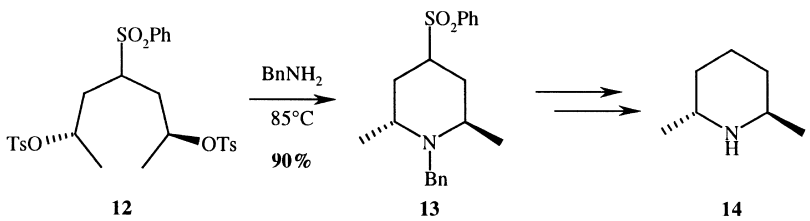
2.1.2. Reaction of amines with acetates and mesylates. Rather than achieving a 6-halogeno displacement by a 2-amino group, it is more common to form a good leaving group such as an acetate[9] or a mesylate from a hydroxy group. Most commonly, mesylates or tosylates are used as



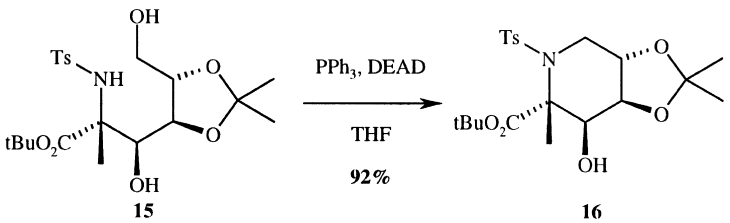
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

the leaving groups to form piperidines via intramolecular cycloaddition. In the synthesis of (−)-ibogamine **11**, White et al.[10] cyclised the amino-tosylate **9** to give the target compound **10** in 71% yield (Scheme 4).

Tertiary mesylates or triflates can also be used and the piperidines are formed with inversion of configuration. Fleet and co-workers[11] demonstrated that polyhydroxy-piperidines can be synthesised from amino-triflates in good yield using sodium acetate in a protic solvent such as ethanol. Holzapfel et al.[12] worked on similar compounds and showed that cyclisation can occur in aprotic solvents without base (e.g., THF, reflux).

Reaction of bis-tosylates with primary amines is also known in the literature and is more common from bis-mesylates/tosylates than halogens. Kurth and co-workers[13] cyclised the bis-tosylate **12** using an excess of benzylamine at 85 °C (Scheme 5). The reaction occurred in 90% yield and gave only the *anti* piperidine **13**.

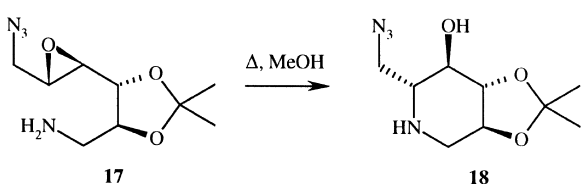
Cyclisation with tosylamine is also known in the literature,[14] but is less common due to its lower reactivity. Finally, coupling with ammonia is possible, but a high pressure is required, as demonstrated by Quallich et al.[15] Reaction with ammonia avoids further steps, such as deprotection, when preparing secondary amines.

2.1.3. Reaction of amines with alcohols. Cyclisation to piperidines can be achieved directly from alcohols. Although, this reaction is less commonly used, it can give very good yields and avoids extra steps such as the formation of halide or mesylate. Kazmaier and co-workers[16] cyclised the *N*-tosylamino alcohol **15** to the desired amine **16** in 92% yield under Mitsunobu conditions (PPh_3, DEAD, THF), (Scheme 6). Cyclisation of the secondary alcohol to give an aziridine did not occur and the desired piperidine **16** was formed as the only reaction product.

When a primary alcohol and an acetate group are present in the same molecule, cyclisation under Mitsunobu conditions only affords the desired piperidine.

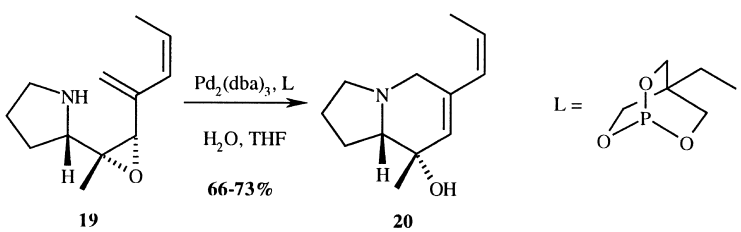
The synthesis of β-lactams using this strategy is more difficult. Ikegami et al.[17] have found that, under Mitsunobu reaction conditions, O-alkylation occurred, rather than N-alkylation.

2.1.4. Reaction of amines with three-membered rings. A very efficient method of forming 3-hydroxypiperidines involves epoxide-opening and subsequent cyclisation. Compernolle and co-workers[18] have used this strategy to prepare the polyhydroxy-piperidine intermediate **18** by refluxing a solution of the primary amino-epoxide **17** in methanol (Scheme 7).

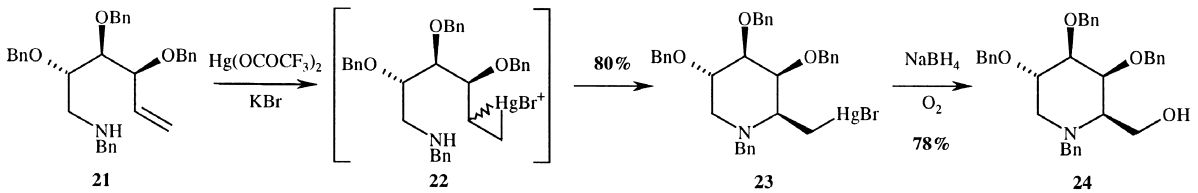


Scheme 7.

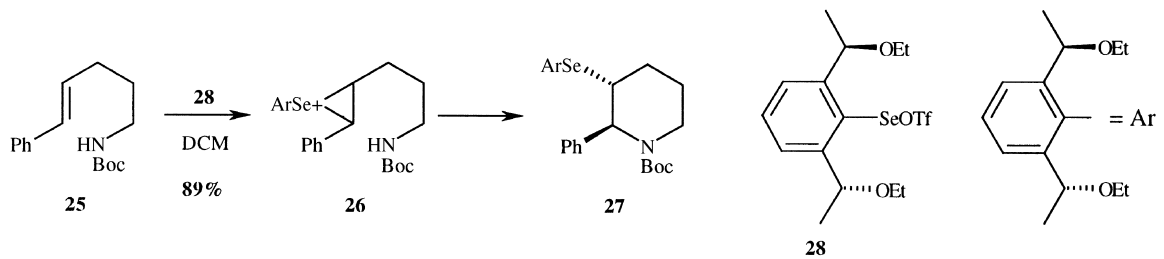
In an approach to catharanthine, Trost et al.[19] used the



Scheme 8.



Scheme 9.



Scheme 10.

formation of a π-allylpalladium intermediate derived from an amino-epoxide. This strategy became more interesting when Trost et al.[20] cyclised the amino-epoxide **19** via a palladium-catalysed reaction equivalent to a '1,4 addition' to the vinyl epoxide **19** (Scheme 8). After optimisation of the palladium catalyst, Trost's group synthesised the indolizidine **20** in 66–73% yield.

D'Angelo and co-workers[21] converted an azido-epoxide to a hydroxypiperidine via a one-step reduction and cyclisation using a Staudinger reduction reaction (PPh_3, THF). Although amines protected with electron-withdrawing groups are less reactive, they can be cyclised under basic conditions.[22] Less commonly, the cyclisation of a bis-aziridine or amino-aziridine can be achieved, this strategy mimicking carbohydrate synthesis.[23]

In a synthesis of aza-analogues of D-galacturonic acid, Ganem et al.[24] used oxymercuration followed by reductive oxygenation of the mercuric salt, to form the 2-hydroxymethylpiperidine **24** (Scheme 9). Treatment of the amino-alkene **21** with mercuric trifluoroacetate and KBr gave the mercuric cation **22**, which immediately cyclised to the piperidine **23** in 80% yield. Reduction of the resulting mercuric intermediate with $NaBH_4$ and O_2 afforded **24** as a single diastereoisomer in 78% yield. Although oxymercuration is a reliable synthetic tool, it is not commonly used, because of its toxicity.

Among the few asymmetric syntheses of piperidines, the method developed by Déziel and co-workers[25] is useful (Scheme 10). The aminoalkene **25** was cyclised in the presence of the chiral arylselenium triflate **28** to give the diastereomerically pure piperidine **27** in 89% yield and 92% ee. The reaction proceeds via an arylselenium cationic intermediate **26**. The resulting selenide can then be reduced, using Ph_3SnH and AIBN, in good yield.

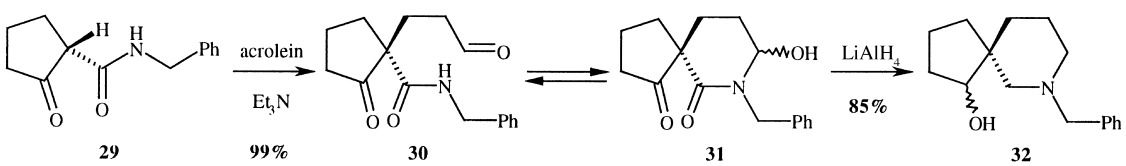
2.2. Reductive amination

One of the most common methods for the synthesis of piperidines, if not the mostly widely used, is reductive amination. Indeed, piperidines can be synthesised from 1,5-amino-aldehydes in a one-pot procedure in the case of secondary amines or a two-pot procedure for primary amines. The two-step process involves the formation of an imine intermediate, followed by its reduction.

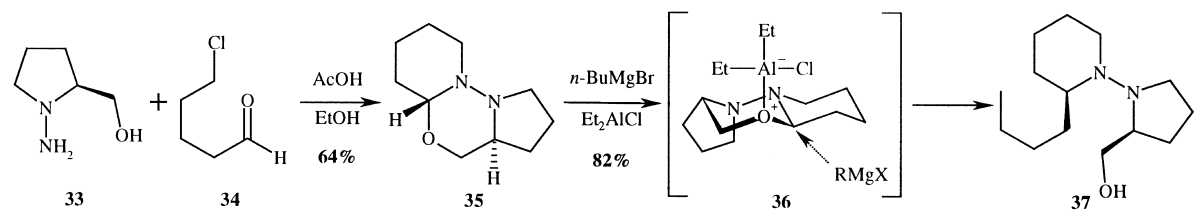
2.2.1. Intramolecular reductive amination. Primary and secondary amino-aldehydes are not highly stable. In most cases, storage leads to mixture of aminals resulting from intramolecular addition of the amine to the formyl function. Reduction of this mixture can afford the secondary amine. Urban et al.[26] achieved the conjugate addition of the β-keto-amide **29** with acrolein to afford the desired aldehyde **30** in 99% yield (Scheme 11). These workers found, however, that complete conversion of **30** to a mixture of aminals **31** occurred on storage over several hours. Reduction of the amino-aldehyde **30** or the aminals **31** with $LiAlH_4$ resulted in a reductive cyclisation, yielding the racemic alcohol **32**.

Other reducing agents such as $NaCNBH_3$ can be used to reduce the aminal or the imine.[27] Moreover, reductive amination can occur during reductive deprotection of tertiary amines.[28]

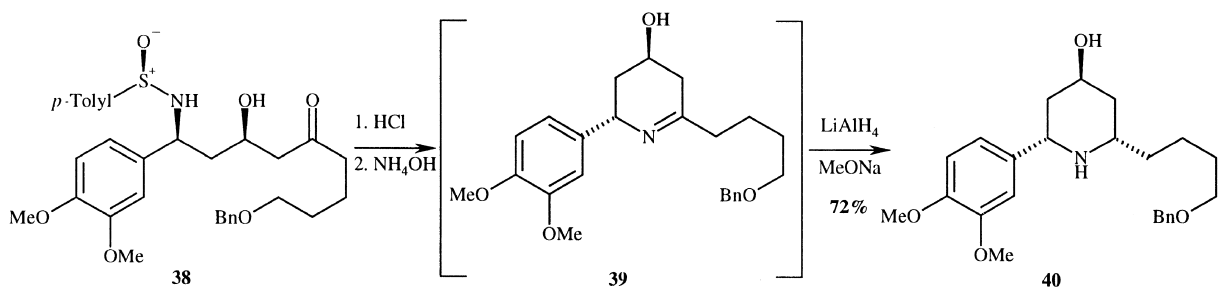
If the imine or an equivalent intermediate can be formed and isolated, addition of organometallics to the 2,3,4,5-tetra-hydropyridine can be completed. Among the enantioselective syntheses of piperidines, the methodology developed by



Scheme 11.



Scheme 12.



Scheme 13.

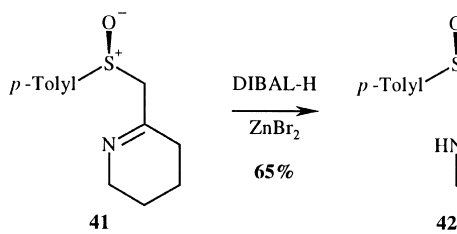
Kibayashi and co-workers[29] is probably the most efficient to synthesise 2-substituted piperidines enantioselectively. When (2*S*)-1-amino-2-pyrrolidinemethanol **33** was refluxed with 5-chloropentanal **34** in acetic acid and ethanol, 1,3,4-oxadiazinane **35** was formed as a single diastereoisomer (Scheme 12). In the presence of a Lewis acid such as Et_2AlCl, **35** exists as the oxonium salt **36**. At low temperature (−80 to −90 °C), the addition of Grignard reagents can occur with good diastereoselectivity (64–98% de). The reaction is believed to occur via an S_N2 process, explaining the good diastereoselectivity and the inversion of configuration at C-2. Using this methodology, **37** was obtained in 82% yield and 98% de. Reductive N–N bond cleavage can easily be achieved using borane in THF, yielding (+)-coniine in 64% yield.

Reductive amination can also be performed with amino-ketones. The usual reduction of the imine intermediate should give a mixture of diastereoisomers. This strategy therefore needs to be complemented with a stereoselective reduction of the imine or needs to be controlled by the formation of the most stable piperidine. This method is very common for preparing *syn* 2,6-piperidines, as the reduction of the 2,6-dialkyl-2,3,4,5-tetrahydropyridine gives the *syn* product. When Davis et al.[30] deprotected the sulphinamide **38**, followed by direct reduction of the imine intermediate **39** with $LiAlH_4$/MeONa, the desired *syn* 2,6-piperidine **40** was obtained in 72% yield (Scheme 13).

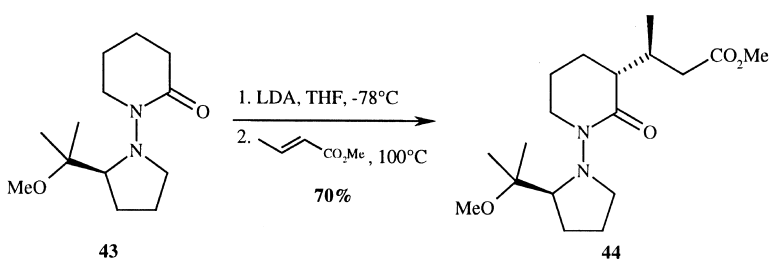
If the diastereoselectivity of the reduction is not satisfactory, a chiral sulphoxide can be used. Ruano et al.[31] developed a stereoselective reduction of α-sulphinyl imines and this methodology can be applied to the synthesis of chiral piperidines. The α-sulphinyl 2,3,4,5-tetrahydropyridine **41** was selectively reduced to the piperidine **42** (65% yield) using DIBAL-H in the presence of $ZnBr_2$ (Scheme 14).

1,5-Amino-esters or acids can be isolated, but undergo rapid cyclisation to lactams under acidic conditions. This can be a good method for forming piperidinones.[32] Moreover, cyclisation can occur when primary or secondary amino-esters are formed. Indeed, reductive hydrogenation of a nitroester by Sas and co-workers[33] afforded the corresponding cyclised piperidinone.

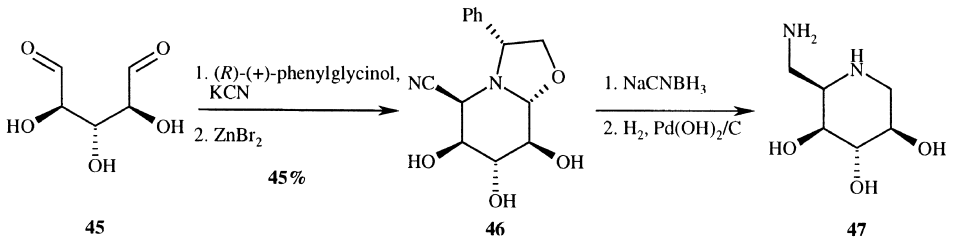
Piperidinones can also be synthesised from an amino-cyanide under acidic conditions. The main problem with this type of cyclisation is the vigorous conditions required that do not tolerate many protecting groups. A saturated solution of HCl in MeOH/H_2O (99:1) was required by



Scheme 14.



Scheme 15.



Scheme 16.

Gmeiner et al.[34] to be able to afford the desired piperidinone in their synthesis of dopamine D_2 receptor agonists.

The advantage of piperidinones is the possibility of functionalisation α to the carbonyl using standard chemistry. Horenstein and co-workers[35] and Yu et al.[36] have used this strategy to synthesise 3,4-di- and 3,4,5-trisubstituted piperidines. Enders and co-workers[37] have been working on the stereoselective synthesis of 3-substituted piperidin-2-ones using a chiral pool strategy. Treatment of the chiral piperidinone **43** with LDA, followed by a Michael electrophile, but-3-enoic acid methyl ester, afforded the piperidinone **44** in 70% yield and 96% ee (Scheme 15).

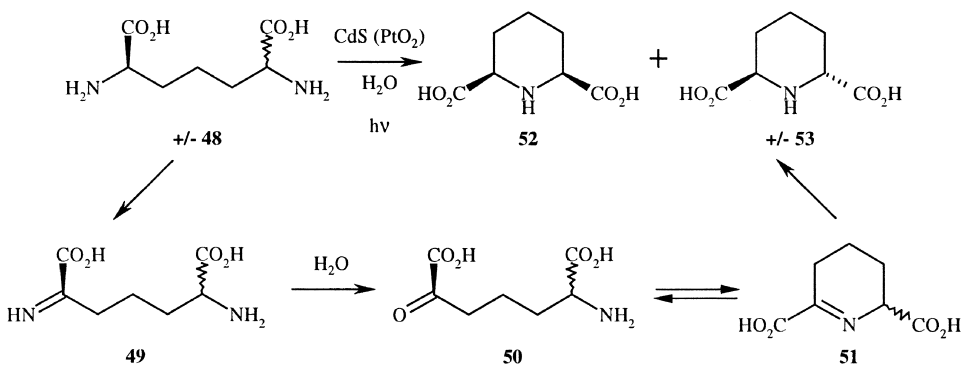
If piperidines are required, piperidinones can be reduced to the desired piperidines with $LiAlH_4$,[38] but problems can be encountered and milder conditions must then be used. In their synthesis of strychnine, Magnus and co-workers[39] reduced a piperidinone in the presence of an ester and an acetal-protected ketone using borane. Nagase et al.[40] reduced a piperidinone to the corresponding enamine using DIBAL-H and treatment with $NaCNBH_3$ afforded the desired piperidine in good yield.

2.2.2. Intermolecular reductive amination. Intermolecular reductive amination can be very useful in the stereoselective synthesis of 3,4,5-trisubstituted piperidines. Husson and co-workers[41] prepared the dialdehyde **45** from the commercially available isopropylidene-α-D-glucofuranose in two steps (Scheme 16). Reaction with (*R*)-(+)-phenylglycinol in the presence of KCN, followed by treatment with $ZnBr_2$, afforded the piperidine **46** in 45% yield. The chirality at the C-2 stereogenic centre is the result of a 1,3-transfer of chirality from the phenyl substituent involving the addition of CN^- from the upper face of the piperidinium chair transition state. Reductive cleavage of the chiral pool component using $NaCNBH_3$ or alane (AlH_3), followed by catalytic hydrogenation with $Pd(OH)_2/C$, afforded the piperidine **47**.[42]

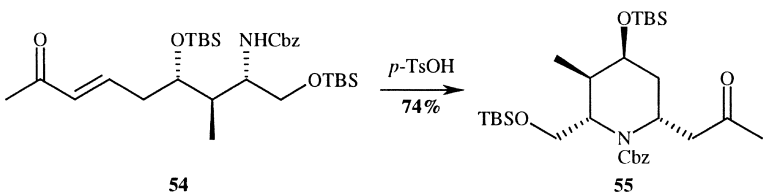
Martin et al.[43] have employed a double reductive amination of a bis-ketone to synthesise piperidines. Reduction of the imine intermediate took place with high diastereoselectivity. The selectivity of the reduction is generally controlled by the formation of the most stable piperidine.

2.2.3. Reaction of bis-amines. Ohtani and co-workers[44] have shown that diamines can undergo photocatalytic deaminocyclisation in a very effective manner. The *syn* or *anti* 2,6-dicarboxylic acid piperidines **52** and **53** can be synthesised from 2,6-diaminopimelic acid (DAP) **48** (1:1:2: (*S*,*R*)/(*R*,*S*)/*meso*). Although photocatalytic deamination with TiO_2 gave the *syn* piperidine **52** as well as a racemic mixture of pipecolinic acid (piperidine-2-carboxylic acid), a negligible amount of the *anti* piperidine **53** was observed (Scheme 17). On the other hand, when CdS (cadmium(II) sulphide) was used in aqueous media, the formation of the *syn* piperidine **52** or the racemic *anti* piperidine **53** could be achieved. When CdS was pre-heated to 300 °C, the racemic *anti* piperidine **53** was mainly formed in 39% yield, along with 48% recovery of the *meso* starting material. When PtO_2-loaded CdS was pre-heated to 300 °C, the *syn* piperidine **52** was mainly formed in 33% yield, with 50% recovery of the *meso* starting material. Although the yields of the *syn* piperidine **52** and the *anti* piperidine **53** were quite low, this was a major improvement, as they are very difficult intermediates to synthesise diastereoselectively. Moreover, they are common intermediates in many syntheses of 2,6-piperidines.

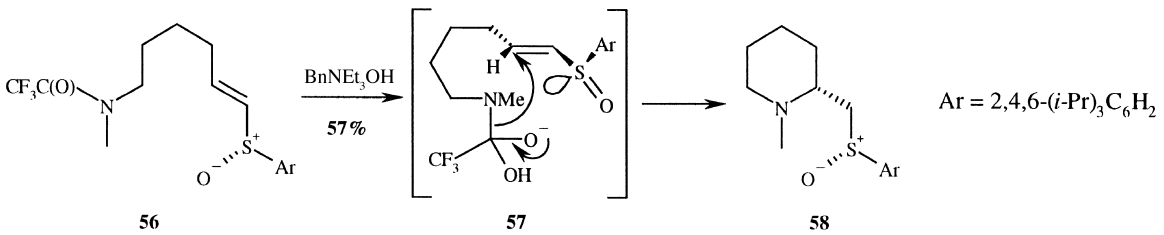
Piperidines can also be synthesised from dicyanide precursors. This method involves reflux under very acidic conditions (H_2SO_4, AcOH) and is therefore only used in the synthesis of very simple piperidines.[45] Moreover, this



Scheme 17.



Scheme 18.



Scheme 19.

method is easy to carry out as the byproduct formed, $(NH_4)_2SO_4$, is simply removed by filtration.

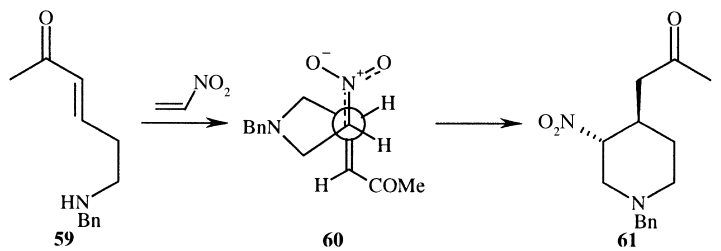
2.3. Reaction of amines with alkenes and alkynes

2.3.1. Intramolecular Michael addition. Michael addition plays an important role in the synthesis of piperidines. Control of the dia- or stereoselectivity is the main difficulty in this type of cyclisation. Armstrong et al.,[46] in their approach towards the synthesis of cylindrospermopsin, synthesised the primary piperidine intermediate **55** via a Michael addition reaction (Scheme 18). Treatment of the compound **54** with a catalytic amount of *p*-TsOH in refluxing benzene gave the most stable N-Cbz-protected piperidine **55**, as a single diastereoisomer in 74% yield.

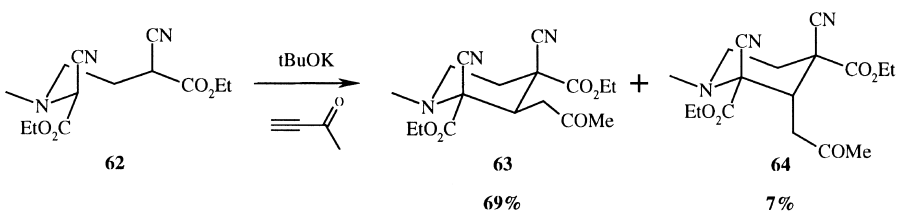
Chiral vinylsulphoxides can also be used in the synthesis of 2-alkylpiperidines. The reaction proceeds via a Michael-type attack of the amine on the vinylsulphoxide. Deprotection of the amino-vinylsulphoxide **56** by Pyne and co-workers[47] under basic conditions using $BnNEt_3OH$ afforded the piperidine **58** in 57% yield (Scheme 19). Only 4% of the undesired diastereoisomer was isolated. The reaction is believed to proceed via the intermediate **57**, where the lone pair of the sulphoxide and the C=C double bond are *syn* coplanar. Attack of the amine occurs on the less hindered face, to afford the desired piperidine **58**.

A one-pot convergent synthesis of 3,4-aminoalkylpiperidines has been developed by Barco et al.[48] The reaction involved an intermolecular addition of a nitrogen nucleophile to an electrophilic olefin, followed by intramolecular trapping of the generated enolate by a built-in α,β-unsaturated acceptor. Indeed, the reaction of the 3-amino-α,β-unsaturated ketone **59** with nitroethylene (generated in situ from 1-benzoyloxynitroethane) afforded the *anti* piperidine **61** in good yield (Scheme 20). The diastereoselectivity of the reaction can be explained via the transition state **60** with an antiperiplanar orientation between the nitro group and the acceptor chain.

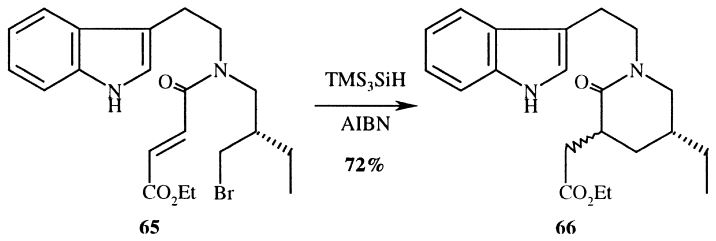
Grossman and co-workers[49] utilised the same type of double Michael addition to synthesise complex functionalised piperidines. Amines of the type **62**, underwent a double Michael addition with 3-butyn-2-one (Scheme 21) in the presence of *tert*-BuOK in DCM, to afford the desired



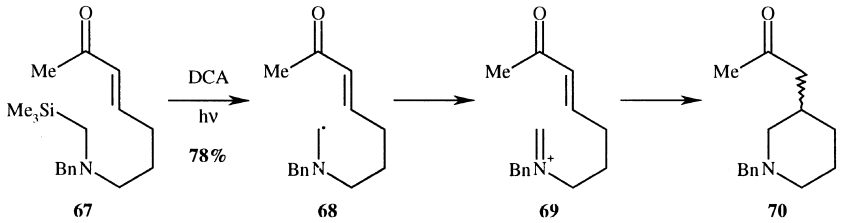
Scheme 20.



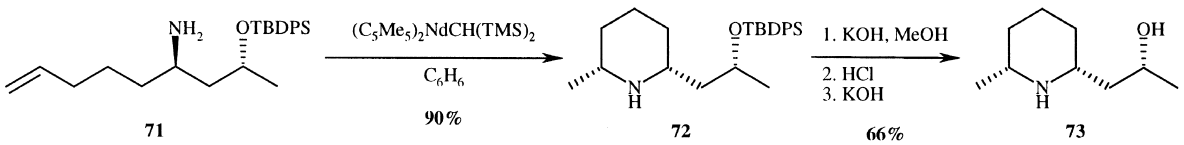
Scheme 21.



Scheme 22.



Scheme 23.



Scheme 24.

piperidine **63** in 69% yield as a single diastereoisomer. Only 7% of the C-3 axial diastereoisomer **64** was obtained. The reaction generally proceeds in relatively good yields and diastereoselectivities, but also gives the 2,3,4-trisubstituted piperidines, which can be easily functionalised to more complex compounds.

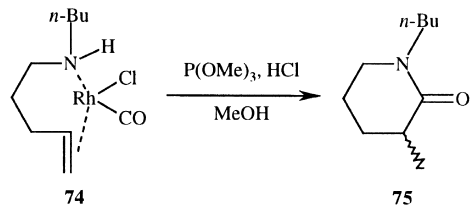
2.3.2. Radical 1,4 reaction of amines with alkenes. 1,4-Radical cyclisation can also be applied to the synthesis of piperidines or piperidinones. In their synthesis of tacamonine, Fukumoto et al.[50] cyclised bromo-vinyl ester **65** to afford the piperidinone **66** in 72% yield as a diastereoisomeric mixture (Scheme 22). With the racemic precursor **65**, the use of TMS_3SiH in the presence of AIBN gave better results than Bu_3SnH. In the same model study, the corresponding iodo-vinyl ester gave a lower yield of the desired piperidine **66**.

The oxidation of silylamino-enones has been studied by Mariano et al.[51] Treatment of the silylamino-enone **67** with 9,10-dicyanoanthracene (DCA) under photosensitisation afforded the piperidine **70** in 78% yield (Scheme 23). The silylamino-enone is believed to first undergo oxidative desilylation, affording the amino radical **68**, followed by oxidative formation of the iminium cation **69**. Cyclisation then occurred, to afford the desired piperidine **70**. This methodology has been extended to the radical cyclisation of bis-silanes. When metal oxidants, such as Ce^{4+} ($nBu_4NCe(NO_3)_6$), were used, better yields were obtained.

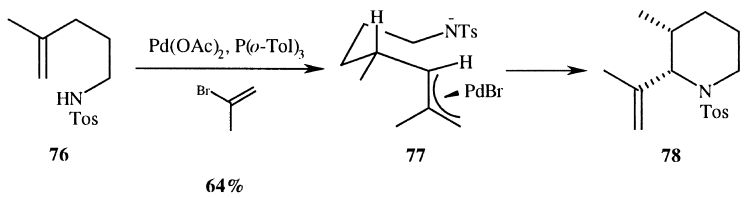
2.3.3. Hydroamination. A diastereoselective lanthanocene-catalysed intramolecular hydroamination has been developed by Molander and co-workers.[52] This methodology is an important procedure for the synthesis of *syn* 2,6-piperidines in high enantiomeric excesses. The aminoalkene **71** was synthesised in a few steps from commercially available reactants (Scheme 24) and was cyclised in 90% yield in the presence of $(C_5Me_5)_2NdCH(TMS)_2$ (9 mol%), to give the piperidine **72**. The presence of bulky ligands and the large size of the metal are believed to be the key factors in determining the diastereoselectivity of the reaction. Deprotection of the alcohol afforded (−)-pinidinol **73** in 66% yield and 99.9% ee.

Yamamoto et al.[53] developed a similar chemistry using $[(\eta^3\text{-}C_3H_5)PdCl]_2$ with 1,1′-bis(diphenylphosphino)ferrocene (dppf), which has been proven to be the best catalyst for the intramolecular hydroamination of allenic alkenes. The desired *syn* 2,6-alkylvinylpiperidine was obtained in modest yield and in up to 90% de.

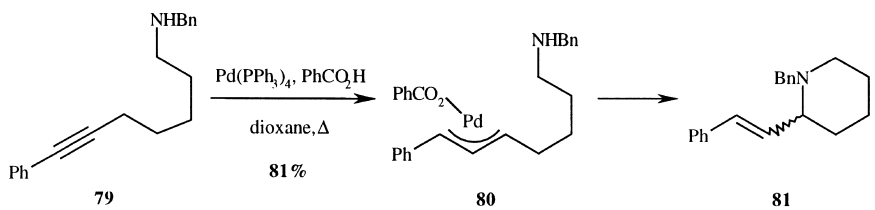
Krafft and co-workers[54] have studied the hydrocarboxylation of aminoalkenes using rhodium. The rhodium complex **74** was synthesised from the corresponding amine and $[(CO)_2RhCl]_2$. Treatment of this complex with an ethereal solution of anhydrous HCl, trimethyl phosphite and MeOH afforded the piperidine **75** in 80% yield (Scheme 25).



Scheme 25.



Scheme 26.



Scheme 27.

Although this methodology is interesting, its applications to the synthesis of complex piperidines are limited, due to the harsh conditions.

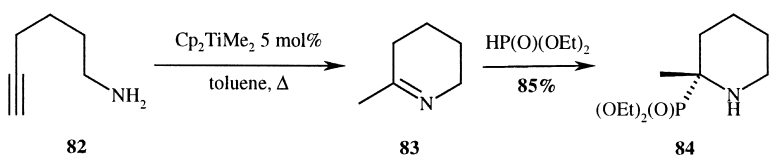
In an investigation by Zang et al.,[55] amino-alkenes in the presence of CO, H_2 and a catalytic amount of $HRh(CO)(PPh_3)_3$, were found to undergo cyclisation to the desired piperidin-2-one, which was reduced in situ to the corresponding piperidine. These conditions are more compatible with the presence of protecting groups, but more studies are required, in order to describe this strategy as a reliable tactic for preparing piperidines.

Larock, Weinreb and co-workers[56] synthesised *syn* 2,3-vinyl-alkylpiperidines via a palladium-catalysed coupling of vinyl bromides and olefinic sulphonamides. Indeed, treatment of the aminoalkene **76** and 2-bromopropene with $Pd(OAc)_2$ (5 mol%) and P(*o*-Tol)$_3$ (10 mol%), afforded the *syn* 2,3-piperidine **78** in 64% yield as a single stereoisomer (Scheme 26). The reaction is believed to occur via the intermediate **77**, in which the π-allylpalladium complex adopts a pseudoaxial position in order to avoid developing a strain in the transition state for ring closure.

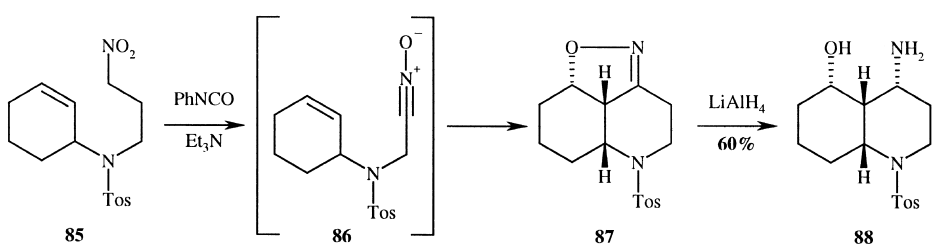
Yamamoto[57] also performed the hydroamination of amino-alkynes with $Pd(PPh_3)_4$ (5 mol%) in the presence of benzoic acid (10 mol%). The first step in the catalytic process is believed to be hydropalladation leading to a vinylpalladium species which undergoes β-elimination, to afford the corresponding allene. Hydropalladation of the intermediate affords the corresponding π-allylpalladium complex of the type **80** (Scheme 27). For the cyclisation of amino-alkynes, such as **79**, to produce analogues of **81**, the nitrogen must be electron rich. Indeed, in the case of a tosyl-protected amine, β-elimination of the π-allylpalladium complex occurred, affording the corresponding aminodiene.

Doye et al.[58] demonstrated that α-phosphate-substituted piperidines could be synthesised using a titanium complex as a catalyst. The aminoalkyne **82** underwent cyclisation in the presence of Cp_2TiMe_2 (5 mol%) in refluxing toluene (Scheme 28). Treatment of the imine intermediate **83** with $HP(O)(OEt)_2$ under acidic conditions (5 mol% Me_2AlCl) afforded the desired piperidine **84** in 85% overall yield.

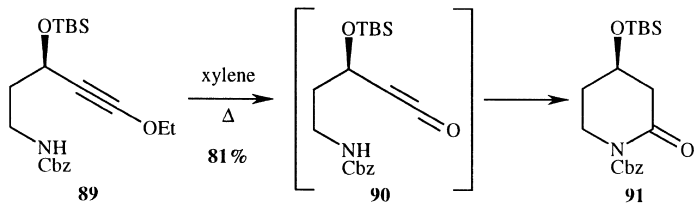
2.3.4. Other reactions of amines with alkenes. Hassner and co-workers[59] studied the reaction of nitro-alkenes such as **85** (Scheme 29) which, in the presence of phenyl isocyanate, afforded the nitrile oxide **86** which spontaneously cyclised to the isoxazoline **87** in good yield. Reductive ring opening with $LiAlH_4$ led to the amino-hydroxypiperidine **88** in 60% overall yield.



Scheme 28.

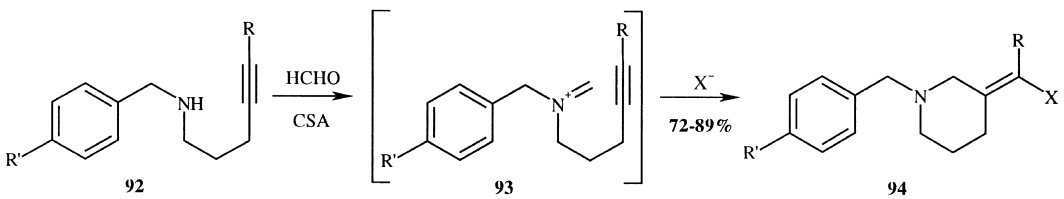


Scheme 29.



89 90 91

Scheme 30.



92 93 94

R = H, Me
R' = H, OMe

R = H, Me
R' = H, OMe
X = I, Br, N_3, SCN

Scheme 31.

2.3.5. Reaction of amines with alkynes. MaGee et al.[60] developed a convenient and general method for the synthesis of cyclic piperidinones via the intramolecular trapping of ketenes. Refluxing the compound **89** in xylene afforded the desired piperidinone **91** in 81% yield (Scheme 30). This reaction is believed to proceed via the ketene **90**, which cyclises spontaneously under the reaction conditions.

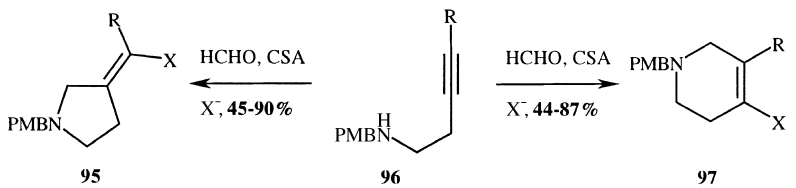
Overman et al.[61] reacted the amino-alkynes **92** with formaldehylde under acidic conditions (CSA), providing the formaldimidium intermediates **93** which, in the presence of a nucleophile (Nu) such as TBAB, NaI, NaN_3 or NaSCN, afforded the corresponding piperidines **94** in good yield (72–89%), (Scheme 31).

Similar studies have been carried out to form pyrrolidines. Treatment of the amino-alkynes **96** (R=Me; X=I, Br, N_3) under the same conditions afforded the pyrrolidines **95** in 45–90% yields (Scheme 32). Treatment of aminoalkynes **96** (R=H, TMS; X=I, Br), under the same conditions, however, afforded piperidines **97** in moderate to good yields (44–87%). Functionalisation of compounds of the type **97** can be very useful in the synthesis of more complex molecules.

2.4. Reaction of dienes, enynes and diynes

2.4.1. Ring-closing metathesis. The synthesis of piperidines via ring-closing metathesis (RCM) has become a widely used approach, providing a reliable synthetic method for the preparation of unsaturated piperidines. Moreover, the double bond formed can easily be further functionalised.

Couty and co-workers[62] published an interesting synthesis of the natural product (−)-β-conhydrine and different analogues using RCM. Metathesis can also be used to



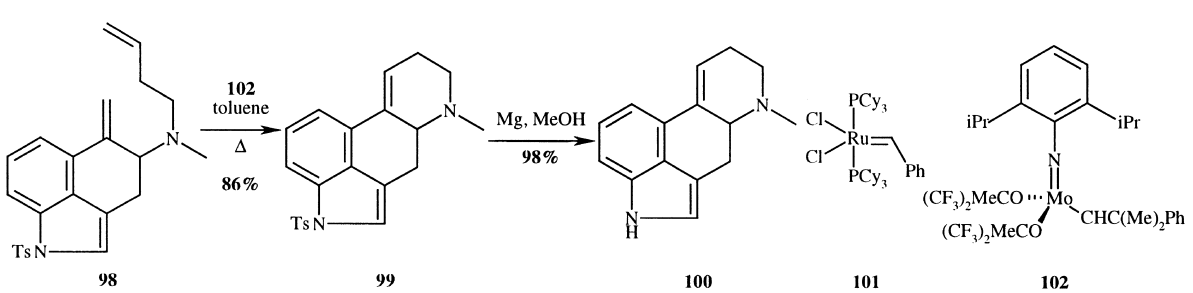
95 96 97

R = Me
X = I, Br, N_3

R = H, Me, TMS

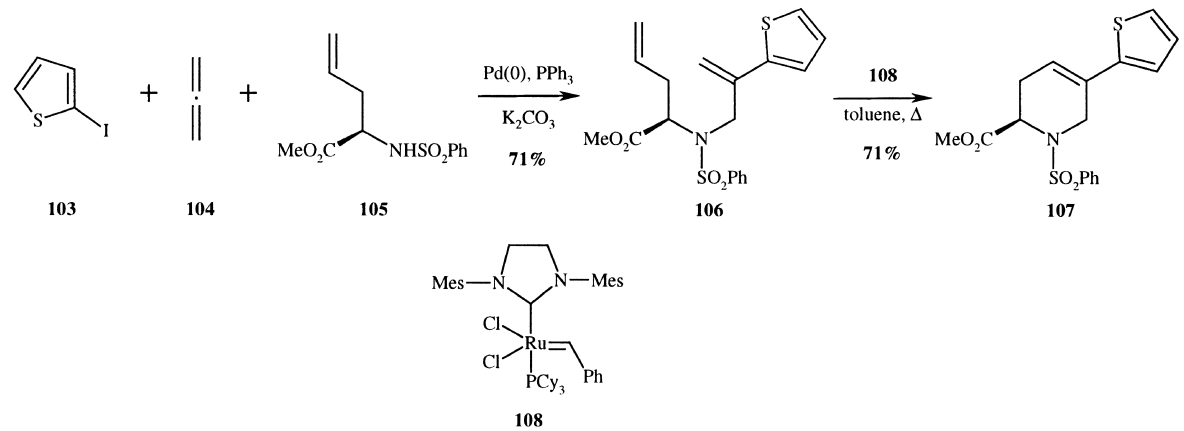
R = H, TMS
X = I, Br

Scheme 32.



98 99 100 101 102

Scheme 33.

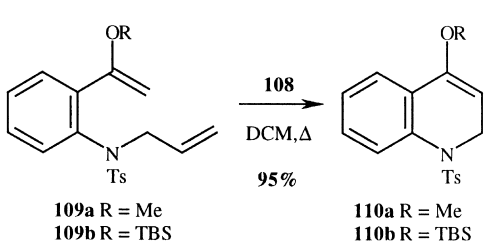


Scheme 34.

synthesise trisubstituted unsaturated six-membered heterocycles. In their synthesis of ergot alkaloids, Martin et al.[63] used RCM as one of the final steps to form the heterocycle **99**. Treatment of the diene **98** with the first generation of Grubbs' catalyst **101** gave only traces of the desired alkaloid **99** (Scheme 33). The more reactive Schrock catalyst **102** was, however, used in this case to afford the tosyl-protected alkaloid **99** in 86% yield. Deprotection of the tosyl protecting group with Mg in methanol afforded ergoline **100** in 98% yield.

Grigg and co-workers[64] have introduced a highly effective synthesis of arylpiperidines via a sequential Pd/Ru-catalysed allene insertion-nucleophile incorporation-olefin metathesis. This strategy involves the reaction of an aryl halide such as **103** with allene **104** and a nucleophile such as the amine **105** in the presence of Pd(0) to afford, in good yields, dienes of type **106** (71% yield for this example), (Scheme 34). RCM using the second generation Grubbs' catalyst **108** (which is more reactive than the Schrock catalyst **102**) was accomplished affording the 1,2,5,6-tetrahydropyridine **107** in good yield (71% in this case). This strategy is a very efficient and short method for the synthesis of 3,4-unsaturated-3-arylpiperidines.

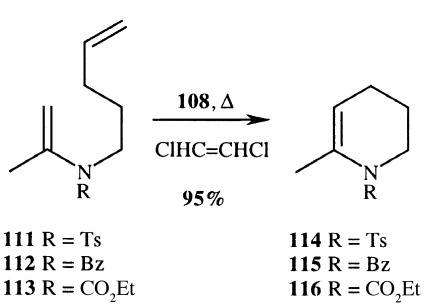
RCM of enol ethers can also be achieved using the highly reactive Grubbs' catalyst **108**. This type of metathesis is still under investigation and examples for the synthesis of piperidines are still limited to simple systems. Although RCM is a very useful synthetic tool for chemists, it does not work for every case. When RCM reactions do not occur, the starting materials are normally recovered. It is still very difficult to understand the reasons for the failure and no general rules have been established. Using RCM of an enol ether as a key step in a total synthesis is therefore still risky,



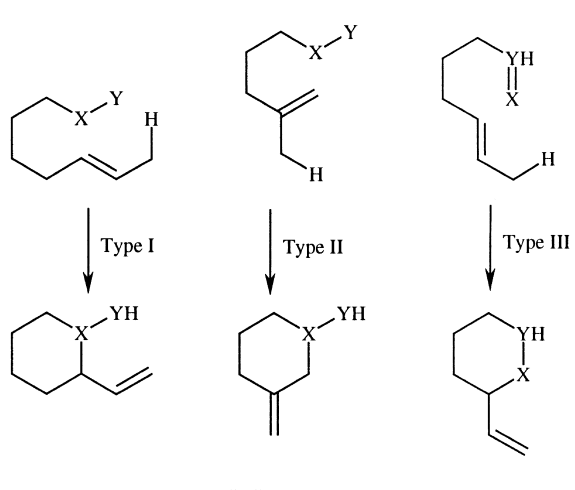
Scheme 35.

as a real understanding of their RCM reactivity is not fully understood. Despite this, Nakagawa et al.[65] realised the synthesis of six-membered heterocycles to afford quinolines via RCM of an enol ether. Both the enol ether **109a** or the silyl enol ether **109b** underwent RCM using the second generation Grubbs' catalyst to provide **110a** and **110b**, each in 95% yield (Scheme 35).

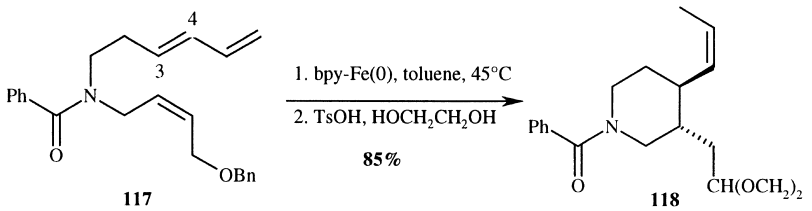
Rutjes and co-workers[66] investigated the RCM of olefinic enamides such as **111** using the Grubbs' catalyst **108** (Scheme 36) to generate 1,2,3,4-tetrahydropyridines. Different electron-withdrawing protecting groups were investigated and the results showed a preference for the



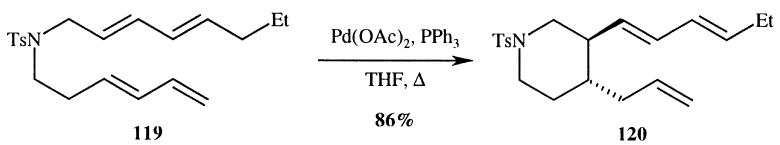
Scheme 36.



Scheme 37.



Scheme 38.



Scheme 39.

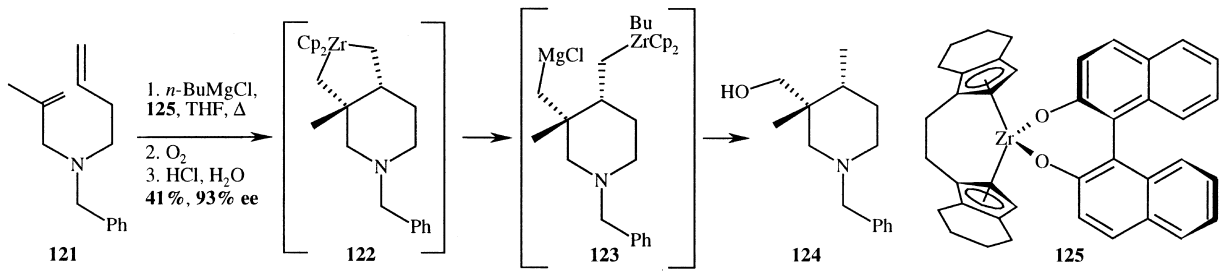
benzoyl protecting group. RCM of the olefinic enamides **111**, **112** and **113** afforded the 1,2,3,4-tetrahydropyridines **114**, **115** and **116** in 75, 93, and 57% yields, respectively.

2.4.2. Intramolecular ene reactions. Intramolecular ene reactions have not been widely applied to the synthesis of piperidines, especially when the desired six-membered-ring heterocycles comprise a relatively complex structure. Nevertheless, a few examples can be found in the literature. Intramolecular ene reactions[67] have been divided by Oppolzer et al. into three different types, I, II and III, depending on the position of attachment of the ene and enophile (Scheme 37).

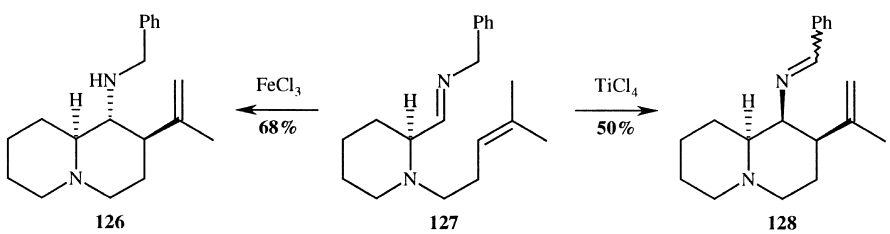
2.4.2.1. Ene reactions (type I). Reactions of the type I are probably the most commonly used intramolecular ene reactions. Takacs and co-workers[68] studied catalytic iron mediated ene reactions and they have applied the ene carbocyclisation to the synthesis of *anti* 3,4-disubstituted piperidines. Indeed, treatment of the triene **117** with 15 mol% of the catalyst bis(2,2′bipyridine)iron(0), (bpy-Fe(0))[69] in toluene, followed by acetylation, afforded the *anti* 3,4-disubstituted piperidiene **118** in 85% overall yield (Scheme 38). According to carbocyclisation studies, the *E*/*Z* geometry of the C3=C4 double bond should control the *syn*–*anti* relation in the resulting piperidine.

The catalytic Pd carbocyclisation of tetraenes has also been investigated by Takacs et al.[70] and, although their study was limited to simple compounds, it is an interesting strategy for the synthesis of *anti* 3,4-disubstituted piperidines. Treatment of the tetraene **119** with $Pd(OAc)_2$ (5 mol%) and PPh_3 afforded the piperidine **120** in 86% yield (Scheme 39). Only the *anti* diastereoisomer was obtained and, interestingly, both newly-formed double bonds had an *E*-geometry.

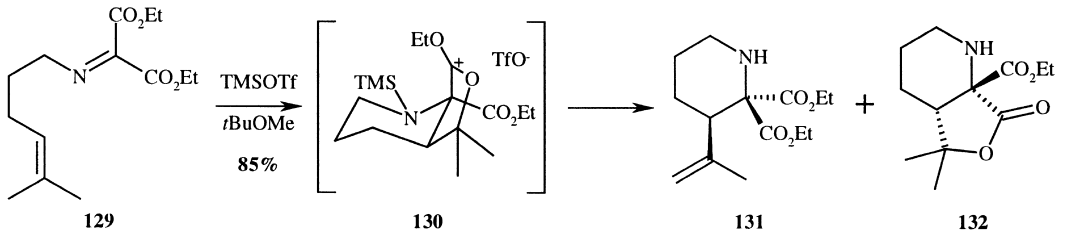
Mori and co-workers[71] worked on an asymmetric version of the zirconocene-mediated synthesis of 3,4-piperidines. Treatment of the diene **121** with *n*-BuMgCl and the zirconocene catalyst **125** (10 mol%), followed by quenching with an electrophile (O_2 in this case), afforded the piperidine **124** in 41% yield and 93% ee (Scheme 40). Although the yield is quite low, this type of reaction is very interesting, as two new chiral centres, one of which is quaternary, have been created. The reaction is believed to proceed via the zirconabicycle **122** and zirconocene **123** intermediates. This chemistry has also been performed with 1,7-enyne and



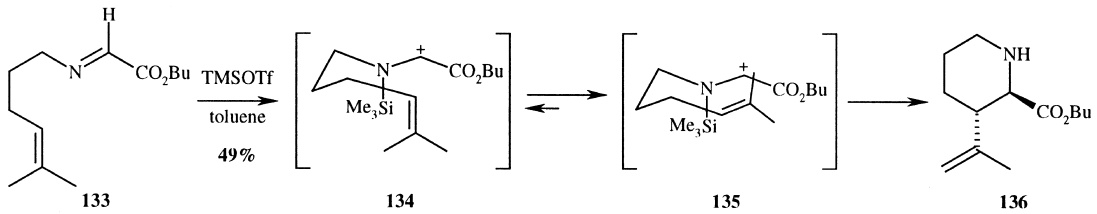
Scheme 40.



Scheme 41.



Scheme 42.



Scheme 43.

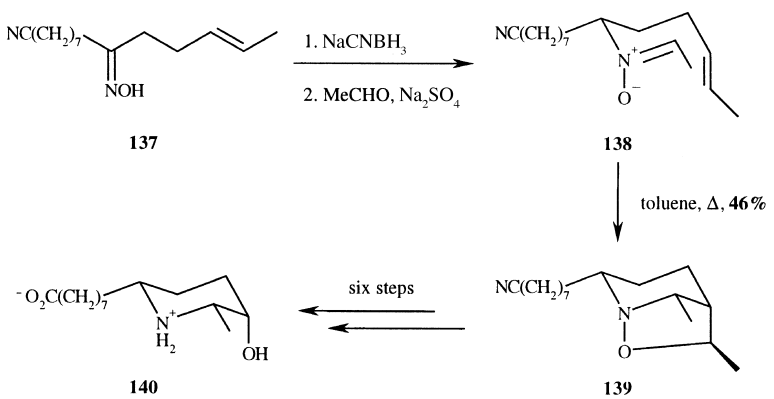
1,7-diyne systems and Whitby et al.[72] generally obtained good yields of the 3,4-disubstituted piperidine products. Trost and co-workers[73] have also reacted 1,7-enynes with CpRu(COD)Cl (10 mol%), to afford similar piperidines in 75% yield.

Imino-ene reactions of type I have been studied for the synthesis of *syn* or *anti* 3,4-diaminopiperidines. Laschat and co-workers[74] investigated the imino-ene reaction of the imino-alkene **127** in the presence of Lewis acids such as $FeCl_3$ or $TiCl_4$ (Scheme 41). The imino-alkene **127** underwent an imino-ene reaction with $FeCl_3$ to give the *anti* piperidine **126** in 68% yield. If, however, $TiCl_4$ was used as the Lewis acid, the *syn* piperidine **128** was formed as the major diastereoisomer in 50% yield.

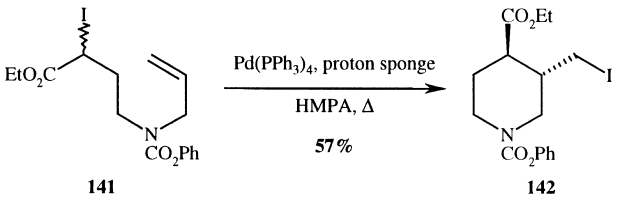
2.4.2.2. Ene reactions (type III). Bratz et al.[75] have used ene reactions of the type III to synthesise 2,3-disubstituted piperidines and they first studied the ene reaction of the dimethylimine **129**, prepared from the corresponding amine (Scheme 42). Treatment of **129** with TMSOTf in *tert*-BuOMe gave a 7.2:1.0 mixture of **131** and **132** in 85% yield. If, however, **129** was treated with TFA in DCM, the ratio of **131** and **132** was reversed, yielding 50% of a 1.0:6.1 mixture of products. The reaction is believed to proceed via the intermediate **130**. The product ratio in the formation of **131** and **132** depends on the nucleophilicity of the counter-ion and the accessibility of the alkyl group in the ester moiety, as well as its ability to form a cation.

Bratz and co-workers[76] then studied the reaction of imino-alkenes of the type **133** (Scheme 43) and the *anti* 2,3-disubstituted piperidines were synthesised in good yield and diastereoselectivity. The best result was obtained when the *n*-butyl ester **133** was treated with TMSOTf in toluene at −78 °C. The 2,3-disubstituted piperidine **136** was obtained in 49% yield and in a 1:33.5 ratio of *syn*/*anti* stereoisomers. The good diastereoselectivity is believed to result from a strong 1,3-diaxial interaction in the intermediate **134**, caused by the bulky trimethylsilyl group, which destabilises **134** severely towards **135**.

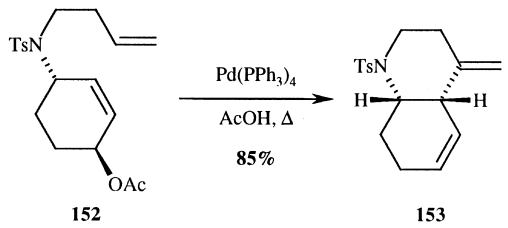
In their synthesis of carpamic acid **140**, Williams and co-workers[77] made use of a type III ene reaction of *N*-oxide alkenes to set up the *syn* 2,3-relationship in the natural product (Scheme 44). Reduction of the oxime **137** afforded the unstable hydroxyamine, which was immediately condensed with acetaldehyde to give the nitrone **138** and the latter compound underwent a type III ene reaction upon reflux in toluene, yielding the desired piperidine **139** in 46% overall yield.



Scheme 44.



Scheme 45.



Scheme 48.

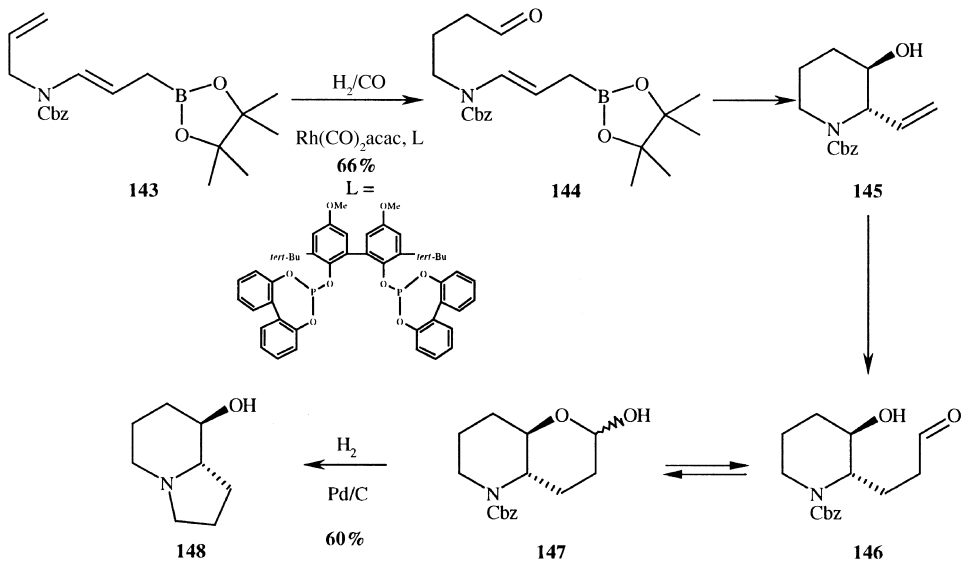
2.4.3. Formal ene reactions

2.4.3.1. Ene halogenocyclisation. Mori et al.[78] studied the palladium-catalysed ene-halogenocyclisations. Treatment of the iodo-alkene **141** with $Pd(PPh_3)_4$ in the presence of a proton sponge afforded the *anti* piperidine **142** (Scheme 45). This strategy is very interesting in the synthesis of 3,4-piperidines which can then be easily functionalised. The reaction, however, shows some disadvantages, as the primary iodide present in the synthesised piperidine can easily be eliminated and a mixture of diastereoisomers can be obtained. A similar cyclisation using $(n\text{-}Bu_3Sn)_2$ has been studied by Curran and co-workers,[79] although a poor yield and a 1:1 mixture of *syn* and *anti* piperidines were obtained.

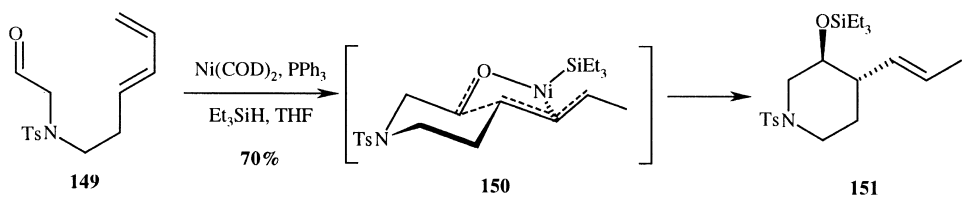
2.4.3.2. π-Allyl complexes. Hoffmann et al.[80] developed an intramolecular allylboration reaction to synthesise *anti* 2-alkylpiperidin-3-ols. The allylamide **143** was hydroformylated to give the aldehyde **144**, which underwent an in situ allylboration to give the vinylpiperidinol **145** (Scheme 46). The reaction does not stop at this stage since **145** has a newly-generated terminal C=C double bond and therefore undergoes a second hydroformylation to expand the carbon skeleton, giving a mixture of **146** and **147** in 66% yield. Hydrogenation of this mixture with Pd/C led to the indolizidine **148** in 60% yield.

In their approach towards the synthesis of (−)-elaeokanine C, Mori et al.[81] investigated the cyclisation of 1,3-dienyl aldehydes via the π-allylnickel complex **150** (Scheme 47). The nickel complex **150** was formed in situ by the treatment of $Ni(COD)_2$ with PPh_3 and Et_3SiH. Treatment of the 1,3-dienyl aldehyde **149** with the desired catalyst and Et_3SiH as the hydride source afforded only the *anti* diastereoisomer **151** in 70% yield.

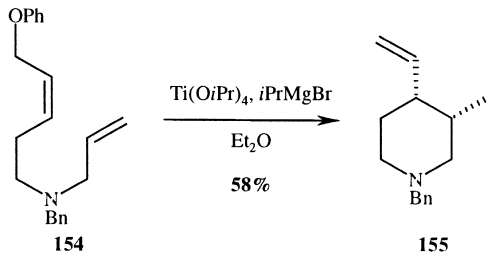
Palladium-catalysed intramolecular olefin allylation is a widely used reaction and it is therefore logical to find it applied to the synthesis of piperidines. Oppolzer and co-workers[82] have studied this process and used $Pd(PPh_3)_4$ in acetic acid to synthesise simple piperidines. In the synthesis of 6,6-bicyclo systems, the *syn*-fused rings were obtained. Indeed, treatment of the compound **152** with $Pd(PPh_3)_4$ (7 mol%) at 80 °C afforded the compound **153** in 85% yield (Scheme 48). Although the choice of solvent limits this strategy to the synthesis of simple piperidines, it



Scheme 46.



Scheme 47.



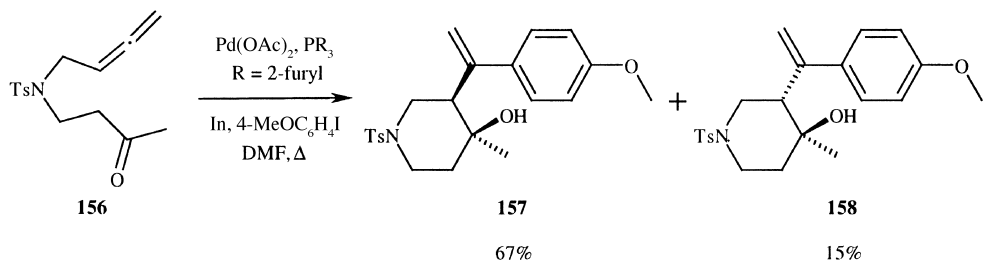
Scheme 49.

can be useful for the synthesis of *syn*-fused rings such as that found in **153**.

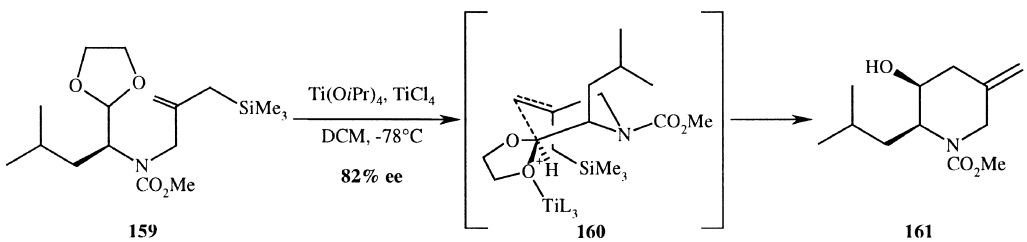
A similar cyclisation of dienes has been investigated by Taylor, who accomplished the cyclisation of the diene **154** to the piperidine **155** in 58% yield (Scheme 49). The diene **154** was treated with $Ti(OiPr)_4$ and *i*PrMgBr, to afford the *syn* piperidine **155**. An asymmetric version of this reaction has been studied using a 1-phenylethyl protecting group instead of the benzyl protecting group, but a 1:1 mixture of *syn* diastereoisomers was obtained. When $ZrCl_2$ was used with *n*-BuLi, an unsatisfactory 1:1.4 mixture of *syn*/*anti* diastereoisomers was obtained.

Barbier allylation has been recently investigated by Kang in the synthesis of piperidines. Interestingly, this strategy is quite general and a wide range of piperidines can be prepared. Both allene aldehydes and ketones can be reacted, to give the 3,4-disubstituted piperidines. 3-Trimethylsilanylvinylpiperidin-4-ol,[83] and 3-arylvinylpiperidin-4-ols[84] have been synthesised using this method. Kang initially treated allene aldehydes and ketones with $(\pi\text{-allyl})_2PdCl_2$ and $Bu_3SnSiMe_3$, to afford the corresponding piperidines in good yields (62–67%). Further studies showed that π-allylpalladium complexes could be formed using $Bu_3SnSnBu_3$ and ArI, leading to the synthesis of 3-arylvinylpiperidin-4-ols. This methodology gave good yields and diastereoselectivity and it could be applied to a wide range of aromatics and aromatic heterocycles. Due to the moderate toxicity of the tributyltin reagents, Kang studied the use of indium in the Barbier allylation. Treatment of a solution of the ketoallene **156** in DMF with $Pd(OAc)_2$, tris(2-furyl)phosphine and indium afforded the desired *syn* piperidine **157** in 67% yield (Scheme 50). Only 15% of the *anti* piperidine **158** was isolated.

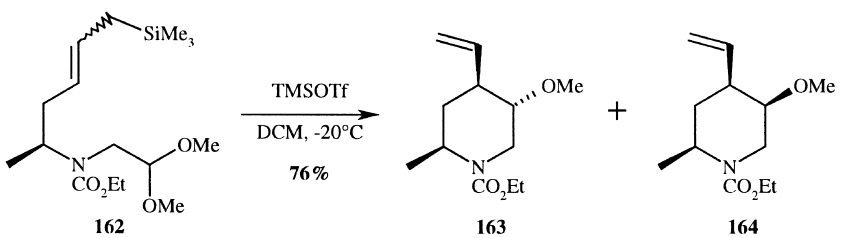
Interesting results were obtained by Kano et al.,[85] who investigated the cyclisation of α-aminoacetal-allylsilanes, resulting in the formation of 2-alkyl-3-hydroxypiperidines. Treatment of the α-aminoacetal-allylsilane **159** with the in situ-generated $Ti(OiPr)Cl_3$ afforded the *syn* piperidinol **161** in 82% ee (Scheme 51). The reaction proceeds via the intermediate **160**, where no interaction between $SiMe_3$ and any of the oxygens is observed. A similar chemistry has been studied by Bonjoch and co-workers,[86] using α,β-unsaturated keto-α-trimethylsilylalkynes. 3-Allene-4-alkyl-disubstituted piperidines were obtained in 57–60% yield using $BF_3{\cdot}Et_2O$ or $TiCl_4$ as Lewis acids. Further



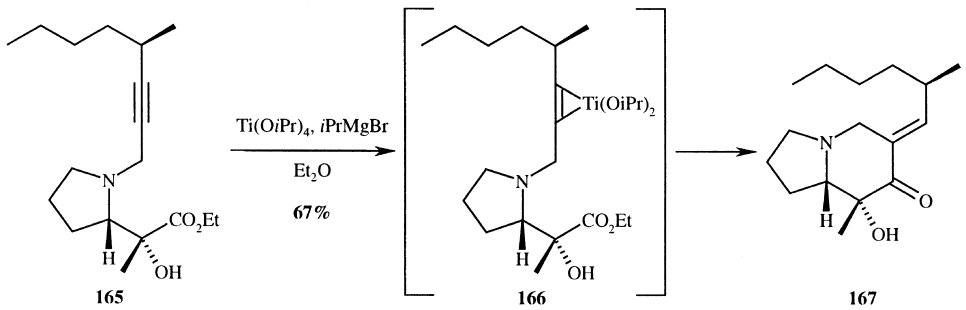
Scheme 50.



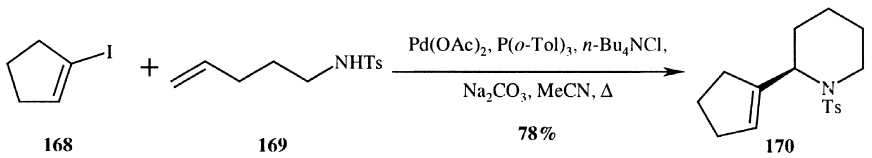
Scheme 51.



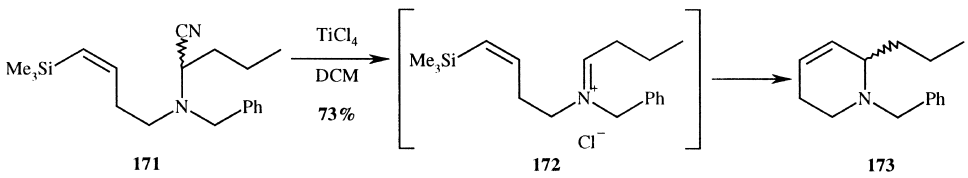
Scheme 52.



Scheme 53.



Scheme 54.



Scheme 55.

functionalisation of the product allenes afforded a range of 3,4-disubstituted piperidines.

Mann et al.[87] have also been working on the synthesis of *anti* 3-hydroxy-4-alkylpiperidines from α-trimethylsilyl-methylalkenes. When the allyltrimethylsilane **162** was treated with a catalytic amount of TMSOTf (10 mol%), only two of the four possible diastereoisomeric piperidines were obtained (Scheme 52) in an 85:15 ratio (**163** and **164**) and in 76% yield. This strategy created two new chiral centres influenced by the stereochemistry present in the starting material.

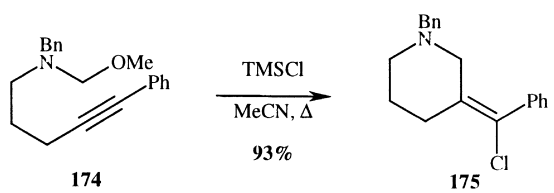
In their synthesis of allopumiliotoxin alkaloid 267A, Sato and co-workers[88] made use of an intramolecular nucleophilic acyl substitution initiated with a low-valent titanium reagent Ti(O*i*Pr)$_2$*i*Pr. Treatment of the ethyl ester **165** with Ti(O*i*Pr)$_4$ and *i*PrMgCl afforded the desired six-membered heterocycle **167** in 67% yield (Scheme 53). The reaction is believed to occur via the intermediate **166**, which undergoes an intramolecular nucleophilic substitution.

2.4.3.3. Palladium cross-coupling. Piperidine synthesis via palladium-catalysed tandem cyclisation cross-coupling can be found in the literature. In their synthesis of ellipticine, Ishikura et al.[89] synthesised the six-membered ring heterocycle via Heck coupling of a vinyl bromide and an alkyne. Crisp and co-workers[90] studied the synthesis of lactams via palladium-catalysed intramolecular carbonyl coupling and reacted an amino enol triflate with carbon monoxide in the presence of Pd(PPh$_3$)$_4$ and (*n*-Bu)$_3$N in acetonitrile. The corresponding lactam was obtained in 72% yield using of *N*-benzyl 3-methylene-piperidin-2-one. Ban et al.[91] worked on a similar synthesis of piperidinones.

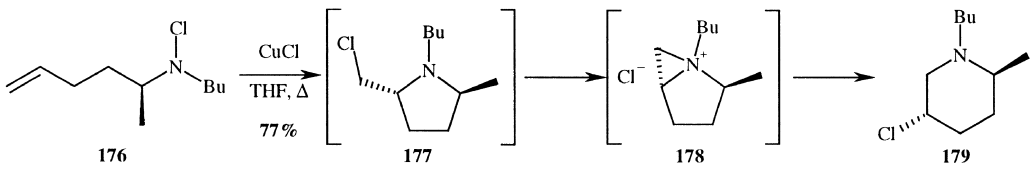
Larock, Weinreb and co-workers[92] studied the palladium cross-coupling of vinyl iodides, vinyl bromides or enol triflates, for example, **168** with *N*-tosyl-pent-4-enylamine **169** (Scheme 54). The 2-substituted-piperidines of type **170** were successfully prepared in modest to good yields.

2.4.3.4. Reactivity of iminium cations. Rotella et al.[93] have investigated the application of TiCl$_4$ in an induced iminium ion cyclisation in order to prepare piperidines. The iminium ion was prepared by the treatment of an α-cyanoamine of type **171** with titanium (IV) chloride (Scheme 55). The corresponding iminium ion **172** underwent cyclisation, to afford the 1,2,5,6-tetrahydropyridine **173** in 73% yield. Reduction of the double bond afforded racemic coniine in 90% yield.

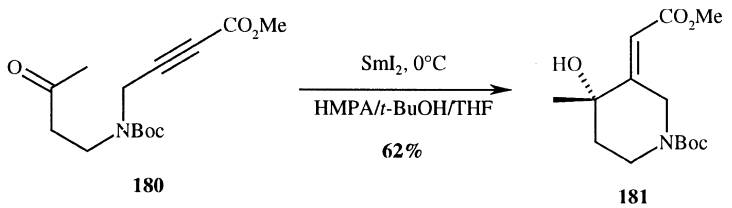
Overman and co-workers[94] worked on a similar methodology and treated *N*-methoxymethyl alkynes such as **174** with TMSCl (Scheme 56). The piperidine **175** was obtained



Scheme 56.



Scheme 57.



Scheme 58.

in 93% yield as a 93:7 mixture of *E*/*Z* isomers. The reaction most probably proceeds via an iminium cation.

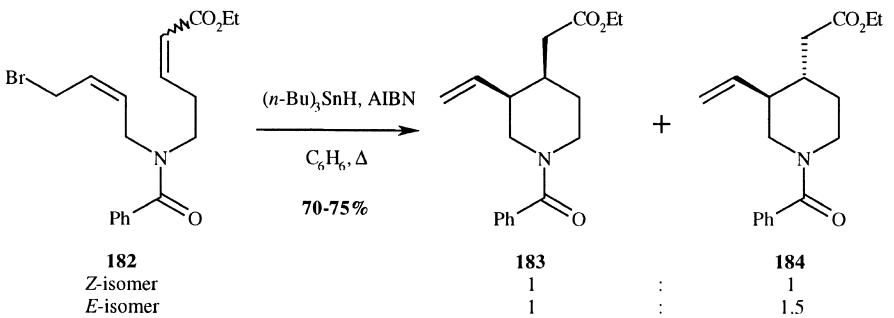
2.5. Radical cyclisations

2.5.1. Radical cyclisation of *N*-chloro amino alkenes. Götflich et al.[95] studied the reactivity of *N*-chloro amino alkenes under radical conditions. The unstable *N*-chloro amine **176** was freshly prepared from the corresponding amine and NCS (Scheme 57). Treatment with a catalytic amount of CuCl (10 mol%) afforded the piperidine **179** in 77% yield as a 7:1 mixture of *syn*/*anti* diastereoisomers. The reaction is believed to proceed via the pyrrolidine **177** and the azonia-bicyclo[3.1.0]hexane **178**. The synthesis of *syn* 3,5-piperidines was also performed in good yield, but the diastereoselectivity was lower (1:4, *anti*/*syn*). Somfai and co-workers[96] studied similar reactions in the presence of a Lewis acid instead of CuCl and obtained good diastereoselectivity (up to 93:7 in favour of the *syn* 3,5-disubstituted piperidine).

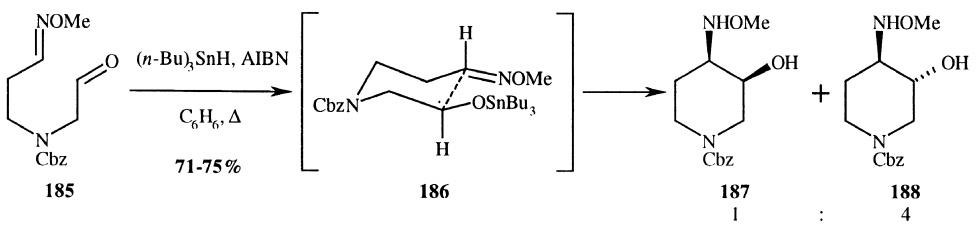
2.5.2. Radical cyclisation using samarium. The use of samarium to synthesise piperidines is rare in the literature. Shim and co-workers[97] have, however, described the synthesis of a 3,4-disubstituted piperidine via an intramolecular reductive cyclisation of aldehydes and ketones with alkynes. Interestingly, the reaction with ketones led to the formation of piperidines containing a quaternary alcohol in position 4. Treatment of the keto-alkyne **180** with SmI_2 in a mixture of HMPA, *tert*-butanol and THF afforded the racemic piperidine **181** in 62% yield (Scheme 58).

2.5.3. Radical cyclisation using tin. Tin allylic radical cyclisation has been investigated in the synthesis of piperidines, although this reaction did not show diastereoselectivity and gave a mixture of diastereoisomers. Indeed, treatment of the allyl bromide **182**[98] with $(n\text{-Bu})_3SnH$ and AIBN afforded a mixture of the diastereoisomers **183** and **184** (Scheme 59).

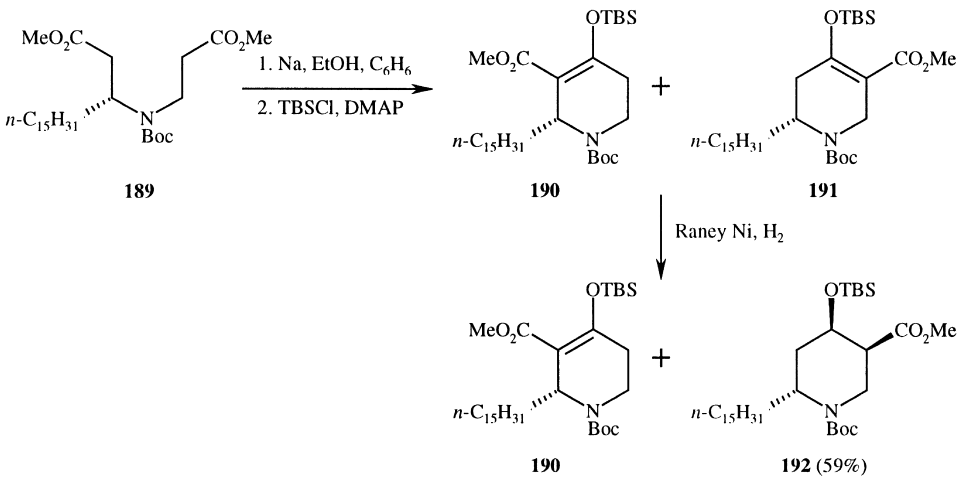
The radical cyclisation of α,β-keto-dienes[99] has also been investigated and, although the yields are relatively high, a low diastereoselectivity was generally obtained. The intramolecular radical cyclisation of oxime ethers with



Scheme 59.



Scheme 60.



Scheme 61.

aldehydes and ketones has been studied by Naito et al.[100] who obtained modest results. Attempts to synthesise 3-amino-4-hydroxypiperidines gave a reasonable yield of 62%, but the diastereoselectivity was poor (1:1.3 in favour of the *anti* diastereoisomer). Treatment of the 'oxime-aldehyde' **185** with $(n\text{-Bu})_3SnH$, and AIBN afforded a 1:4 mixture of the diastereoisomers **187** and **188** (Scheme 60). The most stable intermediate is believed to be the *anti* isomer **186**, where the oxime and tin are *anti* to each other.

2.6. Dieckmann condensation

Dieckmann condensation is an important tool in the synthesis of 3,4-disubstituted piperidines and can provide *syn* piperidines or the more stable *anti* piperidines. This strategy can, however, become problematic with more complex piperidines which contain further substitution in positions 2, 5 or 6. Ma et al.[101] investigated the synthesis of 2,4,6-trisubstituted piperidines and faced problems of diastereoselectivity. Indeed, the bis-methyl ester **189** can undergo two different Dieckmann cyclisations to give after trapping of the intermediate enolate with TBSCl, **190** and **191** in an 1:3.8 diastereomeric mixture (Scheme 61). Fortunately, Ma managed to selectively hydrogenate the less sterically hindered silyl enol ether, to obtain the desired 2,4,6-trisubstituted piperidine **192** in 59% yield from **189**.

In the synthesis of 3,4-disubstituted piperidines, this problem does not occur and the *syn* and *anti* piperidines can be prepared. Pollini and co-workers[102] were able to synthesise *syn* 3,4-disubstituted piperidines and then epimerised them to the more stable *anti* piperidines. This strategy has become very attractive in medicinal chemistry, as both the *syn* and *anti* 3,4-disubstituted piperidines can be easily obtained for testing purposes.

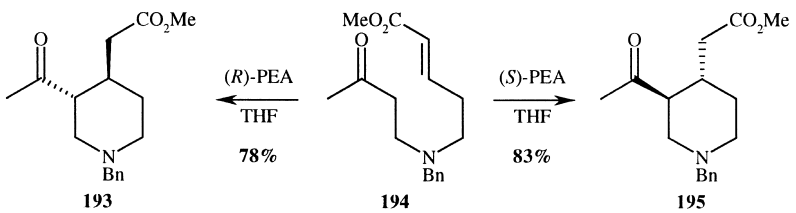
Dieckmann cyclisation can be performed under acidic conditions using Lewis acids such as $TiCl_4$.[103] Chiral bases can be employed to synthesise enantiomerically pure piperidines. Indeed, Hirai et al.[104] realised a 1,4-Michael addition similar to a Dieckmann cyclisation to afford **193** or **195** starting from the ester **194** (Scheme 62). (*R*)- and (*S*)-1-Phenylethylamine (PEA) gave both products in good enantiomeric excess (90% ee). Both enantiomers **193** and **195** were synthesised in 78 and 83% yields, respectively.

3. Cycloadditions

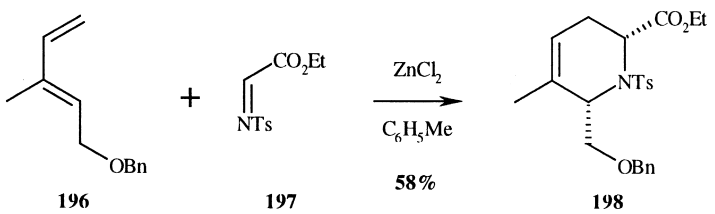
In cycloadditions, the Diels–Alder reaction is one of the most commonly used reactions for preparing six-membered rings. In a similar manner, the aza Diels–Alder reaction is an important tool in the hand of chemists for synthesising piperidines. The method is mostly applied to the reaction of dienes with imines. The reaction of α,β-unsaturated imines (aza dienes) with alkenes is also known in the literature.

3.1. Imino Diels–Alder reactions

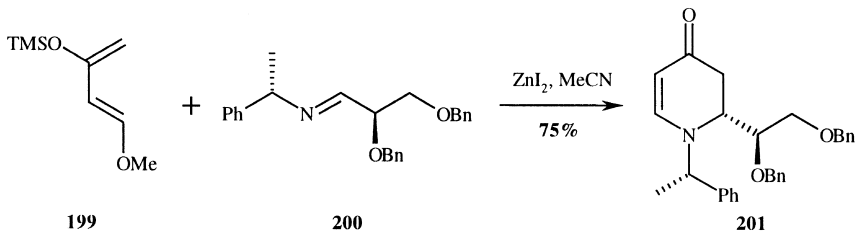
Imino Diels–Alder reactions require an electron-rich diene and an electron-poor imine. In general, the imine is protected as a sulphonamide or as a silylamine, although the reaction of dienes protected as benzylimines is also known. Imino Diels–Alder reactions are generally slow and are typically catalysed by a Lewis acid such as $ZnCl_2$. The



Scheme 62.



Scheme 63.



Scheme 64.

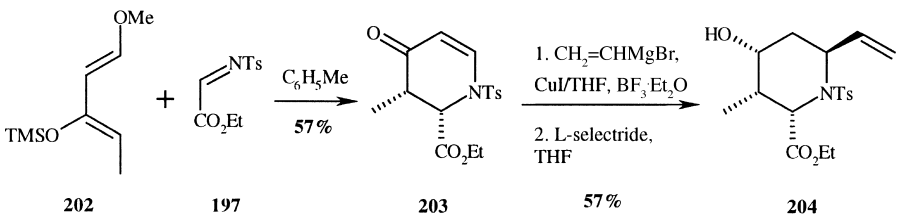
speed of the reaction depends mainly on the reactivity of the starting imine and a wide range of electron-rich dienes can be used.

In their studies towards the synthesis of cylindrospermopsin, Weinreb and co-workers[105] studied the imino Diels–Alder reaction of the diene **196** and the imine **197** (Scheme 63). The piperidine **198** was obtained after 6 days at room temperature in toluene in the presence of $ZnCl_2$ in 58% yield. Although the yield is only modest, a *syn* 2,6-piperidine was synthesised in a one-step process.

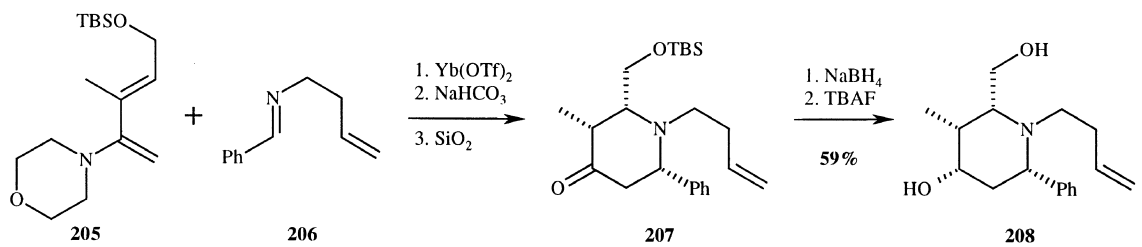
An imino Diels–Alder reaction using Danishefsky's diene has been investigated by Villegas et al.,[106] who studied an enantioselective reaction of the diene **199** with the enantiomerically pure imine **200** (Scheme 64). The reactions in acetonitrile at −40 °C using ZnI_2 were found to be the optimal conditions. The compound **201** was the only diastereoisomer observed and, when the reaction was carried out with the corresponding benzylimine, a 95:5 mixture of diastereoisomers was obtained. Deprotection of the methylbenzyl chiral pool component can accomplished via the usual hydrogenation (H_2, $Pd(OH)_2/C$). Reduction of the α,β-unsaturated piperidinone **201** to the piperidin-4-one can be completed with *L*-selectride.

More interestingly, Weinreb et al.[105] used a 1,4-vinylcopper addition to heterocycle **203** prepared from diene **202**. *L*-selectride reduction of the ketone provided the tetrasubstituted piperidine **204** in 57% yield overall (Scheme 65).

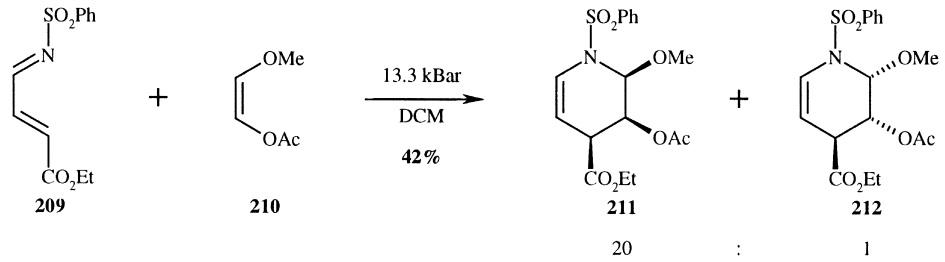
Moreover, aza Diels–Alder reactions can be performed with 2-amino-1,3-butadiene derivatives **205** leading after hydrolysis, to piperidin-4-ones of the type **207** (Scheme 66). The optimal Lewis acid was $Yb(OTf)_3$ and Barluenga and co-workers[107] reported the hydrolysis of the enamine via filtration through a pad of silica. Reduction of the ketone using $NaBH_4$, followed by silyl ether deprotection, led to the tetrasubstituted piperidine **208** in 59% yield overall. In their synthesis towards (−)-nupharamine, Barluenga and co-workers developed an asymmetric version of this type of imino Diels–Alder reaction.[108]



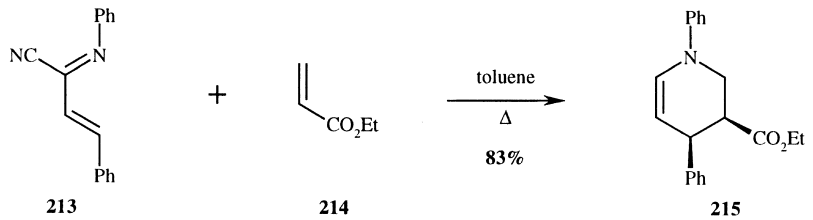
Scheme 65.



Scheme 66.



Scheme 67.



Scheme 68.

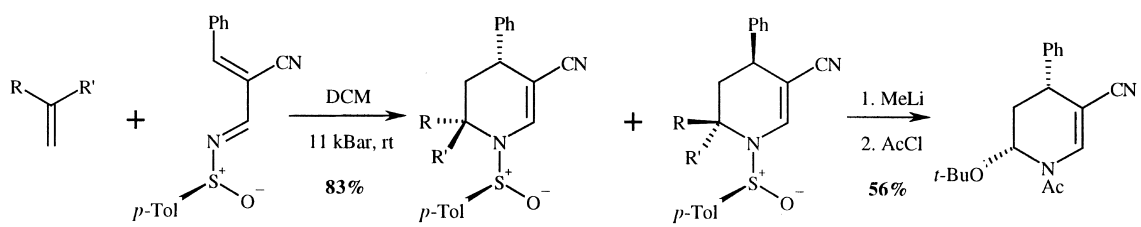
3.2. Aza-diene Diels–Alder reactions

The aza Diels–Alder reaction of a diene with an imine is well known in the synthesis of piperidines, but the aza-diene Diels–Alder reaction is rarely used. Indeed, this type of reaction is difficult to realise as the aza-dienes suffer low conversion and competitive imine addition and/or tautomerisation. Boger and co-workers[109,110] studied the influence of different substituents on the aza-dienes in their reactions with electron-rich alkenes such as enol ethers. Other types of dienophiles are not reactive enough, unless a highly reactive aza-diene is used. According to Boger's studies, an electron-withdrawing group on the nitrogen of the aza-diene facilitates the reaction, substituents in position 2 slow down the reaction and electron-withdrawing groups accelerate it. Groups such as *N*–SO_2Ph and *N*–$P(O)Ph_2$ are good choices, as the starting imine can be easily purified by flash chromatography without decomposition and the steric bulk of the groups prevents the 1,2-imine addition. The *endo* aza Diels–Alder product is favoured (up to 95%) in both the thermal and pressure-promoted (most common) reactions. Both the *anti* and *syn* enol ethers react with conservation of geometry. Alkoxyallenes can also be used, to give the corresponding piperidines with good diastereoselectivity. The solvent does not seem to have any influence on the reactivity or diastereoselectivity of the reaction.

The aza Diels–Alder reaction is very useful for the synthesis of 2,3,4-trisubstituted piperidines. Boger et al.[109] reacted the aza-diene **209** with the dienophile **210**, to afford the desired piperidines **211/212** in 42% yield as a 20:1 ratio of *endo*/*exo* products (Scheme 67).

Fowler and co-workers[111] demonstrated that the aza-diene Diels–Alder reaction is possible with electron-poor dienophiles, although the number of applications is limited. This research group reacted the aza-diene **213** with ethyl acrylate **214** to give the piperidine **215** as a 6:1 *syn*/*anti* mixture of diastereoisomers (Scheme 68). The cyano group in position 2 combined with the presence of the *N*-phenyl group is believed to enhance the 'inverse electron demand' Diels–Alder reaction and therefore the reaction of the aza-diene with electron-poor dienophiles.

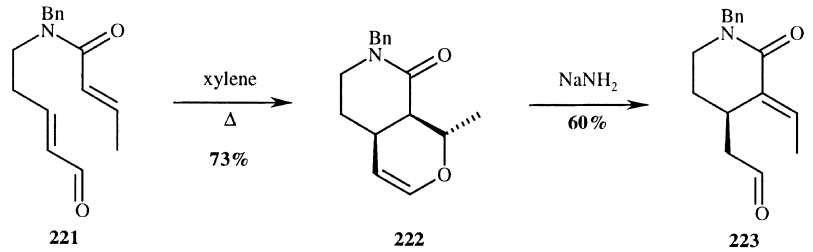
Enantioselective aza Diels–Alder reactions have also been studied, although this work is still in its infancy. Tietze et al.[112] studied the reaction of enantiopure α,β-unsaturated sulphinimines with dienophiles. The reactions were performed with electron-rich dienophiles such as enol or thioenol ethers, whereas the reactions with alkenes did not lead to any tetrahydropyridines. The conformation of the sulphinimine **217** is believed to be that shown in Scheme 69, where the sulphur–oxygen bond is coplanar to the aza-diene. The dienophile approaches the aza-diene from the less hindered face. For simple dienophiles, the *endo*/*exo* ratio was good (100:1, **216a** and **b**). When bulky or



216a R = OEt, R' = H
216b R = SPh, R' = H
216c R = OtBu, R' = H
216d R = OMe, R' = Me

218a R = OEt, R' = H (60%) **219a** R = OEt, R' = H (35%)
218b R = SPh, R' = H (52%) **219b** R = SPh, R' = H (27%)
218c R = OBu, R' = H (60%) **219c** R = OBu, R' = H (26%)
218d R = OMe, R' = Me (37%) **219d** R = OMe, R' = Me (35%)

Scheme 69.



Scheme 70.

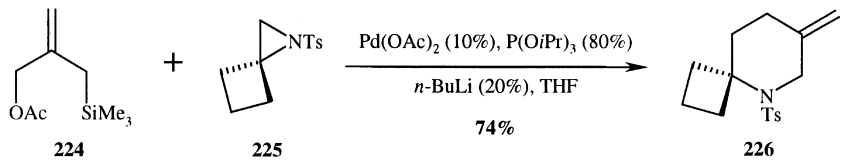
disubstituted enol ethers were reacted, however, the reaction was less diastereoselective (87:13, **216c**; 76:24, **216d**). The facial stereoselectivity was modest and ratios of between 1:1.7 and 1:2.3 were obtained. The piperidine **218a** was therefore formed in 60% yield and only 35% of the other diastereoisomer **219a** was isolated. Intramolecular Diels–Alder reactions seem to proceed more readily, although, in the example studied, the diastereoselectivity was not as good. Removal of the sulphoxide did not occur under conventional conditions ($LiAlH_4$ or Raney Ni), but this group could be removed by nucleophilic substitution with MeLi. After quenching with AcCl, the piperidine **220c** was obtained in 56% yield.

3.3. Other dipolar cycloadditions

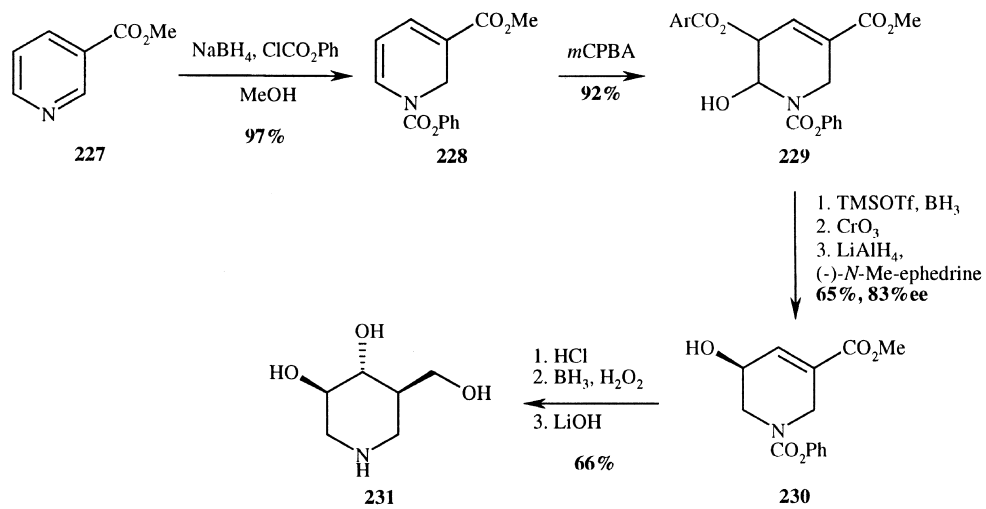
In their approach towards the synthesis of geissoschizine, Martin et al.[113] synthesised the piperidine **223** from **221** via a hetero Diels–Alder reaction (Scheme 70). Cleavage of the dihydropyran **222** gave the 3,4-disubstituted piperidine **223**.

Harrity and co-workers[114] have recently developed a general [3+3] cycloaddition reaction to synthesise 2-substituted piperidines. The reaction proceeds via an intermediate palladium–trimethylenemethane (Pd–TMM) complex **224** (Scheme 71). The study mainly examined the reaction of 1,1-disubstituted aziridines. The reaction seemed to be more efficient when $Pd(OAc)_2$ (10 mol%) was used with $P(OiPr)_3$ (80 mol%) as the ligand in the presence of *n*-BuLi (20 mol%), while THF was found to be the best solvent. A range of alkyl-, aryl- and allyl-aziridines have been investigated, giving modest to good yields of the products (44–82%). Phenylaziridine led to a mixture of diastereoisomers in which the aziridine was preferentially attacked at C-2 rather than C-1 (1.6:1 mixture). Reactions of symmetrical disubstituted aziridines gave similar yields. The reaction with *N*-tosylaziridine **225** afforded the piperidine **226** in 74% yield. When bicyclic aziridines were reacted in order to synthesise fused 5/6-, 6/6- or 7/6-membered rings, disappointing yields were, however, obtained, as the reactions were very slow (0–31%).

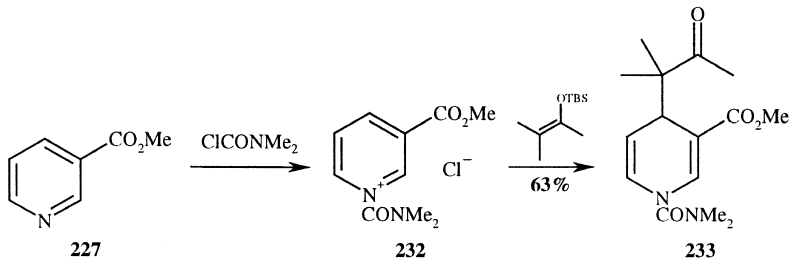
Both nitrones and azides are important building blocks in diastereoselective 1,3-cycloadditions, leading mainly to the 2-substituted piperidines. Further details can be found in previous reviews.[2]



Scheme 71.



Scheme 72.



Scheme 73.

4. Reduction of pyridines

The synthesis of piperidines from pyridines has been widely investigated and shown to be a very important synthetic tool for the preparation of 3,4,5-trisubstituted piperidine derivatives. Access to piperidines containing a quaternary carbon via the reduction of pyridines is, however, not the best strategy. Pyridines can be reduced to dihydropyridines, tetrahydropyridines or piperidines in one- or two-step processes. The most common method of reducing pyridines is by treatment with an electrophile such as phenyl chloroformate and a reducing agent such as $NaBH_4$. The direct hydrogenation of pyridines, however, is also discussed in the literature.

4.1. Reduction to dihydropyridines

Pyridines can be reduced to 1,2-dihydropyridines using $NaBH_4$. This strategy allows the possibility of further functionalisation of the six-membered ring. This type of reduction contains problems of diastereoselectivity and 1,2- or 1,6-reduction can occur. After the investigation, Sundberg et al.[115] have published the possibility of carrying out regioselectively the 1,2-reduction. Indeed, sterically-nondemanding donor substituents lead to 1,2-reduction. Acceptor substituents lead to lower reactivity and a lack of regioselectivity. Formation of the pyridinium salts with alkyl chloroformates, however, led to better results. Moreover, methanol gave a better result, whereas THF led to a mixture of regioisomers and 1,4-reduction.

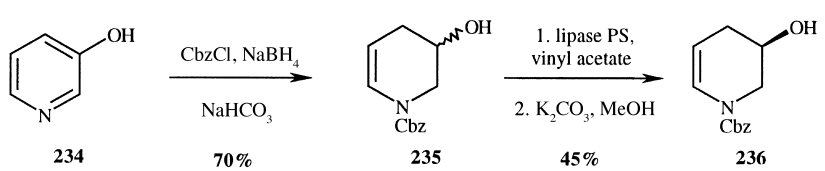
Ganem and co-workers[116] managed to reduce methyl nicotinate **227** to the 1,2-dihydropyridine **228** in 90% yield (Scheme 72). The dihydropyridine **228** was a crucial intermediate in a synthesis of azasugars. Epoxidation using *m*CPBA led to the compound **229** in 92% yield. The alcohol **230** was subsequently obtained in three steps, 65% yield and 83% ee. Saponification, followed by hydroboration and deprotection of the piperidine led to the corresponding azasugar **231** in 66% overall yield.

Formal 1,4-reduction of pyridines can also be performed by the addition of a nucleophile to the pyridinium salts. Akiba and co-workers[117] investigated the synthesis of 1,4-dihydronicotinate by the addition of silyl enol ethers to quaternised pyridines. Indeed, treatment of methyl nicotinate **227** with an electrophile such as dimethylcarbamoyl chloride led to the quaternised nicotinium salt **232** (Scheme 73). Reaction with silyl enol ethers led to 1,4 dihydropyridines such as **233** in 63% yield. 1,2- and 1,6-Dihydropyridines could be observed, depending on the nature of the silyl enol ether. The 1,4 dihydropyridines were, however, always the major isomer. Akiba also demonstrated that copper addition can be performed. The direct 1,4-reduction of pyridinium salts has additionally been achieved by O'Neill et al.[118] using sodium dithionate ($Na_2S_2O_4$) as the reducing agent.

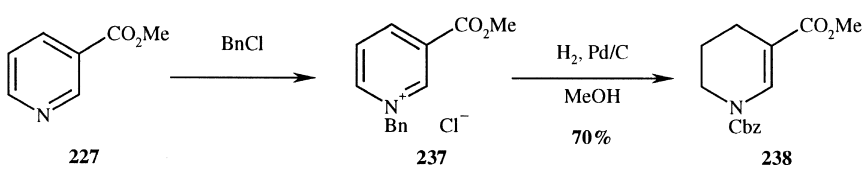
4.2. Reduction to tetrahydropyridine

Reduction to the tetrahydropyridine can also be performed. With substituted pyridines, however, problems of regioselectivity can appear although control can be achieved. Ogasawara and co-workers[119] studied the reduction of 3-hydroxypyridine **234** to the enamide **235** using the usual conditions such as $NaBH_4$ with CbzCl in ethanol (Scheme 74). Resolution of the racemic mixture enzymatically, followed by deprotection, afforded the enantiomerically-pure alcohol **236** in 31% yield over the three steps.

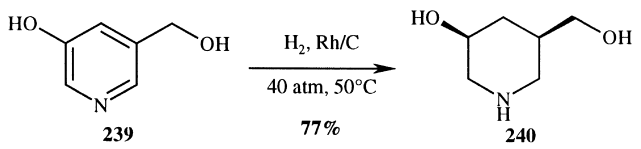
Plaquevent et al.[120] reported the reduction of pyridines having an electron-withdrawing group at C-3. Indeed after



Scheme 74.



Scheme 75.



Scheme 76.

formation of the bromo- or chloropyridinium salt **237**, reduction via hydrogenation afforded the tetrahydropyridine **238** in 70% yield overall (Scheme 75). In the case of the bromide salt, previous treatment with AgCl was necessary as the counteranion could poison the Pd/C catalyst for the hydrogenation.

Liu and co-workers[121] obtained similar 1,4,5,6-tetrahydropyridines from the reduction of 1,4-dihydropyridines using H_2 with 10% Pd/C in a mixture MeOH/THF and 1,2,5,6-tetrahydropyridines[122] can be obtained with sodium borohydride at −15 °C.

4.3. Reduction to piperidines

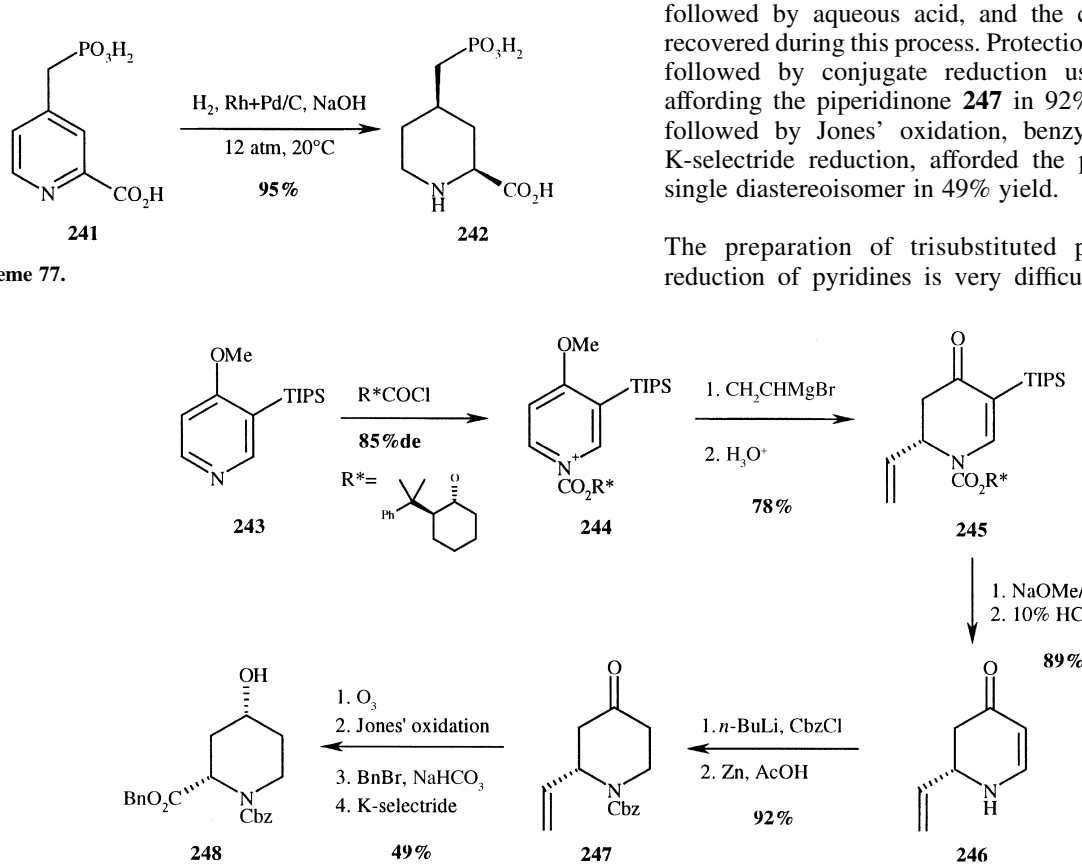
The full reduction of pyridines to piperidines can be achieved using hydrogenation. Different catalysts such as Pd/C, PtO_2 or Rh/C can be used. When substituted pyridines are used, problems with diastereoselectivity can result, with the main product generally being the all-*syn* piperidines, although mixtures of diastereoisomers are observed in most cases. The reduction of the diol **239** by Bols et al.[123] using Rh/C as the catalyst led to *syn* 3,5-hydroxyhydroxymethylpiperidine **240** in 77% yield (Scheme 76). The reduction of 3,5-pyridinedicarboxylic acid diethyl ester using PtO_2 in AcOH afforded a 3:2 mixture of the *anti*/*syn* piperidines.[124]

Steiner et al.[125] studied the reduction of 2,4-pyridines such as **241** using different catalysts, solvents and reaction conditions (Scheme 77). The mixed catalysts gave better results in terms of diastereoselectivity and a 1:9 Rh/Pd ratio was found to be the optimum mixture. Due to solubility reasons, hydrogenation was performed on the corresponding pyridine salt in aqueous solution. The best result in terms of diastereoselectivity was obtained using 1 equiv. of NaOH. An excess of base led to a lower diastereoselectivity. These workers were able to efficiently scale up the reduction of the pyridine **241** to the desired *syn* 2,4-disubstituted piperidine **242**, in 95% yield, which contained 3% of the *anti* diastereoisomer.

The stereoselective reduction of 2-methylnicotinic acid has been investigated by Besson and co-workers,[126] using a chiral auxiliary introduced as an amide. A 4:1 mixture of the *syn*/*anti* diastereoisomers and modest diastereoisomeric excesses of between 17 and 35% were obtained.

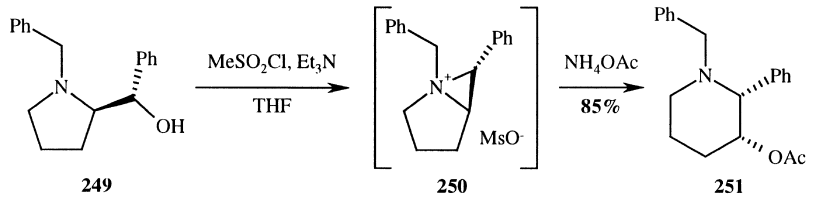
In their approach to the synthesis of palinavir, Comins et al.[127] synthesised 2,4-substituted piperidines enantioselectively from the pyridine **243** (Scheme 78). A chiral pool strategy was used and the enantiomerically-pure (85% de) pyridinium salt **244** was formed. Grignard addition at the C-2 position of the pyridine, followed by methyl ether deprotection, afforded the hydropyridinone **245** as a single diastereoisomer in 78% yield. The hydropyridinone **246** was then formed in 89% yield by treatment with NaOMe, followed by aqueous acid, and the chiral auxiliary was recovered during this process. Protection was then achieved, followed by conjugate reduction using Zn in AcOH, affording the piperidinone **247** in 92% yield. Ozonolysis, followed by Jones' oxidation, benzyl esterification and K-selectride reduction, afforded the piperidine **248** as a single diastereoisomer in 49% yield.

The preparation of trisubstituted piperidines via the reduction of pyridines is very difficult and, as Bols and

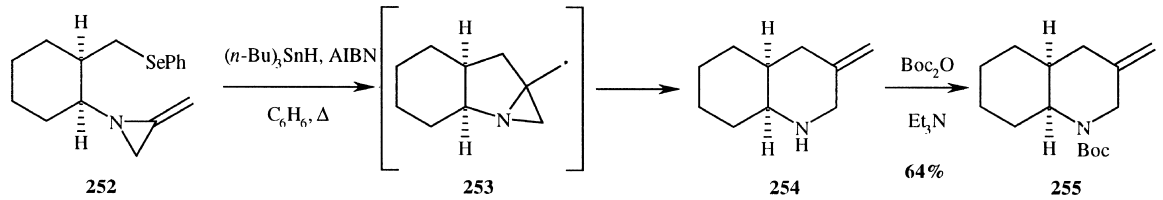


Scheme 77.

Scheme 78.



Scheme 79.



Scheme 80.

co-workers[128] have reported, mixtures of diastereoisomers are formed. Diastereoselective control via this type of reduction is very difficult.

5. Ring expansions and rearrangements

5.1. Ring expansion from pyrrolidines

Lee et al.[129] used an unusual method for making piperidines via a ring expansion of the hydroxymethylpyrrolidine **249** (Scheme 79). This strategy was demonstrated to be a highly stereoselective method for synthesising 2,3-disubstituted piperidines from *N*-benzylpyrrolidines such as **249**. Treatment of the compound **249** with methanesulphonyl chloride and triethylamine is believed to form the azoniabicyclo[3.1.0]hexane intermediate **250**, which, when quenched with ammonium acetate, undergoes a ring expansion to form the acetoxypiperidine **251** in 85% yield and 99% ee.

5.2. Intramolecular radical rearrangement

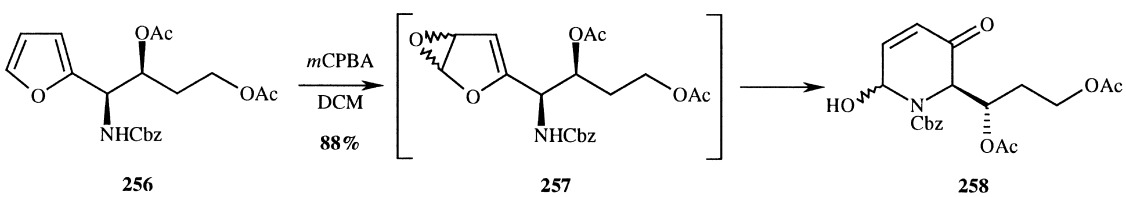
Shipman et al.[130] have been working on the intramolecular 5-*exo* cyclisation of the 3-(2-methyleneaziridin-1-yl)propyl radical generated from the corresponding selenide. Treatment of the 2-methyleneaziridine **252** with $(n\text{-Bu})_3$SnH and AIBN afforded via **253** the corresponding piperidine **254**, which was immediately Boc protected (Scheme 80). The piperidine **255** was obtained in 64% yield over the two steps.

5.3. Oxidation of furans

In their approach towards the synthesis of indolizidines, Padwa et al.[131] oxidised a furan with *m*CPBA to furnish an epoxy intermediate, which rearranged via an aza-Achmatowicz reaction to provide a hemiaminal in 85% yield. Zhou and co-workers[132] used the same strategy in their synthesis of (+)-6-epicastanospermine and demonstrated that rearrangement was favoured over nucleophilic substitution. Indeed, the furan **256** containing both primary and secondary acetates was oxidised with *m*CPBA to afford the hemiaminal **258** via the intermediate **257** in 88% yield (Scheme 81).

6. Conclusions

The synthesis of diversely-functionalised piperidines remains one of the challenges of organic chemistry. Although the synthesis of 2,6-disubstituted piperidines has been widely investigated, the preparations of more complex piperidines such as 3-, 4- and 5-multisubstituted piperidines, as well as piperidines containing quaternary centres, are less prevalent in the literature. The main strategy involved in constructing piperidine rings is via the cyclisation of a linear chain and this method is generally high yielding and reliable, although it demonstrates a lack of convergence. The synthesis of piperidines via the aza Diels–Alder reaction looks promising, but this methodology has not been yet widely applied. The preparation of piperidines through the reduction of pyridines has the advantage that the heterocyclic ring is already present, but the generalisation of this procedure to the synthesis of complex piperidines has been shown to be difficult. Finally, the rearrangement to piperidines is not a commonly-used method, although the technique shows some advantages in the synthesis of 2-mono- or 2,6-disubstituted piperidines. The preparation of piperidines has been widely studied, but their synthesis



Scheme 81.

remains a major challenge as more and more complex piperidine-containing compounds are designed, in order to improve the selectivity and therefore reduce the side effects of potential drugs.

Acknowledgements

I would like to thank Professor E. J. Thomas for his invaluable guidance and encouragement during my time in Manchester. I would also like to thank Dr. Chris Moore who generously volunteered to proofread this report and his input is gratefully welcomed.

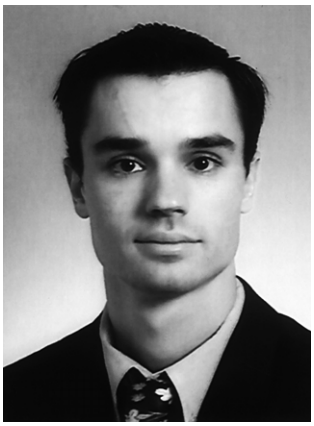
References and notes

1. Baliah, V.; Jeyraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379–423.
2. Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781–1813. Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978.
3. Mao, H.; Joly, G. J.; Peeter, K.; Hoonaert, G. J.; Compernolle, F. *Tetrahedron* **2001**, *57*, 6955–6967.
4. Pearce, H. L.; Bach, N. J.; Cramer, T. L. *Tetrahedron Lett.* **1989**, *30*, 907–910.
5. Hanessian, S.; Griffin, A. M.; Cantin, L. D. *Chirality* **2000**, *12*, 342–345.
6. Fustero, S.; Diaz, M. D.; Carrio, J. C.; Aguilar, E. *Eur. J. Org. Chem.* **2001**, 1195–1201.
7. Suginome, S.; Yamada, S.; Wang, J. B. *J. Org. Chem.* **1990**, *55*, 2170–2176.
8. Mellor, J. M.; Pathirana, R. N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 753–756.
9. Kalaus, G.; Greiner, I.; Kajtar-Peredy, M.; Brlik, J.; Szabo, L.; Szantai, C. *J. Org. Chem.* **1993**, *58*, 1434–1442.
10. White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373–2376.
11. Fleet, G. W. J.; Carpentier, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409–412.
12. Holzapfel, C. W.; Crous, R.; Greyling, H. F.; Verdoorn, G. H. *Heterocycles* **1999**, *51*, 2801–2806.
13. Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279–3282.
14. Mehta, G.; Mohal, N. *Tetrahedron Lett.* **2000**, *41*, 5747–5751.
15. Quallich, G. J.; Makowski, T. W.; Sanders, A. F.; Urban, F. J.; Vazquez, E. *J. Org. Chem.* **1998**, *63*, 4116–4119.
16. Grandel, R.; Kazmaier, U.; Rominger, F. *J. Org. Chem.* **1998**, *63*, 4524–4528.
17. Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995–3000.
18. Kilonda, A.; Compernolle, F.; Peeters, K.; Joly, G. J.; Toppet, S.; Hoornaert, G. J. *Tetrahedron* **2000**, *56*, 1005–1012.
19. Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332–2342.
20. Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988–4990.
21. Sdassi, H.; Revial, G.; Pfau, M.; D'Angelo, J. *Tetrahedron Lett.* **1990**, *31*, 875–879.
22. Asaoka, M.; Ohkura, N.; Yokota, M.; Sonoda, S.; Takei, H. *Heterocycles* **1994**, *38*, 2455–2462.
23. Depezay, J. C. In *Carbohydrate mimics concepts and methods*; Chapleur, Y., Ed.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; pp 307–326. Duréault, A.; Tranchepain, I.; Depezay, J. C. *J. Org. Chem.* **1989**, *54*, 5324–5330.
24. Tong, M. K.; Blumenthal, E. M.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 1683–1684.
25. Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660–4662.
26. Bendl, M.; Eder, M.; Langhammer, I.; Urban, E. *Heterocycles* **2000**, *53*, 115–126.
27. Grigg, R.; Hargreves, S.; Redparth, J.; Turchi, S.; Yoganathan, G. *Synthesis* **1999**, 441–446.
28. Tietze, L. F.; Bachmann, J.; Schul, W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 971–973.
29. Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623–4626.
30. Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623–2625.
31. Garcia Ruano, J. L.; Cifuentes, M. M.; Lorente, A.; Rodriguez Ramos, J. H. *Tetrahedron: Asymmetry* **1999**, *10*, 4607–4618.
32. Jaroch, S.; Matsuoka, R. T.; Overman, L. E. *Tetrahedron Lett.* **1999**, *40*, 1273–1276.
33. Budzinska, A.; Sas, W. *Tetrahedron Lett.* **2001**, *42*, 105–107.
34. Weber, K.; Ohnmacht, U.; Gmeiner, P. *J. Org. Chem.* **2000**, *65*, 7406–7416.
35. Sun, H.; Millar, K. M.; Yang, J.; Abboud, K.; Horenstein, B. A. *Tetrahedron Lett.* **2000**, *41*, 2801–2804.
36. Yu, M. S.; Lantos, I.; Peng, Z. Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647–5651.
37. Enders, D.; Teschner, P.; Raabe, G. *Heterocycles* **2000**, *52*, 733–749. Enders, D.; Gröbner, R.; Raabe, G.; Runsink, J. *Synthesis* **1996**, 941–948.
38. Kirby, A. J.; Komarov, I. V.; Feeder, N. *J. Chem. Soc., Perkin Trans. 2* **2001**, 522–529.
39. Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116–8129.
40. Kawamura, K.; Kawai, K.; Miyamoto, T.; Ooshima, K.; Nagase, H. *Heterocycles* **1998**, *48*, 267–283.
41. Poupon, E.; Luong, B. X.; Chiaroni, A.; Kunesch, N.; Husson, H. P. *J. Org. Chem.* **2000**, *65*, 7208–7210.
42. Amat, M.; Canto, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343–5351.
43. Martin, O. R.; Saavedra, O. M.; Xie, F.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem.* **2001**, *9*, 1269–1278.
44. Ohtani, B.; Kusakabe, S.; Okada, K.; Tsuru, S.; Nishimoto, S.; Amino, Y.; Izawa, K.; Nakato, Y.; Matsumura, M.; Nakaoka, Y.; Nasaka, Y. *J. Chem. Soc., Perkin Trans. 2* **2001**, 201–209. Othani, B.; Kusakabe, S.; Okada, K.; Tsuru, S.; Izawa, K.; Amino, Y.; Nishimoto, S. *Tetrahedron Lett.* **1995**, *36*, 3189–3192.
45. Laeckmann, D.; Rogister, F.; Dejardin, J. V.; Prosperi-Meys, C.; Géczy, J.; Delarge, J.; Masereel, B. *Bioorg. Med. Chem.* **2002**, *10*, 1793–1804.
46. MacAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849–1853.
47. Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086–1093.
48. Barco, A.; Beneti, S.; Casolari, A.; Pollini, G. P.; Spalluto, G. *Tetrahedron Lett.* **1990**, *31*, 3039–3042.
49. Hughes, F., Jr.; Grossman, R. B. *Org. Lett.* **2001**, *3*, 2911–2914.

50. Ihara, M.; Setsu, F.; Shohda, M.; Taniguchi, N.; Takunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 5317–5323.
51. Zhang, X.; Jung, X. S.; Marino, P. S.; Fox, M. A.; Martin, P. S.; Merkert, J. *Tetrahedron Lett.* **1993**, *34*, 5239–5242.
52. Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344–4347.
53. Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421–5424.
54. Krafft, M. E.; Wilson, L. J.; Onan, K. D. *Tetrahedron Lett.* **1988**, *29*, 6421–6424.
55. Zang, Z.; Ojima, I. *J. Organomet. Chem.* **1993**, *454*, 281–289.
56. Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172–4178.
57. Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570–4571.
58. Haak, E.; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2002**, 457–463.
59. Lokantha, K. M.; Hassner, A. *Heterocycles* **1990**, *30*, 817–830.
60. MaGee, D. I.; Ramaseshan, M.; Leach, J. D. *Can. J. Chem.* **1995**, *73*, 2111–2118.
61. Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612–614.
62. Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393–5401.
63. Lee, K. L.; Goh, J. B.; Martin, S. F. *Tetrahedron Lett.* **2001**, *42*, 1635–1638.
64. Donds, H. A.; Balme, G.; Clique, B.; Grigg, R.; Hodgeson, A.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2001**, *42*, 8673–8675.
65. Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029–8033.
66. Kindeman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045–2048.
67. Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.
68. Takacs, B. E.; Takacs, J. M. *Tetrahedron Lett.* **1990**, *31*, 2865–2868.
69. Takacs, J. M.; Anderson, L. G.; Madhavan, G. V. B.; Creswell, M. W.; Seely, F. L.; Devroy, W. F. *Organometallics* **1986**, *5*, 2395–2398.
70. Takacs, J. M.; Zhu, J.; Chandramouli, S. *J. Am. Chem. Soc.* **1992**, *114*, 773–774.
71. Yamaura, Y.; Yakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615–7616.
72. Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synlett* **1994**, 451–453.
73. Trost, B. M.; Tost, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714–715.
74. Laschat, S.; Grehl, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 458–461.
75. Tietze, L. F.; Bratz, M.; Pretor, M. *Chem. Ber.* **1989**, *122*, 1955–1961. Tietze, L. F.; Bratz, M. *Chem. Ber.* **1989**, *122*, 997–1002.
76. Tietze, L. F.; Bratz, M. *Synthesis* **1989**, 439–442.
77. Homes, A. B.; Swithenbank, C.; Williams, S. F. *J. Chem. Soc., Chem. Commun.* **1986**, 265–266.
78. Mori, M.; Kanda, N.; Ban, Y.; Aoe, K. *J. Chem. Soc., Chem. Commun.* **1988**, 12–14. Mori, M.; Kubo, Y.; Ban, Y. *Tetrahedron Lett.* **1985**, *26*, 1519–1522. Mori, M.; Kubo, Y.; Ban, Y. *Tetrahedron* **1988**, *44*, 4321–4330.
79. Curran, D. P.; Chang, C. T. *Tetrahedron Lett.* **1990**, *31*, 933–936.
80. Hoffmann, R. W.; Brückner, D.; Gerusz, V. J. *Heterocycles* **2000**, *52*, 121–124. Hoffmann, R. W.; Hense, A. *Liebigs Ann.* **1996**, 1283–1288.
81. Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153–1168.
82. Oppolzer, W.; Gaudin, J. M.; Bedoya-Zurita, M.; Hueso-Rodriguez, J.; Rayhnam, T. M.; Robyr, C. *Tetrahedron Lett.* **1988**, *29*, 4709–4712. Oppolzer, W.; Swenson, R. E.; Gaudin, J. M. *Tetrahedron Lett.* **1988**, *29*, 5529–5532.
83. Kang, S. K.; Ha, Y. H.; Ko, B. S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 343–345.
84. Ha, Y. H.; Kang, S. K. *Org. Lett.* **2002**, *4*, 1143–1146. Kang, S. K.; Lee, S. W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376–4379.
85. Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1987**, *26*, 2805–2809.
86. Solé, D.; Garcia-Rubio, S.; Bosch, J.; Bonjoch, J. *Heterocyles* **1996**, *43*, 2415–2424.
87. Mann, A.; Nativi, C.; Taddei, M. *Tetrahedron Lett.* **1988**, *29*, 3247–3250.
88. Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984–6990.
89. Ishikura, M.; Hino, A.; Katagiri, N. *Heterocycles* **2000**, *53*, 11–14.
90. Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585–5596.
91. Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058–4067.
92. Larock, R. C.; Yang, H.; Weinreb, S. M.; Herr, R. J. *J. Org. Chem.* **1994**, *59*, 4172–4178.
93. Teng, T. F.; Lin, J. H.; Yang, T. K. *Heterocycles* **1990**, *31*, 1201–1204.
94. Murata, Y.; Overman, L. E. *Heterocycles* **1996**, *42*, 549–553.
95. Göttlich, R. *Synthesis* **2000**, 1561–1564.
96. Hemmerling, M.; Sjöholm, A.; Somfai, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4091–4094. Sjöholm, A.; Hemmerling, M.; Pradeille, N.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 891–899.
97. Shim, S. C.; Hwang, J. T. *Tetrahedron Lett.* **1990**, *31*, 4765–4768.
98. Yoo, S. E.; Yi, K. Y.; Lee, S. H.; Jeong, N. *Synlett* **1990**, 575–576.
99. Parsons, A. F.; Pettifer, R. M. *Tetrahedron Lett.* **1997**, *38*, 5907–5910. Parsons, A. F.; Pettifer, R. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 651–660.
100. Naito, T.; Tajtri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205–2206. Naito, T.; Nakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem.* **1999**, *64*, 2003–2009.
101. Ma, D.; Sun, H. *J. Org. Chem.* **2000**, *65*, 6009–6016.
102. De Risi, C.; Pollini, G.; Piero, G.; Trapella, C.; Peretto, I.; Ronzoni, S.; Giardina, G. A. M. *Bioorg. Med. Chem.* **2001**, *9*, 1871–1877.
103. Deshmukh, M. N.; Sampath Kumar, U.; Rama Rao, A. V. *Synth. Commun.* **1995**, 177–182.
104. Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958–960.
105. Heintzelman, G. R.; Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 4594–4599.
106. Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **1999**, *55*, 7601–7612.

107. Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Org. Lett.* **2002**, *4*, 1971–1974.
108. Barluenga, J.; Aznar, F.; Ribas, C.; Valdès, C. *J. Org. Chem.* **1999**, *64*, 3736–3740.
109. Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, *55*, 2999–3000.
110. Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713–1729. Boger, D. L.; Zang, M. *J. Org. Chem.* **1992**, *58*, 3974–3977. Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839–11849.
111. Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1992**, *58*, 2075–2080.
112. Tietze, L. F.; Schuffenhauer, F. *Eur. J. Org. Chem.* **1998**, 1629–1637.
113. Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986**, *42*, 2903–2910.
114. Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286–4292.
115. Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51*, 3672–3679.
116. Zhao, G.; Deo, U. C.; Ganem, B. *Org. Lett.* **2001**, *3*, 201–203.
117. Akiba, K. Y.; Othani, A.; Yamamoto, Y. *J. Org. Chem.* **1986**, *51*, 5328–5332.
118. O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201–4204.
119. Sakagami, H.; Ogasawara, K. *Synlett* **2001**, 45–48. Tanaka, H.; Sakagami, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 93–96.
120. Trancard, D.; Tout, J. B.; Giard, T.; Chichaoui, I.; Cahard, D.; Plaquevent, J. C. *Tetrahedron Lett.* **2000**, *41*, 3843–3847.
121. Shih, K. S.; Liu, C. W.; Hsieh, Y. J.; Chen, S. F.; Ku, H.; Liu, L. T.; Lin, Y. C.; Huang, H. L.; Jeff Wang, C. L. *Heterocycles* **1999**, *51*, 2439–2444.
122. Drinkuth, S.; Groethsch, S.; Peters, E. M.; Peters, K.; Christl, M. *Eur. J. Org. Chem.* **2001**, 2665–2670.
123. Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, *8*, 1218–1226.
124. Collins, I.; Davey, W. B.; Rowley, M.; Quirk, K.; Bromidge, F. A.; MacKernan, R. M.; Thompson, S. A.; Wafford, K. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1381–1384.
125. Steiner, H.; Giannousis, P.; Pirsche-Jacques, A.; Blaser, H. U. *Top. Catal.* **2000**, *13*, 191–194.
126. Douja, N.; Besson, M.; Gallezot, P.; Pinel, C. *J. Mol. Catal. A: Chem.* **2002**, *186*, 145–151.
127. Brooks, C. A.; Comins, D. L. *Tetrahedron Lett.* **2000**, *41*, 3551–3553.
128. Liang, X.; Lohse, A.; Bols, M. *J. Org. Chem.* **2000**, *65*, 7432–7437.
129. Lee, J.; Askin, D.; Hoang, T. U.S. Pat. Appl. Publ. US 20020019532, 2002.
130. Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383–2385.
131. Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371–4381.
132. Zhang, H. X.; Xia, P.; Zhou, W. S. *Tetrahedron* **2003**, *59*, 2015–2020.

Biographical sketch



Maxime G. P. Buffat was born in 1977 in Tournon-sur-Rhône, France. He graduated from the ECPM, Strasbourg, France in 2000 before moving to the University of Manchester, UK where he carried out his PhD studies under the supervision of Professor E. J. Thomas. His research focused on the synthesis of selective M_1 muscarinic receptor agonists. In 2003, he joined the group of Professor Stephen Hanessian in Montreal.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1731–1748

Inhibitors of biotin biosynthesis as potential herbicides

Ayelet Nudelman,[a] Dana Marcovici-Mizrahi,[b] Abraham Nudelman,[c,*] Dennis Flint[d] and Vernon Wittenbach[e]

[a]*QBI Enterprises Ltd., Weizmann Science Park, Ness Ziona 70400, Israel*
[b]*Department of Organic Chemistry, Israel Institute for Biological Research, PO Box 19, Ness Ziona 74100, Israel*
[c]*Department of Chemistry, Bar Ilan University, Ramat Gan 52900, Israel*
[d]*E. I. Du Pont de Nemours and Company, Central Research and Development, Experimental Station, Wilmington, DE 19880-0328, USA*
[e]*E. I. Du Pont de Nemours and Company, Stine-Haskell Research Center, Newark, DE 19714, USA*

Received 2 December 2003; accepted 18 December 2003

Abstract—Isosteric derivatives and analogues of the 7-keto-8-aminopelargonic acid (KAPA), 7,8-diaminopelargonic acid (DAPA) and desthiobiotin (DTB) vitamer intermediates involved in the biosynthetic pathway of biotin were prepared and evaluated as potential herbicides. The most active compound was desmethyl-KAPA which displayed a GR_{50} (concentration of the active compound that causes a 50% growth inhibition) value of 8 ppm, where values <50 ppm are considered herbicidal. Other KAPA analogs where the terminal Me group was replaced by bulkier substituents such as Et, *i*-Pr and $HOCH_2$ showed moderate activity.

1. Introduction

Biotin, a water soluble vitamin, functions as a coenzyme in carboxylation and transcarboxylation reactions critical to microorganisms, plants and animals.[1] The importance of biotin to metabolism is derived from its participation in many vital metabolic processes, such as gluconeogenesis, biosynthesis of fatty acids and metabolism of amino acids. Perhaps its most important role is in the carboxylation of acetyl-CoA to give malonyl-CoA, which is the first step in

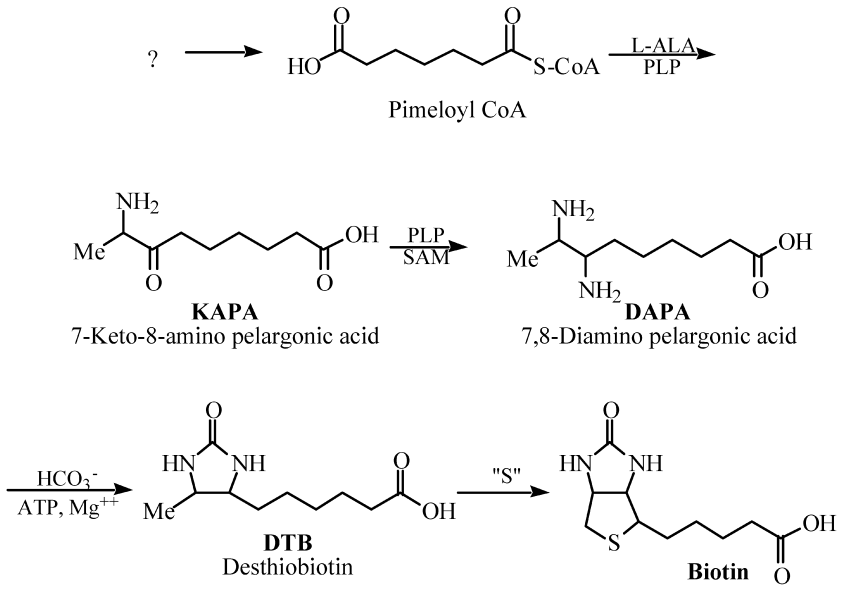
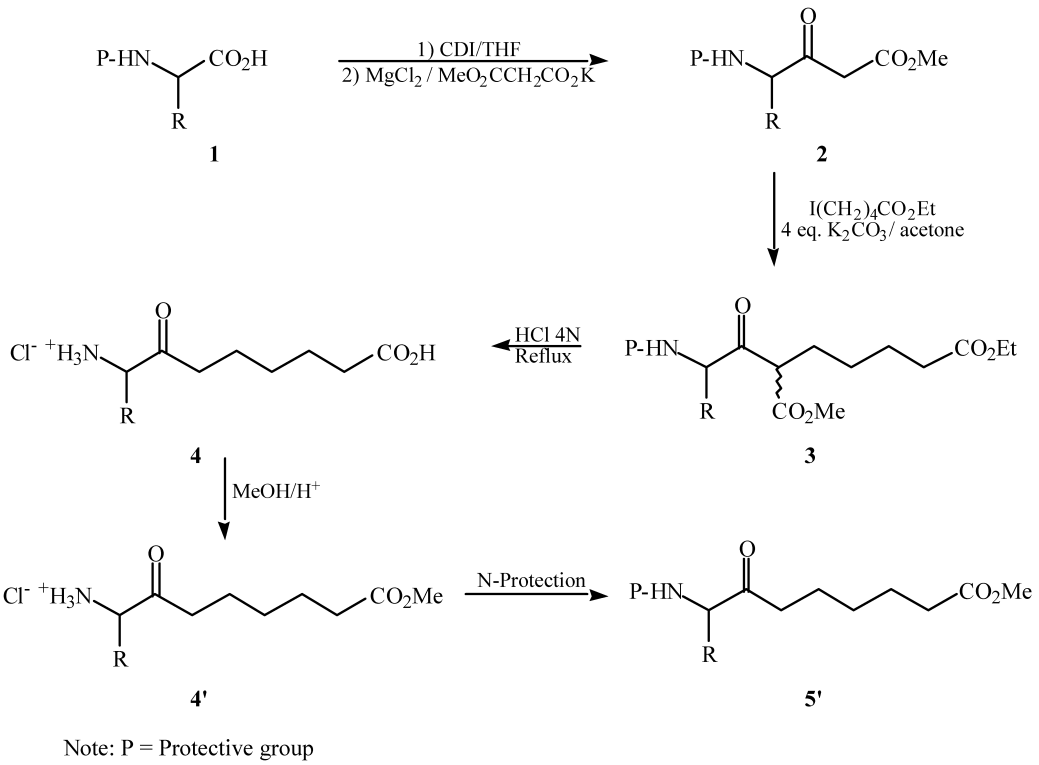


Figure 1. Biosynthetic pathway of biotin.

Keywords: Biotin; Biotin vitamers; 7-Keto-8-aminopelerginic acid (KAPA); 7,8-Diaminopelargonic acid (DAPA); Desthiobiotin (DTB); Herbicides; Enzyme inhibitors.
* Corresponding author. Tel.: +972-3-531-8314; fax: +972-3-535-1250; e-mail address: nudelman@mail.biu.ac.il

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.047

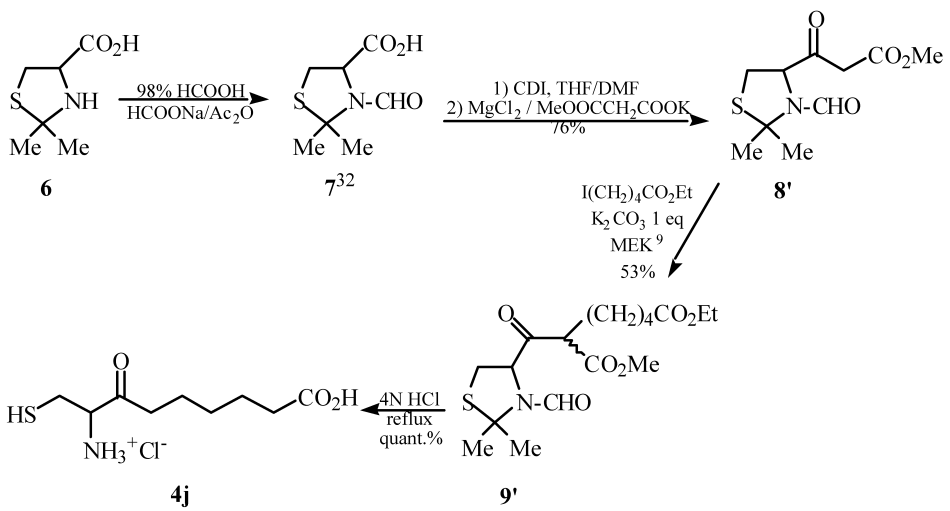


Scheme 1. General synthesis of KAPA analogs.

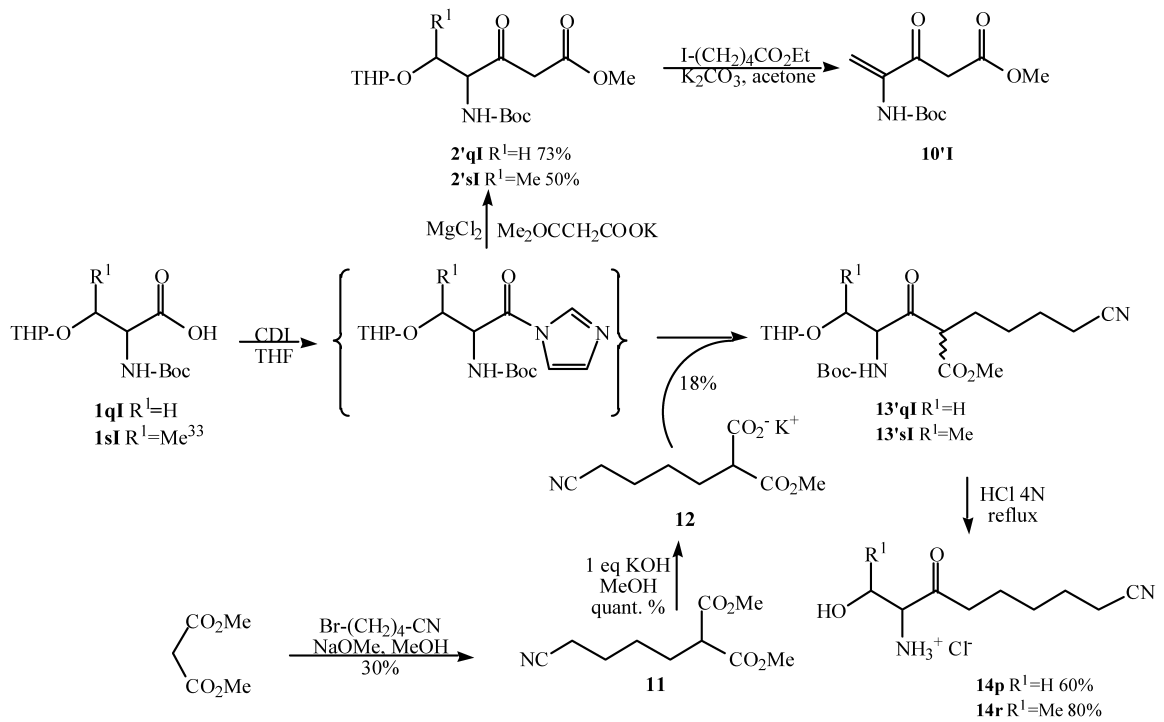
fatty acid biosynthesis. Since fatty-acid synthesis is essential for the growth and development of most organisms, biotin is thus an essential nutrient for plants and animals. Plants, microorganisms and some fungi biosynthesize their own biotin, while animals and man require trace amounts of the vitamin in their diet.

The biotin biosynthetic pathway[2] (Fig. 1), involving the KAPA, DAPA and DTB vitamers, is well understood in microorganisms[3] but has not been clearly elucidated in plants. However, there is increasing evidence that plants synthesize it by a similar route to that used by *E. coli*.[4] Recent studies indicate that the source of the sulfur atom, in the conversion of DTB to biotin, catalyzed by biotin synthase stems from an iron–sulfur cluster found in this enzyme.[5]

Inhibitors of enzymes involved in the biosynthesis of essential plant nutrients can cause irreparable damage to plants, and for this reason such enzymes can be useful targets for the rational design of inhibitors in the hopes of finding new herbicides. We describe the synthesis and biological evaluation of analogs of biotin and biotin vitamers (molecules, such as intermediates in the biotin biosynthetic pathway, that can be converted into biotin in vivo) as potential enzyme inhibitors with the objective of finding some that exhibit herbicidal activity. Moreover, since the enzymes involved in the biotin biosynthetic



Scheme 2. Synthesis of KAPA analogs derived from cysteine.



Scheme 3. Synthesis of KAPA analogs derived from THP-protected serine and threonine.

pathway are absent in higher organisms, it is expected that inhibitors of biotin biosynthesis will possess minimal toxicity in animals and man.

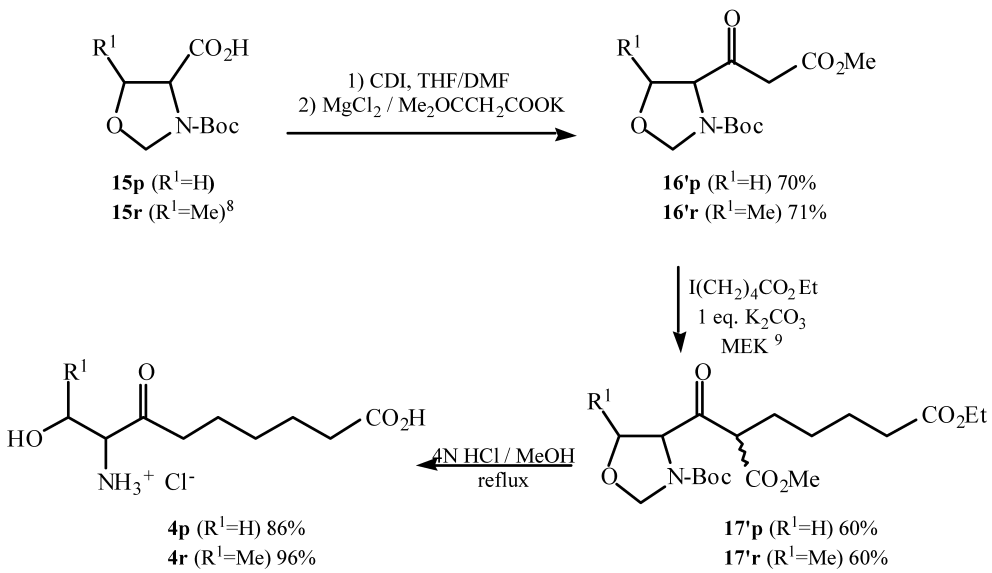
2. Results and discussion

Based on the structures of the vitamers of biotin, several families of analogs were developed, each featuring one or more isosteric modifications. The synthetic approaches to these derivatives were based to a large extent on our earlier synthesis of the vitamers.[6] The compounds described below are analog derivatives of KAPA, DAPA and DTB having chain lengths of nine carbon atoms, focusing primarily on compounds prepared from various amino acids, resulting in modifications of the terminal Me group.

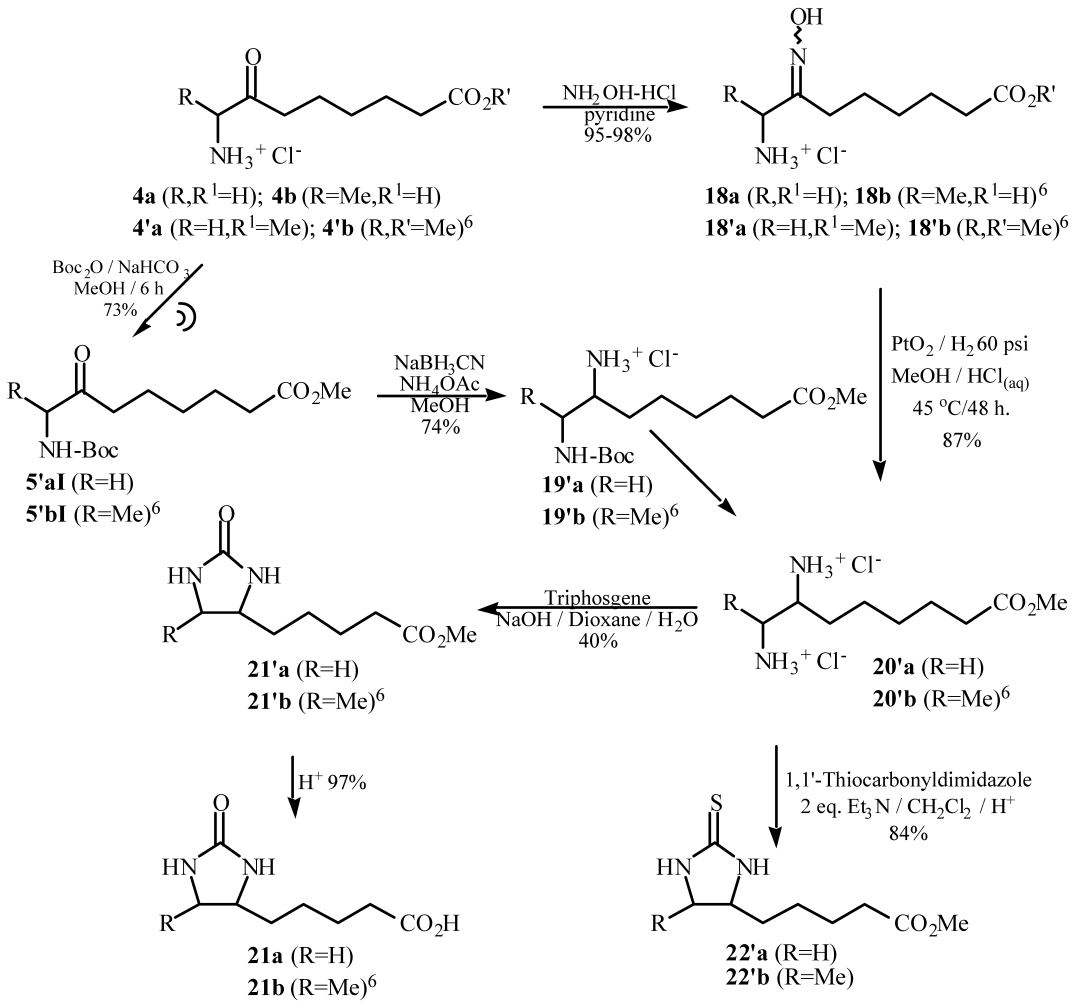
2.1. KAPA analogs

Substrates **1** (Scheme 1, Table 1) were derivatives of natural L-amino acids with the exclusion of the racemic *N*-Boc-α-aminobutyric acid (**1c** R=Et), *S*-benzyl-cysteine (**1k** R=$BnSCH_2$) and *S*-Boc-cysteine (**1k** R=$BocSCH_2$).

The syntheses of KAPA analogs derived from cysteine **4j**, serine **4p** and threonine **4r**, that required additional protection of the *S* and *O* atoms, are shown in Schemes 2–4. An initial attempt to prepare **4j** involved reaction of



Scheme 4. Synthesis of KAPA analogs derived from serine and threonine.



Scheme 5. Synthesis of DTB and thio-DTB derivatives.

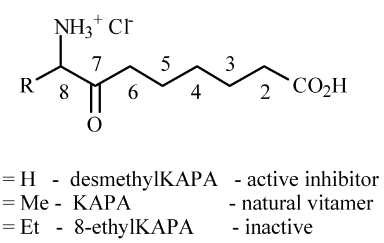
Bn-*S*-cysteine (Bn) to give the desired β-ketoester analog **2m**. However, due to the high nucleophilic character of the *S* atom, alkylation of **2m** with I–$(CH_2)_5$–COOEt took place preferentially at *S* rather than at *C* (Scheme 1). Other cysteine derivatives protected both at the *S* and the *N* with Boc (**1kI**), CBZ (**1lII**) or Ac (**1nIV**)[7] groups, gave poor yields of the respective derivatives **2**. The desired **4j** was finally obtained from thiazolidine **7** that possessed a sterically hindered sulfide group (Scheme 2).

Attempted alkylation on the respective β-ketoester derivatives of *N*-Boc-*O*-THP-protected serine **2′qI** or threonine **2′sI** led to elimination of THP-OH to give compound **10′I**, which was not isolated and was identified only by its characteristic vinylic peaks in the NMR spectrum. To prevent this base catalyzed elimination an alternative approach to **4p** and **4q** involved the coupling of the diprotected *N*-Boc-*O*-THP-serine and threonine with the nitrile derivative **12**. Although the desired cyano esters **13′qI** and **13′sI** were obtained, subsequent hydrolysis and decarboxylation gave KAPA-analogs **14q** and **14s** where the CN group remained intact (Scheme 3).

The desired **4p** and **4r** were finally obtained from the amino acids protected as their respective *N*-Boc oxazolidines **15p** and **15r**,[8] via the intermediate diesters **16′p** and **16′r** (Scheme 4). In contrast to compounds of structure **2**, which were alkylated in acetone in the presence of four equivalents of K_2CO_3, the alkylation of **16′p** and **16′r** readily proceeded with one equivalent of base in 2-butanone (MEK).

2.2. DAPA and DTB analogs

The synthesis of the neighboring diamino functionality found in the DAPA skeleton was approached via oximation of the α-amino-keto group of the KAPA analogs **4**.[6] Although the α-amino-oximes **18a** and **18b** were obtained as mixtures of *syn* and *anti*-isomers, one isomer predominated. This encouraged us to believe that the chiral center at C-8 could induce stereoselectivity upon oximation and would do so in the subsequent reductive step leading to



R = H - desmethylKAPA - active inhibitor
R = Me - KAPA - natural vitamer
R = Et - 8-ethylKAPA - inactive

Figure 2. SAR of KAPA derivatives.

Table 1. P and R substituent assignments

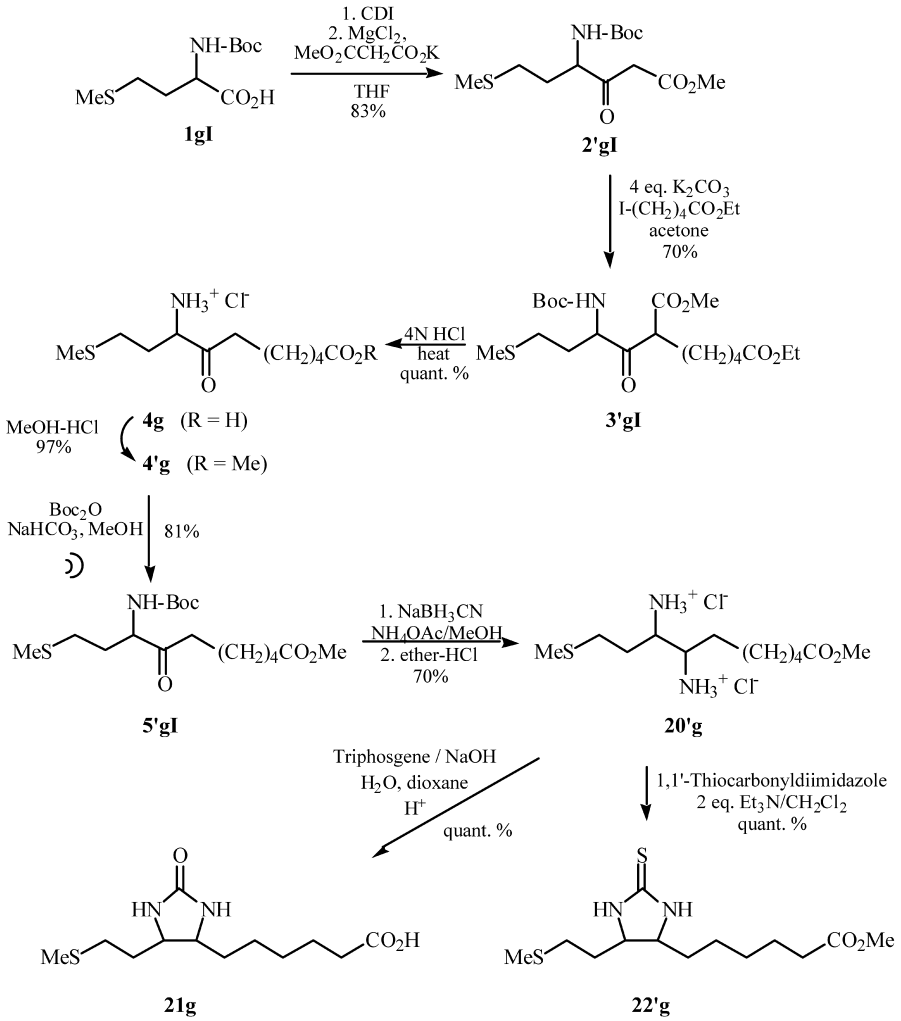
P *N*-Protective group	Code
Boc	I
CBZ	II
MeOCO	III
Ac	IV
R-substituent	Code
H-	a
Me–	b
Et–	c
i-Pr–	d
i-Bu–	e
sec-Bu–	f
$MeSCH_2CH_2$–	g
$MeS(O)CH_2CH_2$–	h
$MeSCH_2$–	i
$HSCH_2$–	j
Boc-SCH_2–	k
CBZ-SCH_2–	l
Bn-SCH_2–	m
Ac-SCH_2–	n
CH_2=CH–	o
$HOCH_2$–	p
THP-OCH_2–	q[28]
HOCH(Me)–	R
THP-OCH(Me)–	s[28]

Note: all Me esters are labeled as #′.

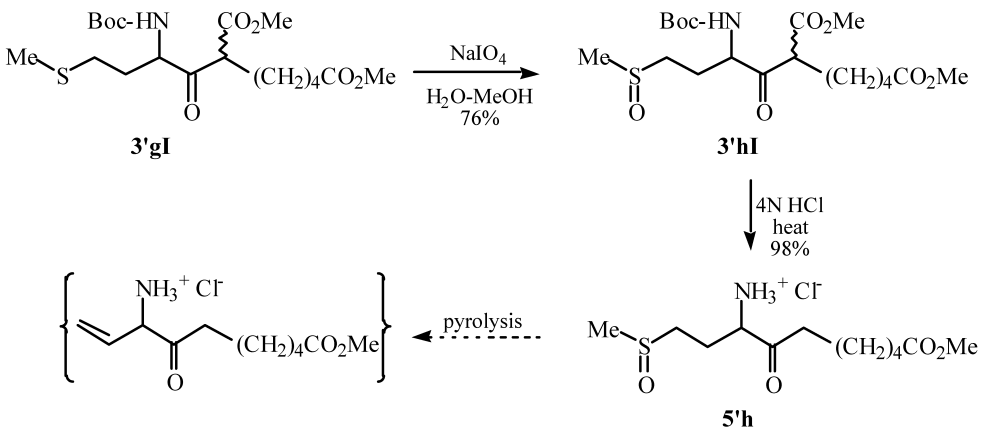
desired *cis*-diamino analogs. Alas, the diamines **19′a** and **19′b** were obtained as equimolar mixtures of two diastereomers. A similar loss of chiral discrimination was described earlier.[6] Based on biological data (see below), derivatives **20′a** and **20′b** were cyclized to the respective DTB analogs **21′a** and **21′b** (Scheme 5). Since *S*-containing KAPA-analogs **5′g–n** were unsuitable to catalytic hydrogenation due to catalyst poisoning, for these compounds an alternative route to the DAPA structure was developed involving reductive amination with $NaBH_3CN$. This procedure was also convenient for the threonine analog **4rI**. Since standard *N*-Boc protection of amines involves basic conditions, to avoid possible decomposition of free amino ketones obtained upon acid neutralization of derivatives **4′**, mild basic conditions coupled with sonnication were found to be satisfactory for the preparation of the *N*-Boc derivatives **5′aI** and **5′bI**. These compounds were amenable to subsequent $NaBH_3CN$ reduction in organic media. The DAPA analogs **21a** and **21b** were found to be racemic at the C-7 centers (Scheme 5).[6]

2.3. Vinyl derivatives

The natural vitamer, KAPA **4b**, possesses a terminal R=Me group. In these studies, the first analog found to possess



Scheme 6. DTB and thio-DTB analogs derived from methionine.



Scheme 7. Attempted synthesis of vinyl-KAPA.

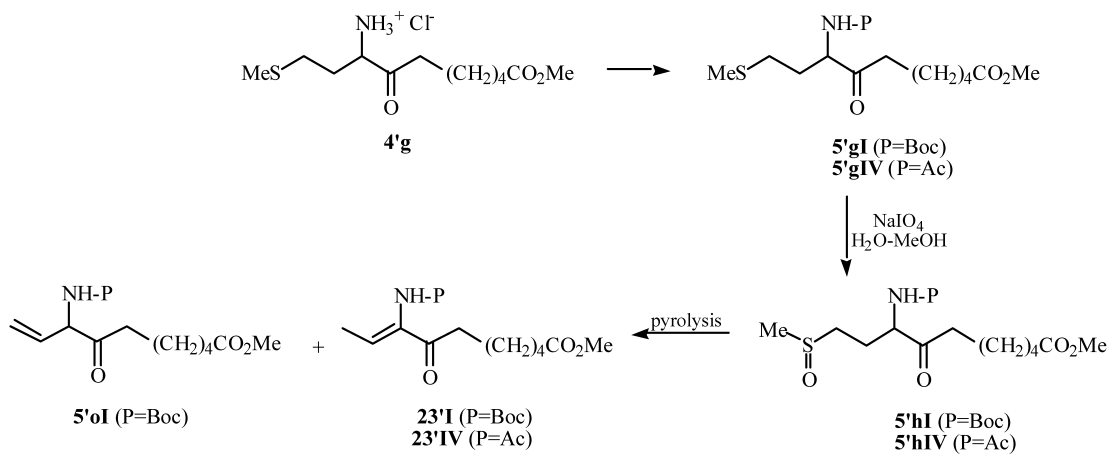
inhibitory effects on plant growth was the analog **4a** where R=H. However when an additional carbon was added, **4c** R=Et, no inhibition was detected. Being that a vinyl group is larger than a Me group, yet smaller than an Et group, introduction of a vinyl substituent at position 8 was expected to provide additional information on the steric demands for molecular fit at this part of the molecule (Fig. 2).

Given that L-alanine was the substrate for KAPA, and glycine was used in the preparation of desmethyl-KAPA,[9] L-vinylglycine,[10] **1o**, was the preferred starting material for the synthesis of the 9-vinyl derivative **4o**. In addition to its enzyme-inhibitory and antibiotic properties L-vinylglycine has become an important chiral starting material for a variety of other amino acid syntheses and optically active products. Since the attempted direct formation of the β-keto ester of vinylglycine, analog of compound **2′o**, failed, apparently due to the acidity of the methine proton of vinylglycine, the β-keto ester of methionine **2′gI** was prepared from *N*-Boc-methionine **1gI** by Mansour's method.[11] By analogous methodology to that described in Scheme 1, **2′gI** was further converted into KAPA, DAPA, DTB and thio-DTB analogs **4g**, **20′g**, **21′g** and **22′g**, respectively (Scheme 6). The lack of herbicidal activity of these derivatives may be attributed to the presence of the $MeSCH_2$-substituent on C-8, being probably too big to fit into the enzymatic 'cavity' suitable for a Me group.

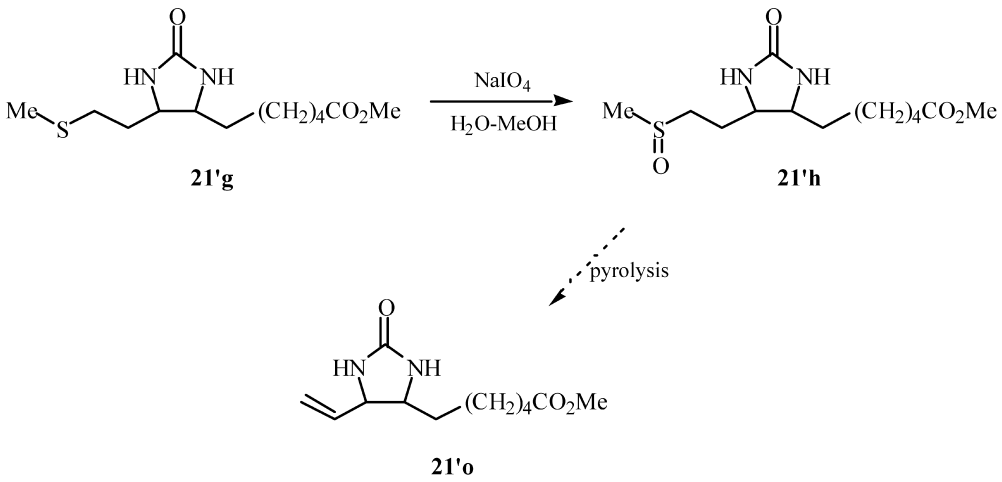
Periodate oxidation of **3′gI** to sulfoxide **3′hI**[12] followed by removal of the *N*-Boc protective group gave the KAPA analog **5′h**. Because the attempted pyrolysis of **5′h** to the corresponding vinylic KAPA derivative failed (Scheme 7), an alternative approach to the vinylic derivative was developed. Reaction of **4′g** with di-*tert*-butyl dicarbonate or acetylimidazole yielded sulfides **5′gI** and **5′gIV**, that were oxidized to sulfoxides **5′hI** and **5′hIV**, respectively. Whereas pyrolysis of **5′hI** afforded a mixture of **5′oI** and **23′I**, the *N*-acetylated **5′hIV** due to the higher acidity of the methine hydrogen α to the amido group, gave only the corresponding **23′IV** (Scheme 8). Although in the former case some of the desired **5′oI** was isolated, because of concomitant loss of the Boc group under the pyrolysis conditions, the overall yield of the mixture of olefins was very low.

In an attempt to avoid the isomerization of the double bond in **5′oI** leading to **23′oI**, attributed to the acidity of the proton α to the carbonyl group, sulfoxide **21′h**, obtained by periodate oxidation of **21′g**, was pyrolyzed, however the reaction was unsuccessful (Scheme 9).

To stay away from ketonic groups having acidic α-protons, DAPA derivatives protected with groups other than *N*-Boc, were examined. Sulfoxide **20′hII** was obtained in excellent yield when **20′gII** suspended in MeOH was dissolved in CH_2Cl_2, and was oxidized with $NaIO_4$ in a mixture of



Scheme 8. Formation of isomeric vinylic derivatives of KAPA.



Scheme 9. Attempted pyrolysis of a DTB-sulfoxide derivative.

MeOH and H_2O. In the course of pyrolysis of **20′hII** partial loss of the CBZ groups was observed, giving a mixture of benzyl alcohol and imidazolones **21′o** and **24′o**. The *N* on to which the CBZ was attached in **24′o** was not determined. In both products only the desired terminal vinyl substituent was found, without a trace of the undesired isomer (Scheme 10).

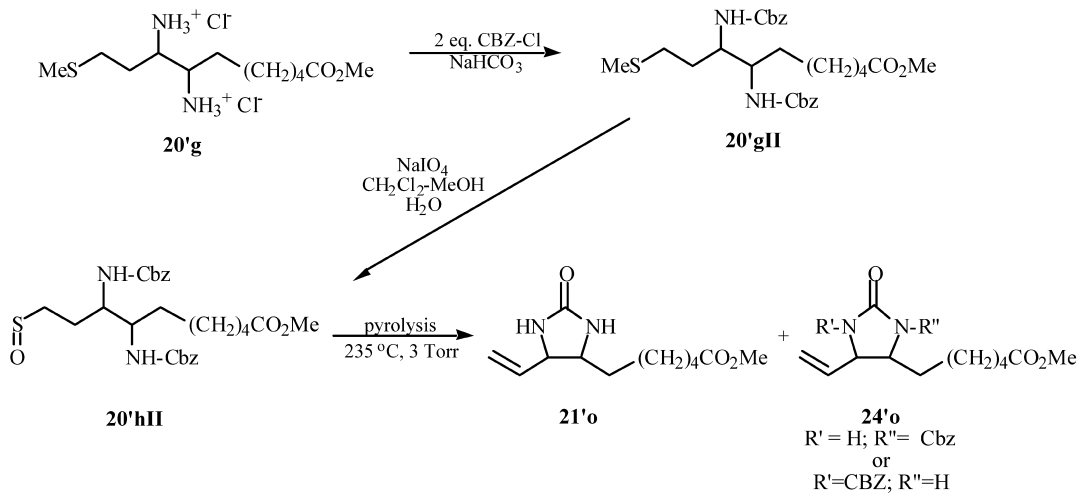
To avoid the cyclization observed in the course of the pyrolysis, the amino groups where protected as methyl carbamates. Although carbamates are usually prepared using methyl chloroformate and NaOH,[13] the bis-carbamate derivative **20′gIII** was prepared in excellent yield using dimethyl dicarbonate, by an analogous procedure to that used with di-*t*-butyl dicarbonate. Oxidation of **20′gIII** gave the sulfoxide **20′hIII**, which was pyrolyzed to give **20′oIII** as a mixture of two diastereomers. Whereas acidic hydrolysis of **20′oIII** gave a mixture of vinylic isomers **20o** and **25o** in a 9:1 ratio, basic hydrolysis led to the mono-carbamoylated cyclic urea isomers **21o** and **26o** where the location of the *N*-carbamate was not established (Scheme 11).

2.4. Biological results

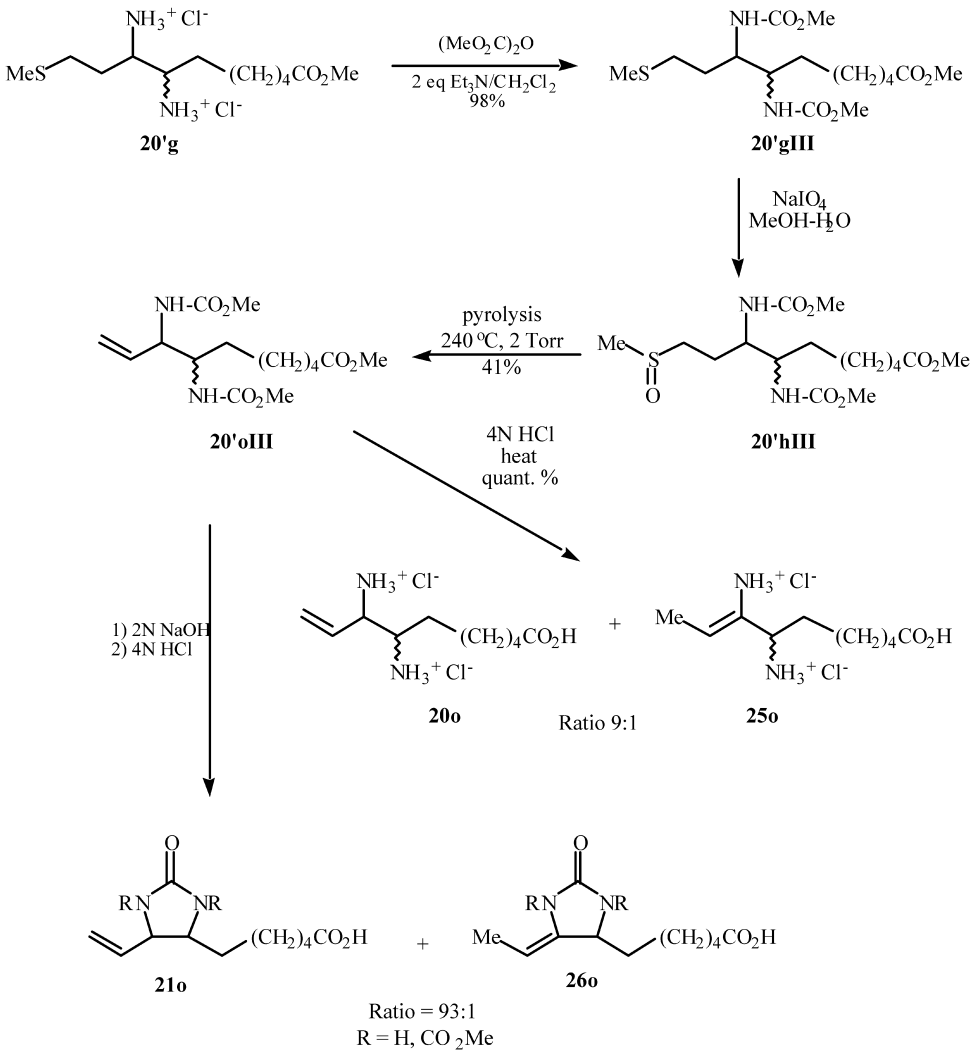
Enzyme assays on compounds described in this paper were not conducted. Instead, herbicidal activity was measured at difference concentrations of the compounds and the results were recorded as GR_{50} values. The term of GR_{50} refers to the concentration of the active compound that causes a 50% growth inhibition. In our tests commercial herbicides gave GR_{50} values of <50 ppm, so compounds with activity in this range were considered herbicidal. When compounds described in this paper exhibited herbicidal activity, reversal tests were carried out by treating the plants with biotin. If the herbicidal activity of a compound was reversed by biotin, it was deemed likely that the compound was active because it disrupted biotin biosynthesis.

Initial herbicidal activity tests were carried out on *Arabidopsis*. Compounds active against *Arabidopsis* where tested further tested on *Lemna*, Back Mexican Sweet Corn Cells (BMS), and Barnyard grass.

In conclusion, the growth inhibitory activities (GR_{50}) of a selected number of compounds are listed in Table 2. The most active compound found was desmethyl-KAPA **4a**. Other KAPA analogs where the terminal Me group was replaced by bulkier substituents such as Et, *i*-Pr and $HOCH_2$ showed moderate activity, whereas the thio-derivatives ($HSCH_2$, $MeSCH_2$ and $Me_2CH_2CH_2$) as well as that derived



Scheme 10. Pyrolysis of a di-Cbz-DAPA sulfoxide derivative.



Scheme 11. Attempted formation of 9-vinyl-DTB.

from threonine (MeCHOH) were considerably weaker inhibitors. DAPA and DTB analogs replacing the Me by H or Et also showed moderate activity. When comparing free acids to their respective more lipophilic Me esters, the latter where found to be more active. Subsequent reports will describe the inhibitory activity of isosters involving additional structural modifications based on the natural vitamers.

3. Experimental

3.1. Biology—methods and materials

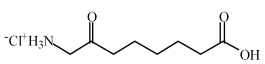
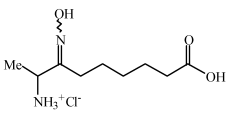
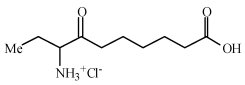
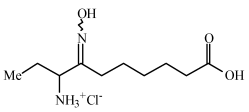
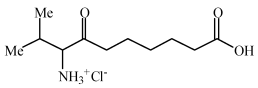
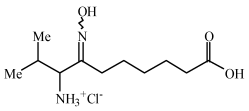
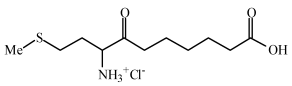
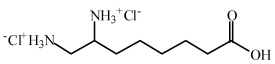
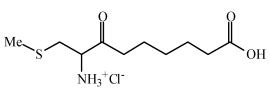
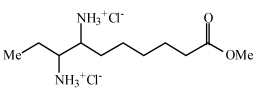
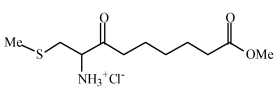
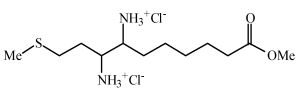
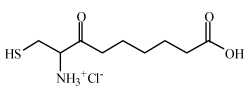
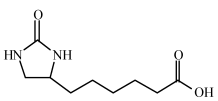
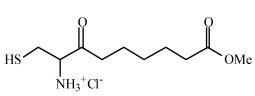
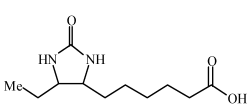
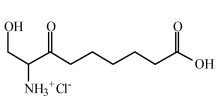
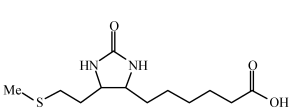
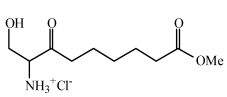
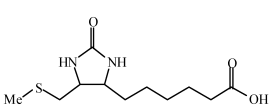
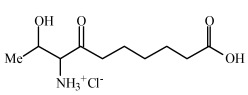
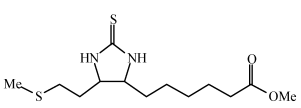
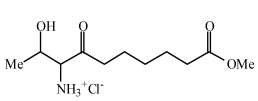
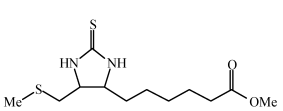
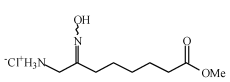
3.1.1. *Arabidopsis* test. *Arabidopsis thaliana* was grown in 12-well titer plates under sterile conditions on 0.8% agar medium containing nutrient solution as described by Somerville and Ogren.[14] Concentrated treatment solutions were filter sterilized and were added to the agar solution while it was still in a liquid state (45 °C). Three mL aliquots of the agar solution were pipetted into the wells. Concentrated treatment solutions were filter sterilized and were added to the agar solution while it was still in a liquid state (45 °C). When the agar had solidified and cooled, seeds were sown on the surface. The plates were placed in a 26 °C incubator under continuous fluorescent lighting with an intensity of 55 $\mu E\ m^{-2}\ s^{-1}$. The plants were rated after three weeks against the controls for growth inhibition due to the inhibitor treatment. These ratings were used to determine the GR_{50} value, which is the concentration that resulted in a 50% growth reduction.

To obtain more tissue for biotin determinations, seven-day old *Arabidopsis* seedlings grown on media without the inhibitor were watered over the foliage with different concentrations of the tested inhibitor in 8 mM phosphate buffer, at a pH 6.5 value. Plants were harvested at 0, 7 and 14 days after treatment and were weighed and extracted for total biotin determination.

3.2. Chemistry—general

^1H NMR spectra 200 and 300-MHz were obtained on Bruker AC-200 and AM-300 spectrometers, respectively. Chemical shifts are expressed in ppm downfield from Me_4Si used as internal standard. When D_2O was used as solvent, its own peak was used as internal standard for ^1H NMR, while additional MeOH was used as an internal standard for ^{13}C NMR. The values are given in δ scale. Mass spectra were obtained on a Varian Mat 731 spectrometer (CI=chemical

Table 2. Growth inhibitory activity (GR_{50}) of selected isosters of the biotin vitamers

Compounds	Structure	GR_{50} (ppm)	Compounds	Structure	GR_{50} (ppm)
4a[29]		8	**18b**[6]		40
4c[30]		43	**18c**		>780
4d		37	**18d**		>780
4g		>780	**20a**[31]		53
4i		>780	**20′c**		76
4′i		250	**20′g**		>780
4j		>780	**21a**[26]		35
4′j		120	**21c**[27]		35
4p		100	**21g**		>780
4′p		53	**21i**		46
4r[20]		250	**22′g**		>780
4′r[20]		100	**22′i**		44
18a		53			

ionization). HRMS were obtained on a VG AutoSpec E spectrometer. Progress of the reactions was monitored by TLC on silica gel (Merck, Art. 5554) or alumina (Riedel-de Haen, Art. 37349). Flash chromatography was carried out on silica gel (Merck, Art. 9385). Commercially available chemicals were used without further purification.

3.3. *N*-Boc protection of amino acids 1

Method A.[15]To a stirred solution of an amino acid (0.03 mol) and NaOH (0.03 mol) in water (4 mL) and *tert*-BuOH (6 mL) was added di-*tert*-butyl dicarbonate (0.03 mol). The mixture was stirred overnight at room

temperature, water (15 mL) was then added and the aqueous phase was washed with hexane (3×50 mL). The aqueous phase was acidified with $KHSO_4$ (to pH=2.5), extracted with EtOAc (4×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford the desired *N*-Boc protected amino acid.

Method B.[16] A suspension of a KAPA.HCl methyl ester derivative (1 mmol), $NaHCO_3$ (3 mmol), and di-*tert*-butyl dicarbonate (1 mmol) in dry MeOH (10 mL), was sonicated at room temperature for 6 h. The resulting mixture was filtered and evaporated to dryness. The residue was dissolved in ether (20 mL) and 1 N HCl (20 mL). The aqueous layer was washed with ether (3×15 mL). The combined organic layer was washed with 5% $NaHCO_3$ (2×20 mL), and brine (2×20 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated to give the desired *N*-Boc product.

Method C.[17] To a solution of L-cystine (4 mmol), NaOH (8 mmol) in 15 mL water at 0 °C, was slowly added DMF (15 mL). The mixture was brought to room temperature and di-*tert*-butyl dicarbonate (8 mmol) was added in one portion. The pH was maintained at ~9 by adding NaOH for 3 h and stirring at room temperature was continued overnight. To the cloudy mixture, water (50 mL) was added and was washed with EtOAc (2×50 mL). To the aqueous solution obtained, EtOAc was added (50 mL). The mixture was cooled to 0 °C and HCl 1 N was added until pH 3 was obtained. The organic phase was separated and washed with water (6×20 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated to give the desired product.

Method D. A mixture of the amino acid ester derivative (1 mmol) and Et_3N (1 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 10 min. Di-*tert*-butyl dicarbonate (1 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The resulting mixture was washed with water (3×25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness, to afford the desired product.

3.4. 2-(3-Formyl-2,2-dimethyl-thiazolidine-4-carbonyl)-heptanedioic acid 7-ethyl ester 1-methyl ester (9′)

C-Alkylation of **8′** with ethyl 5-iodovalerate (53% yield). Note: due to large amounts of O-alkylation products, only one equivalent of K_2CO_3 in 2-butanone (bp 73 °C) was used. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J=7 Hz, 3H, CH_2Me), 1.38 (m, 2H, $CH_2CH_2CH_2CO_2$), 1.63 (superimposed, 5H, *Me*C and $CH_2(CH_2)_3CO_2$), 1.81 (superimposed, 5H, *Me*C and $CH_2CH_2CO_2$), 2.30 (t, J=7.5 Hz, 2H, CH_2CO_2), 3.23 (ABq of d, J_{AB}=13.8 Hz, J_{AX}=5 Hz, J_{BX}=4.8 Hz, 2H, SCH_2), 3.74 and 3.75 (two s, 3H, OMe), 3.75 and 3.93 (two t, J=7 Hz, 1H, $COCHCO_2$), 4.12 (q, J=7 Hz, 2H, CH_2Me), 4.92 (td, J=7, 1 Hz, 1H, CHNH), 8.20 (d, J=1 Hz, 1H, COH).

3.5. General procedure for the preparation of methyl esters, using a diazomethane derivative, trimethylsilyl diazomethane[18]

A 2 M solution of TMS-diazomethane in hexane (0.65 mL, 1.3 mmol) was added dropwise to a solution of an *N*-protected amino acid (1 mmol) in hexane (5 mL) and anhydrous MeOH (2 mL). The mixture was stirred at room temperature overnight, and became cloudy. The solvent was evaporated and the residue was dissolved in $CHCl_3$ and was washed with 5% $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (2×) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated, to give the esters. Although it was not required to wash the product with 5% $NaHCO_3$, this was found convenient to obtain the product without a trace of the starting acid.

3.6. Conversion of N-protected amino acid derivatives to the corresponding β-keto esters

To a solution of an N-protected amino acid (1 mmol) in dry THF (10 mL) under N_2, CDI (1.2 mmol) was added portion wise. The mixture was stirred at room temperature for 1 h, then $MgCl_2$ (1 mmol) and monomethyl malonate K salt (1 mmol) were added at once. The mixture was stirred at 35 °C overnight. The resulting slurry was filtered and the filtrate was evaporated. The residue was dissolved in EtOAc (20 mL) and 1 N HCl (20 mL). The aqueous phase was extracted with EtOAc (3×20 mL). The organic layers were washed with 5% $NaHCO_3$ (2×20 mL), brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated to give the desired product.

3.6.1. 4-*tert*-Butoxycarbonylamino-3-oxo-hexanoic acid methyl ester (2′cI). From *N*-Boc-*dl*-2-aminobutyric acid, **1′cI** (60% yield). ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J=7.5 Hz, 3H, CH_2Me), 1.45 (s, 9H, Me_3C), 1.61 (m, 1H, CH_2Me), 1.95 (m, 1H, CH_2Me), 3.57 (ABq, J=15 Hz, 2H, CH_2CO), 3.75 (s, 3H, OMe), 4.32 (m, 1H, CHNH), 5.16 (m, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 9.5 (CH_2Me), 24.1 (CH_2Me), 28.3 (Me_3C), 46.1 (CH_2CO), 52.4 (OMe), 60.8 (CHNH), 80.1 (C), 155.4 ($HNCO_2$), 167.2 (CO_2Me), 201.9 (CO); MS (EI) *m/e* 260 (MH^+, 34), 204 ($MH^+-C_4H_8$, 100), 186 (MH^+-t-BuOH, 17), 160 (MH^+-Boc, 68); HRMS (DCI, CH_4) calcd for $C_{12}H_{22}NO_5$ (MH^+) 260.1497 found 260.1420.

3.6.2. 3-(3-Formyl-2,2-dimethyl-thiazolidin-4-yl)-3-oxo-propionic acid methyl ester (8′). From 2,2-dimethyl-thiazolidine-4-carboxylic acid hydrochloride, **7** (76% yield). Note: dry DMF (ca. 0.5 mL) was added to the mixture, to allow better solubility of the starting acid. The product was obtained as a single isomer, derived from the major rotamer of the starting material. ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 6H, Me_2C), 3.30 (ABq of d, J_{AB}=12.2 Hz, J_{AX}=7 Hz, J_{BX}=6 Hz, 2H, CH_2S), 3.70 (ABq, J_{AB}=16.1 Hz, 2H, CH_2CO), 3.75 (s, 3H, OMe), 5.04 (ddd, J=7, 6, 1 Hz, 1H, CH_2CH), 8.29 (d, J=1 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ 30.1 (CH_2S), 30.9 (*Me*C), 31.5 (*Me*C), 46.9 (CH_2CO), 52.3 (OMe), 68.1 ($CHCH_2$), 70.3 (Me_2C), 158.90 (CON), 167.3 (CO_2), 198.6 (COCH). MS (CI/NH_3) *m/e* 263 (MNH_4^+, 100), 246 (MH^+, 37).

3.7. C-Alkylation of β-keto esters using K_2CO_3[6]

To a solution of a β-keto ester derivative (1 mmol) in dry acetone (20 mL) and anhydrous K_2CO_3 (4 mmol) or dry 2-butanone (MEK) (20 mL) and K_2CO_3 (1 mmol), was added an alkyl iodide (1 mmol). The resulting suspension

was refluxed under nitrogen for 6–18 h, cooled and filtered. The salts were washed with acetone. The filtrate was evaporated and the residue was flash chromatographed on a silica gel column (hexane/EtOAc 2:1 or 3:1), to give the desired C-alkylated product, containing mixtures of diastereomers.

3.7.1. 2-*tert*-Butoxycarbonylaminoacetyl-heptanedioic acid 7-ethyl ester 1-methyl ester (3′aI). From **2′aI** (55% yield). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J=7 Hz, 3H, OCH_2Me), 1.45 (s, 9H, Me_3C), 1.50–1.78 (m, 4H, $CHCH_2CH_2CH_2$), 1.90 (m, 2H, $CHCH_2CH_2CH_2$), 2.30 (t, J=7 Hz, 2H, CH_2CO_2Et), 3.50 (t, J=7 Hz, 1H, $CHCO_2Me$), 3.73 (s, 3H, OMe), 4.15 (m, superimposed, 4H, CH_2NH, OCH_2Me), 5.20 (m, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.2 (OCH_2Me), 24.4 ($CH_2CH_2CO_2$), 25.1 ($CHCH_2$), 26.8 ($CHCH_2CH_2$), 28.3 (Me_3C), 33.9 (CH_2CO_2), 50.1 (CH_2NH), 52.6 (OMe), 55.9 ($CHCO_2Me$), 60.3 (OCH_2Me), 80.0 (C), 155.5 ($HNCO_2$), 169.4 (CO_2Me), 173.2 (CO_2Et), 200.9 (CO); MS (CI, *i*-Bu) *m/e* 360 (MH^+, 1), 304 ($MH^+-C_4H_8$, 13), 256 (MH^+−Boc, 100); HRMS (DCI, CH_4) calcd for $C_{17}H_{30}NO_7$ (MH^+) 360.2022 found 360.1995.

3.8. Preparation of KAPA·HCl derivatives (hydrolysis and decarboxylation of compounds 3)[6]

A suspension of a C-alkylated ester **3** (1 mmol) in 4 N HCl (2 mL) was refluxed for 2 h. Gas evolution was observed. The resulting dark yellow solution was evaporated under high vacuum. If the color of the resulting product darkened, the residue was dissolved in distilled water (minimum amount) and was treated with charcoal, filtered and the filtrate was evaporated under high vacuum to give a solid residue. Recrystallization was carried out from EtOH–ether, or ether–HCl, to give the desired HCl salt.

3.8.1. 8-Amino-7-oxo-octanoic acid hydrochloride (4a).[19] Hydrolysis and decarboxylation of **3′aI**, isolated as a white solid mp 129–131 °C (84% yield). ^{1}H NMR (D_2O) δ 1.40 (m, 2H, $CH_2CH_2CH_2CO_2$), 1.70 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 2.40 (t, J=7 Hz, 2H, CH_2CO_2), 2.70 (t, J=7 Hz, 2H, CH_2CO), 4.18 (s, 2H, CH_2N); ^{13}C NMR (D_2O) δ 22.9 ($CH_2CH_2CO_2$), 24.6 (CH_2CH_2COCH), 28.2 ($CH_2CH_2CH_2CO$), 34.4 (CH_2CO_2), 39.9 (CH_2COCH), 47.7 (CH_2N), 180.0 (CO_2), 206.9 (CO); MS (CI, NH_3) m/e 174 (MH+, 100); HRMS (DCI, CH_4) calcd for $C_8H_{16}NO_3$ (MH^+) 174.1130 found 174.1140.

3.8.2. 8-Amino-9-methyl-7-oxo-decanoic acid hydrochloride (4d). From **3′dI** (95% yield). ^{1}H NMR (D_2O) δ 0.86 (d, J=7 Hz, 3H, Me), 1.11 (d, J=7 Hz, 3H, Me), 1.33 (m, 2H, $CH_2(CH_2)_2CO_2$), 1.60 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 2.37 (t, J=7.5 Hz, 2H, CH_2CO_2), 2.55 (m, 2H, $CHMe_2$), 2.68 (m, 2H, superimposed, CH_2CO), 4.24 (d, J=3.5 Hz, 1H, CHN); ^{13}C NMR (D_2O) δ 15.8 (Me), 19.0 (Me), 22.8 ($CH_2(CH_2)_3CO_2$), 24.6 ($CH_2CH_2CO_2$), 28.6 ($CHMe_2$), 34.4 (CH_2CO_2), 39.7 (CH_2CO), 64.7 ($CHCO$), 177.7 (CO_2), 209.6 (CO); MS (DCI, NH_3) *m/e* 216 (MH^+, 100); HRMS (DCI, CH_4) calcd for $C_{13}H_{26}NO_3$ (MH^+) 244.1912 found 244.1918.

3.8.3. 8-Amino-9-hydroxy-7-oxo-decanoic acid hydrochloride (4r). Hydrolysis and decarboxylation of **17′b** (96% yield). ^{1}H NMR (D_2O) δ 1.32 (m and d, superimposed, J=6.6 Hz, 5H, Me, $CH_2CH_2CH_2CO_2$), 1.49–1.66 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 2.34 (t, J=7.3 Hz, 2H, CH_2CO_2), 2.70 (dt, J=2.5, 7.2 Hz, 2H, CH_2CO), 4.22 (d, J=2.5 Hz, 1H, CHN), 4.60 (dq, J=2.5, 6.6 Hz, 1H, $CHMe$); ^{13}C NMR (D_2O) δ 19.68 (Me), 22.79 ($CH_2CH_2CO_2$), 24.43 (CH_2CH_2CO), 28.06 ($CH_2(CH_2)_2CO_2$), 34.06 (CH_2CO_2), 39.33 (CH_2CO), 64.44 ($CHMe$), 64.89 (CHN), 179.18 (CO_2), 207.53 (CO); MS (CI, NH_3) *m/e* 218 (MH^+, 18), 200 (MH^+-H_2O, 12), 174 (MH^+-CO_2, 15); HRMS (DCI, CH_4) calcd for $C_{10}H_{20}NO_4$ (MH^+) 218.1392 found 218.1390.

3.8.4. 8-Amino-9-hydroxy-7-oxo-nonanenitrile hydrochloride (14p). From **13′qI**. The reaction mixture was washed with EtOAc (2×10 mL) and then the aqueous solution was evaporated to afford the product (60% yield). ^{1}H NMR (D_2O) δ 1.40 (m, 2H, $CH_2(CH_2)_2CN$), 1.61 (m, 4H, $CH_2CH_2CH_2CH_2CN$), 2.44 (t, J=7 Hz, 2H, CH_2CN), 2.70 (t, J=7 Hz, 2H, CH_2CO), 4.05 (dd, J=3.4, 12.8 Hz, 1H, CH_2OH), 4.17 (dd, J=4, 12.8 Hz, 1H, CH_2OH), 4.35 (t, J=3.7 Hz, 1H, $CHCH_2$); ^{13}C NMR (D_2O) δ 16.8 (CH_2CN), 22.3 (CH_2CH_2CN), 24.7 (CH_2CH_2CO), 27.8 ($CH_2(CH_2)_2CN$), 38.9 (CH_2CO), 59.4 (CH_2OH), 61.3 (CHN), 122.7 (CN), 207.1 (CO).

3.9. Formation of methyl esters of amino acids 4

Method A. Concentrated HCl (1.12 mL) was added to a solution of a KAPA derivative (1 mmol) in 2,2-dimethoxypropane (15 mL). The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in a small amount of MeOH. Addition of dry ether resulted in crystallization. The crystals were filtered and washed with ether to give hydrochloride salt.

Method B. A solution of a KAPA·HCl derivative (1 mmol) in MeOH·HCl (8 mL) was stirred at room temperature overnight. Evaporation under vacuum gave the hydrochloride salt.

Method C. To a solution of a KAPA derivative (1 mmol) in dry MeOH (10 mL) at 0 °C was dropwise added AcCl (3 mL).[20] The resulting mixture was stirred at room temperature overnight. Evaporation yielded the hydrochloride salt.

3.9.1. 8-Amino-7-oxo-octanoic acid methyl ester hydrochloride (5′a). Esterification of DMK·HCl **4a** (quantitative yield). ^{1}H NMR (D_2O) δ 1.30 (m, 2H, $CH_2CH_2CH_2CO_2$), 1.60 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 2.40 (t, J=7.3 Hz, 2H, CH_2CO_2), 2.60 (t, J=7.4 Hz, 2H, CH_2CO), 3.70 (s, 3H, OMe), 4.05 (s, 2H, CH_2N); ^{13}C NMR (D_2O) δ 22.8 ($CH_2CH_2CO_2$), 24.5 (CH_2CH_2CO), 28.2 ($CH_2CH_2CH_2CO_2$), 34.0 (CH_2CO_2), 39.9 (CH_2CO), 52.7 (OMe), 58.1 (CH_2N), 178.0 (CO_2Me), 209.8 (CO); MS (CI, *i*-Bu) *m/e* 187 (MH^+−HCl); HRMS (DCI, CH_4) calcd for $C_9H_{18}NO_3$ (MH^+) 188.1286 found 188.1260.

3.9.2. 8-Acetylamino-10-methylsulfanyl-7-oxo-decanoic acid methyl ester (5′gIV). N-Acetylation of **4′g**—CDI (0.22 g, 1.3 mmol) was added to a solution of AcOH (0.08 g, 1.3 mmol) in dry THF (10 mL) under N_2. The

mixture was stirred at room temperature for 1 h and was transferred via a cannula to a flask containing **4′g** (0.35 g, 1.16 mmol). The mixture was stirred at room temperature under N_2 overnight and was evaporated. The residue was partitioned between 1 N HCl and EtOAc and the aqueous layer was extracted with EtOAc (4×). The combined organic layers were washed with 5% $NaHCO_3$ (2×), brine, dried ($MgSO_4$), filtered and evaporated to give **5′gIV** as an oil, 57% yield). ^{1}H NMR ($CDCl_3$) δ1.34 (m, 2H, $CH_2(CH_2)_2CO_2$), 1.64 (m, 4H, $CH_2(CH_2)_3CO_2$), 2.04 (s, 3H, MeCO), 2.10 (s, 3H, SMe), 2.27 (m, 2H, SCH_2CH_2), 2.32 (t, *J*=7.4 Hz, 2H, CH_2CO_2), 2.50 (superimposed, m, 4H, CH_2S and $CHCOCH_2$), 3.67 (s, 3H, OMe), 4.74 (td, *J*=7.5, 4.5 Hz, 1H, CH), 6.30 (brd, *J*=6.2 Hz, 1H, NH). MS (CI/*i*-Bu) m/e 304 (MH^+, 100), 272 (MH^+-MeOH, 51), 229 ($MH^+-MeSCH_2CH_2$, 71), 146 (91), 104 (67); HRMS (CI/CH_4) calcd for $C_{14}H_{26}NO_4S$ (MH^+), 304.06436 found 304.04163.

3.9.3. 2-(4-Cyanobutyl)-malonic acid dimethyl ester (11).[21] Dimethyl malonate (0.02 mol, 2.64 g) in MeOH (5 mL) was added to an ice-cold solution obtained by addition of NaH (60% in oil, 0.02 mol, 0.98 g) to dry MeOH (20 mL). The mixture was stirred for a few minuets at room temperature and then 5-bromovaleronitrile (0.02 mol, 3.25 g) dissolved in MeOH (5 mL) was added followed by addition of a catalytic amount of KI. The mixture was refluxed for 48 h, filtered and evaporated. The inorganic salts were dissolved in water (20 mL) and were washed with EtOAc (3×20 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated and the residue was flash chromatographed (hexane/EtOAc 2:1), to give the *C*-alkylated product 30% yield. ^{1}H NMR ($CDCl_3$) δ 1.47 (quintet, *J*=7 Hz, 2H, $CH_2(CH_2)_3CN$), 1.70 (quintet, *J*=7 Hz, 2H, $CH_2(CH_2)_2CN$), 1.93 (q, *J*=7.5 Hz, 2H, CH_2CH_2CN), 2.37 (t, *J*=7 Hz, 2H, CH_2CN), 3.37 (t, *J*=7.4 Hz, 1H, CH), 3.74 (s, 6H, OMe); ^{13}C NMR ($CDCl_3$) δ16.7 (CH_2CN), 24.8 (CH_2CH_2CN), 26.1 ($CHCH_2$), 51.1 (OMe), 52.3 (*C*H), 119.1 (CN), 169.3 (CO_2Me); MS (CI, NH_3) *m/e* 231 (MNH_4^+, 100), 214 (MH^+, 6); HRMS (DCI, CH_4) calcd for $C_{10}H_{16}NO_4$ (MH^+) 214.1079 found 214.1074.

3.9.4. 2-(4-Cyanobutyl)-malonic acid monomethyl ester potassium salt (12). KOH (1 mmol) in MeOH (5 mL) was added to a stirred solution of **11** (1 mmol) in MeOH (2 mL). The mixture was stirred overnight, and was then evaporated to dryness to give the product in quantitative yield. ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2H, $CH_2(CH_2)_2CN$), 1.63 (m, 2H, $CH_2(CH_2)_3CN$), 1.88 (m, 2H, CH_2CH_2CN), 2.41 (t, *J*=6.7 Hz, 2H, CH_2CN), 3.18 (t, *J*=6.2 Hz, 1H, CH), 3.71 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$) δ16.9 (CH_2CN), 25.0 (CH_2CH_2CN), 27.0 ($CHCH_2CH_2$), 29.1 ($CHCH_2$), 52.0 (OMe), 55.5 (*C*H), 120.6 (CN), 174.2 (CO_2^-), 174.7 (CO_2Me); MS (CI, NH_3) *m/e* 173 ($MNH_4^+-CO_2K$, 100), 214 (MH^+, 6).

3.10. Acylation of *N*-Boc-amino acids with 12

To a solution of an *N*-Boc-amino acid (0.84 mmol) in dry THF (5 mL), CDI (1 mmol) was added portion wise and the obtained mixture was stirred at room temperature for 1 h. $MgCl_2$ (0.84 mmol) and **12** (0.84 mmol) were then added and the resulting mixture was stirred under reflux overnight. The obtained suspension was filtered, evaporated, and the crude residue was purified by flash chromatography (hexane/EtOAc usually 2:1).

3.10.1. 2-(2-*tert*-Butoxycarbonylamino-propionyl)-6-cyano-hexanoic acid methyl ester (13′b). From **1bI** and **12** The product was obtained as a mixture of two diastereomers, 23% yield). ^{1}H NMR ($CDCl_3$) δ 1.34 (two d, *J*=7.2 Hz, 3H, Me), 1.44–1.45 (two s, 9H, *t*-Bu), 1.44 (m, 2H, $CH_2(CH_2)_2CN$), 1.67 (quintet, *J*=7.4 Hz, 2H, CH_2CH), 1.89 (quintet, *J*=7.4 Hz, 2H, CH_2CH_2CN), 2.36 (t, *J*=7 Hz, 2H, CH_2CN), 3.73 (s and m, superimposed, 4H, OMe, $CHCO_2$), 4.39 (m, 1H, *CH*Me), 5.11 (bt, *J*=7.6 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$) δ16.7 and 16.8 (CH*Me*), 17.4 (CH_2CN), 25.0 and 25.1(CH_2CH_2CN), 26.3 and 26.4 ($CHCH_2CH_2$), 28.2 (Me_3C), 27.6 and 27.9 ($CHCH_2$), 52.4 ($CHCO_2$), 52.46 and 52.52 (OMe), 54.9 (*C*HMe), 80.01 (C), 119.2 (CN), 155.0 (CO_2NH), 169.4 (CO_2Me), 204.4 (CO); MS (CI, NH_3) *m/e* 344 (MNH_4^+, 100), 327 (MH^+, 10.9), 288 ($MNH_4^+-C_4H_8$, 74), 271 ($MH^+-C_4H_8$, 7), 227 (MH^+-Boc, 11); HRMS (DCI, CH_4) calcd for $C_{16}H_{27}N_2O_5$ (MH^+) 327.1920 found 327.1840.

3.10.2. 2-[2-*tert*-Butoxycarbonylamino-3-(tetrahydro-pyran-2-yloxy)-propyl]-6-cyano-hexanoic acid methyl ester (13′qI). From **1q** and **12**. The product was obtained as a mixture of two diastereomers, 18% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H, Me_3C), 1.46–1.94 (m, 12H, $(CH_2)_3CH$ and $(CH_2)_3CH_2CN$), 2.35 (t *J*=7 Hz, 2H, CH_2CN), 3.60 (m, 2H, CH_2CHN), 3.70 and 3.71 and 3.73 and 3.74 (four s, 3H, OMe), 3.85 (m, 3H, CH_2OCH and *CH*COO), 4.59 (m, 2H, *CH*NH and OCHO), 5.63–5.38 (m, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 16.9 (CH_2CN), 19.3 and 19.6 and 19.7 (CH_2CH_2CH), 25.2 (CH_2CH_2CN), 26.4 and 26.5 and 26.8 and 26.9 (CH_2CH_2O and $CH_2(CH_2)_2CN$), 27.2 and 27.5 ($CH_2(CH_2)_3CN$), 28.3 (Me_3C), 30.3 and 30.4 and 30.5 (CH_2CHO), 52.4 and 52.6 (OMe), 54.8 and 55.0 and 55.2 and 55.4 ($CHCO_2$), 59.0 and 59.4 and 59.7 and 60.4 (*C*HNH), 62.3 and 62.8 and 63.0 (CH_2OCH), 67.1 and 67.7 and 68.9 (CH_2O), 80.1 and 80.3 (C), 99.2 and 99.5 and 99.9 (O*C*HO), 119.3 (CN), 155.4 ($NHCO_2$), 169.2 and 169.3 (CO_2Me), 202.2 and 203.5 (CO); MS (CI, NH_3) *m/e* 444 (MNH_4^+, 100), 427 (MH^+, 6), 388 ($MNH_4^+-C_4H_8$, 21), 360 ($MNH_4^+-C_5H_8O$, 85), 343 (MNH_4^+-HBoc, 32).

3.10.3. 2-(2-*tert*-Butoxycarbonylamino-3-hydroxy-butyryl)-6-cyano-hexanoic acid methyl ester (13′r). In the course of the workup of the previous reaction, the THP protective group was removed. The product was obtained as a mixture of two diastereomers, 12% yield. ^{1}H NMR ($CDCl_3$) δ 1.25 (d, *J*=6.3 Hz, 3H, CH*Me*), 1.47 (s, 9H, Me_3C), 1.70 (m, 4H, $(CH_2)_2(CH_2)_2CN$), 1.92 (m, 2H, CH_2CH_2CN), 2.36 (t *J*=7 Hz, 2H, CH_2CN), 3.37 (t, *J*=7.4 Hz, 1H, *CH*Me), 3.73 (m, 1H *CH*CO_2), 3.75 (s, 3H, OMe), 4.31 (m, 1H, *CH*NH), 5.33 (m, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 16.9 (CH_2CN), 19.9 (CH*Me*), 25.1 ($CH_2(CH_2)_3$-CN), 26.4 ($CH_2(CH_2)_2CN$), 28.0 (CH_2CH_2CN), 28.3 (Me_3C), 51.3 ($CHCO_2$), 52.6 (OMe), 68.2 (*C*HMe), 80.2 (C), 119.3 (CN), 169.5 ($NHCO_2$), 171.9 (CO_2OMe), 205.0 (CO).

3.11. Oxidation of KAPA·HCl analogs[22]

To a solution of NH_2OH·HCl (1.5 mmol) in dry pyridine

(0.75 mL) was added to an ice-cold solution of a KAPA·HCl derivative (1 mmol) in dry pyridine (0.75 mL). The mixture was stirred at room temperature for 24 h and was then evaporated to dryness. The residue was dissolved in distilled water (3 mL) and was basified with 0.5 N NaOH to pH=8. This solution was extracted with CH_2Cl_2 (6×5 mL). The aqueous phase was evaporated yielding the desired product.

3.11.1. 8-Amino-7-hydroxyimino-octanoic acid hydrochloride (18a). Oximation of **4a** (98% yield). ^{1}H NMR (D_2O) δ 1.32–1.36 (m, 2H, $CH_2CH_2CH_2CO_2$), 1.55 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 2.20 (t, J=7.3 Hz, 2H, CH_2CO_2), 2.41 (t, J=7.5 Hz, 2H, CH_2CNOH), 3.80 (s, 2H, CH_2N); ^{13}C NMR (D_2O) δ 24.8 ($CH_2CH_2CO_2$), 25.8 (CH_2CH_2CNOH), 26.2 (CH_2CNOH), 29.0 ($CH_2CH_2CH_2CO_2$), 37.4 (CH_2CO_2), 41.2 (CH_2N), 158.0 (CNOH), 183.6 (CO_2); MS (CI, NH_3) *m/e* 206 (MNH_4^+, 2), 189 (MH^+, 48).

3.11.2. 8-Amino-7-hydroxyimino-10-methyl-undecanoic acid hydrochloride (18e). Hydrolysis and decarboxylation of **3e** followed by in situ oximation (34% yield). ^{1}H NMR (D_2O) δ 0.98 (m, 7H, $CHMe_2$), 1.40 (m, 2H, CH_2CHMe_2), 1.72 (m, 8H, $(CH_2)_4CO_2$), 2.22 (t, J=7.3 Hz, 2H, CH_2CO_2), 4.05 (m, 1H, $CHNH_3^+$); MS (CI, NH_3) *m/e* 245 (MH^+, 67), 159 ($MH^+-C_5H_{11}N$, 100).

3.12. Preparation of DAPA derivatives 20 via catalytic reduction of KAPA oximes analogs 18[6]

A solution of the oxime analog (1 mmol) and 4 N HCl (2 mL) in absolute MeOH (10 mL) was hydrogenated in a Parr apparatus at 65 psi/40 °C/48 h over 10% PtO_2 (30 mg). The mixture was filtered through celite and washed with MeOH. The solvent was evaporated yielding the diamine product.

3.12.1. 7,8-Diamino-octanoic acid methyl ester dihydrochloride (20′a). Catalytic reduction of **18′a** (87% yield). ^{1}H NMR (D_2O) δ 1.43 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 1.62 (m, 2H, CH_2CH_2CH), 1.75 (m, 2H, $CH_2CH_2CO_2$), 2.41 (t, J=7.3 Hz, 2H, CH_2CO_2), 3.33 (d, J=6.2 Hz, 2H, CH_2N), 3.63 (m, 1H, CH_2N), 3.68 (s, 3H, OMe); ^{13}C NMR (D_2O) δ 24.3 and 24.4 ($CH_2CH_2CH_2CH_2CO_2$), 28.3 ($CH_2CH_2CH_2CO_2$), 30.4 (CH_2CH), 34.3 (CH_2CO_2), 41.3 (CH_2N), 50.0 (CHN), 52.7 (OMe), 178.1 (CO_2Me); MS (DCI, NH_3) *m/e* 189 (MH^+, 100).

3.12.2. 7,8-Diamino-decanoic acid methyl ester dihydrochloride (20′c). Catalytic reduction of **18′c** (90% yield). ^{1}H NMR (D_2O) δ 1.08 (t, J=7.5 Hz, 3H, Me), 1.42 (m, 4H, $(CH_2)(CH_2)_2CO_2$), 1.77 (m, 6H, CH_2Me, $CH_2(CH_2)_2CH_2CH_2CO_2$), 2.42 (t, J=7.3 Hz, 2H, CH_2CO_2), 3.70 (m and s, superimposed, 5H, two CHN and OMe); ^{13}C NMR (D_2O) δ 9.7 (Me), 20.6 (CH_2Me), 24.3 ($CH_2CH_2CO_2$), 24.8 ($NCHCH_2CH_2$), 28.5 ($CH_2(CH_2)_3CO_2$), 34.1 (CH_2CO_2), 52.9 ($NHCH(CH_2)_2$), 179.2 (CO_2Me); MS (DCI, NH_3) *m/e* 217 (MH^+, 100), 203 (MH^+, 87); HRMS (DCI, CH_4) calcd for $C_{11}H_{25}N_2O_2$ (MH^+) 217.1916 found 217.1910.

3.12.3. 7,8-Diamino-9-methyl-octanoic acid methyl ester dihydrochloride (20′d). Catalytic reduction of **18′d** (92% yield). ^{1}H NMR (D_2O) δ 1.10 (m, 3H, $CHMe_2$), 1.46 (m, 4H, $CH_2(CH_2)_2CH_2CH_2CO_2$), 2.17 (m, 1H, $CHMe_2$), 2.43 (t, J=7 Hz, 2H, CH_2CO_2), 3.42 (m, 1H, $CHCHMe_2$), 3.70 (s, 3H, OMe), 3.82 (m, 1H, CHN); ^{13}C NMR (D_2O) δ 17.0 (Me), 17.5 (Me), 19.6 (CH_2Me_2), 24.4 ($CH_2(CH_2)_3CO_2$), 24.6 ($CH_2CH_2CO_2$), 27.8 ($CH_2(CH_2)_2CO_2$), 28.2 ($CH_2(CH_2)_4CO_2Me$), 34.1 (CH_2CO_2), 51.6 ($CH(CH_2)_5$), 52.3 ($CHCHMe_2$), 58.9 (OMe), 179.2 (CO_2Me); MS (DCI, NH_3) *m/e* 231 (MH^+, 100); HRMS (DCI, CH_4) calcd for $C_{12}H_{27}N_2O_2$ (MH^+) 231.2072 found 231.2110.

3.13. Preparation of DAPA derivatives 20 via sodium cyanoborohydride reductive amination of ketones 5[23]

To a solution of an *N*-Boc-KAPA derivative methyl ester (1 mmol) in dry MeOH (10 mL), NH_4OAc (10 mmol) was added. The solution obtained was stirred at room temperature for 10 min, then $NaBH_3CN$ (3.7 mmol) was added in one portion and the resulting mixture was stirred at room temperature for 48 h. The reaction was quenched with 1 N HCl (20 mL). The solvent was evaporated and the crude residue was dissolved in water. KOH was added till a basic solution was obtained. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine (2×10 mL), dried ($MgSO_4$), filtered and evaporated to give the compound.

3.13.1. 7-Amino-8-*tert*-butoxycarbonylamino-octanoic acid methyl ester (19′aI). Reductive amination of **5′aI** (74% yield). ^{1}H NMR ($CDCl_3$) δ 1.33 (m, 4H, $(CH_2)_2(CH_2)_2CO_2$), 1.44 (s, 9H, Me_3C), 1.62 (m, 4H, $CH_2(CH_2)_2CH_2CH_2CO$), 1.78 (m, 2H, NH_2), 2.31 (t, J=7.5 Hz, 2H, CH_2CO_2), 2.86 (m, 2H, CH_2NH), 3.26 (m, 1H, CH), 3.67 (s, 3H, OMe), 4.98 (m, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 24.8 ($CH_2(CH_2)_3CO_2$), 25.7 ($CH_2CH_2CO_2$), 28.4 (Me_3C), 29.2 ($CH_2(CH_2)_2CO_2$), 34.0 (CH_2CO_2), 35.5 ($CHCH_2CH_2$), 47.0 (CH_2NH), 51.3 (OMe), 51.5 (CH), 79.3 (C), 156.3 (CO_2NH), 174.2 (CO_2Me); MS (CI, NH_3) *m/e* 289 (MH^+, 100), 233 ($MH^+-C_4H_8$, 18), 189 (MH^+-Boc, 4); HRMS (DCI, CH_4) calcd for $C_{14}H_{29}N_2O_4$ (MH^+) 289.2127 found 289.2140.

3.14. Acid cleavage the *N*-Boc protecting group

To a suspension of an *N*-Boc-amino compound (1 mmol) in ether (5 mL), a solution of 1 N HCl–ether (3 mL) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated to give the diamine dihydrochloride product. In some cases, a solution of HCl in EtOAc (prepared from a mixture of EtOAc, EtOH and AcCl was used.[16]

3.14.1. 7,8-Diamino-9-methylsulfanyl-nonanoic acid methyl ester dihydrochloride (20′i). From **5′iI** by reductive amination and hydrolysis (50% yield). ^{1}H NMR (D_2O) δ 1.40 (m, 4H, $(CH_2)_2(CH_2)_2CO_2$), 1.60 (m, 4H, $CH_2(CH_2)_4CO_2$), 2.23 (s, 3H, SMe), 2.42 (t, J=7.4 Hz, 2H, CH_2CO_2), 2.93 (ABq of d, J_{AB}=16 Hz, J_{AX}=9.5 Hz, J_{BX}=5.5 Hz, 2H, CH_2S), 3.70 (s, 3H, OMe), 3.80 (m, 2H, two CH's). ^{13}C NMR (D_2O) δ 15.4 (SMe), 24.4 ($CH_2CH_2CO_2$), 24.8 and 24.9 (two CH_2CH_2CHN), 27.4 ($CH_2(CH_2)_2CO_2$), 28.3 and 28.5 (two CH_2CHN), 31.6 and 32.7 (two CH_2S), 34.0 (CH_2CO_2), 51.4 (OMe), 51.9 and 52.6 (two $CHCH_2S$), 52.7 and 52.8 (two $CHCHCH_2S$), 175.0 (CO_2). MS (CI/NH_3) *m/e* 249 (MH^+-2HCl, 100).

3.15. DTB and derivatives—imidazolone formation

Method A.[24] A mixture of a DAPA·2HCl Me ester derivative (1 mmol) and Et_3N (0.2 g, 2 mmol) in dry CH_2Cl_2 (10 mL) was stirred in an ice bath for 30 min. A solution of CDI (0.2 g, 1.2 mmol) in dry CH_2Cl_2 (5 mL) was added and the mixture was stirred at room temperature overnight. The mixture was evaporated and the residue was partitioned between 1 N HCl and EtOAc. The aqueous layer was extracted with EtOAc (4×) and the combined organic layers were washed with 5% $NaHCO_3$ (2×), brine, dried ($MgSO_4$), filtered and evaporated to give the product, in the form of two diastereomers.

Method B.[25] An aqueous solution (10 mL) of NaOH (0.4 g, 10 mmol) and a DAPA·2HCl derivative (1 mmol) was stirred at room temperature for 10 min. A solution of triphosgene (0.3 g, 1 mmol) in dioxane (10 mL) was added. The mixture became hot and the pH dropped from ~10 to ~8. The resulting mixture was stirred at room temperature for 2 days and was then evaporated. Trituration of the residue with MeOH, filtration and evaporation afforded the product. Note: both the free acid and the ester could be used as substrates. The product was either the pure acid or a mixture of acid and ester. In the case of a mixture, the product was dissolved in 4 N HCl and stirred at room temperature overnight, to afford, after evaporation, the free acid.

3.15.1. 6-(2-Oxo-imidazolidin-4-yl)-hexanoic acid (21a).[26] From **20′a**, method A (97% yield). ^{1}H NMR (CD_3OD) δ 1.4 (m, 4H, (CH_2)$_2$(CH_2)$_2$$CO_2$), 1.64 (m, 4H, CH_2(CH_2)$_2$$CH_2$$CH_2CO_2$), 2.32 (m, 2H, CH_2CO_2), 3.07 (m, 1H, CHN), 3.80 (m, 2H, CH_2N); ^{13}C NMR (D_2O) δ 24.6 and 26.2 (CH_2(CH_2)$_2$$CO_2$ and CH_2(CH_2)$_3$$CO_2$), 29.0 ($CH_2CH_2$-$CO_2$), 35.1 ($CH_2CO_2$), 38.0 ($CH_2$($CH_2$)$_4$$CO_2$), 46.6 ($CH_2$N), 53.3 (CHN), 163.7 (NCON), 184.1 (CO_2); MS (CI, *i*-Bu) *m/e* 201 (MH^+, 100); HRMS (DCI, CH_4) calcd for $C_9H_{17}N_2O_2$ (MH^+) 201.1239 found 201.1200.

3.15.2. 6-(5-Ethyl-2-oxo-imidazolidin-4-yl)-hexanoic acid (21c).[27] Cyclization of **20′c**, method A (97% yield). ^{1}H NMR (D_2O) δ 0.89 (t, *J*=7 Hz, 4H, Me), 1.33 (m, 4H, CH_2CH_2(CH_2)$_2$$CO_2$), 1.52 (m, 6H, CH_2(CH_2)$_2$$CH_2$$CH_2CO_2$ and CH_2Me), 2.16 (t, *J*=7 Hz, 2H, CH_2CO_2), 3.41 (m, 1H, $CHCH_2Me$), 3.73 (m, 2H, CH(CH_2)$_5$); ^{13}C NMR (D_2O) δ 9.1 (Me), 24.6 (CH_2(CH_2)$_3$$CO_2$), 26.3 ($CH_2CH_2CO_2$), 28.4 ($CH_2$($CH_2$)$_2$$CO_2$), 29.1 ($CH_2CO_2$), 35.4 ($CH_2$Me), 38.1 ($CH_2$($CH_2$)$_4$$CO_2$), 58.3 ($CH_2CHN$), 60.1 (CHN), 165.5 (NCON), 175.2 (CO_2); MS (CI, NH_3) *m/e* 243 (MH^+, 42), 211 (MH^+-MeOH, 31); HRMS (DCI, CH_4) calcd for $C_{11}H_{21}N_2O_2$ (MH^+) 229.1552 found 229.1570.

3.16. General procedure for the preparation of imadizolidinethiones

A mixture of a DAPA·2HCl methyl ester derivative **20′** (1 mmol) and Et_3N (0.2 g, 2 mmol) in dry CH_2Cl_2 (10 mL) was stirred at ca. 0 °C for 30 min. A solution of *N*,*N*′-thiocarbonyldiimidazole (0.21 g, 1.2 mmol) in dry CH_2Cl_2 (10 mL) was added and the mixture was stirred at room temperature overnight. The resulting mixture was evaporated to dryness and the residue partitioned between 1 N HCl and EtOAc. The aqueous layer was extracted with EtOAc (4 times) and the combined organic layers were washed with 5% $NaHCO_3$ (twice) and brine (once), dried ($MgSO_4$), filtered and evaporated to give the desired cyclized product, as a mixture of two diastereomers.

3.17. 5-(5-Methyl-2-thioxo-imidazolidin-4-yl)-pentanoic acid methyl ester (22′b)

From **20′b**, as a viscous yellow oil (84% yield). MS (CI/NH_3) *m/e* 245 (MH^+, 100), 213 (MH^+-MeOH, 4); HRMS (CI/CH_4) calcd for $C_{11}H_{21}N_2O_2S$ (MH^+), 245.13238 found 245.06617.

3.17.1. 5-(5-Methyl-2-thioxo-imidazolidin-4-yl)-pentanoic acid (22b). Hydrolysis of **22′b**, yellow solid (quantitative yield). ^{1}H NMR (D_2O) δ cis diastereomer 1.33 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 1.41 (d, *J*=6.5 Hz, 3H, Me), 1.57 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CO_2$), 2.35 (m, 2H, CH_2CO_2), 4.12 (m, 1H, $CHCH_2$), 4.08 (q, *J*=6.5 Hz, 1H, CHMe). trans diastereomer 1.19 (d, *J*=6.6 Hz, 3H, Me), 1.33 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 1.57 (m, 4H, CH_2-$CH_2CH_2CH_2CH_2CO_2$), 2.35 (m, 2H, CH_2CO_2), 3.72 (m, 1H, $CHCH_2$), 4.40 (q, *J*=6.8 Hz, 1H, CHMe). MS (CI/NH_3) *m/e* 231 (MH^+, 100); HRMS (CI/CH_4) calcd for $C_{10}H_{19}N_2O_2S$ (MH^+), 231.11672 found 231.09542; (M^+), 230.10890 found 230.09407.

3.17.2. 5-(5-Methylsulfanylmethyl-2-thioxo-imidazolin-4-yl)-pentanoic acid (22i). From **20′I**, tan crystals (82% yield). ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 4H, $CH_2CH_2CH_2CH_2$-CO_2), 1.64 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CO_2$), 2.14 and 2.15 (two s, 3H, SMe), 2.20 (m, 1H, CH_2S), 2.33 (t, *J*=7.3 Hz, 2H, CH_2CO_2), 2.65 (m, 1H, CH_2S), 3.68 (s, 3H, OMe), 3.70 (m, 1H, CH), 4.03 (m, 1H, CH), 6.60–6.90 (several m, 2H, two NH's). ^{13}C NMR ($CDCl_3$) δ 15.7 and 15.9 (two SMe), 24.63 and 24.9 (two $CH_2CH_2CO_2$), 25.8 and 26.2 (two $CH_2CH_2CH_2CH_2CO_2$), 28.7 and 28.8 (two $CH_2CH_2CH_2CO_2$), 29.7 ($CH_2CH_2CH_2CH_2CH_2CO_2$), 33.8 and 34.0 (two CH_2CO_2), 35.1 and 38.9 (two CH_2S), 51.5 (OMe), 58.4 and 59.9 (two $CHCH_2S$), 61.7 and 62.6 (two $CHCHCH_2S$), 173.9 (CO_2), 182.3 (CS). MS (CI/NH_3) *m/e* 291 (MH^+, 100), 259 (MH^+-MeOH, 4); HRMS (CI/CH_4) calcd for $C_{12}H_{23}N_2O_2S_2$ (MH^+), 291.12010 found 291.08042.

3.17.3. 5-[5-(2-Methylsulfanyl-ethyl)-2-thioxo-imidazolidin-4-yl]-pentanoic acid (22g). From **20′g**, yellow powder (quantitative yield). ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 4H, $CH_2CH_2CH_2CH_2CO_2$), 1.64 (m, 4H, $CH_2CH_2CH_2CH_2CH_2$-CO_2), 1.88 (m, 1H, CH_2CH_2S), 2.11 (s, 3H, SMe), 2.32 (t, *J*=7.3 Hz, 2H, CH_2CO_2), 2.59 (t, *J*=7 Hz, 2H, CH_2S), 2.65 (m, 1H, CH_2CH_2S), 3.67 (s, 3H, OMe), 3.75 (m, 1H, CH), 4.03 (m, 1H, CH), 7.00–7.40 (several m, 2H, two NH's). ^{13}C NMR ($CDCl_3$) δ 15.5 (SMe), 24.7 ($CH_2CH_2CO_2$), 25.0 ($CH_2CH_2CH_2CH_2CO_2$), 28.8 ($CH_2CH_2CH_2CO_2$), 28.9 ($CH_2CH_2CH_2CH_2CH_2CO_2$), 30.3 (CH_2CH_2S), 31.2 (CH_2S), 33.9 (CH_2CO_2), 51.5 (OMe), 59.3 and 60.3 (two $CHCH_2CH_2S$), 62.1 and 63.0 (two $CHCHCH_2CH_2S$), 174.0 (CO_2), 181.8 (CS). MS (CI/NH_3) *m/e* 305 (MH^+, 100), 273 (MH^+-MeOH, 11); HRMS (CI/CH_4) calcd for $C_{13}H_{25}N_2O_2S_2$ (MH^+), 305.13575 found 305.07004.

3.18. General procedure for the preparation of *N*-Cbz amino acid methyl ester derivatives

Benzyl chloroformate (0.16 mL, 1.1 mmol) was added dropwise, during 30 min to an ice-cooled turbid mixture of the amino acid hydrochloride Me ester (1 mmol) and $NaHCO_3$ (0.4 g, 5 mmol) in EtOAc (3 mL)/H_2O (2 mL). The mixture was stirred at room temperature for 3 h and was then decanted. The organic layer was washed with 1 N HCl (2×), H_2O (2×), dried ($MgSO_4$), filtered and evaporated to give the product.

3.18.1. 7,8-Bis-benzyloxycarbonylamino-10-methylsulfanyl-decanoic acid methyl ester (20′gII). Compound **20′gII** was obtained as a viscous oil from **20′g** (63% yield). Note: two equivalents of benzyl chloroformate were used. ^{1}H NMR ($CDCl_3$) δ 1.33 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$CH$_2$CO$_2$), 1.60 (m, 4H, C*H*$_2$(CH$_2$)$_2$CH$_2$CO), 1.75 (m, 2H, C*H*$_2$CH$_2$S), 2.07 (s, 3H, SMe), 2.28 (t, J=7.2 Hz, 2H, CH$_2$CO$_2$), 2.54 (m, 2H, CH$_2$S), 3.66 (s, 3H, OMe), 3.78 (m, 2H, two CH's), 4.70–5.00 (several m, 2H, two NH's), 5.08 (two s, 4H, C*H*$_2$Ar), 7.32 (two m, 10H, Ar). MS (CI/NH_3) *m/e* 548 (MNH_4^+, 67), 531 (MH^+, 100), 456 ($MNH_4^+-CH_2Ph$, 5), 440 (MH^+-CH_2Ph, 4), 397 ($MH^+-CO_2CH_2Ph$, 12); HRMS (CI/CH_4) calcd for $C_{28}H_{39}N_2O_6S$ (MH^+), 531.25228 found 531.25697.

3.18.2. 7,8-Bis-methoxycarbonylamino-10-methylsulfanyl-decanoic acid methyl ester (20′gIII). From **20′g**. Et_3N (0.2 g, 2 mmol) was added to a suspension of **20′g** (0.26 g, 1 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred vigorously until it became homogenous and was further stirred at room temperature for 10 min. Dimethyl dicarbonate (0.26 g, 2 mmol) was added and the mixture was stirred at room temperature for 3.5 h. The resulting mixture was evaporated to dryness and the residue was partitioned between 1 N HCl and EtOAc. The aqueous layer was extracted with EtOAc (4×) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give **20′gIII** (98% yield). ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 4H, CH(C*H*$_2$)$_2$(CH$_2$)$_2$CO$_2$), 1.63 (m, 4H, CHC*H*$_2$(CH$_2$)$_2$C*H*$_2$), 2.11 (m, 1H, C*H*$_2$CH$_2$S), 2.10–2.12 (several s, 3H, SMe), 2.29 (m, 1H, C*H*$_2$CH$_2$S), 2.27 and 2.30 (two t, J=7.5, 7 Hz, 2H, CH$_2$CO$_2$), 2.55 (m, 1H, CH$_2$S), 2.68 (t, J=6.9 Hz, 1H, CH$_2$S), 3.65–3.76 (several s, 9H, CH$_2$CO$_2$*Me* and two NCO$_2$*Me*), 3.75–4.02 (several m, 2H, two CH's), 4.70–5.25 (several m, 2H, two NH's). MS (CI/NH_3) *m/e* 396 (MNH_4^+, 86), 379 (MH^+, 100), 364 (MH^+-MeOH, 10), 347 (MH^+-two MeOH, 45).

3.18.3. 7,8-Bis-benzyloxycarbonylamino-10-methanesulfinyl-decanoic acid methyl ester (20′hII). Periodate oxidation[10e] of **20′gII** (93% yield). Notes: (a) due to the insolubility of **20′gII** in MeOH and H_2O, the starting material was suspended in MeOH, while CH_2Cl_2 was added until complete dissolution and only then was the aqueous solution of $NaIO_4$ added (b) partial NMR spectrum of **20′hII** compared to that of **20′gII**. ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H, SMe) compared to 2.07 (s, 3H, SMe), and 2.71 (m, 2H, CH$_2$S) compared to 2.54 (m, 2H, CH$_2$S). MS (DCI/NH_3) *m/e* 564 (MNH_4^+, 29), 547 (MH^+, 100), 456 (MH^+-CH_2Ph, 12), 439 (MH^+-OCH_2Ph, 61), 412 ($MH^+-CO_2CH_2Ph$, 13), 395 ($MH^+-CO_2CH_2Ph-O$, 44), 321 ($MH^+-CO_2-CH_2Ph-CH_2Ph$, 2), 305 ($MH^+-CO_2CH_2Ph-OCH_2Ph$, 96); HRMS (CI/CH_4) calcd for $C_{28}H_{39}N_2O_7S$ (MH^+), 547.24780 found 547.23947.

3.18.4. 10-Methanesulfinyl-7,8-bis-methoxycarbonylamino-decanoic acid methyl ester (20′hIII). Periodate oxidation[10e] of **20′gIII** (93% yield). Note: partial NMR spectrum of **20′hIII** compared to that of **20′gIII**. ^{1}H NMR ($CDCl_3$) δ 2.58–2.67 (s, 3H, SMe) compared to 2.10–2.13 (s, 3H, SMe) and 2.79 (m, 2H, CH$_2$S), as compared to 2.55 and 2.68 (two m, 2H, CH$_2$S. MS (DCI/NH_3) *m/e* 412 (MNH_4^+, 33), 395 (MH^+, 100), 363 (MH^+-MeOH, 17); HRMS (CI/CH_4) calcd for $C_{16}H_{31}N_2O_7S$ (MH^+), 395.18520 found 395.17896.

3.19. Pyrolysis of sulfoxides to vinyl derivatives

Method A.[10a] A mixture of the sulfoxide (1 mmol) and $CaCO_3$ (0.4 g, 4 mmol) in *o*-dichlorobenzene (5 mL) was stirred at room temperature for 1 h. The mixture was transferred to a pre-heated oil bath (ca. 174 °C). The pyrolysis was monitored by tlc (hexane/EtOAc 4:1, spraying with phosphomolybdic acid). The reaction was complete after 2 h and the product was obtained by in very poor yield flash chromatography.

Method B.[10b] The sulfoxide were distilled in a Kugelrohr apparatus at elevated temperatures (>200 °C) and high vacuum, and were usually obtained as oils that solidified at room temperature. Substrates containing labile Boc groups, or acidic hydrogens (e.g. β-keto esters) could not be pyrolyzed, due to decomposition of the substrate and product. Method B was usually followed, due to better yield.

3.19.1. 8-Acetylamino-7-oxo-dec-8-enoic acid methyl ester (23′IV). Undesired isomer obtained as from **5′hIV** when pyrolyzed at 220 °C and 1 Torr (70% yield). ^{1}H NMR ($CDCl_3$) δ1.34 (m, 2H, C*H*$_2$CH$_2$CH$_2$CO$_2$), 1.64 (m, 4H, C*H*$_2$CH$_2$C*H*$_2$CH$_2$CO$_2$), 1.85 (d, J=7.1 Hz, 3H, *Me*CH), 2.14 (s, 3H, MeCO), 2.32 (t, J=7.4 Hz, 2H, CH$_2$CO$_2$), 2.70 (dd, J=8, 6.7 Hz, 2H, CHCOC*H*$_2$), 3.67 (s, 3H, OMe), 6.67 (q, J=7.1 Hz, 1H, CH), 7.25 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ15.6 (*Me*CH), 24.2 (*Me*CO), 24.7 (*C*H$_2$CH$_2$CO$_2$), 25.0 (*C*H$_2$(CH$_2$)$_2$CO$_2$), 28.7 (*C*H$_2$CH$_2$CH$_2$CO$_2$), 33.8 (*C*H$_2$CO$_2$), 36.3 (*C*H$_2$COCH), 132.6 (CH), 134.5 (CNH), 173.7 (CON), 174.0 (CO$_2$), 197.4 (CH$_2$*C*OCH). MS (EI) m/e 255 (M^+, 18), 224 (M^+-MeOH, 2), 213 (M^+-MeCO$_2$, 100), 196 ($M^+-C_2H_4O_2$, 4), 182 (M^+-MeOH–MeCO$_2$, 48), 153 (M^+-MeCO$_2-C_2H_4O_2$, 20).

3.19.2. 7,8-Bis-methoxycarbonylamino-dec-9-enoic acid methyl ester (20′oIII). From **20′hIII**, at 240 °C and 2 Torr (41% yield). ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 4H, (C*H*$_2$)$_2$-(CH$_2$)$_2$CO$_2$), 1.62 (m, 4H, C*H*$_2$(CH$_2$)$_2$C*H*$_2$CH$_2$CO), 2.32 (m, 2H, CH$_2$CO$_2$), 3.41 and 3.68 (two m, 1H, NC*H*CH$_2$), 3.67 (s, 9H, three OMe's), 3.68 and 4.21 (two m, 1H, CHC*H*CHCH$_2$CH$_2$), 4.50–5.00 (several m, 2H, two NH's), 5.22 and 5.30 (two m, 2H, C*H*$_2$=CH), 5.80 (m, 1H, CH$_2$=C*H*). ^{13}C NMR ($CDCl_3$) δ 23.0–35.0 (chain CH$_2$'s), 51.5 (CH$_2$CO$_2$*Me*), 52.3 and 53.4 (two NCO$_2$*Me*), 56.3 and 57.2 (two=CH*C*H), 59.0 and 61.7 (two N*C*HCH$_2$), 117.4 and 118.4 (two=*C*H), 134.1 and 137.3 (two *C*H$_2$CHN), 155.0 (CON), 174.0 (CO$_2$). MS (CI/NH_3) *m/e* 348 (MNH_4^+,

100), 331 (MH^+, 96), 316 (MNH_4^+-MeOH, 16), 299 (MH^+-MeOH, 41).

Note: experimental procedures for the following compounds may be obtained directly from the corresponding authors.

4-[(*tert*-Butyloxycarbonyl)amino]-5-(methylthio)-3-oxopentanoic acid methyl ester (**2′iI**).

4-[(*tert*-Butyloxycarbonyl)amino]-5-(*tert*-butyloxycarbonyl)thio]-3-oxopentanoic acid methyl ester (**2′kI**).

4-Benzyloxycarbonylamino-5-benzyloxycarbonylsulfanyl-3-oxo-pentanoic acid methyl ester (**2′lII**).

5-Benzylsulfanyl-4-*tert*-butoxycarbonylamino-3-oxo-pentanoic acid methyl ester (**2′mI**).

4-Acetylamino-5-acetylsulfanyl-3-oxo-pentanoic acid methyl ester (**2′nIV**).

4-*tert*-Butoxycarbonylamino-3-oxo-5-(tetrahydro-pyran-2-yloxy)-pentanoic acid methyl ester (**2′qI**).

4-*tert*-Butoxycarbonylamino-3-oxo-5-(tetrahydro-pyran-2-yloxy)-hexanoic acid methyl ester (**2′sI**).

4-Methoxycarbonylacetyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**16′p**).

4-Methoxycarbonylacetyl-5-methyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (**16′r**).

2-(2-*tert*-Butoxycarbonylamino-propionyl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**3′bI**).

2-(2-*tert*-Butoxycarbonylamino-butyryl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**3′cI**).

2-(2-*tert*-Butoxycarbonylamino-3-methyl-butyryl)-heptanedioic acid 7-ethyl ester 1 methyl ester (**3′dI**).

2-(2-*tert*-Butoxycarbonylamino-4-methyl-pentanoyl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**3′eI**).

2-(2-*tert*-Butoxycarbonylamino-3-methyl-pentanoyl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**3′fI**).

2-(2-*tert*-Butoxycarbonylamino-4-methylsulfanyl-butyryl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**3′gI**).

2-(2-*tert*-Butoxycarbonylamino-4-methanesulfinyl-butyryl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**3′hI**).

Ethyl 8-[(*tert*-butyloxycarbonyl)amino]-6-(methoxycarbonyl)-9-(methylthio)-7-oxononanoate (**3′iI**).

2-(3-*tert*-Butoxycarbonyl-oxazolidine-4-carbonyl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**17′p**).

2-(3-*tert*-Butoxycarbonyl-5-methyl-oxazolidine-4-carbonyl)-heptanedioic acid 7-ethyl ester 1-methyl ester (**17′r**).

8-Amino-7-oxo-decanoic acid hydrochloride (**4c**).

8-Amino-10-methylsulfanyl-7-oxo-decanoic acid hydrochloride (**4g**).

8-Amino-10-methanesulfinyl-7-oxo-decanoic acid hydrochloride (**4h**).

8-Amino-9-methylsulfanyl-7-oxo-nonanoic acid hydrochloride (**4i**).

8-Amino-9-mercapto-7-oxo-nonanoic acid hydrochloride (**4j**).

8-Amino-9-hydroxy-7-oxo-nonanoic acid hydrochloride (**4p**).

8-Amino-9-hydroxy-7-oxo-decanenitrile hydrochloride (**14r**).

8-Amino-9-hydroxy-7-oxo-nonanoic acid methyl ester hydrochloride (**5′p**).

8-Amino-9-hydroxy-7-oxo-decanoic acid methyl ester hydrochloride (**5′r**).

8-Amino-10-methylsulfanyl-7-oxo-decanoic acid methyl ester hydrochloride (**5′g**).

8-Amino-9-methylsulfanyl-7-oxo-nonanoic acid methyl ester hydrochloride (**5′I**).

8-Amino-9-mercapto-7-oxo-nonanoic acid methyl ester hydrochloride (**5′j**).

8-*tert*-Butoxycarbonylamino-7-oxo-octanoic acid methyl ester (**5′aI**).

8-(*tert*-Butoxycarbonylamino)-9-hydroxy-7-oxo-decanoic acid methyl ester (**5′qI**).

8-*tert*-Butoxycarbonylamino-10-methylsulfanyl-7-oxo-decanoic acid methyl ester (**5′gI**).

8-*tert*-Butoxycarbonylamino-10-methanesulfinyl-7-oxo-decanoic acid methyl ester (**5′hI**).

8-*tert*-Butoxycarbonylamino-9-methylsulfanyl-7-oxo-nonanoic acid methyl ester (**5′iI**).

8-Amino-7-hydroxyimino-octanoic acid methyl ester hydrochloride (**18′a**).

8-Amino-7-hydroxyimino-octanoic acid hydrochloride (**18c**).

8-Amino-9-methyl-7-hydroxyimino-decanoic acid hydrochloride (**18d**).

8-Amino-7-hydroxyimino-9-methyl-undecanoic acid hydrochloride (**18f**).

8-Amino-7-hydroxyimino-9-mercapto-nonanoic acid hydrochloride (**18j**).

8-Amino-7-hydroxyimino-9-mercapto-nonanoic acid methyl ester hydrochloride (**18′j**).

7-Amino-8-*tert*-butyloxycarbonylamino-9-hydroxy-decanoic acid methyl ester (**19′rI**).

7,8-Diamino-9-hydroxy-decanoic acid methyl ester dihydrochloride (**20′r**).

7,8-Diamino-dec-9-enoic acid dihydrochloride (**20o**).

7,8-Diamino-10-methylsulfanyl-decanoic acid methyl ester dihydrochloride (**20′g**).

6-(2-Oxo-imidazolidin-4-yl)-hexanoic acid methyl ester (**21′a**).

6-[5-(2-Methylsulfanyl-ethyl)-2-oxo-imidazolidin-4-yl]-hexanoic acid (**21g**).

6-(5-Methylsulfanylmethyl-2-oxo-imidazolidin-4-yl)-hexanoic acid (**21i**).

6-[5-(2-Methanesulfinyl-ethyl)-2-oxo-imidazolidin-4-yl]-hexanoic acid (**21h**).

Acknowledgements

Generous support for this work by the 'Marcus Center for Pharmaceutical and Medicinal Chemistry' and the 'Bronia and Samuel Hacker Fund for Scientific Instrumentation' at Bar Ilan University, are gratefully acknowledged.

References and notes

1. (a) Izumi, Y.; Yamada, H. In *Biotechnology of vitamins, pigments and growth factors*; Vadamme, E. J., Ed.; Elsevier: London, 1989; pp 231–256. (b) In *Biotin. Ann. NY Acad. Sci.*, Dakshinamurti, K., Bhagavan, N. H., Eds.;, 1985; 447, pp 1–441. (c) Knowles, J. R. *Annu. Rev. Biochem.* **1989**, *58*, 195–221.
2. (a) Izumi, Y.; Yamada, H. In *Biotechnology of vitamins, pigments and growth factors*; Vadamme, E. J., Ed.; Elsevier: London, 1989; pp 231–256. (b) In *Biotin. Ann. NY Acad. Sci.*, Dakshinamurti, K., Bhagavan, N. H., Eds.;, 1985; 447, pp 1–441. (c) Knowles, J. R. *Annu. Rev. Biochem.* **1989**, *58*, 195–221.
3. Gibson, K. J.; Lorimer, G. H.; Rendina, A. R.; Taylor, W. S.; Cohen, G.; Gatenby, A. A.; Payne, W. G.; Roe, D. C.; Lockett, B. A.; Nudelman, A.; Marcovici, D.; Nachum, A.; Wexler, B. A.; Marsilii, E. L.; Turner, Sr. I. M.; Howel, D.; Kalbach, C. E.; Chi, H. *Biochemistry* **1995**, *34*, 10976–10984.
4. (a) Baldet, P.; Gerbling, H.; Axiotis, S.; Douce, R. *Eur. J. Biochem.* **1993**, *217*, 479–485. (b) Patton, D. A.; Johnson, M.; Ward, E. R. *Plant Physiol.* **1996**, *112*, 371–378. (c) Shellhammer, J.; Meinke, D. *Plant Physiol.* **1990**, *110*, 1021–1028. (d) Patton, D. A.; Volrath, S.; Ward, E. R. *Mol. Gen. Genet.* **1996**, *251*, 261–266. (e) Patton, D. A.; Schetter, A. L.; Franzmann, L. H.; Nelson, K.; Ward, E. R.; Meinke, D. W. *Plant Physiol.* **1998**, *116*, 935–946.
5. (a) Bui, B. T. S.; Florentin, D.; Fournier, F.; Ploux, O.; Méjean, A.; Marquet, A. *FEBS Lett.* **1998**, *440*, 226–230. (b) Marquet, A.; Florentin, D.; Ploux, O.; Bui, B. T. S. *J. Phys. Org. Chem.* **1998**, *11*, 529–535. (c) Méjean, A.; Bui, B. T. S.; Florentin, D.; Ploux, O.; Izumi, Y.; Marquet, A. *Biochem. Biophys. Res. Commun.* **1995**, *217*, 1231–1237.
6. Nudelman, A.; Nudelman, A.; Marcovici-Mizrahi, D.; Flint, D. *Bioorg. Chem.* **1998**, *26*, 157–168.
7. Zervas, L.; Photaki, I.; Ghelis, N. *J. Am. Chem. Soc.* **1963**, *85*, 1337–1341.
8. Conti, S.; Cossu, S.; Giacomelli, G.; Falorni, M. *Tetrahedron* **1994**, *50*, 13493–13500.
9. Nudelman, A. PhD Dissertation, Bar Ilan University, 1996, unpublished results..
10. (a) Hanessian, S.; Sahoo, S. P. *Tetrahedron Lett.* **1984**, *25*, 1425–1428. (b) Barton, D. H. R.; Crich, D.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1985**, *25*, 4347–4357. (c) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817–4820. (d) Pellicciari, R.; Natalini, B.; Marinozzi, M. L-Vinylglycine form L-homoserine; *Synth. Commun.* **1988**, *18*, 1715–1721. (e) Ardakani, A.; Rapoport, H. L-Vinylglycine. *J. Org. Chem.* **1980**, *45*, 4817–4820. (f) Pellicciari, R.; Natalini, B.; Marinozzi, M. *Synth. Commun.* **1988**, *18*, 1715–1721. (g) Carrasco, M.; Jones, R. J.; Kamel, S.; Rapoport, H.; Thien, T. *Org. Synth.* **1992**, *70*, 29–34.
11. Mansour, T. S.; Evans, C. A. *Synth. Commun.* **1990**, *20*, 773–781.
12. Meffre, P.; Vo-Quang, L.; Vo-Quang, Y.; Le-Goffic, F. *Synth. Commun.* **1989**, *19*, 3457–3468.
13. Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157–6163.
14. Somerville, C. R.; Ogren, W. L. *Isolation of photorespiration mutants in arabidopsis thaliana. In Methods in chloroplast molecular biology*; Elsevier: London, 1982.
15. Nudelman, A.; Patchornick, A.; Karoly-Hafely, E.; Braun, F.; Erickson, R. C. *J. Antibiot.* **1980**, *33*, 76–82.
16. Einhorn, J.; Einhorn, C.; Luche, J. L. *Synlett* **1991**, 37–38.
17. Ferraro, *J. Biochem. Prep.* **1971**, *13*, 39–41.
18. Hashimoto, M.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478.
19. Tauchi, M.; Matsumura, I. *Jpn. Kokai Tokkyo Koho*. JP07188133, JP07188203, **1995**..
20. Nudelman, A.; Bechor, Y.; Falb, E.; Fischer, B.; Wexler, B. A.; Nudelman, A. *Synth. Commun.* **1998**, *28*, 471–474.
21. Fonken, G. S.; Johnson, W. S. *J. Am. Chem. Soc.* **1952**, *74*, 831–833.
22. Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn* **1984**, *18*, 777–782.
23. Borch, R. F.; Bernstein, M. D.; Dupont, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
24. Wright, Jr. W. B. *J. Heterocyl. Chem.* **1965**, *2*, 42–43.
25. Falb, E.; Nudelman, A.; Hassner, A. *Synth. Commun.* **1993**, *23*, 2839–2844.
26. (a) Green, M. R. GB Patent GB2114886, **1983**.. (b) Christow, C. P. *Hildesheim, Ger. Ernst Rodenwalt Arch.* **1976**, *3*, 47–50. (c) Balikhina, V. N.; Zav'yalov, S. I.; Rodionova, I. Z.; Gracheva, E. P.; Filippov, V. V. *Uchenye Zapiski—Vladimirskii Gosudarstvennyi Pedagogicheskii Institut imeni P. I. Lebedeva-Polyanskogo, Seriya Fiziologiya Rastenii* **1971**, *31*, 49–55.
27. (a) Andreev, L. N. *Abh. Akad. Wiss. DDR, Abt. Math.; Naturwiss.; Tech* **1983**, 341–344. (b) Trunenkov, I. P.; Fabrichnyi, B. P.; Shalavina, I. F.; Kostrova, S. M.; Gol'dfarb,

Ya. L.; Filippov, V. V. *Uch. Zap.; Vladimirskii Gos. Pedagog. Inst.; Ser. Fiziol. Rast.* **1971**, *31*, 65–71. (c) Balkihina, V. N.; Fabrichnyi, B. P.; Shalavina, I. F.; Kostrova, S. M.; Gol'dfarb, Ya. L.; Filippov, V. V. *Uch. Zap.; Vladimirskii Gos. Pedagog. Inst.; Ser. Fiziol. Rast.* **1971**, *31*, 56–60. (d) Fabrichnyi, B. P.; Shalavina, I. F.; Kostrova, S. M.; Gol'dfarb, Ya. L.; Filippov, V. V. *Zh. Org. Khim.* **1970**, *65*, 1091–1100.

28. Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
29. Tauchi, M.; Matsumura, I. *Jpn. Kokai Tokkyo Koho.* JP07188133, JP07188203, **1995**..
30. Balikhina, V. N.; Zav'yalov, S. I.; Rodionova, I. Z.; Gracheva, E. P.; Filippov, V. V. *Uch. Zap. Vladimirskii Gos. Pedagog. Inst.; Ser. Fiziol. Rast.* **1971**, *31*, 49–55.
31. (a) Rendina, A. R.; Taylor, W. S.; Gibson, K.; Lorimer, G.; Rayner, D.; Lockett, B.; Kranis, K.; Wexler, B.; Marcovici-Mizrahi, D.; Nudelman, A.; Nudelman, A.; Marsilii, E.; Chi, H.; Wawrzak, Z.; Calabrese, J.; Huang, W.; Jia, J.; Schneider, G.; Lindqvist, Y.; Yang, G. *Pesticide Sci.* **1999**, *55*, 236–247. (b) Warshawsky, A.; Wilchek, M.; Altma, J.; Shoef, N. US Patent US4652519, **1987**.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1749–1759

Synthesis and structure of highly substituted pyrazole ligands and their complexes with platinum(II) and palladium(II) metal ions

Elzbieta Budzisz,[a,*,†] Magdalena Malecka[b] and Barbara Nawrot[c]

[a]*Department of Bioinorganic Chemistry, Faculty of Pharmacy, Medical University of Lodz, Muszynskiego 1, 90-151 Lodz, Poland*
[b]*Department of Crystallography and Crystal Chemistry, University of Lodz, Pomorska 149/153, 90-236 Lodz, Poland*
[c]*Department of Bioorganic Chemistry, Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Lodz, Poland*

Received 23 October 2003; revised 27 November 2003; accepted 18 December 2003

Abstract—Reaction of 3-methoxycarbonyl-2-methyl- or 3-dimethoxyphosphoryl-2-methyl-substituted 4-oxo-4*H*-chromones **1** with *N*-methylhydrazine resulted in the formation of isomeric, highly substituted pyrazoles **4** (major products) and **5** (minor products). Intramolecular transesterification of **4** and **5** under basic conditions led, respectively, to tricyclic derivatives **7** and **8**. The structures of pyrazoles **4a** (dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate) and **4b** (methyl 4-oxo-2-methyl-4*H*-chromene-3-carboxylate) were confirmed by X-ray crystallography. Pyrazoles **4a** and **4b** were used as ligands (L) in the formation of ML_2Cl_2 complexes with platinum(II) or palladium(II) metal ions (M). Potassium tetrachloroplatinate(II), used as the metal ion reagent, gave both *trans*-[Pt(**4a**)$_2$Cl$_2$] and *cis*-[Pt(**4a**)$_2$Cl$_2$], complexes with ligand **4a**, and only *cis*-[Pt(**4b**)$_2$Cl$_2$] isomer with ligand **4b**. Palladium complexes were obtained by the reaction of bis(benzonitrile)dichloropalladium(II) with the test ligands. *trans*-[Pd(**4a**)$_2$Cl$_2$] and *trans*-[Pd(**4b**)$_2$Cl$_2$] were the exclusive products of these reactions. The structures of all the complexes were confirmed by IR, ^{1}H NMR and FAB MS spectral analysis, elemental analysis and Kurnakov tests.

1. Introduction

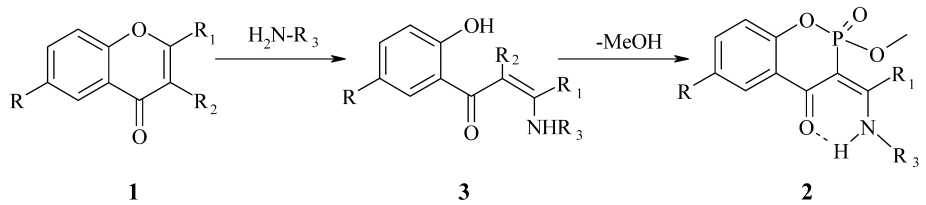
cis-Platin [diamminedichloroplatinum, *cis*-$PtCl_2(NH_3)_2$] is known as a DNA-modifying agent with strong anticancer potency.[1] Despite its wide application as a therapeutic agent in chemotherapy, *cis*-platin is associated with many serious side effects, such as nephrotoxicity, othotoxicity, allergy etc.[2] Thus, various platinum(II) and palladium(II) complexes with nitrogen-containing ligands are the subject of intensive biological evaluation in the search for less toxic and more selective anticancer therapeutics.[3,4] Among them, the class of pyrazole-containing complexes have been reported to possess antitumor activity comparable to that of *cis*-platin.[5] In addition, considerable interest in the pyrazole nucleus has been stimulated by promising pharmacological, agrochemical and analytical applications of pyrazole-containing derivatives.[6–9] Recently, substituted pyrazoles have been used as analytical reagents in the complexation of transition metal ions.[10–13]

Chromone (benzo-γ-pyrone) derivatives form another class of biologically important compounds.[14] These compounds exhibit a wide spectrum of biologically relevant properties including anticonvulsant,[15] antimicrobial[16] and antitumor activities.[17] New chromone derivatives containing a phosphorus atom have been considered as bioisosteric analogues of natural chromones.[18,19] For many years the synthesis of phosphonic derivatives of benzo-γ-pyrone has been a subject of interest in several laboratories.[20–23] However, the biological activity of these compounds has not been investigated.

Thus, recently our research has been focused on the synthesis and pharmacological properties of phosphonic derivatives of chromones of general formulae **1** and **2**.[24] These compounds exhibit noticeable antibacterial, cytotoxic and alkylating activity. In terms of their chemistry, we carried out a detailed investigation of the transformation of dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonates **1** [R=H or CH_3, R_1=CH_3, R_2=P(O)$(OCH_3)_2$] into 2-methoxy-3-[1-(alkylamino)ethylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e][1,2]oxaphosphinanes **2** (R=H or CH_3, R_1=CH_3).[25,26] The reaction involves the action of various primary amines [NH_2CH_3, NH_2CH_2Ph or $NH_2(CH_2)_2OH$] on the chromone system leading to the opening of the γ-pyrone ring, followed by spontaneous cyclisation of the intermediate enamino ketones **3** [R_3=CH_3, CH_2Ph or

Keywords: Phosphonic chromone; Pyrazole; Platinum(II) complex; Palladium(II) complex; X-ray structure.
* Corresponding authors: Tel.: +48-42-677-92-17; fax: +48-42-678-83-98; e-mail address: elora@ich.pharm.am.lodz.pl
† Present address: Department of Medicinal Chemistry, Faculty of Pharmacy, Medical University of Lodz, 90-151 Lodz, Muszynskiego 1, Poland.

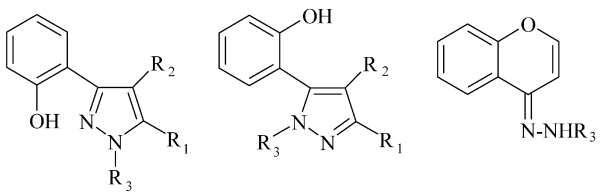
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.044



Scheme 1.

$(CH_2)_2OH$] into cyclic phosphonic isosteres of coumarin **2** (Scheme 1).

An analogous reaction of chromone itself with hydrazine hydrate led to 3- and/or 5-*o*-hydroxyphenylpyrazoles **4** or **5** (R_1, R_2 and R_3=H), and not the hydrazone **6**, as proposed in the early fifties.[27–29] Additional support comes from publications of Takagi[30] and Nawrot-Modranka and Kostka,[31,32] in which reaction of C3–Me, Ph or NO_2 substituted chromones with *N*-methylhydrazine leads to both isomeric products **4** and **5** (R_1=H, CH_3 or C_2H_5, R_2=CH_3, Ph or NO_2; R_3=CH_3). It was assumed that the molar ratio of the isomeric products **4** and **5** depends on the amount of nucleophilic reagent used.



4 **5** **6**

In the present work, we demonstrate that the reaction of phosphonic chromone **1a** [R=H, R_1=CH_3, R_2=$P(O)(OCH_3)_2$], as well as its C-3 methoxycarbonyl analogue **1b** (R_2=$COOCH_3$) with *N*-methylhydrazine leads to the substituted pyrazoles **4** and **5** and to the products of their intramolecular esterification—compounds **7** and **8**. Pyrazoles **4a** and **4b** were used as ligands (L) in the formation of ML_2Cl_2 complexes with platinum(II) or palladium(II) metal ions (M). The structures of the ligands and the resulting complexes were determined by their spectral and elemental analysis.

2. Results

2.1. Chemistry

2.1.1. Synthesis of ligands. An NMR scale reaction of **1a** with an equimolar amount of *N*-methylhydrazine was carried out in methanol. The progress of the conversion of **1a** was monitored by ^{31}P NMR spectroscopy and by thin layer chromatography (TLC). In the ^{31}P NMR spectrum (Fig. 1a), obtained within the first 15 min of the reaction, the signals of two new products at 19.57 (**4a**) and 18.34 ppm

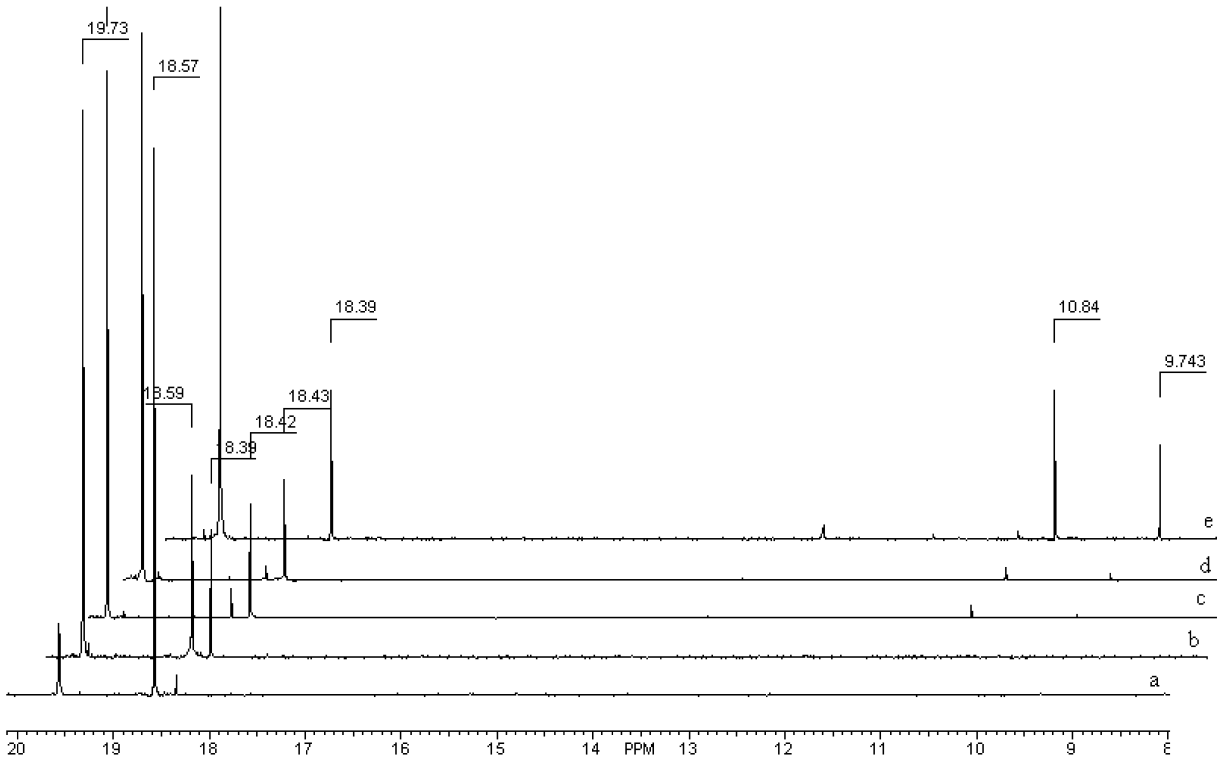


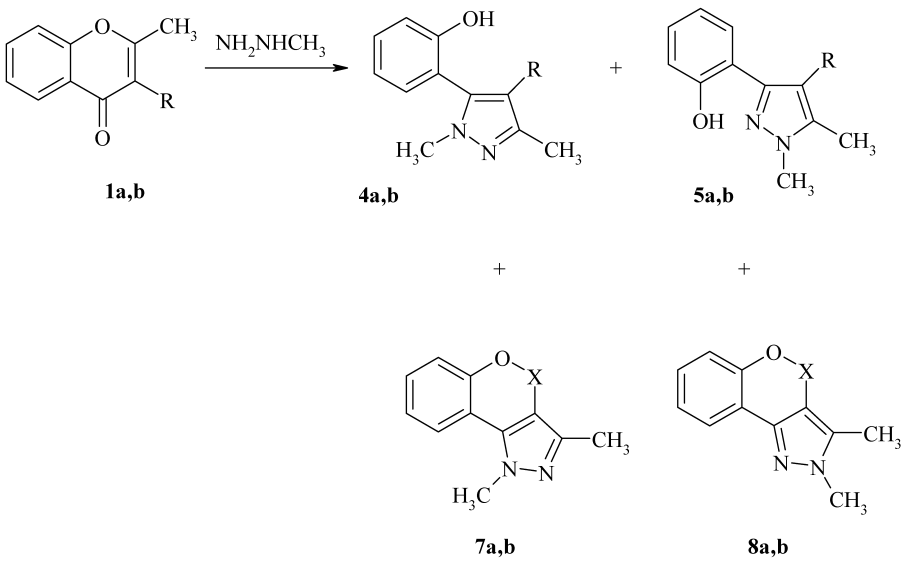
Figure 1. ^{31}P NMR analysis of the reaction products of chromone **1a** with 1 equiv. of *N*-methylhydrazine in methanol. The spectra were measured after 0.25 (a), 2 (b), 24 (c) and 48 h (d) of reaction time. Spectrum e was collected 24 h after addition of a second equivalent of *N*-methylhydrazine to the reaction mixture represented by spectrum d.

(**5a**) were observed, in addition to the signal of the substrate **1a** at 18.57 ppm. The intensity of these signals gradually increased until only traces of substrate were left (48 h, Fig. 1d). The ratio of the products was 4:1, with the major reaction product associated with the downfield resonance. Interestingly, after 24 h two additional minute signals could be seen in NMR spectrum (Fig. 1c). The ratio of these additional signals at 10.92 and 9.81 ppm was also 4:1. Careful chromatographic analysis allowed us to relate the mobility of these four products and their chemical shifts in the ^{31}P NMR spectra. No significant increase in the content of the two minor products was observed in the next 24 h (Fig. 1d); while addition of a second equivalent of *N*-methylhydrazine to the reaction mixture dramatically improved the yield of these products, giving rise to a higher intensity of the upfield signals. All four products were present after 15 min when the reaction was carried out in the absence of solvent or when a twofold molar excess of *N*-methylhydrazine in methanol was used. Similar ratios of both pairs of signals (ca. 4:1) were observed throughout these experiments (as in Fig. 1e).

The reaction of chromone **1a** with an equimolar amount of *N*-methylhydrazine, performed on a larger scale without any solvent, gave three isolated products. The major product (64% yield, δ 19.57 ppm) was isolated from the reaction mixture by addition of acetone, while the two other products, giving rise to signals at 10.92 and 9.81 ppm, respectively, were separated chromatographically from the remaining mixture. The major reaction product was shown to be the 5-(2-hydroxyphenyl)-1,3-dimethyl-4-phosphonyl-substituted pyrazole **4a** (Scheme 2). Unexpectedly, no isomeric 3-(2-hydroxyphenyl)-1,5-dimethyl-4-phosphonyl-substituted pyrazole **5a** (giving ^{31}P NMR signal at 18.34 ppm) was obtained. Instead, compound **8a** was isolated in 20% yield. Probably **5a**, formed in the first step of the reaction, was unstable under the chromatographic conditions and underwent intramolecular cyclisation giving rise to **8a**. The third reaction product, identified as **7a** and originating from an analogous cyclisation of **4a**, was obtained in the lowest yield (16%). The ratio of isolated products **8a** to **7a** (5:4) was much higher than present in ^{31}P NMR spectrum (1:4, Fig. 1e).

A multimilligram reaction of **1b** with one equivalent of *N*-methylhydrazine gave a similar mixture of products **4b** (64%), **7b** (16%) and **8b** (20%). No isomeric product **5b** was isolated, although it was seen during TLC analysis of the crude reaction mixture. Compounds **7b** and **8b** were previously obtained by Collota et al.[33] as by-products of the reaction of 3-acetyl-4-hydroxycoumarin with *N*-methylhydrazine in the presence of acetic acid but were not fully characterised. The reported melting points (194–196 and 210–212 °C) are in agreement with those obtained for our compounds **7b** and **8b** (192–194 and 208–209 °C, respectively).

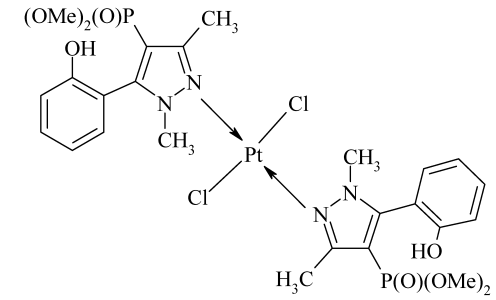
As expected, compound **4b** was readily transformed into tricyclic product **7b** on treatment with an equimolar amount of *N*-methylhydrazine. Thus, we conclude that both pairs of parent products **4a**,**5a** and **4b**,**5b** undergo intramolecular transesterification in the presence of *N*-methylhydrazine to give two pairs of products **7a**,**8a** and **7b**,**8b**, respectively. Moreover, products **5a** and **5b** are unstable under the isolation acidic conditions (silica gel) and are easily transformed into the stable tricyclic products **8a** and **8b**, respectively.



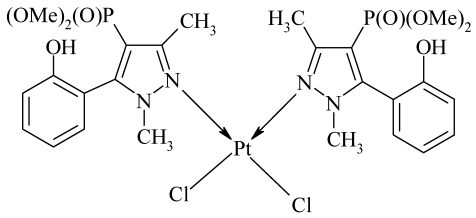
a: R= -P(O)(OCH$_3$)$_2$ X= >P(O)(OCH$_3$)

b: R= -COOCH$_3$ X= >C=O

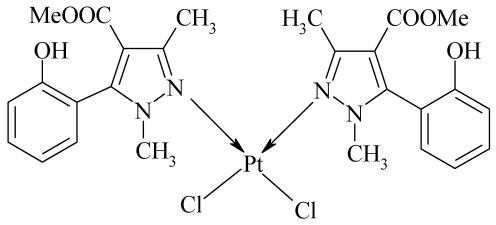
Scheme 2. Reaction of the phosphonic chromone **1a** and its C-3 methoxycarbonyl analogue **1b** with *N*-methylhydrazine.



9a



10a



10b

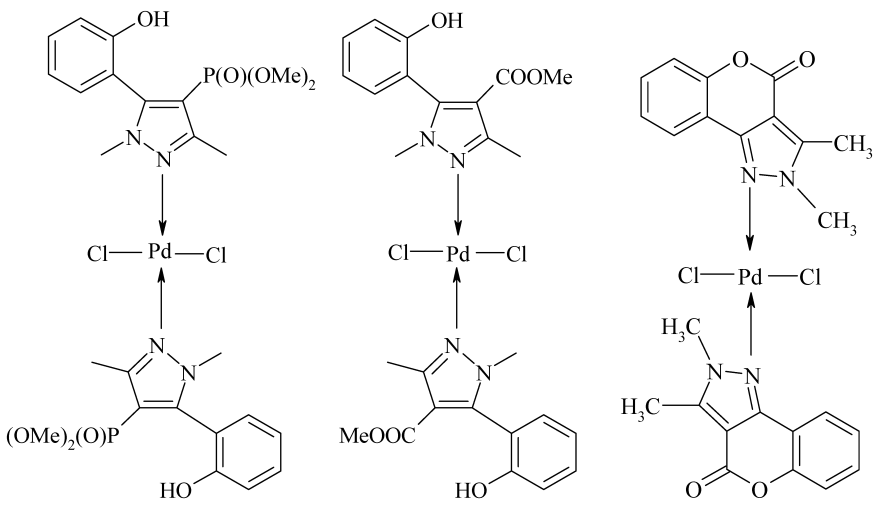
Figure 2. The structures of the platinum(II) complexes of the highly substituted pyrazoles **4a** and **4b**.

2.1.2. Synthesis of Pt(II) and Pd(II) complexes. Potassium tetrachloroplatinate(II) and bis(benzonitrile)dichloropalladium(II) were used as metal ion reagents. Synthesis of the platinum complexes of ligand **4a** was carried out in aqueous acetone at 60 °C for 6 h. Cooling the reaction mixture to ambient temperature, followed by slow removal of part of the solvent afforded a dark-brown precipitate which was filtered off. The remaining yellow solution was cooled in an ice bath and left for 24 h in −12 °C. The resulting yellow solid was filtered off. Both complexes were analysed by their IR spectra and a Kurnakov test.[34] The first compound, which has a melting point above 350 °C was identified as *trans*-[Pt(**4a**)$_2$Cl$_2$] **9a** and the remaining solid, with mp 153–156 °C, was identified as the *cis*-[Pt(**4a**)$_2$Cl$_2$] isomer **10a** (Fig. 2).

An analogous synthesis of the platinum complexes of ligand **4b** was carried out in aqueous ethanol for 72 h at room temperature. In this reaction only one complex was obtained. It was identified as *cis*-[Pt(**4b**)$_2$Cl$_2$] **10b**.

Palladium complexes of ligands **4a** and **4b** were synthesized by addition of a dichloromethane solution of ligand to a solution of bis(benzonitrile)dichloropalladium(II) in the same solvent at RT in 24 h. Only one complex was isolated from each reaction. Spectral analysis of the resulting complexes showed that exclusively the *trans* isomers, **11a** and **11b** were formed (Fig. 3).

We also tested the most available chromone analogue ligand **8b** for its potential to form a palladium complex. Thus an analogous reaction with bis(benzonitrile)dichloropalladium(II) in dichloromethane was performed with this ligand. The resulting solid, mp 334 °C, was identified by FAB MS spectrometry and elemental analysis as the complex [Pd(**8b**)$_2$Cl$_2$]. Its poor solubility in most of the suitable solvents did not allow us to obtain ^{1}H NMR spectrum. However, careful infrared data analysis enabled us to deduce that it is the *trans*-isomer **12b**, since palladium(II) metal ion form predominantly *trans*-complexes,



11a **11b** **12b**

Figure 3. The structures of the palladium(II) complexes of the highly substituted pyrazoles **4a**, **4b** and **8b**.

Table 1. Selected geometric parameters of the crystal structures of **4a** and **4b**

Environment of P atom		Geometric parameters for pyrazole ring			
4a	(Å)	**4a**	(Å)	**4b**	(Å)
P1–O1	1.464(2)	N1–N2	1.356(2)	N1–N2	1.358(2)
P1–O2	1.567(2)	N2–C3	1.321(2)	N2–C3	1.327(3)
P1–O3	1.556(1)	C3–C4	1.420(2)	C3–C4	1.416(3)
P1–C4	1.757(2)	C4–C5	1.393(2)	C4–C5	1.394(3)
O1–P1–O3	114.7(1)	C5–N1	1.347(2)	C5–N1	1.351(2)
O1–P1–O2	107.5(1)	N1–N2–C3	105.5(1)	N1–N2–C3	106.2(2)
O3–P1–O2	107.6(1)	N2–C3–C4	110.8(2)	N2–C3–C4	110.0(2)
O1–P1–C4	115.6(1)	C3–C4–C5	104.9(2)	C3–C4–C5	105.8(2)
O3–P1–C4	103.1(1)	C4–C5–N1	106.0(2)	C4–C5–N1	105.8(2)
O2–P1–C4	108.0(1)	C5–N1–N2	112.8(1)	C5–N1–N2	112.3(2)

Table 2. Hydrogen bonding geometry for structure **4a** and **4b**

	D–H (Å)	H···A (Å)	D···A (Å)	<D–H···A (deg)
Structure **4a**				
O52–H52···O1^{i}	0.82(4)	1.87(4)	2.688(2)	175(3)
Structure **4b**				
O51–H51···N2^{ii}	0.98(2)	1.80(2)	2.763(2)	167(2)

Symmetry code: (i) $x-1$, y, z; (ii) $x+\frac{1}{2}$, $-y+\frac{1}{2}+1$, $-z$.

characterised by a sharp Pd–Cl band in the range of ca. 350 cm^{-1}. In contrast, *cis*-complexes exhibit broad or double IR band in the range of ca. 330 cm^{-1}.[35]

2.2. Structural studies

2.2.1. X-ray crystallographic study of ligands 4a and 4b. X-ray structure investigations were undertaken for the two major ligands **4a** and **4b**. The structure of **4a** shows the pyrazole ring substituted by methyl groups at positions 1 and 3, a dimethyl phosphonate moiety at C-4 and a hydroxyphenyl group at position 5. The pyrazole and phenyl rings are planar. The geometry around the P atom is best described as between a distorted tetrahedron and a trigonal pyramid with a P1–C4 elongated bond (Table 1). An intermolecular hydrogen bond between O52–H52 and O1^{i} [symmetry code: (i) $x-1$, y, z] is observed (Table 2).

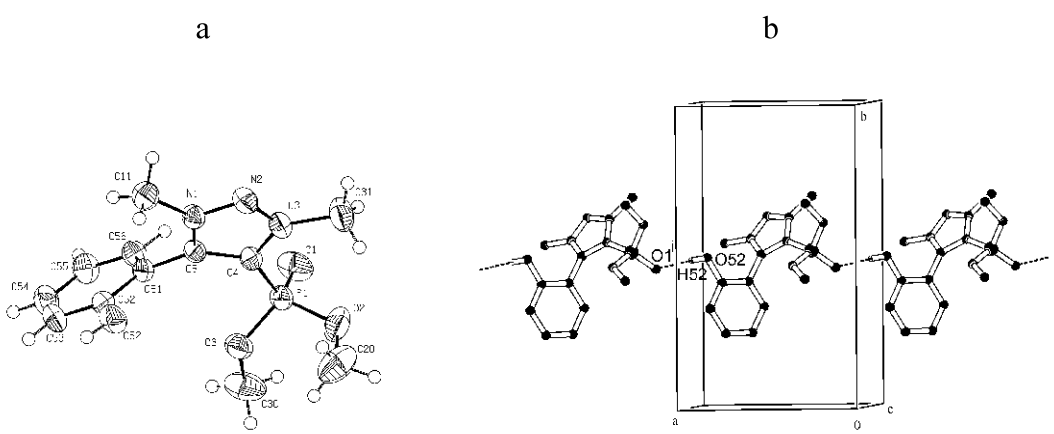


Figure 4. X-ray structure of **4a** (a) single molecule and (b) crystal lattice.

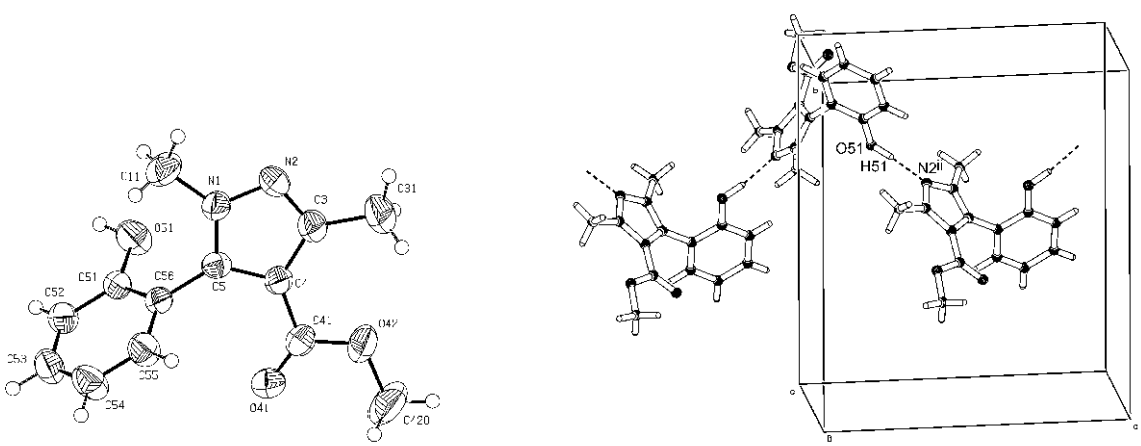


Figure 5. X-ray structure of **4b** (a) single molecule and (b) crystal lattice.

Thus the molecules form chains running along the *a* axis (Fig. 4b).

The structure of molecule **4b** (Fig. 5a) shows a pyrazole ring substituted with methyl groups at positions 1 and 5, a methoxycarbonyl group at C-4 and a hydroxyphenyl group at position 3. The pyrazole and phenyl rings are planar. The dihedral angle between the pyrazole ring and the phenyl ring is 69.07(7)°. In the crystal lattice the molecules are linked by an intermolecular hydrogen bond O51–H51···N2^{ii} [symmetry code: (ii) $x+\frac{1}{2}, -y+\frac{1}{2}+1, -z$] (Table 2 and Fig. 5b).

All intra-molecular bond distances and angles are in a good agreement with expected values.[36]

2.2.2. Spectral characteristics of Pt(II) and Pd(II) complexes. The assignments of the most important IR spectra bands for the ligands **4a** and **4b** and the platinum(II) and palladium(II) complexes **9**–**12** are listed in Tables 3 and 4.

The IR spectrum of ligand **4a** (Table 3) shows a large number of absorption bands in the range 1700–1000 cm^{-1} assigned to different vibration modes of the pyrazole ring and phosphonate function. The band at 1600 cm^{-1}, assigned to the C=N vibration, shifts to higher energy in the IR spectra of complexes **9a**–**11a**, giving rise to the bands at 1614 and 1618 cm^{-1} for the Pt and Pd complexes, respectively. The same tendency in the shift of C=N vibration to higher energy is seen for complexes **10b**–**12b** (Table 4). This phenomenon indicates that the nitrogen atom participates in the coordination of the metal ion.[37] The other characteristic bands of the pyrazole ring of the free ligand shift to higher frequencies upon complexation confirming coordination of the heterocyclic N atoms.

The two new bands at about 400 cm^{-1} in both Pt and Pd complexes may correspond to the metal-nitrogen vibrations involving the N-atoms of the pyrazole ring.[38] The absorption observed in the low-energy region at 310–350 cm^{-1} is assigned to the M−Cl stretching vibration.[39]

Table 3. IR frequencies for pyrazole derivative **4a** and for complexes **9a**, **10a** and **11a**

ν (cm^{-1})	OH	–N=C–	P=O	P–O–C	M–N–	M–Cl
4a	3131	1594	1213	1049	—	—
9a	3449	1637	1228	1038	422	326
10a	3475	1614	1223	1036	487	332
11a	3443	1618	1238	1044	421	354

Table 4. IR frequencies for pyrazole derivatives **4b** and **8b** and for their complexes **10b**–**12b**

1	OH	–C=O	–N=C–	C–O–C	M–N–	M–Cl
4b	3081	1721	1611	1097	—	—
10b	3478	1722	1615	1098	480	330
11b	3342	1714	1614	1124	414	354
8b	—	1737	1592	—	—	—
12b	—	1755	1619	—	420	354

Table 5. ^{1}H and ^{31}P NMR (DMSO-d_6) characteristics of pyrazole **4a** and **4b** and their complexes with Pt(II) and Pd(II) metal ions (chemical shifts are given in ppm). $\Delta\delta$ corresponds to the difference in chemical shifts of protons in the ligands and in the corresponding complexes

	C–CH$_3$	OCH$_3$	O–CH$_3$	N–CH$_3$	OH	^{31}P NMR
4a	2.283	3.363	3.436	3.494	9.986	19.57
9a	2.425	3.523	3.701	3.889	10.145	17.89
$\Delta\delta$	0.142	0.160	0.238	0.395	0.159	1.68
10a	2.385	3.465	3.537	3.780	12.04	18.07
$\Delta\delta$	0.102	0.102	0.101	0.286	2.100	1.50
11a	2.210	3.461	3.513	3.682	10.210	18.30
$\Delta\delta$	0.073	0.098	0.077	0.186	0.224	1.27
4b	2.352	—	3.508	3.355	9.821	—
10b	2.368	—	3.612	3.394	9.954	—
$\Delta\delta$	0.016	—	0.104	0.039	0.133	—
11b	2.348	—	3.504	3.366	9.802	—
$\Delta\delta$	0.004	—	0.004	0.009	0.019	—

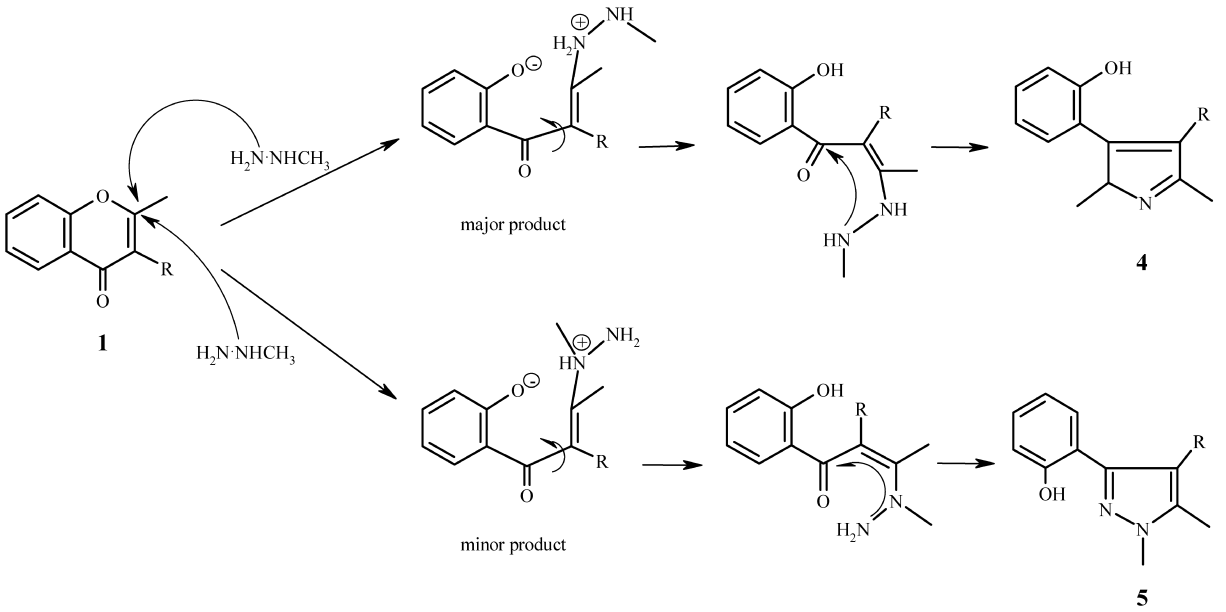
The selected chemical shifts assigned in the ^{1}H NMR spectra of pyrazole **4a** and **4b** and their P(II) and Pd(II) complexes **10** and **11** are shown in Table 5. The spectra are quite similar, however, in the metal complexes, all the signals are shifted downfield.[8] The differences between the chemical shifts of protons in the ligands and in the corresponding complexes are shown as $\Delta\delta$ (in ppm).

Apart from the remarkable values of $\Delta\delta$ for the OH groups the biggest differences in the chemical shifts of complexes **9a**, **10a**, **11a** and **11b** and their parent ligands are observed for the methyl group attached to the nitrogen atom adjacent to the coordinating center. In the spectrum of complex **10b** the most significant shift is observed for the methyl ester group.

3. Discussion

In the present work we describe the synthesis of several novel, highly substituted pyrazole derivatives as well as their complexes with Pt(II) and Pd(II) metal ions. Isomeric pyrazoles **4a**,**b** and **5a**,**b**, containing phosphonic or carboxylic acid residues, were obtained by means of the reaction of phosphonic chromone **1a** or its C-3 methoxycarbonyl analogue **1b**, with *N*-methylhydrazine (Scheme 2). The reaction proceeded according to the general mechanism described for the reaction of chromones with nitrogen nucleophiles,[40,41] including hydrazines.[31,32,42,43] Attack of a nitrogen nucleophile at C-2 of the chromone led to the opening of the γ-pyrone ring. When an alkylamine was used as the nucleophilic agent an enamino ketone derivative (as e.g., **3**) was formed.[25] Further reactions could occur when the initial product contained other reactive groups (as for example reaction of **1a** with methylamine which resulted in the formation of the cyclic phosphonic isostere **2** (R_1, R_3=CH_3) of coumarin). An analogous reaction of chromone **1** (R, R_1, R_2=H) with *N*-methylhydrazine led to both isomeric products **4** and **5** (R_1, R_2=H and R_3=CH_3) and not to the hydrazone **6**, as initially proposed.[27–29] It was also suggested that the molar ratio of the isomeric products **4** and **5** (R_1, R_2=H and R_3=CH_3) depends on the amount of nucleophilic reagent used such a reaction.[31]

In our experiments, the progress of the reaction of chromone derivative **1a** with *N*-methylhydrazine (1:1 molar ratio) in



Scheme 3. Proposed mechanism of the formation of isomeric pyrazoles **4** and **5**.

methanol was monitored by ^{31}P NMR spectroscopy. The ^{31}P NMR spectra monitored after 0.25, 2, 24 and 48 h of the reaction showed the presence of the signals of the two new products identified as **4a** and **5a** (Fig. 1a–d, respectively). Both products were formed in a ratio of 4:1, independently of the reaction time. Thus, according to the general mechanism, we assume that, in the first step, C-2 of the chromone is attacked by the nitrogen nucleophile resulting in opening of the γ-pyrone ring. Both nitrogen atoms of *N*-methylhydrazine may be considered as nucleophiles. Their participation in this reaction is governed by their relative nucleophilicity and their steric accessibility. No pKa value for N-1 of *N*-methylhydrazine has been reported while the value for N-2 was determined as 7.87.[44] It seems that N-1 should be a better nucleophile due to the presence of the electron donating adjacent methyl group. On the other hand, the presence of the methyl group causes steric hindrance which makes N-1 a less effective nucleophile. Thus, two opening products are formed - a major product, resulting from nucleophilic attack of the sterically more accessible N-2, and a minor product, arising from participation of the less sterically accessible although the more basic N-1 (Scheme 3). Both intermediate hydrazines undergo subsequent spontaneous cyclisation with the carbonyl group of the opened γ-pyrone system leading to the major product **4b** and minor product **5b**, respectively. As determined by integration of ^{31}P NMR spectra the ratio of products **4b** to **5b** is 4:1, and is similar to the ratio of products obtained in the reaction carried out without any solvent. Two other products, **7a** and **8a**, are the products of intramolecular transesterification of the parent pyrazoles **4a** and **5a**, respectively.

The proposed earlier mechanism of nucleophilic opening of chromone ring, by which **4a** can be formed exclusively, while its isomer, compound **5a** can be obtained by the reaction of the intermediate major enamine ketone with an additional *N*-methylhydrazine followed by cyclisation of the respective hydrazone,[31] does not explain our data. Our proposed mechanism for the formation of the isomeric pyrazoles is outlined in Scheme 3. An analogous mechanism is proposed for the formation of isomeric pyrazoles **4b** and **5b** and their intramolecular transesterification products **7b** and **8b**.

The structures of the **9a**, **10a**,**b** and **11a**,**b** metal complexes were confirmed by spectral (IR, ^{1}H NMR and FAB MS) and elemental analysis. DMSO-d_6 was the solvent of choice in proton NMR experiments because of the very limited solubility of all complexes in other solvents. For complex **12b** it was impossible to obtain good ^{1}H NMR spectrum due to its very poor solubility, even in DMSO. We should point out that DMSO replaces chlorine atoms in *cis*-and *trans*-platin[45,46] and thus the data obtained in our measurements may not be unequivocally attributed to structures **9**, **10** and **11** but possibly to their DMSO analogues.

4. Conclusions

Several highly substituted pyrazole ligands were obtained by the reaction of dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate and 2-methyl-4-oxo-4*H*-chromene-3-carboxylic acid methyl ester with *N*-methylhydrazine. Selected compounds were used as ligands for the synthesis of novel ML_2Cl_2 type platinum(II) and palladium(II) complexes. The structures of the ligands and the metal complexes were confirmed by spectral and elemental analyses. The structures of ligands **4a** and **4b** were confirmed by X-ray analysis. The biological activities of the palladium(II) and platinum(II) complexes will be reported in due course.

5. Experimental

5.1. General

The melting points were determined using an Electrothermal 1A9100 apparatus and they are uncorrected. The IR spectra were recorded on a Pey-Unicam 200G

Spectrophotometer in KBr or CsI. The ^{1}H NMR spectra were registered at 300 MHz on a Varian Mercury spectrometer. ^{31}P NMR spectra were recorded on a Varian 75 MHz spectrometer. Positive chemical shift values are assigned to compounds resonating downfield of phosphoric acid. The MS data were obtained on a LKB 2091 mass spectrometer (70 eV ionisation energy) and the MS-FAB data were determined on Finnigan Matt 95 mass spectrometer (NBA, Cs^+ gun operating at 13 keV). Satisfactory elemental analyses (±0.3% of the calculated values) were obtained for the new compounds in the Microanalytical Laboratory of the Department of Bioorganic Chemistry (Medical University, Lodz) using a Perkin Elmer PE 2400 CHNS analyser or in the Institute for Physical Chemistry, University of Vienna, Austria. Dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate (**1a**), was prepared according to literature,[20] methyl 2-methyl-4-oxo-4*H*-chromene-3-carboxylate (**1b**) was prepared according to literature.[47]

5.2. Synthesis of compounds 4a, 7a and 8a

To the solution of chromone **1a** 268 mg (1.0 mmol) in methanol (5 mL) *N*-methylhydrazine, 9.2 mg (2.0 mmol) solution in methanol (0.5 mL) was added. The mixture was left overnight at room temperature. The mixture was concentrated to dryness and then dry acetone was added. Crude solid **4a** was filtered off, dried, and recrystallized from acetone. The remaining solution was evaporated to dryness and chromatographed on a silica gel column. Pure **4a** was eluted from the column with chloroform–acetone 5:1, v/v.

5.2.1. Dimethyl [5-(2-hydroxyphenyl)-1,3-dimethyl-1*H*-pyrazol-4-yl]-phosphonate (4a). Yield: 189.6 mg (64%, acetone), mp 176.9–179.2 °C, R_f=0.19 (chloroform–acetone, 5:1). IR (KBr): ν=3131 (OH); 1594 (N=C); 1213 (P=O); 1049 (P–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.41 (s, 3H, CH_3); 3.51 (d, 3H, OCH_3, $^3J_{PH}$=11.7 Hz); 3.59 (s, 3H, N–CH_3); 3.70 (d, 3H, OCH_3, $^3J_{PH}$=11.7 Hz); 7.08–7.31 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$) δ=13.89 (C–CH_3); 36.91 (N–CH_3); 52.57 (P–O–CH_3, $^2J_{PC}$=5.73 Hz); 102.85 (C–P, $^1J_{PC}$=221.6 Hz); 116.49; 117.16; 119.46; 131.2; 146.84; 151.1; 155.42. ^{31}P NMR ($CDCl_3$) δ=19.57. MS (70 eV) *m*/*z* (%): 296 (100, M$^+$), 279 (18.37), 233 (10.38), 201 (9.98), 187 (10.59), 115 (5.25). Anal. found: C, 52.78; H, 5.84; N, 9.58; P, 10.61. Calcd for $C_{13}H_{17}N_2O_4P$ (296.26): C, 52.7; H, 5.78; N, 9.46; P, 10.45%.

5.2.2. 4-Methoxy-1,3-dimethyl-1,4-dihydro[1,2]benzoxaphosphinino[4,3-c]pyrazole-4-oxide (7a). Yield: 42.3 mg (16%), mp 103.0–104.7 °C, R_f=0.38 (chloroform–acetone, 5: 1). IR (KBr): ν=3360 (OH); 1250 (P=O); 1028 (P–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.48 (d, 3H, C–CH_3, J_{PC}=1.19 Hz); 3.80 (d, 3H, OCH_3, $^3J_{PC}$=11.9 Hz); 4.22 (s, 3H, N–CH_3); 7.30–7.86 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ 13.2 (C–CH_3); 37.3 (N–CH_3); 53.0 (P–O–CH_3, $^2J_{PC}$=6.6 Hz); 104.0 (P–C, $^1J_{PC}$=212.7 Hz); 115.9; 121.21; 126.92; 148.73; 149.9; 150.6. ^{31} P NMR ($CDCl_3$): δ 10.86. MS (70 eV) *m*/*z* (%): 264(100, M$^+$); 233(29); 132(8.7); 56(13.19). Anal. found: C, 54.46; H, 5.14; N, 10.53; P, 11.97. Calcd for $C_{12}H_{13}N_2O_3P$ (264.21): C, 54.50; H, 4.96; N, 10.60; P, 11.72%.

5.2.3. 4-Methoxy-2,3-dimethyl-2,4-dihydro[1,2]benzoxaphospinono[4,3-c]pyrazole-4-oxide (8a). Yield: 52.8 mg (20%), mp 147.5–149.0 °C, R_f=0.24 (chloroform–acetone 5:1). IR (KBr): ν=3375 (OH); 1259 (P=O); 1031 (P–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.53 (s, 3H, C–CH_3, J_{PC}=3.9 Hz); 3.74 (d, 3H, OCH_3, $^3J_{PC}$=12.0 Hz); 3.89 (s, 3H, N–CH_3); 7.13–7.98 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=11.68 (C–CH_3); 36.82 (N–CH_3); 53.20 (P–O–CH_3, $^2J_{PC}$=6.58 Hz); 100.42 (P–C, $^1J_{PC}$=212.71 Hz); 117.46; 119.21; 124.21; 130.02; 143.33; 149.09; 151.02. ^{31}P NMR ($CDCl_3$): δ=9.64. MS (70 eV) *m*/*z* (%): 264(100, M$^+$); 249(11); 233(21.52); 132(5.07); 56(13.19). Anal. found: C, 54.56; H, 5.24; N, 10.43; P, 11.54. Calcd for $C_{12}H_{13}N_2O_3P$ (264.21): C, 54.55; H, 4.96; N, 10.60; P, 11.72%.

5.3. Reaction of 3-carboxylic derivatives of chromones with *N*-methylhydrazine

To a solution of **1b** (218.2 mg, 1.0 mmol) in methanol (5 mL) a solution of *N*-methylhydrazine (9.2 mg, 2.0 mmol) in methanol (0.5 mL) was added. The mixture was stirred at room temperature and after 2 h the product **8b** precipitated. The solid was filtered off and than recrystallized from methanol. The filtrate was left at room temperature overnight. After this time the product **4b** was filtered off, and recrystallized from acetone. The filtrate was evaporated to dryness and the residual solid was recrystallized from methanol to give **7b** as a crystalline white solid.

5.3.1. 5-(2-Hydroxyphenyl)-1,3-dimethyl-1*H*-pyrazole-4-carboxylic acid methyl ester (4b). Yield: 169.1 mg (64%), mp 182.5–183.5 °C, R_f=0.29 (chloroform–acetone, 5:1). IR (KBr): ν=3133 (OH); 1721 (C=O); 1611 (N=C); 1097 (C–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.47 (s, 3H, CH_3); 3.62 (s, 3H, N–CH_3); 3.72 (s, 3H, OCH_3); 7.01–7.38 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=14.40 (C–CH_3); 37.23 (N–CH_3); 51.71 (O–CH_3); 111.18; 111.67; 118.16; 120.46; 131.29; 143.62; 150.50; 154.54; 165.55. MS (70 eV) *m*/*z* (%): 247(100, M$^+$); 215 (6.0). Anal. found: C, 63.48; H, 5.81; N, 11.43. Calcd for $C_{13}H_{14}N_2O_3$ (246.26): C, 63.40; H, 5.73; N, 11.38%.

5.3.2. 1,3-Dimethyl-1*H*-chromeno[4,3-*c*]pyrazol-4-one (7b). Yield: 34.3 mg (16%), mp 192.5–193.9 °C, R_f=0.38 (chloroform–acetone, 5:1). IR (KBr): ν=1731 (C=O); 1612 (–N=C–); 1018 (C–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.60 (s, 3H, CH_3); 4.27 (s, 3H, N–CH_3); 7.35–7.94 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=13.11 (C–CH_3); 39.89 (N–CH_3); 112.62; 118.57; 122.28; 124.44; 130.97; 149.54; 158.25 (C=O). MS (70 eV) *m*/*z* (%): 215 (100, M+H$^+$); 203 (14.0); 117 (6.0); 93 (5.25). Anal. found: C, 67.33; H, 4.77; N, 13.35. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.70; N, 13.08%.

5.3.3. 1,5-Dimethyl-1*H*-chromeno[4,3-c]pyrazol-4-one (8b). Yield: 42.8 mg (20%) mp 208–209 °C, R_f=0.27 (chloroform–acetone, 5:1). IR (KBr): ν=1737 (C=O); 1592 (–N=C–) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.69 (s, 3H, CH_3); 3.96 (s, 3H, N–CH_3); 7.25–8.01 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=11.02 (C–CH_3); 37.12 (N–CH_3); 115.22; 117.69; 118.16; 122.46; 124.42; 130.13; 162.30 (C=O). MS (70 eV) *m*/*z* (%): 215 (100, M$^+$+H$^+$), 203

(14.0); 117 (6.0); 93 (5.25). Anal. found: C, 67.13; H, 4.76; N, 13.21. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.70; N, 13.08%.

5.4. Syntheses of complexes *trans*-[Pt(4a)$_2$Cl$_2$] (9a) and *cis*-[Pt(4a)$_2$Cl$_2$] (10a)

$K_2[PtCl_4]$ (83.4 mg, 0.20 mmol) was dissolved in 3 mL of acetone–water (1:1) mixture and the solution was slowly added to solution of pyrazole **4a** (118.5 mg, 0.40 mmol) in acetone (5 mL). A pink solid started to precipitate at the end of the addition. The suspension was heated to reflux at 115 °C with good stirring. After 6 h at reflux, a brown powder precipitated was filtered off and dried to give complex **9a**. The remaining yellow solution was cooled down in an ice bath and left for 24 h in the freezer (−12 °C). The yellow powder was filtered off, washed with cold water and then with diethyl ether, to afford **10a**.

5.4.1. *trans*-[Pt(4a)$_2$Cl$_2$] (9a). Yield: 12.0 mg (7%), mp>350 °C. IR (CsI): ν=3449 (OH); 1637 (N=C); 1228 (P=O); 1038 (P–O–C); 422 (M−N); 326 (M−Cl) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.43 (s, 3H, CH_3); 3.52 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.70 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.89 (s, 3H, N–CH_3); 7.00–8.16 (m, 4H, arom.), 10.15 (s, 1H, OH). ^{31}P NMR (DMSO): δ=17.89. MS-FAB *m/z*: 857. Anal. found: C, 36.66; H, 4.06; N, 6.39. Calcd for $C_{26}H_{34}N_4O_8P_2Cl_2Pt$ (858.51): C, 36.37; H, 3.99; N, 6.53%.

5.4.2. *cis*-[Pt(4a)$_2$Cl$_2$] (10a). Yield: 138.0 mg (80%), mp 153–156 °C. IR (CsI): ν=3461 (OH); 1218.5 (P=O); 1038.4 (P–O–C); 585 (Pt–N); 426.8; 343 (Pt–Cl) cm^{-1}.^{1}H NMR (DMSO): δ=2.39 (s, 3H, CH_3); 3.47 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.54 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.78 (s, 3H, N–CH_3); 6.96–7.84 (m, 4H, arom.), 12.04 (s, 1H, OH). ^{31}P NMR (DMSO): δ=18.07. ^{13}C NMR (DMSO-d_6): δ=14.07 (C–CH_3); 37.09 (N–CH_3); 52.75 (d, P–O–CH_3, $^2J_{PC}$=5.73 Hz); 103.05 (C–P, $^1J_{PC}$=221.6 Hz); 117.09; 117.36; 119.86; 131.43; 147.14; 151.61; 155.96. MS-FAB *m/z*: 857. Anal. Found: C, 36.61; H, 4.11; N, 6.47. Calcd for $C_{26}H_{34}N_4O_8P_2Cl_2Pt$ (858.51): C, 36.37; H 3.99; N 6.53%.

5.5. Syntheses of *cis*-[Pt(4b)$_2$Cl$_2$] complex 10b

$K_2[PtCl_4]$ (41.5 mg, 0.10 mmol) was dissolved in water (5 mL) and ligand **4b** (49.25 mg, 0.2 mmol), dissolved in methanol (15 mL), added slowly dropwise. The mixture was stirred for 48 h at room temperature, and then half of the volume of methanol was removed under reduced pressure at room temperature. A yellow solid started to precipitate at the end of concentration. The solid was filtered off, washed with water and then with diethyl ether and dried in vacuo to give complex **10b**.

5.5.1. *cis*-[Pt(4b)$_2$Cl$_2$] complex 10b. Yield: 25.8 mg (34%)) mp 263 °C dec. IR (CsI): ν=3342 (OH); 1722 (C=O); 1615 (N=C); 1098 (C–O–C); 480 (M−N); 330 (M−Cl) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.37 (s, 3H, C–CH_3); 3.39 (s, 3H, N–CH_3); 3.61 (d, 3H, OCH_3); 7.18–7.74 (m, 4H, arom.); 9.95 (s, 1H, OH). MS-FAB *m/z*: 758.0. Anal. found: C, 41.40; H, 3.96; N, 7.43. Calcd for $C_{26}H_{28}N_4O_6Cl_2Pt$ (758.49): C, 41.2; H, 3.72; N, 7.38%.

5.5.2. Syntheses of the complex *trans*-[Pd(4a)$_2$Cl$_2$] (11a). Compound **4a** (118.5 mg, 0.4 mmol) dissolved in dichloromethane (5 mL) was added to a solution of [Pd(C_6H_5CN)$_2$-Cl_2] (76.7 mg, 0.2 mmol) in the same solvent (5 mL). The reaction mixture was left with stirring at room temperature. After 2 h a yellow powder precipitated from the reaction mixture. The stirring was continued for the next 24 h. The resulting solid was filtered off, washed with water and then with diethyl ether and dried overnight in vacuo.

Yield: 124.7 mg (81%) mp 223 °C dec. IR (CsI): ν=3373 (OH); 1205 (P=O); 1020 (P–O–C); 573 (Pd–N); 382 (Pd–Cl) cm^{-1}. ^{1}H NMR (DMSO): δ=2.98 (s, 3H, CH_3); 3.43 (d, 3H, P–OCH_3, $^3J_{PH}$=11.7 Hz); 3.59 (s, 3H, N–CH_3); 3.68 (d, 3H, $POCH_3$, $^3J_{PH}$=11.7 Hz); 7.21–7.78 (m, 4H, arom.); 10.21 (s_{broad}, 1H, OH). ^{31}P NMR (DMSO): δ=18.3. MS-FAB *m/z*: 769.0. Anal. found: C, 40.34; H, 4.47; N, 7.41; P, 8.31. Calcd for $C_{26}H_{34}N_4O_8P_2Cl_2Pd$ (769.93): C, 40.56; H, 4.45; N, 7.2; P, 8.04%.

5.5.3. Synthesis of Pd(II) complex *trans*-[Pd(4b)$_2$Cl$_2$] (11b). Compound **4b** (123.1 mg, 0.5 mmol) dissolved in dichloromethane (5 mL) was added to the solution of [Pd(C_6H_5CN)$_2$Cl$_2$] (95.9 mg, 0.25 mmol) in the same solvent (5 mL). The mixture was left with stirring at room temperature. After 2 h, a yellow powder precipitated. The stirring was continued for 24 h. The resulting precipitate was filtered off, washed with water and then with diethyl ether, and dried overnight in vacuo.

Yield: 138 mg (83%) mp 336 °C dec. IR (CsI): ν=3342 (OH); 1714 (C=O); 1614 (N=C); 1124 (C–O–C); 414 (M−N); 354 (M−Cl) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.35 (s, 3H, C–CH_3); 3.37 (s, 3H, N–CH_3); 3.50 (d, 3H, OCH_3); 7.21–7.78 (m, 4H, arom.); 9.8 (s, 1H, OH). MS-FAB *m/z*: 669.0. Anal. found: C, 46.47; H, 4.97; N, 8.23. Calcd for $C_{26}H_{28}N_4O_6Cl_2Pd$ (669.84): C, 46.61; H, 4.21; N, 8.36%.

5.5.4. Synthesis of Pd(II) complex 12b. Compound **8b** (150 mg, 0.7 mmol) dissolved in dichloromethane (5 mL) was added to the solution of [Pd(C_6H_5CN)$_2$Cl$_2$] (134 mg, 0.35 mmol) in the same solvent (5 mL). The mixture was left with stirring at room temperature. After 10 min a yellow powder precipitated. The stirring was continued for 24 h. The resulting precipitate was filtered off, washed with water and then with ethyl ether, and dried overnight in vacuo.

Yield: 125 mg (59%), mp 334 °C dec. IR (CsI): ν=1755 (–C=O); 1619(–N=C–); 420 (Pd–N); 354 (Pd–Cl) cm^{-1}. MS-FAB *m/z* (%): 604.5. Anal. found: C, 47.58; H, 3.57; N, 9.02. Calcd for $C_{24}H_{20}N_4O_4Cl_2Pd$ (605.75): C, 47.58; H, 3.32; N, 9.25%.

5.5.5. Crystal data for compound 4a,[48] (Fig. 4). $C_{13}H_{17}N_2O_4P$, Mr=296.26, monoclinic, space group $P2_1/n$, a=8.555(1) b=14.270(1) c=12.242(1) Å β=103.01(1)°, V=1456.1(2) Å^3, Z=4, D_x=1.351 Mg m^{-3}, $F(000)$=624, T=293 K μ(Cu Kα)=1.819 mm^{-1}, colorless crystal of dimensions 0.2×0.3×0.4 mm, cell dimension from 80 reflections in the range θ=39.85–39.97°. The intensities

were collected on a KUMA KM4 diffractometer using graphite-monochromatic Cu Kα radiation, λ=1.54178 Å, ω scans. The intensities were corrected for absorption[49] effect with T_{min}=0.51 and T_{max}=0.69 and Lorentz and polarization effect. Intensities of 3 standard reflections checked every 150 reflections: no decay, θ range 4.83–67.12°, 5250 measured reflections of which 2519 were unique (R_{int}=0.015). The structure was solved by direct methods using SHELXS8650, which revealed the positions of non-H atoms. All H-atoms were located in a difference Fourier map. The structure was refined on F^2 by full-matrix least-squares methods using SHELX9751 none-H atoms refined anisotropically, H-atoms fixed in calculated positions excluding H52. The refinement was carried out on 212 parameters using 2413 observed reflections with $I>2\sigma(I)$ gave $R1$=0.044 $wR2$=0.120 ($w=1/[\sigma^2(F_o^2)+(0.0742P)^2]$, where $P=(F_o^2+2F_c^2)/3$, S=1.0068, max and min residual electron density 0.511, −0.317 e Å^{-3}.

5.5.6. Crystal data for compound 4b,[48] (Fig. 5). $C_{13}H_{14}N_2O_3$, Mr=246.26, orthorhombic, space group $P2_12_12_1$, a=12.456(4) b=14.4589(2) c=7.084(5) Å, V=1287.2(10) Å^3, Z=4, D_x=1.271 Mg m^{-3}, $F(000)$=520, T=293 K, μ(Cu Kα)=0.76 $^{-1}$, colorless crystal of dimensions 0.5×0.1×0.1 mm, AFC5S Rigaku four-circle diffractometer, graphite-monochromatic Cu Kα radiation, λ=1.54178 Å, ω scans, cell constants from 25 reflections in the range θ=22.51–28.78°, intensities of 3 standard reflections: 3 2 0, 2 −1 −1, 2 0 −1 checked every 150 reflections, no decay, θ range 4.67–67.48°, 4866 measured reflections of which 2268 were unique (R_{int}=0.029). The intensities were corrected for absorption[49] effect with T_{min}=0.737 and T_{max}=0.936. Structure solution by direct methods using SHELXS86,[50] and refined 170 parameters on F^2 by full-matrix least-square methods using SHELX97,[51] none-H atoms refined anisotropically, H-atoms fixed in calculated positions and refined using a riding model except H51. Final $R1$=0.0328 and $wR2$=0.0756 (w=exp(3s^2)/$[\sigma^2(F_o^2)+(0.0381P)^2]$), where $P=(F_o^2+2F_c^2)/3$, S=0.854, max and min residual electron density 0.12, −0.15 e Å^{-3}.

Acknowledgements

Financial support from Medical University of Lodz (grant No 502-13-755 to E.B.) and University of Lodz (grant No 505/696 to M.M.) is gratefully acknowledged. We thank Mrs. Agnieszka Rybarczyk-Pirek for skillful experimental assistance.

References and notes

1. Reedijk, J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 236–240.
2. Garnuszek, P.; Licinska, J.; Skierki, J. S.; Koronkiewicz, M.; Mirowski, M.; Wiercioch, R.; Mazurek, A. P. *Nucl. Med.* **2002**, *29*, 169–175.
3. Wong, E.; Giandomenico, M. *Chem. Rev.* **1999**, *99*, 2451–2466.
4. Jakupec, M. A.; Galanski, M.; Keppler, B. K. *Rev. Physiol. Biochem. Pharmacol.* **2003**, *146*, 1–53.
5. Sakai, K.; Tomista, Y.; Ue, T.; Goshima, K.; Ohminato, M.; Tsubomura, T.; Matsumoto, K.; Chmura, K.; Kawakami, K. *Inorg. Chim. Acta* **2000**, *297*, 64–71.
6. Eliguero, J. *Comprehensive heterocyclic chemistry II*; Katritzky, A. R., Pees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 3, p 1.
7. Eicher, T.; Hauptmann, S. The chemistry of heterocycles structure, reaction synthesis and applications; Georg Thime: Stuttgart, 1995; p 184, Translated by Suschitzky, H.; Suschitzky, J.
8. Onoa, G. B.; Moreno, V.; Font-Bardia, M.; Solans, X.; Perez, J. M.; Alonso, C. J. *Inorg. Biochem.* **1999**, *75*, 205–212.
9. Al-Allaf, T. A. K.; Rashan, L. *J. Boll. Chim. Farm.* **2001**, *140*, 205–210.
10. Ahmad, R.; Ahmad, N.; Zia-Ul-Hag, M.; Wahid, A. *J. Chem. Soc. Pak.* **1996**, *18*, 38.
11. Wisniewski, M. Z.; Surga, W. J.; Opozda, E. M. *Trans. Met. Chem.* **1994**, *19*, 353–354.
12. Chruscinski, L.; Mlynarz, P.; Malinowska, K.; Ochocki, J.; Boduszek, B.; Kozlowski, H. *Inorg. Chim. Acta* **2000**, *303*, 47–53.
13. Hassain, A. G. *Inorg. Bioinorg. Phys. Theor. Anal. Chem.* **1996**, *35A*(5), 373–378.
14. *The pharmacology of benzopyrone derivatives and related compounds*; Gabor, M., Ed.; Akademiai Kiado: Budapest, 1988; pp 91–126, see also pp 179–223.
15. El-Nagger, A. M.; Abdel-El-Salam, A. M.; Ahmed, F. S. M.; Latif, M. S. A. *Pol. J. Chem.* **1981**, *55*, 793–797.
16. Ohemeng, K. A.; Schwender, C. F.; Fu, K. P.; Barrett, J. F. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 225–230.
17. Middleton, E.; Kandaswami, C. The impact of plant flavonoids on mammalian biology. Implication for immunity, inflammation and cancer. In *The flavonoids advances in research since 1986*; 1994. Harborne, J. B., Ed.; Chapman & Hall: London, 1994; pp 619–652.
18. *The role of phosphonates in living systems*; Hildebrand, R. L., Ed.; CRC: Boca Raton, FL, 1983.
19. Engel, R. *Synthesis of carbon–phosphorus bond*; CRC: Boca Raton, FL, 1988.
20. Kostka, K.; Pastuszko, S.; Porada, M. *Phosphorus, Sulfur, Silicon* **1992**, *71*, 67–74.
21. Kostka, K.; Modranka, R. *Phosphorus, Sulfur, Silicon* **1991**, *57*, 279–285.
22. Kostka, K.; Modranka, R. *Phosphorus, Sulfur, Silicon* **1992**, *70*, 29–38.
23. Kostka, K.; Modranka, R.; Grabowski, M. J.; Stepien, A. *Phosphorus, Sulfur, Silicon* **1993**, *83*, 209–214.
24. Budzisz, E.; Brzezinska, E.; Krajewska, U.; Rozalski, M. *Eur. J. Med. Chem.* **2003**, *38*, 597–603.
25. Budzisz, E.; Pastuszko, S. *Tetrahedron* **1999**, *55*, 4815–4824.
26. Budzisz, E.; Nawrot, E.; Malecka, M. *Arch. Pharm.* **2001**, *334*, 381–387.
27. Koenigs, E.; Freund, J. *Chem. Ber.* **1947**, *80*, 143–149.
28. Baker, W.; Harborne, J. B.; Ollis, W. D. *J. Chem. Soc.* **1952**, 1303–1309.
29. Schoenberg, A.; Sidky, M. M. *J. Am. Chem. Soc.* **1953**, *75*, 1528–5130.
30. Tagaki, K.; Tanaka, M.; Murakami, Y.; Merita, H.; Aotsuka, T. *Eur. J. Med. Chem.-Chim. Ther.* **1986**, *21*, 65–70.
31. Nawrot-Modranka, J.; Kostka, K. *Pol. J. Chem.* **1988**, *62*, 417–426.
32. Nawrot-Modranka, J.; Kostka, K. *Pol. J. Chem.* **1989**, *63*, 103–111.
33. Colotta, V.; Cecchi, L.; Catarzi, D.; Melani, F.; Filacchioni,

G.; Martini, C.; Tacchi, P.; Lucacchini, A. *Recept. Channels* **1993**, *1*, 111–119.
34. Arpalathi, J.; Lippert, B. *Inorg. Chim. Acta* **1987**, *138*, 171–173.
35. Kettle, S. F. A. *Physical inorganic chemistry*; Oxford University Press, 1996.
36. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A.; Tayler, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1–19.
37. Garcia, J.; Molla, M. C.; Borras, J. *Polyhedron* **1985**, *4*, 757–760.
38. Adams, D. M. *Metal ligand and related vibrations*; 1st ed. Arnold: London, 1967.
39. Van Kralingen, C. G.; De Ridder, J. K.; Reedijk, J. *Inorg. Chim. Acta* **1979**, *36*, 69–77.
40. Kostka, K. *Chem. Anal.* **1969**, *14*, 1145–1160.
41. Kostka, K. *Rocz. Chem.* **1973**, *47*, 305–313.
42. Chila, V. P.; Aitmanbetov, A.; Usmailov, U.; Grishko, L. G. *Khim. Prirodnych Soedin.* **1993**, 629–633.
43. Pinto, Z. *Tetrahedron* **1999**, *55*, 10187–10200.
44. Hinman, R. J. *J. Org. Chem.* **1958**, *23*, 1587–1588.
45. Kerrison, J. S.; Sadler, P. J. *Chem. Commun.* **1997**, 861.
46. Sundquist, W. I.; Ahmed, K. J.; Hollins, L. S.; Lippard, S. J. *Inorg. Chem.* **1987**, *26*, 1524–1528.
47. Coppola, G. M.; Dodsworth, R. W. *Synthesis* **1981**, *7*, 523–524.
48. Crystallographic data for the structure of **4a**, and **4b** have been deposited with the Cambridge Crystallographic Data Bases deposition No CCDC 175437 for **4a** and CCDC 186628 for **4b**. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
49. North, A. C. T.; Phillips, D. C.; Scott Metthews, F. *Acta Crystallogr.* **1968**, *A24*, 351.
50. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
51. Sheldrick, G. M. *Program for the Refinement of Crystal Structures SHELXL97*; University of Göttingen, Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1761–1766
Tetrahedron

Simple NMR method for assigning relative stereochemistry of bridged bicyclo[3.*n*.1]-2-enes and tricyclo[7.*n*.1.0]-2-enes

Olga V. Patrusheva,* German A. Verbitskii and Vladimir I. Vysotskii

Department of Chemistry, Far Eastern National University, Octyabrskaya St. 27, Vladivostok 690600, Russian Federation

Received 21 October 2003; revised 28 November 2003; accepted 18 December 2003

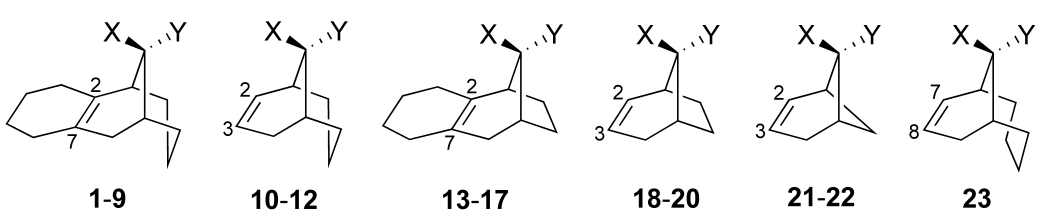
Abstract—The stereochemistry of *syn* and *anti*-forms of bridged bicyclo[3.*n*.1]-2-ene, tricyclo[7.*n*.1.0]-2-ene (n=1–3) and bicyclo[4.3.1]dec-7-ene derivatives can be assigned from the ^{13}C chemical shift difference of the double bond. Both *syn*-9-*R*-bicyclo[3.3.1]non-2-enes and *syn*-13-*R*-tricyclo[7.3.1.0^{2,7}]tridec-2(7)-enes have a large shielding difference between sp^2 carbons, while the corresponding *anti*-forms have a smaller one. In contrast, 8-*R*-bicyclo[3.2.1]oct-2-enes and 12-*R*-tricyclo[7.2.1.0^{2,7}]dodec-2(7)-enes have an inverse correlation. The reason of this specificity is the influence of the γ-*gauche* effect on the chemical shift of C(2) atom. The GIAO theory has been applied to investigate the ^{13}C chemical shifts. The conformational equilibrium in the formamide group of 13-formylamino-tricyclo[7.3.1.0^{2,7}]tridec-2(7)-enes has been studied.

1. Introduction

Up to now, the determination of the relative stereochemistry of molecules has been being a time consuming and sometimes difficult task. This was solved, as a rule, by X-ray crystallography analysis or NMR methods ($^1H-^1H$ and $^1H-^{13}C$ coupling constants data, $^1H-^1H$ NOE measurements). The most common approach involves ^1H NMR through the angular dependence of the vicinal coupling constant.[1,2] However, often the coupling information is not available because either the coupling does not exist or the critical lines in the spectrum are masked by superimposed signals. The use of long-range $^1H-^{13}C$ coupling constants in definition of molecular configuration is an increasingly active area, with numerous methods. Recently developed *J*-based configuration analysis[3] is well suited to such measurements, but requires the protons of interest to be sufficiently resolved, and numerous experiments will be required if many $^nJ_{C,H}$ values are to be determined. Therefore, application of conventional 1D ^{13}C NMR to solve stereochemical problems are sometimes more useful.[4,5] In recent years, efficient techniques for the calculations of NMR parameters by ab initio methods have been developed.[6] The advantage of this approach is the possibility to predict the spectral data in the absence of experimental data. The stereochemistry of substituent placement on a carbon framework is reflected in α, β, γ and δ-substituent effects. Barfield and co-workers previously examined the capability of ab initio calculations to predict substituent effects by using substituted butanes as model systems.[7]

Traditionally, relative stereochemistry determination of 12-*R*-tricyclo[7.2.1.0^{2,7}]dodec-2(7)-ene and 13-*R*-tricyclo-[7.3.1.0^{2,7}]tridec-2(7)-ene systems were carried out either by chemical[8] or by X-ray crystallography analysis.[9,10]

Our objective was to define a simple empirical rule for



Scheme 1. **1**,**10**,**13**,**18**,**21**,**23**: X=H, Y=H; **2**: X=H, Y=NHCHO; **3**: X=NHCHO, Y=H; **4**,**14**: X=H, Y=NH_2; **5**,**15**: X=NH_2, Y=H; **6**: X=H, Y=$NCHC_6H_4OH$; **7**: X=$NCHC_6H_4OH$, Y=H; **8**,**11**,**16**,**19**,**22**: X=H, Y=OH; **9**,**12**,**17**,**20**: X=OH, Y=H.

Keywords: ^{13}C NMR; GIAO-SCF; *Gauche* effect; Bicyclo[3.2.1]octane; Bicyclo[3.3.1]nonane; Tricyclo[7.2.1.02,7]dodecane; Tricyclo[7.3.1.02,7]tridecane; Bicyclo[3.1.1]heptane; Bicyclo[4.3.1]decane.
* Corresponding author. E-mail address: olpatrus@chem.dvgu.ru

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.045

assigning relative stereochemistry of 13-*R*-tricyclo[7.3.1.0^{2,7}]-tridec-2(7)-enes, 9-*R*-bicyclo[3.3.1]non-2-enes, 12-*R*-tricyclo-[7.2.1.0^{2,7}]dodec-2(7)-enes and 8-*R*-bicyclo[3.2.1]oct-2-enes by visual inspection of ^{13}C NMR spectra. With this purpose, we have analyzed ^{13}C NMR spectra for compounds **1**–**20** (Scheme 1).

2. Methodology

All ab initio calculations were performed using the Dalton program package[11] on Beowulf Linux cluster. All geometries employed were fully optimized in the C_1 symmetry at the HF level of theory using the TZ basis set of Ahlrichs and co-workers[12] with two polarization functions. The resulting geometries were characterized at the same levels of theory by performing frequency calculations. The optimal structures were then used to calculate the absolute chemical shielding using the GIAO[13] method, as implemented in Dalton. The calculated ^{13}C NMR shielding values were referenced to $SiMe_4$ ($\sigma_{(C)}$=195.11 ppm at the same computational level).

3. Results and discussion

Skeletal ^{13}C NMR chemical shifts for compounds **1**–**10**, **13**–**21**, **23** were calculated and the experimental spectra (where available) are fully assigned (Tables 1 and 2). The experimental assigned spectra for compounds **1**, **18**–**20** was used for validate computational method. Generally, with the theoretical approach, one isolated molecule in vaccuo in its equilibrium geometry is studied. Consequently, the experimental counterparts to the calculated absolute shielding values should be those measured in the gas phase extrapolated to zero density and temperature. Because the NMR experiments for studied compounds had to be carried out to on samples in $CDCl_3$ solutions, the following issues

Table 1. Skeletal ^{13}C NMR chemical shifts (ppm) of tricyclo[7.3.1.0^{2,7}]tridec-2(7)-ene and bicyclo[3.3.1]non-2-ene derivatives

Compound		^{1}C	^{2}C	^{3}C	^{4}C	^{5}C	^{6}C	^{7}C	^{8}C	^{9}C	^{10}C	^{11}C	^{12}C	^{13}C
1	Calculated	31.05	138.93	26.76	22.77	22.41	27.62	137.25	34.54	25.67	32.06	18.88	26.70	30.59
	Experimental[a]	34.9	130.8	29.2	23.7	23.3	30.0	130.0	37.7	27.9	34.4	19.0	28.9	32.8
2$_Z$	Calculated	33.99	138.86	26.55	22.53	22.17	27.24	136.20	35.98	29.01	27.07	17.95	20.80	43.77
	Experimental[b]	38.05	129.88	27.87	23.08	22.99	29.27	129.05	38.25	31.05	28.70	17.46	22.23	48.08
2$_E$	Calculated	37.89	138.37	26.56	22.39	22.13	27.20	137.37	35.92	31.50	26.81	17.78	21.11	47.37
	Experimental[b,c]	40.35	130.07	27.51	—	22.94	29.21	—	38.36	32.78	—	17.35	21.86	51.88
3$_Z$	Calculated	36.44	135.12	27.07	22.62	22.41	27.47	139.16	31.24	29.90	31.09	17.80	27.08	44.65
	Experimental[b]	40.05	127.19	28.31	23.20	23.07	29.53	130.85	33.17	31.80	33.13	17.15	29.14	49.40
3$_E$	Calculated	38.03	135.71	27.04	22.55	22.14	27.33	138.36	30.88	33.27	31.79	17.59	27.21	49.00
	Experimental[b,d]	41.17	127.00	28.39	—	22.92	29.45	131.03	32.82	34.35	33.32	16.91	29.06	53.75
4	Rotamer −sc, ΔE[e]=3.75	5.41	20.82	3.95	3.37	3.32	4.05	20.24	5.38	5.04	3.84	2.69	3.02	7.01
	Rotamer ap, ΔE=0	24.87	93.39	18.03	15.31	15.11	18.44	92.29	24.10	20.90	17.40	12.57	13.65	31.31
	Rotamer +sc, ΔE=3.32	7.01	24.46	4.75	4.01	3.95	4.82	24.30	6.47	5.36	4.57	3.19	3.61	8.32
	Weighted average[f]	37.29	138.67	26.73	22.69	22.38	27.31	136.83	35.95	31.30	25.81	18.45	20.28	46.64
	Experimental	41.55	129.88	28.89	23.23	23.15	29.33	129.64	39.03	33.89	26.90	17.92	21.21	50.80
5	Rotamer −sc, ΔE=0	19.58	63.38	12.93	10.71	10.54	12.86	64.43	14.46	14.78	51.34	8.46	12.79	22.92
	Rotamer ap, ΔE=4.36	3.05	10.77	2.21	1.86	1.81	2.21	11.09	2.56	2.55	2.55	1.47	2.17	3.96
	Rotamer +sc, ΔE=0.10	16.70	61.54	12.22	10.25	10.10	12.34	61.02	13.88	15.72	14.47	8.10	12.41	22.07
	Weighted average	39.33	135.69	27.36	22.82	22.45	27.41	136.54	30.90	33.05	32.36	18.03	27.37	48.95
	Experimental	43.35	126.94	28.86	23.41	23.25	29.50	129.40	32.86	35.19	34.06	17.30	29.57	53.11
6	Calculated	38.42	138.41	26.67	22.60	22.36	27.39	137.28	35.68	32.65	27.11	18.64	21.60	66.67
	Experimental[b]	41.46	130.10	28.32	23.25	23.17	29.46	129.31	38.36	34.25	28.79	18.28	22.72	69.16
7	Calculated	38.82	135.16	27.20	22.89	22.21	27.38	137.81	32.08	33.12	31.75	18.09	26.62	68.27
	Experimental[b]	41.87	126.64	29.37	23.42	23.28	29.61	130.42	34.13	34.57	33.30	17.56	27.89	70.61
8	Rotamer −sc, ΔE=0	19.11	67.34	13.19	11.14	10.99	13.45	68.02	17.49	14.67	12.67	9.01	10.30	31.54
	Rotamer ap, ΔE=5.03	2.37	8.93	1.73	1.46	1.44	1.76	8.88	2.32	1.99	1.67	1.15	1.33	4.13
	Rotamer +sc, ΔE=0.27	15.78	61.09	11.73	9.97	9.86	12.02	60.14	15.56	14.53	11.59	8.08	8.95	28.28
	Weighted average	37.26	137.36	26.65	22.57	22.29	27.23	137.04	35.37	31.19	25.93	18.24	20.58	63.95
	Experimental	41.15	129.83	28.86	23.12	23.12	29.25	128.54	38.47	33.61	27.21	17.87	21.64	70.49
9	Rotamer −sc, ΔE=6.06	2.56	9.42	1.89	1.60	1.56	1.91	9.50	2.20	2.36	2.17	1.25	1.84	4.63
	Rotamer ap, ΔE=0	31.05	109.31	21.92	18.33	18.08	22.18	111.43	24.73	25.73	25.28	14.35	21.56	52.48
	Rotamer +sc, ΔE=4.70	4.86	16.01	3.30	2.78	2.71	3.31	16.86	3.80	3.68	3.75	2.17	3.18	8.00
	Weighted average	38.47	134.74	27.11	22.71	22.35	27.40	137.79	30.73	31.77	31.20	17.77	26.58	65.11
	Experimental	42.81	126.45	29.25	23.31	23.14	29.59	130.60	32.93	34.43	33.03	16.96	28.30	72.41
10	Calculated	27.16	137.72	136.35	30.00	25.19	31.88	18.07	27.44	29.70				
	Experimental[g]	29.6	130.5	129.4	32.4	27.2	34.2	18.2	29.2	31.8				
11	Experimental[h]	36.20	128.01	129.07	33.61	33.30	27.03	17.07	22.20	69.84				
12	Experimental[h]	37.68	125.97	130.30	28.14	34.16	32.91	16.23	28.98	71.58				

[a] Data taken from Ref. 14.
[b] Data are identically published.[9]
[c] Signals of the C(4), C(7) and C(10) atoms are masked by superimposed signals of the more stable conformer.
[d] Signal of the C(4) atom is masked by superimposed signals of the more stable conformer.
[e] Values in kJ mol^{-1}, relative to the most stable rotamer.
[f] Weighted average for each carbon was calculated based on the sum of the GIAO predicted chemical shift values for each rotamers weighted by the distribution coefficient.
[g] Data taken from Ref. 15.
[h] Data taken from Ref. 16.

Table 2. Skeletal ^{13}C NMR chemical shifts (ppm) of tricyclo[7.2.1.0^{2,7}]dodec-2(7)-ene and bicyclo[3.2.1]oct-2-ene derivatives, bicyclo[3.1.1]hept-2-ene and bicyclo[4.3.1]dec-7-ene

Compound		^{1}C	^{2}C	^{3}C	^{4}C	^{5}C	^{6}C	^{7}C	^{8}C	^{9}C	^{10}C	^{11}C	^{12}C
13[a]	Calculated	37.08	143.84	27.30	22.75	22.41	27.20	132.33	38.52	31.53	28.36	32.02	33.82
14[a]	Rotamer −sc, ΔE[b]=5.34	3.88	13.36	2.51	2.08	2.06	2.48	12.11	3.60	3.75	2.38	2.66	5.11
	Rotamer ap, ΔE=0	34.31	114.01	21.69	18.05	17.83	21.52	105.20	30.58	30.13	21.55	23.82	42.96
	Rotamer +sc, ΔE=4.84	5.17	16.21	3.10	2.56	2.52	3.05	14.99	4.48	4.12	2.95	3.25	6.27
	Weighted average[c]	43.36	143.58	27.30	22.69	22.41	27.05	132.30	38.66	38.00	26.88	29.73	54.34
15	Rotamer −sc, ΔE=0	23.79	76.17	15.38	12.49	12.34	14.83	73.03	18.45	18.65	14.72	16.26	28.08
	Rotamer ap, ΔE=6.29	1.80	5.91	1.20	0.99	0.97	1.16	5.76	1.47	1.51	1.19	1.31	2.17
	Rotamer +sc, ΔE=0.71	16.76	57.85	11.38	9.35	9.23	11.12	53.96	13.89	14.71	11.26	12.12	21.18
	Weighted average	42.35	139.93	27.96	22.83	22.54	27.11	132.75	34.01	34.87	27.17	29.69	51.43
	Experimental[d]	45.9	131.4	30.0	23.2	23.1	29.2	125.0	36.4	37.0	29.6	32.0	55.4
16[a]	Rotamer −sc, ΔE=0	22.02	69.75	13.44	11.13	10.98	13.28	65.71	18.90	17.97	13.11	14.65	35.26
	Rotamer ap, ΔE=5.49	2.30	7.70	1.47	1.21	1.20	1.44	7.14	2.09	2.02	1.37	1.53	3.89
	Rotamer +sc, ΔE=0.21	18.96	64.98	12.32	10.24	10.12	12.20	59.76	17.27	17.93	12.11	13.40	32.47
	Weighted average	43.28	142.43	27.23	22.58	22.30	26.92	132.61	38.26	37.92	26.59	29.58	71.62
17	Rotamer −sc, ΔE=7.86	1.49	5.15	1.03	0.85	0.83	1.00	4.92	1.27	1.30	0.97	1.05	2.51
	Rotamer ap, ΔE=0	36.27	123.72	24.62	20.15	19.92	24.12	119.14	29.83	29.59	22.95	24.81	59.45
	Rotamer +sc, ΔE=6.14	3.16	10.16	2.08	1.71	1.68	2.02	10.10	2.54	2.48	1.93	2.14	5.02
	Weighted average	40.92	139.03	27.73	22.71	22.43	27.14	134.16	33.64	33.37	25.85	28.00	66.98
	Experimental	44.96	130.95	29.80	23.19	23.02	29.26	126.55	36.40	35.90	28.26	30.16	74.38
18	Calculated	32.76	142.21	131.58	34.49	31.15	28.43	33.38	33.30				
	Experimental[e]	35.6	134.7	123.8	37.5	33.6	30.6	35.5	35.5				
19	Rotamer −sc, ΔE=0	20.84	72.15	68.42	17.76	18.76	13.79	16.04	36.75				
	Rotamer ap, ΔE=5.72	1.97	7.23	6.75	1.79	1.92	1.31	1.52	3.68				
	Rotamer +sc, ΔE=0.44	16.27	61.01	56.47	14.70	16.99	11.57	13.30	30.68				
	Weighted average	39.08	140.39	131.64	34.25	37.67	26.67	30.86	71.11				
	Experimental[e]	42.3	132.6	124.2	37.5	40.7	28.3	32.6	78.1				
20	Rotamer −sc, ΔE=8.27	1.13	4.29	4.13	0.95	1.09	0.82	0.93	2.10				
	Rotamer ap, ΔE=0	32.30	121.65	118.44	26.30	29.06	25.89	29.31	58.52				
	Rotamer +sc, ΔE=5.81	3.22	11.39	11.45	2.57	2.80	2.20	2.55	5.64				
	Weighted average	36.65	137.33	134.02	29.82	32.95	28.91	32.79	66.26				
	Experimental[e,f]	39.8	129.9	126.6	31.5	35.7	28.4	32.2	73.5				
21[a]	Calculated	29.71	145.91	130.34	31.59	30.59	31.87	31.87					
23[a]	Calculated	25.73	33.13	24.67	27.35	32.13	30.64	139.23	133.46	31.40	28.52		

[a] Experimental data are absent.
[b] Values in kJ mol^{-1}, relative to the most stable rotamer.
[c] Weighted average for each carbon was calculated based on the sum of the GIAO predicted chemical shift values for each rotamers weighted by the distribution coefficient.
[d] Data taken from Ref. 10.
[e] Data taken from Ref. 17.
[f] Ref. 18.

complicated comparison of the theoretical and experimental data. Gas-to-liquid transition and solvatation effects generate a large shift in shieldings. In general, vibrational motion perturbs chemical shifts,[19] but for many cases, this correction may be negligible.

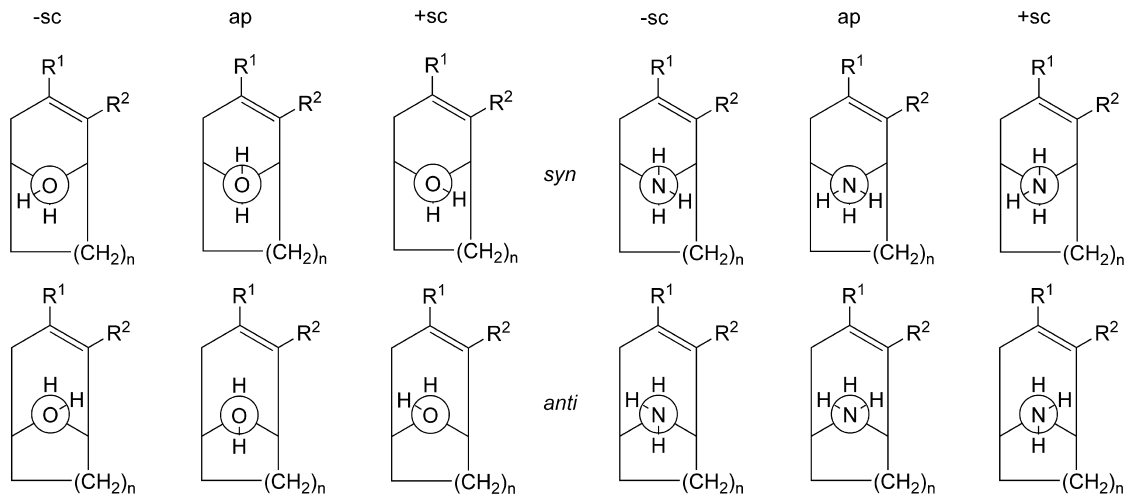
It should be noted that the calculated chemical shifts for all compounds tend, as a rule, to be underestimated for the saturated carbons (0.13–7.4 ppm) and overestimated for the olefinic carbons (6.95–9.06 ppm) than the observed ones. It can be traced back to the neglect of electron correlation contribution in the SCF approach. However, we find fairly reasonable linear correlations ($0.994<R^2<0.999$) between experimental assigned and theoretical chemical shifts for compounds **1**, **18**–**20** (Table 3). The correct order of shifts is given with just one exception for C(1) atom in hydrocarbons **1** and **18**, but its assignment can be easily corrected by NMR experiments with *J*-modulated spin-echo sequence. That procedure was used for correction of C(1) atom assignment for hydrocarbons **10** and **13** also. We proceeded with our work using the assumption that calculated intramolecular chemical shift differences for the two olefinic carbons using identical levels of theory and basis sets can greatly reduce this type of systematic error, and achieve much higher accuracy than chemical shifts calculated relative to a standard.

Table 3. Correlation parameters (slope, intercept and R^2 factor) between experimental assigned and theoretical chemical shifts for compounds **1**, **18**–**20**[a]

Compound	Slope	Intercept	R^2 factor
1	1.0917	−4.675	0.9988
18	1.1060	−6.120	0.9998
19	1.1078	−6.410	0.9995
20	1.1081	−4.908	0.9937

[a] Data are plotted as δ(GIAO)=intercept+slope×δ(exp).

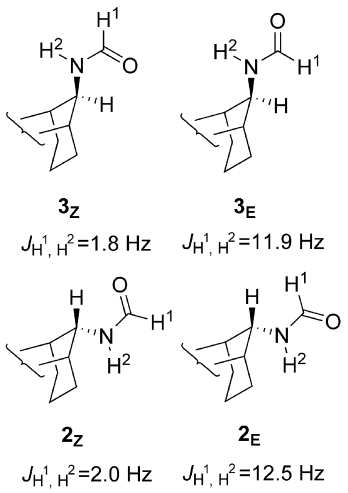
Alcohols and amines introduce the problem of conformational mobility of substituent on a fixed bicyclic framework. The observed chemical shifts at ambient temperature are time-averaged values from weighted average of contributing conformations. It has been recently shown that to reproduce the experimental ^{13}C NMR results for isomeric 2-norbornanols, the conformational-averaged values are used in calculations of chemical shifts.[20] The hydroxyl or amino proton(s) can occupy three different positions associated with the energy minima in rotation about



Scheme 2. **4**,**5**: n=2, R^1+R^2=$(CH_2)_4$; **8**,**9**: n=2, R^1+R^2=$(CH_2)_4$; **11**,**12**: n=2, R^1=R^2=H; **14**,**15**: n=1, R^1+R^2=$(CH_2)_4$; **16**,**17**: n=2, R^1+R^2=$(CH_2)_4$; **19**,**20**: n=1, R^1=R^2=H.

the C–O or C–N bond, shown as ap(antiplanar) and ±sc(synclinal) rotamers with respect to the relationship between H–H or H-lone pair moieties (Scheme 2). The ab initio energies of all rotamers were computed in order to estimate the rotamer populations at 298 K based on the Boltzmann's equation. On the basis of the populations of the rotamers, the weighted average chemical shifts were obtained for compounds **4**, **5**, **8**, **9**, **14**–**17**, **19**, **20**. The conformational behavior of methyl-substituted hydrocarbon chains does not depend on solvation, as has been demonstrated by the analysis of $^3J_{C,C}$ coupling constants for certain model compounds.[21] It can thus be expected that the energetic order of the rotamers does not change significantly when going from the gas phase to a $CDCl_3$ solution.

Experimental ^{13}C NMR spectra of formylamines **2** and **3** have double sets of signals.[9] The existence of an equilibrium mixture of conformers with different amide group orientations has been cited as a possible reason. Our calculations show a ratio of conformers $\mathbf{3}_Z$:$\mathbf{3}_E$=7:1 for isomer **3** and a ratio of conformers $\mathbf{2}_Z$:$\mathbf{2}_E$=3:1 for isomer **2**. The experimental ^{1}H NMR spectra also show the presence of two conformers in a ratio Z:E=3:1 for both compounds. These



Scheme 3.

results are consistent with ^3J coupling of formyl protons[22,23] (Scheme 3). Vicinal constants for protons on adjacent stereogenic centers typically fall in the range $J_{anti(E)} > J_{syn(Z)}$.[24]

Stereoisomeric pairs of 13-*R*-tricyclo[7.3.1.0^{2,7}]tridec-2(7)-ene, 9-*R*-bicyclo[3.3.1]non-2-ene, 12-*R*-tricyclo[7.2.1.0^{2,7}]-dodec-2(7)-ene and 8-*R*-bicyclo[3.2.1]oct-2-ene systems show some distinctions in the chemical shifts of the respective carbons. In particular, the carbon chemical shift difference of the double bond ($\Delta\delta_{(C=C)}$) is specific for each isomer, without dependence on a substituent (Table 4). The reason for this specificity is the influence of the γ-*gauche* effect on the ^{13}C chemical shift of the C(2) atom.[25,26] In

Table 4. ^{13}C NMR chemical shift differences (ppm) of the double bond for various cyclic systems

Compounds	$\Delta\delta_{(C=C)}$ *anti*-isomer	$\Delta\delta_{(C=C)}$ *syn*-isomer
13-R-tricyclo[7.3.1.0 ^{2,7}]tridec-2(7)-ene		
Hydrocarbon	0.8	
Formylamines[a]	0.83	3.66
Amines	0.24	2.46
Shiff bases	0.79	3.78
Alcohols	1.29	4.15
9-R-bicyclo[3.3.1]non-2-ene		
Hydrocarbon	1.1	
Alcohols	1.06	4.33
12-R-tricyclo[7.2.1.0 ^{2,7}]dodec-2(7)-en		
Hydrocarbon	11.51[b]	
Amines	—	6.4
	11.28[b]	7.18[b]
Alcohols	—	4.4
	9.82[b]	4.87[b]
8-R-bicyclo[3.2.1]oct-2-ene		
Hydrocarbon	10.9	
Alcohols	8.4	3.3
7-R-bicyclo[3.1.1]hept-2-ene		
Hydrocarbon	15.57[b]	
10-R-bicyclo[4.3.1]dec-7-ene		
Hydrocarbon	5.77[b]	

[a] Conformers $\mathbf{2}_Z$ and $\mathbf{3}_Z$; paper[8] contains incorrect $\Delta\delta_{(C=C)}$ values.
[b] Based on theoretical spectra.

Table 5. γ-Substituent effects[a] on the skeletal carbon shieldings of various cyclic systems

Compound	γ-*anti*	γ-*gauche*
13-R-tricyclo[7.3.1.0 ^{2,7}]tridec-2(7)-ene		
2$_Z$	−0.92 C(2)	−5.70 C(10)
	0.55 C(8)	−6.67 C(12)
3$_Z$	−1.27 C(10)	−3.61 C(2)
	0.24 C(12)	−4.53 C(8)
4	−0.92 C(2)	−7.50 C(10)
	1.33 C(8)	−7.69 C(12)
5	−0.34 C(10)	−3.86 C(2)
	0.67 C(12)	−4.84 C(8)
6	−0.70 C(2)	−5.61 C(10)
	0.66 C(8)	−6.18 C(12)
7	−1.10 C(10)	−4.16 C(2)
	−1.01 C(12)	−3.57 C(8)
8	−0.97 C(2)	−7.19 C(10)
	0.77 C(8)	−7.26 C(12)
9	−1.37 C(10)	−4.35 C(2)
	−0.60 C(12)	−4.77 C(8)
9-R-bicyclo[3.3.1]non-2-ene		
11	−2.49 C(2)	−7.17 C(6)
	1.21 C(4)	−7.00 C(8)
12	−1.29 C(6)	−4.53 C(2)
	−0.22 C(8)	−4.26 C(4)
12-R-tricyclo[7.2.1.0 ^{2,7}]dodec-2(7)-en[b]		
14	−0.26 C(2)	−1.48 C(10)
	0.14 C(8)	−2.29 C(11)
15	−1.19 C(10)	−3.91 C(2)
	−2.33 C(11)	−4.51 C(8)
16	−1.41 C(2)	−1.77 C(10)
	−0.26 C(8)	−2.44 C(11)
17	−2.51 C(10)	−4.81 C(2)
	−4.02 C(11)	−4.88 C(8)
8-R-bicyclo[3.2.1]oct-2-ene		
19	−2.1 C(2)	−2.3 C(6)
	0 C(4)	−2.9 C(7)
20	−2.2 C(6)	−4.8 C(2)
	−3.3 C(7)	−6.0 C(4)

[a] $\Delta\delta^{X} = \delta_C^{R\text{-}X} - \delta_C^{R\text{-}H}$ where R-H=unsaturated hydrocarbon (in ppm); negative values indicate upfield shifts.
[b] Based on theoretical spectra.

anti-forms the C(2) atom is under the influence of a small γ-*anti* effect, while in *syn*-forms the same atom experiences a large upfield shift as a result of the γ-*gauche* effect (Table 5). The γ effect influences the corresponding aliphatic carbons too, but the application of their signals as a diagnostic sign is inconvenient because the assignment by visual inspection of the experimental spectra is not straightforward.

The relative configuration of tricyclo[7.3.1.0^{2,7}]tridec-2(7)-enes **2**–**9** is established.[8,9] For these compounds a smaller $\Delta\delta_{(C=C)}$ value corresponds to the *anti*-forms, while the *syn*-forms have a larger one (Table 4). The $\Delta\delta_{(C=C)}$ for hydrocarbon **1** is relatively close to the same value for the *anti*-forms (compounds **2**, **4**, **6**, **8**) and significantly farther apart from it for the *syn*-forms (compounds **3**, **5**, **7**, **9**). This finding is a characteristic feature. It is referred that a 2:3 mixture of isomeric bicyclo[3.3.1]non-2-en-9-ols has been received.[17] An assignment of ^{13}C NMR spectra was made, but a relative configuration of these products was not specified. Our finding allows us to assign the major isomer to the *anti*-form **11** and the minor to the *syn*-form **12** (Table 1).

The relative configuration of *syn*-amine **15** is established,[10] but the *anti*-isomer was not isolated. Mathematically, the γ-substituent effect defined as a difference $\delta_C^{R\text{-}X} - \delta_C^{R\text{-}H}$, but the experimental spectrum for hydrocarbon **13** is absent, so a theoretical spectrum was calculated. Also we carried out calculations of spectra for compounds **14**–**17**. The γ effect values based on the theoretical spectra are presented in Table 5. A larger $\Delta\delta_{(C=C)}$ value corresponds to the *anti*-forms (compounds **14**, **16**) and only slightly different from it for hydrocarbon **13**, while a smaller value corresponds to the *syn*-forms (compound **15**). It is noteworthy that the difference between the theoretical and experimental $\Delta\delta_{(C=C)}$ values for 12-*R*-tricyclo[7.2.1.0^{2,7}]dodec-2(7)-ene system does not exceed 0.8 ppm. Thus, obtained compound **17** we have assigned to the *syn*-form. This rule applies also to alcohols **19** and **20**.

The dispersion of $\Delta\delta_{(C=C)}$ values for the *anti*-forms of 13-*R*-tricyclo[7.3.1.0^{2,7}]tridec-2(7)-ene/9-*R*-bicyclo[3.3.1]-non-2-ene systems is 0.24–1.29 ppm and for the *syn*-forms-2.46–4.33 ppm. In the case of 12-*R*-tricyclo[7.2.1.0^{2,7}]-dodec-2(7)-ene/8-*R*-bicyclo[3.2.1]oct-2-ene systems, dispersion of these values for the *anti*-forms is 8.4–11.3 ppm and for the *syn*-forms-3.3–6.4 ppm. Formally, the relative $\Delta\delta_{(C=C)}$ values for isomeric forms of mentioned systems are inverted. This is due to the distinction between $\Delta\delta_{(C=C)}$ values for corresponding unsaturated hydrocarbons. The $\Delta\delta_{(C=C)}$ value for hydrocarbons **1** and **10** does not exceed 1.1 ppm and a large upfield γ-*gauche* effect for the C(2) atom of *syn*-isomers **3**, **5**, **7**, **9**, **12** leads to an increase of that quantity. In the case of *syn*-isomers **15**, **17** and **20**, the same effect leads to a decrease of initially large $\Delta\delta_{(C=C)}$ value (ca. 11 ppm) for hydrocarbons **13** and **18**. In contrast, the *anti*-isomers for all systems showing $\Delta\delta_{(C=C)}$ close to these values for corresponding hydrocarbons.

This finding can be extended to bicyclic systems **21** and **23**. For compound **23**, the two most stable twist–chair conformations of the seven-membered ring were taken into account. Theoretical $\Delta\delta_{(C=C)}$ values for unsaturated hydrocarbons **21** and **23** are 15.57 and 5.77 ppm, respectively. For the *anti*-forms of 7-*R*-bicyclo[3.1.1]hept-2-ene and 10-*R*-bicyclo[4.3.1]dec-7-ene systems, estimated $\Delta\delta_{(C=C)}$ should be near the value of corresponding hydrocarbon, while for the *syn*-forms it should be considerably smaller due to the influence of the γ-*gauche* effect. Compounds **21**[27] and **22**[28] are known, but experimental ^{13}C NMR data were omitted.

4. Conclusions

The comparison of $\Delta\delta_{(C=C)}$ values for some stereoisomer and respective hydrocarbon allows the *syn*-/*anti*-isomers to be distinguished without recourse to the calculations. For the *anti*-isomers of studied systems $\Delta\delta_{(C=C)}$ should be near the value of respective hydrocarbon, and for the *syn*-isomers it should be considerably different. Moreover, the relative order of $\Delta\delta_{(C=C)}$ values is transferable within the same bicyclic carbon framework, without dependence on a substituent. The specificity of $\Delta\delta_{(C=C)}$ values for the two stereoisomers with known relative configurations permit an assignment of relative configuration for the stereoisomers

with another substituent at the bridged carbon, without experimental spectra for corresponding hydrocarbon, even if only one of the unknown isomers is available. Also it is possible to suggest that this rule will be kept for any alkyl substituents on the carbon–carbon double bond.

5. Experimental

The NMR spectra were obtained in the pulse Fourier transform mode using Bruker WM 250 spectrometer operating at 62.9 MHz (^{13}C) and 250.1 MHz (^{1}H). The spectral data were recorded in a $CDCl_3$ solution with solvent or tetramethylsilane as an internal standard. For the preparation of **4**, **5**, **8** and **9** see the literature.[8,9] Alcohol **17** was obtained by $LiAlH_4$ reduction of the appropriate ketone on the analogy with synthesis of **9**.[8]

Acknowledgements

We thank the Research Educational Computational Center of Far Eastern National University and Institute for Automation and Control Processes of Far Eastern branch of Russian Academy of Science for a generous amount of time on the Linux clusters 'ABACUS' and MBC-1000, respectively.

References and notes

1. Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Van Nieuwenhe, M. S.; Gustin, D. J.; Dilley, G. J.; Lane, G. C.; Scheidt, K. A.; Smith, III., W. J. *J. Org. Chem.* **2002**, *67*, 4284–4289.
2. Filippini, M.-H.; Fauer, R.; Rodriguez, *J. Org. Chem.* **1995**, *60*, 6872–6882.
3. Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876.
4. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.
5. Rychnovsky, S.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.
6. Helgaker, T.; Jaszunski, M.; Ruud, K. *Chem. Rev.* **1999**, *99*, 293–352.
7. Barfield, M. *J. Am. Chem. Soc.* **1995**, *117*, 2862–2876.
8. Vysotskii, V. I.; Tilichenko, M. N.; Vysotskaya, T. A. *Zh. Org. Khim. (Russ.)* **1973**, *9*, 947–951.
9. Vysotskii, V. I.; Patrusheva, O. V.; Vysotskaya, T. A.; Isakov, V. V.; *Russ. J. Org. Chem. (Eng.)* **2002**, *38*, 1130–1136.
10. Akimova, T. I.; Ivanenko, Z. A.; Gerasimenko, A. V.; Vysotskii, V. I.; *Russ. J. Org. Chem. (Eng.)* **2001**, *37*, 1232–1237.
11. Written by Helgaker, T.; Jensen, H. J. A; Jørgensen, P.; Olsen, J.; Ruud, K.; Ågren, H.; Auer, A. A.; Bak, K. L.; Bakken, V.; Christiansen, O.; Coriani, S.; Dahle, P.; Dalskov, E. K.; Enevoldsen, T.; Fernandez, B.; Hättig, C.; Hald, K.; Halkier, A.; Heiberg, H.; Hettema, H.; Jonsson, D.; Kirpekar, S.; Kobayashi, R.; Koch, H.; Mikkelsen, K. V.; Norman, P.; Packer, M. J.; Pedersen, T. B.; Ruden, T. A.; Sanchez, A.; Saue, T.; Sauer, S. P. A.; Schimmelpfennig, B.; Sylvester-Hvid, K. O.; Taylor, P. R.; Vahtras, O. *Dalton*, a molecular electronic structure program, Release 1.2. **2001**.
12. Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829–5835.
13. (a) London, F. J. *Phys. Radium* **1937**, *8*, 397–409. (b) Ditchfield, R. *Mol. Phys.* **1974**, *27*, 789–807. (c) Wolinski, K.; Hinton, J. F.; Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260. (d) Häser, M.; Ahlrichs, R.; Baron, H. P.; Weiss, P.; Horn, H. *Theor. Chim. Acta* **1992**, *83*, 455–470. (e) Rauhut, G.; Puycar, S.; Wolinski, K.; Pulay, *J. Phys. Chem.* **1996**, *100*, 6310–6316. (f) Cheeseman, J. R.; Trucks, G. W.; Keith, T. A.; Frisch, *J. Chem. Phys.* **1996**, *104*, 5497–5509.
14. Vysotskaya, T. A.; Vysotskii, V. I.; Pavlenko, O. I. Tilichenko, M. N. *Zh. Org. Khim. (Russ.)* **1985**, *21*, 2527–2529.
15. Okazaki, T.; Terakawa, E.; Kitagawa, T.; Takeuchi, K. *J. Org. Chem.* **2000**, *65*, 1680–1684.
16. Ruano, J. L. G.; Rumbero, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4427–4436.
17. Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1977**, *55*, 841–848.
18. Our assignment of ^{13}C NMR signals for **20** is identically published.[16] But table 1 of the original paper contains an error: chemical shifts for C(2) and C(6) atoms of *endo*-bicyclo-[3.2.1]oct-3-en-8-ol (the numbering differs from IUPAC rules) must be exchanged, because in table 3 of that paper, the values for γ effects are consistent with our assignment.
19. Chesnut, D. B. *Chem. Phys.* **1997**, *214*, 73–79.
20. Forsyth, D. A.; Sebag, A. *J. Am. Chem. Soc.* **1997**, *119*, 9483–9494.
21. Menger, F. M.; D'Angelo, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 8241–8242.
22. Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Martinez-Ruiz, P.; San Antonio, R. M.; Martinez Alcazar, M. P. *Tetrahedron: Asymmetry* **1999**, *10*, 1499–1505.
23. Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Martinez-Ruiz, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2153–2158.
24. Jackman, L. M.; Sternhell, S. *Application of nuclear magnetic resonance spectroscopy in organic chemistry*. 2nd ed. Pergamon: Oxford, 1969.
25. Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315–5318.
26. Eliel, E. L.; Bailey, W. F.; Kopp, L. D.; Willer, R. L.; Grant, D. M.; Bertrand, R.; Christensen, K. A.; Dalling, D. K.; Duch, M. W.; Wenkert, E.; Schell, F. M.; Cochran, D. W. *J. Am. Chem. Soc.* **1975**, *97*, 322–330.
27. Grychtol, K.; Musso, H.; Oth, J. F. M. *Chem. Ber.* **1972**, *105*, 1798–1809.
28. Kirmse, W.; Streu, J. *Chem. Ber.* **1988**, *3*, 551–553.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1767–1771
Tetrahedron

Montmorillonite KSF clay catalyzed one-pot synthesis of α-aminonitriles

J. S. Yadav,* B. V. Subba Reddy, B. Eeshwaraiah and M. Srinivas

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 28 August 2003; revised 2 December 2003; accepted 18 December 2003

Abstract—Aryl imines, formed in situ from aldehydes and amines undergo smoothly nucleophilic addition with trimethylsilyl cyanide on the surface of montmorillonite KSF clay under mild reaction conditions to afford the corresponding α-aminonitriles in excellent yields. The solid acid can be recovered and recycled in subsequent reactions with a gradual decrease of activity.

1. Introduction

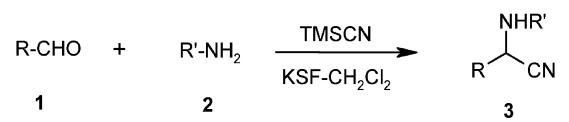
α-Aminonitriles are important intermediates for the synthesis of α-amino acids[1] and various nitrogen containing heterocycles[2] such as imidazoles and thiadiazoles, etc. They are usually prepared by the nucleophilic addition of cyanide anion to the imines.[3] The classical Strecker reaction is generally carried out with alkaline cyanides in aqueous solution. Subsequently, several modifications of the Strecker reaction have been reported using a variety of cyanating agents such as α-trimethylsiloxynitriles, diethyl phosphorocyanidate under various reaction conditions.[4] The use of trimethylsilyl cyanide is a safer and more effective cyanide anion source for the nucleophilic addition reactions of imines under mild conditions.[5] However, many of these methods involve the use of expensive reagents and extended reaction times, harsh conditions and also require tedious aqueous work-up leading to the generation of a large amount of toxic waste.

Furthermore, many of these catalysts are deactivated or some times decomposed by amines and water that exist during imine formation. In order to circumvent some of the problems associated with these procedures recently one-pot procedures have been developed for this transformation.[6] In recent years, the use of solid acid catalysts such as clays, ion-exchange resins and zeolites has received considerable attention in different areas of organic synthesis.[7] Especially, clay catalysts make the reaction process convenient, cost-effective, environmentally benign and act as Brønsted as well as Lewis acids in their natural or ion-exchanged forms, enabling them to function as efficient catalysts for various transformations.[8]

Because of the distinct advantages of solid acids, they can make a great contribution to green chemistry. Although, clay has been used for cyanohydrin formation,[9] there are no examples of the use of clay as catalyst for the synthesis of α-aminonitriles.

2. Results and discussion

In view of the emerging importance of the use of solid acids as environmentally friendly and reusable catalysts,[10] we herein describe a simple and efficient protocol for the three component-coupling reactions of aldehydes, amines and trimethylsilyl cyanide to produce α-aminonitriles using a heterogeneous solid acid catalyst, montmorillonite KSF clay under mild reaction conditions (Scheme 1).



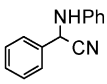
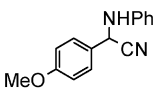
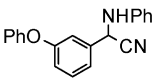
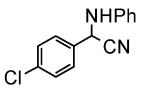
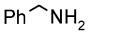
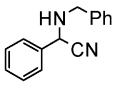
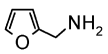
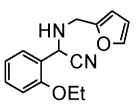
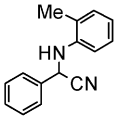
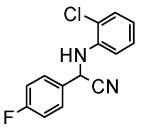
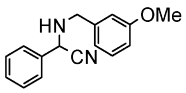
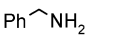
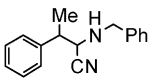
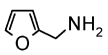
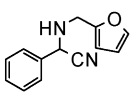
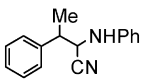
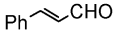
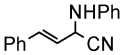
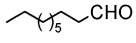
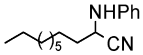
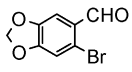
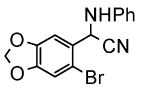
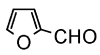
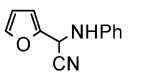
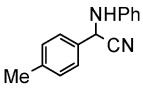
Scheme 1.

The treatment of benzaldehyde and aniline with TMSCN in the presence of KSF clay afforded the corresponding 2-anilino-2-phenylacetonitrile in 90% yield. Similarly, a variety of aldehydes were coupled with a range of amines and trimethylsilyl cyanide in a one-pot operation by using this procedure to produce α-aminonitriles in 85–94% yields. These three-component coupling reactions proceeded efficiently at ambient temperature with high selectivity. No cyanohydrin trimethylsilyl ethers (an adduct between an aldehyde and trimethylsilyl cyanide) were

Keywords: Solid acids; Aryl imines; Trimethylsiyl cyanide; α-Aminonitriles.
* Corresponding author. Tel.: +91-40-27193434; fax: +91-40-27160512; e-mail address: yadav@iict.ap.nic.in

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.043

Table 1. Montmorillonite clay promoted synthesis of α-amino nitriles

Entry	Aldehyde (**1**)	Amine (**2**)	Product (**3**)[a]	Reaction time (h)	Yield (%)[b]
(a)	C_6H_5CHO	$C_6H_5NH_2$		3.5	90
(b)	4-$MeOC_6H_4CHO$	$C_6H_5NH_2$		3.0	92
(c)	3-$PhOC_6H_4CHO$	$C_6H_5NH_2$		2.5	89
(d)	4-ClC_6H_4CHO	$C_6H_5NH_2$		3.5	91
(e)	C_6H_5CHO			4.5	87
(f)	2-$EtOC_6H_4CHO$			3.0	92
(g)	C_6H_5CHO	2-$MeC_6H_4NH_2$		4.0	94
(h)	4-FC_6H_4CHO	2-$ClC_6H_4NH_2$		5.0	85
(i)	C_6H_5CHO	3-$MeOC_6H_4CH_2NH_2$		4.5	89
(j)				3.5	91
(k)	C_6H_5CHO			5.5	92
(l)		$C_6H_5NH_2$		5.0	89
(m)		$C_6H_5NH_2$		4.5	85
(n)		$C_6H_5NH_2$		5.5	87
(o)		$C_6H_5NH_2$		5.0	92
(p)		$C_6H_5NH_2$		5.5	89
(q)	4-MeC_6H_4CHO	$C_6H_5NH_2$		5.0	91

Ph=phenyl.

[a] All products were characterized by ^1H NMR IR and mass spectroscopy.

[b] Isolated and unoptimized yields after purification.

obtained under these reaction conditions. This is because of the rapid formation and activation of the imines by solid acid clay. Both aromatic and aliphatic aldehydes afforded excellent yields of products whereas ketones did not yield any product under these reaction conditions. The reactions are clean and highly selective affording exclusively α-aminonitriles in high yields in a short reaction time. This method is equally effective with aldehydes bearing electron-withdrawing substituents in the aromatic ring. Furthermore, acid sensitive aldehydes such as furfuraldehyde and cinnamaldehyde worked well without any decomposition or polymerization under these reaction conditions. This method does not require any additives or stringent reaction conditions to proceed. The reaction conditions are mild enough to perform these reactions in the presence of either acid or base sensitive substrates. Enolizable aldehydes such as 2-phenylacetaldehyde and decanal also produced the corresponding α-aminonitriles. The scope and generality of this process is illustrated with respect to various amines and aldehydes including aromatic, α,β-unsaturated, heterocyclic and aliphatic aldehydes and the results are presented in Table 1. Finally, the clay was recovered by filtration, washed with methanol and recycled for use in subsequent reactions (after activation at 120 °C for 4–5 h) with gradual decrease in activity; for example, the reaction of benzaldehyde, aniline and trimethylsilyl cyanide under the present reaction conditions afforded α-aminonitriles in 92, 87 and 82% yields over three cycles.

3. Conclusion

In summary, we describe a simple, convenient and practical method for the synthesis of α-aminonitriles through a one-pot three-component coupling of aldehydes, amines and trimethylsilyl cyanide using heterogeneous solid acid KSF clay. The simple experimental and product isolation procedures combined with easy recovery and reuse of this natural clay is expected to contribute to the development of clean and environmentally friendly strategy for the synthesis of α-aminonitriles.

4. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. KSF clay was purchased from Aldrich Co.

4.1. General procedure for the preparation of α-aminonitriles

A mixture of aldehyde (1 mmol), amine (1 mmol), trimethylsilyl cyanide (1.2 mmol) and Mont. KSF clay (1.0 g) in dichloromethane (10 mL) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure α-aminonitrile. Solid clay portion was washed with methanol, dried at 120° under reduced pressure and could be reused in subsequent reactions.

4.2. Spectroscopic data for products

4.2.1. Compound 3a. White crystalline solid, mp 73–74 °C, IR (KBr): ν 3369, 3021, 2954, 2236, 1603, 1505, 1464, 1313, 1142, 995, 751. ^{1}H NMR ($CDCl_3$): δ 4.0 (d, 1H, J=8.1 Hz), 5.40 (d, 1H, J=8.1 Hz), 6.75 (d, 2H, J=8.0 Hz), 6.90 (t, 1H, J=7.8 Hz), 7.25 (t, 2H, J=7.8 Hz), 7.40–7.50 (m, 3H), 7.60–7.70 (m, 2H). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 50.7, 114.8, 118.9, 120.6, 127.8, 129.7, 130.0, 130.2, 134.5, 145.4. EIMS: m/z: 208 M^+, 180, 116, 91, 77. HRMS calcd for $C_{14}H_{12}N_2$: 208.10004. Found: 208.10105.

4.2.2. Compound 3b. White solid, mp 94–95 °C, IR (KBr): ν 3383, 3053, 2932, 2245, 1601, 1502, 1454, 1298, 1118, 1041, 925, 764. ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H), 3.90 (d, 1H, J=8.1 Hz), 5.30 (d, 1H, J=8.1 Hz), 6.75 (d, 2H, J=8.0 Hz), 6.80 (t, 1H, J=7.9 Hz), 6.90 (d, 2H, J=8.0 Hz), 7.25 (t, 2H, J=7.9 Hz), 7.50 (d, 2H, J=8.0 Hz). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 50.0, 55.8, 114.5, 115.0, 118.9, 120.5, 126.3, 129.0, 129.9, 145.1, 160.8. EIMS: m/z: 238 M^+, 211, 181, 167, 141, 104, 77, 51, 40. HRMS calcd for $C_{15}H_{14}N_2O$: 238.11061. Found: 238.11129.

4.2.3. Compound 3c. Pale yellow solid, mp 64–65 °C, IR (KBr): ν 3424, 2924, 2854, 2231, 1603, 1514, 1460, 1270, 1153, 1034, 798. ^{1}H NMR ($CDCl_3$): δ 4.02 (d, 1H, J=8.0 Hz), 5.38 (d, 1H, J=8.0 Hz), 6.78 (d, 2H, J=7.9 Hz), 6.90 (t, 1H, J=7.8 Hz), 7.05–7.65 (m, 11H). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 49.7, 114.1, 117.2, 117.9, 119.1, 119.2, 120.2, 121.5, 123.8, 129.4, 129.8, 130.5, 130.7, 114.4, 156.2, 158.1. EIMS: m/z: 300 M^+, 273, 210, 181, 167, 141, 104, 77. HRMS calcd for $C_{20}H_{16}N_2O$: 300.12626. Found: 300.12593.

4.2.4. Compound 3d. White solid, mp 109–112 °C, IR (KBr): ν 3405, 2927, 2239, 1600, 1515, 1457, 1272, 1161, 1098, 791. ^{1}H NMR ($CDCl_3$): δ 4.0 (d, 1H, J=8.1 Hz), 5.39 (d, 1H, J=8.1 Hz), 6.75 (d, 2H, J=8.0 Hz), 6.90 (t, 1H, J=7.9 Hz), 7.15 (t, 2H, J=7.9 Hz), 7.40 (d, 2H, J=8.0 Hz), 7.60 (d, 2H, J=8.0 Hz). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 49.5, 114.2, 117.8, 120.5, 128.5, 129.4, 129.5, 132.3, 135.5, 144.3. EIMS: m/z: 242 M^+, 213, 149, 114, 91, 73, 59. HRMS calcd for $C_{14}H_{11}ClN_2$: 242.06107. Found: 242.06152.

4.2.5. Compound 3e. Colorless oil, IR (KBr): ν 3409, 2924, 2234, 1648, 1514, 1401, 1108, 1028, 919, 825, 751. ^{1}H NMR ($CDCl_3$): δ 1.80 (brs, 1H, NH), 3.95 (AB q, 2H, J=13.5 Hz), 4.70 (s, 1H), 6.78 (d, 1H, J=8.0 Hz), 7.15 (t, 1H, J=7.8 Hz), 7.25–7.40 (m, 6H), 7.49–7.51 (m, 2H). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 51.7, 53.8, 119.2, 128.1, 128.9, 129.1, 129.5, 130.0, 135.2, 138.5, 143.5. EIMS: m/z: 222 M^+, 195, 141, 131, 116, 106, 91, 77, 51. HRMS calcd for $C_{15}H_{14}N_2$: 222.11569. Found: 222.11603.

4.2.6. Compound 3f. Yellow liquid, IR (KBr): ν 34481, 2981, 2895, 2225, 1638, 1598, 1494, 1248, 1118, 1043, 923, 754. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, 3H, J=6.9 Hz), 1.80 (brs, 1H, NH), 3.90 (AB q, 2H, J=13.5 Hz), 4.15 (q, 2H, J=6.9 Hz), 4.80 (s, 1H), 6.30 (m, 1H), 6.87 (d, 1H, J=8.0 Hz), 7.0 (t, 1H, J=7.8 Hz), 7.30–7.45 (m, 4H). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 14.5, 43.9, 48.9, 63.8, 108.0, 110.1, 111.8, 118.6, 120.6, 122.7, 128.6, 130.3, 142.2, 151.6, 155.9. EIMS: *m/z*: 256 M^+, 227, 198, 173, 146, 120, 104, 95, 80, 52. HRMS calcd for $C_{15}H_{16}N_2O_2$: 256.12117. Found: 256.12148.

4.2.7. Compound 3g. Pale yellow solid, mp 72–73 °C, IR (KBr): ν 3365, 2935, 2857, 2237, 1605, 1517, 1461, 1275, 1035, 791. ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H), 3.38 (brd, 1H, NH, J=8.1 Hz), 5.45 (d, 1H, J=8.1 Hz), 6.80 (t, 2H, J=7.9 Hz), 7.10 (d, 1H, J=8.0 Hz), 7.20 (d, 1H, J=7.9 Hz), 7.40–7.50 (m, 3H), 7.50 (d, 2H, J=8.0 Hz). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 17.8, 50.7, 112.2, 118.9, 120.4, 124.1, 127.7, 127.9, 129.8, 130.0, 131.3, 134.7, 143.4. EIMS: *m/z*: 222 M^+, 194, 155, 141, 116, 106, 91, 73, 65, 45. HRMS calcd for $C_{15}H_{14}N_2$: 222.11569. Found: 222.11607.

4.2.8. Compound 3h. White crystalline solid, mp 95–97 °C, IR (KBr): ν 3410, 2931, 2230, 1610, 1520, 1461, 1269, 1051, 790. ^{1}H NMR ($CDCl_3$): δ 4.65 (d, 1H, J=8.1 Hz), 5.45 (d, 1H, J=8.1 Hz), 6.90–6.95 (m, 2H), 7.15–7.35 (m, 4H), 7.58–7.65 (m, 2H). EIMS: *m/z*: 260 M^+, 234, 135, 100, 75. HRMS calcd for $C_{14}H_{10}ClFN_2$: 260.05165. Found: 260.05123.

4.2.9. Compound 3i. Yellow liquid, IR (KBr): ν 3400, 2941, 2890, 2241, 1616, 1527, 1471, 1283, 1160, 1045, 789. ^{1}H NMR ($CDCl_3$): δ 1.85 (brs, 1H, NH), 3.80 (s, 3H), 3.95 (AB q, 2H, J=13.0 Hz), 4.70 (d, 1H, J=13.0 Hz), 6.80–6.95 (m, 3H), 7.25 (t, 1H, J=7.9 Hz), 7.30–7.55 (m, 5H). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 51.4, 53.6, 55.5, 96.5, 113.4, 114.2, 119.0, 120.9, 127.6, 129.3, 130.0, 135.3, 140.0, 160.2. EIMS: *m/z*: 252 M^+, 225, 122, 91, 77. HRMS calcd for $C_{16}H_{16}N_2O$: 252.12626. Found: 252.12661.

4.2.10. Compound 3j. Pale yellow oil, IR (KBr): ν 3398, 2927, 2860, 2230, 1609, 1530, 1495, 1275, 1159, 1054, 787. ^{1}H NMR ($CDCl_3$): δ 1.45 (d, 3H, J=6.9 Hz), 1.95 (brs, 1H, NH), 3.10–3.20 (m, 1H), 3.58–3.60 (m, 1H), 3.80 (d, 1H, J=13.0 Hz), 4.05 (d, 1H, J=13.0 Hz), 7.20–7.45 (m, 10H). EIMS: *m/z*: 250 M^+, 223, 145, 105, 91, 77, 51. HRMS calcd for $C_{17}H_{18}N_2$: 250.14699. Found: 250.14659.

4.2.11. Compound 3k. Yellow liquid, IR (KBr): ν 3306, 2923, 2851, 2225, 1691, 1575, 1462, 1216, 1141, 1017, 940, 765. ^{1}H NMR ($CDCl_3$): δ 1.80 (brs, 1H, NH), 4.0 (s, 2H), 4.78 (s, 1H), 6.20–6.40 (m, 2H), 7.30–7.55 (m, 6H). EIMS: *m/z*: 212 M^+, 186 105, 81, 77 51, 39. HRMS calcd for $C_{13}H_{12}N_2O$: 212.09496. Found: 212.09523.

4.2.12. Compound 3l. Light brown solid, mp 99–100 °C, IR (KBr): ν 3400, 2967, 2895, 2235, 1601, 1535, 1482, 1280, 1180, 1055, 791. ^{1}H NMR ($CDCl_3$): δ 1.60 (d, 3H, J=6.9 Hz), 3.20–3.37 (m, 1H), 3.45–3.55 (m, 1H), 4.30–4.45 (m, 1H)), 6.65 (d, 2H, J=8.0 Hz), 6.85 (t, 1H, J=7.9 Hz), 7.20–7.45 (m, 7H). EIMS: *m/z*: 236 M^+, 209, 131, 105, 77, 51. HRMS calcd for $C_{16}H_{16}N_2$: 236.13134. Found: 236.13178.

4.2.13. Compound 3m. Pale yellow solid, mp 117–119 °C, IR (KBr): ν 3350, 2929, 2233, 1603, 1505, 1461, 1275, 1030, 976, 897, 746. ^{1}H NMR ($CDCl_3$): δ 3.80 (d, 1H, J=8.1 Hz), 5.05 (m, 1H), 6.30 (dd, 1H, J=6.9, 17.3 Hz), 6.78 (d, 1H, J=8.0 Hz), 6.90 (t, 1H, J=7.9 Hz), 7.08 (dd, 1H, J=1.7, 17.3 Hz), 7.25–7.45 (m, 8H). EIMS: *m/z*: 234 M^+, 206, 128, 115, 77, 51. HRMS calcd for $C_{16}H_{14}N_2$: 234.11569. Found: 234.11515.

4.2.14. Compound 3n. Pale yellow liquid, IR (KBr): ν 3405, 2925, 2854, 2235, 1600, 1505, 1463, 1279, 1160, 1030, 791. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, J=6.8 Hz), 1.20–1.40 (m, 12H), 1.50–1.65 (m, 2H), 1.80–1.90 (m, 2H), 3.80 (brs, NH), 4.05–4.15 (m, 1H), 6.60 (d, 2H, J=8.0 Hz), 6.80 (t, 1H, J=7.9 Hz), 7.20 (t, 2H, J=7.9 Hz). ^{13}C NMR (Proton decoupled, $CDCl_3$): δ 48.9, 112.7, 116.3, 116.6, 117.5, 120.4, 120.5, 127.9, 129.0, 129.1, 129.6, 140.4, 161.6, 164.9. EIMS: *m/z*: 258 M^+, 185, 155, 135, 121, 77, 51. HRMS calcd for $C_{17}H_{26}N_2$: 258.20959. Found: 258.20906.

4.2.15. Compound 3o. Brown solid, mp 93–94 °C, IR (KBr): ν 3364, 2924, 2855, 2233, 1599, 1499, 1406, 1271, 1239, 1127, 1035, 979, 866, 750. ^{1}H NMR ($CDCl_3$): δ 3.90 (brs, 1H, NH), 5.60 (s, 1H), 6.0 (s, 2H), 6.70 (d, 2H, J=8.0 Hz), 6.90 (t, 1H, J=7.9 Hz), 7.08 (m, 1H), 7.20–7.45 (m, 3H). EIMS: *m/z*: 331 M^+, 305, 282, 249, 229, 199, 155, 141, 97, 69, 51, 39. HRMS calcd for $C_{15}H_{11}BrN_2O_2$: 330.00038. Found: 330.00108.

4.2.16. Compound 3p. Dark brown solid, mp 68–70 °C, IR (KBr): ν 3359, 2925, 2235, 1695, 1601, 1501, 1440, 1289, 1248, 1149, 1014, 880, 751. ^{1}H NMR ($CDCl_3$): δ 4.05 (d, 1H, J=8.1 Hz), 5.40 (d, 1H, J=8.1 Hz), 6.40 (m, 1H), 6.55 (m, 1H), 6.80 (d, 2H, J=8.0 Hz), 6.90 (t, 1H, J=7.9 Hz), 7.25 (t, 2H, J=7.9 Hz), 7.40 (m, 1H). EIMS: *m/z*: 198 M^+, 169, 155, 141, 115, 106, 92, 77, 51. HRMS calcd for $C_{12}H_{10}N_2O$: 198.07931. Found: 198.07890.

4.2.17. Compound 3q. Yellow solid, mp 76–78 °C, IR (KBr): ν 3306, 2923, 2851, 2225, 1691, 1575, 1462, 1216, 1141, 1017, 940, 765. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.90 (d, J=8.1 Hz), 5.40 (d, J=8.1 Hz), 6.78 (d, 2H, J=8.0 Hz), 6.90 (t, 1H, J=7.8 Hz), 7.20–7.30 (m, 4H), 7.50 (d, 2H, J=8.0 Hz), 7.50 (d, 2H, J=8.0 Hz). EIMS: *m/z*: 222 M^+, 194, 176, 131, 103, 91, 77 41. HRMS calcd for $C_{15}H_{14}N_2$: 222.11569. Found: 222.11508.

Acknowledgements

B. V. S. thanks CSIR, New Delhi, for the award of fellowships.

References and notes

1. Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148.

2. (a) Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. *J. Org. Chem.* **1967**, *32*, 2823. (b) Matier, W. L.; Owens, D. A.; Comer, W. T.; Deitchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* **1973**, *16*, 901.
3. Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
4. (a) Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *25*, 4583. (b) Harusawa, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1979**, *20*, 4663.
5. (a) Chakraborty, T. K.; Reddy, G. V.; Hussain, K. A. *Tetrahedron Lett.* **1991**, *32*, 7597. (b) Leblanc, J.; Gibson, H. W. *Tetrahedron Lett.* **1992**, *33*, 6295. (c) Heydari, A.; Fatemi, P.; Alizadeh, A. A. *Tetrahedron Lett.* **1998**, *39*, 3049.
6. (a) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 981.
7. (a) Coppola, G. M. *Synthesis* **1984**, 1021. (b) Asakura, J. I.; Robins, M. J.; Asaka, Y.; Kim, T. H. *J. Org. Chem.* **1996**, *61*, 9026. (c) Van Herwijnen, H. W. G.; Brinker, U. H. *J. Org. Chem.* **2001**, *66*, 2874.
8. (a) Balogh, M.; Laszlo, P. *Organic chemistry using clay*; Spinger: New York, 1993. (b) Cornelis, A.; Laszlo, P. *Synlett* **1994**, 155.
9. (a) Onaka, M.; Higuchi, K.; Sugita, K.; Izumi, Y. *Chem. Lett.* **1989**, 1393. (b) Higuchi, K.; Onaka, M.; Izumi, Y. *Bull. Chem. Soc. Jpn* **1993**, *66*, 2016. (c) Somanathan, R.; Rivero, I. A.; Gama, A.; Ochoa, A.; Aguirre, G. *Synth. Commun.* **1998**, *28*, 2043.
10. (a) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Murthy, Ch. V. S. R. *Tetrahedron Lett.* **2001**, *42*, 89. (b) Yadav, J. S.; Reddy, B. V. S.; Patil, K. S.; Reddy, P. S. R. *Tetrahedron Lett.* **2002**, *43*, 3853. (c) Yadav, J. S.; Reddy, B. V. S.; Rasheed, M.; Kumar, H. M. S. *Synlett* **2000**, 487. (d) Yadav, J. S.; Reddy, B. V. S.; Madan, Ch. *Synlett* **2001**, 1131.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1773–1780
Tetrahedron

Synthesis of photoaffinity probes of tautomycin

Masakuni Kurono, Aya Shimomura and Minoru Isobe*

Laboratory of Organic Chemistry, Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

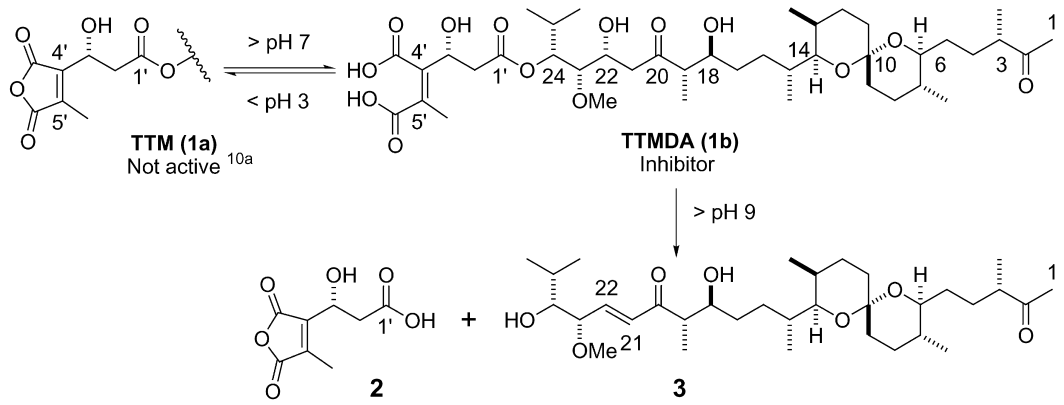
Received 8 December 2003; revised 24 December 2003; accepted 24 December 2003

Abstract—Two types of photoaffinity probe, which possesses a benzophenone or a diazirine photophore on the 2-position of tautomycin, were prepared in order to prove the details of binding site to PP1. These photoaffinity probes were designed on the basis of the structure–activity relationship; thus, the diacid moiety is indispensable. The selective introduction of photolabeling units on the 2-position of tautomycin was achieved through the 2-oxime of tautomycin diacid.

1. Introduction

Tautomycin (TTM, **1**) was isolated in 1987,[1] structurally elucidated in 1990 by Isono (Scheme 1),[2] and shows a specific inhibitor of protein phosphatase (PP) 1 and 2A.[3] It has been reported that PP1 or PP2A were inhibited by natural products such as okadaic acid, calyculin, and microcystin–LR.[4] Each of these three compounds inhibits PP2A much more strongly than does PP1, which TTM inhibits PP1 more selectively than PP2A.[4] In 1995, the X-ray crystallographic structure of the complex of PP1–microcystin–LR provided the details of the interaction between the protein and the toxin.[5] The X-ray structures were reported for PP1 complexes of okadaic acid (2001)[6] and calyculin (2002).[7] However, the X-ray structure of PP1–TTM complex is not yet available, probably due to the nature of TTM. Herein, we describe the synthesis of two types of photoaffinity probe (**4**, **5**, **6**, and **7**), which possesses a benzophenone or a diazirine photophore on the 2-position of TTM in order to study the binding site to PP1 (Scheme 2). These photoaffinity probes were designed according to the structure–activity relationship reported in the various sources with natural and synthetic derivatives:[8–11] (i) Active inhibitor is not the anhydride (**1a**), but the dicarboxylic acids form (**1b**).[10a,11a] (ii) The hydroxyl groups at the C22 and the C′3 are also indispensable for its bioactivity.[10b,11a] (iii) The hydrophobic spiroketal moiety contributes significantly to the selective inhibition of PP.[10b] Thus, we have been introducing the photolabeling units into the 2-position of TTM for the current studies.

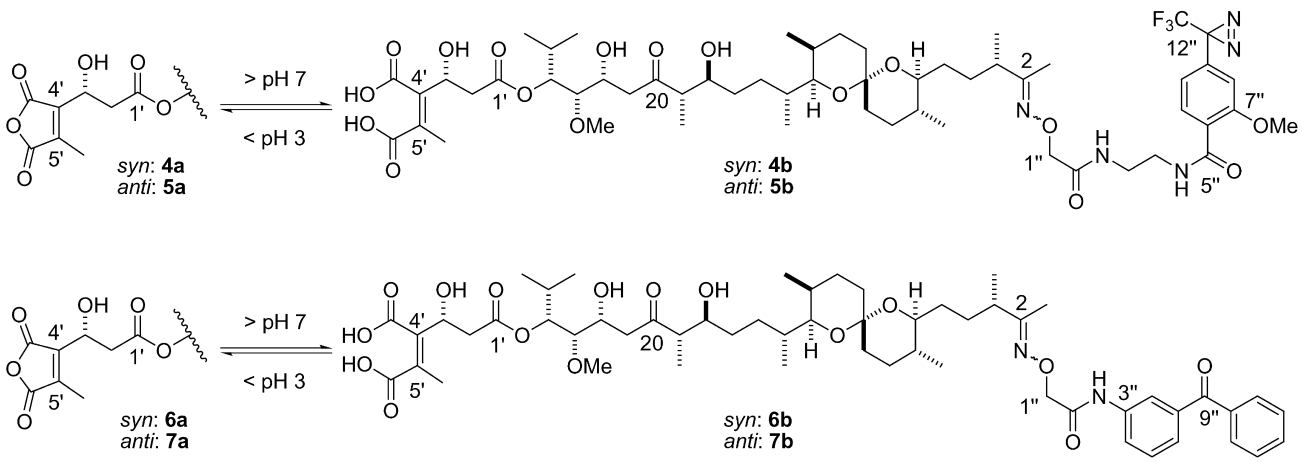
Under mild alkaline conditions (CH_3CN, 3% $NaHCO_3$, pH 8), TTM (**1**) exists predominantly as the diacid form (TTMDA, **1b**), which is the active inhibitor. These two



Scheme 1. Tautomycin (TTM) and tautomycin diacid (TTMDA).

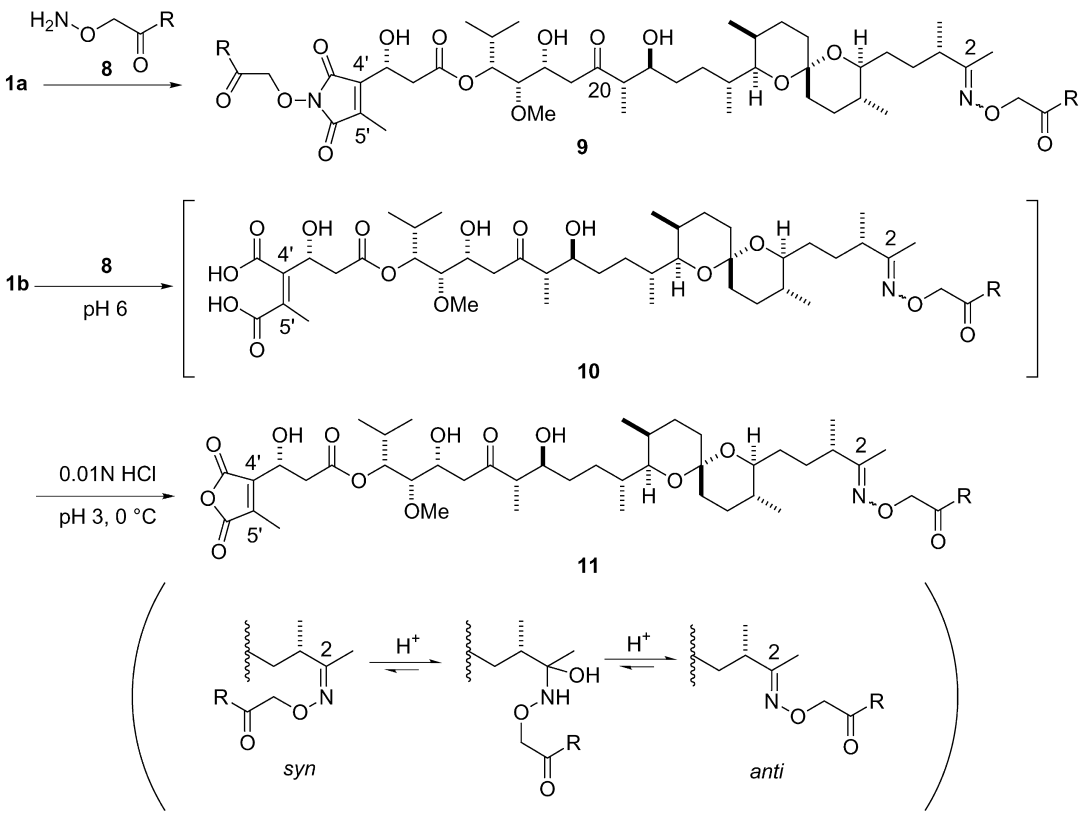
Keywords: Tautomycin; Photoaffinity probe; Protein phosphatase.
* Corresponding author. Tel.: +81-52-789-4109; fax: +81-52-789-4111; e-mail address: isobem@agr.nagoya-u.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.053

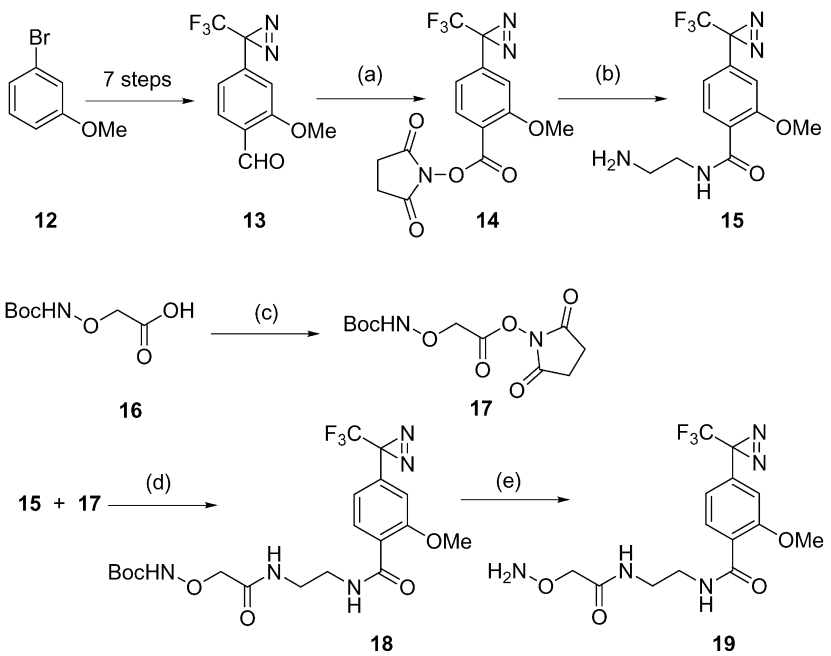


Scheme 2. Photoaffinity probes.

species (TTM and TTMDA) were separable with a short column on HPLC (see Section 7).[10a] However, **1** exhibits an unstable nature under alkaline conditions (MeOH, 20% Cs_2CO_3, pH 9) to cause elimination of C22 hydroxy group (**3**, Scheme 1).[2] This mechanism is suggested to include a trans-esterification before the elimination.[10a] Introduction of photolabeling unit under such a basic condition should be avoided. Therefore, the oxime linkage was selected as a suitable one, because its coupling reaction with **1** could be achieved at pH 6.[12] However, the coupling reaction of **1a** with aminooxy compound **8** raise another serious problem: thus, **8** reacted not only with one of the carbonyl groups, but also with the anhydride moiety of **1** to give the product **9** (Scheme 3). To avoid these problems, we selected the diacid **1b**, for the coupling reaction at pH 6.[10a] The reaction mixture was immediately acidified with 0.01 N hydrochloric acid (HCl) at 0 °C. Under these conditions, The aminooxy compound **8** rapidly receives protonation to oxiammonium salt and loses the nucleophilicity. On the other hand, the diacid moiety in the product **10** was relatively slowly converted into the anhydride oximes **11**, which were separated by HPLC with, for example, MeOH containing 0.1% TFA. During the acidification, the *syn* oxime isomer isomerized to the corresponding *anti* oxime isomer, the latter being is thermodynamically more stable. When the reaction mixture is neutralized, it should be noted that the aminooxy compound **8** recovered the nucleophilicity react with the anhydride moiety of **11**. Therefore, the short column is required to remove the oxiammonium salt from the reaction mixture (see Section 7).



Scheme 3. The strategy for the introduction of photolabeling units.



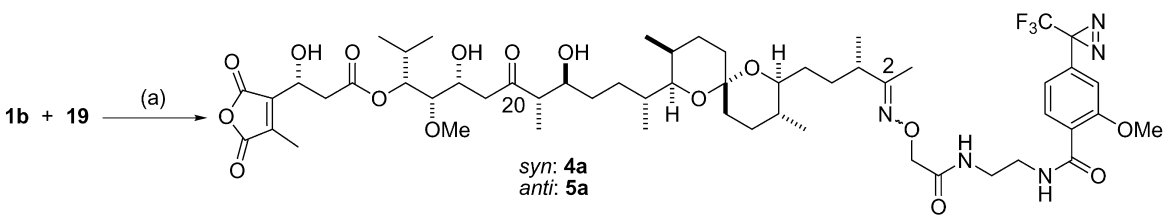
Scheme 4. Synthesis of photolabeling unit bearing the diazirine photophore: (a) (i) $^{n}Bu_4NMnO_4$, pyridine, room temperature, 1 h; (ii) *N*-hydroxysuccinimide, EDC·HCl, DMF, room temperature, 1 h, 74% in two steps; (b) ethylenediamine, MeOH, 0 °C, 7 min, 94%; (c) *N*-hydroxysuccinimide, EDC·HCl, DMF, room temperature, 36 h, 78%; (d) Et_3N, DMF, room temperature, 30 min, 84%; (e) TFA/CH_2Cl_2 (1:1), 0 °C, 30 min.

2. Synthesis of photolabeling unit bearing the diazirine photophore

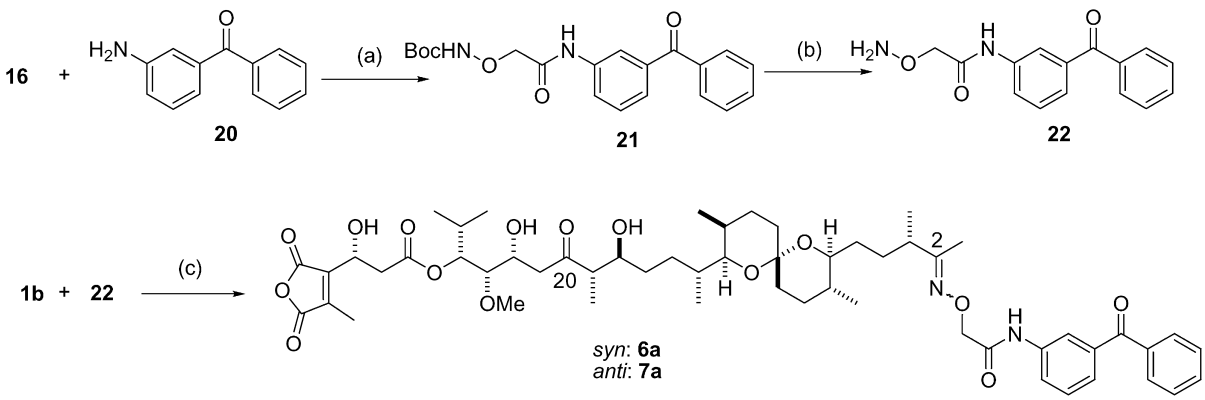
Synthesis of the photolabeling unit (**19**) is illustrated in Scheme 4. According to the method by Hatanaka,[13] we synthesized 2-methoxy-4-(3-trifluoromethyl-3*H*-diazirin-3-yl) benzaldehyde **13** in 34% overall yield from a commercially available 3-bromoanisole **12**. The oxidation of **13** with *n*-tetrabutylammonium permanganate ($^{n}Bu_4MnO_4$)[14] in pyridine was followed by activation of the resulting carboxylic acid with *N*-hydroxysuccinimide in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl) to provide the activated ester **14**. In order to insert a spacer between TTMDA **1b** and photolabeling function, **14** was first connected with the ethylenediamine, to provide the amine **15**. Secondly, **15** was connected with the activated ester **17** in the presence of triethylamine (Et_3N) to furnish the protected photolabeling unit **18**. Finally the protective *t*-butoxycarbonyl (Boc) group of **18** was removed with TFA in CH_2Cl_2 to afford the aminooxy compound **19**, which was used in the coupling reaction with **1b** without further purification.

3. Synthesis of photoaffinity probe bearing the diazirine photophore

The synthesis of the diazirine photoaffinity probe (**4a**, **5a**) is summarized in Scheme 5. The coupling reaction of **1b** with photolabeling unit (**19**) was carried out in 50% *N*,*N*′-dimethylacetamide (DMA)/H_2O at pH 6, which was successively acidified with 0.01 N HCl to furnish the corresponding *E*/*Z* regioisomeric mixture of the photoaffinity probe (**4a**, **5a**). No oxime was found on 20-ketone under this condition presumably due to heavily steric congestion around the 20-ketone. The reaction mixture was separated by HPLC (ODS column, CH_3CN/H_2O) to give the pure *Z* isomer **4a** (1.3 mg, 6% in two steps), and the pure *E* isomer **5a** (6.8 mg, 31% in two steps). The *Z* or *E* oxime configurations were determined from ^{1}H NMR spectroscopy on the basis of Karabatsos report, thus, the deshielding effect (N–O group) or shielding effect (N lone pair) exerted by the oxime moiety.[15] In the *Z* isomer **4a** the H-3 chemical shift (δ 3.35 ppm) was down-field by 0.98 ppm in comparison with the corresponding H-3 chemical shift (δ 2.37 ppm) for the *E* isomer **5a**. On the other hand, the H-1 is more shielded by 0.14 ppm in the *Z* isomer **4a** (δ 1.73 ppm)



Scheme 5. Synthesis of photoaffinity probe bearing the diazirine photophore: (a) 50% DMA/H_2O, pH 6, room temperature, 36.5 h, then 0.01 N HCl, pH 3, room temperature, 4 h, *Z*/*E* (1:4), 37% (two steps).



Scheme 6. Synthesis of photoaffinity probe bearing the benzophenone photophore: (a) EDC·HCl, CH_2Cl_2, room temperature, 1 h, 72%; (b) TFA/CH_2Cl_2 (1:1), 0 °C, 3 h; (c) 50% DMA/H_2O, pH 6, room temperature, 48 h, then 0.01 N HCl, pH 3, room temperature, 3 h, *Z*/*E* (1:4), 47% (two steps).

than the corresponding signal in the *E* isomer **5a** (δ 1.87 ppm).

4. Synthesis of photoaffinity probe bearing the benzophenone photophore

The synthesis of the photoaffinity probe bearing the benzophenone photophore (**6a**, **7a**) is summarized in Scheme 6. Treatment of 3-aminobenzophenone (**20**) with the compound **16** in the presence of EDC·HCl furnished the protected photolabeling unit **21**. The Boc group was removed with TFA/CH_2Cl_2 to provide the aminooxy compound **22**. The coupling reaction of **1b** with photolabeling unit (**22**) was carried out under the similar condition as above, to furnish the corresponding *E*/*Z* regioisomeric mixture of the photoaffinity probe (**6a**, **7a**). The reaction mixture was separated by HPLC to give the pure *Z* isomer **6a** (1.6 mg, 10% in two steps), and the pure *E* isomer **7a** (6.0 mg, 37% in two steps).

The PP1γ inhibitory activity of these photoaffinity probes were measured by the firefly bioluminescence system, which have already established in our laboratry.[16] These photoaffinity probes showed high inhibitory activity for PP1 in the range of K_i=10–200 nM (**1b**: 4.5 nM).[17]

5. Photoreactive experiment

Photochemical reaction was examined with **4a**; one of the synthesized diazirine photoaffinity probes. A solution of **4a** (126 μM) in CH_3CN was irradiated with UV lamp (365 nm, FI-5L) at room temperature. The reaction was monitored in the different photoirradiation time from 0 to 7 min by the ESI (electrospray ionization)-Q-TOF (tandem quadrupole/orthogonal-acceleration time-of-flight) MS. According to the time, a peak increased at *m*/*z* 1137 corresponding to the acetonitrile adduct structure being an equivalent of the possible structure **23** [**4a**-N_2+CH_3CN]$^+$ ion (Scheme 7).[18] This result indicates involvement the carbene which would react with PP1γ by the irradiation of UV light for 7 min.

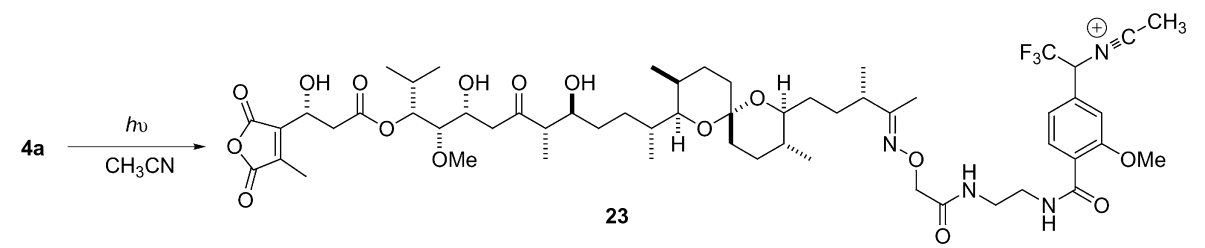
6. Conclusion

Two types of the photoaffinity probe (**4a**, **5a**, **6a**, and **7a**), which possesses a benzophenone or a diazirine photophore on the 2-position of tautomycin, has been accomplished through the selective reaction of the photolabeling units (**19** and **22**) with tautomycin diacid (**1b**). Further studies are in progress in order to detect of modified protein and peptides using matrix assisted laser desorption ionization (MALDI)-TOF-MS as well as HPLC-ESI-Q-TOF-MS and MS/MS.

7. Experimental

7.1. General methods

Melting points were recorded on a Yanaco MP-S3 melting point apparatus. Infrared spectra (IR) were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a BRUKER AMX-600 (600 MHz), or an ARX-400 (400 MHz), and/or an Avance-400 (400 MHz) spectrometers. Chemical shifts are reported in perts per million (ppm) using tetramethylsilane (δ=0.00 ppm) and dimethylslufoxide-d_6 (δ=2.49 ppm) as an internal standard. Data are reported as follows; chemical



Scheme 7. Photochemical reaction of **4a**.

shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, sext=sextet, br=broad, m=multiplet), coupling constant(s), and assignment, respectively. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a BRUKER AMX-600 (150 MHz), an ARX-400 (100 MHz), and/or an Avance-400 (100 MHz) spectrometers. Chemical shifts are reported in ppm using $CDCl_3$ (δ=77.0 ppm) and dimethylslufoxide-d_6 (δ=39.7 ppm) as an internal standard. Data are reported as follows; chemical shift, multiplicity (q=quartet), coupling constant(s), and assignment, respectively. Fluoro nuclear magnetic resonance (^{19}F NMR) spectra were recorded on an Avance-400 (376.5 MHz) spectrometer. Chemical shifts are reported in ppm using $CFCl_3$ (δ=0.00 ppm) as an external standard. 2D NMR (COSY, HMBC, HMQC, and HSQC) spectra were measured at a BRUKER AMX-600 (600 MHz), or a BRUKER ARX-400 (400 MHz) and/or an Avance-400 (400 MHz) spectrometers. Tautomycin and photoaffinity probes numbering corresponding to the front page are employed for assignment of ^{1}H NMR. MS spectra were measured utilizing a Q-TOF mass spectrometer (Micromass, Manchester, UK) equipped with a Z-spray type ESI source. HPLC analyses were performed with combination of Jasco PU-980 pump, a Rheodyne model 7125 sample injector, a Jasco VL-611 Variable loop injector, a Jasco UV-970 UV/VIS detector, and a Jasco 807-IT integrator. Elemental analyses were performed by Mr S. Kitamura in Analytical Laboratory at Bioagricultural Sciences, Nagoya University to whom the authors gratefully acknowledge. Unless otherwise noted, the reaction flask was wrapped with aluminium foil to protect from light, and non-aqueous reactions were carried out under nitrogen or argon atmosphere. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated glass plates $60F_{254}$ using UV light as visualizing agent and 12molybdo(VI)phosphoric acid *n*-hydrate or *p*-anisaldehyde solution and heated as developing agents. Silica gel 60 (particle size 0.063–0.2 mm ASTM) was used for open-column chromatography. Dry CH_2Cl_2 was distilled from CaH_2 under nitrogen atmosphere. Pyridine and Et_3N were dried over anhydrous KOH pellets. All other commercially available reagents were used as received.

Tautomycin (**1**) was kindly provided by Dr. K. Isono (ex-Riken Institute) and further purified by the procedure of the method described previously with slight modification.[19]

7.1.1. Tautomycin diacid (TTMDA, 1b). TTM (**1a**, 24 mg, 30.4 mmol) was dissolved in 1.4 ml of 80% CH_3CN/H_2O, and adjusted to pH 8 with aqueous $NaHCO_3$ (28 mg/ml). After being stirred for 5 h at room temperature, a major compound was detected by HPLC (Develosil ODS-UG-5 (i.d. 4.6×250 mm), 85% CH_3CN/H_2O, 1.0 ml/min, UV 254 nm, and T_r=2.4 min). The reaction mixture was neutralized with 0.01 N HCl at 0 °C, concentrated and then purified by HPLC (Develosil ODS-10/20 (i.d. 4.6×50 mm), 70% CH_3CN/H_2O, 1.0 ml/min, UV 254 nm, and T_r=0.6 min). The fraction was evaporated and lyophilized to give TTMDA (**1b**, 23 mg, 95%) as a white powder.

7.1.2. 2-Methoxy-4-(3-trifluoromethyl-3*H*-diazirin-3-yl)-benzoic acid 2,5-dioxopyrrolidin-1-yl ester (14). To a solution of benzaldehyde **13** (0.75 g, 3.06 mmol) in pyridine (2.0 ml) was added a solution of *n*-tetrabutylammonium permanganate[14] (1.66 g, 3.06 mmol) in pyridine (10.2 ml). After being stirred for 1 h at room temperature, the reaction mixture was diluted with water, acidified with 1 N HCl to pH 3, and saturated aqueous $NaHSO_3$ was added until all the MnO_2 precipitates dissolved. The colorless solution was extracted with Et_2O and the organic layer was combined, washed with sat. $CuSO_4$, water. The combined organic phase was dried over Na_2SO_4 and then concentrated under reduced pressure to afford the crude aromatic acid (0.77 g). To a solution of the crude acid (352 mg, 1.35 mmol) in DMF (10.0 ml) was added *N*-hydroxysuccinimide (164 mg, 1.42 mmol), a solution of EDC·HCl (286 mg, 1.49 mmol) in DMF (24.0 ml) at room temperature. After being stirred for 1 h at room temperature, the solvent was evaporated in vacuo. The reaction mixture was extracted with CH_2Cl_2 (×3) and the organic layer was combined, and washed with water (×3) and brine. The combined organic phase was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (silica gel 8.0 g, ethyl acetate/hexane=1:2, then 2:1) to give the activated ester **14** (357 mg, 74% in two steps) as a yellow oil.

7.1.3. Compound 14. IR (KBr) λ_{max} 1774, 1740, 1297, 1274, 1194, 827 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.89 (4H, s, COC*H*$_2$C*H*$_2$CO), 3.93 (3H, s, 2-OC*H*$_3$), 6.72 (1H, br s, Ar-*H*), 6.87 (1H, br d, *J*=8.4 Hz, Ar-*H*), 8.05 (1H, d, *J*=8.4 Hz, Ar-*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7, 28.5 (q, *J*=40.7 Hz), 56.3, 110.0, 115.6, 118.2, 122.3 (q, *J*=273.1 Hz), 133.2, 136.9, 159.7, 160.4, 169.1. Anal. Calcd for $C_{14}H_{10}F_3N_3O_5$: C, 47.07; H, 2.82; N, 11.76. Found: C, 47.07; H, 2.77; N, 11.63.

7.1.4. *N*-(2-Amino-ethyl)-2-methoxy-4-(3-trifluoromethyl-3*H*-diazirin-3-yl)-benzamide (15). To a solution of the activated ester **14** (103 mg, 0.29 mmol) in MeOH (85 ml) was added ethylenediamine (863 mg, 14.36 mmol) at 0 °C. After being stirred for 7 min, the reaction mixture was concentrated to one-tenth of its original volume. The residue was purified by column chromatography (Silica Gel 60 N (spherical, neutral), 10 g, CH_2Cl_2/MeOH/*i*-PrNH$_2$=20:1:0.3) to give the compound **15** (82 mg, 94%) as a yellow oil.

7.1.5. Compound 15. IR (KBr) λ_{max} 3386, 1647, 1613, 1541, 1260, 1154, 829 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.93 (2H, m, NH$_2$C*H*$_2$C*H*$_2$NH), 3.52 (2H, m, NH$_2$C*H*$_2$C*H*$_2$-NH), 3.98 (3H, s, 2-OC*H*$_3$), 6.71 (1H, d, *J*=1.8 Hz, Ar-*H*), 6.90 (1H, br d, *J*=8.4 Hz, Ar-*H*), 8.07 (1H, s, CON*H*), 8.21 (1H, d, *J*=8.4 Hz, Ar-*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (q, *J*=40.4 Hz), 41.3, 42.6, 56.0, 109.2, 119.1, 121.8 (q, *J*=273.1 Hz), 123.0, 132.7, 133.4, 157.3, 164.3. ESI-Q-TOF-MS Calcd for $C_{12}H_{14}F_3N_4O_2^+$ 303.1069 ([M+H]$^+$). Found 303.1050.

7.1.6. 2-*tert*-Butoxycarbonylaminoxy-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester (17). To a solution of *N*-*tert*-butoxycarbonyl-aminooxy acetic acid **16** (34 mg, 0.18 mmol) in DMF (0.7 ml) was added *N*-hydroxysuccinimide (25 mg, 0.22 mmol) and then a solution of EDC·HCl (41 mg, 0.22 mmol) in DMF (2.0 ml) at room temperature.

After being stirred for 36 h at room temperature, the solvent was evaporated in vacuo. The residual mixture was extracted with AcOEt (×3). The combined organic phase was washed with water (×3), brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (silica gel 1.5 g, ethyl acetate/hexane=1:1, then ethyl acetate) to give the activated ester **17** (40 mg, 78%) as a colorless oil.

7.1.7. Compound 17. IR (KBr) λ_{max} 3280, 2983, 1741, 1371, 1253, 1208, 1163 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (9H, s, C(C*H*$_3$)$_3$), 2.88 (4H, s, COC*H*$_2$C*H*$_2$CO), 4.78 (2H, s, H-2), 7.80 (1H, s, CON*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 28.1, 70.8, 82.7, 156.3, 165.0, 168.7. ESI-Q-TOF-MS calcd for $C_{11}H_{16}N_2NaO_7^+$ 311.0855 ([M+Na]$^+$). Found 311.0913.

7.1.8. *N*-[2-(2-Aminooxy-acetylamino)-ethyl]-*N*-*tert*-butoxycarbonyl-2-methoxy-4-(3-trifluoromethyl-3*H*-diazirin-3-yl)-benzamide (18). A solution of compound **15** (23 mg, 0.08 mmol) in DMF (0.2 ml) was mixed with Et_3N (19 mg, 0.19 mmol) at 0 °C and a solution of compound **17** (32 mg, 0.12 mmol) in DMF (1.2 ml) at room temperature. After being stirred for 30 min at room temperature, the solution was evaporated in vacuo. The reaction mixture was extracted with CH_2Cl_2 (×3). The combined organic phase was washed with water (×3) and brine, dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (silica gel 1.0 g, ethyl acetate/hexane=1:1, then ethyl acetate) to give the protected photolabeling unit **18** (31 mg, 84%) as a colorless oil.

7.1.9. Compound 18. IR (KBr) λ_{max} 3380, 1725, 1653, 1540, 1160, 851 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.43 (9H, s, C(C*H*$_3$)$_3$), 3.57 (2H, m, NHC*H*$_2$C*H*$_2$NH), 3.65 (2H, m, NHC*H*$_2$C*H*$_2$NH), 3.98 (3H, s, OC*H*$_3$), 4.32 (2H, s, COC*H*$_2$ONH), 6.70 (1H, br s, Ar-*H*), 6.89 (1H, br d, *J*=8.2 Hz, Ar-*H*), 8.20 (4H, m, Ar-*H*, amides-N*H*). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.01, 28.33 (q, *J*=40.5 Hz), 39.17, 39.96, 56.07, 76.08, 82.75, 109.24, 119.13, 121.83 (q, *J*=273.0 Hz), 122.50, 132.78, 133.76, 157.56, 157.60, 165.20, 169.58. Anal. Calcd for $C_{19}H_{24}F_3N_5O_4$: C, 47.07; H, 2.82; N, 11.76. Found: C, 47.07; H, 2.77; N, 11.63.

7.1.10. Photoaffinity probe bearing the diazirine photophore (4a, 5a). To a solution of **18** (20.9 mg, 43.96 μmol) in CH_2Cl_2 (1.2 ml) was slowly added TFA (1.2 ml) at 0 °C. After being stirred for 30 min the reaction mixture was evaporated. To remove of TFA, the residue was dissolved in water and concentrated under reduced pressure to provide the aminooxy compound **19**, which was used in the coupling reaction with **1b** without purification.

To a solution of **1b** (15.5 mg, 19.75 μmol) in 50% DMA/H_2O (2.0 ml) was added a solution of **19** in 50% DMA/H_2O (0.6 ml), which had preliminarily and carefully adjusted to pH 6 with 0.1 N NaOH. The progress of reaction was monitored by HPLC (Develosil ODS-UG-5 (i.d. 4.6×250 mm), 85% CH_3CN/H_2O, 1.0 ml/min, and UV 254 nm). After stirring magnetically for 36.5 h at room temperature, the reaction mixture was poured into a cold 0.01 N HCl solution, and stirring for 4 h at room temperature. The two regioisomeric (*E* and *Z*) oximes were detected by HPLC (Develosil ODS-UG-5 (i.d. 4.6×250 mm), 85% CH_3CN/H_2O, 1.0 ml/min, UV 254 nm), the *Z* isomer was the earlier elute (T_r=13 min) and the *E* isomer was the later elute (T_r=15 min). The reaction mixture was separated by short column chromatography on silica gel (Develosil ODS-10/20, CH_3CN/H_2O=1:1, then 3:1) to remove the oxiammonium salt. The fractions were concentrated, and separated by HPLC (Develosil ODS-UG-5 (i.d. 10.0×250 mm), 85% CH_3CN, 4.0 ml/min, T_r=14, 17 min) to give the pure *Z* isomer **4a** (1.3 mg, 6% in two steps) as a colorless oil, and the pure *E* isomer **5a** (6.8 mg, 31% in two steps) as a colorless oil. The total yield was in the range of 30–51% on repeated runs.

7.1.11. Compound 4a. IR (KBr) λ_{msax} 3854, 1767, 1647, 1540, 1259, 1162 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80–1.72 (17H, m), 0.80 (3H, d, *J*=6.7 Hz, 7-C*H*$_3$), 0.88 (3H, d, *J*=7.0 Hz, 13-C*H*$_3$), 0.96 (3H, d, *J*=6.0 Hz, 25-C*H*$_3$), 0.98 (3H, d, *J*=6.0 Hz, H-26), 0.98 (3H, d, *J*=6.5 Hz, 15-C*H*$_3$), 1.04 (3H, d, *J*=7.0 Hz, 3-C*H*$_3$), 1.09 (3H, d, *J*=7.0 Hz, 19-C*H*$_3$), 1.73 (3H, s, H-1), 1.82 (1H, m, H-13), 1.99 (1H, m, H-12b), 2.11 (1H, sext, *J*=5.9 Hz, H-25), 2.26 (3H, d, *J*=1.2 Hz, 5′-C*H*$_3$), 2.66 (1H, m, H-19), 2.67 (1H, dd, *J*=17.4, 4.2 Hz, H-21a), 2.77 (1H, dd, *J*=16.2, 9.8 Hz, H-2′a), 2.92 (1H, dd, *J*=16.4, 3.6 Hz, H-2′b), 2.98 (1H, dd, *J*=17.5, 8.6 Hz, H-21b), 3.17 (1H, m, H-6), 3.23 (1H, dd, *J*=10.0, 2.2 Hz, H-14), 3.27 (1H, dd, *J*=6.0, 2.0 Hz, H-23), 3.35 (1H, q, *J*=7.2 Hz, H-3), 3.44 (3H, s, 23-OC*H*$_3$), 3.49–3.62 (4H, m, H-3″, 4″), 3.72 (1H, m, H-18), 3.99 (3H, s, 7″-OC*H*$_3$), 4.36 (1H, m, H-22), 4.46 (2H, s, H-1″), 4.60–4.65 (1H, br m, 3′-OH), 5.09 (1H, dd, *J*=6.2, 6.0 Hz, H-24), 5.20 (1H, m, H-3′), 6.70 (1H, d, *J*=1.2 Hz, H-8″), 6.74 (1H, m, CON*H*CH$_2$), 6.89 (1H, ddd, *J*=8.2, 1.0, 0.5 Hz, H-10″), 8.12 (1H, m, CH$_2$N*H*COAr), 8.17 (1H, d, *J*=8.0 Hz, H-11″). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.1, 11.0, 13.6, 15.3, 16.8, 17.0, 17.9, 18.0, 19.4, 26.7, 27.2, 27.7, 28.1, 28.7, 29.4, 30.2, 30.7, 31.5, 32.3, 34.6, 34.9, 36.1, 39.0, 40.1, 40.9, 45.7, 52.4, 56.1, 59.1, 63.9, 66.5, 72.3, 74.1, 74.4, 75.0, 76.5, 80.7, 95.7, 109.3, 119.1, 122.4, 132.9, 133.9, 142.2, 142.9, 157.6, 164.8, 165.0, 165.1, 165.8, 169.5, 171.3, 215.2. ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -64.83. ESI-Q-TOF-MS Calcd for $C_{55}H_{81}F_3N_5O_{16}^+$ 1124.5630 ([M+H]$^+$). Found 1124.5548.

7.1.12. Compound 5a. IR (KBr) λ_{max} 3417, 1768, 1653, 1540, 1258, 1160 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75–1.85 (17H, m), 0.89 (3H, d, *J*=6.8 Hz, 7-C*H*$_3$), 0.87 (3H, d, *J*=7.0 Hz, 13-C*H*$_3$), 0.96 (3H, d, *J*=5.0 Hz, 25-C*H*$_3$), 0.97 (3H, d, *J*=5.0 Hz, H-26), 0.97 (3H, d, *J*=6.5 Hz, 15-C*H*$_3$), 1.02 (3H, d, *J*=7.0 Hz, 3-C*H*$_3$), 1.06 (3H, d, *J*=7.0 Hz, 19-C*H*$_3$), 1.80–1.85 (1H, m, H-13), 1.87 (3H, s, H-1), 1.95–2.00 (1H, m, H-12b), 2.11 (1H, m, H-25), 2.26 (3H, d, *J*=1.4 Hz, 5′-C*H*$_3$), 2.37 (1H, q, *J*=7.0 Hz, H-3), 2.68 (1H, dd, *J*=8.0, 7.2 Hz, H-19), 2.72 (1H, dd, *J*=17.4, 4.6 Hz, H-21a), 2.76 (1H, dd, *J*=16.0, 9.8 Hz, H-2′a), 2.90 (1H, dd, *J*=16.0, 3.5 Hz, H-2′b), 2.97 (1H, dd, *J*=17.4, 8.0 Hz, H-21b), 3.16 (1H, td, *J*=9.6, 1.2 Hz, H-6), 3.28 (1H, dd, *J*=5.4, 2.0 Hz, H-14), 3.30 (1H, d, *J*=2.5 Hz, H-23), 3.40–3.64 (6H, m, H-3″, 4″, 18-OH, 22-OH), 3.44 (3H, s, 23-OC*H*$_3$), 3.70 (1H, m, H-18), 3.99 (3H, s, 7″-OC*H*$_3$), 4.38 (1H, m, H-22), 4.45 (2H, s, H-1″), 4.77 (1H, m, 3′-OH), 5.09 (1H, t, *J*=6.2 Hz, H-24), 5.20 (1H, m, H-3′), 6.70 (1H, d, *J*=1.8 Hz, H-8″), 6.91 (1H, dd, *J*=8.4, 1.8 Hz, H-10″), 7.03

(1H, t, J=5.0 Hz, CONHCH$_2$), 8.13 (1H, m, CH$_2$NHCOAr), 8.16 (1H, d, J=8.4 Hz, H-11″). ^{13}C NMR (CDCl$_3$, 100 MHz) δ 10.1, 11.0, 11.3, 13.5, 16.8, 17.0, 17.2, 18.0, 19.4, 26.8, 27.2, 27.6, 28.1, 28.7, 29.4, 30.2, 30.3, 31.8, 35.0, 35.1, 36.1, 38.6, 39.7, 39.8, 41.0, 46.1, 52.5, 56.2, 59.1, 63.8, 66.4, 72.4, 73.4, 74.1, 74.8, 76.5, 80.7, 95.5, 109.3, 119.2, 121.9 (q, J=273.0 Hz), 122.2, 133.0, 134.0, 142.3, 142.9, 157.6, 164.3, 164.8, 165.3, 165.9, 169.4, 171.6, 215.3. ^{19}F NMR (CDCl$_3$, 376.5 MHz) δ -64.83. ESI-Q-TOF-MS Calcd for $C_{55}H_{81}F_3N_5O_{16}^+$ 1124.5630 ([M+H]$^+$). Found 1124.5658.

7.1.13. 2-(*N*-*tert*-Butoxycarbonyl-aminooxy)-*N*-(3-benzoyl-phenyl)-acetamide (21). To a solution of *N*-*tert*-butoxycarbonyl-aminooxy acetic acid (**16**, 101 mg, 0.53 mmol) in CH$_2$Cl$_2$ was added 3-aminobenzophenone (**20**, 219 mg, 1.06 mmol) and EDC·HCl (253 mg, 1.32 mmol). The mixture was stirred for 1 h at room temperature, diluted with CH$_2$Cl$_2$ and washed with 5% NaHCO$_3$ aqueous solution. The organic layer was dried over Na$_2$SO$_4$. After evaporation of the solvent, the residue was purified by column chromatography (silica gel 2.0 g, ethyl acetate/hexane=1:3, then 1:1) to give **21** (140.0 mg, 72%) as a colorless solid.

7.1.14. Compound 21. Mp 129–130 °C (as white tiny needles from ether-hexane). IR (KBr) λ_{max} 3262, 2980, 2934, 1725, 1663, 1591, 1559, 1486, 1448, 1321, 1286, 1256, 1163, 1114, 721 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.45 (9H, s, C(CH$_3$)$_3$), 4.43 (2H, s, COCH$_2$O), 7.46 (1H, dd, J=8.0, 5.5 Hz, Ar-*H*), 7.48 (2H, ddd, J=8.0, 5.5, 2.0 Hz, Ar-*H*), 7.55–7.59 (2H, m, Ar-*H*), 7.82 (2H, m, Ar-*H*), 8.01 (1H, ddd, J=8.0, 2.0, 1.0 Hz, Ar-*H*), 8.06 (1H, t, J=2.0 Hz, Ar-*H*), 8.10 (1H, s, CONH), 10.52 (1H, s, CH$_2$ONH). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 28.0, 76.6, 83.6, 121.5, 123.8, 125.7, 128.2, 128.9, 130.0, 132.4, 137.4, 137.9, 138.2, 158.5, 167.5, 169.3. Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99, N, 7.56. Found: C, 64.86; H, 5.95, N; 7.52.

7.1.15. Photoaffinity probe bearing the benzophenone photophore (6a, 7a). To a solution of **21** (12.0 mg, 32.40 μmol) in CH$_2$Cl$_2$ (0.8 ml) was slowly added TFA (0.8 ml) at 0 °C. After being stirred for 3 h, the reaction mixture was evaporated. To remove TFA, the residue was dissolved in water and concentrated under reduced pressure to provide the aminooxy compound **22**, which was used in the coupling reaction with **1b** without purification.

To a solution of **1b** (12.7 mg, 16.08 μmol) in 50% DMA/H$_2$O (0.1 ml) was added a solution of **22** in 50% DMA/H$_2$O (0.8 ml). This mixture was carefully maintained at pH 6 with 0.1 N NaOH. The progress of reaction was monitored by HPLC (Develosil ODS-UG-5 (i.d. 4.6×250 mm), 85% CH$_3$CN/H$_2$O, 1.0 ml/min, and UV 254 nm). After stirring magnetically for 48 h at room temperature, the reaction mixture was poured into a cold 0.01 N HCl solution, and stirring magnetically for 3 h at room temperature. The two regioisomeric (*E* and *Z*) oximes were detected by HPLC (Develosil ODS-UG-5 (i.d. 4.6×250 mm), 85% CH$_3$CN/H$_2$O, 1.0 ml/min, and UV 254 nm), the *Z* isomer eluted at 12 min, while the *E* isomer eluted at 14 min. The reaction mixture was separated by short column chromatography on silica gel (Develosil ODS-10/20, CH$_3$CN/H$_2$O=1:1, then 3:1) to remove the oxiammonium salt, the fractions were concentrated, and separated by HPLC (Develosil ODS-UG-5 (i.d. 10.0×250 mm), 85% CH$_3$CN/H$_2$O, 4.0 ml/min, T_r=15, 17 min) to give the pure *Z* isomer **6a** (1.6 mg, 10% in two steps) as a light yellow oil, and the pure *E* isomer **7a** (6.0 mg, 37% in two steps) as a light yellow oil. The total yield was in the range of 30–56% on repeated runs. The *Z* or *E* configurations for the above reported oximes were assessed by ^{1}H NMR spectroscopy. In the *Z* isomer **6a** the H-3 chemical shift (3.41 ppm) is down-field by 0.94 ppm in comparison with the corresponding H-3 chemical shift (2.47 ppm) for the *E* isomer **7a**. Conversely, the H-1 is more shielded (0.1 ppm) in the *Z* isomer **6a** (1.83 ppm) than the corresponding signal in the *E* isomer **7a** (1.93 ppm).

7.1.16. Compound 6a. IR (KBr) λ_{max} 3406, 2930, 1768, 1700, 1541, 1282, 1077, 987 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.79 (3H, d, J=6.8 Hz, 7-CH$_3$), 0.84–1.82 (19H, m), 0.87 (3H, d, J=7.0 Hz, 13-CH$_3$), 0.97 (3H, d, J=7.0 Hz, 25-CH$_3$), 0.97 (3H, d, J=7.0 Hz, H-26), 0.98 (3H, d, J=7.0 Hz, 15-CH$_3$), 1.09 (3H, d, J=7.1 Hz, 19-CH$_3$), 1.11 (3H, d, J=7.0 Hz, 3-CH$_3$), 1.83 (3H, s, H-1), 1.99 (1H, tt, J=10.0, 4.2 Hz, H-12b), 2.12 (1H, m, H-25), 2.26 (3H, d, J=0.8 Hz, 5′-CH$_3$), 2.54 (1H, br s, 18-OH), 2.66 (1H, m, H-19), 2.66 (1H, dd, J=17.3, 4.1 Hz, H-21a), 2.77 (1H, dd, J=16.3, 9.8 Hz, H-2′a), 2.92 (1H, dd, J=16.3, 3.2 Hz, H-2′b), 2.98 (1H, dd, J=17.5, 8.3 Hz, H-21b), 3.17 (1H, td, J=9.4, 2.5 Hz, H-6), 3.23 (1H, dd, J=10.0, 2.1 Hz, H-14), 3.27 (1H, dd, J=5.6, 2.0 Hz, H-23), 3.41 (1H, sext, J=7.0 Hz, H-3), 3.43 (3H, s, OCH$_3$), 3.70 (1H, td, J=8.0, 1.5 Hz, H-18), 4.36 (1H, m, H-22), 4.55 (1H, br s, 3′-OH), 4.59 (2H, s, H-1″), 5.09 (1H, t, J=6.0 Hz, H-24), 5.21 (1H, d, J=9.1 Hz, H-3′), 7.45 (1H, t, J=7.9 Hz, H-7″), 7.49 (1H, t, J=7.9 Hz, H-12″), 7.49 (1H, t, J=7.9 Hz, H-14″), 7.51 (1H, t, J=7.9 Hz, H-6″), 7.60 (1H, t, J=7.5 Hz, H-13″), 7.81 (1H, t, J=6.4 Hz, H-11″), 7.81 (1H, t, J=6.4 Hz, H-15″), 7.82 (1H, dd, J=2.0, 1.4 Hz, H-4″), 7.93 (1H, dd, J=7.5, 1.9 Hz, H-8″), 8.12 (1H, br s, CONHAr). ^{13}C NMR (150 MHz, CDCl$_3$) δ 10.2, 10.9, 13.7, 15.4, 16.9, 17.3, 18.0, 18.0, 19.4, 26.7, 27.3, 27.6, 28.0, 28.7, 29.5, 30.1, 30.8, 31.5, 32.5, 34.5, 34.9, 36.0, 41.0, 45.8, 52.4, 59.0, 63.9, 66.4, 72.6, 74.1, 74.4, 75.0, 76.4, 80.6, 95.7, 121.0, 123.9, 126.3, 128.3, 128.4, 129.0, 130.1, 130.1, 132.7, 137.2, 137.4, 138.4, 142.1, 143.0, 164.8, 165.8, 165.9, 168.9, 169.5, 196.2, 215.3. ESI-Q-TOF-MS calcd for $C_{56}H_{79}N_2O_{15}^+$ 1019.5480 ([M+H]$^+$). Found 1019.5478.

7.1.17. Compound 7a. IR (KBr) λ_{max} 3432, 2933, 1767, 1661, 1540, 1283, 1099, 918 cm^{-1}. ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.77 (3H, d, J=6.8 Hz, 7-CH$_3$), 0.88–1.68 (19H, m), 0.79 (3H, d, J=7.0 Hz, 13-CH$_3$), 0.96 (3H, d, J=7.0 Hz, 25-CH$_3$), 0.97 (3H, d, J=7.1 Hz, H-26), 0.97 (3H, d, J=6.5 Hz, 15-CH$_3$), 1.07 (3H, d, J=7.0 Hz, 19-CH$_3$), 1.09 (3H, d, J=7.0 Hz, 3-CH$_3$), 1.82 (1H, tt, J=13.1, 5.5 Hz, H-12b), 1.93 (3H, s, H-1), 2.11 (1H, m, H-25), 2.26 (3H, d, J=0.8 Hz, 5′-CH$_3$), 2.47 (1H, sext, J=6.9 Hz, H-3), 2.69 (1H, m, H-19), 2.75 (1H, dd, J=17.5, 4.8 Hz, H-21a), 2.76 (1H, dd, J=16.3, 9.8 Hz, H-2′a), 2.92 (1H, dd, J=16.3, 3.1 Hz, H-2′b), 2.97 (1H, dd, J=17.5, 8.3 Hz, H-21b), 3.15 (1H, t, J=9.8 Hz, H-6), 3.24 (1H, dd, J=10.0, 2.2 Hz, H-14), 3.26 (1H, br s, 18-OH), 3.28 (1H, dd, J=5.6, 2.8 Hz, H-23), 3.44 (3H, s, OCH$_3$), 3.70 (1H, td, J=8.0, 2.0 Hz, H-18), 4.38 (1H, m, H-22), 4.55 (1H, d, J=16.2 Hz, H-1″a),

4.57 (1H, d, J=16.2 Hz, H-1″b), 4.65 (1H, br s, 3′-OH), 5.10 (1H, dd, J=6.8, 6.0 Hz, H-24), 5.21 (1H, d, J=9.1 Hz, H-3′), 7.45 (1H, t, J=7.9 Hz, H-7″), 7.49 (1H, t, J=7.9 Hz, H-12″), 7.49 (1H, t, J=7.9 Hz, H-14″), 7.50 (1H, t, J=7.9 Hz, H-6″), 7.60 (1H, t, J=7.5 Hz, H-13″), 7.80 (1H, m, H-11″), 7.80 (1H, m, H-15″), 7.80 (1H, m, H-4″), 7.98 (1H, dd, J=7.8, 1.9 Hz, H-8″), 8.14 (1H, br s, CON*H*Ar). ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.1, 10.8, 11.5, 13.5, 16.8, 17.1, 18.0, 18.0, 19.4, 26.6, 27.1, 27.5, 28.0, 28.7, 29.3, 30.1, 30.1, 31.9, 35.0, 35.0, 36.0, 38.6, 41.0, 46.3, 52.3, 59.0, 63.8, 66.3, 72.6, 73.2, 74.2, 74.9, 76.4, 80.6, 95.5, 120.6, 123.5, 126.3, 128.3, 128.4, 129.0, 130.1, 130.1, 132.7, 137.2, 137.4, 138.4, 142.2, 142.9, 164.8, 165.5, 165.8, 169.3, 169.4, 196.1, 215.5. ESI-Q-TOF-MS calcd for $C_{56}H_{79}N_2O_{15}^+$ 1019.5480 ($[M+H]^+$). Found 1019.5416.

Acknowledgements

This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Technology. We are grateful to Professor K. Isono at ex-Riken Institute for supplying a crude tautomycin. We also thank Mr. S. Kitamura (analytical laboratory in this school) for elemental analyses, Mr. K. Koga for special NMR spectroscopy.

References and notes

1. Cheng, X.-C.; Kihara, T.; Kusakabe, H.; Magae, J.; Kobayashi, Y.; Fang, R.-P.; Ni, Z.-F.; Shen, Y.-C.; Ko, K.; Yamaguchi, I.; Isono, K. *J. Antibiot.* **1987**, *40*, 907–909.
2. For structure of tautomycin, see: (a) Ubukata, M.; Cheng, X.-C.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1990**, 244–246. (b) Cheng, X.-C.; Ubukata, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 809–819. (c) Ubukata, M.; Cheng, X.-C.; Isobe, M.; Isono, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 617–624.
3. Protein phosphatase type 1 (PP1) and type 2A (PP2A) are two of the four major enzymes that dephosphorylate serine/threonine residues of proteins in eukaryotic cells (a) Cohen, P. *Annu. Rev. Biochem.* **1989**, *58*, 453–508. (b) Shenolikar, S.; Nairn, A. C. *Adv. Second Messenger Phosphoprotein Res.* **1991**, *23*, 1–121.
4. Takai, A.; Sasaki, K.; Nagai, H.; Mieskes, G.; Isobe, M.; Isono, K.; Yasumoto, T. *Biochem. J.* **1995**, *306*, 657–665.
5. Goldberg, J.; Huang, H.; Kwon, Y.; Greengard, P.; Nairn, A. C.; Kuriyan, J. *Nature* **1995**, *376*, 745–753.
6. Maynes, J. T.; Bateman, K. S.; Cherney, M. M.; Das, A. K.; Luu, H. A.; Holmes, C. F. B.; James, M. N. G. *J. Biol. Chem.* **2001**, *276*, 44078–44082.
7. Kita, A.; Matsunaga, S.; Takai, A.; Kataiwa, H.; Wakimoto, T.; Fusetani, N.; Isobe, M.; Miki, K. *Structure* **2002**, *10*, 715–724.
8. For Ubukata's structure–activity investigations, see: Nishiyama, U.; Ubukata, M.; Magae, J.; Kataoka, T.; Erdodi, F.; Hartshorne, D. J.; Isono, K.; Nagai, K.; Osada, H. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 103–107.
9. For Oikawa and Ichihara's structure–activity investigations, see: (a) Kawamura, T.; Matsuzawa, S.; Mizuno, Y.; Kikuchi, K.; Oikawa, H.; Oikawa, M.; Ubukata, M.; Ichihara, A. *Biochem. Pharmacol.* **1998**, *55*, 995–1003. (b) Oikawa, H. *Curr. Med. Chem.* **2002**, *9*, 2033–2054.
10. For Isobe's structure–activity investigations, see: (a) Sugiyama, Y.; Ohtani, I. I.; Isobe, M.; Takai, A.; Ubukata, M.; Isono, K. *Bioorg. Med. Chem, Lett.* **1996**, *6*, 3–8. (b) Takai, A.; Tsuboi, K.; Koyasu, M.; Isobe, M. *Biochem. J.* **2000**, *350*, 81–88.
11. For Chamberlin's structure–activity investigations, see: (a) Liu, W.; Sheppeck, J. E., II; Colby, D. A.; Huang, H.-B.; Nairn, A. C.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1597–1600. (b) Colby, D. A.; Liu, W.; Sheppeck, J. E., II; Huang, H.-B.; Nairn, A. C.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1601–1605.
12. (a) Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63–128. (b) Shao, J.; Tam, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3893–3899.
13. Hatanaka, Y.; Hashimoto, M.; Kurihara, H.; Nakayama, H.; Kanaoka, Y. *J. Org. Chem.* **1994**, *59*, 383–387.
14. Hashimoto, M.; Kanaoka, Y.; Hatanaka, Y. *Heterocycles* **1997**, *46*, 119–122.
15. (a) Karabatsos, G. J.; Taller, R. A.; Vane, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 2327–2328. (b) Karabatsos, G. J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079–1095. (c) Karabatsos, G. J.; Taller, R. A. *Tetrahedron* **1968**, *24*, 3347–3360.
16. (a) Isobe, M.; Sugiyama, Y.; Ito, T.; Ohtani, I. I.; Toya, Y.; Nishigohri, Y.; Takai, A. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 2235–2238. (b) Sugiyama, Y.; Fujimoto, K.; Ohtani, I. I.; Takai, A.; Isobe, M. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1260–1264.
17. The corresponding bioorganic studies including the inhibitory activity for PP will be published.
18. (a) Naito, I.; Nakamura, K.; Kumagai, T.; Oku, A.; Hori, K.; Matsuda, K.; Iwamura, H. *J. Phys. Chem. A* **1999**, *103*, 8187–8192. (b) Admasu, A.; Gudmundsdóttir, A. D.; Platz, M. S.; Watt, D. S.; Kwiatkowski, S.; Crocker, P. J. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1093–1099.
19. Kurono, M.; Isobe, M. *Tetrahedron* **2003**, *59*, 9609–9617.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1781–1789
Tetrahedron

Use of diamines containing the α-phenylethyl group as chiral ligands in the asymmetric hydrosilylation of prochiral ketones

Virginia M. Mastranzo,[a,b] Leticia Quintero,[b] Cecilia Anaya de Parrodi,[a,*] Eusebio Juaristi[c,*] and Patrick J. Walsh[d,*]

[a]*Centro de Investigaciones Químico Biológicas, Universidad de las Américas-Puebla, Santa Catarina Mártir, Cholula, 72820 Puebla, Mexico*
[b]*Centro de Investigación de la Facultad de Ciencias Químicas, Universidad Autónoma de Puebla, Puebla 72570, Mexico*
[c]*Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico, D.F. 07000, Mexico*
[d]*Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, USA*

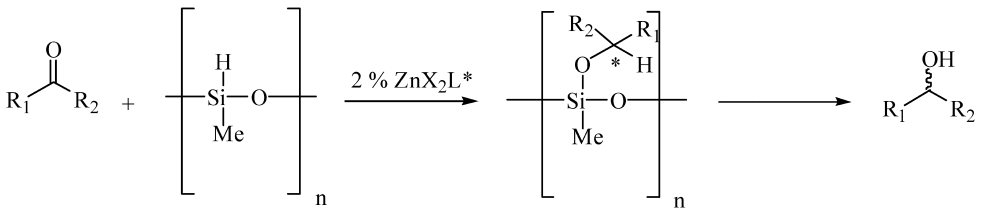
Received 18 November 2003; revised 15 December 2003; accepted 15 December 2003

Abstract—Chiral diamines **1**–**7** were used in the enantioselective hydrosilylation of prochiral aromatic and aliphatic ketones. Some of these ligands combine chiral backbones and chiral *N*,*N*′-α-phenylethyl substituents that give rise to synergistic effects between these two groups and lead to catalysts that exhibit high enantioselectivity.

1. Introduction

The catalytic reduction of prochiral ketones to secondary alcohols with high enantioselectivity is an important goal in synthetic organic chemistry. Among the most efficient catalysts for this transformation are the ruthenium-BINAP hydrogenation catalysts developed by Noyori[1] and the chiral oxazaborolidine complexes of Itsuno,[2a] Corey,[2b] and others.[2c] A practical alternative to these methodologies is the asymmetric hydrosilylation of ketones, which affords secondary alcohols upon work-up. Several catalysts promote this reaction in an enantioselective fashion.[3] In some cases, polymethylhydrosiloxane (PMHS) has been used as the hydrosilylating reagent.[4] PMHS is a coproduct of the silicone industry that is inexpensive and can be easily handled in air. PMHS has been used with chiral *ansa*-titanocene catalysts in the reduction of ketones with high enantioselectivity by the Buchwald group.[5a] Additionally, the use of copper hydride in the hydrosilylation of aryl ketones has been reported by Lipschutz with excellent results.[5b,c]

Recent work in the enantioselective hydrosilylation of ketones by Mimoun and co-workers[6] has demonstrated that an efficient and enantioselective catalyst can be prepared from zinc precursors such as diethylzinc and zinc carboxylates in combination with homochiral diamine ligands and PMHS Eq. (1). The active species in the reduction is proposed to be L*ZnH_2, where L* is the chiral bidentate ligand. From a structure-enantioselectivity study, it was found that the ligands with the stilbene diamine backbone afforded better enantioselectivity than ligands derived from *trans*-1,2-diaminocyclohexane. They also observed that the catalyst generated from *N*,*N*′-ethylene bis(1-phenylethylamine) **1** (Chart 1), gave high enantioselectivities. Their results demonstrated that ligands with chiral backbones and achiral *N*,*N*′-dialkyl groups gave similar results to ligands with achiral backbones and chiral *N*,*N*′-dialkyl groups.[6]



PMHS (1)

Keywords: Asymmetric reactions; Enantioselective hydrosilylation; Chiral ligands; Chiral auxiliaries; α-Phenylethylamine; Enantioselective reduction.
* Corresponding authors. Tel.: +2-2292067; fax: +2-2292419 (CAdP); e-mail addresses: anaya@mail.pue.udlap.mx; juaristi@chem.cinvestav.mx; pwalsh@sas.upenn.edu

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.039

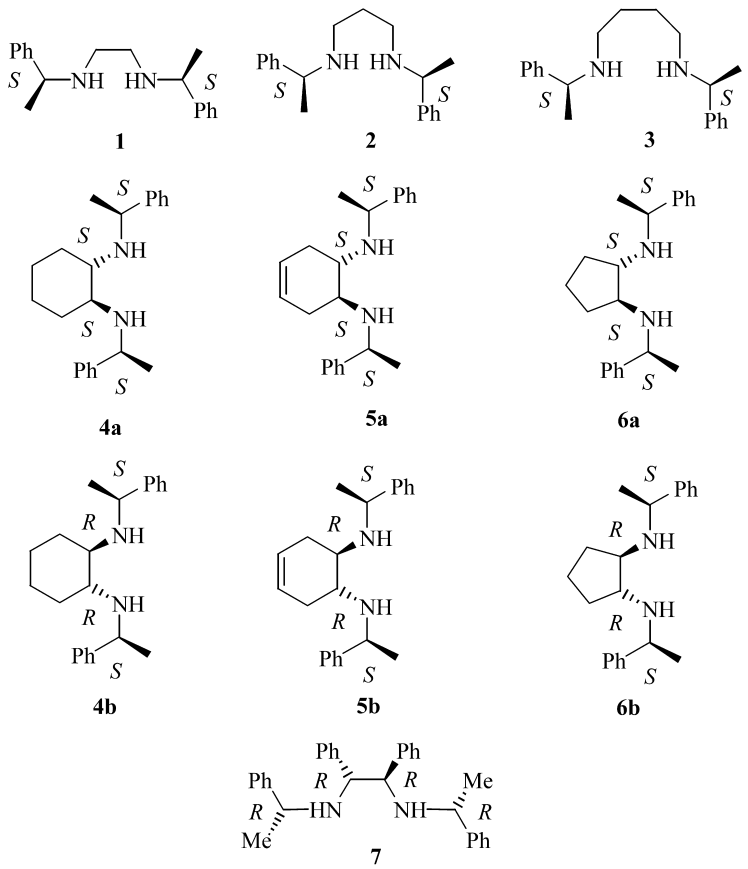


Chart 1.

Inspired by these results, we thought it would be informative to explore the structure-enantioselectivity relationship of ligands bearing both chiral backbones and chiral *N*,*N*′-dialkyl groups in the asymmetric hydrosilylation of ketones. We have, therefore, synthesized a series of such diamines and found that there is indeed a strong synergistic effect between these moieties in the catalytic asymmetric reduction of ketones.

Chiral diamines **1**–**7** (Chart 1) were selected with two considerations in mind: (1) The presence of C_2-symmetry was expected to confer a high degree of enantiotopic differentiation.[7] (2) Incorporation of the α-phenylethylamino group was deemed attractive as chiral moieties, because they have proven quite effective in asymmetric synthesis.[8]

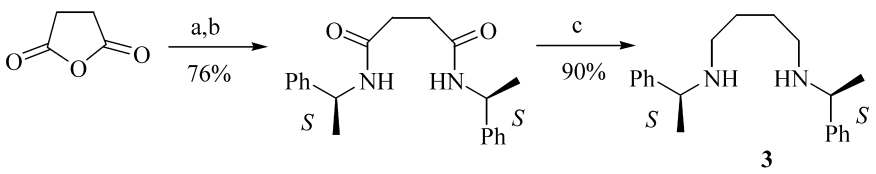
2. Results and discussion

2.1. Synthesis of chiral diamines 1–7

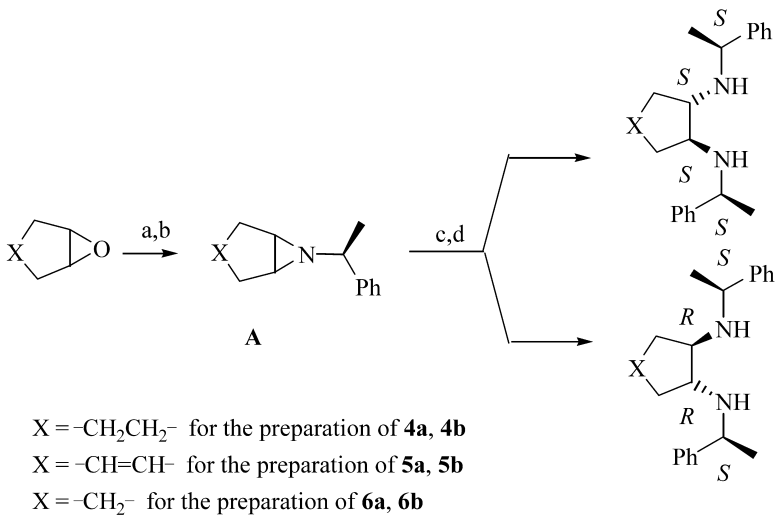
Convenient procedures for the preparation of *N*,*N*′-ethylene bis(1-phenylethylamine) **1** are available in the literature.[9] Higher homolog **2**[9b] was prepared according to our procedure.[10] The synthesis of diamine **3** was prepared from succinic acid as shown in Scheme 1.[11]

trans-Cyclohexane-1,2-diamines **4a** and **4b**, as well as unsaturated analogs **5a** and **5b** and *trans*-cyclopentane 1,2-diamines **6a** and **6b** were prepared from the appropriate epoxide precursors, via chiral aziridine intermediates **A**, as outlined in Scheme 2.[12b] The major products were **4a**, **5a** and **6a**, and the diastereomeric ratios were 2:1 in all cases.

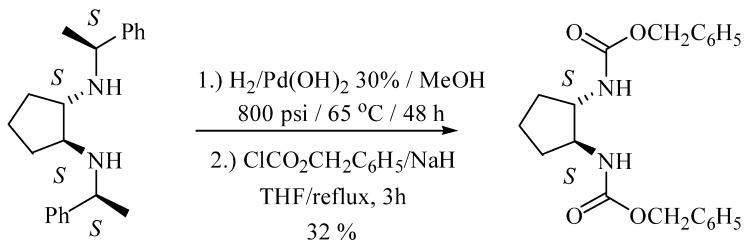
The separation of the diastereomeric pairs **4a/4b**, **5a/5b**, and **6a/6b** was accomplished by flash chromatography [hexane–EtOAc (12:1)]. The assignment of configuration of cyclopentane diamines **6a** (all *S* configurations) and **6b** [(*S*,*R*,*R*,*S*) isomer] was achieved by chemical correlation of **6a** with the known[10] *trans*-diamide (*S*,*S*)-**8** (Scheme 3). Likewise, the configuration of cyclohexene diamines **5a** and **5b** was possible via chemical correlation with **4a** and **4b**, respectively, by simple hydrogenation of the double bond (Scheme 4).



Scheme 1. Reagents and conditions: (a) (*S*)-$CH_3CH(Ph)NH_2$/Et_2O/rt/12 h. (b) (*S*)-$CH_3CH(Ph)NH_2$DCC/DMAP/CH_2Cl_2/rt/16 h. (c) $LiAlH_4$/THF/reflux/48 h.

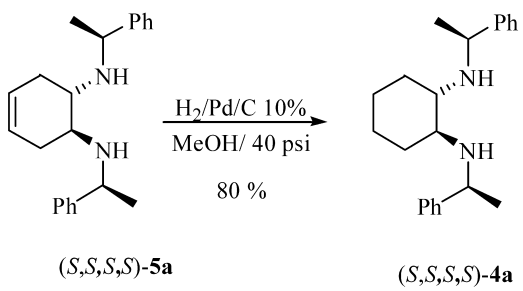


Scheme 2. Reagents and conditions: (a) (*S*)-α-Phenylethylamine/$LiClO_4$/CH_3CN/reflux/18 h. (b) $CH_3SO_2Cl/Et_3N/CH_2Cl_2$/rt/24 h. (c) (*S*)-α-Phenylethylamine/$LiClO_4$/CH_3CN/reflux/50 h. (d) Flash chromatography [hexane–EtOAc (12:1)].



Scheme 3.

Finally, the preparation of (*R*,*R*,*R*,*R*)-*N*,*N*′-di(α-phenylethyl)-1,2-diphenyl-1,2-ethylenediamine **7**[14a] was accomplished following the procedure described in the literature, which involves the stereoselective addition of phenylmagnesium bromide to the chiral bis-imine,[14b,c] derived from glyoxal and 2 equiv. of (*R*)-α-phenylethylamine.



Scheme 4.

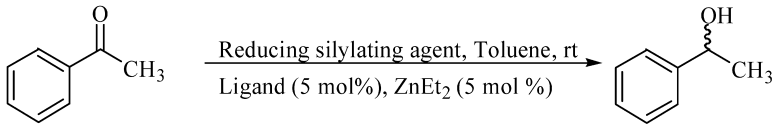
3. Enantioselective reduction of aromatic and aliphatic prochiral ketones

According to the general procedures described for the enantioselective reduction of prochiral ketones,[6] acetophenone was treated with 5 mol% of diethylzinc (1.0 M in hexanes), and 5 mol% of the chiral ligand in toluene solvent at ambient temperature in the presence of 2 equiv. of PMHS for 24 h (method A) or 1.5 equiv. of $(EtO)_3SiH$ for 18 h (method B). The results are collected in Table 1.

Examination of Table 1 indicates that highest enantioselection is achieved with chiral ligands **4a**, **5a** and **6a** where the α-phenylethylamino chiral groups are bonded to a fairly rigid cycloalkane (or cycloalkene in the case of **5a**) framework. As can be appreciated in entries 4, 5, 7, 8, and 11 in Table 1, the use of ligands **4a**, **5a** and **6a** (all *S*-configuration) afforded consistently high enantioselectivities (80–84%). In contrast, ligands **4b**, **5b** and **6b** [(*S*,*R*,*R*,*S*) configuration] led to reduced carbinol products of low enantiopurity (10–29%). These results demonstrate that the stereogenic centers of phenylethyl groups are important in the enantioselectivity determining step.[15]

Whereas ethylene diamine derivative **1** induces high enantioselectivity in the reduction process (79% ee, entry 1 in Table 1), higher homologs **2** and **3** proved to be inefficient ligands (5% ee and 17% ee, respectively). It has been known since early studies by Knowles and coworkers[16] that chiral ligands with stereogenic centers directly attached to the metal center can exhibit excellent enantioselectivities. We believe that a key factor in the control of enantioselectivity in the asymmetric hydrosilylation of ketones is the stereochemistry of coordination of the amino groups to the zinc center. Upon coordination nitrogen inversion ceases and the bound nitrogens become stereogenic centers. It is possible that the ligand **1** binds to the metal with high diastereoselectivity and that the chiral phenylethyl groups and stereogenic nitrogens contribute constructively to the enantioselectivity of the catalyst. In contrast, ligands **2** and **3**, with longer, more flexible

Table 1. Enantioselective reduction of acetophenone in the presence of diethylzinc and a chiral ligand



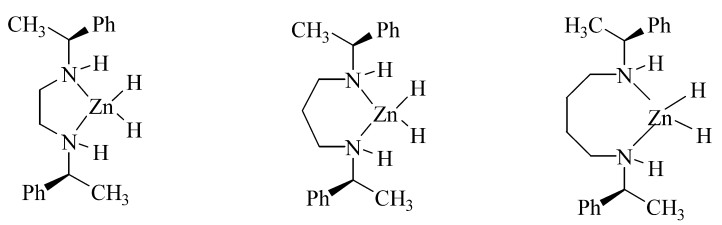
Entry	Chiral ligand	Reducing silylating agent[a]	Reaction time (h)	Yield (%)	ee (%)[b]
1	**1**	PMHS	24	100	79 (*R*)[c]
2	**2**	PMHS	24	85	5 (*R*)
3	**3**	PMHS	24	20	17 (*R*)
4	**4a**	$(EtO)_3SiH$	18	100	80 (*R*)
5	**4a**	PMHS	24	90	83 (*R*)
6	**4b**	PMHS	24	40	18 (*S*)
7	**5a**	$(EtO)_3SiH$	18	99	84 (*R*)
8	**5a**	PMHS	24	90	82 (*R*)
9	**5b**	$(EtO)_3SiH$	18	100	29 (*R*)
10	**5b**	PMHS	24	40	10 (*R*)
11	**6a**	PMHS	24	95	83 (*R*)
12	**6b**	PMHS	24	50	21 (*S*)
13	**7**	PMHS	24	18	2 (*R*)

[a] Experiments were carried out using 1.0 equiv. of acetophenone and 2.0 equiv. of PMHS or 1.5 equiv. of $(EtO)_3SiH$.
[b] The enantiomeric excess was determined by HPLC with a Chiralcel OD column.
[c] Mimoun et al.[6] reported 75% ee in this reaction using 2 mol% zinc-ligand catalyst, in the presence of 1.1 equiv. of PMHS.

backbones, may permit formation of diastereomeric catalysts (Chart 2) that are less enantioselective. The magnitude of the difference in enantioselectivity between the match and mismatched diastereoisomers is surprisingly large, being 101% (**4a/4b**), 92% (**5a/5b**), and 104% (**6a/6b**). We believe these results indicate that the enantioselectivities of the catalysts are highly sensitive to their chiral environments. It is also noteworthy that the mismatched ligands resulted in much slower catalysts. Although catalysts derived from **4a**, **5a** and **6a** proceeds to at least 90% yield in 24 h, those using catalysts prepared from **4b**, **5b** and **6b** did not exceed 50% in this time. It is also clear that the difference in enantioselectivities between the catalysts derived from (*S*,*S*,*S*,*S*)- and (*R*,*S*,*S*,*R*)-configured ligands arises from a mismatched combination between the stereogenic nitrogens and the phenylethyl groups. Amino groups that become stereochemically fixed on coordination have been shown to have a powerful impact on enantioselectivity in zinc(diamine)-based catalysts.[17]

It is also informative to compare the enantioselectivities of our matched and mismatched ligands with a ligand that has chirality in the diamine backbone and achiral *N*,*N*′-dialkyl groups. In the reduction of acetophenone with matched catalyst derived from **4a** and mismatched catalyst derived from **4b** the enantioselectivities and configurations were 83% (*R*) and 18% (*S*), respectively. The previously reported ligand (*R*,*R*)-*N*,*N*′-bis(1-naphthylenemethyl)-*trans*-1,2-cyclohexanediamine gave 70% enantioselectivity with acetophenone under the same conditions. These results suggest that the synergistic effects of the chiral *N*,*N*′-α-phenylethyl groups with the diamine backbone in **4a** can raise the level of enantioselectivity of the catalyst over that of a similar catalysts bearing only achiral *N*,*N*′-dialkyl groups. The poor stereoinduction achieved with ligand **7** (all *R*-configured) show again that a proper combination of stereogenic center on the α-phenylethylamino groups and the ligand's backbone is essential for good enantiofacial differentiation in this system.

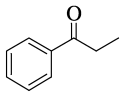
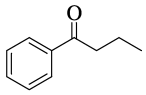
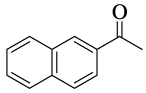
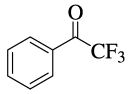
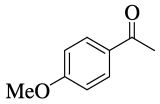
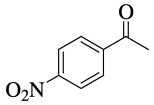
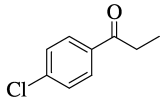
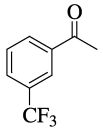
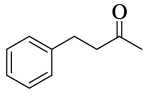
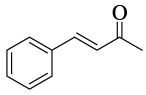
Since there is not a significant difference in the enantioselectivity of acetophenone reduction with diamines **4a**, **5a** and **6a** (Table 1), and **4a** can be prepared more economically, the use of diamine **4a** in the enantioselective reduction of other prochiral ketones with PMHS in the presence of $ZnEt_2$ has been explored (Table 2). Prochiral ketones were treated with 2 mol% diethylzinc (1.0 M in toluene), and 2 mol% of the chiral ligand in toluene solvent at ambient temperature and in the presence of 2 equiv. of PMHS for 24 h (method C). From Table 2, it can be seen that with aryl alkyl ketones better enantioselectivities were obtained with longer alkyl groups, that is, *n*-Pr>Et>Me (Table 2 entries 1 and 2, Table 1 entry 5). The enantioselectivity with β-acetonaphthone gave similar results to



1·ZnH$_2$ **2·ZnH$_2$** **3·ZnH$_2$**

Chart 2.

Table 2. Enantioselective reduction of prochiral ketones by PMHS in the presence of $ZnEt_2$ (2 mmol%) and diamine **4a** (2 mmol%)[a]

Entry	Ketones	Yield (%)	ee (%)
1		75	84 (*R*)[b]
2		80	89 (*R*)[b]
3		72	84 (*R*)[b]
4		95	19 (*S*)[c]
5		87	11 (*R*)[c]
6		80	68 (*R*)[b]
7		81	84 (*R*)[c]
8		95	82 (*R*)[c]
9		67	15 (*R*)[b]
10		70	84 (*R*)[b]

[a] Experiments were carried out using 1.0 equiv. of prochiral ketone and 2.0 equiv. of PMHS.
[b] The enantiomeric excess were determined by HPLC after purification on silica gel (hexane–ethyl acetate, 10:1).
[c] The enantiomeric excess were determined by GC on a β-Dex column.

acetophenone (entry 3). However, the enantioselective reduction of trifluoroacetophenone proceeded with low selectivity due to the electronic effect of the trifluoromethyl group (entry 4). Additionally, the reduction of prochiral ketones with substituents on the aromatic ring was performed. Enantioselectivity was significantly diminished when *p*-MeO and *p*-NO_2 group were present (entries 5 and 6). Nevertheless, *p*-Cl or *m*-CF_3-acetophenones were very good substrates, exhibiting (82–84% ee, entries 7 and 8). To examine the effect of substrate unsaturation on the catalyst enantioselectivity, we examined the use of 4-phenyl-2-butanone and *trans*-4-phenyl-3-buten-2-one (entries 9 and 10). The saturated derivative gave low enantioselectivity (15%). This is not surprising, given that the lone pair environments of the substrate are so similar and the catalyst cannot readily differentiate between them. On the other hand, the unsaturated substrate give very good enantioselectivity (84%) indicating the importance of the double bond in this asymmetric reduction.

In conclusion, chiral diamines **1**–**7** were used in the enantioselective hydrosilylation of prochiral acetophenone. Diamines **4a**, **5a**, and **6a** combine chiral backbones and chiral *N*,*N*′-α-phenylethyl substituents that give rise to synergistic effect between these two groups and lead to catalysts that exhibit high enantioselectivities. The enantioselectivities of prochiral aromatic ketones in the presence of **4a** were found to range from poor with dialkyl ketones to very good with acetophenone derivatives and α,β-unsaturated ketones.

4. Experimental

4.1. General

Melting points were determined on a Fischer Jones apparatus and are uncorrected. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were measured on a Varian Mercury spectrometer, with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm) and coupling constants *J* are given in Hz. Optical rotations $[\alpha]_D$ were measured at ambient temperature in 0.1 dm cells, using a Perkin–Elmer 241 spectrophotometer. IR-FT spectra were recorded on a BioRad instrument. Mass spectra were recorded on a Saturn Varian GC-mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. All reagents were purchased from Aldrich Chemical Co.

4.1.1. *N*,*N*′-Bis[(*S*)-α-phenylethyl]propane-1,3-diamine, 2. In a dry two-necked flask fitted with an addition funnel, condenser, and magnetic stirrer was placed (*S*)-α-phenylethylamine (3.3 mL, 26 mmol) under a nitrogen atmosphere. The reaction flask was heated to 100 °C with stirring followed by slow addition of 2.0 g (13.0 mmol) of freshly prepared 1-mesylate-3-chloro-propane (prepared from 3-chloro-propanol) over 2 h. Stirring of the mixture was continued for 16 h at 100 °C, followed by cooling to 60 °C, and addition of 2 mL of saturated aqueous KOH. The resulting mixture was allowed to cool to ambient temperature and extracted with three 20 mL portions of CH_2Cl_2. The combined organic layers were washed with brine and dried over anh. Na_2SO_4, and concentrated in a rotary evaporator. The excess (*S*)-α-phenylethylamine was removed by vacuum distillation (40 °C/5 mm Hg) affording the desired product as a colorless liquid 1.3 g (50% yield). $[\alpha]_D=-64.6$ (c=1.1, $CHCl_3$); $[\alpha]_D=-66.3$ (c=0.55, $CHCl_3$).[9b] ^{1}H NMR ($CDCl_3$) δ: 1.3 (m, 2H), 1.4 (d, 6H, J=7 Hz), 2.1 (m, 2H), 3.7 (q, 1H, J=7 Hz), 7.2–7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 30.3, 46.4, 58.4, 126.5, 126.7, 128.3, 145.7.

4.1.2. *N*,*N*′-Bis[(*S*)-α-phenylethyl]butane-1,4-diamine, 3.[11] Succinic anhydride 0.7 g (7.0 mmol) was dissolved in 10 mL of diethyl ether at rt and a solution of (*S*)-α-phenylethylamine (0.90 mL, 7.0 mmol) in 2 mL of diethyl ether was added dropwise over 10 min with stirring. The mixture was stirred overnight at rt. The product was purified

by column chromatography [hexane–EtOAc (1:1)] and isolated as a white solid (1.4 g, 95% yield), mp=102–103 °C, $[\alpha]_D=-86.6$ (c=1.0, CH_3OH). ^1H NMR (CD_3OD) δ: 1.4 (d, 3H, J=6.6 Hz), 2.4 (m, 2H), 2.6 (m, 2H), 5.1 (q, 1H, J=6.6 Hz), 6.4 (m, 1H), 7.3 (m, 5H), 10.5 (b, 1H). ^{13}C NMR (CD_3OD) δ: 21.8, 29.7, 30.7, 49.2, 126.1, 127.4, 126.7, 142.8, 171.5, 176.6.[11a]

To a stirred solution of *N*-(*S*)-α-phenylethylsuccinamidic acid (0.44 mg, 2.1 mmol) in anhydrous CH_2Cl_2 (20 mL) under nitrogen at 0 °C was added 4-dimethylaminopyridine (10.3 g, 2.1 mmol), and 1,3-dicyclohexylcarbodiimide (10.4 g, 2.1 mmol). Then, (*S*)-α-phenylethylamine (0.27 mL, 2.1 mmol) was added. The reaction mixture was stirred at rt over 16 h, and filtered to remove the white precipitate. The filtrate was extracted with water and CH_2Cl_2 (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography [hexane–EtOAc (4:1)]. (1*S*,1′*S*)-*N*,*N*′-Bis-(α-phenylethyl)-1,4-succinil-diamide was obtained as a colorless solid (0.58 g, 80% yield), mp 206–207 °C, $[\alpha]_D=66.9$ (c=1.0, CH_3OH). ^1H NMR (CD_3OD) δ: 1.4 (d, 6H, J=7.0 Hz), 2.5 (m, 4H), 4.8 (q, 2H, J=7.0 Hz), 7.2–7.3 (m, 10H). ^{13}C NMR (CD_3OD) δ: 21.4, 31.0, 48.9, 125.9, 126.8, 128.3, 144.0, 172.4. MS (*m*/*z*): 42, 77, 195, 120 (base peak), 160, 188, 204, 221, 281, 303, 324.[11a]

A solution of (1*S*,1′*S*)-*N*,*N*′-bis-(α-phenylethyl)-1,4-succinildiamide (0.23 g, 0.70 mmol) in THF (2 mL) was added slowly to a vigorously stirred suspension of $LiAlH_4$ (0.13 g, 3.5 mmol) in THF (10 mL). The resulting mixture was refluxed over 48 h, and quenched by careful addition of an aqueous 10% NaOH solution (10 mL). The mixture was stirred vigorously for 30 min and filtered. The filtrate was concentrated, dissolved in CH_2Cl_2 (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography [hexanes–EtOAc (1:1)]. *N*,*N*′-Bis[(*S*)-α-phenylethyl]butane-1,4-diamine, **3**, was obtained as a colorless liquid (0.19 g, 90% yield), $[\alpha]_D=-67.5$ (c=1.0, $CHCl_3$), (*R*,*R*), $[\alpha]_D^{lit.}=+60$ (c=1.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.2 (s, 2H), 1.6 (d, 6H, J=6.6 Hz), 1.7 (m, 2H), 2.4 (m, 4H), 3.7 (q, 2H, J=6.6 Hz), 4.5 (b, 2H), 7.2–7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 23.2, 27.0, 46.9, 58.2, 126.7, 127.3, 128.6, 143.8.[11b]

4.1.3. (1*S*,2*S*,1′*S*,1″*S*)- and (1*R*,2*R*,1′*S*,1″*S*)-*N*,*N*′-Di(α-phenylethyl)-4-cyclohexene-1,2-diamines, 5a and 5b. Diamines **5a** and **5b** were prepared following the general procedure. The diastereomeric mixture of β-aminoalcohols were prepared from 1,4-cyclohexadiene monoxide (98% yield).[12a] The crude mixture was used immediately for the synthesis of 4-cyclohexen-1-aziridine following the literature procedure.[10] The product was obtained as a colorless liquid, 80% yield, after purification by flash chromatography [hexanes–ethyl acetate (30:1)], $[\alpha]_D=-90.0$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.4 (d, 3H, J=7 Hz), 1.6–1.8 (m, 2H), 2.2–2.4 (m, 4H), 2.6 (q, 1H, J=7 Hz), 5.5 (s, 2H), 7.2–7.5 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.2, 23.2, 23.6, 35.1, 36.4, 68.4, 121.3, 121.7, 125.1, 125.2, 126.6, 143.6. MS (*m*/*z*): 39, 41, 55, 67, 77, 79, 95, 96, 105, 120, 136, 154, 184, 198, 200 (M^++H). HRMS (FAB+) calcd for $C_{14}H_{17}N_1$ (M^++H) 200.1439 found 200.1446.

After purification, the aziridine was used to obtain the 1,2-diamines, which were separated by flash chromatography [hexanes–ethyl acetate (12:1)].

1,2-Diamine **5a** dihydrochloride. White crystals, mp 177–178 °C. Anal. calcd $C_{22}H_{28}N_2{\cdot}2HCl{\cdot}H_2O$: C 64.22%, H 7.84%; found C 64.55%, H 7.65%.

*Free 1,2-diamine (1S,2S,1′S,1″S)-**5a***. The main product is the *all-S* yielding 55%, $[\alpha]_D=+36.2$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.3 (d, 6H, J=6 Hz), 1.7–1.8 (m, 4H), 2.2 (d, 2H), 2.6 (t, 2H), 3.8 (q, 2H, J=6 Hz), 5.4 (s, 2H), 7.1–7.3 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 32.5, 55.3, 56.5, 125.1, 126.7, 126.8, 128.4, 147.2.

1,2-Diamine **5b** dihydrochloride. White crystals, mp 240 °C. MS (*m*/*z*): 42, 79, 82, 105 (base peak), 120, 134, 161, 187, 201, 217, 266, 305, 321, 322 (M^+).

*Free 1,2-diamine (1R,2R,1′S,1″S)-**5b***. 18% yield, $[\alpha]_D=-75.0$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.3 (d, 6H, J=6 Hz), 1.6–1.8 (m 4H), 1.9 (s, 1H), 2.2–2.5 (m, 3H), 3.9 (q, 2H, J=6 Hz), 5.5 (s, 2H), 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 25.6, 31.7, 53.9, 54.6, 124.8, 126.5, 126.6, 128.3, 145.7. HRMS (FAB+) calcd for $C_{22}H_{28}N_2$ (M^++H) 321.2331; found 321.2332.

4.1.4. (1*S*,2*S*,1′*S*,1″*S*)- and (1*R*,2*R*,1′*S*,1″*S*)-*N*,*N*′-Di(α-phenylethyl)cyclopentane-1,2-diamines, 6a and 6b. Following the general procedure, the diastereomeric mixture of β-aminoalcohols was prepared from cyclopentene oxide, affording a yellow liquid (98% yield). Immediately, the mixture was used to prepare the *N*-[(*S*)-α-phenylethyl]-cyclopenteneaziridine. The crude product was purified by flash chromatography [hexanes–ethyl acetate (30:1)] to provide the aziridine (1.5 g, 80.0% yield) as a yellow liquid, $[\alpha]_D=-10.5$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.3 (d, 3H, J=7 Hz), 1.2–1.4 (m, 4H), 1.7–2.1 (m, 4H), 2.5 (q, 1H, J=7 Hz), 7.1–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 21.3, 23.5, 27.4, 27.8, 44.5, 45.2, 66.8, 126.4, 126.0, 128.0, 145.8. MS (*m*/*z*): 42, 53, 55, 68, 83, 91, 105 (base peak), 119, 130, 143, 144, 158, 172, 187 (M^+). HRMS (FAB+) calcd for $C_{13}H_{17}N_1$ (M^++H) 188.1439; found 188.1442.

The aziridine was then used to obtain the 1,2-diamines, which were separated by flash chromatography [hexanes–ethyl acetate (12:1)].

*Free 1,2-diamine (1S,2S,1′S,1″S)-**6a***. The main product is the *all-S* yielding 55%, $[\alpha]_D=+63.1$ (c=1.0, $CHCl_3$). ^1H NMR δ: 1.1 (m, 2H), 1.3 (d, 6H, J=6 Hz), 1.5 (m, 2H), 1.7 (m, 2H), 2.0 (broad, 2H), 2.7 (t, 2H), 3.8 (q, 2H, J=6 Hz), 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 21.1, 24.1, 31.5, 57.0, 63.6, 126.6, 126.7, 128.2, 146.4. IR (cm^{-1}) 3100, 2954–2862, 1450.

1,2-Diamine **6a** dihydrochloride. White crystals, mp 230–232 °C. MS (*m*/*z*): 308, 208, 189, 160, 120, 105 (base peak), 79, 56. Anal. calcd $C_{21}H_{28}N_2{\cdot}2HCl{\cdot}H_2O$: C 63.14%, H 8.07%; found C 62.92%, H 8.19%.

*Free 1,2-diamine (1R,2R,1′S,1″S)-**6b***. 22% yield, $[\alpha]_D=-83.4$ (c=1.0, $CHCl_3$). ^1H NMR δ: 1.1 (m, 2H),

1.3 (d, 6H, J=6 Hz), 1.5 (m 2H), 1.9 (m, 4H), 2.4 (t, 2H), 3.7 (q, 2H, J=6 Hz), 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 21.0, 25.5, 30.3, 56.1, 62.2, 126.4, 126.5, 128.1, 146.1. MS (m/z): 27, 41, 43, 55, 77, 91, 105, 120, 136, 154, 160, 187, 188, 203, 224, 231, 252, 267, 289, 309 (M^++1). HRMS (FAB+) calcd for $C_{21}H_{28}N_2$ (M^++H) 309.2331; found 309.2332.

1,2-Diamine **6b** dihydrochloride. White crystals, mp 240–243 °C.

4.1.5. (1*R*,2*R*,1′*R*,1″*R*)-*N*,*N*′-Di(α-phenylethyl)-1,2-diphenyl-1,2-ethylenediamine, 7. The *N*,*N*′-bis-[(*R*)-1-phenylethyl]-ethanediimine was prepared from 40% aqueous glyoxal and (*R*)-α-phenylethylamine (2 equiv.) following the reported procedure.[14b]

^{1}H NMR δ: 1.5 (d, 6H, J=6.5 Hz), 4.4 (q, 2H, J=6.5 Hz), 7.3 (m, 10H), 8.0 (s, 2H). ^{13}C NMR δ: 23.9, 69.6, 126.6, 127.2, 128.5, 160.6.[13c]

To a stirred solution of *N*,*N*′-bis-[(*R*)-1-phenylethyl]-ethanediimine (170 mg, 0.64 mmol) in Et_2O (3 mL) at −70 °C under a nitrogen atmosphere was added PhMgBr (2.57 mL of a 2 M solution in THF) over 10 min. A white precipitate formed immediately, and the mixture was then allowed to warm to rt over a period of 5 h. The mixture was then cooled to 0 °C, quenched by the addition of a saturated aqueous solution of NH_4Cl, and the organic product extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, the solvent removed under reduced pressure, and the residue was purified by column chromatography [hexanes–EtOAc (10:1)] to yield a yellowish oil 76 mg, 45% yield, $[\alpha]_D$=+190.0 (c=1.0, $CHCl_3$), 93% ee, $[\alpha]_D$=+205.0 (c=0.7, $CHCl_3$).[14a] ^{1}H NMR δ: 1.2 (d, 6H, J=6.6 Hz), 2.4 (broad, 2H), 3.4 (s, 2H), 3.5 (q, 2H, J=6.6 Hz), 6.9–7.4 (m, 20H). ^{13}C NMR δ: 25.2, 54.9, 65.7, 126.8, 127.7, 127.8, 128.20, 128.2, 141.5, 141.5.[14a]

4.1.6. (1*S*,2*S*)-*N*,*N*′-Cyclopentane-1,2-dibenzyldicarbamate, (*S*,*S*)-8. The hydrogenation flask was rinsed with methanol and 30 mol% palladium hydroxide was added followed by **5a** (100 mg, 0.3 mmol) in methanol (15 mL). The reaction vessel was purged three times with nitrogen, three times with hydrogen, pressurized with 800 psi of hydrogen, and heated with stirring to 60 °C for 48 h. After completion of the reduction the catalyst was filtered over celite and the solvent was removed in vacuo.

The reaction mixture was dissolved in THF (2 mL). NaH (14.4 mg, 0.6 mmol) and benzyl chloroformate (0.086 mL, 0.6 mmol) were added and the mixture was refluxed for 3 h. The resulting solution was extracted with CH_2Cl_2 (3×20 mL), dried, and evaporated under reduced pressure. The product was purified by flash chromatography [EtOAc–hexanes (1:10)] to afford an oil (35 mg, 32% yield), $[\alpha]_D$=+8.1 (c=1.75, $CHCl_3$), ee=69%. [mp=147–149 °C, $[\alpha]_D$=+10.2 (c=0.47, $CHCl_3$), ee=87%]. ^{1}H NMR ($CDCl_3$) δ: 1.4 (m, 2H), 1.7 (m, 2H), 2.2 (m, 2H), 3.7 (m, 2H), 4.9 (m, 2H, NH), 5.1 (m, 4H), 7.3 (s, 10H). ^{13}C NMR ($CDCl_3$) δ: 19.1, 28.6, 54.4, 66.3, 126.3, 127.7, 128.4, 136.1, 156.3.[13]

4.2. Enantioselective reduction of prochiral ketones. General procedure

Method A. In a Schlenk flask $ZnEt_2$ (0.08 mL, 1 M in hexanes, 0.082 mmol) and chiral ligand (0.082 mmol) were dissolved in 1 mL of toluene and stirred under nitrogen atmosphere for 10 min. Then 1.66 mmol of the corresponding ketone was added, and PMHS (0.13 g, 2 mmol) was added slowly to the mixture. The reaction was kept at rt for 24 h. The reaction mixture was poured on KOH 15% aqueous solution (5 mL) and extracted with CH_2Cl_2 (3 mL×3). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography on silica gel, with hexanes–EtOAc, 10:1, as eluent.

Method B. In a Schlenk flask $ZnEt_2$ (0.08 mL, 1 M in toluene, 0.082 mmol) and chiral ligand (0.082 mmol) were dissolved in 1 mL of toluene and stirred under nitrogen atmosphere for 10 min. Then 1.66 mmol of the corresponding ketone was added, and $(EtO)_3SiH$ (2 mmol) was added slowly to the mixture. The reaction was kept at rt for 18 h. The reaction mixture was poured on KOH 15% aqueous solution (5 mL) and extracted with CH_2Cl_2 (3 mL×3). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo.). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography on silica gel, with hexanes–EtOAc, 10:1, as eluent.

Method C. In a Schlenk flask $ZnEt_2$ (0.03 mL, 1 M in toluene, 0.033 mmol) and chiral diamine **4a** (0.033 mmol) were dissolved in 1 mL of toluene and stirred under nitrogen atmosphere for 10 min. Then 1.66 mmol of the corresponding ketone was added, and PMHS (0.13 g, 2 mmol) was added slowly to the mixture. The reaction was kept at rt for 24 h. The reaction mixture was poured on KOH 15% aqueous solution (5 mL). The organic layer was washed with water (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography on silica gel, with hexanes–EtOAc, 10:1, as eluent.

4.3. Conditions for the analysis and assignment of configuration of the chiral secondary alcohol products from the enantioselective reductions

Chiral capillary GC: Supelco β-Dex 120 column 30 m×0.25 mm (i.d.), 0.25 μm film. Carrier gas He. Detector FID, 270 °C. Injector 250 °C.

Chiral HPLC: Chiralcel OB or Chiralcel OD column, 254 nm UV detector.

Specific optical rotations of the secondary alcohols were measured and compared with those reported on the literature to assign configuration.[18]

The racemic alcohol products were obtained by addition of $NaBH_4$ to the ketones in MeOH. The retention times of the racemic products under the given conditions are listed below.

4.3.1. 1-Phenyl-1-ethanol. t_R=19.90 min, t_S=24.80 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). (*R*)-1-Phenyl-1-ethanol: $[\alpha]_D^{lit.}$=+33.0 (*c*=1, $CHCH_3$).[18a]

4.3.2. 1-Phenyl-1-propanol. t_R=21.47 min, t_S=29.27 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D$=+34 (*c*=1, $CHCl_3$). (*R*)-1-Phenyl-1-propanol: $[\alpha]_D^{lit.}$=+48 (*c*=1, $CHCl_3$).[18a]

4.3.3. 1-Phenyl-1-butanol. t_R=18.01 min, t_S=20.72 min (HPLC OD column, hexanes–*i*-PrOH 97:3, 0.5 mL/min). $[\alpha]_D$=+34 (*c*=1, $CHCl_3$). (*S*)-1-Phenyl-1-butanol: $[\alpha]_D^{lit.}$=−48 (*c*=1, $CHCl_3$).[18b]

4.3.4. 1-(β-Naphtyl)-ethanol. t_R=36.84 min, t_S=40.10 min (HPLC OB column, hexanes–*i*-PrOH 98:2, 0.5 mL/min). $[\alpha]_D$=+29 (*c*=1, $CHCl_3$). (*S*)-1-(β-Naphtyl)-ethanol: $[\alpha]_D^{lit.}$=−31 (*c*=1, $CHCl_3$).[18c]

4.3.5. 2,2,2-Trifluoro-1-phenyl-ethanol. t_S=14.44 min, t_R=15.85 min (GC 115 °C, 2.8 mL/min). $[\alpha]_D$=+6 (*c*=0.5, $CHCl_3$). (*S*)-2,2,2-Trifluoro-1-phenyl-ethanol: $[\alpha]_D^{lit.}$=+30.4 (*c*=1.56, $CHCl_3$).[18d]

4.3.6. 1-(*p*-Methoxyphenyl)-ethanol. t_R=61.75 min, t_S=65.6 min (GC 120 °C, 1.0 mL/min). $[\alpha]_D$=+5 (*c*=0.7, $CHCl_3$). (*S*)-1-(*p*-Methoxyphenyl)-ethanol: $[\alpha]_D^{lit.}$=−40.6 (*c*=1.12, $CHCl_3$).[18c]

4.3.7. 1-(*p*-Nitrophenyl)-ethanol. t_R=32.21 min, t_S=34.11 min (HPLC OB column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D$=+18 (*c*=1, $CHCl_3$). (*S*)-1-(*p*-Nitrophenyl)-ethanol: $[\alpha]_D^{lit.}$=−30.5 (*c*=1, $CHCl_3$).[18e]

4.3.8. 1-(*p*-Chlorophenyl)-propanol. t_R=18.38 min, t_S=19.76 min (GC 136 °C, 2.6 mL/min). $[\alpha]_D$=+23 (*c*=1.6, C_6H_6). (*S*)-1-(*p*-Chlorophenyl)-propanol: $[\alpha]_D^{lit.}$=+28.59 (*c*=5.1, C_6H_6).[18f]

4.3.9. 1-(*m*-Trifluoromethylphenyl)-ethanol. t_R=13.56 min, t_S=14.64 min (GC 115 °C, 1.6 mL/min). $[\alpha]_D$=+14 (*c*=0.9, MeOH). (*S*)-1-(*m*-Trifluoromethylphenyl)-ethanol: $[\alpha]_D^{lit.}$=−17.1 (*c*=2.92, MeOH).[18g]

4.3.10. *trans*-4-Phenyl-3-buten-2-ol. t_R=27.66 min, t_S=46.17 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D$=+27 (*c*=0.5, $CHCl_3$). (*S*)-*trans*-4-Phenyl-3-buten-2-ol: $[\alpha]_D^{lit.}$=−32.16 (*c*=5, $CHCl_3$).[18h]

4.3.11. 4-Phenyl 2-butanol. t_R=19.17 min, t_S=28.07 min (HPLC OD column, hexanes–*i*-PrOH 95:5, 0.5 mL/min). $[\alpha]_D^{lit.}$=−2.0 (*c*=0.5, $CHCl_3$). (*S*)-4-Phenyl-2-butanol: $[\alpha]_D^{lit.}$=+15.8 (*c*=1.00, $CHCl_3$).[18i]

Acknowledgements

We thank CONACyT for financial support (Project No. 39500-E and Grant No. 144937), P. J. W. thanks NIH (National Institute of General Medical Sciences) for additional support.

References and notes

1. Ohkuma, T.; Noyori, R. Hydrogenation of carbonyl compounds. *Comprehensive asymmetric catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, 1999; Vol. 1, p 199 and Refs. 8, 9, 18, 19 and 20 therein.
2. (a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, S. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Itsuno, S. In *Hydroboration of carbonyl groups. Comprehensive asymmetric catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p 267.
3. (a) For a review, see: Nishiyama, H. In *Hydrosilylation of C=O and C=N. Comprehensive asymmetric catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, p 289. (b) Fu, G.; Tao, B. *Angew. Chem., Int. Ed.* **2002**, *41*, 3892. and references cited therein. (c) Carpentier, J.-F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, 913. and references cited therein.
4. For a review, see: Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.
5. (a) Carter, M. B.; Schiott, B.; Gutiérrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667. (b) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8799. (c) Lipshutz, B. H.; Caires, C. C.; Kuipers, P.; Chrisman, W. *Org. Lett.* **2003**, *5*, 3085.
6. Mimoun, H.; de Saint Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158.
7. (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Juaristi, E. *Introduction to stereochemistry and conformational analysis*. Wiley: New York, 1991; p 208. (c) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed.* **1994**, *33*, 497. (d) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.
8. (a) Jaen, J. *Encyclopedia of reagents for organic synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 5, p 3427. (b) Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715. (c) Juaristi, E.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.
9. (a) Horner, L.; Dickerhof, L. *Liebigs Ann. Chem.* **1984**, 124. (b) Hulst, R.; de Vries, K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1995**, *5*, 699.
10. Anaya de Parrodi, C.; Moreno, G. E.; Quintero, L.; Juaristi, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2093.
11. (a) Potapov, V. M.; Koval', G. N.; Solov'eva, L. D. *J. Org. Chem. USSR* **1985**, *21*, 705. (b) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2002**, *4*, 411.
12. (a) Anaya de Parrodi, C.; Juaristi, E.; Quintero-Cortés, L. *An. Quim., Int. Ed.* **1996**, *92*, 400. (b) Anaya de Parrodi, C.; Vazquez, V.; Quintero, L.; Juaristi, E. *Synth. Commun.* **2001**, *31*, 3295.
13. Luna, A.; Alfonso, I.; Gotor, V. *Org. Lett.* **2002**, *4*, 3627.
14. (a) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391. (b) Dieck, H.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694. (c) Alvaro, G.; Grepioni, F.; Savoia, D. *J. Org. Chem.* **1997**, *62*, 4180.
15. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.
16. Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.
17. Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 6929.
18. (a) Sato, S.; Watanabe, H.; Asami, M. *Tetrahedron:*

Asymmetry **2000**, *11*, 4329. (b) Salvi, N. A.; Chattopadhyay, S. *Tetrahedron* **2001**, *57*, 2833. (c) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7490. (d) Yong, K. H.; Chong, M. *Org. Lett.* **2002**, *4*, 4139. (e) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880. (f) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (g) Naemura, K.; Murata, M.; Tanaka, R.; Yano, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 3285. (h) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (i) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1791–1801
Tetrahedron

Regioselective synthesis of substituted 1-indanols, 2,3-dihydrobenzofurans and 2,3-dihydroindoles by electrochemical radical cyclization using an arene mediator

Nobuhito Kurono,* Eiichi Honda, Fumikazu Komatsu, Kazuhiko Orito and Masao Tokuda

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, kita-ku kita13 Nishi8, Sapporo 060-8628, Japan

Received 12 November 2003; revised 13 December 2003; accepted 15 December 2003

Abstract—Electrochemical reduction of haloarenes carrying 2-(1-hydroxybut-3-enyl), 2-allyloxy or *N*-allyl-*N*-methylamino group in the presence of phenanthrene as a mediator generated the corresponding aryl radicals and gave the corresponding 5-*exo* cyclization products in good yields. Higher regio- and stereoselectivities than those of usual radical cyclization using AIBN-Bu_3SnH were achieved.

1. Introduction

Radical cyclization is a useful method for synthesizing cyclic compounds. Carbon radicals are usually generated by the reaction of organic halides with AIBN-organotin reagents such as tributyltin hydride (Bu_3SnH).[1] However, there are several drawbacks in this method, such as toxicity of tin compounds and difficulty in isolating products due to contamination of R_3SnX. Many methods[2] have been reported to overcome the drawbacks. On the other hand, electrochemical reaction is an environmentally benign method for organic synthesis since it can be carried out under mild conditions by using electrons as clean reagents. Therefore, electrochemical generation of carbon radicals from the corresponding organic halides and its use in cyclization reactions would be of synthetic importance. However, usual electrochemical reduction of organic halides gives the corresponding carbanions by their preferential two-electron reduction and, finally, gives simple reduction products.[3] Only a few methods for electrochemical generation of radicals to give cyclization products have been reported: i.e. direct electrochemical reduction of 2-halo-*N*-arylbenzamide derivatives[4] and arenediazonium salts carrying prop-3-enylamino groups[5] and electrochemical reduction of alkenyl and aryl halides using Ni(II) or Co(II) catalyst[6] and of *N*-(2-iodophenyl)-*N*-alkylcinnamides using an oxygen mediator.[7]

Recently, we developed an electrochemical method for the generation of aryl radicals from the corresponding aryl halides by the use of arene as a single electron transfer mediator and reported in a communication that these aryl radicals could be used to intramolecular cyclization reaction.[8] In this paper, we report the detailed results of the electrochemical generation of aryl radicals as well as its application to 5-*exo* radical cyclizations to give substituted 1-indanols, 2,3-dihydrobenzofurans and 2,3-dihydroindoles. We also report that these cyclizations undergo in more regio- and stereoselective manner than that of usual radical cyclizations using AIBN-Bu_3SnH. Similar electrochemical cyclization of *N*-allyl-2-chloroacetanilide using (*E*)-stilbene as an electron transfer agent was reported by Grimshaw et al.[9]

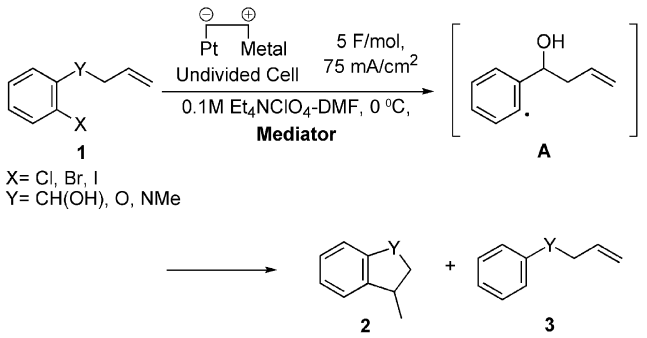
2. Results and discussion

2.1. Generation of aryl radicals

Electrochemical reduction of 1-(2-iodophenyl)-3-buten-1-ol (**1a**: X=I, Y=CH(OH)) in the presence of arene mediator generated the corresponding aryl radical (A) and gave the corresponding 5-*exo* cyclization product **2a** and simple reduction product (**3a**) (Scheme 1). This radical cyclization reaction was first examined under various conditions to optimize the reaction conditions. These results are summarized in Tables 1 and 2. Electrolysis was carried out at a constant current in an undivided cell equipped with a platinum cathode and a sacrificial anode. An anode material used as a sacrificial anode was very effective for the reactions. It was found that the use of Mg or Zn metal as an anode gave an *exo*-cyclized product **2a**, although electrolysis using a Pt anode gave **2a** only in 12% yield (Table 1). Therefore, a platinum cathode and a magnesium anode were

Keywords: Electrolysis; Radical cyclization; 5-*exo* Cyclization; Arene mediator; Regioselectivity.
* Corresponding author. Tel.: +81-11-706-6601; fax: +81-11-706-6598; e-mail address: chlono@org-mc.eng.hokudai.ac.jp

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.038



Scheme 1.

Table 1. Effect of anode materials on electrochemical cyclization of **1a**[a]

Entry	Anode (metal)	Yields (%)[b]	
		2a (*syn*:*anti*)[c]	**3a**
1	Pt	12 (2.2:1)	18
2	Zn	60 (1.7:1)	28
3	Mg	76 (2.5:1)	14

[a] Electrolysis of **1a** in 0.1 M Et_4NClO_4-DMF was carried out at 0 °C in the presence of 6 equiv. of naphthalene using a Pt cathode (75 mA/cm^2, 5 F/mol).
[b] Isolated yields.
[c] Isomer ratios of *syn* and *anti* were determined by ^{1}H NMR analysis.

used in the following electrolyses. The effect of current density was also examined, and the electrolysis of **1a** at current densities of 45, 60, 75 and 90 mA/cm^2 gave **2a** in yields of 67, 69, 76 and 58%, respectively. Electricity of 5 F/mol was needed for complete consumption of **1a**.

Effects of various mediators and their amounts on the cyclization of **1a** were also examined, and the results are summarized in Table 2. Electrolysis of **1a** in the absence of any mediator gave the cyclization product **2a** only in 11% yield (entry 1). Use of 6 equiv. of naphthalene gave **2a** in 76% yield (entry 2). When phenanthrene was used as a mediator, **2a** was obtained in 73% yield even when 2 equiv. of phenanthrene was used (entry 5). When 9,10-diphenylanthracene, 9-phenylanthracene or 9-cyanophenanthrene was used, the cyclized product was obtained in low to moderate yields (entries 8–10). Finally, all of the following electrolyses were carried out in a one-compartment cell equipped with a Pt cathode and an Mg anode in 0.1 M Et_4NClO_4-DMF solution containing a substrate and phenanthrene as a mediator at a current density of 75 mA/cm^2. Electricity of 5 F/mol was passed (Scheme 1).

2.2. Synthesis of substituted 1-indanols

The present radical cyclization by electrolysis was applied to a synthesis of substituted 1-indanols (**2**). Electrolysis of aryl iodide (**1a**), bromide (**1b**), or chloride (**1c**) in 0.1 M Et_4NClO_4-DMF containing 2.0 or 4.0 equiv. of phenanthrene at 75 mA/cm^2 using a Pt cathode and Mg anode gave the 5-*exo* cyclization product **2a** having *syn* and *anti*-isomers in yields of 62–80% (Table 3). Conventional radical cyclization of **1c** using AIBN-Bu_3SnH gave no **2a** and the starting **1c** was recovered unreacted (Table 3, entry 8). Substituted indanols **2b** and **2c**, tricyclic indanol (**2d**) were also obtained in good yields. Cyclization of **1g** having α,β-unsaturated ester group proceeded smoothly without the reduction of carbon–carbon double bond in the ester moiety. It has also been found that a higher diastereomeric ratio of *syn*- and *anti*-**2a**[10] (2.3:1) was obtained in the electrochemical cyclization of **1a** (Table 3, entries 1 and 2), although a similar cyclization using AIBN-Bu_3SnH gave *syn*- and *anti*-**2a** in a ratio of 1.4:1 (entry 3). It is not clear about the reason why the difference of diastereoselectivity appeared in the present stage. However, various reaction conditions, such as mediator compounds or equivalents of mediator, affected on the diastereomeric ratio (Table 2). Particularly, remarkable effect of anode materials on the diastereomeric ratio of the electrochemical cyclization was observed. Electrolysis of **1a** using an Mg anode gave the higher diastereomeric ratio of *syn*- and *anti*-**2a** (2.5:1) than that using a Zn anode (1.7:1) (Table 1, entries 1 and 2).

2.3. Synthesis of substituted 2,3-dihydrobenzofurans

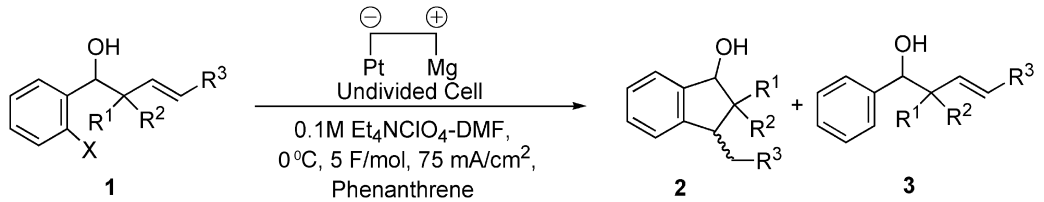
5-*exo* Cyclization of aryl radical proceeded efficiently by

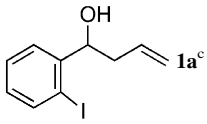
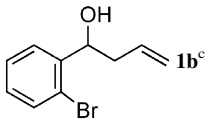
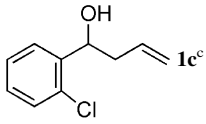
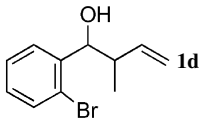
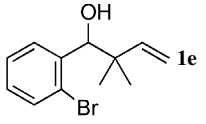
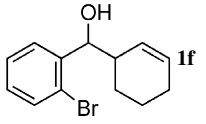
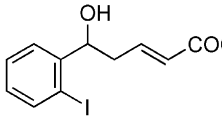
Table 2. Effects of various polyaromatic compounds on electrochemical radical cyclization of **1a**[a]

Entry	Mediator	Reduction potential[b] (V vs. Ag/Ag$^+$)	Equivalent[c]	Yield (%)[d]		
				2a (*syn*:*anti*)[e]	**3a**	Recov. **1a**
1	None	—	—	11 (1.7:1)	78	0
2	Naphthalene	−2.94	6.0	76 (2.5:1)	14	0
3	Naphthalene		2.0	59 (2.4:1)	8	18
4	Phenanthrene	−2.87	4.0	80 (2.3:1)	14	0
5	Phenanthrene		2.0	73 (2.3:1)	12	0
6	Phenanthrene		1.0	58 (2.2:1)	4	22
7	Phenanthrene		0.5	36 (2.5:1)	3	44
8	9,10-Diphenylanthracene	−2.27	2.0	48 (1.1:1)	8	23
9	9-Phenylanthracene	−2.31	2.0	30 (4.4:1)	15	21
10	9-Cyanophenanthrene	−2.22	2.0	47 (2.2:1)	4	22

[a] Electrolysis of **1a** in 0.1 M Et_4NClO_4-DMF was carried out at 0 °C with a constant current of 75 mA/cm^2 (5 F/mol) in a one-compartment cell equipped with a Pt cathode and Mg anode.
[b] Reduction potentials of **1a** and arene compounds were measured by cyclic voltammetry in 0.1 M Et_4NClO_4-DMF using Ag/Ag$^+$ reference electrode. Reduction potential of **1a** was −2.50 V vs. Ag/Ag$^+$.
[c] Equivalents of mediator to **1a**.
[d] Isolated yields.
[e] Determined by ^{1}H NMR analysis.

Table 3. Synthesis of substituted 1-indanols by electrochemical radical cyclizations



Entry	Substrate	Equiv.[a]	Yield (%)[b]	
			2 (*syn*:*anti*)	**3**
1	 **1a**[c]	2.0	64 (2.3:1)	11
2		4.0	80 (2.3:1) **2a**	14 **3a**
3		AIBN-TBTH[d]	86 (1.4:1)	
4	 **1b**[c]	2.0	64 (2.4:1) **2a**	11 **3a**
5		4.0	73 (2.4:1)	10
6	 **1c**[c]	2.0	62 (2.1:1)	10
7		4.0	69 (2.5:1) **2a**	8 **3a**
8		AIBN-TBTH[d]	No reaction	
9	 **1d**	2.0	64 (nd[e]) **2b**	11 **3b**
10		4.0	72 (nd[e])	10
11	 **1e**	2.0	61 (1.6:1) **2c**	15 **3c**
12		4.0	69 (1.5:1)	14
13	 **1f**	2.0	63 (nd[f]) **2d**	20 **3d**
14		4.0	65 (nd[f])	14
15	 **1g**	2.0	72 (1.7:1) **2e**	
16		4.0	82 (1.7:1)	

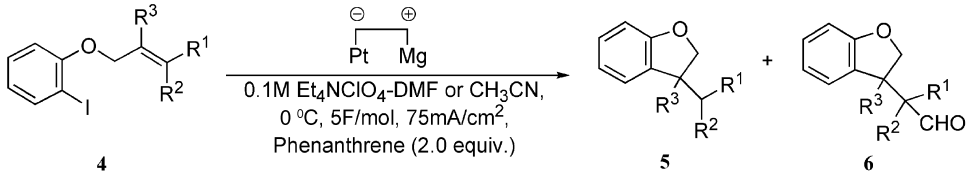
[a] Equivalents of mediator to substrate.
[b] Isolated yields. Diastereomer ratios were determined by ^{1}H NMR.
[c] Reduction peak potentials of **1a**, **1b** and **1c** were −2.50, −2.96 and −3.18 V vs. Ag/Ag$^+$, respectively.
[d] Reaction of **1a** or **1c** (0.5 mmol) was carried out in toluene (25 ml) under reflux by using 0.2 equiv. of AIBN and 1.1 equiv. of tributyltin hydride.
[e] Four diastereomers were obtained. The ratios were not determined.
[f] Two diastereomers were obtained. The ratios were estimated to be of 5.8:1 (entry 13) and 5.0:1 (entry 14), respectively, by ^{1}H NMR spectra.

using the electrochemical method and, therefore, this reaction was applied to a synthesis of benzofuran. Similar electrochemical reduction of allyl *o*-iodophenyl ethers using phenanthrene mediator gave the corresponding 2,3-dihydrobenzofurans **5a**–**d** and **6a**–**c**. The results are summarized in Table 4. The products carrying formyl group (**6a**–**c**) were also obtained in 20–27%, when DMF was used as a solvent. The use of acetonitrile as a solvent in the electrochemical cyclization of **4c** prevented the introduction of a formyl group and a cyclized product **5c** was obtained as a sole product in 72% yield (Table 4, entry 4). Similarly, electrolysis of **4d** and **4e** in acetonitrile solvent gave the cyclized products **5d** and **5e** in 64 and 69% yield, respectively, without a formation of the corresponding formylated products.

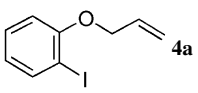
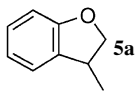
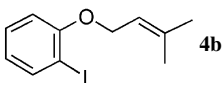
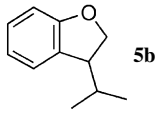
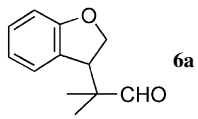
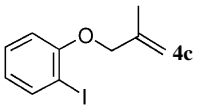
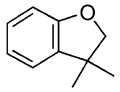
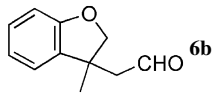
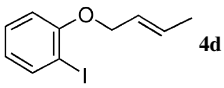
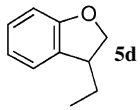
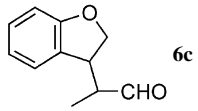
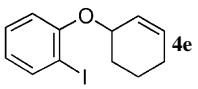
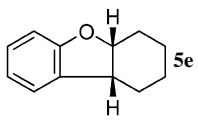
2.4. Synthesis of substituted 2,3-dihydroindoles

The results described above suggested that the electrolysis in acetonitrile gave the desired cyclization products in higher yields than those in DMF. Therefore, the following electrolyses were carried out in acetonitrile. Electrolysis of *N*-methyl-2-iodoanilines carrying various *N*-allyl substituents (**7a**–**e**) gave the corresponding substituted

Table 4. Synthesis of substituted 2,3-dihydrobenzofurans



4 **5** **6**

Entry	Solvent	Substrate	Product and yield (%)[a]		
1	DMF	 **4a**	 **5a**	41	
2	DMF	 **4b**	 **5b**	53	 **6a** 27
3	DMF	 **4c**	 **5c**	59	 **6b** 20
4	AN			72	0
5	DMF	 **4d**	 **5d**	54	 **6c** 25
6	AN			64	0
7	AN	 **4e**	 **5e**	69	

[a] Isolated yields.

2,3-dihydroindoles (**8a**–**8e**) in 48–73% yields (Table 5). It is noteworthy that the electrolysis of **7e** provided the cyclized product **8e** in 73% yield, although the electrolysis of similar substrate, *N*-cinnamyl-2-chloroacetanilide, using (*E*)-stilbene as a mediator was reported to give a low yield of the cyclization product along with a larger amount of decomposed product, 2-chloroacetanilide.[7]

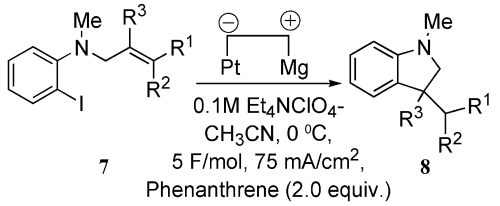
2.5. Regioselective radical cyclization

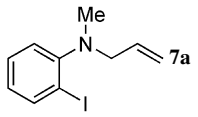
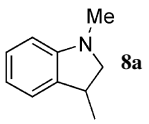
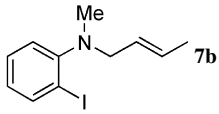
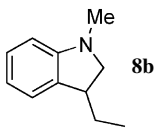
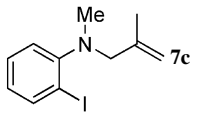
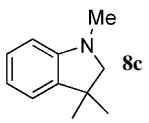
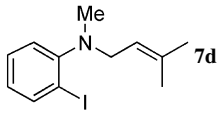
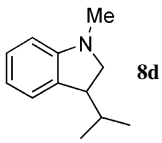
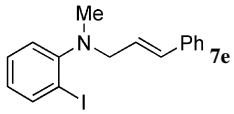
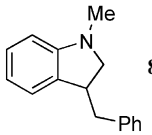
Regioselectivity of the present electrochemical cyclization is interesting from a synthetic viewpoint. In carbon radical cyclizations, 6-*endo* cyclization preferentially occurs to give a six-membered ring when there are any substituents at the C-5 position of 5-hexenyl radical.[11] Conventional radical cyclization of **1h** using AIBN-Bu_3SnH in refluxing toluene gave 5-*exo* (**2f**) and 6-*endo* cyclization products (**9a**) in a ratio of 45:55 (Table 6, entry 3). It has been reported that the ratio in the 5-*exo*/6-*endo* cyclization varied depending on the reaction conditions.[12] Effect of the reaction temperature was examined by the use of benzene as a solvent, **2f** and **9a** were obtained in the ratio of 48:52 (Table 6, entry 4). Effect of the concentration of Bu_3SnH was also examined (Table 6, entries 3, 5 and 6). These results show that the ratio of 5-*exo*/6-*endo* was slightly affected by the reaction temperature and the concentration of Bu_3SnH. When the radical cyclizaions of **4c** or **7c** using AIBN-Bu_3SnH was carried out, the corresponding 6-*endo* cyclization products (**9b** or **9c**) was also obtained (entries 5 and 7). However, the electrochemical cyclization of **1h** preferentially gave 5-*exo* cyclization product **2f** (entry 1). Similar electrochemical cyclization of 2-methallyloxyphenyl iodide (**4c**) and 2-iodo-*N*-methallyl-*N*-methylaniline (**7c**) gave exclusively 5-*exo* cyclization product **5c** and **8c**, respectively (entries 4 and 6). 5-*exo* Cyclized product **5c** was also obtained in the Ni-catalyzed electrochemical cyclization that was carried out at 20 °C.[6e,f] These higher regioselectivity are probably due to a lower reaction temperature in the present electrochemical radical cyclizations. Effect of the reaction temperature on a ratio of 5-*exo*/6-*endo* in the radical cyclization reaction has been reported by Walling et al.[13] In the present electrochemical radical cyclization, the electrolysis at higher temperature resulted in an increase of 6-*endo* cyclization although a total yield of two products was decreased (Table 6, entry 2).

2.6. Reaction pathways

One of the speculated reaction pathways are shown in Scheme 2. It has already been reported that the radical anion generated by electrochemical reduction of arene mediator can reduce aryl halides to give the corresponding aryl radicals or aryl anion.[14] In the present electrochemical reaction, aryl radicals **A** are also generated by a one-electron reduction of aryl halides with phenanthrene radical anions. This is supported by the result that a dark-blue color of the phenanthrene radical anion appeared on the surface of the platinum cathode. Two-electron reduction of aryl halides occurs preferentially in the absence of arene mediator to give the corresponding aryl anions which are protonated to

Table 5. Synthesis of substituted 2,3-dihydroindoles



Entry	Substrate	Product and yield (%)[a]
1		 60
2		 62
3		 51
4		 48
5		 73

[a] Isolated yields.

afford simple reduction products **3** (Table 2, entry 1). Dissolution of an Mg anode prevents a reoxidation of the radical anion. 5-*exo* Cyclization of **A** to give cyclized radical **B** proceeds faster than a further reduction of the aryl radicals. Carbon radicals **B** resulted from the radical cyclization are reduced to give anionic intermediates **C** that finally afford 1-indanol, 2,3-dihydrobenzofuran or 2,3-dihydroindole derivatives. Formylated products **6a–c** are obtained by an attack of the anionic intermediates **C** to DMF molecules (Table 2, entries 2, 3, 5). No formylated product was obtained in the electrolysis of **1a–h** even when DMF was used as a solvent (Table 3 and Table 6, entry 1). This is probably due to a ready protonation of anionic intermediates **C** with a hydroxy group in the starting substrates **1a–h**.

3. Conclusion

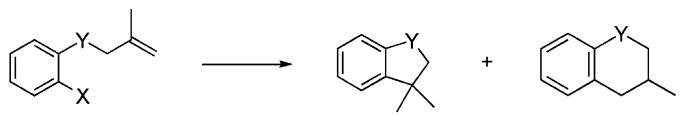
In conclusion, electrochemical reduction of halobenzenes carrying *o*-(1-hydroxy-3-butenyl), *o*-allyloxy or *o*-allylamino group in the presence of phenanthrene mediator generated the corresponding aryl radicals efficiently and gave various 5-*exo* cyclized products, substituted 1-indanols, 2,3-dihydrobenzofurans or 2,3-dihydroindoles, in moderate to good yields. Higher regio- and stereoselectivities than those of usual radical cyclizations using AIBN-Bu_3SnH were observed in the present electrochemical radical cyclization. Exclusive 5-*exo* cyclization proceeded to give substituted 1-indanols, 2,3-dihydrobenzofurans and 2,3-dihydroindoles.

4. Experimental

4.1. General procedures

The NMR spectra were recorded on a JEOL JNM-EX270 (^{1}H, 270 MHz; ^{13}C, 67.8 MHz) FT NMR spectrometer. ^{1}H and ^{13}C Chemical shifts were represented as δ-values relative to the internal standard, tetramethylsilane. IR spectra were recorded on a JASCO IR-810 infrared spectrometer. High and low resolution mass spectra were determined with a JEOL JMS-AX500 or JEOL JMS-SX102A spectrometer. Cyclic voltammetry was carried out with BAS-50W using Pt disc electrode (1 mm ∅ as a

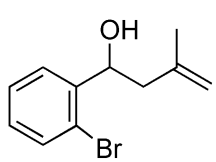
Table 6. Regioselectivity in the electrochemical and the conventional radical cyclizations



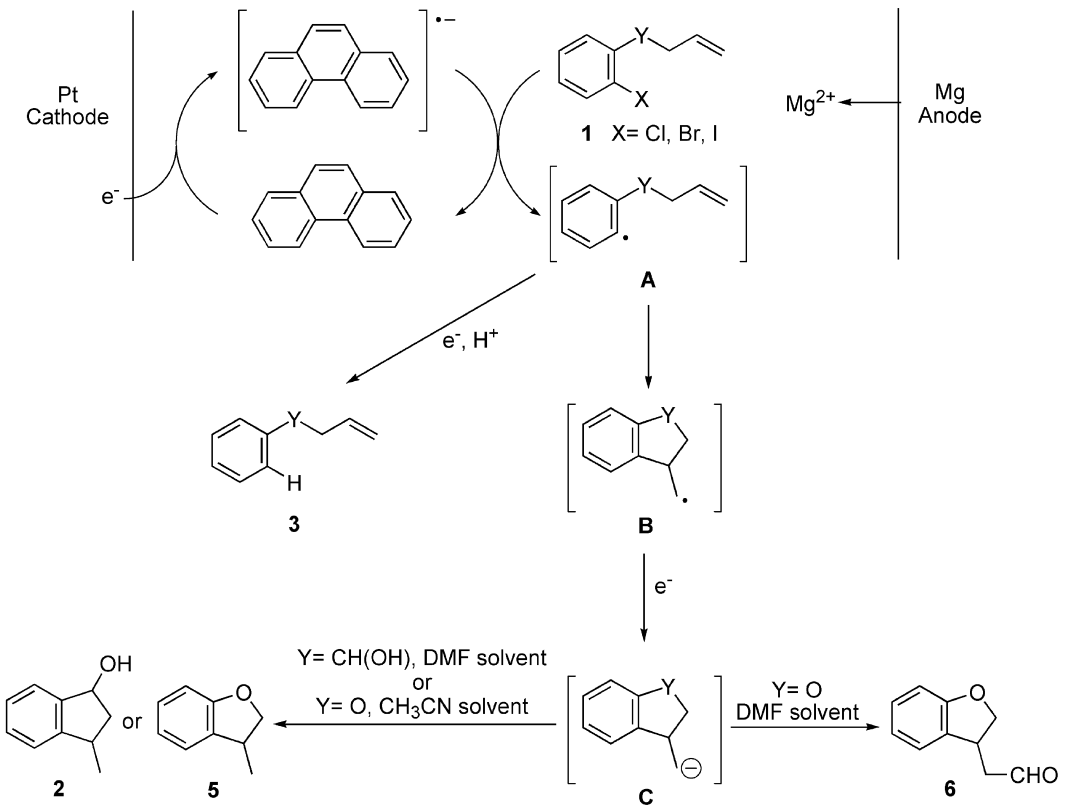
1h X=Br,Y=CH(OH)
4c X=I,Y=O
7c X=I, Y=NCH_3

2f, 5c, 8c
5-*exo* cyclized product

9a-c
6-*endo* cyclized product

Entry	Substrate	Conditions	Yield (%)[a]	Product	Ratio (5-*exo*/6-*endo*)[b]
1		Electrolysis at 0 °C	68		78/22
2		Electrolysis at 100 °C	27		64/36
3		AIBN-TBTH (0.022 M), toluene, reflux	71	**2f/9a**	45/55
4		AIBN-TBTH (0.022 M), benzene, reflux	76		48/52
5		AIBN-TBTN (0.05 M), toluene, reflux	63		52/48
6		AIBN-TBTH (0.5 M), toluene, reflux	33		55/45
7	**4c**	Electrolysis at 0 °C	79	**5c/9b**	100/0
8		AIBN-TBTH (0.022 M), toluene, reflux	56		82/18
9	**7c**	Electrolysis at 0 °C	51	**8c/9c**	100/0
10		AIBN-TBTH (0.022 M), toluene, reflux	68		51/49

[a] Isolated yields.
[b] Ratios of regioisomers were determined by ^{1}H NMR.



Scheme 2.

working electrode and Pt wire as a counter electrode in 0.1 M Et_4NClO_4-DMF solution (Ag/Ag^+ reference electrode). Thin-layer chromatography and column chromatography were carried out on a Merck Silica gel 60 PF_{254}. Anhydrous *N*,*N*-dimethylformamide (DMF) and tetraethylammonium perchlorate (TEAP) were commercially available and were used without further purification. Acetonitrile was freshly distilled under nitrogen from P_2O_5. Metal plates for electrodes are commercially available in more than 99.9% purities, and they were washed with 2 N HCl, methanol, and acetone and dried before electrolysis.

4.2. Preparation of 1-(2-halophenyl)-3-buten-1-ols

1-(2-Halophenyl)-3-buten-1-ol derivatives (**1a**–**h**) were prepared by allylation of 2-halobenzaldehydes with the corresponding substituted allyl bromides using electrochemically generated reactive zinc (EGZn).[15]

4.2.1. 2-Iodobenzaldehyde. To a solution of pyridinium chlorochromate (9.7 g, 45.0 mmol), silica gel (20 g) and CH_2Cl_2 (120 ml) were added 2-iodobenzyl alcohol (7.03 g, 30.0 mmol). The solution was stirred at room temperature for 4 h. The reaction mixture was filtrated and evaporated. The residue was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$. Concentration gave 6.80 g of the crude product, which was purified by recrystallization from hexane to give 5.91 g (85%) of 2-iodobenzaldehyde.

Mp 34 °C; IR (nujol) 2922, 1689, 1460, 1202, 1016 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.07 (1H, S), 7.96 (1H, d, J=7.9 Hz), 7.88 (1H, dd, J=1.7, 7.9 Hz), 7.47 (1H, t, J=7.9 Hz), 7.29 (1H, t, J=7.9 Hz); EIMS *m*/*z* (relative intensity) 248 (100), 231 (62), 203 (18), 76 (29), 65 (25). Anal. calcd for C_7H_5IO: C, 36.24; H, 2.17. Found: C, 36.12; H, 2.20.

4.2.2. 1-(2-Iodophenyl)-3-buten-1-ol (1a). Mp 42 °C; IR (nujol) 3368, 1640, 1462, 1436, 1011 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (1H, dd, J=1.3, 7.6 Hz), 7.52 (1H, dd, J=1.3, 7.6 Hz), 7.37 (1H, dt, J=1.3, 7.6 Hz), 6.97 (1H, dt, J=1.3, 7.6 Hz), 5.90 (1H, m), 5.21 (2H, m), 4.93 (1H, dt, J=3.3, 8.9 Hz), 2.62 (1H, m), 2.27 (2H, m). Anal. calcd for $C_{10}H_{11}OI$: C, 43.82; H, 4.04; I, 46.30. Found: C, 43.90; H, 4.05; I, 46.57.

4.2.3. 1-(2-Bromophenyl)-3-buten-1-ol (1b). Bp 68 °C/0.5 mm Hg; IR (neat) 3372, 1640, 1568, 1467, 1439, 1023 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (2H, m), 7.34 (1H, dt, J=1.7, 6.9 Hz), 7.13 (1H, dt, J=1.7, 6.9 Hz), 5.89 (1H, m), 5.16 (3H, m), 2.65 (1H, m), 2.36 (1H, m), 2.13 (1H, d, J=3.3 Hz); HRMS calcd for $C_{10}H_{10}BrO$ (M^+-1). *m*/*z* 224.9915. Found *m*/*z* 224.9924. Anal. calcd for $C_{10}H_{11}BrO$: C, 52.99; H, 4.88; Br, 35.18. Found: C, 52.74; H, 4.88; Br, 35.25.

4.2.4. 1-(2-Chlorophenyl)-3-buten-1-ol (1c). Bp 68 °C/0.27 mm Hg; IR (neat) 3376, 1641, 1474, 1439, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (1H, dd, J=1.7, 7.6 Hz), 7.30 (2H, m), 7.20 (1H, dt, J=1.7, 7.6 Hz), 5.86 (1H, m), 5.18 (3H, m), 2.64 (1H, m), 2.38 (1H, m), 2.13 (1H, d, J=3.6 Hz). Anal. calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.41. Found: C, 65.69; H, 6.19; Cl, 19.29.

4.2.5. 1-(2-Bromophenyl)-2-methyl-3-buten-1-ol (1d). Bp 80 °C/0.2 mm Hg; IR (neat) 3410, 1641, 1568, 1468, 1440, 1012 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (2H, m), 7.33 (1H, dt, J=1.3, 7.6 Hz), 7.13 (1H, m), 5.90 (1H, m), 5.20–4.91 (3H, m), 2.78–2.59 (1H, m), 2.14 (*syn*, 1H, d, J=3.6 Hz), 1.94 (*anti*, 1H, d, J=3.6 Hz), 1.05 (*syn*, 3H, d, J=6.9 Hz), 0.98 (*anti*, 3H, d, J=6.9 Hz); EIMS *m/z* (relative intensity) 242 ([M+2], 3), 187 (90), 185 (100), 159 (17), 157 (21), 105 (10), 77 (53). Anal. calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Br, 33.14. Found: C, 54.67; H, 5.46; Br, 33.17.

4.2.6. 1-(2-Bromophenyl)-2,2-dimethyl-3-buten-1-ol (1e). IR (neat) 3432, 1638, 1468, 1434, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (1H, dd, J=1.3, 7.9 Hz), 7.48 (1H, dd, J=1.3, 7.9 Hz), 7.30 (1H, dt, J=1.3, 7.9 Hz), 7.12 (1H, dt, J=1.3, 7.9 Hz), 6.03 (1H, dd, J=10.9, 17.5 Hz), 5.15–5.05 (3H, m), 2.01 (1H, d, J=3.3 Hz), 1.27 (3H, s), 1.04 (3H, s); HRMS calcd for $C_{12}H_{15}BrO$ *m/z* 254.0306. Found *m/z* 254.0321. Anal. calcd for $C_{12}H_{15}BrO$: C, 56.49; H, 5.93; Br, 31.32. Found: C, 56.56; H, 6.00; Br, 31.15.

4.2.7. 2-Bromo-α-(2-cyclohexenyl)benzyl alcohol (1f). Mixture of diastereomers. IR (neat) 3404, 1650, 1469, 1437, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (2H, m), 7.33 (1H, dt, J=1.3, 7.3 Hz), 7.13 (1H, dt, J=1.3, 7.3 Hz), 5.94 (1H, m), 5.67 (0.15H, dd, J=1.7, 9.9 Hz), 5.52 (0.85H, dd, J=1.7, 9.9 Hz), 5.06 (0.85H, m), 4.92 (0.15H, m), 2.68 (1H, m), 2.03 (1H, m), 1.92 (1H, d, J=2.3 Hz), 1.78 (1H, m), 1.60–1.44 (3H, m); ^{13}C NMR ($CDCl_3$) δ 142.4, 141.4, 132.8, 132.6, 131.2, 130.4, 128.7 (two signals), 128.5, 128.1, 128.0, 127.4, 127.3, 125.4, 122.4, 122.3, 75.8, 75.3, 41.3, 40.8, 26.5, 25.2 (two signals), 22.7, 21.8, 21.3; HRMS calcd for $C_{13}H_{15}BrO$ *m/z* 266.0306. Found *m/z* 266.0306. Anal. calcd for $C_{13}H_{15}BrO$: C, 58.44; H, 5.66; Br, 29.91. Found: C, 58.61; H, 5.76; Br, 29.82.

4.2.8. Ethyl 5-(2-iodophenyl)-5-hydroxy-2-pentenoate (1g). IR (neat) 3450, 1700, 1655, 1269, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (1H, dd, J=1.7, 7.9 Hz), 7.54 (1H, dd, J=1.7, 7.9 Hz), 7.39 (1H, dt, J=1.7, 7.9 Hz), 7.05 (1H, d, J=15.8 Hz), 6.99 (1H, td, J=1.7, 7.9 Hz), 5.97 (1H, d, J=15.8 Hz), 5.03 (1H, dt, J=3.6, 8.6 Hz), 4.29 (2H, q, J=7.3 Hz), 2.70 (1H, m), 2.49 (1H, m), 2.13 (1H, d, J=3.6 Hz), 1.30 (3H, t, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 145.1, 144.5, 139.4, 129.5, 128.7, 126.8, 124.2, 97.2, 76.1, 60.3, 40.3, 14.2; HRMS calcd for $C_{13}H_{15}IO$ *m/z* 346.0066. Found *m/z* 346.0062. Anal. calcd for $C_{13}H_{15}IO$: C, 45.11; H, 4.37; I, 36.66. Found: C, 45.16; H, 4.27; I, 36.88.

4.2.9. 1-(2-Bromophenyl)-3-methyl-3-buten-1-ol (1h). IR (neat) 3388, 1648, 1441, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (1H, dd, J=1.7, 7.9 Hz), 7.52 (1H, dd, J=1.7, 7.9 Hz), 7.34 (1H, td, J=1.7, 7.9 Hz), 7.13 (1H, td, J=1.7, 7.9 Hz), 5.16 (1H, dt, J=2.6, 9.9 Hz), 4.96 (1H, m), 4.91 (1H, s), 2.60 (1H, dd, J=1.3, 13.9 Hz), 2.22 (1H, d, J=1.32 Hz), 2.20 (1H, dd, J=9.9, 13.9 Hz), 1.88 (3H, s); HRMS calcd for $C_{11}H_{13}BrO$ *m/z* 240.0149. Found *m/z* 240.0150. Anal. calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Br, 33.14. Found: C, 54.82; H, 5.43; Br, 33.29.

4.3. Typical procedure for preparation of allyl aryl ethers

Alk-2-enyl *o*-iodophenyl ethers (**4a–e**) were prepared according to literature.[16] To a solution of 2-iodophenol (4 mmol), anhydrous potassium carbonate (8 mmol) and DMF (10 ml) was added allyl bromide (6 mmol) at room temperature. The solution was stirred for 4 h at 70 °C. The reaction mixture was filtrated and extracted with Et_2O. The combined ether extracts were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column or distillation.

4.3.1. Allyl *o*-iodophenyl ether (4a). IR (neat) 1582, 1472, 1276, 1248, 1018, 996 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (1H, dd, J=1.3, 7.9 Hz), 7.28 (1H, dt, J=1.3, 7.9 Hz), 6.81 (1H, dd, J=1.3, 7.9 Hz), 6.71 (1H, dt, J=1.3, 7.9 Hz), 6.10 (1H, m), 5.52 (1H, d, J=1.7 Hz), 5.31 (1H, d, J=1.7 Hz), 4.60 (2H, dt, J=1.7, 4.6 Hz); EIMS *m/z* (relative intensity) 260 (6), 133 (15), 105 (18), 92 (13), 77 (7), 63 (21), 50 (8), 41 (100), 39 (36); HRMS calcd for C_9H_9IO *m/z* 259.9698. Found *m/z* 259.9678.

4.3.2. Prenyl *o*-iodophenyl ether (4b).[16] IR (neat) 1677, 1471, 1241, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1H, dd, J=1.3, 7.9 Hz), 7.27 (1H, m), 6.81 (1H, dd, J=1.3, 7.9 Hz), 6.69 (1H, td, J=1.3, 7.9 Hz), 5.50 (1H, m), 4.58 (2H, d, J=6.6 Hz), 1.79 (3H, s), 1.74 (3H, s).

4.3.3. Methallyl *o*-iodophenyl ether (4c).[17] IR (neat) 1660, 1583, 1245, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (1H, dd, J=1.7, 7.9 Hz), 7.27 (1H, m), 6.80 (1H, dd, J=1.3, 8.3 Hz), 6.70 (1H, dt, J=1.3, 7.9 Hz), 5.19 (1H, d, J=0.7 Hz), 5.02 (1H, t, J=1.3 Hz), 4.48 (2H, s), 1.87 (3H, d, J=0.7 Hz).

4.3.4. Crotyl *o*-iodophenyl ether (4d). *E* and *Z* mixture.[16] IR (neat) 1676, 1582, 1471, 1244, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1H, dd, J=1.7, 7.9 Hz, *E* and *Z*), 7.31–7.24 (1H, m, *E* and *Z*), 6.81 (1H, dd, J=1.7, 7.9 Hz, *E* and *Z*), 6.69 (1H, dt, J=1.7, 7.9 Hz, *E* and *Z*), 5.98–5.68 (1H, m, *E* and *Z*), 4.66 (1H, d, J=4.3 Hz, *Z*), 4.52 (1H, d, J=5.6 Hz, *E*), 1.87 (3H, d, J=1.7 Hz, *Z*), 1.32 (3H, d, J=1.7 Hz, *E*).

4.3.5. Cyclohex-2-enyl *o*-iodophenyl ether (4e). IR (neat) 1649, 1580, 1468, 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1H, dd, J=1.7, 7.9 Hz), 7.25 (1H, m), 6.88 (1H, dd, J=1.0, 8.3 Hz), 6.69 (1H, dt, J=1.7, 7.9 Hz), 6.02–5.95 (1H, m), 5.93–5.87 (1H, m), 4.78 (1H, m), 2.24–2.03 (2H, m), 2.02–1.85 (3H, m), 1.74–1.60 (1H, m); EIMS *m/z* (relative intensity) 300 (5), 220 (11), 81 (58) 80 (100); HRMS calcd for $C_{12}H_{13}IO$ *m/z* 300.0011. Found *m/z* 300.0009. Anal. calcd for $C_{12}H_{13}IO$: C, 48.02; H, 4.37; I, 42.28. Found: C, 48.19; H, 4.39; I, 42.32.

4.4. Preparation of *N*-alk-2-enyl-*N*-methyl-2-iodoanilines (7a–7e)

N-Alk-2-enyl-*N*-methyl-2-iodoanilines (**7a–e**) were prepared by *N*-allylation of *N*-methyl-2-iodoaniline or *N*-methylation of *N*-allyl-2-iodoaniline.[18,19]

4.4.1. *N*-Methyl-2-iodoaniline.[18] Bp 68–72 °C/0.6 mm Hg; IR (neat) 3400, 1515, 1316 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65

(1H, dd, *J*=1.3, 7.6 Hz), 7.23 (1H, dt, *J*=1.3, 7.6 Hz), 6.55 (1H, dd, *J*=1.3, 7.6 Hz), 6.44 (1H, dt, *J*=1.3, 7.6 Hz), 4.19 (1H, br), 2.88 (3H, d, *J*=5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 148.14, 138.85, 129.45, 118.46, 109.97, 85.10, 30.96; EIMS *m/z* (relative intensity) 233 (100), 232 (37), 105 (23), 77 (22); HRMS calcd for C_7H_8NI *m/z* 232.9702. Found *m/z* 232.9704.

4.4.2. *N*-Allyl-*N*-methyl-2-iodoaniline (7a).[20] Bp 90 °C/1.0 mm Hg; IR (neat) 1643, 1580, 1470, 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, dd, *J*=1.3, 7.6 Hz), 7.30 (1H, dt, *J*=1.3, 7.6 Hz), 7.06 (1H, dd, *J*=1.3, 7.6 Hz), 6.77 (1H, dt, *J*=1.3, 7.6 Hz), 5.88–6.03 (1H, m), 5.15–5.29 (2H, m), 3.55 (2H, d, *J*=6.3 Hz), 2.69 (1H, s); ^{13}C NMR ($CDCl_3$) δ 153.94, 140.07, 135.27, 128.84, 125.14, 121.82, 117.75, 98.26, 60.22, 41.03; EIMS *m/z* (relative intensity) 273 (49), 252 (37), 246 (33), 146 (100), 144 (36), 132 (34), 131 (32), 91 (32), 77 (34), 44 (38); HRMS calcd for $C_{10}H_{12}NI$ *m/z* 273.0015. Found *m/z* 273.0026.

4.4.3. *N*-Crotyl-*N*-methyl-2-iodoaniline (7b). Mixture of *E* and *Z* isomers (4.3:1). IR (neat) 1672, 1357 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, dd, *J*=1.3, 7.6 Hz), 7.30 (1H, dt, *J*=1.3, 7.6 Hz), 7.06 (1H, dd, *J*=1.3, 7.6 Hz), 6.77 (1H., dt, *J*=1.3, 7.6, Hz), 5.72–5.54 (m, 2H), 3.60 (minor, 1H, dd, *J*=0.7, 5.6 Hz), 3.46 (major, 1H, dd, *J*=0.7, 5.4 Hz), 2.70 (minor, 3H, s), 2.67 (major, 3H, s), 1.72 (major, 3H, dd, *J*=0.7, 5.4 Hz), 1.64 (minor, 3H, dd, *J*=0.7, 5.6 Hz); ^{13}C NMR ($CDCl_3$) (major isomer) δ 154.16, 140.04, 128.81, 127.92, 127.08, 124.96, 121.74, 98.24, 59.60, 40.68, 17.79 (minor isomer) δ 153.94, 140.04, 128.97, 127.92, 127.19, 125.07, 121.82, 98.24, 53.41, 41.10, 13.12; EIMS *m/z* (relative intensity) 287 (42), 273 (32), 160 (100), 144 (71), 132 (67), 104 (20), 77 (22); HRMS calcd for $C_{11}H_{14}NI$ *m/z* 287.0171. Found *m/z* 287.0164. Anal. calcd for $C_{11}H_{14}NI$: C, 46.01; H, 4.91; N, 4.88; I, 44.20. Found: C, 46.19; H, 4.87; N, 4.89, I, 44.37.

4.4.4. *N*-Methallyl-*N*-methyl-2-iodoaniline (7c). IR (neat) 1655, 1579, 1470, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, dd, *J*=1.6, 7.6 Hz), 7.30 (1H, dt, *J*=1.6, 7.6 Hz), 7.09 (1H, dd, *J*=1.6, 7.6 Hz), 6.78 (1H, dt, *J*=1.6, 7.6 Hz), 5.00 (1H, d, *J*=0.7 Hz), 4.9 (1H, d, *J*=0.7 Hz), 3.48 (2H, s), 2.61 (3H, s), 1.82 (3H, s); ^{13}C NMR ($CDCl_3$) δ 154.50, 142.75, 140.00, 128.95, 125.32, 122.10, 113.30, 98.65, 63.02, 42.18, 20.74; EIMS *m/z* (relative intensity) 287 (48), 246 (100), 160 (88), 144 (26), 118 (25); HRMS calcd for $C_{12}H_{16}NI$ *m/z* 287.0171. Found *m/z* 287.0170.

4.4.5. *N*-Methyl-*N*-prenyl-2-iodoaniline (7d). IR (neat) 1671, 1580, 1469, 1359 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, dd, *J*=1.3, 7.6 Hz), 7.30 (1H, dt, *J*=1.3, 7.6 Hz), 7.06 (1H, dd, *J*=1.3, 7.6 Hz), 6.76 (1H, dt, *J*=1.3, 7.6 Hz), 5.34 (1H, m), 3.52 (1H, d, *J*=6.9 Hz), 2.68 (3H, s), 1.74 (3H, d, *J*=1.3 Hz), 1.64 (3H, s); ^{13}C NMR ($CDCl_3$) δ 154.16, 140.03, 135.34, 128.77, 124.94, 121.74, 121.27, 98.33, 54.88, 40.86, 25.86, 18.02; EIMS *m/z* (relative intensity) 301 (32), 286 (22), 233 (15), 175 (14), 174 (100), 132 (49); HRMS calcd for $C_{12}H_{16}NI$ *m/z* 301.0327. Found *m/z* 301.0323.

4.4.6. *N*-Cinnamyl-*N*-methyl-2-iodoaniline (7e). IR (neat) 1650, 1598, 1580, 1469, 1360, 1337 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87 (1H, dd, *J*=1.3, 7.6 Hz), 7.42–7.20 (6H, m), 7.10 (1H, dd, *J*=1.3, 7.6 Hz), 6.78 (1H, dt, *J*=1.3, 7.6 Hz), 6.60 (1H, d, *J*=15.8 Hz), 6.35 (1H, dt, *J*=6.3, 15.8 Hz), 3.70 (2H, d, *J*=6.3 Hz), 2.74 (3H, s); ^{13}C NMR ($CDCl_3$) δ 153.96, 140.13, 137.00, 132.78, 128.91, 128.52 (two signals), 127.44, 126.97, 126.36 (two signals), 125.19, 121.82, 98.22, 59.79, 41.03; EIMS *m/z* (relative intensity) 349 (10), 233 (13), 222 (100), 144 (28), 132 (56), 117 (65), 115 (29), 91 (50), 77 (16); HRMS calcd for $C_{16}H_{16}NI$ *m/z* 349.0328. Found *m/z* 349.0326.

4.5. Typical procedure for electrochemical radical cyclization. Cyclization of 1a

A mixture of **1a** (0.5 mmol) and phenanthrene (1 mmol) in 0.1 M Et_4NClO_4-DMF (10 ml) was electrolyzed at 0 °C with a Pt cathode and an Mg anode under nitrogen atmosphere. Electrolysis was carried out at 75 mA/cm^2, and an electricity of 5 F/mol of substrate was passed. The reaction mixture was quenched with 2 N HCl and diluted with water, and extracted with Et_2O. The combined ether extracts were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by TLC.

4.5.1. 3-Methylindan-1-ol (2a). Mixture of *syn* and *anti* diastereomers.[10] IR (neat) 3316, 1609, 1477, 1459, 1330, 1088, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31 (4H, m), 5.24 (*anti*, 1H, m), 5.18 (*syn*, 1H, m), 3.45 (*syn*, 1H, sextet, *J*=6.9 Hz), 3.05 (*syn*, 1H, sextet, *J*=6.9 Hz), 2.77 (*syn*, 1H, dt, *J*=6.9, 12.9 Hz), 2.26 (*anti*, 1H, m), 1.97 (*anti*, 1H, dt, *J*=6.9, 12.9 Hz), 1.82 (*syn*, 1H, br), 1.63 (*anti*, 1H, br), 1.44 (*anti*, 1H, m), 1.36 (*anti*, 3H, d, *J*=6.9 Hz), 1.27 (*syn*, 3H, d, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 148.63, 147.33, 145.00, 144.28, 128.72, 128.10, 126.83, 126.74, 124.40, 123.76, 123.61, 123.31, 75.13, 45.70, 44.71, 36.66, 36.25, 20.25, 20.15; EIMS *m/z* (relative intensity) 148 (81), 147 (100), 133 (50), 131 (27), 130 (87), 129 (84), 128 (36), 127 (16), 116 (11), 115 (64), 105 (34), 103 (12), 91 (28), 79 (12), 77 (22), 64 (10), 51 (14); HRMS calcd for $C_{10}H_{12}O$ *m/z* 148.0888. Found *m/z* 148.0880.

4.5.2. 2,3-Dimethylindan-1-ol (2b). Mixture of diastereoisomers. IR (neat) 3350, 1477, 1459, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (4H, m), 5.05 (1H, d, *J*=6.6 Hz), 4.94 (1H, d, *J*=5.6 Hz), 4.79 (1H, d, *J*=6.3 Hz), 4.68 (1H, d, *J*=6.3 Hz), 3.32–2.54 (1H, m), 2.34–1.80 (2H, m), 1.34–0.92 (6H, m); EIMS *m/z* (relative intensity) 162 (39), 161 (28), 147 (21), 144 (65), 143 (28), 133 (12), 129 (100), 128 (41), 127 (13), 119 (10), 115 (16), 105 (18), 91 (18), 77 (14); HRMS calcd for $C_{11}H_{14}O$ *m/z* 162.1045. Found *m/z* 162.1048.

4.5.3. 2,2,3-Trimethylindan-1-ol (*syn*-2c). Configuration of **2c** was determined by comparison of ^{1}H NMR and DIFNOE spectra of two isomers. IR (neat) 3258, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.13 (4H, m), 4.72 (1H, s), 2.72 (1H, q, *J*=6.9 Hz), 1.7 (1H, s), 1.22 (3H, s), 1.21 (3H, d, *J*=6.9 Hz), 1.11 (3H, s), 0.68 (3H, s); ^{13}C NMR ($CDCl_3$) δ 145.3, 143.7, 127.7, 126.6, 123.0, 129.9, 83.4, 49.6, 45.8, 24.6, 14.6, 12.4; EIMS *m/z* (relative intensity) 176 (29), 158 (51), 143 (100), 133 (69), 128 (38), 115 (25),

105 (31) 91 (27), 77 (20); HRMS calcd for $C_{12}H_{16}O$ *m/z* 176.1201. Found *m/z* 176.1210.

4.5.4. 2,2,3-Trimethylindan-1-ol (*anti*-2c). IR (neat) 3268, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.15 (4H, m), 4.60 (1H, s), 3.02 (1H, q, *J*=7.3 Hz), 1.51 (1H, s), 1.16 (3H, d, *J*=7.3 Hz), 1.12 (3H, s), 0.87 (3H, s); ^{13}C NMR ($CDCl_3$) δ 147.7, 143.5, 128.5, 126.6, 124.7, 123.9, 82.9, 46.4, 46.0, 21.6, 21.2, 13.3; EIMS *m/z* (relative intensity) 176 (28), 158 (48), 143 (100), 133 (60), 128 (38), 115 (23), 105 (25) 91 (23), 77 (16); HRMS calcd for $C_{12}H_{16}O$ *m/z* 176.1201. Found *m/z* 176.1209.

4.5.5. 1,2,3,4,4a,9a-Hexahydrofluoren-9-ol (2d). Mixture of two diasteromers. Analytical data of one isomer; IR (neat) 3336, 1450, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (1H, dd, *J*=2.3, 5.9 Hz), 7.42–7.18 (4H, m), 5.15 (1H, d, *J*=5.6 Hz), 3.10 (1H, m), 2.61 (1H, m), 2.20 (1H, m), 1.83–1.48 (5H, m), 1.20 (2H, m), 0.94 (1H, m); ^{13}C NMR ($CDCl_3$) δ 145.2, 142.8, 127.6, 126.4, 123.8, 122.7, 77.9, 46.1, 40.3, 25.6, 24.3, 21.9, 21.3; EIMS *m/z* (relative intensity) 188 (100), 170 (62), 145 (22), 142 (52), 141 (42), 129 (33), 120 (21), 115 (20), 105 (20), 91 (25); HRMS calcd for $C_{13}H_{16}O$ *m/z* 188.1201. Found *m/z* 188.1214.

Analytical data of another isomer; IR (neat) 3336, 1450, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (1H, dd, *J*=2.3, 5.9 Hz), 7.27–7.16 (3H, m), 4.89 (1H, d, *J*=6.3 Hz), 3.19 (1H, q, *J*=6.3 Hz), 2.23 (1H, quint, *J*=6.3 Hz), 1.86 (2H, m), 1.60 (2H, m), 1.51–1.36 (5H, m); ^{13}C NMR ($CDCl_3$) δ 147.2, 144.3, 128.1, 126.5, 124.7, 123.4, 77.7, 49.2, 41.4, 29.5, 24.9, 23.6, 22.8; EIMS *m/z* (relative intensity) 188 (100), 187 (68), 170 (80), 145 (27), 142 (61), 141 (49), 129 (33), 120 (22), 115 (21), 91 (22); HRMS calcd for $C_{13}H_{16}O$ *m/z* 188.1201. Found *m/z* 188.1206.

4.5.6. Ethyl (3-hydroxyindan-1-yl)acetate (*syn*-2e). Configurations of **2e** was determined by the comparison of ^1H NMR and DIFNOE spectra of two isomers. IR (neat) 3362, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (1H, m), 7.30–7.19 (3H, m), 5.20 (1H, d, *J*=5.0 Hz), 4.16 (2H, q, *J*=7.3 Hz), 3.48 (1H, dt, *J*=7.6, 13.5 Hz), 2.92–2.77 (2H, m), 2.58 (1H, dd, *J*=8.6, 15.8 Hz), 2.15 (1H, br, s), 1.69 (1H, ddd, *J*=5.9, 7.3, 13.5 Hz), 1.26 (3H, t, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 172.6, 145.1, 144.6, 128.5, 127.5, 124.3, 123.6, 75.0, 60.6, 42.8, 40.3, 38.4, 14.3; EIMS *m/z* (relative intensity) 202 ($M-H_2O$, 29), 131 (27), 129 (49), 128 (100), 115 (20). Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.18; H, 7.26.

4.5.7. Ethyl (3-hydroxyindan-1-yl)acetate (*anti*-2e). IR (neat) 3424, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (1H, m), 7.33–7.21 (3H, m), 5.28 (1H, dd, *J*=4.0, 6.3 Hz), 4.18 (2H, q, *J*=7.3 Hz), 3.83 (1H, quint, *J*=5.9 Hz), 2.73 (1H, dd, *J*=5.9, 15.2 Hz), 2.41 (1H, dd, *J*=8.9, 15.2 Hz), 2.31 (1H, ddd, *J*=4.0, 7.9, 13.9 Hz), 2.16 (1H, dt, *J*=6.3, 13.9 Hz) 1.73 (1H, br,s), 1.27 (3H, t, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 172.4, 145.4, 144.6, 128.8, 127.5, 124.6, 124.0, 74.9, 60.5, 42.6, 40.2, 38.8, 14.2; EIMS *m/z* (relative intensity) 220 (8), 202 (72), 146 (33), 132 (96), 128 (100), 115 (18); HRMS calcd for $C_{13}H_{16}O_3$ *m/z* 220.1099. Found *m/z* 220.1107.

4.5.8. 3,3-Dimethylindan-1-ol (2f). IR (neat) 3332, 1455, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (1H, dd, *J*=1.3, 5.9 Hz), 7.35–7.18 (3H, m), 5.26 (1H, t, *J*=6.3 Hz), 2.38 (1H, dd, *J*=6.9, 12.9 Hz), 1.83 (1H, dd, *J*=6.3, 12.9 Hz), 1.80 (1H, br, s), 1.39 (3H, s), 1.22 (3H, s); EIMS *m/z* (relative intensity) 162 (38), 147 (100), 129 (56); HRMS calcd for $C_{11}H_{14}O$ *m/z* 162.1045. Found *m/z* 162.1062.

4.5.9. 1-Phenyl-3-buten-1-ol (3a).[21] IR (neat) 3398, 1642, 1494, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.23 (5H, m), 5.81 (1H, m), 5.19 (2H, m), 4.76 (1H, m), 2.51 (1H, m), 2.07 (1H, t, *J*=2.6 Hz).

4.5.10. 2-Methyl-1-phenyl-3-buten-1-ol (3b).[21] IR (neat) 3404, 1640, 1604, 1495, 1455, 1020, 914 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.22 (5H, m), 5.78 (1H, m), 5.19 (1H, m), 5.05 (1H, m), 4.60 (*anti*, 1H, m), 4.35 (*syn*, 1H, m), 2.54 (1H, m), 2.16 (*syn*, 1H, m), 1.96 (*anti*, 1H, m), 0.99 (*anti*, 3H, d, *J*=6.9 Hz), 0.87 (*syn*, 3H, d, *J*=6.9 Hz); EIMS *m/z* (relative intensity) 162 (1), 145 (9), 129 (17), 107 (100), 79 (83), 51 (10).

4.5.11. 2,2-Dimethyl-1-phenyl-3-buten-1-ol (3c).[21] IR (neat) 3452, 1730, 1639, 1495, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.28 (5H, m), 5.91 (1H, d, *J*=10.6 Hz), 5.13 (2H, m), 4.43 (1H, d, *J*=2.0 Hz), 2.00 (1H, d, *J*=2.0 Hz), 1.02 (3H, s), 0.96 (3H, s).

4.5.12. α-(2-Cyclohexenyl)benzyl alcohol (3d). IR (neat) 3384, 1690, 1465, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.23 (5H, m), 5.81 (1H, m), 5.38 (1H, dd, *J*=2.3, 9.9 Hz), 4.58 (1H, d, *J*=6.3 Hz), 2.49 (1H, m), 1.99 (2H, m), 1.85–1.66 (2H, m), 1.58–1.47 (2H, m); EIMS *m/z* (relative intensity) 107 (100) 79 (33); HRMS calcd for $C_{13}H_{16}O$ *m/z* 188.1201. Found *m/z* 188.1201.

4.5.13. 2,3-Dihydro-3-methylbenzofuran (5a). Bp 60 °C/5 mm Hg; IR (neat) 1598, 1482, 1463, 1450, 1228, 967 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (2H, m), 6.85 (1H, dt, *J*=1.0, 7.9 Hz), 6.77 (1H, d, *J*=7.9 Hz), 4.66 (1H, dd, *J*=6.9, 15.8 Hz), 4.06 (1H, dd, *J*=6.9, 15.8 Hz), 3.54 (1H, sixt, *J*=6.9 Hz), 1.32 (3H, d, *J*=6.9 Hz); EIMS *m/z* (relative intensity) 134 (85), 119 (100), 91 (64); HRMS calcd for $C_9H_{10}O$ *m/z* 134.0732. Found *m/z* 134.0726. Anal. calcd for $C_9H_{10}O$: C, 80.56; H; 7.51. Found: C, 80.31; H, 7.54.

4.5.14. 2,3-Dihydro-3-isopropylbenzofuran (5b).[16] IR (neat) 1596, 1484, 1233 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19–7.09 (2H, m), 6.84 (1H, dt, *J*=1.0, 7.3 Hz), 6.77 (1H, d, *J*=7.3 Hz), 4.51 (1H, t, *J*=8.9 Hz), 4.37 (1H, dd, *J*=5.3, 8.9 Hz), 3.34 (1H, dt, *J*=5.3, 8.9 Hz), 2.02–1.90 (1H, m), 0.95 (3H, d, *J*=6.93 Hz), 0.87 (3H, d, *J*=6.60 Hz).

4.5.15. 2,3-Dihydro-3,3-dimethylbenzofuran (5c).[22] IR (neat) 1600, 1480, 1191 cm^{-1}; ^1H NMR ($CDCl_3$) 7.15–7.09 (2H, m), 6.88 (1H, td, *J*=1.0, 7.6 Hz), 6.79 (1H, d, *J*=7.6 Hz), 4.23 (2H, s), 1.34 (6H, s).

4.5.16. 3-Ethyl-2,3-dihydrobenzofuran (5d).[23] IR (neat) 1597, 1482, 1229 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19–7.09 (2H, m), 6.85 (1H, dt, *J*=1.0, 7.9 Hz), 6.79 (1H, d, *J*=7.9 Hz), 4.63 (1H, t, *J*=8.9 Hz), 4.21 (1H, dd, *J*=6.6, 8.9 Hz), 3.37 (1H, m), 1.86–1.73 (1H, m), 1.68–1.52 (1H, m), 0.97 (3H, t, *J*=7.6 Hz).

4.5.17. 1,2,3,4,4a,9b-Hexahydrodibenzofuran (5e). Configurations of **5e** was determined by DIFNOE spectrum. IR (neat) 1596, 1474, 1226 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.08 (2H, m), 6.87 (1H, dd, J=1.0, 7.6 Hz), 6.80 (1H, d, J=7.6 Hz), 4.67 (1H, dt, J=5.0, 7.3 Hz), 3.19 (1H, q, J=7.3 Hz), 2.04–1.75 (3H, m), 1.62–1.44 (4H, m), 1.42–1.26 (1H, m); EIMS m/z (relative intensity) 174 (100), 159 (33), 145 (56), 131 (84), 120 (36), 91 (21); HRMS calcd for $C_{12}H_{14}O$ m/z 174.1045. Found m/z 174.1048. Anal. calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.50; H, 8.01.

4.5.18. 2,3-Dihydro-3-(1-formyl-1-methylethyl)benzofuran (6a). IR (neat) 1723, 1594, 1484, 1460, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.56 (1H, s), 7.15 (2H, m), 6.86 (1H, dd, J=1.0, 7.6 Hz), 6.80 (1H, m), 4.56 (1H, dd, J=4.0, 9.2 Hz), 4.38 (1H, dd, J=4.0, 9.2 Hz), 3.66 (1H, dd, J=4.0, 9.2 Hz), 1.12 (3H, s), 1.03 (3H, s); EIMS m/z (relative intensity) 190 (17), 119 (100), 91 (78); HRMS calcd for $C_{12}H_{14}O_2$ m/z 190.0994. Found m/z 190.0986. Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.54; H, 7.42.

4.5.19. 2,3-Dihydro-3-formylmethyl-3-methylbenzofuran (6b).[24] IR (neat) 1722, 1598, 1481, 1460, 1243 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.70 (1H, dd, 1.7, 2.3 Hz), 7.16 (2H, m), 6.91 (1H, dt, J=1.0, 8.3 Hz), 6.81 (1H, d, J=8.3 Hz), 4.44 (1H, d, J=9.2 Hz), 4.35 (1H, d, J=9.2 Hz), 4.34 (1H, d, J=9.2 Hz), 2.85 (1H, dd, J=2.3, 16.8 Hz), 2.72 (1H, dd, J=1.7, 16.8 Hz), 1.46 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.8, 159.0, 133.8, 128.7, 122.8, 120.9, 120.7, 110.1, 82.2, 53.5, 25.3; EIMS m/z (relative intensity) 176 (66), 133 (100), 105 (53), 77 (26); HRMS calcd for $C_{11}H_{12}O_2$ m/z 176.0837. Found m/z 176.0835.

4.5.20. 3-(1-Formylethyl)-2,3-dihydrobenzofuran (6c). IR (neat) 1723, 1596, 1483, 1461, 1230, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.76 (0.4H, s), 9.72 (0.6H, s), 7.15 (2H, m), 6.93–6.79 (2H, m), 4.62 (1H, m), 4.30 (1H, m), 3.94 (0.4H, m), 3.83 (0.6H, m), 2.84 (0.4H, m), 2.70 (0.6H, quint, J=7.3 Hz), 1.14 (1.8H, d, J=7.3 Hz), 1.06 (1.2H, d, J=7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4, 160.4, 128.8, 126.9, 125.4, 120.5, 109.7, 75.0, 50.4, 41.9, 10.4; EIMS m/z (relative intensity) 176 (35), 119 (100), 91 (98); HRMS calcd for $C_{11}H_{12}O_2$ m/z 176.0837. Found m/z 176.0843.

4.5.21. 2,3-Dihydro-1,3-dimethylindole (8a). IR (neat) 3048, 1610, 1492, 1462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (2H, m), 6.70 (1H, dt, J=0.7, 7.6 Hz), 6.49 (1H, dd, J=0.7, 7.6 Hz), 3.52 (1H, t, J=8.3 Hz), 3.27 (1H, m), 2.79 (1H, t, J=8.3 Hz), 2.74 (3H, s), 1.31 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 152.88, 135.31, 127.42, 122.91, 117.93, 107.35, 64.13, 36.23, 35.31, 18.22; EIMS m/z (relative intensity) 147 (62), 146 (16), 143 (15), 132 (100), 131 (16), 117 (34); HRMS calcd for $C_{10}H_{13}N$ m/z 147.1048. Found m/z 147.1041.

4.5.22. 3-Ethyl-2,3-dihydro-1-methylindole (8b). IR (neat) 3046, 1609, 1492, 1461 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07 (2H, m), 6.58 (1H, dt, J=0.7, 7.6 Hz), 6.48 (1H, dd, J=0.7, 7.6 Hz), 3.38 (1H, t, J=8.3 Hz), 3.11 (1H, m), 2.92 (1H, t, J=8.3 Hz), 2.74 (3H, s), 1.88 (1H, m), 1.55 (1H, m) 1.00 (3H, t, J=7.6 Hz); ^{13}C NMR ($CDCl_3$)δ 153.19, 134.05, 127.48, 123.43, 117.61, 107.21, 61.89, 42.37, 36.17, 26.65, 11.93; EIMS m/z (relative intensity) 161 (32), 133 (11), 132 (100), 131 (10), 130 (11), 117 (37), 40, (21); HRMS calcd for $C_{11}H_{15}N$ m/z 161.1204. Found m/z 161.1221.

4.5.23. 2,3-Dihydro-1,3,3-trimethylindole (8c).[25] IR (neat) 3022, 1608, 1491, 1462 cm^{-1}; ^1H NMR ($CDCl_3$) 7.09 (1H, dt, J=1.3, 7.6 Hz), 7.01 (1H, dd, J=1.3, 7.6 Hz), 6.70 (1H, dt, J=1.3, 7.6 Hz), 6.49 (1H, dd, J=1.3, 7.6 Hz), 3.06 (2H, s), 2.75 (3H, s), 1.30 (6H, s); ^{13}C NMR ($CDCl_3$) δ 151.97, 139.21, 127.42, 121.49, 117.82, 107.29, 70.30, 40.23, 35.97, 27.37 (two signals).

4.5.24. 3-Isopropyl-2,3-dihydro-1-methylindole (8d). IR (neat) 3046, 1609, 1491, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (2H, m), 6.66 (1H, dt, J=0.7, 7.3 Hz), 6.46 (1H, dd, J=0.7, 7.3 Hz), 3.30 (1H, t, J=8.2 Hz), 3.12 (2H, m), 2.73 (3H, s), 2.02 (1H, m), 0.99 (3H, d, J=6.9 Hz), 0.88 (3H, d, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 153.91, 132.85, 127.71, 124.60, 117.50, 107.21, 58.55, 47.35, 36.35, 30.73, 20.83, 19.10; EIMS m/z (relative intensity) 175 (23), 158 (19), 133 (11), 132 (100), 117 (30); HRMS calcd for $C_{12}H_{17}N$ m/z 175.1361. Found m/z 1751355.

4.5.25. 3-Benzyl-2,3-dihydro-1-methylindole (8e). IR (neat) 3026, 1607, 1492, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.21 (5H, m), 7.11 (1H, dt, J=0.7, 7.6 Hz), 6.93 (1H, dd, J=0.7, 7.3 Hz), 6.66 (1H, dt, J=0.7, 7.3 Hz), 6.51 (1H, dd, J=0.7, 7.3 Hz), 3.49 (1H, m), 3.28 (1H, t, J=8.6 Hz), 3.11 (1H, dd, J=6.0, 13.5 Hz), 3.02 (1H, dd, J=6.6, 8.6 Hz), 2.78 (1H, dd, J=9.6, 13.5 Hz), 2.73 (3H, s); ^{13}C NMR ($CDCl_3$) δ 153.14, 140.20, 133.30, 128.97 (two signals), 128.39 (two signals), 127.78, 126.15, 123.65, 117.68, 107.37, 61.69, 42.37, 60.06, 36.08; EIMS m/z (relative intensity) 223 (12), 132 (100), 117 (25), 91 (10); HRMS calcd for $C_{16}H_{17}N$ m/z 223.1361. Found m/z 223.1361.

4.5.26. 3-Methy-1,2,3,4-tetrahydro-1-naphthol (9a).[26] IR (neat) 3332, 1455, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.18 (4H, m), 2.80 (1H, m), 2.41 (1H, m), 2.19 (1H, m), 1.88 (2H, m), 1.08 (1H, d, J=6.3 Hz).

4.5.27. 3-Methychroman (9b).[27] IR (neat) 2922, 1734, 1456, 1261 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.7–7.2 (4H, m), 4.17 (1H, ddd, J=2.0, 5.6, 10.6 Hz), 3.68 (1H, t, J=9.6 Hz), 2.83 (1H, ddd, J=2.0, 5.6, 16.2 Hz), 2.44 (1H, dd, J=9.6, 16.2 Hz), 2.15 (1H, m), 1.04 (3H, d, J=6.6 Hz).

4.5.28. 1,3-Dimethy-1,2,3,4-tetrahydroquinoline (9c).[28] IR (neat) 3024, 1605, 1492, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07 (1H, t, J=9.8 Hz), 6.95 (1H, d, J=6.8 Hz), 6.59 (2H, m), 3.15 (1H, ddd, J=2.0, 4.2, 11.0 Hz), 2.88 (3H, s), 2.72–2.79 (2H, m), 2.41 (1H, dd, J=10.7, 15.8 Hz), 2.12 (1H, m), 1.03 (3H, d J=6.5 Hz).

4.6. Typical procedure for radical cyclization using Bu_3SnH and AIBN

To a solution of substrate (0.5 mmol) and toluene (25 ml) was added n-Bu_3SnH (0.55 mmol) and AIBN (0.1 mmol) at room temperature. The solution was heated under reflux for 4 h. The solvent was evaporated and diluted with hexane. The solution was extracted with CH_3CN. The combined CH_3CN extracts were washed with hexane, dried over

Na_2SO_4 and concentrated in vacuo. The crude product was purified by TLC.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (B) (No. 11450342) from The Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

1. Neumann, W. P. *Synthesis* **1987**, 665–683.
2. (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072–3082. (b) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726–5733. (c) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080–3082. (d) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2003**, *59*, 6627–6635. (e) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838–6842. (f) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415–2416. (g) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn* **2001**, *74*, 225–235. (h) Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910–1911. (i) Inoue, R.; Nakao, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn* **1997**, *70*, 2039–2049. (j) Clark, A. J.; Davies, D. I.; Jones, K.; Millbanks, C. *J. Chem. Soc., Chem. Commun.* **1994**, 41–42.
3. Fry, A. J. Synthetic organic electrochemistry; Wiley: New York, 1989; pp 136–156.
4. Generation of aryl radicals by the direct electrochemically reduction of aryl halides has been reported. Yields of the corresponding simple reduction products and cyclized products were dependent on the structure of the substrates and the electrochemical conditions. (a) Grimshaw, J.; Trocha-Grimshaw, J. *Tetrahedron Lett.* **1974**, *12*, 993–996. (b) Grimshaw, J.; Haslett, R. J.; Trocha-Grimshaw, J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2448–2455. (c) Grimshaw, J.; Mannus, D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2456. (d) Donnelly, S.; Grimshaw, J.; Trocha-Grimshaw, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2171–2172.
5. LeStrat, F.; Murphy, J. A.; Hughes, M. *Org. Lett.* **2002**, *4*, 2735–2738.
6. (a) Ozaki, S.; Matsushita, H.; Ohmori, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1120–1122. (b) Ozaki, S.; Matsushita, H.; Ohmori, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2339–2344. (c) Ozaki, S.; Horiguchi, J.; Matsushita, H.; Ohmori, H. *Tetrahedron Lett.* **1994**, *35*, 725–728. (d) Ihara, M.; Katsumata, A.; Setsu, F.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 677–684. (e) Sandra, O.; Clinet, J. C.; Duñach, E. *Tetrahedron Lett.* **1995**, *36*, 4429–4432. (f) Clinet, J. C.; Duñach, E. *J. Organomet. Chem.* **1995**, *503*, C48–C50. (g) Gómez, M.; Muller, G.; Penyella, D.; Rocamora, M. *Organometallics* **1997**, *16*, 5900–5908. (h) Sandra, O.; Rolland, J-P.; Duñach, E. *Organometallics* **1998**, *17*, 3747–3753. (i) Torii, S.; Inokuchi, T.; Yukawa, T. *J. Org. Chem.* **1985**, *50*, 5875–5877.
7. Munusamy, R.; Dhathathreyan, K. S.; Balasubramanian, K. K.; Venkatachalam, C. H. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1154–1166.
8. Kurono, N.; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Chem. Lett.* **2003**, *32*, 720–721.
9. Dias, M.; Gibson, M.; Grimshaw, J.; Hill, I.; Trocha-Grimshaw, J.; Hammerich, O. *Acta Chem. Scand.* **1998**, *52*, 549–554.
10. Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* **2001**, 2235–2243.
11. (a) Rigollier, P.; Young, J. R.; Fowley, L. A.; Still, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 9441–9442. (b) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn* **1989**, *62*, 143–147.
12. Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072–4078.
13. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059–6064.
14. Peters, D. G. Halogenated organic compounds. In *Organic electrochemistry*; Lund, H., Baizer, M. M., Eds.; Marcel Dekker: New York, 1991; pp 390–392.
15. (a) Tokuda, M.; Kurono, N.; Mimura, N. *Chem. Lett.* **1996**, 1091–1092. (b) Kurono, N.; Sugita, K.; Takasugi, S.; Tokuda, M. *Tetrahedron* **1999**, *55*(19), 6097–6108. (c) Jalil, A. A.; Kurono, N.; Tokuda, M. *Synlett* **2001**(12), 1944–1946. (d) Jalil, A. A.; Kurono, N.; Tokuda, M. *Tetrahedron* **2002**, *58*, 7477–7484. (e) Jalil, A. A.; Kurono, N.; Tokuda, M. *Synthesis* **2002**(18), 2681–2686.
16. Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050–6058.
17. Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2000**, *56*, 7553–7560.
18. Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662.
19. Stevens, R. V.; Bisacchi, G. S.; Goldsmith, L.; Strouse, C. E. *J. Org. Chem.* **1980**, *45*, 2709–2710.
20. Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 795–802.
21. Hosomi, A.; Kohra, S.; Ogata, K.; Yanagi, T.; Tominaga, Y. *J. Org. Chem.* **1990**, *55*, 2415–2420.
22. Janusz, J. M.; Young, P. A.; Scherz, M. W.; Enzweiler, K.; Wu, L. I.; Gan, L.; Pikul, S.; McDow-Dunham, K. L.; Johnson, C. R.; Senanayake, C. B.; Kellstein, D. E.; Green, S. A.; Tulich, J. L.; Rosario-Jansen, T.; Magrisso, I. J.; Wehmeyer, K. R.; Kuhlenbeck, D. L.; Eichhold, T. H.; Dobson, R. L. M. *J. Med. Chem.* **1998**, *41*, 1124–1137.
23. Rajesh, C. S.; Thanulingam, T. L.; Das, S. *Tetrahedron* **1997**, *53*, 16817–16834.
24. Brown, S.; Clarkson, S.; Grigg, R.; Thomas, W. A.; Sridharam, V.; Wilson, D. M. *Tetrahedron* **2001**, *57*, 1347–1359.
25. Nishio, T.; Okuda, N.; Kashima, C. *Helv. Chim. Acta* **1990**, *73*, 1719–1723.
26. Mitsui, S.; Kasahara, A.; Hanaya, K. *Bull. Chem. Soc. Jpn* **1968**, *41*, 2526–2527.
27. Wipf, P.; Ribe, S. *Org. Lett.* **2001**, *3*, 1503–1505.
28. Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1995**, *60*, 7631–7640.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1803–1816
Tetrahedron

An efficient and general method for resolving cyclopropene carboxylic acids☆

Lian-an Liao, Fan Zhang, Ni Yan, James A. Golen† and Joseph M. Fox*

Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, USA

Received 10 November 2003; revised 15 December 2003; accepted 15 December 2003

Abstract—A general method is described for the resolution of cycloprop-2-ene carboxylic acids via diastereomeric *N*-acyloxazolidines prepared from enantiomerically pure oxazolidinones. Although a number of oxazolidinones were shown to resolve cyclopropene carboxylic acids, the oxazolidinones of *S*-phenylalaninol, *S*-phenylglycine and (1*S*,2*R*)-*cis*-1-amino-2-indanol are optimal in terms of resolving power and cost effectiveness. Separations were performed using simple flash chromatography, and because there is typically a large difference in R_f values it is possible to separate gram quantities of pure diastereomers in a single chromatogram. The cycloprop-2-ene carboxylic acids that can be resolved include those that are substituted at the 1-position by H, Ph, α-naphthyl, CO_2Me, CH_2OMOM, and trans-styryl; alkene substituents include Me, *n*-alkyl, Ph and tethered alkynes. Remarkably, 2-methyl-3-propylcycloprop-2-ene carboxylic acid can also be resolved with ease. The relative configurations of four diastereomerically pure oxazolidines were determined by X-ray crystallography. Reduction of the *N*-acyloxazolidinones with $LiBH_4$ give enantiomerically pure derivatives of 3-hydroxymethylcyclopropene that react with either MeMgCl or vinylMgCl and catalytic CuI to give enantiomerically pure products of *syn*-addition.

1. Introduction

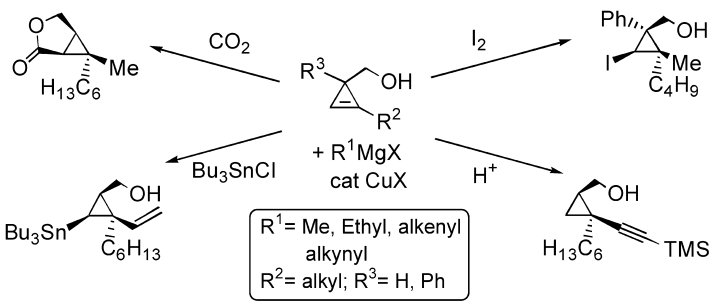
Although the unusual reactivity of cyclopropenes makes them interesting tools for synthesis,[1–7] methods that produce enantiomerically enriched cyclopropenes are rare.[8–18] Racemic cyclopropenecarboxylic esters[19,20] can be prepared easily and in quantity by the reactions of stabilized diazo compounds with alkynes,[21] and the groups of Doyle and Müller have described enantioselective versions of the process using chiral-catalysts.[9–14,17,22,23] For intermolecular catalytic asymmetric cyclopropenation reactions, excellent enantioselectivities have been obtained for the reactions of propargylethers (≥94% ee) acetals (88–95% ee) and amines (≥97% ee) with diazoacetates or *N*,*N*-dimethyldiazoacetamide using $[MEPY]_4Rh_2$.[9,10,17] High selectivity could also be achieved in the enantioselective cyclopropenation of *t*-butylacetylene (89% ee) or the diastereoselective cyclopropenation of 1-hexyne (86% de with *d*-menthyldiazoacetate).[9]

Although the Doyle/Müller system for enantioselective cyclopropenation represents a significant advance, there are a number of challenges that must be addressed before cyclopropene carboxylic acids can be generally useful as chirons.[24] Most importantly, the enantioselective reactions that have been described so far have been restricted to those that utilize unsubstituted diazoacetates or *N*,*N*-dimethyldiazoacetamide. Reactions that produce enantiomerically enriched cyclopropenes with quaternary centers are unknown. Furthermore, when applied to internal alkynes the chiral catalysts produce cyclopropenes with very low enantiomeric excess.[9] Because of renewed interest in the development of stereoselective reactions of cyclopropenes,[6,25–29] including that of our own group,[30] we sought to develop a simple and inexpensive procedure for obtaining numerous derivatives of cyclopropene carboxylic acids in enantiomerically pure form. For example, facially selective carbometallation (Scheme 1)[30] and hydrometallation reactions[27] are powerful new methods for preparing diverse types of cyclopropane products from common chiral precursors. The multicomponent nature of such reactions makes them attractive for complex molecule synthesis and drug discovery. However, before the present work was undertaken, there was no general method for obtaining the enantiomerically pure starting materials. We show here that a variety of cycloprop-2-ene carboxylic acids can be resolved through conversion to diastereomeric *N*-acyloxazolidinones and separated by column chromatography to provide gram quantities of diastereomerically pure cyclopropenes. The method is notably general and reliable, and it significantly enhances the value of the processes in

☆ Supplementary data associated with this article can be found in the online version at doi: 10.1016/S0040-4020(03)02036-2

Keywords: Cyclopropene; Enantiomerically pure oxazolidione.
* Corresponding author. Tel.: +1-302-831-0191; fax: +1-302-831-6335; e-mail address: jmfox@udel.edu
† To whom inquires regarding X-ray crystallography should be addressed. Current Address: Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, North Dartmouth, MA 02747-2300, USA.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.042



Scheme 1.

Scheme 1 and new reactions of chiral cyclopropenes that are under development.

2. Results and discussion

A rational starting point for the resolution of cyclopropene carboxylic acids was via diastereomeric esters, because Kass and co-workers had previously shown that diastereomeric-*l*-menthyl 2-phenyl-3-*t*-butyl-1-trimethylsilyl-cyclopropene carboxylates were separable by MPLC.[18] Accordingly, we reacted a number of enantiomerically pure alcohols with acid chloride **1**, but disappointingly none of the diastereomeric esters were separable by TLC (Fig. 1).

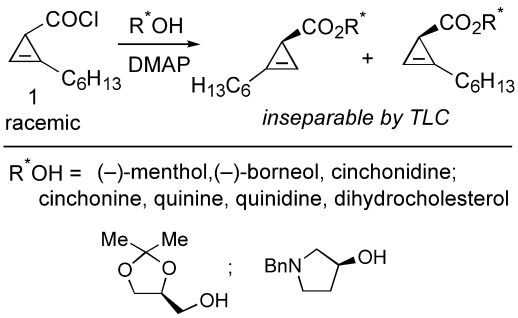


Figure 1. Attempted resolution of diastereomeric esters.

Given the lack of success in these screening efforts, further work was preceded by computational screening of various auxilaries using molecular mechanics. Based on these models, it was surmised that chiral oxazolidinones would be excellent resolving groups for cyclopropene carboxylic acids because of the difference in the relative orientations of the alkene and oxazolidinone substituents for the diastereomers (Fig. 2). The models assumed that the preferred conformations of the *N*-acyloxazolidinones would place the carbonyls in an *anti* orientation,[31] and that like other cyclopropylcarbonyl compounds[32] the cyclopropene and the attached carbonyl would align in an *s-cis* conformation. Another possibility is that materials would separate readily because the carbonyl oxygens of the acyloxazolidinone

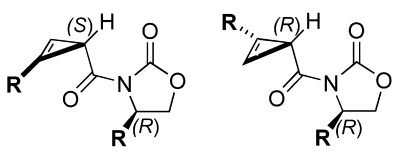
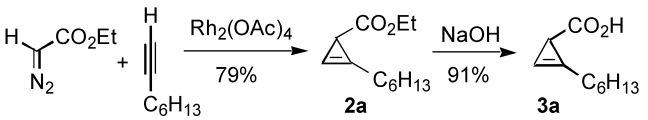
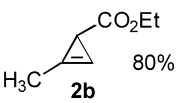
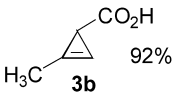
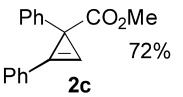
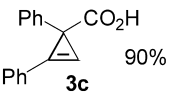
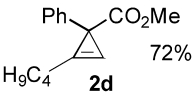
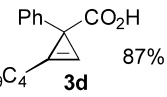
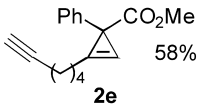
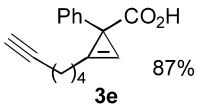
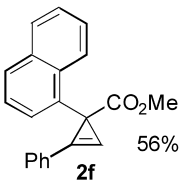
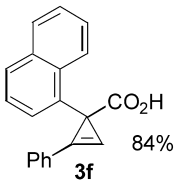
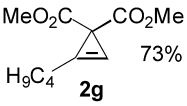
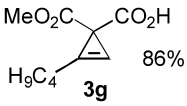
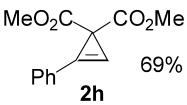
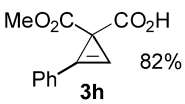
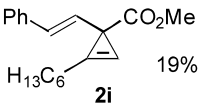
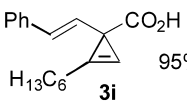
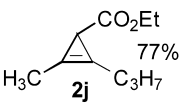
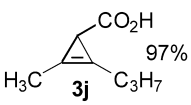


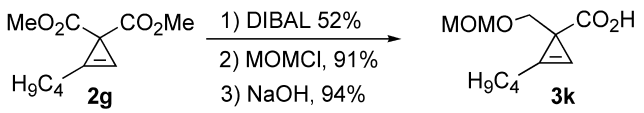
Figure 2. Conformations of diastereomeric oxazolidinones.

Table 1. Synthesis of cyclopropene carboxylic acids



 **2b** 80%	 **3b** 92%
 **2c** 72%	 **3c** 90%
 **2d** 72%	 **3d** 87%
 **2e** 58%	 **3e** 87%
 **2f** 56%	 **3f** 84%
 **2g** 73%	 **3g** 86%
 **2h** 69%	 **3h** 82%
 **2i** 19%	 **3i** 95%
 **2j** 77%	 **3j** 97%

could chelate to the hydrated surface of silica. Again, because the carbonyls would be held in the same plane, the diastereomers would have distinct shapes and should separate readily.

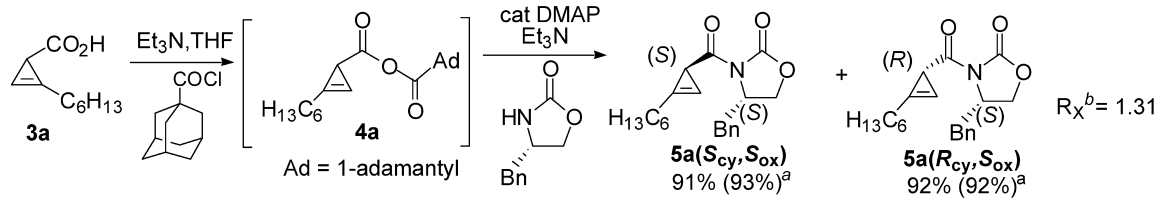


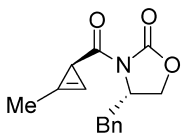
Scheme 2.

Cycloprop-2-ene carboxylic acids were synthesized by $Rh_2(OAc)_4$ catalyzed reaction of appropriate diazo compounds with alkynes[20] followed by saponification[33] (Table 1). All but one of the cyclopropenes in Table 1 was easily prepared and purified in good yield and in multigram quantities. The exception was **2i**, which could still be made easily on a 0.5 g scale even though it was produced in only 19% yield. For the cyclopropenes that were derived from malonate, hydrolysis was selective and gave monoacids[34] **3g** and **3h** in 86 and 82% yields, respectively. DIBAL reduction of **2g** was less selective but still gave the monoalcohol in 52% yield (Scheme 2). Of the commercially available oxazolidinones that were surveyed, the best auxilaries in terms of resolving ability and cost effectiveness are those from (*S*)-phenylalaninol, (*S*)-phenylglycinol and (1*R*,2*S*)-1-amino-2-indanol (Table 2). Regarding the use of stoichiometric quantities of these auxilaries, we note that all three oxazolidinones are commercially available and inexpensive if purchased in quantity. (*S*)-Benzyloxazolidinone and (*S*)-phenyloxazolidinone cost ca. 85 cents/gram when purchased in bulk, and (1*R*,2*S*)-1-amino-2-indanol can be purchased for ca. $2.50 per gram.[35] We also note that large scale preparations have been reported for all three oxazolidinones.[36–39]

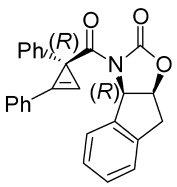
In the optimized procedures for preparing the *N*-acyloxazolidinones, the cycloprop-2-ene carboxylic acid was allowed to react with either pivaloyl chloride or adamantoyl chloride, and the resulting mixed anhydride was combined either with the oxazolidinone and Et_3N/LiCl[40]/cat. DMAP[41]

Table 2. Resolution of cyclopropene carboxylic acids

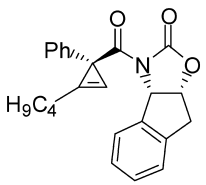




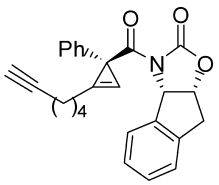
5b(fast[c]) 88%
5b(slow[c]) 88%
R_X=1.06



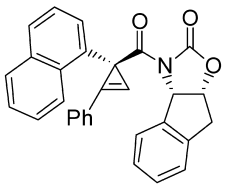
5c(S_{cy},R_{ox}) 91%
5c(R_{cy},R_{ox}) 90%
R_X=1.25



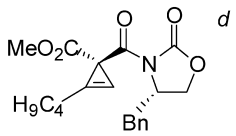
5d(fast) 88% (90%)[a]
5d(slow) 89% (88%)[a]
R_X=1.14



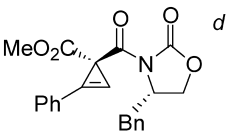
5e(fast) 90%
5e(slow) 89%
R_X=1.15



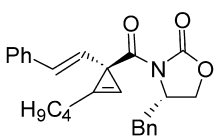
5f(fast) 90% (87%)[a]
5f(slow) 88% (85%)[a]
R_X=1.22



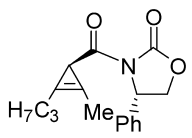
5g(fast) 93%
5g(slow) 92%
R_X=1.50



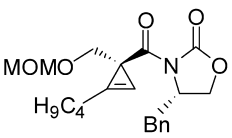
5h(fast) 86%
5h(slow) 89%
R_X=1.58



5i(fast) 73%
5i(slow) 73%
R_X=1.19



5j(fast) 93%
5j(slow) 92%
R_X=1.33



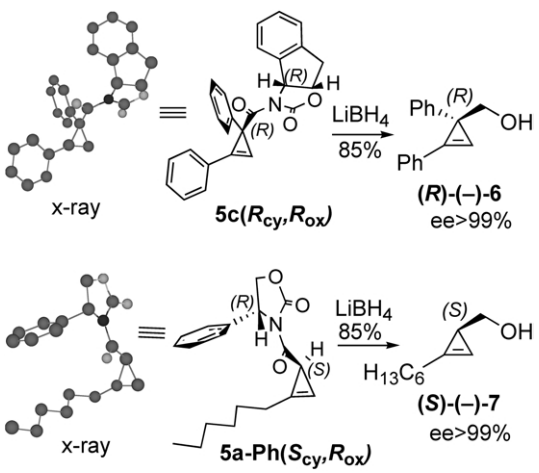
5k(fast) 86%
5k(slow) 86%
R_X=1.50

[a] Yields in parentheses refer to those obtained using (*S*)-phenyloxazolidine as the resolving group.
[b] R_x=R_f(fast)/R_f(slow).
[c] For compounds with unassigned absolute stereochemistry, the designations 'fast' and 'slow' refer to the relative speed with which the diastereomers elute by chromatography.
[d] For these examples, the lithium salt of the oxazolidinone was used instead of Et_3N/DMAP.

or directly with the lithium salt of the oxazolidinone.[42,43] 1-Adamantoyl chloride has not been used previously for the synthesis of *N*-acyloxazolidinones. In most cases, we found adamantoyl chloride to be superior to pivaloyl chloride because minor amounts of *N*-pivaloyloxazolidinones were usually formed with the latter reagent. The use of slightly more hindered adamantoyl chloride ameliorates the selectivity issue. The addition of a catalytic amount of DMAP was necessary in order to obtain both diastereomeric products in good yield. For example, although mixed anhydride **4c** (formed in situ) reacts cleanly at rt to give **5c(R_{cy},R_{ox})** in the absence of DMAP, **5c(S_{cy},R_{ox})** is formed in less than 10% yield. Both diastereomers were formed at equal rates when DMAP was added.[41] Obviously, the former process of distinguishing the enantiomers of **4a–k** by kinetic resolution is of interest—optimization of that process is underway and will be the subject of a future manuscript.

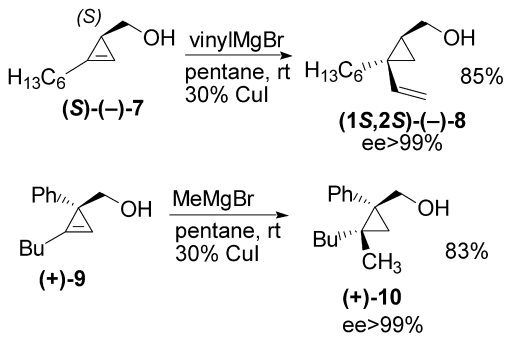
The notable feature about using oxazolidinones to resolve cycloprop-2-ene carboxylic acids is the generality of the method for structurally varied cyclopropenes. This is true even when the alkene substituents are very similar in terms of sterics (example **5j** of Table 2). For the 11 pairs of diastereomers **5a–k**, it was never necessary to test more than two auxilaries in order to find a suitable resolving agent. Furthermore, the syntheses are straightforward and separations were carried out using simple flash chromatography to provide significant amounts of diastereomerically pure material. For example, a single chromatograph (column diameter=1.5″) afforded 1.5 g of **5a(S_{cy},S_{ox})** and an equal amount of **5a(R_{cy},S_{ox})**. Using this as a calibration point with respect to the amount of material that can be purified quickly, it is useful to quantitatively compare the resolving abilities of oxazolidinone auxilaries toward different cyclopropene carboxylic acids via their R_x values.[44] As shown in Table 2, the separations for most of the *N*-acyloxazolidinones is excellent (R_f difference >15%), and even in the worst case (**5b**), 0.7 g of each pure diastereomer was obtained after two chromatograms (first column diameter=1.5″; second column diameter=1″).

X-ray crystallography revealed the absolute configurations of four of the diastereomers from Table 2. Two of those structures are displayed in Scheme 3; their diastereomers **5c(S_{cy},R_{ox})** and **5a-Ph(R_{cy},R_{ox})** are displayed in the Supporting Information. The reduction of the *N*-acyloxazolidinones in Scheme 3 gave 3-hydroxymethylcyclopropenes (*R*)-(−)-**6** and (*S*)-(−)-**7** that were enantiomerically pure within the detection limits (ee >99%) of our analysis by chiral HPLC.



Scheme 3.

The enantiomerically pure 3-hydroxymethylcyclopropenes that were prepared in this manner were subjected to facially selective Cu-catalyzed additions of Grignard reagents as shown in Scheme 4.[30] In each case, the addition occurred with high facial selectivity and with complete preservation of enantiomeric purity.



Scheme 4.

3. Conclusions

A method has been described for the resolution of cycloprop-2-ene-carboxylic acids via diastereomeric *N*-acyloxazolidines prepared from enantiomerically pure oxazolidinones. The method is remarkably general, and can be used to resolve significant quantities of cyclopropenes even when the alkene substituents are very similar. The relative configurations of four diastereomerically pure oxazolidines were established by X-ray crystallography. Reduction of the *N*-acyloxazolidinones with $LiBH_4$ give enantiomerically pure derivatives of 3-hydroxymethylcyclopropene that react with either MeMgCl or vinylMgCl and catalytic CuI to give enantiomerically pure products of *syn*-addition.

4. Experimental

4.1. General

All reactions were carried out in nitrogen atmosphere in glassware that was flame-dried under vacuum and cooled under nitrogen. GC analyses were performed using either an HP5 or HP1 column and a FID detector. Pentane, toluene, THF, ether and CH_2Cl_2 were dried with columns packed with activated neutral alumina. Alternatively, solvents were distilled from Na/benzophenone or CaH_2 (for CH_2Cl_2). Triethylamine was distilled from CaH_2. Copper(I)iodide (98%) was purchased from Acros. Ethyl diazoacetate (90% purity), Propyne, 1,7-Octadiyne, phenylacetylene, 1-hexyne, 1-octyne, Pivaloyl chloride and 1-adamantoyl chloride were purchased from Aldrich (we recommend that the purity of 1-adamantoyl chloride be verified by ^{13}C NMR

prior to use). (*S*)-phenyloxazolidione, (*S*)-benzyloxazolidinone and (1*S*,2*R*)-1-amino-2-indanol were purchased from Chemicrea Inc., Tokyo, JAPAN. (3a*S*)-*cis*-Tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one was prepared according to the literature precedent[39] from (1*S*,2*R*)-1-amino-2-indanol, and (3a*R*)-*cis*-Tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one was purchased from Aldrich. $Rh_2(OAc)_4$ was purchased from Pressure Chemical Co. Chromatography was performed on silica gel (ICN SiliTech 32-62D, 60 Å). For ^1H NMR, the abbreviation 'app' stands for apparent (e.g., 'app d'= apparent doublet). For ^{13}C NMR, multiplicities were distinguished using an APT pulse sequence: typical methylene and quaternary carbons appear 'up' (u); methine and methyl carbons 'down' (dn). Exceptions are methine carbons of alkynes and cyclopropenes, which usually have the same phase as 'normal' methylenes and quaternary carbons.[45] Yields in this paper refer to isolated yields (average of 2 runs) of compounds estimated to be >95% pure by ^1H, ^{13}C NMR. Diastereomer purities were determined using normal phase silica HPLC columns, and enantiomeric excesses were determined by HPLC using CHIRACEL OD, OJ or AD columns, or by GC using Chiraldex G-TA or B-PH columns. All HPLC runs were preformed at a rate of 1.0 mL/min.

The synthesis of **2a** has been reported previously.[30,46]

4.1.1. Ethyl 2-methylcycloprop-2-ene-1-carboxylate (2b). A 250 mL 3-neck flask was charged with $Rh_2(OAc)_4$ (256 mg, 0.58 mmol) and 100 mL CH_2Cl_2. The flask was sealed with three rubber septa, connected to an oil bubbler, and purged with N_2. The solution was then sparged (using a long needle) with propyne gas for 10 min. The addition of propyne was then ceased and the outlet to the oil bubbler was removed and replaced by a balloon filled with propyne. A solution of ethyl diazoacetate (6 mL, 90% purity (Aldrich), 51.3 mmol) in 4 mL CH_2Cl_2 was added over the course of 7 h via syringe pump. About once an hour, the balloon was emptied and refilled with propyne. After the addition was complete, the mixture was filtered through a pad of silica gel, concentrated (care should be taken not to distil away the product), and then chromatographed on silica gel (5% ether in pentane). Not all of the solvent from the chromatography was removed because of the volatility of the product. ^1H NMR analysis of the colorless solution (9.03 g) indicated that it contained ca. 5.3 g (42.0 mmol, 82%) of **2b**, 2.6 g of ether and 1.2 g of pentane. This solution was used for the preparation of **3b** without further purification. A similar experiment gave **2b** in 77% yield. ^1H NMR ($CDCl_3$, 400 MHz, δ): 6.34 (m, J=1.3 Hz, 1H), 4.12–4.15 (m, 2H), 2.16–2.17 (d, J=1.3 Hz, 3H), 2.11–2.12 (d, J=1.6 Hz, 1H), 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 176.5 (u), 111.6(u), 94.6(u), 60.1(u), 20.0(dn), 14.3(dn), 10.5(dn); IR (neat, cm^{-1}): 3135, 2975, 1809, 1729, 1251, 1186; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_7H_{11}O_2$, 127.0759; found, 127.0753.

4.2. General procedures for cyclopropenation

A solution of the diazoacetate (10 mmol) in 20 mL CH_2Cl_2 was added at rt via syringe pump (0.5–1.0 mL/h) to a stirred mixture of $Rh_2(OAc)_4$ (0.10 mmol) and alkyne (30 mmol). After the syringe pump addition was complete, the mixture was allowed to stir for 1 h and then filtered through celite, concentrated, and chromatographed (eluting with 3–10% ethyl acetate in hexane) to give the corresponding cyclopropene derivative.

4.2.1. Methyl 1,2-diphenylcycloprop-2-ene-1-carboxylate (2c). The general procudure for cyclopropenation with methyl phenyldiazoacetate[47] (1.76 g, 10 mmol) and phenylacetylene (3.06 g, 30 mmol) gave 1.85 g (7.40 mmol, 73%) of **2c**, a pale yellow oil. A similar experiment that started with 5.0 g methyl phenyldiazoacetate gave **2c** in 71% yield. ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.62–7.59 (m, 2H), 7.41–7.35 (m, 5H), 7.30–7.26 (m, 2H), 7.20 (m, 2H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 175.1(u), 140.9(u), 130.1(dn), 130.0(dn), 128.9(dn), 128.3(dn), 128.1(dn), 125.6(dn), 125.4(u), 117.3(u), 100.4(u), 52.3(dn), 33.6(u); IR (DCM, cm^{-1}): 3211, 2916, 1766, 1721, 1506, 1213; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{17}H_{14}O_2$, 250.0630; found, 250.0643.

4.2.2. Methyl 2-butyl-1-phenylcycloprop-2-ene-1-carboxylate (2d).[48] The general procedure for cyclopropenation with methyl phenyldiazoacetate[47] (1.76 g, 10 mmol) and 1-hexyne (2.46 g, 30 mmol) gave 1.64 g (7.1 mmol, 71%) of **2d**, a colorless oil. A similar experment that started with 3.0 g of methyl phenyldiazoacetate gave **2d** in 72% yield. ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.25–7.28 (m, 4H), 7.16–7.21 (m, 1H), 6.64 (t, J=1.5 Hz, 1H), 3.66 (s, 3H), 2.54 (app dt, J=7.4, 1.4 Hz, 2H), 1.58–1.53 (app quintet, J=7.4 Hz, 2H), 1.37–1.31 (m, 2H), 0.89–0.85 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.1(u), 141.8(u), 128.3(dn), 128.1(dn), 126.3(dn), 121.0(u), 97.0(u), 52.0(dn), 33.1(u), 28.9(u), 24.2(u), 22.3(u), 13.8(dn); IR (neat, cm^{-1}): 3131, 2959, 1719, 1494, 1222, 1023; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{15}H_{19}O_2$, 231.1385; found, 231.1396.

4.2.3. Methyl 1-phenyl-2-(hexyn-5-yl)-cycloprop-2-ene-1-carboxylate (2e). A 100 mL flask was charged with $Rh_2(OAc)_4$ (22 mg, 0.05 mmol), 50 mL CH_2Cl_2 and 1,7-octadiyne (2.00 g, 2.50 mL, 18.46 mmol). A solution of methyl phenyldiazoacetate (1.62 g, 9.23 mmol) in 10 mL CH_2Cl_2 was added via syringe pump at a rate of 0.7 mL/h at rt. The crude mixture was filtered through a pad of silica, concentrated and then chromatographed (the eluent was 5% ethyl acetate in hexane) to give 1.37 g (5.39 mmol, 58%) of the title compound as a colorless oil. A similar experiment also gave **2e** in 58% yield. ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.31–7.24 (m, 4H), 7.22–7.18 (m, 1H), 6.71 (t, J=1.4 Hz, 1H), 3.68 (s, 3H), 2.58 (dt, J=7.3, 1.4 Hz, 2H), 2.14–2.18 (app dt, J=7.0, 2.7 Hz, 2H), 1.93 (t, J=2.7 Hz, 1H), 1.76–1.65 (m, 2H), 1.60–1.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 175.9(u), 141.6(u), 128.2(dn), 128.0(dn), 126.3(dn), 120.6(u), 97.4(u), 84.0(u), 68.6(u), 52.0(dn), 33.0(u), 27.7(u), 25.8(u), 24.0(u), 18.0(u); IR (neat, cm^{-1}): 3289, 2947, 1718, 1224, 1021, 701, 647; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{17}H_{19}O_2$, 255.1385; found, 255.1391.

4.2.4. Methyl 2-phenyl-1-(α-naphthyl)cycloprop-2-ene-1-carboxylate (2f). The general procudure for cyclopropenation with methyl (α-naphthyl)diazoacetate[49] (1.13 g, 5.0 mmol) and phenylacetylene (1.53 g, 15 mmol) gave 843 mg (2.81 mmol, 56%) of **2f**, a pale yellow oil. A similar experiment with 2.0 g of (α-naphthyl)diazoacetate gave a

55% yield of **2f**. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.17 (dd, J=7.9, 0.6 Hz, 1H), 7.86 (dd, J=7.5, 0.5 Hz, 1H), 7.77–7.74 (m, 3H), 7.56–7.42 (m, 7H), 7.36–7.32 (m, 1H), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 176.5(u), 139.3(u), 134.2 (u, 2 carbons), 132.9(u), 130.5(dn), 130.3(dn), 129.5(dn), 129.4(dn), 128.4(dn), 126.6(dn), 126.3(u), 126.2(dn), 126.1(dn), 125.1(dn), 118.9(u), 104.0(u), 53.0(dn), 33.2(u); IR (CH_2Cl_2, cm^{-1}): 3065, 2951, 1720, 1596, 1506, 1222, 1093; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{21}H_{16}O_2$, 300.1150; found, 300.1130.

4.2.5. Dimethyl 2-butylcycloprop-2-ene-1,1-dicarboxylate (2g).[26] The general procudure for cyclopropenation with dimethyl diazomalonate (3.33 g, 21.08 mmol) and a solution of $Rh_2(OAc)_4$ (56 mg, 0.13 mmol) and 1-hexyne (6.93 g, 84.3 mmol) in CH_2Cl_2 (20 mL) gave 3.2 g (15.10 mmol, 72%) of the title compound as pale yellow oil. The spectral data were in accord those reported previously.[26] ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.35 (t, J=1.4 Hz, 1H), 3.72 (s, 6H), 2.55 (dt, J=1.4, 7.3 Hz, 2H), 1.58 (m, 2H), 1.39 (m, 2H), 0.92 (t, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 172.3 (u), 114.9 (u), 93.8 (u), 52.6 (dn), 32.8 (u), 28.8 (u), 24.1 (u), 22.6 (u), 14.1 (dn).

4.2.6. Dimethyl 2-phenylcycloprop-2-ene-1,1-dicarboxylate (2h). The general procudure for cyclopropenation with dimethyl diazomalonate(6.64 g, 40.0 mmol) and a solution of $Rh_2(OAc)_4$ (106 mg, 0.24 mmol) and phenylacetylene (21.4 g, 210.0 mmol) in CH_2Cl_2 (80 mL) gave 6.5 g (28.0 mmol, 67%) of the title compound as pale yellow solid, mp 70.5–71.5 (lit[50] 67–70°). The spectral data were in accord with those reported previously.[50] ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.64 (m, 2H), 7.45 (m, 3H), 6.90 (s, 1H), 3.72 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 171.2, 130.6, 130.4, 128.9, 123.9, 112.2, 95.2, 52.4, 32.8.

4.2.7. Methyl 2-hexyl-1-*trans*-styrylcycloprop-2-ene-1-carboxylate (2i). The general procedure for cyclopropenation with methyl (*E*)-2-diazo-4-phenyl butenoate[51] (2.12 g, 10.5 mmol), 1-octyne (4.63 g, 42 mmol) and $Rh_2(OAc)_4$ (28 mg, 0.063 mmol) gave 0.54 g (20%) of the title compound as pale yellow oil. A similar experiment that started with 240 mg of methyl (*E*)-2-diazo-4-phenyl butenoate gave **2i** in 18% yield. ^{1}H NMR ($CDCl_3$, 360 MHz, δ): 7.40–7.17 (m, 6H), 6.33 (t, J=1.2 Hz, 1H), 6.05 (d, J=16.2 Hz, 1H), 3.73 (s, 3H), 2.52 (app dt, J=7.2, 1.1 Hz, 2H), 1.61 (m, 2H), 1.30–1.60 (m, 6H), 0.90 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.1 (u), 137.7 (u), 131.8 (dn), 128.4 (dn), 127.9 (dn), 127.1 (dn), 126.8 (dn), 116.9 (u), 93.3 (u), 52.1(dn), 31.6 (u), 30.6 (u), 29.0 (u), 27.1 (u), 23.7 (u), 22.7 (u), 14.2 (dn); IR (CCl_4, cm^{-1}): 3025, 2952, 2931, 2360, 2336, 1722, 1244, 1226, 1060, 964, 765; HRMS-CI (NH_3) *m/z*: [M+H] calcd for $C_{19}H_{24}O_2$, 285.1854; found, 285.1849.

4.2.8. Ethyl 2-propyl-3-methyl-cycloprop-2-ene-1-carboxylate (2j). The general procedure for cyclopropenation with ethyl diazoacetate (2.53 g, 2.3 mL, 20 mmol) in 2.7 mL CH_2Cl_2 and a solution of 2-hexyne (2.46 g, 3.4 mL, 30 mmol) and $Rh_2(OAc)_4$ (88 mg, 0.2 mmol) in 150 mL CH_2Cl_2 gave 2.60 g (15.5 mmol, 78%) of the title compound as a colorless oil. A similar experiment gave **2j** in 76% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 4.10–4.15 (q, J=7.1 Hz, 2H), 2.41–2.37 (m, 2H), 2.06 (t, J=1.5 Hz, 3H), 2.03 (s, 1H), 1.62–1.56 (m, 2H), 1.26 (t, J=7.1 Hz, 3H), 0.95–0.99 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.4(u), 106.6(u), 102.2(u), 60.2(u), 26.8(u), 23.1(dn), 20.7(u), 14.8(dn), 14.2(dn), 10.2(dn); IR (neat, cm^{-1}): 2961, 2935, 1721, 1457, 1367, 1335, 1241, 1179, 1179, 1044; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{10}H_{17}O_2$, 169.1229; found, 169.1236.

4.3. General procedures for ester saponification

Aqueous KOH (30 mL of an 8.5% solution) was added to a 100 mL round bottomed flask that contained the cycloprop-2-ene-1-carboxylate (17.8 mmol), and 30 mL MeOH. The mixture was stirred overnight at the indicated temperature, concentrated to remove the bulk of the MeOH, acidified to pH 1–3 with conc. HCl, extracted (4×30 mL CH_2Cl_2), dried (Na_2SO_4) filtered, and concentrated. The residue was chromatographed on silica gel (20–40% ethyl acetate in hexane) to provide the cycloprop-2-ene-1-carboxylic acid.

4.3.1. 2-Hexylcycloprop-2-ene-1-carboxylic acid (3a). The general procedure for ester saponification conducted at rt with **2a** (3.2 g, 16.4 mmol) gave 2.55 g (15.1 mmol, 92%) of **3a** as a clear oil. A similar experiment with 1.0 g of **2a** gave **3a** in 90% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.31 (m, 1H), 2.48–2.52 (m, 2H), 2.12 (d, J=1.5 Hz, 1H), 1.61–1.55 (m, 2H), 1.38–1.25 (m, 6H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 183.7(u), 115.4(u), 93.6(u), 31.6(u), 28.9(u), 26.7(u), 25.1(u), 22.7(u), 19.7(dn), 14.2(dn); IR (neat, cm^{-1}): 3510, 2973, 1698, 1425, 1273, 1125; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{10}H_{17}O_2$, 169.1229; found, 169.1230.

4.3.2. 2-Methyl-cycloprop-2-ene-1-carboxylic acid (3b). The general procedure for ester saponification with **2b** [1.50 g (2.55 g of a ~59% mixture in Et_2O/pentane), 11.9 mmol] was conducted at 0 °C during the addition of KOH and subsequently at rt. The yield was 1.08 g (110 mmol, 92%) of **3b**, a colorless oil. A similar experiment gave **3b** in 91% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.34 (m, 1H), 2.17 (d, J=1.3 Hz, 3H), 2.11 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 183.1(u), 111.2(u), 94.2(u), 19.8(dn), 10.4(dn); IR (neat, cm^{-1}): 2977, 1813, 1700, 1423, 1283, 1248, 1121, 711; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_5H_7O_2$, 99.0446; found, 99.0451.

4.3.3. 1,2-Diphenylcycloprop-2-ene-2-carboxylic acid (3c). The general procedure for ester saponification conducted at 35 °C with **2c** (3.0 g, 12.0 mmol) gave 2.58 g (10.9 mmol, 91%) of **3c** as a white solid, mp 136–138 °C. A similar experiment with 730 mg of **2c** gave **3c** in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.63–7.59 (m, 2H), 7.43–7.36 (m, 5H), 7.28–7.24 (m, 2H), 7.19–7.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 180.6(u), 140.4(u), 130.6(dn), 130.4(dn), 129.3(dn),128.8(dn), 128.5(dn), 127.1(dn), 125.4(u), 117.3(u), 100.2(u), 33.5(u); IR (KBr, cm^{-1}): 3589, 3033, 2868, 1787, 1664, 1496, 1409, 1222, 1099; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{16}H_{12}O_2$, 236.0837; found, 236.0833.

4.3.4. 2-Butyl-1-phenylcycloprop-2-ene-1-carboxylic acid (3d). The general procedure for ester saponification

conducted at rt with **2d** (3.0 g, 13.0 mmol) gave 2.48 g (11.5 mmol, 88%) of **3d** as a clear oil. A similar experiment with 520 mg of **2d** gave **3d** in 85% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.30–7.19 (m, 5H), 6.64 (app t, J=1.6 Hz, 1H), 2.56–2.52 (m, 2H), 1.59–1.56 (m, 2H), 1.32–1.30 (m, 2H), 0.86 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 181.9(u), 140.8(u), 128.8(dn), 128.3(dn), 126.4(dn), 120.7(u), 96.3(u), 29.2(u), 28.7(u), 24.2(u), 22.2(u), 13.7(dn); IR (neat, cm^{-1}): 3513, 2953, 1696, 1605, 1506, 1245, 1046; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{14}H_{17}O_2$, 217.1229; found, 217.1229.

4.3.5. 1-Phenyl-2-(5-hexynyl)-cycloprop-2-ene-1-carboxylic acid (3e). The general procedure for ester saponification with **2e** (1.29 g, 5.10 mmol) was conducted at 0 °C during the addition of KOH and subsequently at rt. The yield was 1.06 g (4.42 mmol, 87%) of **3e**, a colorless oil. A similar experiment also gave **3e** in 87% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.30–7.27 (m, 4H), 7.23–7.18 (m, 1H), 6.70 (t, J=1.5 Hz, 1H), 2.59 (app dt, J=7.3 Hz, 1.5 Hz, 2H), 2.16 (app dt, J=6.9 Hz, 2.6 Hz, 2H), 1.93 (t, J=2.7 Hz, 1H), 1.77–1.70 (m, 2H), 1.61–1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 182.0(u), 140.7(u), 128.4(dn), 128.0(dn), 126.5(dn), 120.2(u), 96.7(u), 83.9(u), 68.6(u), 32.7(u), 27.7(u), 25.7(u), 24.0(u), 18.0(u); IR (neat, cm^{-1}): 3312, 2944, 1688, 1254, 804, 744, 696, 633; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{16}H_{17}O_2$, 241.1229; found, 241.1226.

4.3.6. 2-Phenyl-1-(α-naphthyl)cycloprop-2-ene-1-carboxylic acid (3f). The general procedure for ester saponification conducted at 50 °C with **2f** (3.00 g, 10.0 mmol) gave 2.38 g (8.32 mmol, 83%) of **3f** as a pale yellow solid, mp 126–129 °C. A similar experiment with 1.20 g of **2f** gave **3f** in 85% yield. ^{1}H NMR ($CDCl_3$, 360 MHz, δ): 8.22 (app d, J=8.3 Hz, 1H), 7.90–7.86 (app dd, J=8.3, 1.1 Hz, 1H), 7.78–7.76 (m, 3H), 7.58–7.45 (m, 7H), 7.34 (dd, J=8.3, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 181.6(u), 138.0(u), 133.8(u), 132.1(u), 130.1(dn), 129.9(dn), 129.0(dn), 128.8(dn), 128.1(dn),126.1(dn), 125.9(dn), 125.8(u), 125.7(dn), 125.5(dn), 124.6(dn), 118.1(u), 102.9(u), 32.3(u); IR (KBr, cm^{-1}): 3556, 3036, 2928, 1703, 1600, 1503, 1247, 1019; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{20}H_{14}O_2$, 286.0994; found, 286.0984.

4.3.7. 2-Butylcycloprop-2-ene-1,1-dioic acid monomethyl ester (3g). A solution of **2g** (5.04 g, 23.8 mmol) in 50 mL methanol was added dropwise to a solution of KOH (1.33 g, 23.8 mmol) in 15 mL water that was cooled in an ice bath. The reaction mixture was allowed to stir rt for 2 d, at which point it was concentrated to remove MeOH and diluted with 20 mL water. Three extractions with ether (3×10 mL) removed unchanged **2g** (0.82 g, 16%). The remaining aqueous layer was acidified with 10% HCl (aq) and extracted with ether (3×20 mL). The organics were combined, sequentially washed with water and brine, dried (Na_2SO_4), filtered and concentrated to give **3g** (3.90 g, 83%) as a pale yellow oil. A similar experiment that started with 1.27 g of **2g** gave **3g** in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.17 (app t, J=1.5 Hz, 1H), 3.76 (s, 3H), 2.52 (m, 2H), 1.58 (m, 2H), 1.40 (m, 2H), 0.92 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 178.1 (u), 173.2 (u), 110.6(u), 89.9(u), 53.6 (dn), 31.2 (u), 28.7 (u), 23.7 (u), 22.5 (u), 14.0 (dn); IR (neat, cm^{-1}): 3147, 2955, 2874, 2360, 2095, 1749, 1668, 1435, 1315, 1065, 850; HRMS-CI *m/z* [M+H] calcd for $C_{10}H_{15}O_4$, 199.0970; found, 199.0963.

4.3.8. 2-Phenylcycloprop-2-ene-1,1-dioic acid monomethyl ester (3h). The procedure was identical to that used to prepare **3g**, except that **2h** (4.00 g, 17.25 mmol), KOH (0.97 g, 17.25 mmol), MeOH (40 mL), water (10 mL) were used. The protocol gave 3.14 g (83%) of the title compound as a pale yellow solid, mp 88–89 °C. Additionally, unchanged **2h** (0.40 g, 10%) was recovered. A similar experiment that started with 9.5 g of **2h** gave **3h** in 85% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.52–7.46 (m, 5H), 6.75 (s, 1H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.2 (u), 172.5 (u), 131.5 (dn), 130.8 (dn), 129.5 (dn), 122.9 (u), 108.6 (u), 92.4 (u), 53.9 (dn), 31.3 (u); IR (neat, cm^{-1}): 3164, 3054, 2987, 2958, 2685, 2361, 2055, 1756, 1675, 1441, 1420, 1317, 1264, 1071, 705; Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.76; H, 4.60.

4.3.9. 2-Hexyl-1-*trans*-styrylcycloprop-2-ene-1-carboxylic acid (3i). A mixture of **2i** (0.42 g, 1.48 mmol), MeOH (4 mL) and 2 N KOH (aq) (6 mL) was stirred at 50 °C for 3 h. The mixture was extracted with ether (3×5 mL), and the aqueous layer was acidified with 10% HCl (aq) and extracted with ether (3×10 mL). The organics were combined, washed with water and brine, dried (Na_2SO_4), filtered and concentrated to give 370 mg (93%) of **3i** as a pale yellow oil. A similar experiment that started with 0.58 g of **2i** gave **3i** in 96% yield. ^{1}H NMR ($CDCl_3$, 400 Hz, δ): 7.37–7.18 (m, 6H), 6.31 (app t, J=1.4 Hz, 1H), 6.03 (d, J=16.1 Hz, 1H), 2.52 (app dt, J=7.3, 1.4 Hz, 2H), 1.61 (m, 2H), 1.40–1.26 (m, 6H), 0.87 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 182.7 (u), 137.8 (u), 131.1 (dn), 128.9 (dn), 128.3 (dn), 127.4 (dn), 126.5 (dn), 116.6 (u), 92.8 (u), 31.9 (u), 30.6 (u), 29.3 (u), 27.3 (u), 23.9 (u), 23.0 (u), 14.5 (dn); IR (CCl_4, cm^{-1}): 3026, 2957, 2931, 2860, 2360, 2335, 1686, 1419, 1289, 1264, 964, 803, 746; HRMS-CI, *m/z*: [M] calcd for $C_{18}H_{22}O_2$, 270.1620; found, 270.1614.

4.3.10. 2-Propyl-3-methyl-cycloprop-2-ene-1-carboxylic acid (3j). The general procedure for ester saponification with **2j** (0.888 g, 5.28 mmol) was conducted at 0 °C during the addition of KOH and subsequently at rt. The procedure gave 0.711 g (5.08 mmol, 96%) of **3j** as a colorless oil. A similar experiment gave **3j** in 98% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.41–2.37 (m, 2H), 2.06 (app t, J=1.5 Hz, 3H), 2.02 (s, 1H), 1.64–1.55 (m, 2H), 0.96 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 184.4(u), 106.2(u), 101.8(u), 26.8(u), 22.9(dn), 20.7(u), 14.2(dn), 10.1(dn); IR (neat, cm^{-1}): 2962, 2628, 1691, 1420, 1286, 1236, 1123; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_8H_{13}O_2$, 141.0916; found, 141.0920.

4.3.11. Methyl 2-butyl-1-hydroxymethylcycloprop-2-ene-1-carboxylate. A 250 mL round bottomed flask containing a solution of **2g** (3.27 g, 15.4 mmol) in 40 mL THF was cooled in an ice bath, and a solution of DIBAL (30.3 mmol; 60.6 mL of a 0.5 M solution in pentane) was added dropwise via an additional funnel. The mixture was stirred for 1 h and then quenched with water, acidified with

10% HCl (aq) and extracted with ether (3×20 mL). The organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography (10% ethyl acetate in hexanes) gave 1.48 g (8.04 mmol, 56%) of the title compound, a colorless oil. Additionally, 0.84 g of **2g** (26%) was recovered. A similar experiment with 5.50 g of **2g** gave the title compound in 57% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.43 (t, J=1.2 Hz, 1H), 3.74 (m, 2H), 3.63 (s, 3H), 2.52 (bs, 1H), 2.48 (app dt, J=1.2, 7.1 Hz, 2H), 1.53 (m, 2H), 1.36 (m, 2H), 0.88 (t, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.8 (u), 119.9 (u), 97.3 (u), 67.3 (u), 51.8 (dn), 31.1 (u), 29.0 (u), 24.6 (u), 22.3 (u), 13.8 (dn); IR (CH_2Cl_2, cm^{-1}): 2958, 2934, 2873, 1703, 1458, 1436, 1387, 1288, 1190, 1162, 1087, 1020, 975, 832, 791; HRMS-CI, *m/z*: [M] calcd for $C_{10}H_{16}O_3$, 184.1099; found, 184.1096.

4.3.12. Methyl 2-butyl-1-(methoxymethoxymethyl)cycloprop-2-ene-1-carboxylate. To a dry 25 mL round bottomed flask was added methyl 2-butyl-1-hydroxymethylcycloprop-2-ene-1-carboxylate (1.48 g, 8.04 mmol), *N*,*N*-diisopropylethylamine (1.25 g, 9.65 mmol), and CH_2Cl_2 (15 mL). The flask was swept with nitrogen and then cooled in an ice bath. Methyl chloromethylether (970 mg, 12.06 mmol) was added via syringe, and the ice bath was removed. The mixture was allowed to stir at rt for 5 h. Concentration and chromatography (20% ethyl acetate in hexanes) gave 1.64 g (91%) of the title compound, a pale yellow oil. A similar experiment that started with 0.41 g of the starting alcohol gave the title compound in 90% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.43 (app t, J=1.3 Hz), 4.60 (s, 2H), 3.84 (d, J=10.3 Hz, 1H), 3.67 (d, J=10.3 Hz, 1H), 3.63 (s, 3H), 3.33 (s, 3H), 2.48 (app dt, J=7.4, 1.5 Hz), 1.54 (m, 2H), 1.36 (m, 2H), 0.89 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.3 (u), 119.5 (u), 97.5 (u), 96.7 (u), 71.9 (u), 55.4 (dn), 52.2 (dn), 29.5 (u), 29.3 (u), 24.9 (u), 22.6 (u), 14.1 (dn); IR (CH_2Cl_2, cm^{-1}): 2952, 2934, 2874, 1715, 1466, 1288, 1243, 1149, 1104, 1046, 799; HRMS-CI *m/z*: [M−OMe] calcd for $C_{12}H_{20}O_4$, calcd, 197.1178; found, 197.1169.

4.3.13. 1-Methoxymethoxymethyl-2-butylcycloprop-2-ene-1-carboxylic acid (3k). A mixture of methyl 2-butyl-1-(methoxymethoxymethyl)cycloprop-2-ene-1-carboxylate (1.64 g, 7.20 mmol), MeOH (8 mL) and 2 N KOH (aq) (10 mL) was stirred at 50 °C under nitrogen for 3 h. The mixture was extracted with ether (3×5 mL). The aqueous phase was acidified with 10% HCl (aq) and extracted with ether (3×10 mL). The combined organics were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated to give 1.44 g (94%) of the title compound as a pale yellow oil. A similar experiment that started with 420 mg of the ester gave the title compound in 96% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 6.45 (app t, J=1.3 Hz, 1H), 4.63 (s, 1H), 3.85 (d, J=10.4 Hz, 1H), 3.69 (d, J=10.4 Hz, 1H), 3.35 (s, 3H), 2.52 (app dt, J=1.6, 7.3 Hz, 2H), 1.57 (m, 2H), 1.40 (m, 2H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 182.6 (u), 119.0(u), 97.0 (u), 96.7(u), 71.5 (u), 55.5(dn), 29.3 (u), 29.2(u), 24.8(u), 22.6(u), 14.1(dn); IR (neat, cm^{-1}): 3135, 2934, 2875, 2572, 2059, 1803, 1585, 1415, 1295, 1150, 1105, 917; Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.45; H, 8.58.

4.4. General procedures for resolution

A stirred solution of the cycloprop-2-ene-1-carboxylic acid (1 equiv.) in THF (50 mL/mmol acid) was cooled to −30 °C. Triethylamine (3.5 equiv.) and adamantoyl chloride (1.05 equiv.) were added sequentially and stirring was continued at −30 °C for 1 h. Lithium chloride (5.0 equiv.), the appropriate oxazolidinone (1.1 equiv.) and DMAP (0.1 equiv.) were then added and the cold bath was removed. The mixture was allowed to gradually rise to rt while stirring continued overnight. The solvents were removed and the residue was partitioned between ether and water. The aqueous layer was extracted twice with ether, and the combined organics were dried (Na_2SO_4), filtered, and concentrated. Chromatography separated the diastereomeric products.

4.4.1. (4*S*)-4-Benzyl-3-[(1*R*)-2-hexylcycloprop-2-en-1-oyl]-oxazolidinone [5a(R_{cy},S_{ox})] and (4*S*)-4-benzyl-3-[(1*S*)-2-hexylcycloprop-2-en-1-oyl]oxazolidinone [*5a*(S_{cy},S_{ox})]. The general procedure for resolution using (*S*)-benzyl-oxazolidinone (390 mg, 2.2 mmol) and **3a** (336 mg 2.0 mmol) gave 298 mg (0.91 mmol, 91%) of **5a(S_{cy},S_{ox})** and 301 mg (0.92 mmol, 92%) of **5a(R_{cy},S_{ox})** after chromatography with a gradient (5–15%) of ethyl acetate in hexane. **5a(S_{cy},S_{ox})** eluted first. The R_f difference in MTBE:toluene:hexane (1:1:2) was 27%. A similar experiment with 890 mg of **3a** gave **5a(S_{cy},S_{ox})** in 92% yield and **5a(R_{cy},S_{ox})** in 90% yield.

The absolute configuration of **5a(S_{cy},S_{ox})** was determined by reduction with $LiBH_4$, which gave (*S*)-(−)-**7** in 85% yield. The same alcohol was obtained in 81% yield from $LiBH_4$ reduction of crystallographically characterized **5a-Ph(S_{cy},R_{ox})**.

Similarly, the absolute configuration of **5a(R_{cy},S_{ox})** was determined by reduction with $LiBH_4$, which gave (*R*)-(+)-**7** in 75% yield. The same alcohol was obtained in 83% yield from $LiBH_4$ reduction of crystallographically characterized **5a-Ph(R_{cy},R_{ox})**.

5a(S_{cy},S_{ox}): A semisolid. $[\alpha]_D^{23}$=+105° (*c* 1.00, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.18–7.32 (m, 5H), 6.28 (m, 1H), 4.67–4.62 (m, 1H), 4.22–4.13 (m, 2H), 3.43 (d, J=1.1 Hz, 1H), 3.29 (dd, J=10.1, 3.2 Hz, 1H), 2.73 (dd, J=9.8, 3.5 Hz, 1H), 2.52–2.47 (m, 2H), 1.62–1.55 (m, 2H), 1.38–1.23 (m, 6H), 0.88–0.85 (t, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.5(u), 154.5(u), 136.0(u), 129.9(dn), 129.3(dn), 127.6(dn), 114.6(u), 92.6(u), 66.7 (u), 56.1(dn), 38.5 (u), 31.9 (u), 29.2 (u), 27.2(u), 25.3 (u), 22.9 (u), 20.4(dn), 14.5(dn); IR (CCl_4, cm^{-1}): 3031, 2958, 1777, 1688, 1363, 1209; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{20}H_{25}NO_3$, 327.1834; found, 327.1826.

5a(R_{cy},S_{ox}): A semisolid. $[\alpha]_D^{23}$=+46° (*c* 1.03, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.33–7.18 (m, 5H), 6.26 (m, 1H), 4.67–4.62 (m, 1H), 4.22–4.13 (m, 2H), 3.43 (d, J=1.4 Hz, 1H), 3.27 (dd, J=10.0, 3.3 Hz, 1H), 2.77 (dd, J=9.6, 3.7 Hz, 1H), 2.55–2.51(m, 2H), 1.62–1.57(m, 2H), 1.38–1.26(m, 6H), 0.86 (t, J=5.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.0(u), 154.0(u), 135.5(u), 129.4(dn), 128.9(dn), 127.2(dn), 113.9(u), 92.4(u), 66.3(u), 55.7(dn),

38.0(u), 31.5(u), 28.8(u), 26.8(u), 24.9(u), 22.5(u), 20.0(dn), 14.0(dn); IR (CCl_4, cm^{-1}): 3051, 2957, 1784, 1590, 1361, 1205; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{20}H_{25}NO_3$, 327.1834; found, 327.1826.

4.4.2. (4*R*)-3-[(1*S*)-2-Hexylcycloprop-2-en-1-oyl]-4-phenyloxazolidinone [5a-Ph(S_{cy},R_{ox})] and (4*R*)-3-[(1*R*)-2-hexylcycloprop-2-en-1-oyl]-4-phenyloxazolidinone [5a-Ph(R_{cy},R_{ox})]. The general procedure for resolution using (*R*)-phenyloxazolidinone (1.44 g, 8.8 mmol) and **3a** (1.35 g, 8.0 mmol) gave 1.165 g (3.72 mmol, 93%) of **5a-Ph(R_{cy}, R_{ox})** and 1.153 g (3.68 mmol, 92%) of **5a-Ph(S_{cy},R_{ox})** after chromatography with a gradient of 5–15% ethyl acetate in hexane. **5a-Ph(R_{cy},R_{ox})** eluted first. Relative configurations for both diastereomers were determined by X-ray crystallography of crystals that were grown from ethyl acetate/hexane. A similar experiment with 356 mg of **3a** gave **5a-Ph(R_{cy},R_{ox})** in 92% yield and **5a-Ph(S_{cy},R_{ox})** in 92% yield.

5a-Ph(R_{cy},R_{ox}): White needles, mp 50.5–52.5 °C. $[\alpha]_D^{23}=-168°$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.34–7.28 (m, 5H), 6.13 (m, 1H), 5.42 (dd, *J*=4.7, 4.0 Hz, 1H), 4.68 (app t, *J*=8.7 Hz, 1H), 4.27 (dd, *J*=4.8, 4.1 Hz, 1H), 3.41 (d, *J*=1.5 Hz, 1H), 2.45–2.43 (m, 2H), 1.55–1.53 (m, 2H), 1.32–1.24 (m, 6H), 0.86 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.9(u), 154.7(u), 139.7(u), 129.5(dn), 129.0(dn), 126.5(dn), 114.4(u), 92.5(u), 70.5(u), 58.4(dn), 31.9(u), 29.2(u), 27.1(u), 25.3(u), 22.9(u), 20.6(dn), 14.5(dn); IR (CCl_4, cm^{-1}): 3056, 2931, 1766, 1695, 1363, 1241, 1204, 1071; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{19}H_{24}NO_3$, 314.1756; found, 314.1762.

5a-Ph(S_{cy},R_{ox}): White needles, mp 83–86 °C. $[\alpha]_D^{23}=-73°$ (*c* 1.05, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.34–7.27 (m, 5H), 6.19 (m, 1H), 5.42 (dd, *J*=4.8, 3.8 Hz, 1H), 4.68 (app t, *J*=8.8 Hz, 1H), 4.26 (dd, *J*=5.0, 3.8 Hz, 1H), 3.43 (d, *J*=1.6 Hz, 1H), 2.39–2.34 (m, 2H), 1.39–1.37 (m, 2H), 1.24–1.16(m, 6H), 0.84 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.8(u), 154.7(u), 139.8(u), 129.5(dn), 128.9(dn), 126.3(dn), 114.2(u), 92.5(u), 70.5(u), 58.4(dn), 31.8(u), 29.1(u), 27.0(u), 25.2(u), 22.9(u), 20.4(dn), 14.5(dn); IR (CCl_4, cm^{-1}): 3021, 2926, 1775, 1692, 1382, 1195; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{19}H_{23}NO_3$, 313.1834; found, 313.1826.

4.4.3. Diastereomers of (4*S*)-4-benzyl-3-(2-methylcycloprop-2-en-1-oyl)oxazolidinone: 5b(fast) and 5b(slow). The general procedure for resolution using (*S*)-benzyloxazolidinone (1.38 g, 7.80 mmol) and **3b** (0.637 g, 6.5 mmol) gave 0.732 g (2.85 mmol, 88%) of **5b(fast)** (the diastereomer that elutes more quickly) and 0.740 g (2.88 mmol, 89%) of **5b(slow)** (the diastereomer that elutes more slowly). The chromatography eluent was 1:1:1:8 MTBE:CH_2Cl_2:toluene:hexane. A second chromatograph of the 'mixed' fractions was required. The R_f difference in MTBE:toluene:hexane (1:1:2) was 6%. A similar experiment gave **5b(fast)** in 89% yield and **5b(slow)** in 86% yield.

5b(fast): White solid, mp=96–98.5 °C. $[\alpha]_D^{23}=+201°$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.31–7.19 (m, 5H), 6.30 (m, 1H), 4.65–4.62 (m, 1H), 4.20–4.14 (m, 2H), 3.44 (d, *J*=1.4 Hz, 1H), 3.29 (dd, *J*=10.1, 3.2 Hz, 1H), 2.77–2.71 (m, 1H), 2.18 (d, *J*=1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.3(u), 154.5(u), 136.0(u), 129.9(dn), 129.3(dn), 127.7(dn), 110.5(u), 93.4(u), 66.8(u), 56.1(dn), 38.5(u), 20.7(dn), 10.8(dn); IR (KBr, cm^{-1}): 3140, 2921, 1762, 1687, 1491, 1357, 1214, 1103, 769, 714; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{15}H_{16}NO_3$, 258.1130; found, 258.1118.

5b(slow): White solid, mp=73–75 °C. $[\alpha]_D=+112°$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.31–7.18(m, 5H), 6.28 (m, 1H), 4.65–4.64 (m, 1H), 4.20–4.14 (m, 2H), 3.43 (d, *J*=1.6 Hz, 1H), 3.27 (dd, *J*=10.0, 3.3 Hz, 1H), 2.81–2.75 (m, 1H), 2.19 (d, *J*=1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.3(u), 154.5(u), 136.0(u), 129.9(dn), 129.3(dn), 127.7(dn), 110.2(u), 93.8(u), 66.8(u), 56.1(dn), 38.5(u), 20.7(dn), 10.9(dn); IR (KBr, cm^{-1}): 3135, 2975, 1772, 1679, 1375, 1189, 736, 701; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{15}H_{16}NO_3$, 258.1130; found, 258.1143.

4.4.4. Preparation of *5c(R_{cy},R_{ox})* and *5c(S_{cy},R_{ox})*. The general procedure for resolution using (3a*R*)-*cis*-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (385 mg, 2.20 mmol) and **3c** (472 mg, 2.0 mmol) gave two diastereomers after chromatography with a gradient of 10–20% ethyl acetate in hexane. **5c(S_{cy},R_{ox})** (353 mg, 0.90 mmol, 90%) eluted first, followed by **5c(R_{cy},R_{ox})** (358 mg, 0.91 mmol, 91%). Relative configurations for both diastereomers were determined by X-ray crystallography of crystals that were grown from acetone/hexane. The R_f difference in MTBE:toluene:hexane (1:1:2) was 22%. A similar experiment that started with 95 mg of **3c** gave **5c(S_{cy},R_{ox})** in 90% yield and **5c(R_{cy},R_{ox})** in 93% yield.

5c(S_{cy},R_{ox}): White crystals, mp 73–75 °C. $[\alpha]_D^{23}=-378°$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.78–7.75 (m, 2H), 7.65–7.63 (m, 1H), 7.43–7.30 (m, 4H), 7.27–7.17(m, 8H), 5.99 (d, *J*=6.8 Hz, 1H), 5.26–5.23 (m, 1H), 3.35–3.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 174.5(u), 151.9(u), 141.5(u), 140.0(u), 139.5(u), 130.6(dn), 130.3(dn), 130.2(dn), 129.5(dn), 129.2(dn), 128.6(dn), 128.5(dn), 127.8(dn), 126.8(dn), 126.5(u), 125.6(dn), 121.8(u), 101.5(u), 78.5(dn), 63.8(dn), 38.4(u), 37.3(u); IR (KBr, cm^{-1}): 3057, 2921, 1782, 1768, 1595, 1192; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{26}H_{19}NO_3$, 393.1365; found, 393.1352.

5c(R_{cy},R_{ox}): White crystals, mp 96–98 °C. $[\alpha]_D^{23}=+44°$ (*c* 1.03, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.89–7.86 (m, 1H), 7.80–7.77(m, 2H), 7.43–7.34 (m, 4H), 7.29–7.13 (m, 8H), 5.97 (d, *J*=7.0 Hz, 1H), 5.29–5.26 (m, 1H), 3.37–3.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 174.2(u), 152.0(u), 141.4(u), 140.1(u), 139.5(u), 130.6(dn), 130.4(dn), 130.3(dn), 129.2(dn), 128.6(dn), 128.5(dn), 127.7(dn), 126.6(dn), 126.5(dn), 126.3(u), 125.7(dn), 122.3(u), 101.1(u), 78.6(dn), 63.6(dn), 38.5(u), 36.6(u); IR (KBr, cm^{-1}): 3037, 2906, 1787, 1760, 1595, 1195; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{26}H_{19}NO_3$, 393.1365; found, 393.1352.

4.4.5. Preparation of 5d(fast) and 5d(slow). The general procedure for resolution using (3a*S*)-*cis*-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (385 mg, 2.20 mmol) and **3d**

(432 mg, 2.00 mmol) gave 328 mg (0.88 mmol, 88%) of **5d(fast)** (the diastereomer that elutes more quickly) and 332 mg (0.89 mmol, 89%) of **5d(slow)** (the diastereomer that elutes more slowly). Chromatography was performed with a gradient of 10–20% ethyl acetate in hexane. The R_f difference in MTBE:toluene:hexane (1:1:2) was 11%.

5d(fast): A semisolid. $[\alpha]_D^{23}=-171°$ (*c* 1.0, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.70 (d, *J*=7.6 Hz, 1H), 7.34–7.12 (m, 6H), 7.05–7.02 (m, 2H), 6.76 (t, *J*=1.5 Hz, 1H), 5.95–5.90 (d, *J*=6.9 Hz, 1H), 5.22–5.21 (m, 1H), 3.34–3.31 (m, 2H), 2.62–2.60 (m, 2H), 1.57–1.56 (m, 2H), 1.36–1.34 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 175.5(u), 151.8(u), 142.8(u), 140.1(u), 139.5(u), 130.2(dn), 128.4(dn), 128.4(dn), 127.8(dn), 126.4(dn), 126.3(dn), 125.6(dn), 124.0(u), 100.7(u), 78.4(dn), 63.5(dn), 38.5(u), 36.2(u), 29.5(u), 24.9(u), 22.7(u), 14.2(dn); IR (KBr, cm^{-1}): 3054, 2912, 1789, 1695, 1267; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{24}H_{23}NO_3$, 373.1678; found, 373.1674.

5d(slow): A semisolid. $[\alpha]_D=-10.4°$ (*c* 1.01, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.79 (dd, *J*=7.0, 1.1 Hz, 1H), 7.36–7.33 (m, 2H), 7.26 (d, *J*=7.1 Hz, 1H), 7.19–7.15 (m, 2H), 7.12–7.10 (m, 1H), 7.03–7.01(m, 2H), 6.79 (t, *J*=1.3 Hz, 1H), 5.96 (d, *J*=7.0 Hz, 1H), 5.25–5.22 (m, 1H), 3.34–3.31 (m, 2H), 2.65–2.61 (m, 2H), 1.57–1.53 (m, 2H), 1.35–1.29 (m, 2H), 0.84 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 175.4(u), 151.9(u), 142.8(u), 140.1(u), 139.6(u), 130.2(dn), 128.5(dn), 128.4(dn), 127.6(dn), 126.3(dn), 126.2(dn), 125.6(dn), 124.4(u), 100.4(u), 78.4(dn), 63.4(dn), 38.5(u), 36.0(u), 29.4(u), 24.7(u), 22.7(u), 14.1(dn); IR (KBr, cm^{-1}): 3055, 2933, 1786, 1693, 1202; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{24}H_{23}NO_3$, 373.1678; found, 373.1674.

4.4.6. Preparation of 5e(fast) and 5e(slow). The general procedure for resolution was followed using (3a*S*)-*cis*-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (84 mg, 0.48 mmol), **3e** (96 mg, 0.40 mmol), triethylamine (142 mg, 0.2 mL, 1.4 mmol), 1-adamantoyl chloride (98 mg, 0.44 mmol), LiCl (84 mg, 2.0 mmol) and DMAP (5 mg, 0.04 mmol). Chromatography (the eluent was 5% ethyl acetate in hexane) gave 70 mg (0.18 mmol, 88%) of **5e(fast)** (the diastereomer that elutes more quickly) and 68 mg (0.17 mmol, 86%) of **5e(slow)** (the diastereomer that elutes more slowly). A similar experiment gave **5e(fast)** in 92% yield and **5e(slow)** in 92% yield. The R_f difference in MTBE:toluene:hexane (1:1:2) was 14%.

5e(fast): A semisolid. $[\alpha]_D^{23}=+188°$ (*c* 0.98, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.72 (d, *J*=7.4 Hz, 1H), 7.36–7.26 (m, 3H), 7.23–7.19 (m, 2H), 7.16–7.14 (m, 1H), 7.06–7.04 (m, 2H), 6.82 (app s, 1H), 5.95 (d, *J*=6.9 Hz, 1H), 5.25–5.21(m, 1H), 3.40–3.28 (m, 2H), 2.66 (t, *J*=7.2 Hz, 2H), 2.18 (app dt, *J*=7.0, 2.6 Hz, 2H), 1.95–1.94 (m, 1H), 1.77–1.73 (m, 2H), 1.61–1.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 174.9(u), 151.4(u), 142.2(u), 139.7(u), 139.0(u), 129.8(dn), 128.1(2 carbons, dn), 127.3(dn), 126.0(2 carbons, dn), 125.2(dn), 123.2(u), 100.7(u), 84.1(u), 78.0(dn), 68.5(u), 63.1(dn), 38.0(u), 35.8(u), 27.9(u), 26.0(u), 24.3(u), 18.1(u); IR (CCl_4, cm^{-1}): 3313, 2933, 1793, 1683, 1359, 1297, 1190, 767, 697; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{26}H_{24}NO_3$, 398.1756; found, 398.1769.

5e(slow): A semisolid. $[\alpha]_D^{23}=+14.8°$ (*c* 1.00, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.78 (d, *J*=7.4 Hz, 1H), 7.37–7.32 (m, 2H), 7.28–7.26 (m, 1H), 7.19–7.15 (m, 2H), 7.13–7.10 (m, 1H), 7.03–7.01 (m, 2H), 6.83 (app t, *J*=1.3 Hz, 1H), 5.96 (d, *J*=7.0 Hz, 1H), 5.27–5.23 (m, 1H), 3.40–3.28 (m, 2H), 2.68–2.64 (m, 2H), 2.12 (app dt, *J*=7.1, 2.8 Hz, 2H), 1.91 (t, *J*=2.7 Hz, 1H), 1.72–1.68 (m, 2H), 1.68–1.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 174.8(u), 151.4(u), 142.2(u), 139.6(u), 139.1(u), 129.8(dn), 128.1(dn), 128.0(dn), 127.1(dn), 125.9(dn), 125.8(dn), 125.2(dn), 123.6(u), 100.4(u), 84.1(u), 78.0(dn), 68.4(u), 63.0(dn), 38.1(u), 35.5(u), 27.8(u), 26.0(u), 24.1(u), 18.0(u); IR (CCl_4, cm^{-1}): 3313, 2931, 1792, 1684, 1359, 1191, 810, 735, 634; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{26}H_{24}NO_3$, 398.1756; found, 398.1776.

4.4.7. Preparation of 5f(fast) and 5f(slow). The general procedure for resolution using (3a*S*)-*cis*-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (385 mg, 2.20 mmol) and **3f** (572 mg, 2.0 mmol) gave 399 mg (0.90 mmol, 90%) of **5f(fast)** (the diastereomer that elutes more quickly) and 390 mg (0.88 mmol, 88%) of **5f(slow)** (the diastereomer that elutes more slowly). Chromatography was performed with a gradient of 10–20% ethyl acetate in hexane. The R_f difference in MTBE:toluene:hexane (1:1:2) was 20%. A similar experiment that started with 115 mg of **3f** gave **5f(fast)** in 89% yield and **5f(slow)** in 90% yield.

5f(fast): A pale yellow semisolid. $[\alpha]_D^{23}=+38.7°$ (*c* 0.95, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.38–8.35 (m, 1H), 7.81–7.75 (m, 3H), 7.72–7.69 (m, 2H), 7.54 (s, 1H), 7.50 (dd, *J*=6.0, 1.2 Hz, 1H), 7.41–7.35 (m, 6H), 7.26–7.24 (m, 1H), 7.17–7.11 (m, 2H), 5.80 (d, *J*=7.0 Hz, 1H), 5.03–4.99 (m, 1H), 3.22 (dd, *J*=17.7, 6.6 Hz, 1H), 3.06 (app d, *J*=17.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.4(u), 152.2(u), 140.3(u), 138.7(u), 138.0(u), 134.0(u), 132.6(u), 130.3(2 carbons, dn), 130.2(dn), 129.3(dn), 129.2(dn), 128.7(dn), 128.3(dn), 128.2(dn), 128.2(dn), 126.8(u), 126.5(dn), 126.0(dn), 125.7(dn), 125.4(dn), 124.4(dn), 121.8(u), 104.1(u), 78.7(dn), 64.4(dn), 38.4(u), 37.5(u); IR (CH_2Cl_2, cm^{-1}): 3029, 2926, 1784, 1676, 1362, 1265, 1190; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{30}H_{21}NO_3$, 443.1521; found, 443.1503.

5f(slow): A pale yellow solid, mp 78–80 °C. $[\alpha]_D^{23}=+8.7°$ (*c* 1.07, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.27 (d, *J*=8.4 Hz, 1H), 7.90–7.87 (m, 2H), 7.78–7.81(m, 1H), 7.74–7.76(d, *J*=7.6 Hz, 1H), 7.69–7.71(d, *J*=8.1 Hz, 1H), 7.62(s, 1H), 7.51–7.53(dd, *J*=6.1, 1.1 Hz, 1H), 7.32–7.41(m, 5H), 7.26–7.28(m, 1H), 7.15–7.21(m, 2H), 5.74–5.75(d, *J*=6.6 Hz, 1H), 4.94–4.98(m, 1H), 3.10–3.23(m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 177.1(u), 152.1(u), 140.1(u), 139.0(u), 138.3(u), 134.0(u), 132.4(u), 130.39 (dn), 130.33(dn), 130.2(dn), 129.3(dn), 129.3(dn), 128.7(dn), 128.4(dn), 128.4(dn), 128.2(dn), 126.9(u), 126.5(dn), 125.9(dn), 125.7(dn), 125.4(dn), 124.3(dn), 120.2(u), 105.5(u), 79.1(dn), 65.1(dn), 38.0(u), 37.2(u); IR (CCl_4, cm^{-1}): 3029, 2924, 1785, 1680, 1362, 1262, 1190; HRMS-CI(NH_3) *m/z*: [M+], calcd for $C_{30}H_{21}NO_3$, 443.1521; found, 443.1503.

4.4.8. Diastereomers of (4*S*)-4-benzyl-3-(2-butyl-1-methoxycarbonyl-cycloprop-2-en-1-oyl)oxazolidinone:

5g(fast) and 5g(slow). A solution of **3g** (204 mg, 1.03 mmol) and triethylamine (1.42 mmol) in 10 mL THF was stirred in a 25 mL flask and cooled in a bath of dry ice/acetone. Pivaloyl chloride (124 mg, 1.03 mmol) was added via syringe, and the solution was stirred at −78 °C for 5 min and then warmed to 0 °C for 1 h. The mixture was once again cooled in the dry ice/acetone bath.

In a separate 10 mL flask, a solution of (*S*)-benzyloxazolidinone (273 mg, 1.55 mmol) in 4 mL THF, cooled in a bath of dry ice/acetone. n-BuLi (1.5 mL of a 2.5 M solution in hexanes, 1.55 mmol) was added dropwise. This solution was stirred at −78 °C for 0.5 h, and then transferred via cannula to the 25 mL flask that contained the mixed anhydride. The reaction mixture was stirred at −78 °C for 5 min then warmed to 0 °C for 0.5 h. The reaction was carefully quenched with water, and 2 mL of 1% HCl was added. Three extracts with ether (3×20 mL) were combined and washed with water and brine, dried (Na_2SO_4), filtered and concentrated. Chromatography (20% MTBE in petroleum ether) gave **5g(fast)** (171 mg, 0.48 mmol, 93%) and **5g(slow)** (169 mg, 0.47 mmol, 92%). The R_f difference in MTBE:petroleum ether (4:6) was 40%. A similar experiment with 1.00 g of **3g** gave **5g(fast)** in 92% yield and **5g(slow)** in 91% yield.

5g(fast): Colorless oil. $[\alpha]_D^{23}=+48.6°$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.36–7.21 (m, 5H), 6.53 (app t, *J*=1.4 Hz, 1H), 4.68 (m, 1H), 4.24–4.19 (m, 2H), 3.69 (s, 3H), 3.38 (dd, *J*=13.5, 3.4 Hz, 1H), 2.80 (dd, *J*=13.5, 9.8 Hz, 1H), 2.61 (m, 2H), 1.63 (m, 2H), 1.41 (m, 2H), 0.93 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 172.7 (u), 171.7 (u), 153.8 (u), 135.7 (u), 129.9 (dn), 129.3 (dn), 127.7 (dn), 117.3 (u), 95.4 (u), 66.8 (u), 55.5 (dn), 52.6 (dn), 38.0 (u), 35.7 (u), 29.1 (u), 24.5 (u), 22.6 (u), 14.1 (dn); IR (CCl_4, cm^{-1}): 3153, 3055, 2958, 2933, 2873, 2359, 2332, 1785, 1734, 1716, 1695, 1436, 1387, 1310, 1261, 1214, 789, 756, 703; HRMS-CI *m/z* [M] calcd for $C_{20}H_{23}NO_5$, 357.1576; found, 357.1580.

5g(slow): Colorless oil. $[\alpha]_D^{23}=+56.8°$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.34–7.21 (m, 5H), 6.52 (t, *J*=1.1 Hz, 1H), 4.67 (m, 1H), 4.25–4.19 (m, 2H), 3.68 (s, 3H), 3.32 (dd, *J*=13.5, 3.2 Hz, 1H), 2.83 (dd, *J*=13.5, 9.5 Hz, 1H), 2.62 (m, 2H), 1.66 (m, 2H), 1.43 (m, 2H), 0.94 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 172.7 (u), 171.6 (u), 153.8 (u), 135.7 (u), 129.9 (dn), 129.3 (dn), 127.7 (dn), 117.2 (u), 95.6 (u), 66.8 (u), 55.5 (dn), 52.6 (dn), 37.9 (u), 35.6 (u), 29.0 (u), 24.4 (u), 22.6 (u), 14.1 (dn); IR (CCl_4, cm^{-1}): 3153, 3058, 2958, 2933, 2873, 2363, 2321, 1785, 1734, 1717, 1693, 1436, 1387, 1312, 1251, 1213, 701; HRMS-CI *m/z* [M] calcd for $C_{20}H_{23}NO_5$, 357.1576; found, 357.1561.

4.4.9. Diastereomers of (4*S*)-4-benzyl-3-(2-phenyl-1-methoxycarbonyl-cycloprop-2-en-1-oyl)oxazolidinone: 5h(fast) and 5h(slow). The procedure was identical to that used to resolve **3g**, except that adamantoyl chloride (99 mg, 0.5 mmol) was used in place of pivaloyl chloride. The other materials were used in the following quantities: **3h** (109 mg, 0.5 mmol), Et_3N (61 mg, 0.084 mL, 0.6 mmol), THF (7 mL), (*S*)-benzyloxazolidinone (233 mg, 0.75 mmol), n-BuLi (0.3 mL of a 2.5 M solution in hexane, 0.75 mmol). Chromatography (20% MTBE in Petroleum Ether) gave **5h(fast)** (81 mg, 0.21 mmo1, 86%) and **5h(slow)** (84 mg, 0.22 mmo1, 89%). The R_f difference in MTBE:petroleum ether (1:1) was 45%. A similar experiment with 1.62 g of **3h** gave **5h(fast)** in 81% yield and **5h(slow)** in 79% yield.

5h(fast): A semisolid. $[\alpha]_D^{23}=+137.9$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.76 (m, 2H), 7.45(m, 3H), 7.32–7.18 (m, 5H), 7.00 (s, 1H), 4.71 (m, 1H), 4.30–4.21 (m, 1H), 3.70 (s, 3H), 3.35 (dd, *J*=13.4, 3.2 Hz, 1H), 2.81 (dd, *J*=13.4, 9.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 172.0 (u), 170.8 (u), 154.0 (u), 135.6 (u), 131.04 (dn), 130.97 (dn), 129.9(dn), 129.37 (dn), 129.32(dn), 127.8, (dn), 124.9 (u), 114.5 (u), 97.0 (u), 67.0 (u), 55.7 (dn), 52.9 (dn), 38.0 (u), 36.6(u); IR (CH_2Cl_2, cm^{-1}): 3154, 3066, 3031, 2953, 2359, 2338, 2274, 1784, 1739, 1718, 1695, 1387, 1354, 1312, 1214, 1111, 1083, 766; HRMS-CI *m/z* [M] calcd for $C_{22}H_{19}NO_5$, 377.1263; found, 377.1259.

5h(slow): A semisolid. $[\alpha]_D^{23}=-22.2$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.78 (m, 2H), 7.45(m, 3H), 7.24–7.17 (m, 5H), 7.00 (s, 1H), 4.68 (m, 1H), 4.26–4.20 (m, 2H), 3.71 (s, 3H), 3.35 (dd, *J*=13.6, 3.3 Hz, 1H), 2.91 (dd, *J*=13.6, 9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 172.0 (u), 170.7 (u), 154.0 (u), 135.6 (u), 131.04 (dn), 131.02 (dn), 129.95(dn), 129.34 (dn), 129.31(dn), 127.7 (dn), 124.9 (u), 114.4 (u), 97.1 (u), 67.0 (u), 55.7 (dn), 52.9 (dn), 37.9 (u), 36.5(u); IR (CH_2Cl_2, cm^{-1}): 3154, 3065, 3031, 2953, 2359, 2322, 2283, 1784, 1739, 1719, 1694, 1390, 1355, 1311, 1214, 1112, 1083, 768; HRMS-CI *m/z* [M] calcd for $C_{22}H_{19}NO_5$, 377.1263; found, 377.1256.

4.4.10. Diastereomers of (4*S*)-4-benzyl-3-(2-hexyl-1-*trans*-styryl-cycloprop-2-en-1-oyl)oxazolidinone: 5i(fast) and 5i(slow). The general procedure for resolution was followed using **3i** (108 mg, 0.4 mmol), 1-adamantoyl-chloride (84 mg, 0.42 mmol), Et_3N (202 mg, 2.0 mmol), LiCl (85 mg, 2.0 mmol), DMAP (5 mg, 0.04 mmol), (*S*)-benzyloxazolidione (75 mg, 0.42 mmol) and THF (30 mL). Chromatography (10% MTBE in Petroleum Ether) gave **5i(fast)** (64 mg, 0.15 mmol, 73%) and **5i(slow)** (63 mg, 0.15 mmol, 73%) of the title compounds as pale yellow oils. The purities of **5i(fast)** and **5i(slow)** were estimated by ^1H NMR to be >95 and >96%, respectively. The R_f difference in toluene:MTBE:petroleum ether (2:1:2) was 17%. A similar experiment with 1.62 g of **3i** gave **5i(fast)** in 73% yield and **5i(slow)** in 73% yield.

5i(fast): A pale yellow oil. $[\alpha]_D^{23}=+32.3°$ (*c* 1.00, THF). ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.32–7.16 (m, 10H), 6.71 (t, *J*=1.3 Hz, 1H), 6.55 (d, *J*=16.0 Hz, 1H), 6.18 (d, *J*=16.0 Hz, 1H), 4.73 (m, 1H), 4.23–4.15 (m, 2H), 3.34 (dd, *J*=13.4, 3.3 Hz, 1H), 2.79 (dd, *J*=13.4, 9.3 Hz, 1H), 2.58 (m, 2H), 1.64 (m, 2H), 1.40–1.26 (m, 6H), 0.87 (t, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.1 (u), 153.0 (u), 137.7 (u), 135.6 (u), 132.7 (dn), 129.9 (dn), 129.4 (dn), 128.9 (dn), 128.3 (dn), 127.8 (dn), 127.4 (dn), 126.5 (dn), 123.0 (u), 98.6 (u), 66.8 (u), 55.6 (dn), 38.2 (u), 35.1 (u), 31.9 (u), 29.3 (u), 27.4 (u), 25.1 (u), 23.0 (u), 14.5 (dn); IR (CH_2Cl_2, cm^{-1}): 3054, 2957, 2931, 2859, 2305, 1786, 1687, 1600, 1448, 1388, 1351, 1259, 1215, 1076, 959, 896, 757, 713; HRMS-CI, *m/z*: [M+Na]: calcd for $C_{28}H_{31}NO_3$, 452.2226; found, 452.2218.

5i(slow): A pale yellow oil. $[\alpha]_D^{23}$=+42.6 (*c* 1.00, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.31–7.16 (m, 10H), 6.68 (app s, 1H), 6.45 (d, *J*=16.1 Hz, 1H), 6.20 (d, *J*=16.1 Hz, 1H), 4.62 (m, 1H), 4.18–4.13 (m, 2H), 3.37 (dd, *J*=13.3, 3.1 Hz, 1H), 2.84 (dd, 1H), 2.62 (app t, *J*=7.2 Hz, 2H), 1.64 (m, 2H), 1.40–1.26 (m, 6H), 0.88 (t, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 175.6 (u), 152.8 (u), 137.8 (u), 135.8 (u), 132.9 (dn), 130.0 (dn), 129.4 (dn), 128.9 (dn), 128.4 (dn), 127.8 (dn), 127.5 (dn), 126.5 (dn), 123.1 (up), 99.7 (u), 66.7 (u), 56.1 (dn), 38.1 (u), 34.7 (u), 32.0 (u), 29.4 (u), 27.4 (u), 25.1 (u), 23.1 (u), 14.6 (dn); IR (CH_2Cl_2, cm^{-1}): 3054, 2958, 2931, 2858, 2305, 1788, 1686, 1600, 1385, 1350, 1270, 1076, 959, 909, 756, 710; HRMS-CI, *m/z*: [M+Na]: calcd for $C_{28}H_{31}NO_3$, 452.2226; found, 452.2187.

4.4.11. Diastereomers of (4*S*)-4-phenyl-3-[2-methyl-3-propylcycloprop-2-en-1-oyl]oxazolidinone: 5j(fast) and 5j(slow). The general procedure for resolution was followed using **3j** (400 mg, 2.86 mmol), 1-adamantoylchloride (622 mg, 3.14 mmol), Et_3N (1.01 g, 1.4 mL, 10 mmol), LiCl (600 mg, 14.3 mmol), DMAP (5 mg, 0.04 mmol), (*S*)-phenyloxazolidinone (75 mg, 0.42 mmol) and THF (30 mL). Chromatography (10% MTBE in hexane) gave **5j(fast)** (378 mg, 1.33 mmol, 93%) and **5j(slow)** (0.375 g, 1.32 mmol, 92%). A similar experiment gave **5j(fast)** in 92% yield and **5j(slow)** in 93% yield. The R_f difference in MTBE:toluene:hexane (1:1:2) was 28%.

5j(fast): White solid, 66.5–68 °C. $[\alpha]_D^{25}$=+143° (*c* 1.0, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.37–7.29 (m, 5H), 5.44 (dd, *J*=8.7, 4.0 Hz, 1H), 4.69 (app t, *J*=8.7 Hz, 1H), 4.26 (dd, *J*=8.8, 3.9 Hz, 1H), 3.35 (s, 1H), 2.39–2.34 (m, 2H), 1.95 (m, 3H), 1.61–1.54 (m, 2H), 0.95 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 177.2(u), 154.9(u), 140.0(u), 129.5 (dn), 128.9(dn), 126.3(dn), 105.3(u), 100.7(u), 70.4(u), 58.4(dn), 26.8(u), 23.5(dn), 20.9(u), 14.3(dn), 10.0(dn); IR (KBr, cm^{-1}): 3034, 2964, 1907, 1775, 1686, 1453, 1375, 1305, 1189, 1093, 765, 699; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{17}H_{20}NO_3$, 286.1443; found, 286.1453.

5j(slow): White solid, 43–46.5 °C. $[\alpha]_D$=+132° (*c* 1.0, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.36–7.26 (m, 5H), 5.45 (dd, *J*=8.7, 3.9 Hz, 1H), 4.69 (app t, *J*=8.8 Hz, 1H), 4.26 (dd, *J*=8.8, 4.0 Hz, 1H), 3.35 (s, 1H), 2.29–2.25 (m, 2H), 2.03–2.04 (t, *J*=1.5 Hz, 3H), 1.43–1.37 (m, 2H), 0.83 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ): 176.7(u), 154.4(u), 139.5(u), 129.0(dn), 128.4(dn), 125.9(dn), 104.8(u), 100.1(u), 70.0(u), 58.0(dn), 26.1(u), 23.0(dn), 20.3(u), 13.7(dn), 9.6(dn); IR (KBr, cm^{-1}): 3030, 2960, 1772, 1685, 1451, 1376, 1303, 1182, 1106, 166, 705; HRMS-CI(NH_3) *m/z*: [M+H], calcd for $C_{17}H_{20}NO_3$, 286.1443; found, 286.1453.

4.4.12. Diastereomers of (4*S*)-4-benzyl-3-(2-butyl-1-methoxymethoxymethyl-cycloprop-2-en-1-oyl)oxazolidinone: 5k(fast) and 5k(slow). The general procedure for resolution was followed using **3k** (86 mg, 0.4 mmol), 1-adamantoylchloride (83 mg, 0.42 mmol), Et_3N (202 mg, 0.28 mL, 2.0 mmol), LiCl (85 mg, 2.0 mmol), DMAP (5 mg, 0.04 mmol), (*S*)-benzyloxazolidinone (75 mg, 0.42 mmol) and THF (30 mL). Chromatography (20% MTBE in petroleum ether) gave **5k(fast)** (64 mg, 0.17 mmol, 86%) and **5k(slow)** (65 mg, 0.17 mmol, 86%). The R_f difference in MTBE:petroleum ether (4:6) was 40%. A similar experiment gave **5k(fast)** in 91% yield and **5k(slow)** in 90% yield.

5k(fast): A pale yellow oil. $[\alpha]_D$=+10.9 (*c* 1.0, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.34–7.20 (m, 5H), 6.78 (app t, *J*=1.2 Hz, 1H), 4.65–4.60 (m, 1H), 4.63 (s, 2H), 4.21 (m, 1H), 4.14 (m, 1H), 4.06 (d, *J*=11.3 Hz, 1H), 3.57 (d, *J*=11.3 Hz, 1H), 3.36 (m, 1H), 3.34 (s, 3H), 2.71 (dd, *J*=13.3, 9.7 Hz, 1H), 2.55 (app dt, *J*=1.0, 7.4 Hz, 2H), 1.60 (m 2H), 1.39 (m, 2H), 0.92 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 176.1 (u), 153.6 (u), 135.8 (u), 129.8 (dn), 129.3 (dn), 127.7 (dn), 123.3 (u), 100.1 (u), 96.4 (u), 72.9 (u), 67.0 (u), 55.67 (dn), 55.66(dn), 38.3 (u), 33.5 (u), 29.4 (u), 25.5 (u), 22.7 (u), 14.2 (dn); IR (CCl_4, cm^{-1}): 2956, 2930, 2875, 2228, 1784, 1691, 1605, 1454, 1386, 1350, 1215, 1150, 971; Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.26; H, 7.27; N, 3.68.

5k(slow): A pale yellow oil. $[\alpha]_D$=+31.5 (*c* 1.0, THF). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.32–7.20 (m, 5H), 6.72 (app t, *J*=1.2 Hz, 1H), 4.63 (s, 2H), 4.63–4.60 (m, 1H), 4.21 (m, 1H), 4.16 (m, 1H), 3.80 (s, 2H), 3.34 (s, 3H), 3.34 (dd, *J*=13.4, 3.2 Hz, 1H), 2.80 (dd, *J*=13.4, 9.5 Hz, 1H), 2.62 (m, 2H), 1.65 (m, 2H), 1.40 (m, 2H), 0.94 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 175.6 (u), 153.4 (u), 135.8 (u), 129.9 (dn), 129.3 (dn), 127.7 (dn), 123.9 (u), 101.5 (u), 96.4 (u), 73.1 (u), 67.0 (u), 56.1 (dn), 55.7(dn), 38.1 (u), 33.0 (u), 29.5 (u), 25.5 (u), 22.7 (u), 14.2 (dn); IR (CCl_4, cm^{-1}): 2957, 2930, 2874, 2232, 1787, 1690, 1604, 1454, 1386, 1350, 1213, 1150, 971; Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.67; H, 7.47; N, 3.76.

4.5. General procedures for reduction

A solution of the cycloprop-2-en-1-oyl oxazolidinone (1.0 mmol) in THF (30 mL) was cooled in an ice bath. Methanol (32 mg, 40 μL, 1.0 mmol) and $LiBH_4$(4.0 mmol, 2.0 mL of a 2.0 M solution in THF) were added sequentially. The ice bath was removed, and stirring was continued for 4 h while the mixture warmed to rt. The reaction was quenched by NH_4Cl (aq) and extracted with ether (3×30 mL). The organics were combined, dried (Na_2SO_4), filtered, concentrated, and chromatographed (10–30% ethyl acetate in hexane) to provide the 3-hydroxymethyl-cycloprop-1-ene.

4.5.1. (3*S*)-(−)-1-Hexyl-3-hydroxymethylcycloprop-1-ene [*S*-(−)-7]. The general procedure for reduction with **5a(S_{cy},S_{ox})** (327 mg, 1.0 mmol) gave 131 mg (0.85 mmol, 85%). The general procedure with **5a-Ph(S_{cy},R_{ox})** (313 mg, 1.0 mmol) gave 131 mg product, 85%. A similar experiment with 800 mg of **5a(S_{cy},S_{ox})** gave *S*-(−)-**7** in 86% yield. The specific rotation of the colorless oil was $[\alpha]_D$=−34.3° (*c* 1.03, THF). Analysis by HPLC (CHIRACEL OD using 15% IPA in hexane) showed the material to be of >99% ee. Other spectral data were identical to those reported for the racemate.[30]

4.5.2. (3*R*)-1,3-Diphenyl-3-hydroxymethylcycloprop-1-ene [*R*-(−)-6] and (3*S*)-1,3-diphenyl-3-hydroxymethyl-cycloprop-1-ene [*S*-(+)-6]. The general procedure for

reduction with **5c(R_{cy},R_{ox})** (320 mg, 0.81 mmol) gave 163 mg (91%) of *R*-(−)-**6**, a semisolid, $[\alpha]_D=-18.9°$ (*c* 1.1, THF). A similar experiment with 250 mg of **5c(R_{cy},R_{ox})** gave *R*-(−)-**6** in 86% yield. Analysis by HPLC (CHIRACEL OD using 15% IPA in hexane) showed the material to be of >99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.58–7.56 (m, 2H), 7.39–7.26 (m, 8H), 7.19–7.21(m, 1H), 4.29–4.33(m, 1H), 4.21–4.25(m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 145.2(u), 130.1(dn), 129.9(dn), 129.3(dn), 128.7(dn), 127.6(u), 126.9(dn), 126.3(dn), 123.0(u), 105.4(u), 68.1(u), 32.8(u); IR (CCl_4, cm^{-1}): 3595, 3282, 2875, 1717, 1508, 1265, 1065; HRMS-CI(NH_3) *m*/*z*: [M+H] calcd for $C_{16}H_{13}O$, 221.0966; found, 221.0960.

Similarly, reduction of **5c(S_{cy},R_{ox})** (320 mg, 0.81 mmol) gave 160 mg (89%) of *S*-(+)-**6**, $[\alpha]_D=+18.7°$ (*c* 1.0, THF), >99% ee. A similar experiment with 200 mg of **5c(S_{cy},R_{ox})** gave *R*-(+)-**6** in 85% yield

4.5.3. (+)-1-Butyl-3-hydroxymethyl-3-phenylcycloprop-1-ene [(+)-9]. The general procedure for reduction with **5d(fast)** (373 mg, 1.0 mmol) gave 167 mg (0.83 mmol, 83%) of (+)-**9**, a colorless oil. A similar experiment that started with 500 mg of **5d(fast)** gave (+)-**9** in 82% yield. Analysis by HPLC (CHIRACEL OD using 15% IPA in hexane) showed the material to be of >99% ee. $[\alpha]_D=+23.1°$ (*c* 1.0, THF). Other spectral data were identical to those reported for the racemate.[30]

4.5.4. (1*S*,2*S*)-(−)-1-Hexyl-2-hydroxymethyl-1-vinylcyclopropane [(1*S*,2*S*)-(−)-8] was prepared from (*S*)-(−)-7 in the same way as the racemate.[30] Gas Chromatography on a Chiraldex B-PH column showed the material to be of >99% ee. The injection temperature for the GC was 120 °C. The GC oven temperature was increased from 70° to 90° at a rate of 1.0 °C/min, from 90 °C to 110 °C at 0.2 °C/min, and then from 110 °C to 150 °C at 5.0 °C/min. The product is a clear oil, $[\alpha]_D=-3.0°$ (*c* 1.0, THF). Other spectral data were identical to those reported for the racemate.[30]

4.5.5. (+)-1α-Butyl-2β-hydroxymethyl-1β-methyl-2α-phenylcyclopropane (+)-10]. Was prepared from (+)-(**9**) in the same way as the racemate.[30] Gas Chromatography with a Chiraldex B-PH column showed the material to be of >99% ee. The injection temperature for the GC was 120 °C. The GC oven temperature was increased from 90° to 110° at a rate of 1.0 °C/min, from 110 °C to 140 °C at 0.5 °C/min, and then from 140 °C to 150 °C at 1.0 °C/min. The product is a clear oil, $[\alpha]_D=+7.8°$ (*c* 1.0, THF). Other spectral data were identical to those reported for the racemate.[30]

Acknowledgements

The project described was supported by NIH Grant Number P20 RR017716-01 from the COBRE Program of the National Center for Research Resources.

References and notes

1. Halton, B.; Banwell, M. G. In *The chemistry of the cyclopropyl group*. Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1987; pp 1224–1339.
2. Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 137.
3. Baird, M. S.; Schmidt, T.; 4th ed. *Carbocyclic three-membered ring compounds*, de Meijere, A., Ed.; Georg Thieme: Stuttgart, 1996; Vol. E17a, pp 114–255.
4. Baird, M. S.; Bushby, R. J.; Schmidt, T.; 4th ed. *Carbocyclic three-membered ring compounds*, de Meijere, A., Ed.; Georg Thieme: Stuttgart, 1996; Vol. E17d, pp 2695–2860.
5. Hopf, H. *Carbocyclic three-membered ring compounds*, de Meijere, A., Ed.; Georg Thieme: Stuttgart, 1996; Vol. E17d, pp 2745–2746.
6. Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295.
7. Padwa, A.; Fryxell, G. E. *Advances in strain in organic chemistry*, Halton, B., Ed.; Jai: Greenwich, CT, 1991; Vol. 1.
8. York, E. J.; Dittmar, W.; Stevenson, J. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 5680.
9. Doyle, M. P.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492.
10. Müller, P.; Imogai, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419.
11. Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Pillow, T. H. *Chem. Commun.* **1999**, 1691.
12. Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617*, 98.
13. Doyle, M. P.; Hu, W. *Tetrahedron Lett.* **2000**, *41*, 6265.
14. Doyle, M. P.; Hu, W. H. *Synlett* **2001**, 1364.
15. Schöllkopf, U.; Hupfeld, B.; Küper, S.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 433.
16. Baird, M. S.; Fitton, H. L.; Clegg, W.; McCamley, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 321.
17. Imogai, H.; Bernardinelli, G.; Granicher, C.; Moran, M.; Rossier, J. C.; Muller, P. *Helv. Chim. Acta* **1998**, *81*, 1754.
18. Arrowood, T. L.; Kass, S. R. *J. Am. Chem. Soc.* **1999**, *121*, 7272.
19. Diaz-Requejo, M. M.; Mairena, M. A.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Chem. Commun.* **2001**, 1804. and references cited therein.
20. Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssie, P. H. *Tetrahedron Lett.* **1978**, *14*, 1239.
21. Protopopova, M. N.; Shapiro, E. A. *Russ. Chem. Rev. (Engl. Transl.)* **1989**, *58*, 667.
22. The report that a chiral Cu-catalyst also gives non-racemic cyclopropenes seems to be in error, based on the reported NMR spectra: Cho, D.-J.; Jeon, S.-J.; Kim, H. S.; Cho, C.-S.; Shim, S.-C.; Kim, T.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 3833.
23. Doyle, M. P.; Ene, D. G.; Peterson, C. S.; Lynch, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 700.
24. Hanessian, S. *Pure Appl. Chem.* **1993**, *65*, 1189.
25. Baird, M. S.; Huber, F. A. M.; Clegg, W. *Tetrahedron* **2001**, *57*, 9849.
26. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198.
27. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566.
28. Araki, S.; Shiraki, F.; Tanaka, T.; Nakano, H.; Subburaj, K.; Hirashita, T.; Yamamura, H.; Kawai, M. *Chem. Eur. J.* **2001**, *7*, 2784.
29. Boger, D. L.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453. and references therein.
30. Liao, L.-a.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322.
31. For representative crystal structures of *N*-acyloxazolidnones,

see: (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (b) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009. (c) Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 5107.
32. Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3511. and references therein.
33. Donaldson, W. A.; Hughes, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 4846.
34. Wheeler, T. N.; Ray, *J. Org. Chem* **1987**, *52*, 4875.
35. (*S*)-phenyloxazolidione, (*S*)-benzyloxazolidinone and (1*R*,2*S*)-1-amino-2-indanol were purchased from Chemicrea Inc., Tokyo, JAPAN.
36. Gage, J. R.; Evans, D. A. *Org. Syn.* **1993**, Coll. Vol. 8, p 528.
37. Pridgen, L. N.; Prol, Jr. J.; Alexander, B.; Gillyard, L. *J. Org. Chem.* **1989**, *54*, 3231.
38. Verhoeven, T. R.; Ryan, K. M.; Senanayake, C. H.; Reider, P. J.; Jacobsen, E. N. *Org. Synth.* **1999**, *76*, 46.
39. Mühlman, A.; Lindberg, J.; Classon, B.; Unge, T.; Hallsberg, A.; Samuelsson, B. *J. Med. Chem.* **2001**, *44*, 3407.
40. Ho, G.-J.; Mathre, J. *J. Org. Chem.* **1995**, *60*, 2271.
41. Ager, D. J.; Allen, D. R.; Schaad, D. R. *Synthesis* **1996**, 1283.
42. Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063.
43. Dharanipragada, R.; Nicolas, E.; Toth, G.; Hruby, V. J. *Tetrahedron Lett.* **1989**, *30*, 6841.
44. R_x=R_f(fast)/R_f(slow).
45. Taber, D. F.; Yu, H. *J. Org. Chem.* **1996**, *62*, 1687.
46. Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1993**, *76*, 521.
47. Starmans, W. A. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 629.
48. Müller, P.; Pautex, N.; Doyle, M. P.; Bagheri, V. *Helv. Chim. Acta* **1990**, *73*, 1223.
49. Davies, H. M. L.; Townsend, *J. Org. Chem.* **2001**, *66*, 6595–6603.
50. Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947.
51. Davies, H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1817–1826
Tetrahedron

Wittig approach to carbohydrate-derived vinyl sulfides, new substrates for regiocontrolled ring-closure reactions

Vincent Aucagne, Arnaud Tatibouët and Patrick Rollin*

Institut de Chimie Organique et Analytique-UMR CNRS 6005, Université d'Orléans, BP 6759, F-45067 Orléans Cedex 2, France

Received 1 October 2003; revised 12 December 2003; accepted 15 December 2003

Abstract—Reaction of methyl- and phenylthiomethylidene phosphoranes **1** and **2** with a variety of reducing sugars has been explored. Furano-type carbohydrates afforded with good yields the corresponding open-chain vinyl sulfides, whereas pyrano derivatives produced elimination compounds together with the expected vinyl sulfides, depending on the nature of the protective groups.

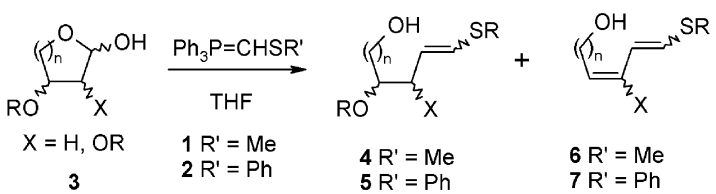
1. Introduction

Carbohydrate-derived open-chain vinyl sulfides have been recognized as useful intermediates for the synthesis of diverse carbohydrate mimics or derivatives.[1–5] Since vinyl sulfides can easily be converted into other interesting functionalities and/or selectively activated with various electrophiles,[6] formation of such carbohydrate building blocks appeared essential to be studied. Carbohydrate-based vinyl sulfides have previously been prepared using diverse methodologies including Vasella's fragmentation reaction,[1] Grignard reagent-induced Grob-type fragmentation[2] or various eliminative methodologies.[7] Whereas the Wittig reaction applied to reducing sugars has been routinely used in glycochemistry,[8] only a limited number of examples involving thiofunctionalized phosphoranylidene reagents have been reported.[5] We have therefore explored the applicability of the Wittig reaction to produce various vinyl sulfides in different carbohydrate series.

2. Results and discussion

A range of protected reducing sugars were prepared from commercially available precursors and reacted with phosphoranes **1** and **2** generated in situ, from their respective phosphonium salts precursors using *n*-butyllithium in anhydrous THF. The results for these Wittig condensations (Scheme 1) on lactols under standard conditions (THF, room temperature) are summarized in Table 1.

As a first observation, it appeared that pyrano- or furano-lactols containing one or more extra free hydroxyl groups—as for 4,6-*O*-benzylidene-D-glucopyranose or 2,3-*O*-isopropylidene-D-ribose—did not react correctly with either ylide **1** or **2** under standard conditions and applying heat to the reactions only resulted in complex mixtures of products. In contrast, Table 1 shows that lactols **3a–f** can react smoothly at room temperature with both ylides to deliver **4a–f** with good to excellent yields in the form of *E*/*Z* isomeric mixtures. Among the above lactols, only **3a** produced a small amount of a mixture of conjugated dienes **7a** resulting from base-induced α,β-elimination close to the anomeric group prior to Wittig reaction[9] (entry a, R=Ph). Due to the high complexity of their NMR spectra, all mixtures of such isomeric dienes further evocated in this paper were only characterized using HRMS.



X = H, OR
3

1 R' = Me
2 R' = Ph

4 R' = Me
5 R' = Ph

6 R' = Me
7 R' = Ph

Scheme 1. Standard Wittig reaction and elimination side-reaction.

Keywords: Carbohydrates; Wittig reaction; Vinyl sulfides; Ring-closure reaction.
* Corresponding author. Tel.: +332-38-41-73-70; fax: +332-38-41-72-81; e-mail address: patrick.rollin@univ-orleans.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.040

The apparent lack of coherence in *Z*/*E* selectivity observed during this process is usual for reactions of phosphoranylidene reagents with chiral lactols. Some authors have shown the influence of hydrogen bonding between the free hydroxyl group and the oxaphosphetane intermediate obtained from a stabilized phosphorane.[10]

In the case of compound **3c**, the Wittig reaction proved to be applicable in the presence of a pivaloyl protecting group to afford **4c** or **5c** in reasonable yield while also producing appreciable amounts of the de-acylated compounds **8** and **9**—isolated and characterized as their respective di-*O*-acetyl derivatives **10** and **11**—and of the bis-pivaloates **12** and **13** resulting from transesterification processes. Application of catalytic basic conditions (NaH 0.1 equiv., THF, RT, 5 h) to the vinyl sulfide **4c** also led to the formation of **8** and **12** (Scheme 2).

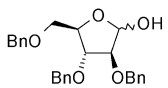
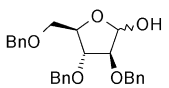
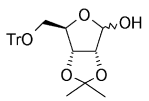
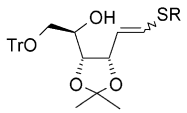
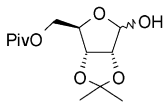
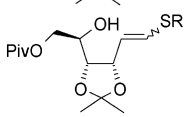
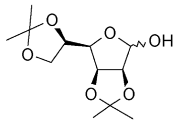
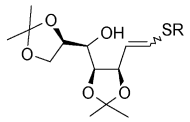
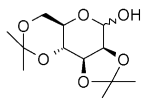
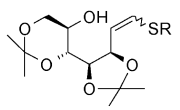
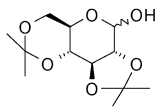
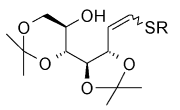
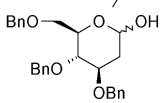
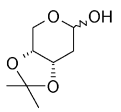
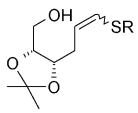
In some cases, direct purification was not effective, as with compound **5e** which could not be obtained exempt from triphenylphosphine oxide contamination. A subsequent acetylation (intermediate **14**)/deacetylation two-step sequence had to be applied to afford pure **5e** in excellent yield.

Considering all the results obtained, it clearly appeared that within the furano-lactol series, whatever the protecting group, the Wittig reaction was quite efficient. In only one case, a small amount of elimination product was obtained. In contrast, with pyrano derivatives, the condensation seemed to be much more complex. 2-Deoxy pyranoses **3g** and **3h** appeared more prone to elimination: 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose **3g** quantitatively furnished mixtures of the elimination products **6g** or **7g**, whereas 4,5-*O*-isopropylidene-D-ribopyranose **3h** led to mixtures of the expected vinyl sulfides **4h** or **5h** and elimination products **6h** or **7h**. All our attempts to obtain **4g** under modified conditions were unsuccessful: either pretreatment of lactols by *n*-butyllithium in THF[11] or addition of tributyltin chloride[12] to the reaction mixture failed to prevent elimination.

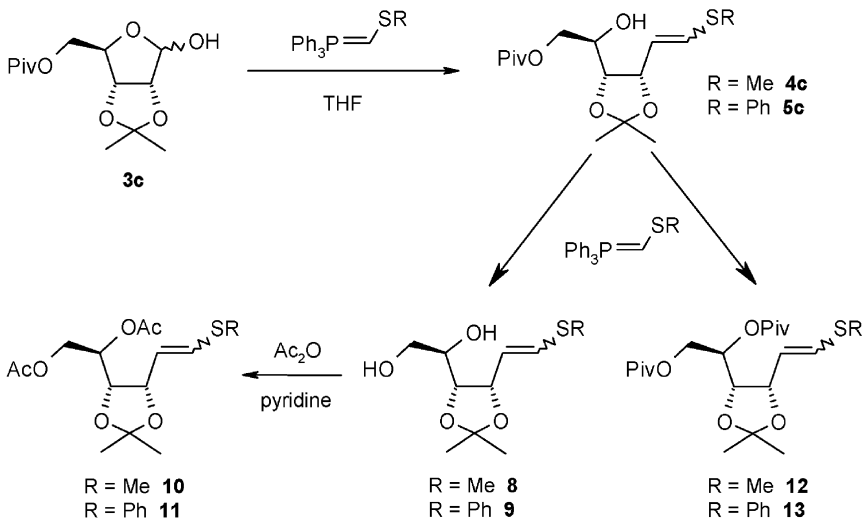
A similar outcome was obtained when starting from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose or 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose, which are known for their low reactivity and their ability to eliminate or epimerize under such Wittig conditions.[9]

From the above results, it can be seen that furano-lactols

Table 1.

Entry	Reducing sugar **3**	Vinyl sulfides	**4**, R=Me **5**, R=Ph Yield (%)		**4**, R=Me **5**, R=Ph *E*/*Z* ratio		**6**, R=Me **7**, R=Ph Yield (%)	
a			96	77	>95/5	85/15	—	6
b			86	94	57/43	17/83	—	—
c			64[a]	57[b]	45/55	20/80	—	—
d			92	86	81/19	41/59	—	—
e			98	87[c]	4/96	13/87	—	—
f			75	71	19/81	5/95	—	—
g		—	—	—	—	—	96	95
h			64	62	75/25	40/60	23	18

[a] 23% of the 5,6-diol resulting from de-*O*-pivaloylation was also isolated as its diacetate derivative **10**.
[b] 28% of the 5,6-diol resulting from de-*O*-pivaloylation was also isolated as its diacetate derivative **11**.
[c] Yield including acetylation and deacetylation steps.



Scheme 2. Application to a 5-*O*-pivaloylated sugar.

constitute suitable substrates for the thio-functionalized phosphoranylidene-type Wittig reaction when no free hydroxyl is present. In the case of pyrano-lactols, protecting groups are critical to favor the Wittig reaction. To avoid the elimination process with alkoxy groups such as *O*-benzyl, cyclic ketals such as *O*-isopropylidene might be used and are less detrimental to the Wittig reaction.

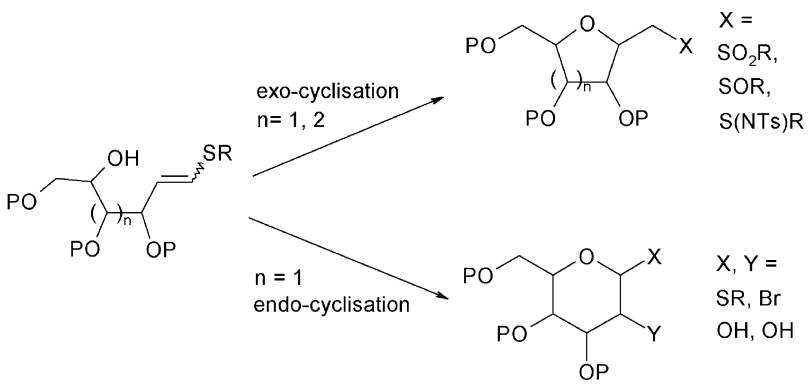
Vinyl sulfides are a functional class which has offered substantial applications in organic synthesis.[6] Deliberately stepping aside from standard solvolytic type C–S cleavages, which have previously been explored,[4,5a,13,14] we have undertaken a preliminary exploration of the ability of our multi-chiral vinyl sulfides to undergo regio- and stereoselective ring-closure: ring-formation via *endo*- or *exo*-cyclisation pathways can be achieved selectively, depending on the reaction conditions (Scheme 3). The *E*/*Z* mixtures of isomers should be considered in ring closing reactions, as *E* or *Z* isomers could produce opposite results in the stereochemical outcome.[15]

exo-Type cyclisations are under current development using a somewhat simple two-step procedure: oxidation of the sulfide moiety into sulfone—or another electron-withdrawing thio-function—followed by base-promoted intramolecular Michael addition led to *exo*-products.[16] This work opening a stereoselective access to novel thio-functionalized *C*-glycosides will shortly be published.[17]

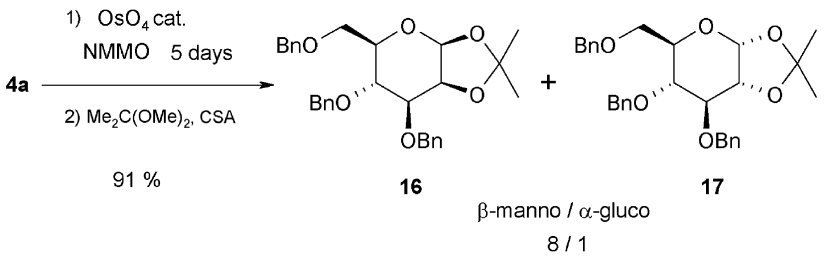
Various methodologies have been explored to perform *endo*-type cyclisation of the above vinyl sulfides: NBS-induced ring closure inspired by the pioneering work of Gallucci et al.[18] gave promising results which are being currently developed in the laboratory.[19] Osmium tetroxide assisted cyclisation has also been investigated: as an illustration, treatment of vinyl sulfide **4a** by a catalytic amount of OsO_4 using *N*-methyl morpholine as co-oxidant led to the diastereoselective formation of α-hydroxy lactols **15** which were characterized as their isopropylidene derivatives **16** and **17** (Scheme 4).[20] To our knowledge, this constitutes the first report on the osmylation of a vinyl sulfide derivative.

In order to clarify the mechanism of this process, the reaction medium was quenched and processed before completion. ^{1}H NMR spectroscopy of the crude allowed indirect follow-up of the reaction pathway.

At the early stage of the process, vinyl sulfone **18** was formed through the transient vinyl sulfoxide **19**.[21] This oxidative process was in competition with the fast direct osmylation of vinyl sulfide **4a** leading to a mixture of α- and



Scheme 3. Regioselective ring closures of the vinyl sulfides.



Scheme 4. Osmylation of vinyl sulfide **4a**.

β-lactols **15**. After 4 h reaction, **15** and **18** were the two sole components of the reaction mixture (4:6 ratio). In a second stage, the consumption of **18** was concomitant with the formation of lactols **15**. The kinetic of this transformation was quite slow due to electron deficiency of the double bond in sulfone **18**. After few days, lactols **15** had become essentially the sole product. With a view to better categorizing the process, osmium tetroxide oxidation was separately performed on vinyl sulfoxide **19** and vinyl sulfone **18**, which both similarly gave lactol **15** in a nearly quantitative yield. This led us to suggest the following mechanism for this oxidative ring-closing process (Scheme 5).

After the first oxidation stages, the resulting unstable *O*,*S*-hemiketal rearranged into the corresponding aldehyde, which is the tautomeric form of lactol **15**. Stereoselectivity of the reaction is therefore attributed to the osmylation step and is in complete agreement with Kishi's empirical rule for dihydroxylation of allylic alcohol derivatives.[22]

3. Conclusions

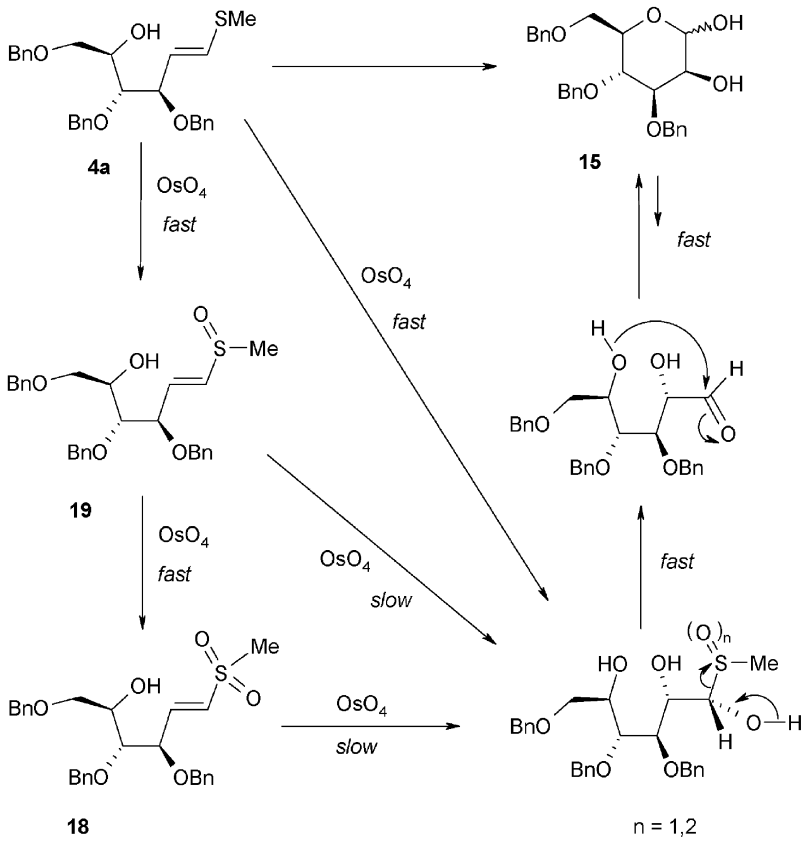
The synthesis of open-chain γ-hydroxy vinyl sulfides can efficiently be performed by treating suitably protected furano- or pyrano-lactols by thiofunctionalized phosphoranylidene reagents. The results for this Wittig reaction are more contrasted in the case of pyrano-lactols, depending on the protective groups.

Preliminary experiments allow to spot out the above vinyl sulfides as promising intermediates for the elaboration of stereoselectively functionalized carbohydrate mimics, and in particular new and selectively protected lactols.

4. Experimental

4.1. General methods

Melting points were determined on a Köfler hot-stage



Scheme 5. Proposed mechanism for the osmylation of vinyl sulfide **4a**.

apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX250 at 250 and 62.89 MHz, respectively. The chemical shifts (δ) are reported in ppm downfield from TMS as the internal standard. Coupling constants (J) are reported in Hz. Specific rotations were measured at 20 °C using a Perkin–Elmer polarimeter 141. HR-ESI-TOF-mass spectra were recorded on a Micromass LC TOF spectrometer. Evaporation was conducted in vacuo with a Büchi rotary evaporator. Analytical TLC was carried out on precoated silica gel 60F-254 plates (E. Merck) and spots were detected by UV light (254 nm) and by heat treatment with a 10:85:5 mixture of sulfuric acid, ethanol and water. Flash column chromatography was performed on Kieselgel 60 (230–400 mesh) silica gel (E. Merck). Methylthiomethyl triphenylphosphonium chloride was prepared from methylthiomethyl chloride.[23] Phenylthiomethyl triphenylphosphonium chloride was purchased from Lancaster.

4.2. Chemical procedure

4.2.1. General method for the synthesis of vinyl sulfides. A 1.6 M *n*-butyllithium solution in hexanes (2.19 mL, 3.5 mmol) was added slowly to an ice-cold suspension of 3.5 mmol methylthiomethyl or phenylthiomethyl triphenylphosphonium chloride in 10 mL dry THF. After 30 min stirring at room temperature, 1 mmol lactol was added. Non-solid lactols were solubilized in a small volume of dry THF prior to addition. The solution was stored at room temperature for 48 h, quenched with water (10 mL), extracted (3×10 mL ethyl acetate) then dried over $MgSO_4$. Evaporation of the solvents gave a brownish solid which was purified by flash column chromatography.

4.2.2. 1-(*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-methylthio-D-*arabino*-hex-1-enitol (4a). Prepared from commercial 2,3,5-tri-*O*-benzyl-D-arabinofuranose **3a**. Eluent: petroleum ether–ethyl acetate 85:15; yellow oil; $[\alpha]_D$=+30 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, MeS), 3.54–3.62 (m, 3H, H-4, H-6a, H-6b), 4.01 (m, 1H, H-5), 4.11 (dd, 1H, J_{2-3}=8.1 Hz, J_{3-4}=3.9 Hz, H-3), 4.34 (d, 1H, J_{gem}=11.9 Hz, CH_2Ph), 4.47–4.65 (m, 5H, CH_2Ph), 5.43 (dd, 1H, J_{1-2}=15.3 Hz, H-2), 6.28 (d, 1H, H-1), 7.22–7.37 (m, 15H, H_{Ar}). ^{13}C NMR: δ 14.8 (MeS), 70.8 (C-5 and CH_2Ph), 71.4 (C-6), 73.8, 74.6 (CH_2Ph), 80.2 (C-3), 81.4 (C-4), 121.5 (C-1), 130.4 (C-2), 128.2, 128.3, 128.5, 128.6, 128.8, 128.9, 138.4, 138.5, 138.6 (C_{Ar}). HRMS: $C_{28}H_{32}O_4S$ calcd. 464.2021; found 464.2032.

4.2.3. 3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-phenylthio-D-*arabino*-hex-1-enitols (5a). Prepared from commercial 2,3,5-tri-*O*-benzyl-D-arabinofuranose **3a**. Eluent: petroleum ether–ethyl acetate 85:15; colorless oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 2.73–2.83 (m, 1H, OH), 3.54–3.62 (m, 3H, H-4, H-6a, H-6b), 4.01 (m, 1H, H-5), 4.16 (ddd, 1H, J_{1-3}=0.6 Hz, J_{2-3}=7.5 Hz, J_{3-4}=3.5 Hz, H-3), 4.34 and 4.63 (2d, 2H, J_{gem}=11.2 Hz, CH_2Ph), 4.48 (s, 2H, CH_2Ph), 4.52 and 4.58 (2d, 2H, J_{gem}=11.4 Hz, CH_2Ph), 5.84 (dd, 1H, J_{1-2}=15.4 Hz, H-2), 6.42 (dd, 1H, H-1), 7.22–7.47 (m, 20H, H_{Ar}); *Z* isomer: δ 2.96 (m, 1H, OH), 3.54–3.62 (m, 2H, H-6a, H-6b), 3.69 (dd, 1H, J_{3-4}=3.8 Hz, J_{4-5}=6.6 Hz, H-4), 4.01 (m, 1H, H-5), 4.35–4.78 (m, 7H, H-3, 3×CH_2Ph), 5.95 (dd, 1H, J_{1-2}=9.7 Hz, J_{2-3}=9.7 Hz, H-2), 6.50 (dd, 1H, J_{1-3}=0.6 Hz, H-1), 7.22–7.47 (m, 20H, H_{Ar}). ^{13}C NMR: *E* isomer: δ 70.3 (C-5), 70.9 (CH_2Ph), 71.0 (C-6), 73.4, 74.3 (CH_2Ph), 79.4 (C-3), 80.7 (C-4), 128.0 (C-1), 128.5 (C-2), 127.2, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 134.4, 137.8, 138.1 (C_{Ar}); *Z* isomer (selected peaks): δ 70.7 (C-5), 71.1 (CH_2Ph), 71.2 (C-6), 73.4, 74.1 (CH_2Ph), 75.9 (C-3), 80.4 (C-4). HRMS: $C_{33}H_{34}O_4S$ calcd. 526.2178; found 526.2183.

4.2.4. 1,2-Dideoxy-3,4-*O*-isopropylidene-1-methylthio-6-*O*-trityl-D-*ribo*-hex-1-enitols (4b). Prepared from 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose **3b**.[24] Eluent: petroleum ether–ethyl acetate 90:10; colorless oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.32 (s, 6H, Me_2C), 2.17 (s, 3H, SMe), 2.64 (m, 1H, OH), 3.25–3.42 (m, 2H, H-6a, H-6b), 3.68–3.85 (m, 1H, H-5), 4.03–4.24 (m, 1H, H-4), 4.71 (dd, 1H, J_{2-3}=7.8 Hz, J_{3-4}=6.7 Hz, H-3), 5.47 (dd, 1H, J_{1-2}=14.9 Hz, H-2), 6.35 (dd, 1H, H-1), 7.12–7.52 (m, 5H, HAr); *Z* isomer: δ 1.32, 1.35 (2s, 2×3H, Me_2C), 2.17 (s, 3H, SMe), 2.64 (m, 1H, OH), 3.25–3.42 (m, 2H, H-6a, H-6b), 3.68–3.85 (m, 1H, H-5), 4.03–4.24 (m, 1H, H-4), 5.06 (dd, 1H, J_{2-3}=9.2 Hz, J_{3-4}=6.4 Hz, H-3), 5.61 (dd, 1H, J_{1-2}=9.4 Hz, H-2), 6.16 (dd, 1H, H-1), 7.12–7.52 (m, 5H, HAr). ^{13}C NMR: *E* isomer: δ 14.4 (MeS), 25.3, 27.8 (2*Me), 65.1 (C-6), 69.2 (C-5), 77.9 (C-4), 78.6 (C-3), 86.7 (*C*Ph_3), 108.4 (C_{IV}-iPrd), 120.0 (C-2), 127.0, 127.8, 128.6 (C_{Ar}), 129.2 (C-1), 143.8 (C_{Ar}); *Z* isomer: δ 17.4 (MeS), 25.3, 27.7 (2*Me), 65.1 (C-6), 69.8 (C-5), 74.7 (C-3), 77.8 (C-4), 86.6 (*C*Ph_3), 108.6 (C_{IV}-iPrd), 123.6 (C-2), 127.0, 127.8, 128.6 (C_{Ar}), 131.9 (C-1), 143.8 (C_{Ar}). HRMS: $C_{29}H_{32}O_4S$ calcd 476.2021; found 476.2013.

4.2.5. 1,2-Dideoxy-3,4-*O*-isopropylidene-1-phenylthio-6-*O*-trityl-D-*ribo*-hex-1-enitols (5b). Prepared from 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose **3b**.[24] Eluent: petroleum ether–ethyl acetate 90:10; colorless oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.33, 1.36 (2s, 2×3H, Me_2C), 2.50 (m, 1H, OH), 3.32–3.37 (m, 2H, H-6a, H-6b), 3.62–3.75 (m, 1H, H-5), 4.14 (dd, 1H, J_{3-4}=8.7 Hz, J_{4-5}=6.3 Hz, H-4), 4.74 (dd, 1H, J_{2-3}=7.0 Hz, H-3), 5.92 (dd, 1H, J_{1-2}=15.1 Hz, H-2), 6.49 (dd, 1H, H1); *Z* isomer: δ 1.36, 1.37 (2s, 2×3H, Me_2C), 2.34 (m, 1H, OH), 3.32–3.37 (m, 2H, H-6a, H-6b), 3.72–3.85 (m, 1H, H-5), 4.24 (dd, 1H, J_{3-4}=8.1 Hz, J_{4-5}=6.5 Hz, H-4), 5.20 (dd, 1H, J_{2-3}=8.7 Hz, H-3), 5.83 (dd, 1H, J_{1-2}=9.3 Hz, H-2), 6.45 (dd, 1H, H-1), 7.22–7.37 (m, 15H, H_{Ar}). ^{13}C NMR: *E* isomer (selected peaks): δ 21.6, 27.9 (2*Me), 65.2 (C-6), 69.3 (C-5), 78.1 (C-4), 78.4 (C-3), 86.9 (*C*Ph_3), 109.0 (C_{IV}-iPrd), 125.4 (C-2), 130.0 (C-1); *Z* isomer (selected peaks): δ 25.5, 27.9 (2*Me), 65.0 (C-6), 69.9 (C-5), 75.0 (C-3), 78.1 (C-4), 86.9 (*C*Ph_3), 109.0 (C_{IV}-iPrd), 126.9 (C-2), 128.5 (C-1). HRMS: $C_{34}H_{34}O_4S$ calcd 538.2178; found 538.2190.

4.2.6. 1,2-Dideoxy-3,4-*O*-isopropylidene-1-methylthio-6-*O*-pivaloyl-D-*ribo*-hex-1-enitols (4c). Reaction of 2,3-*O*-isopropylidene-5-*O*-pivaloyl-D-ribofuranose **3c**[25] with phosphorane **1** afforded a mixture of **4c**, a de-*O*-acylated compound **8** and its di-*O*-pivaloylated derivative **12** that could easily be separated using standard flash column chromatography. Due to its contamination with reaction side-products including triphenylphosphine oxide, **8** could not be satisfactorily characterized: it was therefore, peracetylated under standard procedure to give pure **10**.

Vinyl sulfide **4c**. Eluent: petroleum ether–ethyl acetate 80:20; yellowish oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.24 (s, 9H, Me_3C), 1.36, 1.47 (2s, 2×3H, Me_2C), 2.33 (m, 1H, OH), 2.29 (s, 3H, SMe), 3.75–3.92 (m, 1H, H-5), 4.01–4.21 (m, 3H, H-6b, H-5, H-4), 4.30–4.43 (m, 1H, H-6a), 5.08 (ddd, 1H, J_{2-3}=8.8 Hz, J_{3-4}=6.0 Hz, J_{1-3}=0.9 Hz, H-3), 5.70 (dd, 1H, J_{1-2}=15.1 Hz, H-2), 6.35 (dd, 1H, H-1); *Z* isomer: δ 1.23 (s, 9H, Me_3C), 1.37, 1.47 (2s, 2×3H, Me_2C), 2.33 (m, 1H, OH), 2.31 (s, 1H, SMe), 3.75–3.92 (m, 1H, H-5), 4.01–4.21 (m, 3H, H-6b, H-5, H-4), 4.30–4.43 (m, 1H, H-6a), 4.76 (ddd, 1H, J_{2-3}=7.3 Hz, J_{3-4}=6.0 Hz, J_{1-3}=1.0 Hz, H-3), 5.51 (dd, 1H, J_{1-2}=15.1 Hz, H-2), 6.35 (dd, 1H, H-1). ^{13}C NMR: *E* isomer: δ 14.7 (MeS), 25.4, 27.8 (2*Me), 27.3 (Me_3C), 39.0 (CMe_3), 66.7 (C-6), 69.5 (C-5), 77.4 (C-4), 78.6 (C-3), 109.2 (C_{IV}-iPrd), 119.7 (C-2), 132.6 (C-1), 179.2 (CO); *Z* isomer: δ 17.6 (MeS), 25.4, 27.8 (2*Me), 27.3 (Me_3C), 39.0 (CMe_3), 65.5 (C-6), 69.1 (C-5), 74.7 (C-3), 77.7 (C-4), 108.9 (C_{IV}-iPrd), 123.4 (C-2), 130.2 (C-1), 179.0 (CO). HRMS: $C_{15}H_{26}O_5S$ calcd 318.1501; found 318.1497.

4.2.7. 5,6-Di-*O*-acetyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-methylthio-D-*ribo*-hex-1-enitols (10). Obtained from acetylation of raw **8**. Eluent: petroleum ether–ethyl acetate 90:10; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.37, 1.48 (2s, 2×3H, Me_2C), 2.02, 2.06 (2s, 2×3H, CH_3CO), 2.23 (s, 3H, SMe), 4.04–4.16 (m, 1H, H-6b), 4.25 (dd, 1H, J_{3-4}=9.0 Hz, J_{4-5}=6.4 Hz, H-4), 4.47–4.62 (m, 1H, H-6a), 4.75 (ddd, 1H, J_{2-3}=8.2 Hz, J_{3-4}=6.1 Hz, J_{1-3}=0.9 Hz, H-3), 4.95–5.13 (m, 1H, H-5), 5.25 (dd, 1H, J_{1-2}=14.7 Hz, H-2), 6.43 (dd, 1H, H-1); *Z* isomer: δ 1.39, 1.48 (2s, 2×3H, Me_2C), 2.02, 2.06 (2s, 2×3H, CH_3CO), 2.29 (s, 3H, SMe), 4.04–4.16 (m, 1H, H-6b), 4.30 (dd, 1H, J_{3-4}=8.3 Hz, J_{4-5}=6.4 Hz, H-4), 4.47–4.62 (m, 1H, H-6a), 4.95–5.13 (m, 2H, H-3, H-5), 5.56 (dd, 1H, J_{1-2}=9.8 Hz, H-2), 6.20 (dd, 1H, H-1). ^{13}C NMR: *E* isomer: δ 14.1 (MeS), 20.8, 21.1 (CH_3CO), 25.1, 27.6 (2*Me), 63.3 (C-6), 69.3 (C-5), 75.4 (C-4), 81.6 (C-3), 109.0 (C_{IV}-iPrd), 122.8 (C-1), 130.9 (C-2), 169.9, 170.8 (CO); *Z* isomer: δ 17.5 (MeS), 20.8, 20.9 (CH_3CO), 25.2, 27.6 (2*Me), 63.3 (C-6), 69.7 (C-5), 74.5 (C-3), 75.3 (C-4), 109.2 (C_{IV}-iPrd), 117.8 (C-1), 132.4 (C-2), 170.0, 170.8 (CO). HRMS: $C_{14}H_{22}O_6S$ calcd 318.1137; found 318.1124.

4.2.8. 1,2-Dideoxy-3,4-*O*-isopropylidene-1-methylthio-5,6-di-*O*-pivaloyl-D-*ribo*-hex-1-enitols (12). Eluent: petroleum ether–ethyl acetate 85:15; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.16 (s, 9H, Me_3C), 1.20 (s, 9H, Me_3C), 1.25 (s, 3H, Me_2C), 1.36 (s, 3H, Me_2C), 2.23 (s, 3H, SMe), 4.09 (dd, 1H, J_{6a-6b}=12.3 Hz, J_{5-6b}=5.1 Hz, H-6b), 4.27 (dd, 1H, J_{4-5}=9.4 Hz, J_{3-4}=6.3 Hz, H-4), 4.51 (dd, 1H, J_{5-6a}=2.2 Hz, H-6a), 4.70 (ddd, J_{2-3}=8.4 Hz, J_{1-3}=0.6 Hz, H-3), 5.01–5.17 (m, 1H, H-5), 5.25 (dd, 1H, J_{1-2}=15.0 Hz, H-2), 6.39 (dd, 1H, H-1); *Z* isomer: δ 1.17 (s, 9H, Me_3C), 1.20 (s, 9H, Me_3C), 1.38 (s, 3H, Me_2C), 1.48 (s, 3H, Me_2C), 2.27 (s, 3H, SMe), 4.09 (dd, 1H, J_{6a-6b}=12.3 Hz, J_{5-6b}=5.1 Hz, H-6b), 4.28 (dd, 1H, J_{2-3}=7.9 Hz, J_{3-4}=6.3 Hz, H-4), 4.37 (dd, 1H, J_{5-6a}=2.3 Hz, H-6a), 5.01–5.17 (m, 2H, H-3, H-5), 5.57 (dd, 1H, J_{1-2}=9.7 Hz, J_{2-3}=8.8 Hz, H-2), 6.39 (dd, 1H, H-1). ^{13}C NMR ($CDCl_3$): *E* isomer: δ 14.2 (MeS), 25.3 (Me_2C), 27.1 (2*Me_3C), 27.8 (Me_2C), 38.9 (2*Me_3C), 63.8 (C-6), 68.1 (C-5), 75.6 (C-4), 78.8 (C-3), 109.0 (C_{IV}-iPrd), 122.2 (C-1), 133.4 (C-2), 176.6, 177.0 (CO); *Z* isomer: δ 17.6 (MeS), 25.2 (Me_2C), 27.1 (2*Me_3C), 27.8 (Me_2C), 39.0 (2*Me_3C), 63.5 (C-6), 69.6 (C-5), 74.3 (C-3), 75.5 (C-4), 109.1 (C_{IV}-iPrd), 124.1 (C-1), 131.6 (C-2), 176.6, 177.0 (CO). HRMS: $C_{20}H_{34}O_6S$ calcd 402.2076; found 402.2068.

4.2.9. 1,2-Dideoxy-3,4-*O*-isopropylidene-1-phenylthio-6-*O*-pivaloyl-D-*ribo*-hex-1-enitols (5c). Reaction of 2,3-*O*-isopropylidene-5-*O*-pivaloyl-D-ribofuranose **3c**[25] with phosphorane **2** afforded a mixture of **5c**, a de-*O*-acylated compound **9** and its di-*O*-pivaloylated derivative **13** that could easily be separated using standard flash column chromatography. Due to its contamination with reaction side-products including triphenylphosphine oxide, **9** could not be satisfactorily characterized: it was therefore peracetylated under standard procedure to give pure **11**.

Vinyl sulfide **5c**. Eluent: petroleum ether–ethyl acetate 80:20; yellowish oil. ^{1}H NMR ($CDCl_3$): *E* isomer: 1.23 (s, 9H, Me_3C), 1.35, 1.46 (2s, 2×3H, Me_2C), 2.37 (m, 1H, OH), 3.77–3.95 (m, 1H, H-5), 4.02–4.24 (m, 3H, H-4, H-5, H-6b), 4.33–4.42 (m, 1H, H-6a), 4.78 (dd, 1H, J_{2-3}=J_{3-4}=6.6 Hz, H-3), 5.92 (dd, 1H, J_{1-2}=14.9 Hz, H-2), 6.57 (dd, 1H, H-1), 7.18–7.42 (m, 5H, HAr); *Z* isomer: δ 1.23 (s, 9H, Me_3C), 1.39, 1.50 (2s, 2×3H, Me_2C), 2.37 (m, 1H, OH), 3.75–3.92 (m, 1H, H-5), 4.12–4.21 (m, 3H, H-4, H-5, H-6b), 4.30–4.43 (m, 1H, H-6a), 5.23 (dd, 1H, J_{2-3}=J_{3-4}=7.7 Hz, H-3), 5.91 (dd, 1H, J_{1-2}=9.6 Hz, H-2), 6.52 (dd, 1H, H-1), 7.18–7.42 (m, 5H, HAr). ^{13}C NMR: *E* isomer: δ 25.4, 27.9 (2*Me), 27.3 (Me_3C), 66.9 (C-6), 69.0 (C-5), 77.6 (C-3), 77.8 (C-4), 109.2 (C_{IV}-iPrd), 127.1 (C_{Ar}), 127.2 (C-1), 127.7 (C-2), 129.2, 130.2, 134.6 (C_{Ar}), 179.1 (CO); *Z* isomer: δ 25.4, 27.9 (2*Me), 27.3 (Me_3C), 66.7 (C-6), 69.5 (C-5), 74.8 (C-3), 78.1 (C-4), 109.3 (C_{IV}-iPrd), 126.7 (C-1), 129.1 (C-2), 127.1, 129.2, 129.8, 135.3 (C_{Ar}), 179.1 (CO). HRMS: $C_{20}H_{28}O_5S$ calcd 380.1657; found 380.1670.

4.2.10. 5,6-Di-*O*-acetyl-1,2-dideoxy-3,4-*O*-isopropylidene-1-phenylthio-D-*ribo*-hex-1-enitols (11). Obtained from acetylation of raw **9**. Eluent: petroleum ether–ethyl acetate 90:10; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.37, 1.47 (2s, 2×3H, Me_2C), 2.03, 2.07 (2s, 2×3H, CH_3CO), 4.11 (dd, 1H, J_{6a-6b}=12.4 Hz, J_{5-6b}=4.9 Hz, H-6b), 4.27 (dd, 1H, J_{3-4}=8.9 Hz, J_{4-5}=6.2 Hz, H-4), 4.55 (dd, 1H, J_{5-6a}=2.6 Hz, H-6a), 4.75 (ddd, 1H, J_{2-3}=7.25 Hz, J_{1-3}=1.1 Hz, H-3), 4.95 (ddd, 1H, H-5), 5.66 (dd, 1H, J_{1-2}=15.2 Hz, H-2), 6.43 (dd, 1H, H-1), 7.20–7.47 (m, 5H, HAr); *Z* isomer: δ 1.42, 1.51 (2s, 2×3H, Me_2C), 2.04, 2.08 (2s, 2×3H, CH_3CO), 4.12 (dd, 1H, J_{6a-6b}=12.6 Hz, J_{5-6b}=5.8 Hz, H-6b), 4.35 (dd, 1H, J_{3-4}=8.5 Hz, J_{4-5}=6.2 Hz, H-4), 4.56 (dd, 1H, J_{5-6a}=2.6 Hz, H-6a), 5.04 (ddd, 1H, H-5), 5.19 (ddd, 1H, J_{2-3}=9.2 Hz, J_{1-3}=0.9 Hz, H-3), 5.77 (dd, 1H, J_{1-2}=9.4 Hz, H-2), 6.46 (dd, 1H, H-1), 7.20–7.47 (m, 5H, HAr). ^{13}C NMR ($CDCl_3$): *E* isomer: δ 22.9, 23.0 (CH_3CO), 27.3, 29.7 (2*Me), 65.0 (C-6), 71.4 (C-5), 77.4 (C-4), 79.9 (C-3), 111.3 (C_{IV}-iPrd), 126.1 (C-1), 130.8 (C-2), 129.2, 131.3, 131.6, 137.0 (C_{Ar}), 171.7, 172.0 (CO); *Z* isomer: δ 23.0, 23.2 (CH_3CO), 27.4, 29.7 (2*Me), 65.3 (C-6), 71.7 (C-5), 76.6 (C-3), 77.4 (C-4), 111.5 (C_{IV}-iPrd), 127.8 (C-1), 131.0 (C-2), 129.4, 131.3, 132.7, 138.9 (C_{Ar}), 171.7, 172.0 (CO). HRMS: $C_{19}H_{24}O_6S$ calcd 380.1293; found 380.1301.

4.2.11. 1,2-Dideoxy-3,4-*O*-isopropylidene-1-phenylthio-5,6-di-*O*-pivaloyl-D-*ribo*-hex-1-enitols (13). Eluent: petroleum ether–ethyl acetate 92:8; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.17 (s, 9H, Me_3C), 2.21 (s, 3H, Me_2C), 1.26 (s, 3H, Me_2C), 1.37 (s, 3H, Me_2C), 4.12 (dd, 1H, J_{6a-6b}=12.2 Hz, J_{6a-5}=5.3 Hz, H-6b), 4.27–4.38 (m, 1H, H-4), 4.45–4.57 (m, 1H, H-6a), 4.71 (dd, 1H, J_{2-3}=7.5 Hz, J_{3-4}=6.3 Hz, H-3), 4.96–5.05 (m, 1H, H-5), 5.66 (dd, 1H, J_{1-2}=14.9 Hz, H-2), 6.50 (d, 1H, H-1), 7.20–7.48 (m, 5H, HAr); *Z* isomer: δ 1.17 (s, 9H, Me_3C), 2.21 (s, 9H, Me_2C), 1.41 (s, 3H, Me_2C), 1.51 (s, 3H, Me_2C), 4.12 (dd, 1H, J_{6a-6b}=12.2 Hz, J_{6a-5}=5.3 Hz, H-6b), 4.27–4.38 (m, 1H, H-4), 4.52 (dd, J_{6a-5}=2.4 Hz, H-6a), 5.15 (m, 2H, H-3, H-5), 5.78 (dd, 1H, J_{1-2}=9.6 Hz, H-2), 6.45 (dd, 1H, J_{1-3}=0.6 Hz, H-1), 7.20–7.48 (m, 5H, HAr). ^{13}C NMR ($CDCl_3$): *E* isomer: δ 25.5 (Me_2C), 27.2 (2^*Me_3C), 27.8 (Me_2C), 38.9 (2^*CMe_3), 63.2 (C-6), 69.3 (C-5), 75.5 (C-4), 78.2 (C-3), 109.2 (C_{IV}-iPrd), 124.5 (C-2), 127.4, 129.5, 130.1 (C_{Ar}), 129.5 (C-1), 134.2 (C_{Ar}); *Z* isomer: δ 25.5 (Me_2C), 27.2 (2^*Me_3C), 27.8 (Me_2C), 38.9 (2^*CMe_3), 63.5 (C-6), 69.5 (C-5), 74.3 (C-3), 75.7 (C-4), 109.4 (C_{IV}-iPrd), 124.9 (C-2), 127.2, 129.3, 129.8 (C_{Ar}), 130.8 (C-1), 135.1 (C_{Ar}). HRMS: $C_{25}H_{36}O_6S$ calcd 464.2232; found 464.2221.

4.2.12. 1,2-Dideoxy-3,4,6,7-di-*O*-isopropylidene-1-methylthio-D-*manno*-hept-1-enitols (4d). Prepared from commercial 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **3d**. Eluent: petroleum ether–ethyl acetate 85:15; yellowish oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.35, 1.40, 1.52 (3s, 4×3H, Me_2C), 2.22 (d, 1H, OH, J_{OH-5}=7.4 Hz), 2.29 (s, 3H, SMe), 3.45 (ddd, 1H, J_{5-6}=7.4 Hz, J_{4-5}=1.4 Hz, H-5), 3.95–4.12 (m, 3H, H-6, H-7a, H-7b), 4.34 (dd, 1H, J_{3-4}=7.5 Hz, H-4), 4.78 (dd, 1H, J_{2-3}=8.5 Hz, H-3), 5.62 (dd, 1H, J_{1-2}=14.9 Hz, H-2), 6.47 (dd, 1H, H-1); *Z* isomer: δ 1.35, 1.40, 1.42, 1.53 (4s, 4×3H, Me_2C), 2.13 (d, 1H, OH, J_{OH-5}=7.4 Hz), 2.31 (s, 3H, SMe), 3.40 (ddd, 1H, J_{5-6}=7.6 Hz, J_{4-5}=1.2 Hz, H-5), 3.95–4.12 (m, 3H, H-6, H-7a, H-7b), 4.44 (dd, 1H, J_{3-4}=7.5 Hz, H-4), 5,11 (ddd, 1H, J_{2-3}=8.7 Hz, J_{1-3}=0.9 Hz, H-3), 5.83 (dd, 1H, J_{1-2}=9.6 Hz, H-2), 6.22 (dd, 1H, H-1). ^{13}C NMR: *E* isomer: δ 14.4 (MeS), 24.5, 25.3, 26.7, 26.9 (4^*Me), 67.1 (C-7), 70.7 (C-5), 76.2 (C-6), 76.2 (C-4), 79.2 (C-3), 108.2, 109.4 (2^*C_{IV}-iPrd), 119.4 (C-2), 132.4 (C-1); *Z* isomer: 17.5 (MeS), 24.4, 25.4, 26.6, 26.9 (4^*Me), 66.8 (C-7), 70.4 (C-5), 74.7 (C-3), 76.1 (C-6), 76.6 (C-4), 108.6, 109.3 (2^*C_{IV}-iPrd), 124.7 (C-2), 131.5 (C-1). HRMS: $C_{14}H_{24}O_5S$ calcd 304.1344; found 304.1349.

4.2.13. 1,2-Dideoxy-3,4,6,7-di-*O*-isopropylidene-1-phenylthio-D-*manno*-hept-1-enitols (5d). Prepared from commercial 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **3d**. Eluent: petroleum ether–ethyl acetate 85:15; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.35, 1.40, 1.51 (3s, 4×3H, Me_2C), 2.14 (d, 1H, OH, J_{OH-5}=7.7 Hz), 3.45 (ddd, 1H, J_{5-6}=7.7 Hz, J_{4-5}=1.5 Hz, H-5), 3.95–4.15 (m, 3H, H-6, H-7a, H-7b), 4.36 (dd, 1H, J_{3-4}=7.3 Hz, H-4), 4.78 (dd, 1H, J_{2-3}=8.3 Hz, H-3), 6.02 (dd, 1H, J_{1-2}=15.1 Hz, H-2), 6.57 (dd, 1H, H-1); 7.20–7.41 (m, 5H, HAr); *Z* isomer: δ 1.36), 1.42, 1.44, 1.55 (4s, 4×3H, Me_2C), 2.18 (d, 1H, OH, J_{OH-5}=7.7 Hz), 3.44 (ddd, 1H, J_{5-6}=7.7 Hz, J_{4-5}=0.8 Hz, H-5), 3.97–4.15 (m, 3H, H-6, H-7a, H-7b), 4.51 (dd, 1H, J_{3-4}=7.7 Hz, H-4), 5.24 (ddd, 1H, J_{2-3}=7.8 Hz, J_{3-4}=7.7 Hz, H-3), 6.07 (dd, 1H, J_{1-2}=9.5 Hz, H-2), 6.49 (dd, 1H, H-1); 7.20–7.41 (m, 5H, HAr). ^{13}C NMR: *E* isomer: δ 24.4, 25.5, 26.7, 27.1 (4^*Me), 67.0 (C-7), 70.6 (C-5), 74.7 (C-3), 76.2 (C-6), 76.5 (C-4), 108.9, 109.5 (2^*C_{IV}-iPrd), 127.2 (C-2), 128.1 (C_{Ar}), 128.2 (C-1), 129.3, 129.6, 135.0 (C_{Ar}),; *Z* isomer: δ 24.6, 25.4, 26.8, 26.9 (4^*Me), 67.2 (C-7), 70.7 (C-5), 76.2 (C-6), 76.9 (C-4), 78.6 (C-3), 108.7, 109.5 (2^*C_{IV}-iPrd), 126.5 (C-2), 130.4 (C-1), 127.4, 129.3, 130.6, 134.4 (C_{Ar}). HRMS: $C_{19}H_{26}O_5S$ calcd 366.1501; found 366.1511.

4.2.14. 1,2-Dideoxy-3,4,5,7-di-*O*-isopropylidene-1-methylthio-D-*manno*-hept-1-enitols (4e). Prepared from 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose **3e**.[26] Eluent: petroleum ether–ethyl acetate 85:15; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.38, 1.42, 1.48, 1.53 (4s, 4×3H, Me_2C), 2.27 (s, 3H, SMe), 3.52–3.69 (m, 2H, H-5, H-7b), 3.85–3.98 (m, 2H, H-6, H-7a), 4.39 (dd, 1H, J_{3-4}=7.0 Hz, J_{4-5}=1.3 Hz, H-4), 4.79 (dd, 1H, J_{2-3}=6.7 Hz, H-3), 5.76 (dd, 1H, J_{1-2}=14.9 Hz, H-2), 6.17 (dd, 1H, H-1); *Z* isomer: δ 1.39, 1.40, 1.42, 1.53 (4s, 4×3H, Me_2C), 2.31 (s, 3H, SMe), 2.92–3.05 (m, 1H, OH), 3.43 (dd, 1H, J_{5-6}=8.9 Hz, J_{4-5}=1.5 Hz, H-5), 3.55–3.67 (m, 1H, H-7b), 3.78–3.93 (m, 2H, H-6, H-7a), 4.48 (dd, 1H, J_{3-4}=7.2 Hz, H-4), 5.12 (ddd, 1H, J_{2-3}=7.7 Hz, J_{1-3}=1.3 Hz, H-3,), 5.76 (dd, 1H, J_{1-2}=9.8 Hz, H-2), 6.17 (dd, 1H, H-1). ^{13}C NMR: δ *E* isomer: 14.3 (MeS), 21.1, 26.0, 26.4, 28.6 (4^*Me), 60.5 (C-7), 62.7 (C-6), 73.0 (C-5), 75.7 (C-4), 79.0 (C-3), 98.6, 109.3 (2^*C_{IV}-iPrd), 118.8 (C-2), 131.9 (C-1); *Z* isomer: δ 17.5 (MeS), 19.2, 26.0, 26.4, 28.6 (4^*Me), 62.8 (C-6), 64.9 (C-7), 73.0 (C-5), 74.7 (C-3), 75.1 (C-4), 98.6, 109.4 (2^*C_{IV}-iPrd), 124.5 (C-2), 130.9 (C-1). HRMS: $C_{14}H_{24}O_5S$ calcd 304.1344; found 304.1331.

4.2.15. 1,2-Dideoxy-3,4,5,7-di-*O*-isopropylidene-1-phenylthio-D-*manno*-hept-1-enitols (5e). Reaction of **3e** with phosphorane **2** afforded **5e** contaminated with side-products including triphenylphosphine oxide; the crude mixture was first acetylated under standard procedure to give pure 6-*O*-acetyl-1,2-dideoxy-3,4,5,7-di-*O*-isopropylidene-1-phenylthio-D-*manno*-hept-1-enitols **14**. Eluent: petroleum ether–ethyl acetate 90:10; colorless oil. ^{1}H NMR (C_6D_6): *E* isomer: δ 1.24 (s, 3H, Me_2C), 1.29 (s, 3H, Me_2C), 1.35 (s, 3H, Me_2C), 1.60 (s, 3H, Me_2C), 1.59 (s, 3H, CH_3CO), 3.54 (dd, 1H, J_{7a-7b}=12.0 Hz, J_{6-7b}=6.0 Hz, H-7b), 3.70 (dd, 1H, J_{4-5}=1.3 Hz, J_{5-6}=8.5 Hz, H-5), 4.07 (dd, 1H, J_{6-7a}=4.5 Hz, H-7a), 4.19 (dd, 1H, J_{3-4}=7.2 Hz, H-4), 4.59 (dd, 1H, J_{2-3}=7.9 Hz, H-3), 5.34 (ddd, 1H, H-6), 6.12 (dd, 1H, J_{1-2}=15.1 Hz, H-2), 6.32 (d, 1H, H-1), 7,22–7,42 (m, 5H, HAr); *Z* isomer: δ 1.23 (s, 3H, Me_2C), 1.29 (s, 3H, Me_2C), 1.30 (s, 3H, Me_2C), 1.55 (s, 3H, Me_2C), 1.59 (s, 3H, CH_3CO), 3.50 (dd, 1H, J_{7a-7b}=11.9 Hz, J_{6-7b}=6.2 Hz, H-7b), 3.70 (dd, 1H, J_{4-5}=1.0 Hz, J_{5-6}=8.0 Hz, H-5), 4.02 (dd, 1H, J_{6-7a}=5.0 Hz, H-7a), 4.44 (dd, 1H, J_{3-4}=7.2 Hz, H-4), 5.25 (ddd, 1H, H-6), 5.35 (dd, 1H, J_{2-3}=6.2 Hz, H-3), 6.09 (dd, 1H, J_{1-2}=9.5 Hz, H-2), 6.15 (d, 1H, H-1), 7,22–7,42 (m, 5H, HAr). ^{13}C NMR (C_6D_6): *E* isomer: δ 20.5, 21.0, 26.1, 26.8 (Me_2C), 62.4 (C-7), 68.0 (C-6), 70.2 (C-5), 76.9 (C-4), 78.6 (C-3), 99.7, 109.7 (C_{IV}-iPrd), 127.36 (C_{Ar}), 125.0 (C-2), 126.3 (C-1), 129.5, 130.8, 132.4 (C_{Ar}), 169.5 (CO); *Z* isomer: δ 20.5, 21.0, 26.7, 27.0 (Me_2C), 62.4 (C-6), 67.6 (C-7), 70.3 (C-5), 75.2 (C-3), 76.4 (C-4), 99.6, 109.9 (C_{IV}-iPrd), 126.1 (C-2), 127.1, 129.5, 129.6 (C_{Ar}), 129.9

(C-1), 135.6 (C_{Ar}), 169.5 (CO). HRMS: $C_{21}H_{28}O_6S$ calcd 408.1606; found 408.1599.

A solution of **14** (409 mg, 1 mmol) in 5 mL methanol was treated at RT by sodium methoxide (1 M in methanol, 50 μL, 0.05 equiv.). The reaction mixture was let to stand for 4 h then quenched by silica gel and the solvent was removed in vacuo. The residue was purified by flash column chromatography (petroleum ether–ethyl acetate 70:30) to afford a diastereomeric mixture of vinyl sulfides **5e** (348 mg, 95%). NMR spectra were recorded in C_6D_6 due to the slow isomerisation in chloroform of **5e** into the more stable **5d** through *O*-isopropylidene migration promoted by traces of HCl in commercial $CDCl_3$. ^{1}H NMR (C_6D_6): *E* isomer: δ 1.23, 1.38, 1.65 (3s, 4×3H, Me_2C), 2.01 (m, 1H, OH), 3.43–3.54 (m, 2H, H-5, H-7b), 3.78 (dd, 1H, J_{7a-7b}=11.3 Hz, J_{6-7a}=5.5 Hz, H-7a), 3.85–3.90 (m, 1H, H-6), 4.42 (dd, 1H, J_{4-5}=1.3 Hz, J_{3-4}=7.2 Hz, H-4), 4.61 (dd, 1H, J_{2-3}=J_{1-3}=7.5 Hz, H-3), 6.15 (dd, 1H, J_{1-2}=15.1 Hz, H-2), 6.33 (d, 1H, H-2), 7.20–7.41 (m, 5H, HAr); *Z* isomer: δ 1.27, 1.38, 1.46, 1.69 (4s, 4×3H, Me_2C), 2.50 (m, 1H, OH), 3.51–3.62 (m, 2H, H-5, H-7b), 3.87 (dd, 1H, J_{7a-7b}=11.0 Hz, J_{6-7a}=5.2 Hz, H-7a), 3.96–4.08 (m, 1H, H-6), 4.75 (dd, 1H, J_{4-5}=1.0 Hz, J_{3-4}=7.5 Hz, H-4), 5.48 (ddd, 1H, J_{2-3}=7.7 Hz, J_{1-3}=1.2 Hz, H-3), 6.13–6.25 (m, 2H, H-1, H-2), 7.20–7.41 (m, 5H, HAr). ^{13}C NMR: *E* isomer: δ 19.2, 26.2, 26.9, 28.7 (4*Me), 63.3 (C-6), 65.2 (C-7), 73.3 (C-5), 76.3 (C-4), 78.8 (C-3), 98.8, 109.5 (2*C_{IV}-iPrd), 127.9 (C-2), 128,3 (C-1), 127.3, 129.5, 130.7, 134.8 (C_{Ar}); *Z* isomer: δ 19.2, 26.1, 26.9, 28.9 (4*Me), 63.2 (C-6), 65.3 (C-7), 73.6 (C-5), 75.4 (C-3), 76.1 (C-4), 98.7, 109.8 (2*C_{IV}-iPrd), 126.1 (C-2), 130.0 (C-1), 127.0, 129.4, 129.6, 135.8 (C_{Ar}). HRMS: $C_{19}H_{26}O_5S$ calcd 366.1501; found 366.1498.

4.2.16. 1,2-Dideoxy-3,4,5,7-di-*O*-isopropylidene-1-methylthio-D-*gluco*-hept-1-enitols (4f). Prepared from 2,3:4,6-di-*O*-isopropylidene-D-glucopyranose **3f**.[27] Eluent: petroleum ether–ethyl acetate 90:10; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.38–1.51 (m, 12H, 2Me_2C), 2.27 (s, 3H, SMe), 3.55–3.68 (m, 2H, H-5, H-7b), 3.80–4.02 (m, 3H, H-4, H-6, H-7a), 4.62 (dd, 1H, J_{2-3}=9.0 Hz, J_{3-4}=8.5 Hz, H-3), 5.33 (dd, 1H, J_{1-2}=14.9 Hz, H-2), 6.43 (dd, 1H, H-1); *Z* isomer: δ 1.42, 1.44, 1.50 (3s, 4×3H, Me_2C), 2.29 (s, 3H, MeS), 2.92 (m, 1H, OH), 3.55–3.68 (m, 2H, H-5, H-7b), 3.80–3.95 (m, 2H, H-6, H-7a), 4.02 (dd, 1H, J_{3-4}=8.2 Hz, J_{4-5}=2.3 Hz, H-4), 5.00 (dd, 1H, J_{2-3}=8.5 Hz, H-3), 5.56 (dd, 1H, J_{1-2}=9.4 Hz, H-2), 6.22 (d, 1H, H-1). ^{13}C NMR: *E* isomer: δ 14.4 (MeS), 19.6, 26.5, 27.2, 28.2 (4*Me), 63.7 (C-6), 64.6 (C-7), 71.1 (C-5), 77.2 (C-3), 79.3 (C-4), 99.0, 109.2 (2*C_{IV}-iPrd), 125.9 (C-2), 130.9 (C-1); *Z* isomer: δ 17.5 (MeS), 19.5, 26.3, 27.3, 28.4 2 (4*Me), 63.6 (C-6), 64.6 (C-7), 71.3 (C-5), 72.6 (C-3), 79.2 (C-4), 99.0, 109.7 (2*C_{IV}-iPrd), 124.7 (C-2), 133.3 (C-1). HRMS: $C_{14}H_{24}O_5S$ calcd 304.1344; found 304.1351.

4.2.17. 1,2-Dideoxy-3,4,5,7-di-*O*-isopropylidene-1-phenylthio-D-*gluco*-hept-1-enitols (5f). Prepared from 2,3:4,6-di-*O*-isopropylidene-D-glucopyranose **3f**.[27] Eluent: petroleum ether–ethyl acetate 90:10; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer (selected peaks): δ 4.62 (dd, 1H, J_{2-3}=6.9 Hz, J_{3-4}=8.3 Hz, H-3), 5.80 (dd, 1H, J_{1-2}=15.1 Hz, H-2), 6.54 (dd, 1H, H-1); *Z* isomer: δ 1.44 (s, 3×3H, Me_2C), 1.53 (s, 3H, Me_2C), 2.39 (m, 1H, OH), 3.64–3.74 (m, 2H, H-5, H-7b), 3.89–3.99 (m, 2H, H-6, H-7a), 4.10 (dd, 1H, J_{3-4}=8.2 Hz, J_{4-5}=2.5 Hz, H-4), 5.13 (dd, 1H, J_{2-3}=9.1 Hz, H-3), 5.78 (dd, 1H, J_{1-2}=9.4 Hz, H-2), 6.48 (d, 1H, H-1), 7.22–7.42 (m, 5H, HAr). ^{13}C NMR: *Z* isomer: δ 19.6, 26.5, 27.3, 28.4 (4*Me), 63.9 (C-6), 64.6 (C-7), 71.4 (C-5), 72.8 (C-3), 79.4 (C-4), 99.2, 109.2 (2*C_{IV}-iPrd), 128.0 (C-2), 129.8 (C-1), 127.1, 129.3, 135.5, 139.7 (C_{Ar}). HRMS: $C_{19}H_{26}O_5S$ calcd 366.1501; found 366.1507.

4.2.18. 1,2,3-Trideoxy-3,4-*O*-isopropylidene-1-methylthio-D-*erythro*-hex-1-enitols (4h). Prepared from 2-deoxy-3,4-*O*-isopropylidene-D-ribopyranose **3h**.[28] Eluent: petroleum ether–ethyl acetate 90:10; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.37 (s, 1H, Me_2C), 1.48 (s, 3H, Me_2C), 2.24 (s, 3H, SMe), 2.25–2.51 (m, 2H, H-3a, H-3b), 3.61–3.72 (m, 2H, H-6a, H-6b), 4.13–4.28 (m, 2H, H-4, H-5), 5.41 (ddd, 1H, J_{1-2}=15.1 Hz, J_{2-3a}=7.5 Hz, J_{2-3b}=6.3 Hz, H-2), 6.12 (ddd, 1H, J_{1-3a}=J_{1-3b}=1.3 Hz, H-1); *Z* isomer: δ 1.37 (s, 3H, Me_2C), 1.48 (s, 3H, Me_2C), 2.29 (s, 3H, SMe), 2.25–2.51 (m, 2H, H-3a, H-3b), 3.61–3.72 (m, 2H, H-6a, H-6b), 4.13–4.28 (m, 2H, H-4, H-5), 5.57 (ddd, 1H, J_{1-2}=9.4 Hz, J_{2-3a}=8.2 Hz, J_{2-3b}=6.6 Hz, H-2), 6.12 (ddd, 1H, J_{1-3a}=J_{1-3b}=1.5 Hz, H-1). ^{13}C NMR: *E* isomer: δ 14.9 (MeS), 25.5, 28.2 (2*Me), 33.2 (C-3), 61.7 (C-6), 76.1, 78.0 (C-4 and C-5), 108.4 (C_{IV}-iPrd), 121.6 (C-2), 127.1 (C-1); *Z* isomer: δ 17.1 (MeS), 25.5, 28.2 (2*Me), 29.4 (C-3), 61.7 (C-6), 76.6, 77.8 (C-4 and C-5), 108.4 (C_{IV}-iPrd), 123.5 (C-2), 129.6 (C-1). HRMS: $C_{10}H_{18}O_3S$ calcd 218.0977; found 218.0988.

4.2.19. 1,2,3-Trideoxy-3,4-*O*-isopropylidene-1-phenylthio-D-*erythro*-hex-1-enitols (5h). Prepared from 2-deoxy-3,4-*O*-isopropylidene-D-ribopyranose **3h**.[28] Eluent: petroleum ether–ethyl acetate 90:10; yellow oil. ^{1}H NMR ($CDCl_3$): *E* isomer: δ 1.38 (s, 3H, Me_2C), 1.50 (s, 3H, Me_2C), 1.97 (m, 1H, OH), 2.32–2.58 (m, 2H, H-3a, H-3b), 3.61–3.76 (m, 2H, H-6a, H-6b), 4.13–4.35 (m, 2H, H-4, H-5), 5.95 (ddd, 1H, J_{1-2}=15.0 Hz, J_{2-3a}=7.3 Hz, J_{2-3b}=6.5 Hz, H-2), 6.28 (ddd, 1H, J_{1-3a}=J_{1-3b}=1.2 Hz, H-1), 7.18–7.42 (m, 5H, HAr); *Z* isomer: δ 1.37 (s, 3H, Me_2C), 1.49 (s, 3H, Me_2C), 1.86–2.08 (m, 1H, OH), 2.32–2.58 (m, 2H, H-3a, H-3b), 3.61–3.76 (m, 2H, H-6a, H-6b), 4.13–4.35 (m, 2H, H-4, H-5), 5.87 (ddd, 1H, J_{1-2}=9.5 Hz, J_{2-3a}=J_{2-3b}=7.3 Hz, H-2), 6.34 (ddd, 1H, J_{1-3}=1.4 Hz, H-1), 7.18–7.42 (m, 5H, HAr). ^{13}C NMR: *E* isomer: δ 28.2, 29.6 (2*Me), 33.2 (C-3), 61.8 (C-6), 76.3, 77.9 (C-4 and C-5), 108.6 (C_{IV}-iPrd), 126.0 (C-1), 127.8 (C-2), 126.7, 129.1, 129.3 (C_{Ar}); *Z* isomer: δ 25.5, 28.2 (2*Me), 33.2 (C-3), 61.7 (C-6), 76.2, 77.8 (C-4 and C-5), 108.5 (C_{IV}-iPrd), 124.8 (C-1), 131.0 (C-2), 126.6, 129.1, 129.2, 135.9 (C_{Ar}). HRMS: $C_{15}H_{20}O_3S$ calcd 280.1133; found 280.1124.

4.2.20. 3,4,6-Tri-*O*-benzyl-1,2-*O*-isopropylidene-β-D-mannopyranose (16) and 3,4,6-tri-*O*-benzyl-1,2-*O*-isopropylidène-α-D-glucopyranose (17). Vinyl sulfide **4a** (300 mg, 0.647 mmol) was dissolved in a 3:1 mixture of acetone and water (4 mL). A 2.5% solution of OsO_4 in *t*BuOH was added (363 μL, 0.05 equiv.), followed by a 1:1 mixture of *N*-methylmorpholine *N*-oxide (1.33 mL, 10 equiv.). The resulting dark solution was stirred at room temperature during 3 days. The reaction mixture was then cooled to 0 °C and quenched by the addition of a saturated

solution of $NaHSO_3$ (3 mL). The resulting solution was stirred during 10 min at RT, then extracted by AcOEt (3×5 mL) and the organic phases were dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was purified by flash column chromatography (petroleum ether–ethyl acetate 70:30 then 20:80) to afford a mixture of lactols **15** that could not be satisfactorily characterized, due to the anomeric equilibrium of both *gluco* and *manno* lactols. To overcome this problem, the yellowish oil was dissolved in 2,2-dimethoxypropane (5 mL) and CSA was added (15 mg, 0.1 equiv.). The solution was stirred overnight then quenched by a saturated solution of $NaHCO_3$ (5 mL) and extracted with AcOEt (3×5 mL). Organic phases were dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was purified by flash column chromatography (petroleum ether–ethyl acetate 85:15) to afford 32 mg (10%) of **17** then 257 mg of **16** (81%).

Isomer **17**. Colorless oil; $[\alpha]_D$=+35 (*c* 1.0, $CHCl_3$) (lit.[20a] +37.3, *c*=2.9, $CHCl_3$, lit.[20b] +39.4, *c*=1.0, $CHCl_3$). Spectroscopic data were identical to previous description.[20b] ^{1}H NMR ($CDCl_3$): 1.36 and 1.54 (2s, 2×3H, Me_2C), 3.63–3.67 (m, 2H, H-6a and H-6b), 3.71 (dd, 1H, H-4, J_{3-4}=3.8 Hz, J_{4-5}=9.6 Hz), 3.86–3.98 (m, 2H, H-3 and H-5), 4.26 (dd, 1H, H-2, J_{1-2}=4.9 Hz, J_{2-3}=4.2 Hz), 4.39 (d, 1H, CH_2Ph, J_{gem}=11.5 Hz), 4.49 (d, 1H, CH_2Ph, J_{gem}=12.2 Hz), 4.54–4.65 (m, 3H, CH_2Ph), 4.71 (d, 1H, CH_2Ph, J_{gem}=11.9 Hz), 5.64 (d, 1H, H-1), 7.15–7.43 (m, 15H, H_{Ar}) ^{13}C NMR ($CDCl_3$): δ 26.1 and 27.1 (Me_2C); 69.4 (C-6); 70.5 (C-5); 72.1, 73.1 and 73.5 (CH_2Ph); 75.3 (C-4); 75.9 (C-2); 79.4 (C-3); 97.5 (C-1); 109.2 (CMe_2); 127.7, 127.9, 128.0, 128.1, 128.2, 128.5, 128.6, 138.0, 138.1 and 138.9 (CAr).

Isomer **16**. White solid; $[\alpha]_D$=+38 (*c* 1.0, $CHCl_3$); mp (Et_2O) 106–108 °C. ^{1}H NMR ($CDCl_3$): δ 1.38 and 1.62 (2s, 2×3H, Me_2C), 3.37 (ddd, 1H, H-5, J_{4-5}=9.5 Hz, J_{5-6a}=4.0 Hz, J_{5-6b}=2.4 Hz), 3.37–3.81 (m, 3H, H-3, H-6a and H-6b), 3.99 (dd, 1H, J_{3-4}=9.5 Hz), 4.19 (dd, 1H, H-2, J_{1-2}=2.0 Hz, J_{5-6a}=3.7 Hz), 4.53 (d, 1H, CH_2Ph, J_{gem}=12.2 Hz), 4.54–4.67 (m, 2H, CH_2Ph), 4.78 (s, 1H, CH_2Ph), 4.90 (d, 1H, CH_2Ph, J_{gem}=10.9 Hz), 5.15 (d, 1H, H-1), 7.17–7.43 (m, 15H, H_{Ar}) ^{13}C NMR ($CDCl_3$): δ 25.9 and 28.1 (Me_2C); 69.0 (C-6); 72.1 and 73.3 (CH_2Ph); 74.2 (C-5); 74.5 (C-4); 75.2 (CH_2Ph); 76.5 (C-2); 79.0 (C-3); 97.3 (C-1); 112.2 (CMe_2); 127.4, 127.5, 127.7, 127.9, 128.0, 143.2 and 143, 6 (CAr). HRMS: $C_{30}H_{34}O_6$ calcd 490.2355; found 490.2343.

4.2.21. 1(*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-methylsulfonyl-D-*arabino*-hex-1-enitol (18). To an ice-cold solution of vinyl sulfide **4a** (464 mg, 1.00 mmol) in dry CH_2Cl_2 (10 mL), dry *m*-CPBA (518 mg, 3.0 equiv.) was added and the reaction mixture was warmed slowly to RT. After 4 h stirring at this temperature, the mixture was cooled to 0 °C and quenched by a saturated solution of $NaHSO_3$ (10 mL). The resulting biphasic mixture was vigorously stirred during 10 min, then extracted by CH_2Cl_2 (3×20 mL). The organic phases were pooled, washed with a saturated solution of $NaHCO_3$ (3×5 mL) then dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was purified by flash column chromatography (petroleum ether–ethyl acetate 65:35) to afford the desired vinyl sulfone **18** (452 mg, 91%) as a colorless oil; $[\alpha]_D$=+21 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.70–2.85 (s, 1H, OH), 3.55–3.68 (m, 3H, H-4, H-6a, H-6b), 3.90–4.00 (m, 1H, H-5), 4.39–4.44 (m, 1H, H-3), 4.45–4.63 (m, 6H, CH_2Ph), 6.65 (dd, 1H, J_{1-2}=15.3 Hz, J_{1-3}=1.6 Hz, H-1), 7,00 (dd, 1H, J_{2-3}=4.4 Hz, H-2), 7.17–7.48 (m, 15H, HAr). ^{13}C NMR ($CDCl_3$): δ 42.7 ($MeSO_2$), 70.2 (C-5), 71.4 (C-6), 73.8, 74.6 (CH_2Ph), 77.7 (C-3), 79.8 (C-4), 128.1, 128.2, 128.4, 128.6, 128.7 (C_{Ar}), 131.1 (C-1), 137.2, 137.6, 137.8 (C_{Ar}), 145.4 (C-2). HRMS: $C_{28}H_{32}O_6S$ calcd 496.1919; found 496.1923.

4.2.22. 1(*E*)-3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1-methylsulfinyl-D-*arabino*-hex-1-enitols (19). To an ice-cold solution of vinyl sulfide **4a** (1.00 g, 2.16 mmol) in dry CH_2Cl_2 (20 mL), dry *m*-CPBA (373 mg, 1.0 equiv.) was added and the reaction mixture was warmed slowly to RT. After 20 h stirring at this temperature, a saturated solution of $NaHCO_3$ (20 mL) was carefully added. The reaction medium was extracted by CH_2Cl_2 (3×20 mL) and the organic phases were dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was purified by flash column chromatography (petroleum ether–ethyl acetate 30:70) to afford a 1:1 mixture of *S*-epimers of vinyl sulfoxides **19** (894 mg, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.47, 2.51 (2s, MeSO), 3.52–3.68 (m, H-4, H-6a, H-6b), 3.89–4.05 (m, H-5), 4.36–4.67 (m, H-3, CH_2Ph), 6.50–6.57 (m, H-1, H-2), 7.16–7.38 (m, HAr). ^{13}C NMR ($CDCl_3$): δ 40.6, 40.7 (MeSO), 70.2 (C-5), 70.9 (C-6), 72.4, 72.6, 73.6, 74.3, 74.5 (CH_2Ph), 78.3 (C-3), 80.0 (C-4), 128.0, 128.2, 128.3, 128.4, 128.5, 128.6 (C_{Ar}), 135.8, 136.3, 136.4, 136.5 (C-1, C-2), 137.5, 137.5, 137.8, 137.9, 138.0 (C_{Ar}). HRMS: $C_{28}H_{32}O_5S$ calcd 480.1970; found 480.1981.

Acknowledgements

V. A. would like to thank the French MENRT for a grant.

References and notes

1. (a) Fürstner, A.; Baumgartner, J. *Tetrahedron* **1993**, *49*, 8541–8560. (b) Ferrier, R. J.; Furneaux, R. H.; Prasit, P.; Tyler, P. C.; Brown, K. L.; Gainsford, G. J.; Dielh, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1621–1628.
2. Brochard, L.; Lorin, C.; Spiess, N.; Rollin, P. *Tetrahedron Lett.* **1998**, *39*, 4267–4270, and references cited.
3. Hatanaka, M.; Ueda, I. *Chem. Lett.* **1981**, 61–64.
4. Tolman, R. L.; Peterson, L. H. *Carbohydr. Res.* **1989**, *189*, 113–122.
5. (a) Bestmann, H. J.; Angerer, J. *Tetrahedron Lett.* **1969**, 3665–3666. (b) Lee, T. *Tetrahedron Lett.* **1985**, *26*, 4995–4996. (c) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 490–491. (d) Bestmann, H. J.; Bauriegel, L. *Tetrahedron Lett.* **1995**, *36*, 853–856.
6. Trofimov, B. A.; Shaynian, B. A. *Chemistry of sulphur-containing functional groups*; Wiley: London, 1993; pp 659–797.
7. Trost, B. M.; Nübling, C. *Carbohydr. Res.* **1990**, *202*, 1–12.
8. (a) Zhdanov, Y. A.; Alexeev, Y. E.; Alexeeva, V. G. *Adv.*

Carbohydr. Chem. Biochem. **1972**, *27*, 227–299. (b) Postema, M. H. *C-glycosides synthesis*; Wiley: London, 1995; pp 91–110.
9. (a) Pougny, J. R.; Nassr, M. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375–376. (b) Nicotra, F.; Ronchetti, F.; Russo, G. *J. Org. Chem.* **1982**, *47*, 5381–5382. (c) Allevi, P.; Ciuffreda, P.; Colomb, D.; Monti, D.; Speranza, G.; Mannito, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1281–1283. (d) Nicotra, F.; Russo, G.; Toma, L. *Tetrahedron Lett.* **1984**, *25*, 5697–5700.
10. Webb, T. H.; Thomasco, L. S.; Schlachter, S. T.; Gaudino, J.; Wilcox, C. R. *Tetrahedron Lett.* **1988**, *29*, 6823–6826.
11. Lancelin, J. M.; Pougny, J. R.; Sinaÿ, P. *Carbohydr. Res.* **1985**, *136*, 369–374.
12. Costantino, V.; Imperatore, C.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett.* **2001**, *42*, 8185–8818.
13. (a) Mura, A. J.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4433. (b) Mura, A. J.; Majetich, G.; Grieco, P.; Cohen, T. *Tetrahedron Lett.* **1975**, 4437.
14. Tronchet, J. M. J.; Jaccard-Thorndahl, S.; Baehler, B. *Helv. Chim. Acta* **1969**, *52*, 817–820.
15. Ramirez, M. A.; Padron, J. M.; Palazon, J. M.; Martin, V. S. *J. Org. Chem.* **1997**, *62*, 4584–4590.
16. (a) For pioneering work, see: Marot, C.; Rollin, P. *Phosphorus, Sulfur Silicon* **1994**, *95–96*, 503–504. (b) Marot, C.; Rollin, P. *Tetrahedron Lett.* **1994**, *35*, 8377–8380.
17. Aucagne, V.; Tatibouët, A.; Rollin, P. In preparation.
18. Gallucci, J. C.; Ha, D.-C.; Hart, D. J. *Tetrahedron* **1989**, *45*, 1283–1292.
19. Aucagne, V.; Lorin, C.; Tatibouët, A.; Rollin, P. In preparation.
20. (a) The D-gluco isomer **17** was previously described: Boullanger, P.; Martin, J. C.; Descotes, G. *J. Heterocycl. Chem.* **1975**, *12*, 91–94. (b) Crich, D.; Lim, L. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2209–2214.
21. Kaldor, S. W.; Hammond, M. *Tetrahedron Lett.* **1991**, *32*, 5043–5046.
22. (a) Sha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946. (b) Sha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255.
23. Cameron, A. G.; Hewson, A. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2979–2982.
24. Marek, D.; Wadouachi, A.; Beaupère, D. *Tetrahedron: Asymmetry* **1997**, *8*, 3223–3230.
25. Mahmood, K.; Vasella, A.; Bernet, B. *Helv. Chim. Acta* **1991**, *74*, 1555–1584.
26. Drew, K. N.; Gross, P. H. *J. Org. Chem.* **1991**, *56*, 509–513.
27. Gomez, A. M.; Danelon, G. O.; Valverde, S.; Lopez, J. C. *Carbohydr. Res.* **1999**, *320*, 138–142.
28. Barbat, J.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1983**, *116*, 312–316.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1827–1839
Tetrahedron

Highly diastereoselective cycloaddition reactions of variously substituted 1-thia- and 1-thia-3-aza-buta-1,3-dienes. Synthesis of enantiomerically pure 5,6-dihydro-4*H*-[1,3]thiazines and 3,4-dihydro-2*H*-thiopyrans

Anne Harrison-Marchand,[a,†] Sylvain Collet,[a] André Guingant,[a,*] Jean-Paul Pradère[a] and Loïc Toupet[b]

[a]*Laboratoire de Synthèse Organique, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208-44322 Nantes Cedex 03, France*
[b]*Groupe Matière Condensée et Matériaux, Université de Rennes 1-Beaulieu, 35042 Rennes, France*

Received 30 September 2003; revised 12 December 2003; accepted 15 December 2003

Abstract—The cycloaddition of 2- or 2,3-substituted 1-thia- and 1-thia-3-aza-4-dimethylamino-buta-1,3-dienes with various dienophiles in the presence of a Lewis acid provides a rapid and diastereoselective access to the 3,4-dihydro-2*H*-thiopyran and 5,6-dihydro-4*H*-[1,3]thiazine backbones. The generally observed *trans* relationship between the two newly created strereogenic centres was demonstrated to be the expression of a thermodynamic control of the reaction. The use of chiral dienophile derived from chiral oxazolidin-2-ones allowed us to prepare enantiopure 5,6-dihydro-4*H*-[1,3]thiazines and 3,4-dihydro-2*H*-thiopyrans. In the asymmetric synthetic process the chiral auxiliary removal step was best accomplished in the presence of samarium triflate in methanol.

1. Introduction

Heterocycles containing nitrogen or sulphur (or both) are common features incorporated in the structures of numerous natural products and pharmaceutical compounds and the development of simple and effective methods for their preparation is a point of major concern in medicinal chemistry. In this regard, the utilisation of the hetero Diels–Alder reaction undoubtedly represents one of the most attractive route for preparing these heterocycles with maximum atom economy and high selectivity.[1]

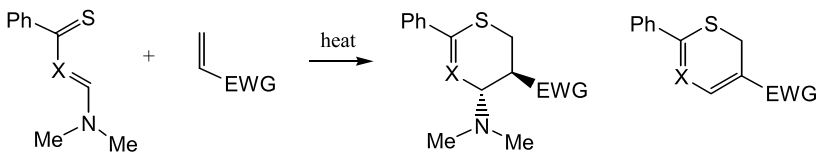
In our laboratory there has been a long-standing interest for heterodienes incorporating sulphur or sulphur and nitrogen atoms in their structures such as the 1-thia- and 1-thia-3-aza-buta-1,3-dienes **1** and **2**, respectively. In particular, it was demonstrated[2] that these dienes experienced thermal Diels–Alder cycloadditions with electrophilic olefins to give the adducts **3** or their evolution products **4** resulting from the facile loss of dimethylamine as illustrated in general terms in Scheme 1.

Since in the early investigations the major synthetic objective to be pursued was to find routes to the synthesis of cephem analogues from 6*H*-[1,3]thiazines,[3] little attention had been paid to the relative stereochemistry in cycloadducts **3** although it was recognised in two occasions that the two substituents at the newly created chiral centres adopted a *trans* relative disposition.[2c,4]

As part of our continuing program towards the reactivity of heterodienes and the synthesis of potentially pharmacologically active heterocycles we have now investigated the possibility of preparing 5,6-dihydro-4*H*-[1,3]thiazines **3** (X=N) and 3,4-dihydro-2*H*-thiopyran analogues **3** (X=CH) in chiral non-racemic form. Since, based on a large body of literature data, the asymmetric synthesis of labile heterocycles **3** could most certainly not be achieved without the help of a Lewis acid, the question arises of knowing whether such acidic conditions are compatible with the maintenance of their integrity. In this context, we decided to reinvestigate the cycloaddition reaction depicted in Scheme 1 under different activation protocols, paying particular attention in its stereochemical aspects. The results of this study are

Keywords: Diastereoselective hetero Diels–Alder reaction; Lewis acids; Chiral non-racemic 5,6-dihydro-4*H*-1,3-thiazines and 3,4-dihydro-2*H*-thiopyrans; Thermodynamic control; Samarium triflate.
* Corresponding author. Tel.: +33-2-51-12-54-92; fax: +33-2-51-12-54-02; e-mail address: andre.guingant@chimie.univ-nantes.fr
† Present address: Laboratoire des fonctions azotées et oxygénées, Université de Rouen, IRCOF—76131—Mont Saint Aignan Cedex (France).

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.041



1 X = CH
2 X = N

3 (X = CH, N) **4**

Scheme 1.

presented in this paper along with the successful achievement of the first asymmetric synthesis of heterocycles **3**. Additionally, we will offer arguments proving that the high propensity of this cycloaddition reaction to deliver, in most examples, adducts of relative *trans* stereochemistry is the result of a readily established thermodynamic control.

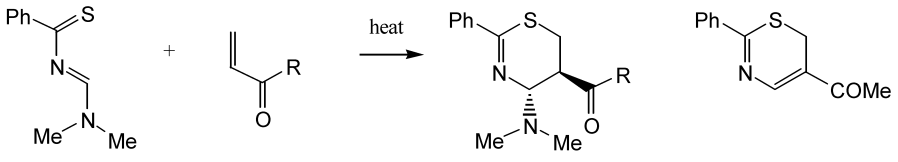
2. Results and discussion

2.1. Cycloaddition reaction of heterodienes 1, 2 and 10

The cycloaddition reactions of diene **2**[5] to methyl vinyl ketone, methyl acrylate and 3-acryloyl-oxazolidin-2-one, **5a**–**c**, under thermal and Lewis acid activations were considered first (Scheme 2).[6]

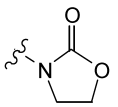
The thermal cycloaddition of diene **2** with a 10-fold excess of methyl vinyl ketone **5a** in toluene (80 °C, 2 h) led mainly to the 6*H*-1,3-thiazine **7** as a result of a dimethylamine elimination process (ratio *trans*-**6a**/**7**=10:90). The initiation of such a facile elimination seems to be attributable to the basicity of the diene. Indeed, when *trans*-**6a** (prepared under Lewis acid activation, vide infra) was heated in toluene (80 °C, 2 h) it was recovered unchanged whereas, in the presence of 1 molar equivalent of diene **2**, in the same conditions as above, the elimination product **7** was quantitatively formed. As expected from the observation, slow addition of diene **2** to an excess of methyl vinyl ketone heated at 80 °C in toluene solution gave adduct *trans*-**6a** though in an always synthetically unfavourable ratio (*trans*-**6a**/**7**=1:1). The reaction of **2** with methyl acrylate **5b** and 3-acryloyl-oxazolidin-2-one **5c** in toluene solution (60 °C, 2 h and reflux, 20 h, respectively) led to *trans*-adducts **6b**,**c** in good chemical yields (80%) when an excess of the dienophile was used. No traces of elimination products were detected in the crude materials by ^{1}H NMR.

Attention was next turned to the approach of forming the adducts **6** under Lewis acid activation. We were initially apprehensive for the success of this activation mode due to the possibility of Lewis acid-induced $NHMe_2$ elimination in the adducts. Fortunately, our concerns proved unfounded since several Lewis acids could be employed to activate the

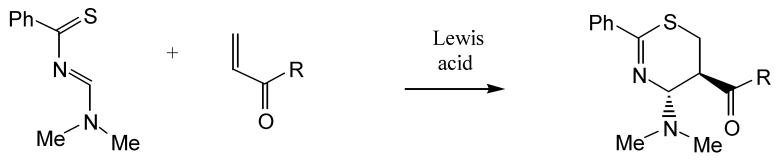


2 **5** *trans*-**6** **7**

a: R=Me; **b**: R=OMe; **c**: R=



Scheme 2.



2 **5** *Trans*-**6 a-c**

a: R = Me
- $TiCl_2(OiPr)_2$, THF, -78°C to -20°C — 78%
- $ZnCl_2$, THF, -10°C to 0°C — 75%

b: R = OMe, **c**: R=

- $MgBr_2$, CH_2Cl_2, 20°C — **b**: 95 % ; **c**: 68%
- Et_2AlCl, CH_2Cl_2, -60°C — **b**: 61 % ; **c**: 0%

Scheme 3.

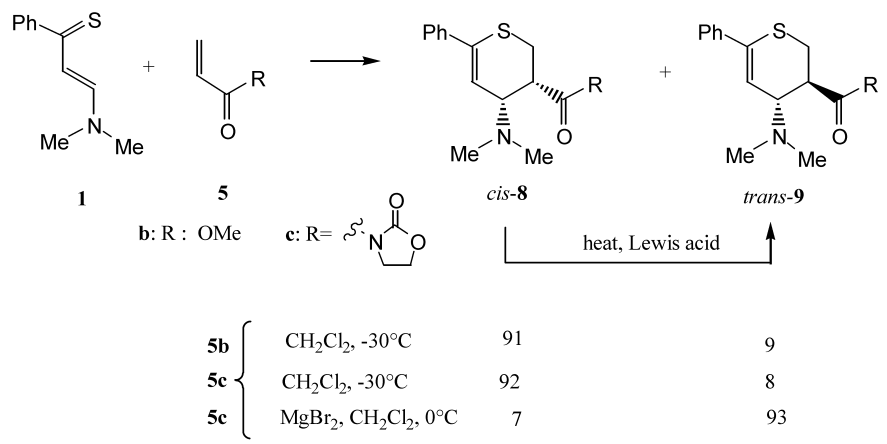
cycloaddition reactions and deliver the adducts in good to excellent chemical yields. Of the various Lewis acids examined, titanium and zinc derivatives (typically 1 molar equivalent with respect to a dienophile) were the best promotors for obtaining adduct *trans*-**6a** when used at low temperature whereas the syntheses of adducts *trans*-**6b**,**c** were best accomplished in the presence of magnesium bromide at room temperature (Scheme 3).

At this point it seems important to notice that the thermal and Lewis acid-promoted reactions are all highly stereoselective and led to the exclusive formation of *trans* adducts irrespective of the activation mode, the solvent and temperature employed. This remarkable feature is somewhat striking because closely related dienes were reported to give predominantly *cis* adducts in the cycloaddition with various electron-poor dienophiles, even at relatively high temperatures.[7] We will return to this problem later.

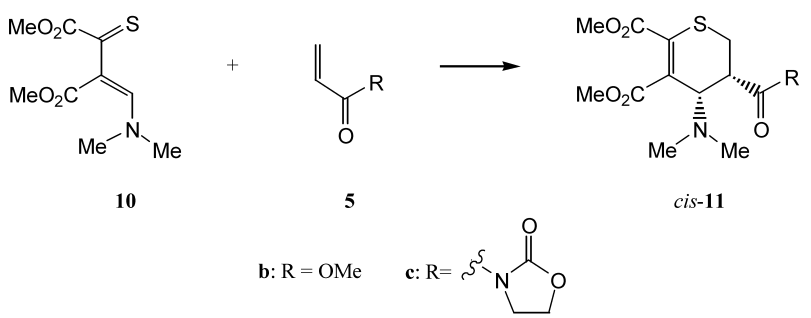
For comparison purposes we next examined the behaviour of diene **1**[8,9] toward the same set of dienophiles as above (Scheme 4). The main differences between the two dienes reside in the greater reactivity of **1** and its marked tendency to give *cis* adducts predominantly at low temperatures. Thus, whereas diene **2** needed long reaction time and elevated temperature to undergo cycloaddition with methyl acrylate, the reaction with diene **1** was complete within 1.5 h at −30 °C producing a mixture of adducts **8b** and **9b** (ratio *cis*-**8b**/*trans*-**9b**: 91:9) in almost quantitative yield. A similar result was also achieved with 3-acryloyl-oxazolidin-2-one as the dienophile. Another noticeable point associated with the reactivity of **1** is the reversal in stereochemistry of the *cis* adducts as the reaction temperature is raised. Thus, when a sample of the initially formed 90:10 mixture of adducts *cis*-**8b**/*trans*-**9b** was heated at 80 °C in toluene for 3 h, the *trans* adduct **9b** only resulted. The reversal in stereochemistry was even more easier for adduct *cis*-**8c** since it occurred on standing the corresponding *cis*-**8c**/*trans*-**9c** mixture at 20 °C for 3 h.

By recourse to competitive crossover experiments, for instance by exposing *cis*-**8b** to a large excess of 3-acryloyl-oxazolidin-2-one **5c** or, conversely, *cis*-**8c** to an excess of methyl acrylate, the evolution of the *cis*-adducts toward the more stable *trans*-adducts was demonstrated to arise via a sequential retro Diels–Alder—Diels–Alder sequence (thermodynamic control). The equilibration process was facilitated under Lewis acid conditions. For instance, the reaction of **1** with 3-acryloyl-oxazolidin-2-one **5c** in the presence of magnesium bromide in methylene chloride at −78 °C gave a ca. 1 to 1 mixture of the corresponding adducts *cis*-**8c** and *trans*-**9c**, whereas adduct *trans*-**9c** was largely predominant at 0 °C (ratio *cis*-**8c**/*trans*-**9c**=7:93). The ease with which the thermodynamic control establishes also depends on the nature of the substituents in the diene. Thus, the cycloaddition reactions of diene **10**[10] with methyl acrylate **5b** and 3-acryloyl-oxazolidin-2-one **5c** afforded the sole *cis*-adducts **11** at 20 °C (Scheme 5). *Trans* adducts were formed, however, in the presence of magnesium bromide (vide infra).

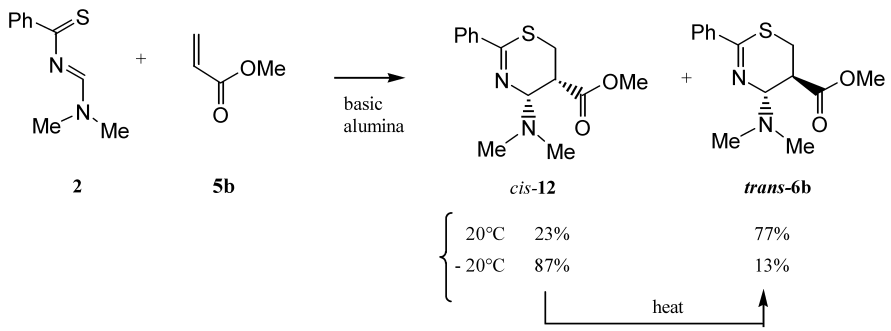
The results displayed by diene **1** now bring us to the



Scheme 4. Ratios of diastereomers were derived by integration of the NMe_2 peaks (or CO_2Me, if present) in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.



Scheme 5.



Scheme 6. Ratios of diastereomers were derived by integration of the NMe_2 peaks (or CO_2Me peaks) in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.

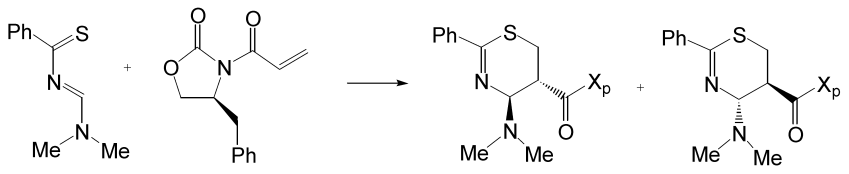
question of whether *trans*-adducts **6**, originating from diene **2**, were also the result of an equilibration process that would establish rapidly, even at very low temperature. The answer to that question emerged fortuity as we studied the condensation of **2** with methyl acrylate on basic alumina (Scheme 6). In these particular conditions the cycloaddition reaction continued to give preference to the *trans*-adduct **6b** although, for the first time, small amount of the *cis*-adduct **12** could be detected in the NMR spectrum of the crude material. Interestingly, decrease of the reaction temperature favoured the formation of the *cis*-adduct (ratio *trans*-**6b**/*cis*-**12**=13:87 at − 20 °C). Without real surprise, brief heating of the *cis*/*trans* adduct mixture in chloroform at 40 °C transformed the *cis*-adduct **12** towards its more stable *trans*-diastereomer **6b**,[11] thereby demonstrating its high thermodynamic instability. Thus, by comparison with the behaviour of *cis*-adducts **8**, it may be concluded that the nitrogen N-3 greatly accelerates the conversion of primary (generally not appeared) *cis*-adducts resulting from the cycloaddition of diene **2** with dienophiles, into their most stable *trans* diastereomers **6**.[12]

Two salient points emerged from the studies reported above: (1) the cycloaddition reactions of diene **2** can be realised in the presence of a Lewis acid without compromising the structural integrity of the adducts formed (no loss of dimethylamine), (2) rapid establishment of the thermodynamic control results in isolation of the sole *trans*-adducts. These observations will be now exploited to develop an efficient route to prepare the 5,6-dihydro-4*H*-1,3-thiazine and 3,4-dihydro-2*H*-thiopyran heterocycles in chiral non-racemic form.

2.2. Asymmetric cycloaddition reactions

When designing an asymmetric diastereoselective synthesis of heterocycle **6b**, two strategies presented itself, i.e. (1) recourse to a chiral heterodiene or (2) utilisation of a chiral dienophile. At first glance, the first strategy seems attractive since it may be envisaged to exchange the dimethylamino group to a chiral amine and excellent selectivities in [4+2] cycloaddition processes had already been displayed with chiral 1-aza-buta-1,3-dienes[13,14] bearing a proline-derived amino-substituent at the N-1 position. However, in the case at hand, any attempts to recover the chiral amino moiety would most certainly be thwarted by a chirality destructive β-elimination process. Attachment of a chiral auxiliary at carbon C-2 represents a second distinct possibility to introducing chirality on the diene. This possibility was already tested in our laboratory[3] but the results were rather disappointing in terms of diastereoselectivity. For all the above reasons it finally appeared to us that a strategy based on an appropriately chosen chiral dienophile would certainly be the most secured method for achieving our goal. Within this context the chiral acrylate derived from ethyl-(*S*)-lactate could be a good candidate as it is easily prepared and reported to give excellent diastereoselectivities in Diels–Alder reactions.[15] While its cycloaddition with diene **2** in the presence of $TiCl_4$ proceeded in a respectable yield of 80% the diastereoselectivity was poor. The weakness of this route prompted us to explore a different approach based on the utilisation of chiral 3-acryloyl-oxazolidin-2-one as a dienophile. If these dienophiles were known, in combination with chelating Lewis acids, to react with carbodienes to give adducts with good to excellent diastereoselectivities,[16] there existed, somewhat surprisingly, no reported examples of their use in hetero Diels–Alder reactions at the outset of our study. However, when our work was in progress, Saito and colleagues[17] reported the Lewis-acid-promoted hetero Diels–Alder reaction of a variety of α,β-unsaturated thiocarbonyl compounds (1-thia-buta-1,3-dienes) with some (4*S*)-benzyl-3-alkenoyl-oxazolidin-2-ones to give [4+2] cycloadducts with fair to excellent diastereomeric excesses.

Cycloaddition reaction of diene **2** with (4*S*)-3-acryloyl-4-benzyl-oxazolidin-2-one **13** was studied under thermal and Lewis acid activations.[18] Thus, when diene **2** and an excess (1.5 equiv.) of chiral **13** was heated in toluene for 20 h, a 20:80 mixture of *trans* diastereomeric adducts **14** and **15** was produced in 75% yield (Scheme 7). This diastereoselectivity was reasonably high for an uncatalysed process and each of the diastereomers was obtained in pure form after simple flash-chromatography on silica gel. In light of our previous investigations (vide supra) we next performed the reaction in the presence of magnesium bromide-etherate in CH_2Cl_2. In these conditions we were gratified to find that the reaction was regulated with much higher diastereoselectivity than that previously observed under thermal conditions, and led to the formation of a single *trans* diastereomer **15**. Thus, depending on the way the reaction is performed, it was possible to direct the process toward the formation of either *trans*-**14** or *trans*-**15**. The absolute configurations at carbons C-4 and C-5 of **15**, and therefore **14**, were firmly established by single crystal X-ray analysis[19,20] of *trans*-**15** (Fig. 1).



2 **13** *trans*-**14** *trans*-**15** (X-ray)

110°C, toluene	85	15
$MgBr_2$-Et_2O in CH_2Cl_2, 0°C	0	100

Scheme 7. Ratios of diastereomers were derived by integration of the NMe_2 peaks in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.

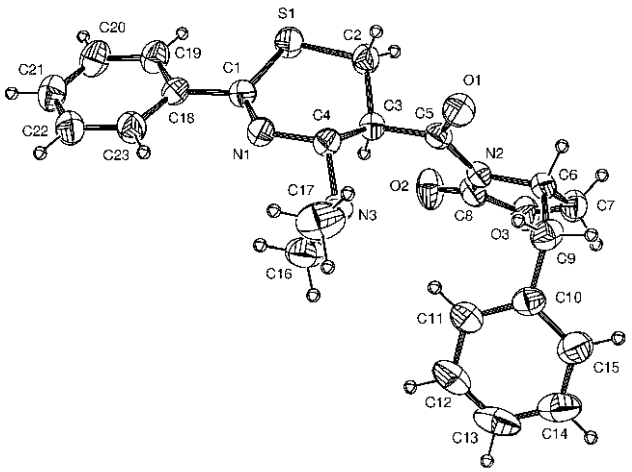


Figure 1. ORTEP drawing of **15**.

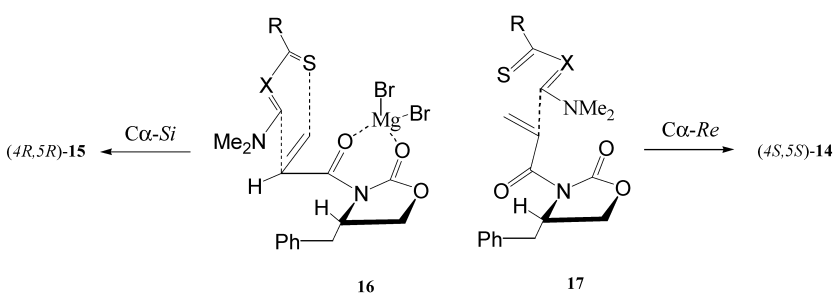
The preferential formation of the (4*R*,5*R*)-adduct **15** under Lewis acid activation may be interpreted by recourse to the Evans model[16] in which magnesium bromide acts as the chelating species. In chelate **16** (R=Ph, X=N), the benzyl group efficiently blocks one diastereotopic face (C_α-*Re*) of the *s-cis* disposed double bond, forcing the heterodiene **2** to approach from the opposite C_α-*Si* face, as depicted in Scheme 8. Under thermal activation, the stereochemical bias provided by the benzyl group in a reactive dienophile conformation close from that shown in **17** (R=Ph, X=N) leads to the preferential formation of the diastereomer (4*S*,5*S*)-**14** (Scheme 8).

The cycloaddition reaction of diene **1** to chiral olefin **13** was less rewarding from a synthetic point of view because each of the four possible *cis* and *trans* stereomers **18**–**21** were formed. If none of these diastereomers could be easily separated from the three others, it was nevertheless possible to determine the diastereomeric ratios for each of the *cis* and *trans* pairs by inspection of the NMR spectra of the crude reaction mixtures (Scheme 9).

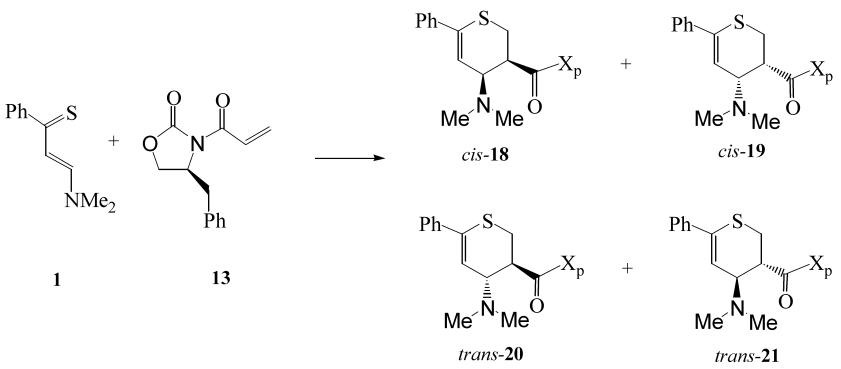
The structures attributed to adducts **18**–**21** were made, as for **14** and **15**, on the basis of the Evans model.[16] As the data indicate, the diastereomeric ratios for *trans* adducts **20** and **21** are quite close to those of the *trans* **14** and **15** adducts obtained under the thermal and Lewis acid-promoted conditions, whereas the corresponding diastereomeric ratios of the *cis* adducts **18** and **19**, respectively, indicate less selective reactions.

More interesting results were obtained in the reaction of **10** with the 3-acryloyl-4-benzyl-oxazolidin-2-one **13**. Scheme 10 and the accompanying data show that the presence (or the absence) of a Lewis acid as well as the reaction temperature are crucial parameters for the establishment of the *cis*/*trans* ratios. Similarly to the precedent reported examples, the cycloaddition reaction can be carried out with high level of diastereoselection when magnesium bromide is the Lewis acid promotor. In these conditions *cis*-**22** and *trans*-**24** are the sole diastereomers formed. Changing the nature of the Lewis acid did not alter the diastereoselectivity for the *trans* adducts (once again **25** was the sole adduct formed when Et_2AlCl was used in place of $MgBr_2$) while the diastereoselectivity for the *cis* adducts **22** and **23** was significantly affected.

Each of the three diastereomers **22**, **23** and **24** that were detected in the above reactions could be easily isolated in pure form by simple flash chromatography on silica. Moreover, the structure of *trans*-**24** was fully ascertained by X-ray analysis.[21] Its formation can be accounted for by

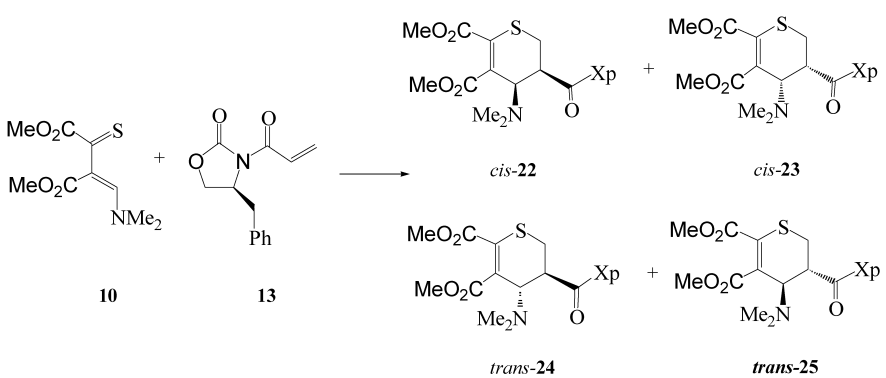


Scheme 8.



Cis:Trans	18:19	20:21
20°C, CH_2Cl_2, 1.5h	75 : 25	25 : 75	15 : 85
$MgBr_2$-Et_2O in CH_2Cl_2, 0°C, 1.5h	55 : 45	80 : 20	**98 : 2**

Scheme 9. Ratios of diastereomers were derived by integration of the NMe_2 peaks in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.



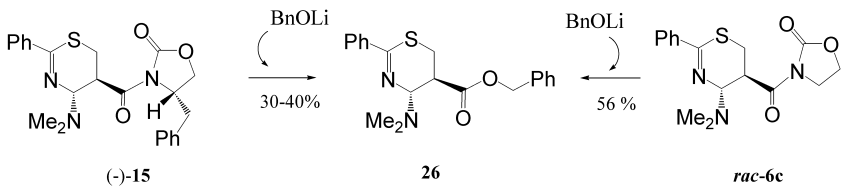
Cis:Trans	22:23	24:25
20°C, CH_2Cl_2, 16h	100:0	15:85	-
$MgBr_2$-Et_2O in CH_2Cl_2 , -10°C, 3h	30:70	100:0	100:0
Et_2AlCl (2 equiv), -60°C, CH_2Cl_2, 3h	78:22	83:17	100:0

Scheme 10. Ratios of diastereomers were derived by integration of the NMe_2 peaks (or CO_2Me peaks) in the ^1H NMR spectra (400 MHz) of the unpurified cycloaddition products.

the Evans transition state model[16] **16** (R=CO_2Me, X=C–CO_2Me) already invoked for the formation of *trans*-**15** adduct (Scheme 8). The structures attributed to the adducts *cis*-**22** and *cis*-**23**, respectively, are based on the reasonable assumption that Evans model is also operative in transition state topographies leading to *cis* adducts.

2.3. Removal of the chiral auxiliary: synthesis of chiral non-racemic heterocycles (+)-6b, (−)-6b, (−)-10b, (−)-27

We have demonstrated that the association (4*S*)-3-acryloyl-4-benzyl-oxazolidin-2-one $MgBr_2$, permitted the highly diastereoselective formation of 5,6-dihydro-4*H*-thiopyrans and 5,6-dihydro-4*H*-[1,3]thiazines when reacted with dienes **1**, **10** and **2**, respectively. It remains now to be demonstrated that the chiral 4-benzyl-oxazolidin-2-one moiety can be easily recovered from the primary Diels–Alder adducts by a simple and high yielding operation. To achieve this ultimate goal, it is necessary that an appropriately chosen nucleophile may be selectively directed to the exocyclic carbonyl of these adducts. While several procedures do succeed in achieving this chemoselective operation,[16] many of them suffer from low efficiency as soon as steric hindrance is involved. Thus, it has been already reported that, in the case where the exocyclic carbonyl is hindered by substituents affixed on the six-membered ring, the nucleophile may well be directed mainly, if not exclusively, to the endocyclic carbonyl, thereby leading to the undesired oxazolidinone ring opening.[16] Due to the presence of the dimethylamino substituent in the vicinity of the exocyclic carbonyl we were thus not surprised to experience some difficulties with adduct **15** upon attempting to recover the chiral auxiliary. To circumvent that problem, the use of lithium peroxide or lithium benzylate, ultimately leading to the replacement of the chiral oxazolin-2-one moiety by an acid or a benzylester,



Scheme 11.

has been equally recommended.[16] In the case at hand, treatment of adduct **15** with lithium peroxide in THF proved unsuccessful, leading to unidentified decomposition products. However, the action of lithium benzylate in THF did afford the expected benzylic ester (−)-**26** in enantiomeric pure form[22] though in unsatisfying low yields (30–40%). At this stage it is not without interest to note that, under the action of the same reagent, the racemic adduct **6c** led to racemic **26** in 56% isolated yield (Scheme 11). This suggests that not only the dimethylamino residue but also the chiral auxiliary benzyl substituent exert an undesirable shielding of the external carbonyl, forcing the benzylate anion to preferentially attack the oxazolidinone ring carbonyl.

After several unsuccessful attempts we were delighted to find that chiral auxiliary removal could be achieved in an acceptable yield of 75% by exposure of adduct **15** to a catalytic amount (0.1 equiv.) of samarium triflate in a 1:1 CH_2Cl_2/MeOH mixture[23] to give (−)-**6b**.[21] Due to the high oxophilicity of samarium, this reaction proceeds most certainly via a chelated intermediate **27** as shown in Scheme 12.

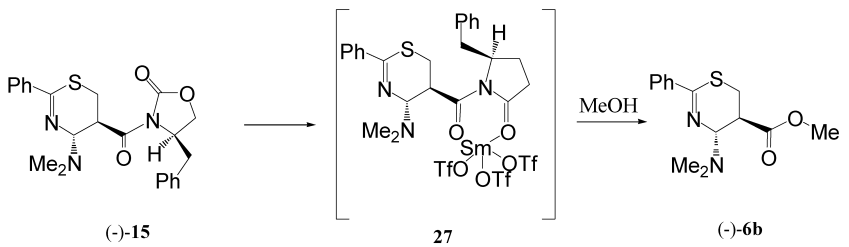
The use of this procedure was also successfully achieved in several other examples, showing its general applicability for substituted 5,6-dihydro-4*H*-[1,3]thiazine and 5,6-dihydro-4*H*-thiopyran compounds (Scheme 13, ee>95% in all examples[21]).

The ability of samarium triflate to form six-membered ring chelates prompts us to determine if this Lewis acid is capable of effecting the [4+2] cycloaddition of diene **2** with chiral dienophile **13** (cf. Scheme 7). Admixture of both components in the presence of a catalytic amount of $Sm(OTf)_3$ in dichloromethane solution led to the expected formation of *trans* adducts **14** and **15** with an encouraging diastereoselection of 89:11 in favour of **15**. By contrast, almost no selectivity was obtained under ytterbium and scandium triflate activations. The preferred formation of adduct **15** in the presence of $Sm(OTf)_3$ can be accounted for by invoking a transition state topography similar to that depicted in Scheme 8 (**15**, R=Ph, X=N, samarium triflate for magnesium bromide). A distinct feature of the $Sm(OTf)_3$ procedure is that the primary adduct need not to be isolated but can be directly transformed in its methyl ester derivative (one pot transformation) by simply adding methanol to the reactional mixture after completion of the cycloaddition. This was demonstrated for the reaction depicted in Scheme 14.

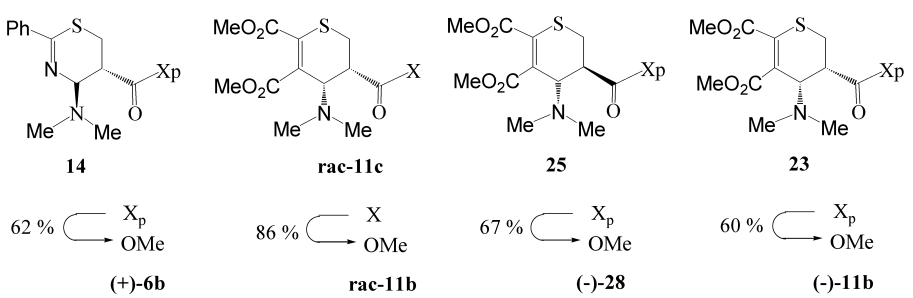
Another potential interest is that the utilisation of samarium triflate in catalytic amount opens the door for achieving a catalytic asymmetric synthesis of the above adducts, using a in situ generated chiral Lewis acid as the reaction promotor.

3. Conclusions

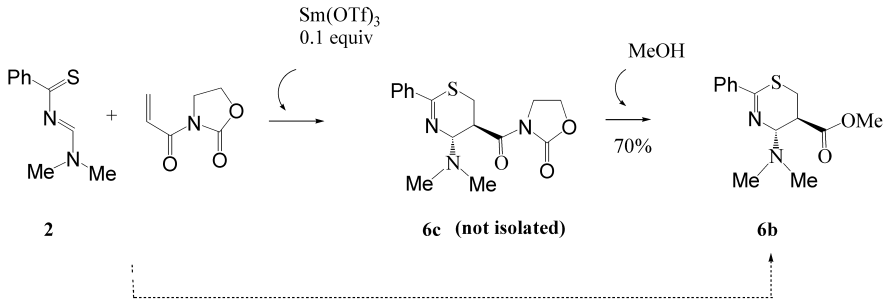
We have described the first approach towards the asymmetric synthesis of the 5,6-dihydro-4*H*-[1,3]thiazine skeleton. The strategy featured the use of the chiral



Scheme 12.



Scheme 13.



Scheme 14.

non-racemic (4*S*)-3-acryloyl-4-benzyl-oxazolidin-2-one **13** which was condensed with the 1-thia-3-aza-buta-1,3-diene **2**. The cycloaddition reaction can be carried out with a very high level of diastereoselection provided magnesium bromide is added to form a chelate with **13**. The only formation of adduct *trans*-**15** in these conditions may be rationalised on the basis of the Evans model. The decisive role of magnesium bromide was also appreciated when chiral dienophile **13** was reacted with 1-thia-buta-1,3-dienes **1** and **10** to give 5,6-dihydro-4*H*-thiopyrans with the same high level of diastereoselection as above. Interestingly, in the absence of a Lewis acid, a still synthetically useful diastereoselectivity of 70% was recorded in all the examples studied. The removal of the chiral auxiliary moiety from the adducts proved to be a non-trivial operation. We discovered that it could be accomplished at best by employing a catalytic amount of samarium triflate in a 1:1 CH_2Cl_2/MeOH mixture. Under these reaction conditions the resulting adducts bearing a methyl ester functionality at C-5 were isolated in yields ranging from 60 to 86%. Finally, it was demonstrated that the general trend of diene **2** to lead to the most stable *trans* adducts, even at low temperatures and in the absence of a Lewis acid, was the result of a thermodynamic control of the cycloaddition reaction.

4. Experimental

4.1. General

Melting points were determined using a Reichert-Jung Thermo Galen Kofler block. Optical rotations were measured at ambient temperature using an Optical Activity Ltd AA-10 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Microanalysis was carried out at the 'Services de Microanalyses du CNRS de Vernaison—France'. IR spectra were recorded on a Bruker IFS 45 WHR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC200 spectrometer at 200 MHz or on a Bruker ARX400 spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer at 50 MHz or on a Bruker ARX400 spectrometer at 100 MHz. All NMR spectra used tetramethylsilane as the internal standard and were run in deuterated solvents. *J* Values are given in Hz. The mass spectra were obtained in GC/MS mode (EI, 70 eV). Thin layer chromatography (TLC) was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates. Flash chromatography was performed with silica gel (Merck Geduran SI 60 Art.11567).

Reactions carried out under an inert atmosphere refer to the use of argon or nitrogen. Diethyl ether, tetrahydrofuran (THF) and benzene were dried by being distilled from sodium and benzophenone. Dichloromethane, toluene, acetone and carbon tetrachloride were dried by distillation from calcium hydride. All other reagents were purified by distillation, the pressure being reduced if the boiling point of the compound was greater than 110 °C at atmospheric pressure.

4.2. Synthesis of racemic heterocycles

4.2.1. 1-(2-Phenyl-6*H*-1,3-thiazin-5-yl)-ethanone: 7. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene (*N*-[(dimethyl-amino)methylene]-benzene-carbothioamide) **2** (0.25 g, 1.3×10^{-3} mol) in dry toluene (10 mL) were added methyl vinyl ketone (1 mL, 12×10^{-3} mol) and hydroquinone (few crystals). The reaction mixture was stirred for 2 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Analysis of the crude product by ^{1}H NMR showed the presence of both **6a** and **7** in a 1:9 ratio. Purification of the residue by chromatography on silica (petroleum ether/ethyl acetate 4:1) gave **7** (90%) as a yellow solid; R_f 0.59 (petroleum ether/ethyl acetate 4:1); mp 108–109 °C (diethyl ether/petroleum ether); ν_{max}/cm^{-1} 1689, 1648, 1504, 693; δ_H (200 MHz; $CDCl_3$): 2.46 (3H, s), 3.70 (2H, s), 7.50 and 8.05 (6H, 2m); δ_C (50 MHz; $CDCl_3$): 21.1, 25.7, 116.4, 129.0, 129.1, 132.9, 137.2, 147.9, 169.4, 196.4; *m/z* (EI) 217 ($M^{+\cdot}$, 31), 202 (27), 175 (100), 174 (54), 121 (19), 105 (83), 77 (58), 51 (20), 43 (14), 39 (7), 15 (3).

4.2.2. *trans*-1-[4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazin-5-yl]ethanone: 6a. *Zinc chloride activation.* A 1 M zinc chloride solution in diethyl ether (1 mL, 10^{-3} mol) was diluted at room temperature in dry THF (4 mL) placed under inert atmosphere. Methyl vinyl ketone (0.21 mL, 2.5×10^{-3} mol) was added and the mixture was stirred for 10 min. After cooling at −20 °C, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.2 g, 1.04×10^{-3} mol) in dry THF (1 mL) was syringed in. The reaction mixture was stirred for 2 h between −20 and −10 °C. After dilution with ethyl acetate (10 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×10 mL) and brine (2×10 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by crystallisation (diethyl ether/petroleum ether) gave **6a** as yellow crystals (0.2 g, 75%).

Titanium dichlorodiisopropoxide activation. Titanium tetrachloride (0.22 mL, 2×10^{-3} mol) then titanium

tetraisopropoxide (0.6 mL, 2×10^{-3} mol) were sequentially added at room temperature to dry THF (20 mL) placed under inert atmosphere. The mixture was stirred for 10 min then cooled at −78 °C. Methyl vinyl ketone (0.32 mL, 3.8×10^{-3} mol) was added. After 20 min, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) in dry THF (4 mL) was syringed in. The reaction mixture was stirred for 3 h allowing to warm to −20 °C. After dilution with ethyl acetate (20 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×20 mL) and brine (2×20 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by crystallisation (diethyl ether/petroleum ether) gave **6a** as yellow crystals (0.53 g, 78%); mp 73–74 °C; ν_{max}/cm^{-1} 1710, 1700, 690; δ_H (200 MHz; $CDCl_3$): 2.30 (3H, s), 2.42 (6H, s), 2.83 (1H, ddd, J=3.8, 10.0, 11.9 Hz), 2.94 (1H, dd, J=3.8, 12.1 Hz), 3.44 (1H, dd, J=11.9, 12.1 Hz), 4.39 (1H, d, J=10.0 Hz), 7.38 and 7.83 (5H, 2m); δ_C (50 MHz; $CDCl_3$) 27.8, 30.4, 40.3, 45.0, 79.8, 126.6, 128.4, 129.1, 138.5, 157.5, 210.3; m/z (EI) 262 ($M^{+}\cdot$, 1), 192 (100), 159 (80), 121 (79), 89 (85), 77 (35), 44 (66); Anal. calcd for $C_{14}H_{18}N_2OS$: C, 64.09; H, 6.92; N, 10.68; found: C, 63.87; H, 6.85; N, 10.58.

4.2.3. *trans*-Methyl 4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate: 6b. *Thermal activation*. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) in dry dichloromethane (30 mL) were added methyl acrylate (2.1 mL, 23.3×10^{-3} mol) and hydroquinone (few crystals). The reaction mixture was stirred for 24 h at 40 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 80:20) gave **6b** as a pale yellow solid (0.59 g, 81%).

Magnesium bromide activation. Magnesium turnings (0.08 g, 3.29×10^{-3} mol) in dry diethyl ether (4 mL) were placed under inert atmosphere. 1,2-Dibromoethane (0.28 mL, 3.25×10^{-3} mol) was added dropwise and the reaction mixture was slightly heated to induce the formation of magnesium bromide. When all the magnesium turnings were consumed, diethyl ether was removed by several pumping and venting cycles (argon) to leave a white powder. Dichloromethane (8 mL), then methyl acrylate (0.175 mL, 1.94×10^{-3} mol) were syringed in at room temperature. After 10 min, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.25 g, 1.3×10^{-3} mol) in dry dichloromethane (2 mL) was added and the reaction mixture was stirred at room temperature for 3 h. After dilution with dichloromethane (10 mL) then successive washings with 10% aqueous potassium hydrogen carbonate (2×10 mL) and brine (2×10 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 4:1) gave **6b** as a pale yellow solid (0.34 g, 95%).

Diethylaluminium chloride activation. Diethylaluminium chloride (1 M in hexane) (1.95 mL, 1.95×10^{-3} mol) was added under inert atmosphere to dichloromethane (10 mL) cooled at −78 °C followed by methyl acrylate (0.175 mL, 1.94×10^{-3} mol). The mixture was stirred for 10 min allowing to warm to −20 °C. After cooling at −78 °C, a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.25 g, 1.3×10^{-3} mol) in dry dichloromethane (2 mL) was added and the reaction mixture was stirred at −60 °C for 3 h. After dilution with dichloromethane (10 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×10 mL) and brine (2×10 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 4:1) gave **6b** as a pale yellow solid (0.22 g, 61%); R_f 0.32 (petroleum ether/ethyl acetate 4:1); mp 78 °C (ethyl acetate/petroleum ether); ν_{max}/cm^{-1} 1725, 1612, 1356, 690; δ_H (400 MHz; $CDCl_3$) 2.42 (6H, s), 2.73 (1H, ddd, J=3.8, 10.2, 12.1 Hz), 3.10 (1H, dd, J=3.8, 12.2 Hz), 3.52 (1H, dd, J=12.1, 12.2 Hz), 3.78 (3H, s), 4.44 (1H, d, J=10.2 Hz), 7.40 and 7.84 (5H, 2m); δ_C (50 MHz; CD_3COCD_3) 28.7, 40.3, 40.8, 52.4, 80.1, 127.2, 129.3, 131.6, 139.5, 158.2, 174.1; m/z (EI): 278 ($M^{+}\cdot$, 1), 192 (80), 159 (59), 121 (44), 89 (100), 77 (19), 51 (8), 44 (56).

4.2.4. *trans*-3-{[4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-yl]carbonyl}-1,3-oxazolidin-2-one: 6c. *Thermal activation*. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.05 g, 2.6×10^{-4} mol) in dry toluene (2 mL) was added a solution of 3-(prop-2-enoyl)-oxazolidin-2-one (0.055 g, 3.9×10^{-4} mol) in dry toluene (8 mL). The reaction mixture was stirred for 20 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/acetone 2:3) gave **6c** as white needles (0.07 g, 81%).

Magnesium bromide activation. Compound **6c** was prepared according to the same procedure as compound **6b**. Flash-chromatography on silica (petroleum ether/acetone 2:3) produced the title compound as white needles (0.16 g, 68%); R_f 0.67 (petroleum ether/acetone 2:3); mp 108–109 °C (ethyl acetate/petroleum ether); ν_{max}/cm^{-1} 1768, 1700, 1616, 1393, 1225, 685; δ_H (200 MHz; $CDCl_3$): 2.41 (6H, s), 3.10 (1H, dd, J=3.8, 12.2 Hz), 3.47 (1H, dd, J=12.2, 12.2 Hz), 4.10 (2H, m), 4.33 (1H, ddd, J=3.8, 10.2, 12.2 Hz), 4.45 (2H, m), 4.68 (1H, d, J=10.2 Hz), 7.60 and 7.85 (5H, 2m); δ_C (50 MHz; $CDCl_3$): 28.5, 36.7, 40.7, 43.1, 62.1, 79.5, 126.7, 128.5, 130.9, 138.6, 153.6, 157.5, 174.6; m/z (EI): 333 ($M^{+}\cdot$, 1), 192 (100), 159 (70), 141 (13), 121 (83), 113 (32), 89 (56), 77 (32), 44 (54).

4.2.5. *cis* and *trans* Methyl 4-(dimethylamino)-6-phenyl-3,4-dihydro-2*H*-1,3-thiopyran-3-carboxylate: 8b and 9b. The title compounds and **8c** and **9c** were prepared according to the same procedure as compounds **6b** and **6c**. They were separated and obtained pure (except for **8c**) by chromatography on silica (petroleum ether/ethyl acetate 3:2) and isolated in yields greater than 90% (see text for information about the *cis*/*trans* ratios).

Compound **8b**. Pale yellow solid; R_f 0.40 (petroleum ether/ethyl acetate 3:2); mp 83–84 °C (ethyl acetate); ν_{max}/cm^{-1} 1734, 1342, 691; δ_H (400 MHz; $CDCl_3$): 2.37 (6H, s), 2.90 (1H, ddd, J=3.4, 5.0, 13.1 Hz), 3.00 (1H, dd, J=3.4, 13.1 Hz), 3.36 (1H, dd, J=13.1, 13.1 Hz), 3.76 (3H, s and

1H, m), 6.16 (1H, d, J=6.0 Hz), 7.34 and 7.50 (5H, 2m); δ_H (400 MHz; C_6D_6): 2.21 (6H, s), 2.71 (1H, ddd, J=3.4, 5.0, 13.1 Hz), 2.80 (1H, dd, J=3.4, 13.1 Hz), 3.41 (1H, m and 3H, s), 3.62 (1H, dd, J=5.0, 6.0 Hz), 6.01 (1H, d, J=6.0 Hz), 7.12 and 7.55 (5H, 2m); δ_C (50 MHz; $CDCl_3$): 24.3, 44.7, 46.0, 51.8, 58.3, 116.8, 126.7, 128.5, 137.6, 139.7 (2C), 173.4; *m/z* (EI): 277 ($M^{+}\cdot$, 1), 233 (6), 191 (50), 158 (100), 121 (13), 115 (18), 77 (8); Anal. calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; found: C, 65.15; H, 6.67; N, 5.05.

Compound **9b**. Pale yellow solid; R_f 0.21 (petroleum ether/ethyl acetate 3:2); mp 60–61 °C (diethyl ether/petroleum ether); ν_{max}/cm^{-1} 1740, 1347; δ_H (400 MHz; $CDCl_3$): 2.36 (6H, s), 2.99 (1H, dd, J=2.8, 12.4 Hz), 3.03 (1H, ddd, J=2.8, 9.3, 10.5 Hz), 3.30 (1H, dd, J=10.5, 12.4 Hz), 3.75 (3H, s), 3.82 (1H, dd, J=2.9, 9.3 Hz), 6.04 (1H, d, J=2.9 Hz), 7.33 and 7.48 (5H, 2m); δ_C (50 MHz; $CDCl_3$): 29.4, 41.0, 42.6, 52.4, 61.9, 118.4, 126.6, 128.6, 137.1, 139.4 (2C), 174.6; *m/z* (EI): 277 ($M^{+}\cdot$, 6), 262 (14), 246 (2), 233 (9), 191 (34), 158 (100); Anal. calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; found: C, 65.18; H, 6.89; N, 4.83.

4.2.6. *cis* and *trans* 3-{[4-(Dimethylamino)-6-phenyl-3,4-dihydro-2*H*-thiopyran-3-yl]carbonyl}-1,3-oxazolin-2-one: 8c and 9c. *Compound* **8c**. δ_H (400 MHz; C_6D_6): 2.19 (6H, s), 2.76 (1H, dd, J=3.2, 13.2 Hz), 3.18 (4H, m), 3.60 (1H, dd, J=13.2, 13.2 Hz), 4.16 (1H, ddd, J=3.2, 6.9, 13.2 Hz), 4.36 (1H, dd, J=5.0, 6.9 Hz), 6.14 (1H, d, J=5.0 Hz), 7.11 and 7.57 (5H, 2m).

Compound **9c**. R_f 0.36 (ethyl acetate/acetone 1:1); mp 131–132 °C (ethyl acetate/petroleum ether); ν_{max}/cm^{-1} 1770, 1693, 694; δ_H (400 MHz; $CDCl_3$): 2.35 (6H, s), 2.98 (1H, dd, J=2.8, 12.7 Hz), 3.25 (1H, dd, J=11.0, 12.7 Hz), 4.07 (3H, m), 4.44 (2H, ddd, J=2.5, 7.7, 8.6 Hz), 4.47 (1H, ddd, J=2.8, 10.1, 11.0 Hz), 6.07 (1H, d, J=2.7 Hz), 7.33, 7.48 (5H, 2m); δ_H (400 MHz; C_6D_6): 2.25 (6H, s), 2.78 (1H, dd, J=2.8, 12.6 Hz), 3.00 (4H, m), 3.24 (1H, dd, J=11.2, 12.6 Hz), 4.10 (1H, dd, J=2.6, 10.4 Hz), 4.82 (1H, ddd, J=2.8, 10.4, 11.2 Hz), 6.04 (1H, d, J=2.6 Hz), 7.12 and 7.60 (5H, 2m); δ_C (100 MHz; $CDCl_3$): 29.9, 40.3, 41.2, 43.1, 62.1, 62.2, 117.8, 126.7, 128.6, 137.2, 139.5, 131.9, 153.5, 174.5; *m/z* (EI: 332 ($M^{+}\cdot$, 1), 191 (49), 158 (100), 143 (21), 121 (26), 115 (34), 55 (98); Anal. calcd for $C_{17}H_{20}N_2O_3S$: C, 61.43; H, 6.06; N, 8.43; found: C, 61.00; H, 6.09; N, 8.22.

4.2.7. *cis*-Trimethyl-4-(dimethylamino)-3,4-dihydro-2*H*-thiopyran-3,5,6-tricarboxylate: 11b. To a solution of 4-dimethylamino-2,3-dimethoxycarbonyl-1-thia-buta-1,3-diene **10** (0.1 g, 4.33×10^{-4} mol) in dry dichloromethane (5 mL) was added methyl acrylate (0.06 mL, 6.66×10^{-4} mol). The reaction mixture was stirred for 4 h at room temperature then concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 1:1) gave **11b** as white crystals (0.124 g, 91%); R_f 0.66 (petroleum ether/ethyl acetate 1:1; mp 76 °C (diethyl ether); ν_{max}/cm^{-1} 1735, 1725, 1440, 1314, 1247, 729; δ_H (400 MHz; $CDCl_3$): 2.34 (6H, s), 2.59 (1H, ddd, J=3.2, 3.6, 13.2 Hz), 3.08 (1H, ddd, J=1.6, 3.2, 13.2 Hz), 3.31 (1H, dd, J=13.2, 13.2 Hz), 3.77 (3H, 3s), 3.79 (3H, 3s), 3.84 (3H, 3s), 4.33 (1H, dd, J=1.6, 3.3 Hz); δ_C (100 MHz; $CDCl_3$): 22.8, 44.7, 44.9, 52.1, 52.5, 53.3, 56.8, 123.0, 142.1, 166.0, 166.3, 172.0; *m/z* (EI): 317 ($M^{+}\cdot$, 11), 286 (7), 270 (7), 258 (17), 231 (50), 213 (20), 199 (100), 184 (19), 172 (61), 141 (40), 129 (13), 113 (13), 72 (24), 42 (32), 15 (22); Anal. calcd for $C_{13}H_{19}NO_6S$: C, 49.20; H, 6.03; N, 4.41; found: C, 49.34; H, 6.26; N, 4.51.

4.2.8. *cis*-Dimethyl 4-(dimethylamino)-3-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate: 11c. The title compound was prepared according to the same procedure as compound **11b** starting from 0.2 g of diene **10**. White crystals (0.216 g, 75%); R_f 0.25 (petroleum ether/ethyl acetate 3:7; mp 114 °C (petroleum ether/ethyl acetate); ν_{max}/cm^{-1} 1776, 1739, 1710, 1693, 1447, 1333, 1262, 1242, 719; δ_H (200 MHz; $CDCl_3$): 2.32 (6H, s), 2.89 (1H, dd, J=3.0, 13.0 Hz), 3.47 (1H, dd, J=2.1, 13.0 Hz), 3.72 (1H, ddd, J=3.0, 3.0, 13.0 Hz), 3.77 (3H, s), 3.84 (3H, s), 4.09 (2H, m), 4.40 (1H, d, J=3.0 Hz), 4.46 (1H, m); δ_C (100 MHz; $CDCl_3$): 22.9, 42.8, 44.5, 44.6, 52.4, 53.2, 57.0, 62.4, 123.5, 141.7, 153.1, 165.7, 166.1, 172.1; *m/z* (EI): 372 ($M^{+}\cdot$, 6), 231 (50), 199 (100), 172 (65), 141 (37), 113 (28), 55 (39); calcd for $C_{14}H_{20}N_2O_6S$: C, 48.83; H, 5.85; N, 8.13; found: C, 49.03; H, 6.47; N, 8.25. HRMS (LSIMS): *m/z*=373 $[M+H]^+$, calcd for $C_{15}H_{21}N_2O_7S$: 373.1070; found: 373.1066.

4.3. Cycloaddition of diene 2 with methyl acrylate catalysed by alumina: obtention of the *cis*- and *-trans* methyl 4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylates 12 and 6b

A solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) and methyl acrylate (2.3 mL, 26×10^{-3} mol) in dry dichloromethane (5 mL) was added to 1.5 g of basic alumina (Merck, type E). The reaction mixture was vigorously stirred for 1 h at 20 °C (or 0 °C). After addition of dichloromethane (40 mL) the resulting slurry was filtered on a pad of celite and the solvent concentrated (no heating!) under reduced pressure. NMR analysis of the crude mixture revealed, next to unreacted material, the presence of two diastereomeric adducts, **6b** and **12**, in a ratio depending on the reaction temperature (see text). Flash chromatography on silica (petroleum ether/ethyl acetate 80:20) gave **6b** (0.477 g, 66%). Due to its extremely facile conversion into *trans*-**6b**, the *cis* adduct **12** could not be isolated. Main NMR characteristic values for **12** (cf. **6b**): δ_H (200 MHz; $CDCl_3$): 2.52 (3H, s); 3.75 (3H, s); 4.62 (1H, d, J=4.0 Hz).

4.4. Synthesis of chiral non-racemic heterocycles

Thermal activation. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.05 g, 2.6×10^{-4} mol) in dry toluene (2 mL) was added a solution of (4*S*)-4-benzyl-3-(prop-2-enoyl)-oxazolidin-2-one **13** (0.09 g, 3.9×10^{-4} mol) in dry toluene (10 mL). The reaction mixture was stirred for 20 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 1:1 then 1:4) gave **14** and **15** (ratio: 85:15) as white needles (0.082 g, 75%).

Magnesium bromide activation. Magnesium turnings (0.021 g, 8.6×10^{-4} mol) in dry diethyl ether (4 mL) were

placed under inert atmosphere. 1,2-Dibromoethane (0.073 mL, 8.47×10^{-4} mol) was added dropwise and the reaction mixture was slightly heated to start the formation of the catalyst $MgBr_2$. When all the magnesium turnings were consumed, diethyl ether was removed by several pumping and venting cycles (argon) to leave a white powder. Dichloromethane (8 mL) was syringed in, then the temperature was cooled to 0 °C. A solution of (4*S*)-4-benzyl-3-(prop-2-enoyl)-oxazolidin-2-one **13** (0.09 g, 3.9×10^{-4} mol) in dry dichloromethane (1 mL) was added followed, after 15 min, by a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.05 g, 2.6×10^{-4} mol) also in dry dichloromethane (1 mL). The reaction mixture was stirred at 0 °C for 3 h. After dilution with dichloromethane (10 mL) at room temperature then successive washings with 10% aqueous potassium hydrogen carbonate (2×15 mL) and brine (2×15 mL), the organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. A washing of the residue with cold diethyl ether gave **15** as white needles (0.075 g, 68%).

4.4.1. (4*S*)-3-{[(4*S*,5*S*)-4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-yl] carbonyl}-4-benzyl-1,3-oxazolidin-2-one: 14. *Compound* **14**. R_f 0.40 (petroleum ether/ethyl acetate 1:4); mp 107–108 °C (diethyl ether/petroleum ether); $[\alpha]_D^{21.5}=+196.4$ (*c* 0.28, $CHCl_3$); ν_{max}/cm^{-1} 1762, 1692, 1616, 1396, 1256, 690; δ_H (400 MHz; $CDCl_3$): 2.40 (6H, s), 2.82 (1H, dd, *J*=8.6, 13.7 Hz), 3.14 (1H, dd, *J*=3.7, 12.0 Hz), 3.30 (1H, dd, *J*=3.2, 13.7 Hz), 3.47 (1H, dd, *J*=12.0, 12.0 Hz), 4.24 (2H, m), 4.26 (1H, ddd, *J*=3.7, 10.1, 12.0 Hz), 4.71 (1H, d, *J*=10.1 Hz), 4.79 (1H, m), 7.32 and 7.85 (10H, 2m); δ_C (100 MHz; $CDCl_3$): 28.5, 37.0, 38.1, 40.7, 55.8, 66.5, 79.2, 126.7, 127.5, 128.4, 129.1, 129.5, 130.8, 135.2, 138.5, 153.5, 157.5, 174.2; *m*/*z* (CI): 423 ($M^{+}\cdot$); (EI): 192 (28), 159 (20), 121 (24), 55 (100), 44 (25); Anal. calcd for $C_{23}H_{25}N_3O_3S$: C, 65.23; H, 5.95; N, 9.92; found: C, 64.69; H, 5.93; N, 9.87.

4.4.2. (4*S*)-3-{[(4*R*,5*R*)-4-(Dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-yl] carbonyl}-4-benzyl-1,3-oxazolidin-2-one: 15. *Compound* **15**. R_f 0.88 (petroleum ether/ethyl acetate 1:4); mp 125–126 °C (diethyl ether/petroleum ether); $[\alpha]_D^{20}=-65.4$ (*c* 0.52, $CHCl_3$); ν_{max}/cm^{-1} 1762, 1692, 1616, 1396, 690; δ_H (400 MHz; $CDCl_3$): 2.47 (6H, s), 2.88 (1H, dd, *J*=8.6, 13.7 Hz), 3.10 (1H, dd, *J*=3.7, 12.0 Hz), 3.26 (1H, dd, *J*=3.2, 13.7 Hz), 3.55 (1H, dd, *J*=12.0, 12.0 Hz), 4.20 (2H, m), 4.38 (1H, ddd, *J*=3.7, 10.1, 12.0 Hz), 4.69 (1H, d, *J*=10.1 Hz), 4.79 (1H, m), 7.35 and 7.85 (10H, 2m); δ_C (100 MHz; $CDCl_3$): 28.3, 36.7, 37.4, 40.7, 55.3, 65.9, 80.5, 126.7, 127.4, 128.4, 129.0, 129.8, 130.8, 135.3, 138.6, 153.5, 157.5, 174.9; *m*/*z* (CI): 423 ($M^{+}\cdot$); (EI): 192 (28), 159 (20), 121 (24), 55 (100), 44 (25); HRMS (LSIMS): *m*/*z*=424 $[M+H]^+$, calcd for $C_{23}H_{25}N_3O_3S$: 424.1695; found: 424.1694.

Thermal activation. A mixture of dimethyl (2*E*)-[(dimethylamino)methylene]-3-thiosuccinate **10** (1.10 mmol) and (4*S*)-3-acryloyl-4-benzyl-1,3-oxazolidin-2-one **13** (1.10 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature during 16 h. The concentrated crude mixture was then flash-chromatographed on silica (eluent: petroleum ether/AcOEt, 7:3) to afford *cis*-**23** (310 mg, 61%) along with its diastereoisomer *cis*-**22** (50 mg, 10%).

Magnesium bromide activation. To a suspension of activated magnesium turnings (3.25 mmol) in dry Et_2O was added 1,2-dibromoethane (3.25 mmol). The resulting mixture was stirred until disappearance of all magnesium turnings and solvent evaporated under N_2 draught. After addition of dry CH_2Cl_2 (10 mL), (4*S*)-3-acryloyl-4-benzyl-1,3-oxazolidin-2-one **13** (1.10 mmol) in anhydrous CH_2Cl_2 (3 mL) was added at −10 °C. After 15 min stirring at −10 °C, dimethyl (2*E*)-[(dimethylamino)methylene]-3-thiosuccinate **10** (1.10 mmol) was slowly added. The reaction mixture was then stirred at −10 °C for 3 h. Saturated $NaHCO_3$ (5 mL) was added and the organic layer was washed with saturated $NaHCO_3$ (2×5 mL), water (5 mL) and brine (5 mL). The CH_2Cl_2 extract was then dried over anhydrous $MgSO_4$, filtered and concentrated. The crude mixture was flash-chromatographed on silica (eluent: petroleum ether/AcOEt, 7:3) to afford *trans*-**25** (285 mg, 57%) as white crystals along with its diastereoisomer *cis*-**22** (142 mg, 28%).

4.4.3. Dimethyl (3*R*,4*R*)-4-(dimethylamino)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl] carbonyl}-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate: 22. *Compound* (3*R*,4*R*)-**22**. $[\alpha]_D^{20}=+371.0$ (*c* 0.52, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 2.39 (6H, s); 2.70 (1H, dd, *J*=13.0, 11.4 Hz); 2.92 (1H, ddd, *J*=12.4, 2.3, 1.6 Hz); 3.50–3.57 (2H, m); 3.67 (1H, m); 3.79, 3.84 (6H, 2s); 4.20 (2H, m); 4.56 (1H, dd, *J*=3.3, 1.6 Hz); 4.74 (1H, m); 7.25–7.37 (5H, m); δ_C (100 MHz; $CDCl_3$): 23.2, 38.5, 44.9, 45.1, 52.5, 53.3, 55.6, 60.5, 66.9, 123.9, 127.5, 129.2, 129.4, 135.5, 141.4, 153.2, 166.1, 172.0, 184.9; HRMS (LSIMS): *m*/*z*=463 $[M+H]^+$, calcd for $C_{22}H_{27}N_2O_7S$: 463.1539; found: 463.1534.

4.4.4. Dimethyl (3*S*,4*S*)-4-(dimethylamino)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl] carbonyl}-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate: 23. *Compound* (3*S*,4*S*)-**23**. $[\alpha]_D^{20}=-310.4$ (*c* 0.52, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 2.35 (6H, s), 2.78 and 3.41 (2H, AB part of an ABX system, *J*=13.3, 9.8, 3.2 Hz), 2.97 and 3.52 (2H, AB part of an ABX system, *J*=13.1, 13.0, 3.0 Hz), 3.72–3.82 (1H, m), 3.76, 3.84 (6H, 2s), 4.23 (2H, m), 4.30 (1H, dd, *J*=3.4, 1.2 Hz), 4.63 (1H, m), 7.22–7.36 (5H, m); δ_C (100 MHz; $CDCl_3$): 23.1, 37.8, 44.8, 52.5, 53.3, 56.4, 57.2, 66.6, 123.4, 127.6, 129.1, 129.5, 135.3, 141.9, 153.0, 165.8, 166.2, 172.1; HRMS (LSIMS): *m*/*z*=463 $[M+H]^+$, calcd for $C_{22}H_{27}N_2O_7S$: 463.1539; found: 463.1535.

4.4.5. Dimethyl (3*R*,4*S*)-4-(dimethylamino)-3-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl] carbonyl}-3,4-dihydro-2*H*-thiopyran-5,6-dicarboxylate 24. *Compound* (3*R*,4*S*)-**24**. Mp 134 °C. $[\alpha]_D^{20}=-102.1$ (*c* 0.52, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 2.36 (6H, s), 2.70 and 3.31 (2H, AB part of an ABX system, *J*=12.8, 9.8, 3.2 Hz), 3.14 (2H, d, *J*=4.7 Hz), 3.80, 3.81 (6H, 2s), 4.17–4.26 (3H, m), 4.53 (1H, dd, *J*=4.9, 4.7 Hz), 4.69 (1H, m), 7.20–7.35 (5H, m); δ_C (100 MHz; $CDCl_3$): 27.2, 37.6, 38.8, 41.9, 52.5, 53.1, 55.6, 60.1, 66.5, 127.5, 129.1, 129.5, 135.2, 130.7, 136.4, 153.3, 165.2, 167.5, 171.5; HRMS (LSIMS): *m*/*z*=463 $[M+H]^+$, calcd for $C_{22}H_{27}N_2O_7S$: 463.1539. Found:

463.1534; Anal. calcd for $C_{22}H_{26}N_2O_7S$ (462.52): C, 57.13; H, 5.67; N, 6.06; found: C, 57.22; H, 5.79; N, 5.98.

4.5. Chiral auxiliary removal

4.5.1. Preparation of an authentic sample of benzyl-4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate: 26. To a solution of 4-dimethylamino-2-phenyl-1-thia-3-aza-buta-1,3-diene **2** (0.5 g, 2.6×10^{-3} mol) in dry toluene (30 mL) were added benzyl acrylate (1 g, 6.17×10^{-3} mol) and hydroquinone (few crystals). The reaction mixture was stirred for 5 h at 110 °C then, after cooling at room temperature, concentrated under reduced pressure. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 7:3) gave the title compound as a white solid (0.87 g, 95%).

4.5.2. Benzyl (4*R*,5*R*)-4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylate: 26. Benzyl alcohol (0.073 mL, 7×10^{-4} mol) was diluted in dry THF (6 mL) and placed under inert atmosphere. The solution was cooled to −78 °C and *n*-butyllithium (1.6 M in hexane, 0.33 mL, 5.28×10^{-4} mol) was added dropwise. After 5 min, a solution of adduct **15** (0.15 g, 3.5×10^{-4} mol) in dry THF (0.45 mL) was syringed in. The temperature was allowed to warm to room temperature and after 5 h, saturated aqueous ammonium chloride (3 mL) was added. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (10 mL) and washed with brine (1×10 mL). The organic layer was extracted, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (petroleum ether/ethyl acetate 7:3) gave **26** as white needles (0.04 g, 32%); R_f 0.47 (petroleum ether/ethyl acetate 1:1); mp 88–89 °C (diethyl ether/petroleum ether); $[\alpha]_D^{20}=-123.1$ (*c* 0.26, $CHCl_3$); ν_{max}/cm^{-1} 1733, 1612; δ_H (400 MHz; $CDCl_3$): 2.41 (6H, s), 2.76 (1H, ddd, *J*=3.9, 10.1, 12.2 Hz), 3.11 (1H, dd, *J*=3.9, 12.2 Hz), 3.54 (1H, dd, *J*=12.2, 12.2 Hz), 4.45 (1H, d, *J*=10.1 Hz), 5.20 (1H, d, *J*=12.4 Hz), 5.25 (1H, d, *J*=12.4 Hz), 7.38 and 7.83 (10H, 2m); δ_C (100 MHz; $CDCl_3$): 28.3, 40.1, 40.3, 66.8, 79.2, 126.6, 128.2, 128.3, 128.4, 128.6, 130.8, 136.0, 138.5, 157.8, 173.4; *m/z* (EI): 354 ($M^{+}\cdot$, 3), 192 (100), 159 (68), 121 (55), 89 (89), 77 (34), 55 (33), 44 (52); Anal. calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; found: C, 67.40; H, 6.29; N, 7.89.

4.5.3. General procedure with $Sm(OTf)_3$. To a mixture of cycloadduct (0.2 mmol) in anhydrous CH_2Cl_2 (2 mL) was added samarium triflate (0.25 equiv.). The resulting solution was stirred for 15 min at room temperature before the addition of MeOH (2 mL). After an additional 18 h of stirring the reaction mixture was concentrated to a residue that was purified by silica gel chromatography (petroleum ether/AcOEt 4:1).

Trimethyl (3*S*,4*S*)-4-dimethylamino-3,4-dihydro-2*H*-thiopyran-3,5,6-dicarboxylate: (−)-**11b**

White solid; mp 99 °C. $[\alpha]_D^{20}=-440.0$ (*c* 0.75, $CHCl_3$).

4.5.4. Trimethyl (3*R*,4*S*)-4-dimethylamino-3,4-dihydro-2*H*-thiopyran-3,5,6-dicarboxylate: (−)-28. $[\alpha]_D^{20}=-162.2$ (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 1734, 1716, 1700, 1436, 1258, 730; δ_H (400 MHz; $CDCl_3$): 2.31 (6H, s); 3.09–3.13 (1H, m); 3.21–3.28 (2H, m,); 3.72 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 4.16 (1H, dd, *J*=1.2, 5.2 Hz); δ_C (100 MHz; $CDCl_3$): 26.3, 39.3, 42.0, 52.4, 52.5, 53.1, 59.2, 129.6, 136.6, 165.3, 167.2, 171.9; HRMS (ESI+), $[M+H]^+$ calcd for $C_{13}H_{20}NO_6S$: 318.1011; found: 318.1016.

4.5.5. Methyl (*R*,*R*)- and methyl (*S*,*S*)-4-(dimethylamino)-2-phenyl-5,6-dihydro-4*H*-1,3-thiazine-5-carboxylates. (+)-**6b**. $[\alpha]_D^{20}=+155.5$ (*c*=0.67, $CHCl_3$).

(−)-**6b**. $[\alpha]_D^{20}=-156.2$ (*c*=0.86, $CHCl_3$).

Acknowledgements

We thank Drs. G. Trippé and J. Perron for performing some preliminary experiments.

References and notes

1. For recent reviews on the enantioselective (hetero) Diels–Alder reaction, see: (a) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698. (c) Tietze, L. F.; Kettschau, G. *In Topics in current chemistry*; Springer: Berlin, 1997; Vol. 189. (d) Boger, D. L. *Comprehensive organic synthesis*; Trost, B. M., Flemming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 451–512.
2. (a) Pradère, J. P.; Quiniou, H. *Ann. Chim.* **1973**, *63*, 563. (b) Pradère, J.-P.; N'Guessan, Y. T.; Quiniou, H.; Tonnard, F. *Tetrahedron* **1975**, *31*, 3059–3064. (c) Meslin, J. C.; Quiniou, H. *Bull. Soc. Chim. Fr.* **1979**, *II*, 347.
3. (a) Hudhomme, P.; Toupet, L.; Duguay, G. *Tetrahedron: Asymmetry* **1990**, *1*, 611–620. (b) Hudhomme, P.; Duguay, G. *Bull. Soc. Chim. Fr.* **1991**, *128*, 760–772.
4. Pradère, J.-P.; Hadjukovic, G. *C. R. Acad. Sci. (Paris) Série C* **1978**, *t.286*, 553–556.
5. For a recent hetero Diels–Alder reaction of a 1-thia-3-aza-buta-1,3-diene related to **2**, see: Bogdanowicz-Szwed, K.; Budzowski, A. *Monatshefte für Chemie* **2001**, *132*, 947–957.
6. Meslin, J.-C.; Quiniou, H. *Bull. Soc. Chim. Fr.* **1979**, *7-8*, 347–349.
7. (a) Barluenga, J.; Tomás, M.; Ballesteros, A.; López, L. A. *Tetrahedron Lett.* **1989**, *49*, 6923–6926. (b) Barluenga, J.; Tomás, M.; Ballesteros, A.; López, L. A. *Synthesis* **1995**, 985–988. (c) The same authors showed, however, that an '*exo*' transition state is operative in the intramolecular version of the HDA with 2-*N*,*N*-disubstituted amino-1-thia-3-aza-buta-dienes-1.3: Barluenga, J.; Tomás, M.; Ballesteros, A.; López, L. A. *J. Org. Chem.* **1991**, *56*, 5680–5684.
8. Bignebat, J.; Quiniou, H.; Lozac'h, N. *Bull. Soc. Chim. Fr.* **1969**, *1*, 127–135.
9. Marchand, A.; Guingant, A.; Pradère, J. P. *Tetrahedron Lett.* **1997**, *38*, 1033–1036.
10. Tea Gokou, C.; Pradère, J.-P.; Quiniou, H. *J. Org. Chem.* **1985**, *50*, 1545–1547.
11. Calculations at the PM3 level have shown that the *trans* adducts are significantly more stable than their *cis* diastereomers (>12 kJ mol^{-1}).

12. For other experimental arguments, see: Trippé, G.; Perron, J.; Harrison-Marchand, A.; Dupont, V.; Guingant, A.; Pradère, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6067–6069.
13. Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry* **1994**, *5*, 557.
14. For recent reviews of the Diels–Alder reaction and synthetic applications of azadienes, see: (a) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259–5288. (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471.
15. (a) Poll, T.; Helmchen, G.; Bauer, B. *Tetrahedron Lett.* **1984**, *25*, 2191–2194. (b) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 112–114.
16. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.
17. Asymmetric synthesis of chiral 3,4-dihydro-2*H*-thiopyrans is mainly due to the group of Saito. For some recent publications, see: (a) Saito, T.; Fujii, H.; Hayashibe, S.; Matsushita, T.; Kato, H.; Kobayashi, K. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1897. (b) Saito, T.; Kawamura, M.; Nishimura, J. *Tetrahedron Lett.* **1997**, *38*, 3231–3234. (c) Saito, T.; Suda, H.; Kawamura, M.; Nishimura, J.; Yamaya, A. *Tetrahedron Lett.* **1997**, *38*, 6035–6038. (d) Saito, T.; Takekawa, K.; Nishimura, J.; Kawamura, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2957. (e) Saito, T.; Takekawa, K.; Takahashi, T. *Chem. Commun.* **1999**, 1001–1002. (f) Saito, T.; Nishimura, J.; Akiba, D.; Kusuoku, H.; Kobayashi, K. *Tetrahedron Lett.* **1999**, *40*, 8383–8386. (g) Saito, T.; Furuie, H.; Ishigo-oka, Y.; Watanabe, I.; Kobayashi, K. *Heterocycles* **2000**, *53*, 1685–1690. See also: (h) Bell, A. S.; Fishwick, C. W. G.; Reed, J. E. *Tetrahedron Lett.* **1996**, *37*, 123–126. (i) Bell, A. S.; Fishwick, C. W. G.; Reed, J. E. *Tetrahedron* **1998**, *54*, 3219–3234.
18. Marchand, A.; Mauger, D.; Guingant, A.; Pradère, J.-P. *Tetrahedron: Asymmetry* **1995**, *6*, 853–856.
19. Structure analysis of compound **15**. $SC_{23}H_{24}O_3N_3$, Mr=422.51, orthorhombic, *P* $2_12_12_1$, *a*=6.481(1), *b*=14.741(2), *c*=22.795(2) Å, *V*=2177.8(5) $Å^{-3}$, *Z*=4, D_x=1.289 mg m^{-3}, λ(Mo Kα)=0.71073 Å, μ=1.78 cm^{-1}, *F*(000)=892, *T*=293 K. The sample (0.50×0.50×0.20 mm^3) is studied on an automatic diffractometer CAD4 NONIUS with graphite monochromatized Mo Kα radiation (Fair, 1990). The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\Theta_{max}$=54°, scan $\omega/2\Theta$=1, t_{max}=60 s, range HKL: H −3,7; K −5,17; L −10,27) gives 6745 unique reflections from which 2939 with $I>2.0\sigma(I)$. After Lorenz and polarization corrections (Spek, 1997)[20] the structure was solved with SIR-97 (Altomare et al., 1998)[20] which reveals the non-hydrogen atoms of the compound. After anisotropic refinement a Fourier difference reveals many hydrogen atoms. The whole structure was refined with SHELXL97 (Sheldrick, 1997)[20] by the full-matrix least-square techniques (use of F square magnitude; *x*, *y*, *z*, β_{ij} for S, O, C and N atoms, *x*, *y*, *z* in riding mode for H atoms; 272 variables and 2939 observations with $I>2.0\sigma(I)$; calc $w=1/[\sigma^2(F_o^2)+(0.058P)^2+0.148P]$ where $P=(F_o^2+2F_c^2)/3$ with the resulting *R*=0.031, R_w=0.083 and S_w=1.024 (residual $\Delta\rho\leq 0.39$e $Å^{-3}$). The absolute configuration is unambiguously determined: Flack parameter=0.03(9). Atomic scattering factors from International tables for X-ray crystallography (1992).[20] Ortep views realized with PLATON98 (Spek, 1998)[20] and Ortep-3 for windows (Farrugia, 1997).[20].
20. (a) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. Sir97: a new tool for crystal structure determination and refinement. *J. Appl. Crystallogr.* **1999**, *32*, 115–119. (b) *International tables for X-ray crystallography*; Vol. C, Wilson, A. J. C., Ed.; Kluwer Academic: Dordrecht, 1992. (c) Fair, C. K. *MolEN, an interactive intelligent system for crystal structure analysis, user manual*; Enraf-Nonius: Delft, The Netherlands, 1990. (d) Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565. (e) Sheldrick, G. M. *SHELX97. Program for the refinement of crystal structures*; University of Göttingen: Germany, 1997. (f) Spek, A. L. *PLATON. A multipurpose crystallographic tool*; Utrecht University: Utrecht, The Netherlands, 1998. (g) Spek, A. L. *HELENA. Program for the handling of CAD4-diffractometer output SHELX(S/L)*; Utrecht University: Utrecht, The Netherlands, 1997.
21. Evain, M.; Collet, S.; Guingant, A. *Acta Crystallogr.* **2002**, *E58*, 1123–1124.
22. Enantiomeric excesses were determined by using (*S*)-mandelic acid derivatives as chiral solvating agents Prestat, G.; Marchand, A.; Lebreton, J.; Guingant, A.; Pradère, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 197–201.
23. Evans, D. A.; Coleman, P. J.; Carlos Dias, L. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2738–2741.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1841–1847
Tetrahedron

Oxidative free radical reactions of enamino esters

Che-Ping Chuang* and Yi-Lung Wu

Department of Chemistry, National Cheng Kung University, Tainan 70101, Taiwan

Received 6 November 2003; accepted 11 December 2003

Abstract—Oxidative free radical reactions of enamino esters are described. Electrophilic carbon-centered radicals produced by the cerium(IV) ammonium nitrate (CAN) oxidation of β-dicarbonyl compounds undergo efficient addition to the C–C double bond of enamino esters. This CAN mediated free radical reaction between enamino esters and β-dicarbonyl compounds provides a novel method for the synthesis of highly substituted pyrroles. The direct CAN oxidation of β-enaminocinnamates gave the dimerization products effectively.

1. Introduction

Free radical reactions have become increasingly important in organic synthesis in the last two decades.[1] The oxidative addition of an electrophilic carbon-centered radicals to alkenes mediated by metal salts has received considerable attention in the organic synthesis for the construction of carbon–carbon bonds. Among these, manganese(III) acetate and cerium(IV) ammonium nitrate (CAN) have been used most efficiently.[1d–f,2,3] These reactions can be performed intermolecularly and intramolecularly. Pyrroles are important substructures of pharmaceutically important compounds and also of numerous natural products.[4] Accordingly, substantial attention has been paid to develop efficient methods for the synthesis of pyrroles.[5] We describe here a novel method for the synthesis of highly substituted pyrroles via the oxidative free radical reactions of enamino esters.

2. Results and discussion

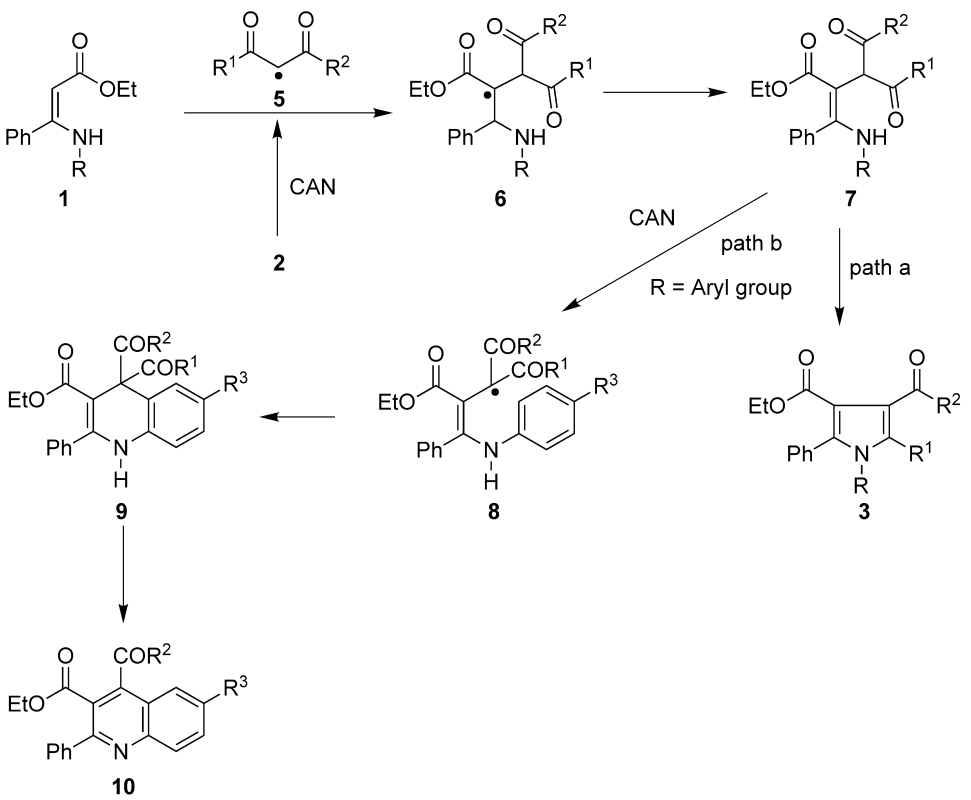
The CAN mediated reaction between β-aminocinnamate **1** and β-dicarbonyl compound **2** was first examined (Eq. 1). When β-anilinocinnamate **1a** was treated with ethyl acetoacetate (**2a**) and CAN in methanol at room temperature, **3a** was obtained in 54% yield (Table 1, entry 1). A plausible mechanism for this reaction is shown in Scheme 1. Initiation occurs with CAN oxidation of **2a** to produce radical **5a**. This radical intermediate **5a** undergoes intermolecular addition followed by oxidation to give **7a**, which undergoes condensation reaction to produce **3a** (path a). There is no trace of another expected product **10a** can be detected, which is presumably derived from the intramolecular cyclization followed by retro Claisen condensation and oxidation of radical intermediate **8a** (path b). This high selectivity for the formation of pyrrole **3a** can be ascribed to the strong oxaphilicity of cerium salt and it enhances the condensation rate of **7a**.[6] With other β-keto esters (R^2=OR), in addition to the desired major product **3**, a competitive oxidative dimerization product **4** was also obtained (entries 2–4). The ratios of **3/4** decrease as the size of substituents (R^1) on β-keto esters increases. This is presumably due to the steric effect exerted by R^1 group—the addition rate (**1→6**) was retarded by the larger R^1 and the oxidative dimerization of **1a** occurred. With 1,3-diones, the reaction of **1a** resulted in the formation of **3** and **4** (entries 5 and 6). The scope of this reaction was explored using a variety of β-aminocinnamate **1** and the results were also shown in Table 1. In all cases, β-aminocinnamate **1** was smoothly converted to the corresponding pyrrole **3** as the major (only) product (entries 7–13). In addition, when β-anilinocrotonate **11** was treated with ethyl acetoacetate (**2a**) and CAN under similar reaction conditions, no desired

Table 1. Free radical reactions of β-aminocinnamate **1**

Entry	Cinnamate	β-Dicarbonyl compound	Product (yield (%))	
1	**1a**	**2a**: R^1=Me, R^2=OEt	**3a** (54)	**4a** (0)
2	**1a**	**2b**: R^1=Et, R^2=OMe	**3b** (51)	**4a** (trace)
3	**1a**	**2c**: R^1=Pr, R^2=OEt	**3c** (44)	**4a** (9)
4	**1a**	**2d**: R^1=^{i}Pr, R^2=OEt	**3d** (29)	**4a** (12)
5	**1a**	**2e**: R^1=Me, R^2=Me	**3e** (36)	**4a** (10)
6	**1a**	**2f**: R^1=Et, R^2=Et	**3f** (35)	**4a** (14)
7	**1b**	**2a**: R^1=Me, R^2=OEt	**3g** (54)	**4b** (0)
8	**1b**	**2f**: R^1=Et, R^2=Et	**3h** (33)	**4b** (18)
9	**1c**	**2a**: R^1=Me, R^2=OEt	**3i** (54)	**4c** (0)
10	**1c**	**2f**: R^1=Et, R^2=Et	**3j** (37)	**4c** (16)
11	**1d**	**2a**: R^1=Me, R^2=OEt	**3k** (45)	**4d** (0)
12	**1e**	**2a**: R^1=Me, R^2=OEt	**3l** (53)	**4e** (0)
13	**1e**	**2f**: R^1=Et, R^2=Et	**3m** (39)	**4e** (9)

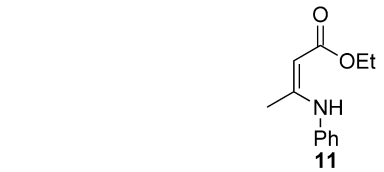
Keywords: Cerium(IV) ammonium nitrate; Oxidative; Free radical; Enamino esters.
* Corresponding author. Fax: +886-6-2740552; e-mail address: cpchuang@mail.ncku.edu.tw

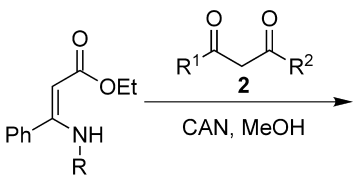
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.035



Scheme 1.

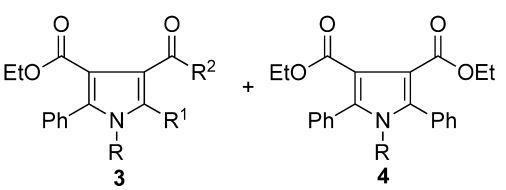
product could be found. It is probably due to the CAN liability of **11**.



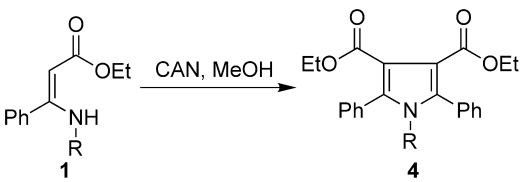


1a: R = p-chlorophenyl
1b: R = p-bromophenyl
1c: R = p-ethoxycarbonylphenyl
1d: R = phenyl
1e: R = cyanomethyl

(1)



The preparation of highly substituted C_2-symmetric pyrroles by the oxidative dimerization of enamino esters has been reported.[7] On the basis of the generation of **4** in above reaction, we expected that the direct oxidation of **1** would produce **4** effectively. Indeed, the formation of **4a** (48%) was achieved by the reaction of **1a** with CAN in methanol at room temperature (Eq. 2). Results of the CAN mediated oxidative dimerization of **1** are summarized in Table 2. While β-anilinocinnamates **1a**–**1d** were converted to the corresponding dimerization products in fair yields (entries 1–4), the dimerization of β-alkylaminocinnamate **1e** was less productive (entry 5).



(2)

Table 2. Oxidative dimerizations of β-aminocinnamate **1**

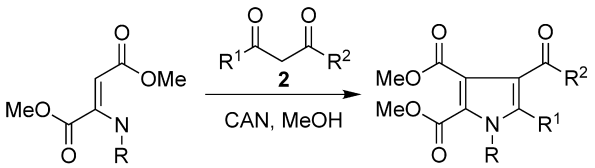
Entry	Cinnamate	Product (yield (%))
1	**1a**	**4a** (48)
2	**1b**	**4b** (46)
3	**1c**	**4c** (56)
4	**1d**	**4d** (58)
5	**1e**	**4e** (22)

We next study this oxidative free radical reaction with 2-aminofumarate **12** (Eq. 3). The reaction of 2-anilinofumarate **12a** with ethyl acetoacetate (**2a**) and CAN in methanol at room temperature afforded **13a** in 60% yield (Table 3, entry 1). Pyrrole **13a** was formed presumably via a similar route shown in Scheme 1. The results of this reaction with a variety of β-dicarbonyl compounds are summarized in Table 3. In contrast to **1**, pyrrole **13** was obtained as the only product and no dimerization product **14**[8] could be

Table 3. Free radical reactions of 2-aminofumarate **12**

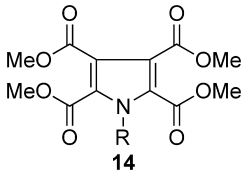
Entry	Fumarate	β-Dicarbonyl compound	Product (yield (%))
1	**12a**	**2a**: R^1=Me, R^2=OEt	**13a** (60)
2	**12a**	**2b**: R^1=Et, R^2=OMe	**13b** (65)
3	**12a**	**2c**: R^1=Me, R^2=Me	**13c** (41)
4	**12a**	**2d**: R^1=Et, R^2=Et	**13d** (61)
5	**12b**	**2a**: R^1=Me, R^2=OEt	**13e** (69)
7	**12b**	**2c**: R^1=Me, R^2=Me	**13f** (33)
8	**12b**	**2d**: R^1=Et, R^2=Et	**13g** (62)
9	**12c**	**2a**: R^1=Me, R^2=OEt	**13h** (67)
10	**12c**	**2b**: R^1=Et, R^2=OMe	**13i** (61)
11	**12c**	**2c**: R^1=Me, R^2=Me	**13j** (41)
12	**12c**	**2d**: R^1=Et, R^2=Et	**13k** (53)
13	**12d**	**2a**: R^1=Me, R^2=OEt	**13l** (57)
14	**12d**	**2c**: R^1=Me, R^2=Me	**13m** (32)
15	**12e**	**2a**: R^1=Me, R^2=OEt	**13n** (68)
16	**12e**	**2b**: R^1=Et, R^2=OMe	**13o** (70)
17	**12e**	**2c**: R^1=Me, R^2=Me	**13p** (40)

found. We speculate that it may be due to some unknown effects of the additional methoxycarbonyl group of **12**. For unknown reason, the reaction yield was rather poor when this reaction was performed with 2,4-pentanedione (**2c**) (entries 3, 7, 11, 14 and 17).



(3)

12a: R = p-ethoxycarbonylphenyl
12b: R = p-cyanophenyl
12c: R = p-bromophenyl
12d: R = benzyl
12e: R = methoxycarbonylmethyl



In conclusion, radical **5** generated from the CAN oxidation of β-dicarbonyl compounds undergoes efficient addition to the C–C double bond of enamino esters. This free radical reaction provides a novel method for the synthesis of highly substituted pyrroles from readily available enamino esters and β-dicarbonyl compounds. The dimerization product **4** can also be synthesized effectively by the direct CAN oxidation of β-aminocinnamates.

3. Experimental

3.1. General considerations

Melting points are uncorrected. Infrared spectra were taken with a Hitachi 260-30 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 or AVANCE-300 spectrometer. Chemical shifts are reported in ppm relative to TMS as internal reference. Elemental analyses were performed with Heraeus CHN-Rapid Analyzer. Analytical thin-layer chromatography was performed with precoated silica gel 60 F-254 plates (0.25 mm thick) from EM Laboratories and visualized by UV. The reaction mixture was purified by column chromatography over EM Laboratories silica gel (70–230 mesh). The starting enamino esters **1**[7b,9b] and **12**[7a,9a] were synthesized according to literature procedures.

3.2. Typical experimental procedure for the reaction between β-aminocinnamate 1 and β-dicarbonyl compounds

A solution of 134 mg (0.44 mmol) of **1a**, 349 mg (2.68 mmol) of ethyl acetoacetate, 223 mg (2.65 mmol) of sodium bicarbonate and 729 mg (1.33 mmol) of CAN in 10 mL of methanol was stirred at room temperature for 10 min. The reaction mixture was diluted with 100 mL of ethyl acetate, washed with 50 mL of saturated aqueous sodium bisulfite, three 50 mL portions of water, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with 1:8 ethyl acetate–hexane) followed by recrystallization (hexane–ethyl acetate) to give 99 mg (54%) of **3a**.

3.3. Typical experimental procedure for the oxidative dimerization reaction of β-aminocinnamate 1

A solution of 135 mg (0.44 mmol) of **1a**, 145 mg (1.72 mmol) of sodium bicarbonate and 541 mg (0.98 mmol) of CAN in 10 mL of methanol was stirred at room temperature for 10 min. The reaction mixture was diluted with 100 mL of ethyl acetate, washed with 50 mL of saturated aqueous sodium bisulfite, three 50 mL portions of water, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with 1:7 ethyl acetate–hexane) followed by recrystallization (hexane–ethyl acetate) to give 52 mg (48%) of **4a**.

3.4. Typical experimental procedure for the reaction between 2-aminofumarate 12 and β-dicarbonyl compounds

A solution of 122 mg (0.40 mmol) of **12a**, 218 mg (1.68 mmol) of ethyl acetoacetate and 430 mg (0.79 mmol) of CAN in 10 mL of methanol was stirred at room temperature for 15 min. The reaction mixture was diluted with 100 mL of ethyl acetate, washed with 50 mL of saturated aqueous sodium bisulfite, three 50 mL portions of water, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with 1:3.5 ethyl acetate–hexane) followed by recrystallization (hexane–ethyl acetate) to give 100 mg (60%) of **13a**

3.4.1. 1-(*p*-Chlorophenyl)-3,4-diethoxycarbonyl-2-methyl-5-phenylpyrrole 3a. Colorless crystals; mp 112–113 °C; IR($CHCl_3$) 2990, 1705, 1535, 1495, 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, J=7.1 Hz, 3H, CH_3), 1.35 (t, J=7.1 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.32 (q, J=7.1 Hz, 2H, OCH_2), 6.99 (d, J=8.6 Hz, 2H, ArH), 7.09–7.22 (m, 5H, ArH), 7.30 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.2

(q), 13.9 (q), 14.2 (q), 60.2 (t), 60.7 (t), 112.4 (s), 116.1 (s), 127.8 (d), 127.9 (d), 129.4 (d), 129.7 (d), 130.1 (s), 130.3 (d), 134.4 (s), 134.5 (s), 135.5 (s), 136.0 (s), 164.7 (s), 165.8 (s). Anal. calcd for $C_{23}H_{22}ClNO_4$: C, 67.07; H, 5.38; N,3.40. Found: C, 67.04; H, 5.36; N, 3.38.

3.4.2. 1-(*p*-Chlorophenyl)-3-ethoxycarbonyl-2-ethyl-4-methoxycarbonyl-5-phenylpyrrole 3b. Colorless crystals; mp 121–122 °C; IR($CHCl_3$) 2990, 1710, 1495, 1440, 1295 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, J=7.4 Hz, 3H, CH_3), 1.15 (t, J=7.1 Hz, 3H, CH_3), 2.74 (q, J=7.4 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 7.03 (d, J=8.6 Hz, 2H, ArH), 7.09–7.14 (m, 2H, ArH), 7.15–7.21 (m, 3H, ArH), 7.30 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0 (q), 14.3 (q), 19.0 (t), 51.3 (q), 60.7 (t), 111.4 (s), 116.1 (s), 127.8 (d), 127.9 (d), 129.3 (d), 129.9 (d), 130.1 (s), 130.4 (d), 134.6 (s), 134.7 (s), 135.4 (s), 142.0 (s), 165.0 (s), 165.8 (s). Anal. calcd for $C_{23}H_{22}ClNO_4$: C, 67.07; H, 5.38; N, 3.40. Found: C, 67.18; H, 5.46; N, 3.35.

3.4.3. 1-(*p*-Chlorophenyl)-3,4-diethoxycarbonyl-2-phenyl-5-propylpyrrole 3c. Colorless crystals; mp 92–93 °C; IR($CHCl_3$) 2975, 1705, 1495, 1435, 1280, 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J=7.6 Hz, 3H, CH_3), 1.14 (t, J=7.1 Hz, 3H, CH_3), 1.35 (t, J=7.1 Hz, 3H, CH_3), 1.43 (sextet, J=7.6 Hz, 2H, CH_2), 2.66–2.72 (m, 2H, CH_2), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.32 (q, J=7.1 Hz, 2H, OCH_2), 7.01 (d, J=8.6 Hz, 2H, ArH), 7.09–7.13 (m, 2H, ArH), 7.15–7.20 (m, 3H, ArH), 7.29 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (q), 14.0 (q), 14.2 (q), 23.2 (t), 27.5 (t), 60.1 (t), 60.7 (t), 112.1 (s), 116.3 (s), 127.7 (d), 127.9 (d), 129.2 (d), 130.0 (d), 130.1 (s), 130.4 (d), 134.5 (s), 135.5 (s), 140.5 (s), 164.5 (s), 165.9 (s). Anal. calcd for $C_{25}H_{26}ClNO_4$: C, 68.25; H, 5.96; N, 3.18. Found: C, 68.24; H, 6.02; N, 3.20.

3.4.4. 1-(*p*-Chlorophenyl)-3,4-diethoxycarbonyl-2-isopropyl-5-phenylpyrrole 3d. Colorless needles; mp 154–155 °C; IR($CHCl_3$) 2985, 1715, 1495, 1270, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J=7.2 Hz, 3H, CH_3), 1.25 (d, J=7.1 Hz, 6H, CH_3), 1.38 (t, J=7.1 Hz, 3H, CH_3), 2.87 (septet, J=7.1 Hz, 1H, CH), 4.11 (q, J=7.2 Hz, 2H, OCH_2), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 7.00 (d, J=8.6 Hz, 2H, ArH), 7.09–7.13 (m, 2H, ArH), 7.14–7.21 (m, 3H, ArH), 7.27 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (q), 14.2 (q), 21.5 (q), 26.6 (d), 60.3 (t), 60.8 (t), 113.1 (s), 114.8 (s), 127.5 (d), 128.0 (d), 129.2 (d), 130.3 (d), 130.5 (s), 130.8 (d), 134.6 (s), 135.78 (s), 135.81 (s), 141.9 (s), 164.8 (s), 166.2 (s). Anal. calcd for $C_{25}H_{26}ClNO_4$: C, 68.25; H, 5.96; N, 3.18. Found: C, 68.27; H, 6.01; N, 3.21.

3.4.5. 3-Acetyl-1-(*p*-chlorophenyl)-4-ethoxycarbonyl-2-methyl-5-phenylpyrrole 3e. Colorless crystals; mp 127–128 °C; IR($CHCl_3$) 3010, 1705, 1660, 1495, 1415 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J=7.1 Hz, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.13 (q, J=7.1 Hz, 2H, OCH_2), 6.98 (q, J=8.6 Hz, 2H, ArH), 7.10–7.15 (m, 2H, ArH), 7.16–7.25 (m, 3H, ArH), 7.29 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.4 (q), 13.8 (q), 31.0 (q), 60.6 (t), 114.4 (s), 123.1 (s), 127.6 (d), 128.1 (d), 129.4 (d), 129.7 (d), 130.5 (s), 130.8 (d), 134.2 (s), 134.6 (s), 135.3 (s), 136.9 (s), 165.2 (s), 197.7 (s). Anal. calcd for $C_{22}H_{20}ClNO_3$: C, 69.20; H, 5.28; N, 3.67. Found: C, 69.20; H, 5.30; N, 3.62.

3.4.6. 1-(*p*-Chlorophenyl)-3-ethoxycarbonyl-5-ethyl-2-phenyl-4-propionylpyrrole 3f. Colorless needles; mp 123–124 °C; IR($CHCl_3$) 2985, 1700, 1495, 1420, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J=7.4 Hz, 3H, CH_3), 1.05 (t, J=7.1 Hz, 3H, CH_3), 1.20 (t, J=7.3 Hz, 3H, CH_3), 2.59 (q, J=7.4 Hz, 2H, CH_2), 2.84 (q, J=7.3 Hz, 2H, CH_2), 4.10 (q, J=7.1 Hz, 2H, OCH_2), 7.02 (d, J=8.5 Hz, 2H, ArH), 7.09–7.13 (m, 2H, ArH), 7.15–7.22 (m, 3H, ArH), 7.28 (d, J=8.5 Hz (2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.6 (q), 13.8 (q), 14.6 (q), 18.8 (t), 36.5 (t), 60.3 (t), 113.7 (s), 112.6 (s), 127.5 (d), 128.0 (d), 129.2 (d), 130.0 (d), 130.7 (s), 130.9 (d), 134.6 (s), 135.4 (s), 137.1 (s), 138.8 (s), 165.1 (s), 201.8 (s). Anal. calcd for $C_{24}H_{24}ClNO_3$: C, 70.32; H, 5.90; N, 3.42. Found: C, 70.27; H, 5.90; N, 3.36.

3.4.7. 1-(*p*-Bromophenyl)-3,4-diethoxycarbonyl-2-methyl-5-phenylpyrrole 3g. Colorless crystals; mp 109–110 °C; IR($CHCl_3$) 2990, 1705, 1495, 1425, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J=7.1 Hz, 3H, CH_3), 1.35 (t, J=7.1 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.32 (q, J=7.1 Hz, 2H, OCH_2), 6.92 (d, J=8.5 Hz, 2H, ArH) (7.08–7.23 (m, 5H, ArH), 7.45 (d, J=8.5 Hz(2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.2 (q), 14.0 (q), 14.3 (q), 60.2 (t), 60.7 (t), 112.4 (s), 116.2 (s), 122.5 (s), 127.8 (d), 128.0 (d), 130.0 (d), 130.1 (s), 130.4 (d), 132.4 (d), 134.5 (s), 135.97 (s), 136.00 (s), 164.7 (s), 165.8 (s). Anal. calcd for $C_{23}H_{22}BrNO_4$: C, 60.54; H, 4.86; N, 3.07. Found: C, 60.62; H, 4.96; N, 3.08.

3.4.8. 1-(*p*-Bromophenyl)-3-ethoxycarbonyl-5-ethyl-2-phenyl-4-propionylpyrrole 3h. Colorless needles; mp 131–132 °C; IR($CHCl_3$) 2985, 1695, 1490, 1420, 1170, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J=7.4 Hz, 3H, CH_3), 1.05 (t, J=7.1 Hz, 3H, CH_3), 1.20 (t, J=7.3 Hz, 3H, CH_3), 2.59 (q, J=7.4 Hz, 2H, CH_2), 2.84 (q, J=7.3 Hz, 2H, CH_2), 4.10 (q, J=7.1 Hz, 2H, OCH_2), 6.96 (d, J=8.6 Hz, 2H, ArH), 7.09–7.13 (m, 2H, ArH), 7.16–7.23 (m, 3H, ArH), 7.43 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.6 (q), 13.8 (q), 14.7 (q), 18.8 (t), 36.5 (t), 60.4 (t), 113.7 (s), 122.57 (s), 122.63 (s), 127.6 (d), 128.1 (d), 130.2 (d), 130.6 (s), 130.8 (d), 132.2 (d), 135.9 (s), 137.1 (s), 138.8 (s), 165.1 (s), 201.9 (s). Anal. calcd for $C_{24}H_{24}BrNO_3$: C, 63.44; H, 5.32; N, 3.08. Found: C, 63.45; H, 5.37; N, 3.12.

3.4.9. 3,4-Diethoxycarbonyl-1-(*p*-ethoxycarbonylphenyl)-2-methyl-5-phenylpyrrole 3i. Colorless crystals; mp 117–118 °C; IR($CHCl_3$) 2990, 1715, 1485, 1270, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J=7.1 Hz, 3H, CH_3), 1.35 (t, J=7.1 Hz, 3H, CH_3), 1.37 (t, J=7.1 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.33 (q, J=7.1 Hz, 2H, OCH_2), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 7.09–7.20 (m, 7H, ArH), 8.01 (d, J=8.5 Hz (2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.2 (q), 14.0 (q), 14.2 (q), 14.3 (q), 60.2 (t), 60.7 (t), 61.3 (t), 112.7 (s), 116.4 (s), 127.8 (d), 128.0 (d), 128.5 (d), 130.0 (s), 130.36 (d), 130.41 (d), 134.4 (s), 135.9 (s), 140.9 (s), 164.7 (s), 165.5 (s), 165.7 (s). Anal. calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.45; H, 6.05; N, 3.04.

3.4.10. 3-Ethoxycarbonyl-1-(*p*-ethoxycarbonylphenyl)-5-ethyl-2-phenyl-4-propionylpyrrole 3j. Colorless needles; mp 111–112 °C; IR($CHCl_3$) 2990, 1715, 1485, 1415, 1280 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 0.95 (t, J=7.4 Hz, 3H, CH_3), 1.06 (t, J=7.1 Hz, 3H, CH_3), 1.21 (t, J=7.3 Hz, 3H, CH_3), 1.38 (t, J=7.1 Hz, 3H, CH_3), 2.60 (q, J=7.4 Hz, 2H, CH_2), 2.85 (q, J=7.3 Hz, 2H, CH_2, 4.11 (q, J=7.1 Hz, 2H, OCH_2), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 7.09–7.23 (m, 7H, ArH), 7.99 (d, J=8.5 Hz (2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.6 (q), 13.8 (q), 14.2 (q), 14.6 (q), 18.9 (t), 36.6 (t), 60.4 (t), 61.4 (t), 113.8 (s), 122.8 (s), 127.6 (d), 128.1 (d), 128.7 (d), 130.3 (d), 130.6 (s), 130.9 (d), 137.1 (s), 138.7 (s), 140.8 (s), 165.1 (s), 165.5 (s), 201.9 (s). Anal. calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.42; H, 6.55; N, 3.06.

3.4.11. 3,4-Diethoxycarbonyl-2-methyl-1,5-diphenylpyrrole 3k. Colorless crystals; mp 94–95 °C; IR($CHCl_3$) 2990, 1705, 1495, 1425, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J=7.1 Hz, 3H, CH_3), 1.35 (t, J=7.1 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 4.32 (q, J=7.1 Hz, 2H, OCH_2), 7.02–7.08 (m, 2H, ArH), 7.14 (s, 5H, ArH), 7.28–7.35 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.2 (q), 13.9 (q), 14.2 (q), 60.0 (t), 60.6 (t), 112.0 (s), 115.9 (s), 127.6 (d), 127.7 (d), 128.41 (d), 128.43 (d), 129.0 (d), 130.3 (d), 134.5 (s), 136.2 (s), 136.9 (s), 164.8 (s), 166.0 (s). Anal. calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.14; H, 6.13; N, 3.71.

3.4.12. 1-Cyanomethyl-3,4-diethoxycarbonyl-2-methyl-5-phenylpyrrole 3l. Colorless crystals; mp 79–80 °C; IR($CHCl_3$) 2990, 1710, 1445, 1425, 1300, 1240, 1185 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J=7.1 Hz, 3H, CH_3), 1.34 (t, J=7.1 Hz, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.10 (q, J=7.1 Hz, 2H, OCH_2), 4.30 (q, J=7.1 Hz, 2H, OCH_2), 4.55 (s, H, NCH_2), 7.36–7.42 (m, 2H, ArH), 7.44–7.50 (m, 3H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.0 (q), 13.8 (q), 14.2 (q), 32.5 (t), 60.4 (t), 60.6 (t), 113.5 (s), 113.9 (s), 116.3 (s), 128.8 (d), 129.0 (s), 129.5 (d), 130.4 (d), 134.4 (s), 134.7 (s), 164.3 (s), 164.7 (s). Anal. calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.99; H, 5.93; N, 8.22.

3.4.13. 1-Cyanomethyl-3-ethoxycarbonyl-5-ethyl-2-phenyl-4-propionylpyrrole 3m. Colorless needles; mp 84–85 °C; IR($CHCl_3$) 2990, 1700, 1485, 1430, 1285, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=7.2 Hz, 3H, CH_3), 1.17 (t, J=7.3 Hz, 3H, CH_3), 1.30 (t, J=7.5 Hz, 3H, CH_3), 2.79 (q, J=7.3 Hz, 2H, CH_2), 2.81 (q, J=7.5 Hz, 2H, CH_2), 4.05 (q, J=7.2 Hz, 2H, OCH_2), 4.53 (s, 2H, NCH_2), 7.36–7.41 (m, 2H, ArH), 7.46–7.52 (m, 3H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.5 (q), 13.6 (q), 14.5 (q), 18.5 (t), 32.1 (t), 36.7 (t), 60.3 (t), 114.0 (s), 114.3 (s), 123.6 (s), 128.6 (d), 129.5 (d), 129.7 (s), 130.6 (d), 136.8 (s), 136.9 (s), 164.1 (s), 202.0 (s). Anal. calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.93; H, 6.58; N, 8.32.

3.4.14. 1-(*p*-Chlorophenyl)-3,4-diethoxycarbonyl-2,5-diphenylpyrrole 4a. Colorless crystals; mp 174–175 °C; IR($CHCl_3$) 2990, 1715, 1490, 1375, 1280 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, J=7.1 Hz, 6H, CH_3), 4.19 (q, J=7.1 Hz, 4H, OCH_2), 6.76 (d, J=8.5 Hz, 2H, ArH), 7.05 (d, J=8.5 Hz, 2H, ArH), 7.14–7.27 (m, 10H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 13.9 (q), 60.0 (t), 115.4 (s), 127.7 (d), 128.2 (d), 128.8 (d), 129.9 (d), 130.2 (s), 130.8 (d), 133.7 (s), 135.5 (s), 136.4 (s), 164.8 (s). Anal. calcd for $C_{28}H_{24}ClNO_4$: C, 70.98; H, 5.10; N, 2.96. Found: C, 70.95; H, 5.18; N, 3.04.

3.4.15. 1-(*p*-Bromophenyl)-3,4-diethoxycarbonyl-2,5-diphenylpyrrole 4b. Colorless crystals; mp 165–166 °C; IR($CHCl_3$) 2990, 1715, 1490, 1375, 1275 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J=7.1 Hz, 6H, CH_3), 4.18 (q, J=7.1 Hz, 4H, OCH_2), 6.70 (d, J=8.3 Hz, 2H, ArH), 7.31–7.14 (m, 12H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 13.9 (q), 60.6 (t), 115.5 (s), 121.8 (s), 127.8 (d), 128.2 (d), 130.2 (d), 130.8 (d), 131.8 (d), 136.1 (s), 136.4 (s), 164.8 (s). Anal. calcd for $C_{28}H_{24}BrNO_4$: C, 64.87; H, 4.67; N, 2.70. Found: C, 64.98; H, 4.71; N, 2.73.

3.4.16. 3,4-Diethoxycarbonyl-1-(*p*-ethoxycarbonylphenyl)-2,5-diphenylpyrrole 4c. Colorless crystals; mp 183–184 °C; IR($CHCl_3$) 2990, 1715, 1485, 1275, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), 1.16 (t, J=7.1 Hz, 6H, CH_3), 1.33 (t, J=7.1 Hz, 3H, CH_3), 4.19 (q, J=7.1 Hz, 4H, OCH_2), 4.29 (q, J=7.1 Hz, 2H, OCH_2), 6.89 (d, J=8.6 Hz, 2H, ArH), 7.15–7.25 (m, 10H, ArH), 7.76 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (q), 14.2 (q), 60.6 (t), 61.2 (t), 115.7 (s), 127.7 (d), 128.3 (d), 128.7 (d), 129.6 (s), 129.8 (d), 130.1 (s), 130.8 (d), 136.4 (s), 140.9 (s), 164.8 (s), 165.5 (s). Anal. calcd for $C_{31}H_{29}NO_6$: C, 72.78; H, 5.71; N, 2.74. Found: C, 72.80; H, 5.80; N, 2.82.

3.4.17. 3,4-Diethoxycarbonyl-1,2,5-triphenylpyrrole 4d. Colorless crystals; mp 139–140 °C; IR($CHCl_3$) 2990, 1715, 1485, 1270, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J=7.1 Hz, 6H, CH_3), 4.19 (q, J=7.1 Hz, 4H, OCH_2), 6.81–6.86 (m, 2H ArH), 7.04–7.11 (m, 3H, ArH), 7.16–7.24 (m, 10H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (q), 60.5 (t), 115.1 (s), 127.5 (d), 127.8 (d), 128.0 (d), 128.5 (d), 128.8 (d), 130.5 (s), 130.8 (d), 136.6 (s), 137.0 (s), 165.0 (s). Anal. calcd for $C_{28}H_{25}NO_4$: C, 76.52; H, 5.93; N, 3.19. Found: C, 76.45; H, 5.80; N, 3.17.

3.4.18. 1-Cyanomethyl-3,4-diethoxycarbonyl-2,5-phenylpyrrole 4e. Colorless needles; mp 155–156 °C; IR($CHCl_3$) 2990, 1725, 1485, 1445, 1310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J=7.1 Hz, 6H, CH_3), 4.13 (q, J=7.1 Hz, 4H, OCH_2), 4.37 (s, 2H, NCH_2), 7.52 (s, 10H, ArH), ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8 (q), 33.6 (t), 60.6 (t), 114.7 (s), 116.0 (s), 128.8 (d), 129.2 (s), 129.7 (d), 130.6 (d), 136.6 (s), 164.1 (s). Anal. calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.51; H, 5.52; N, 6.96.

3.4.19. 3-Ethoxycarbonyl-1-(*p*-ethoxycarbonylphenyl)-4,5-dimethoxycarbonyl-2-methylpyrrole 13a. Colorless needles; mp 141–142 °C; IR($CHCl_3$) 2990, 1715, 1610, 1510, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J=7.1 Hz, 3H, CH_3), 1.42 (t, J=7.1 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.30 (q, J=7.1 Hz, 2H, OCH_2), 4.42 (q, J=7.1 Hz, 2H, OCH_2), 7.28 (d, J=8.2 Hz, 2H, ArH), 8.20 (d, J=8.2 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.2 (q), 14.1 (q), 14.2 (q),

51.7 (q), 52.6 (q), 60.4 (t), 61.3 (t), 111.7 (s), 120.2 (s), 125.9 (s), 127.7 (d), 130.5 (d), 131.3 (s), 141.1 (s), 141.6 (s), 159.1 (s), 163.0 (s), 165.4 (s), 166.4 (s). Anal. calcd for $C_{21}H_{23}NO_8$: C, 60.43; H, 5.55; N, 3.36; Fond: C, 60.39; H, 5.60; N, 3.30.

3.4.20. 1-(*p*-Ethoxycarbonylphenyl)-2-ethyl-3,4,5-trimethoxycarbonylpyrrole 13b. Colorless needles; mp 97–98 °C; IR($CHCl_3$) 2990, 1715, 1510, 1465, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=7.4 Hz, 3H, CH_3), 1.42 (t, J=7.1 Hz, 3H, CH_3), 2.69 (q, J=7.4 Hz, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.42 (q, J=7.1 Hz, 2H, OCH_2), 7.31 (d, J=8.4 Hz, 2H, ArH), 8.20 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.8 (q), 14.3 (q), 19.1 (t), 51.6 (q), 51.8 (q), 52.8 (q), 61.3 (t), 110.9 (s), 120.2 (s), 126.1 (s), 127.9 (d), 130.4 (d), 131.4 (s), 141.0 (s), 147.4 (s), 159.1 (s), 163.2 (s), 165.4 (s), 166.6 (s). Anal. calcd for $C_{21}H_{23}NO_8$: C, 60.43; N, 3.36; H, 5.55. Found: C, 60.42; N, 3.34; H, 5.61.

3.4.21. 3-Acetyl-1-(*p*-ethoxycarbonylphenyl)-4,5-dimethoxycarbonyl-2-methylpyrrole 13c. Colorless crystals; mp 129–130 °C; IR($CHCl_3$) 3010, 1720, 1670, 1445, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J=7.1 Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.42 (q, J=7.1 Hz, 2H, OCH_2), 7.28 (d, J=8.2 Hz, 2H, ArH), 8.20 (d, J=8.2 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.0 (q), 14.3 (q), 29.6 (q), 51.9 (q), 52.9 (q), 61.4 (t), 120.85 (s), 120.93 (s), 125.0 (s), 127.8 (d), 130.6 (d), 131.4 (s), 140.6 (s), 141.0 (s), 159.3 (s), 165.4 (s), 167.0 (s), 193.2 (s). Anal. calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.90; H, 5.42; N, 3.57.

3.4.22. 1-(*p*-Ethoxycarbonylphenyl)-2-ethyl-4,5-dimethoxycarbonyl-3-propionylpyrrole 13d. Colorless needles; mp 104–105 °C; IR($CHCl_3$) 2990, 1720, 1670, 1495, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.4 Hz, 3H, CH_3), 1.16 (t, J=7.1 Hz, 3H, CH_3), 1.42 (t, J=7.1 Hz, 3H, CH_3), 2.66 (q, J=7.4 Hz, 2H, CH_2), 2.76 (q, J=7.1 Hz, 2H, CH_2), 3.62 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.42 (q, J=7.1 Hz, 2H, OCH_2), 7.31 (d, J=8.2 Hz, 2H, ArH), 8.20 (d, J=8.2 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.8 (q), 13.8 (q), 14.2 (q), 19.5 (t), 34.1 (t), 51.8 (q), 52.9 (q), 61.3 (t), 119.9 (s), 120.8 (s), 124.6 (s), 127.9 (d), 130.3 (d), 131.4 (s), 140.9 (s), 146.1 (s), 159.3 (s), 165.4 (s), 167.3 (s), 196.1 (s). Anal. calcd for $C_{22}H_{25}NO_7$: C, 63.60; N, 3.37; H, 6.07. Found: C, 63.46; N, 3.35; H, 6.07.

3.4.23. 1-(*p*-Cyanophenyl)-3-ethoxycarbonyl-4,5-dimethoxycarbonyl-2-methylpyrrole 13e. Colorless crystals; mp 156–157 °C; IR($CHCl_3$) 3010, 2235, 1715, 1510, 1445, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J=7.1 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.30 (q, J=7.1 Hz, 2H, OCH_2), 7.34 (d, J=8.4 Hz, 2H, ArH), 7.83 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.2 (q), 14.1 (q), 51.9 (q), 52.7 (q), 60.5 (t), 112.2 (s), 113.5 (s), 117.6 (s), 120.2 (s), 126.2 (s), 128.8 (d), 133.1 (d), 141.2 (s), 141.5 (s), 159.1 (s), 162.8 (s), 166.1 (s). Anal. calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; N, 7.56; H, 4.90. Found: C, 61.64; N, 7.54; H, 5.01.

3.4.24. 3-Acetyl-1-(*p*-cyanophenyl)-4,5-dimethoxycarbonyl-2-methylpyrrole 13f. Colorless crystals; mp 200–201 °C; IR($CHCl_3$) 3010, 2955, 2235, 1720, 1670, 1495, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.35 (d, J=8.4 Hz, 2H, ArH), 7.83 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.0 (q), 29.5 (q), 52.0 (q), 53.0 (q), 113.6 (s), 117.6 (s), 120.7 (s), 121.2 (s), 125.2 (s), 128.9 (d), 133.2 (d), 140.5 (s), 141.1 (s), 159.2 (s), 166.8 (s), 193.1 (s). Anal. calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; N, 8.23; H, 4.74. Found: C, 63.44; N, 8.11; H, 4.70.

3.4.25. 1-(*p*-Cyanophenyl)-2-ethyl-4,5-dimethoxycarbonyl-3-propionylpyrrole 13g. Colorless needles; mp 117–118 °C; IR($CHCl_3$) 2990, 2235, 1720, 1670, 1495, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.4 Hz, 3H, CH_3), 1.16 (t, J=7.1 Hz, 3H, CH_3), 2.65 (q, J=7.4 Hz, 2H, CH_2), 2.75 (q, J=7.1 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.37 (d, J=8.2 Hz, 2H, ArH), 7.83 (d, J=8.2, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) (7.8 (q), 13.8 (q), 19.5 (t), 34.2 (t), 52.0 (q), 53.0 (q), 113.6 (s), 117.6 (s), 120.1 (s), 120.6 (s), 124.9 (s), 129.0 (d), 133.0 (d), 141.0 (s), 146.1 (s), 159.2 (s), 167.1 (s), 196.0 (s). Anal. calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; N, 7.60; H, 5.47. Found: C, 65.26; N, 7.50; H, 5.52.

3.4.26. 1-(*p*-Bromophenyl)-3-ethoxycarbonyl-4,5-dimethoxycarbonyl-2-methylpyrrole 13h. Colorless crystals; mp 151–152 °C; IR($CHCl_3$) 3005, 2955, 1710, 1510, 1495, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J=7.1 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.29 (q, J=7.1 Hz, 2H, OCH_2), 7.07 (d, J=8.6 Hz, 2H, ArH), 7.63 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.2 (q), 14.1 (q), 51.8 (q), 52.6 (q), 60.4 (t), 111.6 (s), 120.2 (s), 123.3 (s), 125.8 (s), 129.2 (d), 132.4 (d), 136.3 (s), 141.8 (s), 159.1 (s), 163.0 (s), 166.4 (s). Anal. calcd for $C_{18}H_{18}BrNO_6$: C, 50.96; H, 4.28; N, 3.30. Found: C, 50.97; H, 4.30; N, 3.30.

3.4.27. 1-(*p*-Bromophenyl)-2-ethyl-3,4,5-trimethoxycarbonylpyrrole 13i. Colorless crystals; mp 122–123 °C; IR($CHCl_3$) 3010, 2955, 1715, 1510, 1495, 1465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.4 Hz, 3H, CH_3), 2.69 (q, J=7.4 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.10 (d, J=8.4 Hz, 2H, ArH), 7.63 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9 (q), 19.0 (t), 51.6 (q), 51.9 (q), 52.8 (q), 110.8 (s), 120.1 (s), 123.5 (s), 126.0 (s), 129.4 (d), 132.4 (d), 136.1 (s), 147.6 (s), 159.2 (s), 163.2 (s), 166.6 (s). Anal. calcd for $C_{18}H_{18}BrNO_6$: C, 50.96; H, 4.28; N, 3.30; Found: C, 50.96; H, 4.34; N, 3.29.

3.4.28. 3-Acetyl-1-(*p*-bromophenyl)-4,5-dimethoxycarbonyl-2-methylpyrrole 13j. Colorless crystals; mp 176–177 °C; IR($CHCl_3$) 3010, 2955, 1725, 1670, 1495, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.08 (d, J=8.6 Hz, 2H, ArH), 7.64 (d, J=8.6 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.1 (q), 29.6 (q), 51.9 (q), 52.9 (q), 120.8 (s), 123.5 (s), 124.9 (s), 129.3 (d), 132.5 (d), 136.2 (s), 140.8 (s), 159.3 (s), 167.1 (s), 193.2 (s). Anal. calcd for $C_{17}H_{16}BrNO_5$: C, 51.79; H, 4.09; N, 3.55. Found: C, 51.75; H, 4.09; N, 3.51.

3.4.29. 1-(*p*-Bromophenyl)-2-ethyl-4,5-dimethoxycarbonyl-3-propionylpyrrole 13k. Colorless crystals; mp 91–92 °C; IR($CHCl_3$) 2985, 2955, 1725, 1670, 1495, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.4 Hz, 3H, CH_3), 1.16 (t, J=7.1 Hz, 3H, CH_3), 2.66 (q, J=7.4 Hz, 2H, CH_2), 2.75 (q, J=7.1 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.10 (d, J=8.5 Hz, 2H, ArH), 7.63 (d, J=8.5 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.8 (q), 13.9 (q), 19.5 (t), 34.2 (t), 51.9 (q), 52.9 (q), 119.8 (s), 120.8 (s), 123.5 (s), 124.6 (s), 129.5 (d), 132.4 (d), 136.1 (s), 146.4 (s), 159.4 (s), 167.4 (s), 196.2 (s). Anal. calcd for $C_{19}H_{20}BrNO_5$: C, 54.04; H, 4.77; N, 3.32. Found: C, 54.06, H, 4.83; N, 3.33.

3.4.30. 1-Benzyl-3-ethoxycarbonyl-4,5-dimethoxycarbonyl-2-methylpyrrole 13l. Colorless crystals; mp 111–112 °C; IR($CHCl_3$) 3010, 2955, 1705, 1470, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.26 (q, J=7.1 Hz, 2H, OCH_2), 5.63 (s, 2H, NCH_2), 6.93–6.99 (m, 2H, ArH), 7.21–7.33 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3 (q), 14.1 (q), 48.4 (t), 51.8 (q), 52.4 (q), 60.2 (t), 111.3 (s), 118.9 (s), 125.8 (d), 126.2 (s), 127.4 (d), 128.8 (d), 136.2 (s), 141.6 (s), 160.0 (s), 163.2 (s), 166.8 (s). Anal. calcd for $C_{19}H_{21}NO_6$: C, 63.50; N, 3.90; H, 5.89. Found: C, 63.41; N, 3.85; H, 5.95.

3.4.31. 3-Acetyl-1-benzyl-4,5-dimethoxycarbonyl-2-methylpyrrole 13m. Colorless crystals; mp 138–139 °C; IR($CHCl_3$) 3010, 1715, 1665, 1505, 1445 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.63 (s,2H, NCH_2), 6.94–6.99 (m, 2H, ArH), 7.22–7.34 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.0 (q), 29.5 (q), 48.3 (t), 51.9 (q), 52.7 (q), 119.5 (s), 120.6 (s), 125.1 (s), 125.8 (d), 127.5 (d), 128.8 (d), 136.1 (s), 140.6 (s), 160.1 (s), 167.5 (s), 193.4 (s). Anal. calcd for $C_{18}H_{19}NO_5$: C, 65.64; N, 4.25; H, 5.81. Found: C, 65.68; N, 4.18; H, 5.88.

3.4.32. 3-Ethoxycarbonyl-4,5-dimethoxycarbonyl-1-methoxycarbonylmethyl-2-methylpyrrole 13n. Colorless crystals; mp 121–122 °C; IR($CHCl_3$) 3005, 2960, 1745, 1715, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.26 (q, J=7.1 Hz, 2H, OCH_2), 5.08 (s, 2H, NCH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (11.0 (q), 14.1 (q), 46.5 (t), 51.9 (q), 52.4 (q), 52.7 (q), 60.3 (t), 112.2 (s), 118.8 (s), 126.0 (s), 141.5 (s), 160.2 (s), 163.0 (s), 166.5 (s), 167.8 (s). Anal. calcd for $C_{15}H_{19}NO_8$: C, 52.78; N, 4.10; H, 5.61. Found: C, 52.77; N, 4.07; H, 5.68.

3.4.33. 2-Ethyl-3,4,5-trimethoxycarbonyl-1-methoxycarbonylmethylpyrrole 13o. Colorless crystals; mp 113–114 °C; IR($CHCl_3$) 3010, 2960, 1745, 1710, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J=7.5 Hz, 3H, CH_3), 2.96 (q, J=7.5 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.05 (s, 2H, NCH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.2 (q), 18.4 (t), 46.5 (t), 51.5 (q), 51.9 (q), 52.5 (q), 52.7 (q), 110.5 (s), 118.9 (s), 126.1 (s), 146.8 (s), 160.2 (s), 163.2 (s), 166.6 (s), 168.0 (s). Anal. calcd for $C_{15}H_{19}NO_8$: C, 52.78; N, 4.10; H, 5.61. Found: C, 52.81; N, 4.06; H, 5.64.

3.4.34. 3-Acetyl-4,5-dimethoxycarbonyl-1-methoxycarbonylmethyl-2-methylpyrrole 13p. Colorless crystals; mp 101–102 °C; IR($CHCl_3$) 3010, 2955, 1740, 1715, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.09 (s, 2H, NCH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) (11.8 (q), 29.5 (q), 46.4 (t), 52.0 (q), 52.8 (q), 119.2 (s), 120.5 (s), 125.1 (s), 140.6 (s), 160.3 (s), 167.2 (s), 167.8 (s), 193.3 (s). Anal. calcd for $C_{14}H_{17}NO_7$: C, 54.02; N, 4.50; H, 5.50. Found: C, 54.04; N, 4.47; H, 5.57.

Acknowledgements

We are grateful to the National Science Council of the ROC for financial support (Grant No. NSC-91-2113-M-006-008).

References and notes

1. (a) Hart, D. J. *Science* **1984**, *223*, 883. (b) Neumann, W. P. *Synthesis* **1987**, 665. (c) Curran, D. P. *Synthesis* **1988**, *417*, 489. (d) Melikyan, G. G. *Synthesis* **1993**, 833. (e) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (f) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.
2. (a) Oumar-Mahamat, H.; Moustrou, C.; Surzur, J.-M.; Berstrand, M. P. *J. Org. Chem.* **1989**, *54*, 5684. (b) Snider, B. B.; Wan, B. Y. F.; Buckman, B. O.; Foxman, B. M. *J. Org. Chem.* **1991**, *56*, 328.
3. (a) Citterio, A.; Sebastiano, R.; Carvayal, M. C. *J. Org. Chem.* **1991**, *56*, 5335. (b) Citterio, A.; Sebastiano, R.; Nicolini, M. *Tetrahedron* **1993**, *49*, 7743. (c) Jiang, M.-C.; Chuang, C.-P. *J. Org. Chem.* **2000**, *65*, 5409. (d) Wu, Y.-L.; Chuang, C.-P.; Lin, P.-Y. *Tetrahedron* **2001**, *57*, 5543.
4. Gossauer, A. *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R. R., Ed.; Thieme: Stuttgart, 1994; Vol. E 6a, pp 556–798, Part 1.
5. (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849. (b) Borger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (c) Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992. (d) Kelin, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (e) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **2002**, *43*, 4491. (f) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2003**, *44*, 8417.
6. Similar rate enhancement by cerium salt has been reported. See: (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. (c) Tseng, C.-C.; Wu, Y.-L.; Chuang, C.-P. *Tetrahedron* **2002**, *58*, 7625.
7. (a) Carr, R. M.; Norman, R. O. C.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 156. (b) Sukari, M. A.; Vernon, J. M. *Tetrahedron* **1983**, *39*, 793. (c) Zhang, P.-F.; Chen, Z.-C. *Synth. Commun.* **2001**, *31*, 1619.
8. Reaction of **12c** with CAN in methanol only resulted in the decomposition of starting material and no desired dimerization product **14c** could be isolated.
9. (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613. (b) Toda, J.; Fuse, T.; Kishikawa, E.; Ando, N.; Negishi, R.; Horiguchi, Y.; Sano, T. *Heterocycles* **1994**, *38*, 2091.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1849–1861
Tetrahedron

Copper(II)salen catalysed, asymmetric synthesis of α,α-disubstituted amino acids

Yuri N. Belokon,[a] Devayani Bhave,[b] Daniela D'Addario,[b] Elisabetta Groaz,[b] Michael North[b,*] and Valeria Tagliazucca[b]

[a]*A.N. Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences, 117813 Moscow, Vavilov 28, Russian Federation*
[b]*Department of Chemistry, King's College London, Strand, London WC2R 2LS, UK*

Received 10 October 2003; revised 24 November 2003; accepted 11 December 2003

Abstract—Cu(salen) complex **1** was found to be a versatile catalyst for the asymmetric alkylation of a range of enolates derived from α-amino acids, leading to α,α-disubstituted amino acids. The enantioselectivity of the process decreases as the size of the amino acid sidechain increases, but functionalized amino acids such as allylglycine and aspartic acid are substrates for the process. Benzylic bromides are found to be more enantioselective alkylating agents than propargylic bromides. As an example of the utility of this chemistry, an α-propargylic allylglycine derivative is prepared and subjected to ene–yne metathesis using Grubbs' catalyst to give a non-racemic cyclopentenyl amino acid.

1. Introduction

Phase transfer methodology offers many possibilities in allowing otherwise unfavourable reactions to be carried out.[1] In particular, liquid–liquid phase transfer catalysis allows reactions to be carried out involving reagents for which no convenient mutual solvent is available. Solid–liquid phase transfer catalysis is potentially even more general as a solvent only needs to be found for one component of a reaction.

Recently, there has been an upsurge of interest in asymmetric phase transfer catalysis in which a chiral, non-racemic phase transfer catalyst is used to induce the enantioselective conversion of a prochiral substrate into an enantiomerically enriched product. Most work in this area has focused upon the asymmetric synthesis of α-amino acids or α,α-disubstituted amino acids by the alkylation of achiral enolates of glycine or alanine derivatives, though other classes of reactions can also be catalysed. The first reports in this area were due to O'Donnell who demonstrated that quaternary ammonium salts derived from cinchona alkaloids could catalyse the asymmetric alkylation of a glycine enolate, leading to α-amino acids with moderate enantiomeric excesses.[2] This chemistry was subsequently developed simultaneously by Lygo[3] and Corey,[4] who both showed that the use of a 9-anthracenylmethyl group to quaternize the cinchona alkaloid resulted in a catalyst that exhibited enhanced enantioselectivity.[5] In addition to enolate alkylations,[6] this catalyst will also catalyse Michael additions,[7,8] aldol reactions,[9] and enone epoxidations.[10] It can also be used in conjunction with achiral palladium complexes to induce the asymmetric allylation of enolates.[11] However, only glycine derived imines give products with high enantiomeric excesses.[12] Recently, polymer supported[8,13] and oligomeric[14] versions of the cinchona derived phase transfer catalysts have been developed and used for asymmetric amino acid synthesis. The catalysts have also been used under micellar conditions.[15]

Maruoka has developed a class of binaphthyl derived quaternary ammonium salts and has shown that they act as asymmetric phase transfer catalysts for both the alkylation and dialkylation (with two different alkylating agents) of a glycine derived imine, leading to both α-amino acids and α,α-disubstituted amino acids with excellent enantiomeric excesses.[16] Aldol reactions,[17] Michael additions,[18] and the alkylation of β-keto esters[19] are also catalysed by this class of asymmetric phase transfer catalysts. Other groups have also investigated the use of synthetic ammonium[20] and guanidinium[21] salts and crown ethers[22] as asymmetric phase transfer catalysts.

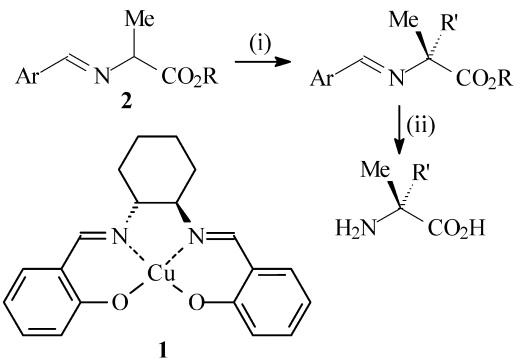
In 1998, Belokon' and Kagan were the first to demonstrate that a metal complex could act as an asymmetric phase transfer catalyst. The sodium salt of TADDOL was found to catalyse the alkylation of alanine derivatives leading to

Keywords: Cu(salen) complex; Phase transfer methodology; Alkylation.
* Corresponding author. Tel.: +44-207-848-1164; fax: +44-870-131-3783; e-mail address: michael.north@kcl.ac.uk

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.031

α-methyl-α-amino acids with up to 82% enantiomeric excess.[23] It was subsequently shown that the sodium salts of both NOBIN[24] and BINOLAM[25] could act as asymmetric phase transfer catalysts for the same reaction.

Although chiral transition metal complexes have been used to catalyse a wide range of asymmetric transformations, we were the first to show that they could be used to catalyse the asymmetric alkylation of amino acid enolates under phase transfer conditions. In particular, we have shown that copper(II)salen complex **1** will catalyse the asymmetric alkylation of the enolate of alanine derivative **2** leading to α-methyl, α-amino acids with up to 90% enantiomeric excess as shown in Scheme 1.[26] The key alkylation reaction is carried out under solid–liquid phase transfer conditions using solid sodium hydroxide as base, and toluene as the solvent. One of the advantages of this chemistry compared to the quaternary ammonium salt methodologies is the ability to use the readily available and inexpensive methyl ester of alanine as substrate, as the nature of the ester appears to make no significant difference to the level of asymmetric induction observed in the reactions. Although the methyl ester is hydrolysed under the reaction conditions, this appears to be slower than the enolate formation and alkylation and the product can readily be re-esterified as part of the work-up procedure.[27] In this manuscript, we report the extension of this chemistry to substrates derived from amino acids other than alanine.[28]

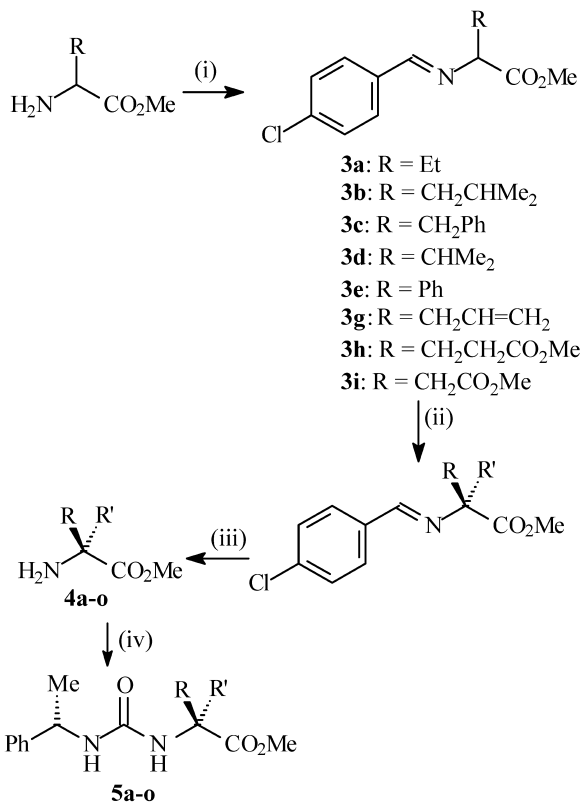


Scheme 1. (i) NaOH/R′X/**1** (2 mol%), toluene, R.T (ii) H_3O^+.

2. Results and discussion

The first substrate that we chose to investigate was aminobutyric acid derivative **3a** as this involved only a small change in the sidechain from methyl to ethyl. Imine **3a** was prepared from (*R*,*S*)-aminobutyric acid methyl ester and *para*-chlorobenzaldehyde (Scheme 2), and was then alkylated with allyl bromide under the standard conditions for the use of catalyst **1**, to give α-ethyl allylglycine methyl ester **4a** with 80% enantiomeric excess (Table 1 entry 1). By doubling the amount of allyl bromide used to 2.4 equiv., the yield of compound **4a** increased to >50%, though at the expense of a decrease in the enantiomeric excess (Table 1: entry 2).

The enantiomeric excess of all the α,α-disubstituted amino esters prepared in this work was determined by reaction of a sample of the amino ester with an excess of (*S*)-α-methyl



4/5a: R = Et, R' = $CH_2CH{=}CH_2$
4/5b: R = Et, R' = CH_2Ph
4/5c: R = Et, R' = 4-$O_2NC_6H_4CH_2$
4/5d: R = CH_2CHMe_2, R' = CH_2Ph
4/5e: R = CH_2CHMe_2, R' = 4-$O_2NC_6H_4CH_2$
4/5f: R = CH_2CHMe_2, R' = $CH_2CH{=}CH_2$
4/5g: R = CH_2Ph, R' = $CH_2CH{=}CH_2$
4/5h: R = CH_2Ph, R' = 4-$O_2NC_6H_4CH_2$
4/5i: R = Ph, R' = $CH_2CH{=}CH_2$
4/5j: R = Ph, R' = CH_2Ph
4/5k: R = $CH_2CH{=}CH_2$, R' = CH_2Ph
4/5l: R = $CH_2CH{=}CH_2$, R' = 4-$O_2NC_6H_4CH_2$
4/5m: R = $CH_2CH{=}CH_2$, R' = CH_2CCMe
4/5n: R = $CH_2CH{=}CH_2$, R' = CH_2CCH
4/5o: R = CH_2CO_2Me, R' = $CH_2CH{=}CH_2$
4/5p: R = CH_2CO_2Me, R' = CH_2Ph

Scheme 2. (i) 4-$ClC_6H_4CHO/MgSO_4$; (ii) NaOH/R′X/**1**, toluene, R.T., then MeOH/AcCl; (iii) SiO_2; (iv) excess (*S*)-PhCHMe-N=C=O, $CDCl_3$, RT.

benzylisocyanate followed by analysis of the resulting diastereomeric ureas **5** by ^1H NMR spectroscopy. When substrate **3a** was alkylated using benzyl bromide to give α-ethyl phenylalanine methyl ester **4b**, the standard conditions (Table 1: entry 3) gave a product with good enantiomeric excess but in very low yield. Simply extending the reaction time from 1 to 2 days increased the chemical yield to >90% whilst leaving the enantiomeric excess of the product essentially unchanged (Table 1: entry 4). The final alkylating agent studied in conjunction with substrate **3a** was 4-nitrobenzyl bromide. In this case, the standard conditions (Table 1: entry 5) again gave the product **4c** with ca. 80% enantiomeric excess but in low yield. Doubling either the reaction time (Table 1: entry 6) or the amount of

Table 1. Alkylation of amino acid derivatives **3a–i**

Entry	Substrate	Alkylating agent (equivalents) (product)	Catalyst (mol%)	Time (days)	Yield (%)	Enantiomeric excess (%)
1	**3a**	Allyl bromide (1.2) (**4a**)	2	1	46	80
2	**3a**	Allyl bromide (2.4) (**4a**)	2	1	54	70
3	**3a**	Benzyl bromide (1.2) (**4b**)	2	1	39	80
4	**3a**	Benzyl bromide (1.2) (**4b**)	2	2	91	82
5	**3a**	*Para*-nitro-benzyl bromide (1.2) (**4c**)	2	1	23	78
6	**3a**	*Para*-nitro-benzyl bromide (1.2) (**4c**)	2	2	83	79
7	**3a**	*Para*-nitro-benzyl bromide (2.4) (**4c**)	2	1	95	75
8	**3b**	Benzyl bromide (1.2) (**4d**)	2	1	0	
9	**3b**	Benzyl bromide (1.2) (**4d**)	10	1	41	27
10	**3b**	Benzyl bromide (1.2) (**4d**)	10	7	54	55
11	**3b**	*Para*-nitro-benzyl bromide (1.2) (**4e**)	10	1	46	40
12	**3b**	*Para*-nitro-benzyl bromide (1.2) (**4e**)	10	7	63	56
13	**3b**	*Para*-nitro-benzyl bromide (2.4) (**4e**)	10	1	64	47
14	**3b**	*Para*-nitro-benzyl bromide (2.4) (**4e**)	2	1	47	43
15	**3b**	Allyl bromide (1.2) (**4f**)	10	1	46	22
16	**3c**	Allyl bromide (1.2) (**4g**)	2	1	30	17
17	**3c**	Allyl bromide (1.2) (**4g**)	2	5	44	17
18	**3c**	Allyl bromide (2.4) (**4g**)	2	1	53	15
19	**3c**	Allyl bromide (4.8) (**4g**)	2	1	74	18
20	**3c**	Allyl bromide (4.8) (**4g**)	10	1	87	20
21	**3c**	Allyl bromide (1.2) (**4g**)	10	1	40	31
22	**3c**	Allyl bromide (1.2) (**4g**)	25	1	68	27
23	**3c**	Allyl bromide (1.2) (**4g**)	50	1	70	19
24	**3c**	*Para*-nitro-benzyl bromide (1.2) (**4h**)	10	1	67	34
25	**3d**	Allyl bromide (2.4)	2	7	0	
26	**3d**	Allyl bromide (2.4)	10	2	0	
27	**3d**	Benzyl bromide (2.4)	10	2	0	
28	**3e**	Allyl bromide (1.2) (**4i**)	2	1	31	48
29	**3e**	Benzyl bromide (1.2) (**4j**)	2	1	38	42
30	**3f**	Benzyl bromide (1.2) (**4k**)	2	1	66	57
31	**3f**	Benzyl bromide (2.4) (**4k**)	2	1	67	57
32	**3f**	Benzyl bromide (1.2) (**4k**)	10	1	38	43
33	**3f**	*Para*-nitro-benzyl bromide (1.2) (**4l**)	2	2	45	47
34	**3f**	1-Bromo-but-2-yne (**4m**)	2	2	46	25
35	**3f**	Propargyl bromide (**4n**)	2	2	49	20
36	**3g**	1-Bromo-but-2-yne (**4m**)	2	2	44	25
37	**3h**	Benzyl bromide (**7**)	2	2	52	
38	**3i**	Allyl bromide (1.2) (**4o**)	2	1	25	17
39	**3i**	Benzyl bromide (1.2) (**4p**)	2	1	75	10

4-nitrobenzyl bromide used (Table 1: entry 7) increased the chemical yield to >80% without significantly reducing the enantiomeric excess of the product. Thus, by choice of appropriate concentrations and/or reaction times it was possible to convert imine **3a** into α-ethyl amino acids in high yield and with ca. 80% enantiomeric excess in each case. Peptides incorporating α-ethyl amino acids have recently been shown to adopt unique conformations.[29] To further extend the scope of the chemistry, leucine derivative **3b** was used as substrate (Scheme 2, R=CH_2CHMe_2). The presence of a branch at the γ-carbon makes this a more hindered substrate than aminobutyric acid derivative **3a**, which was anticipated to affect the enantioselectivity of the alkylation reaction. Under the standard conditions (Table 1: entry 8) no reaction occurred when substrate **3b** was treated with benzyl bromide. Only by increasing the amount of catalyst to 10 mol% (Table 1: entry 9) could α-benzyl leucine methyl ester (**4d**) be isolated in moderate yield and with low enantiomeric purity. Interestingly, increasing the reaction time from 1 to 7 days (Table 1: entry 10) resulted in only a small increase in the isolated yield of compound **4d**, but doubled its enantiomeric purity to a respectable 55%.

para-Nitrobenzyl bromide also reacted with substrate **3b**, giving α,α-disubstituted amino ester **4e** with up to 56% enantiomeric excess (Table 1: entries 11–14). Employing 1.2 equiv. of the alkylating agent (Table 1: entries 11 and 12) gave results which are very similar to those obtained when benzyl bromide was used as the alkylating agent, with optimal yield and enantioselectivity being observed after a reaction time of 7 days. However, by increasing the amount of alkylating agent to 2.4 equiv., it was possible to reduce the reaction time to one day (Table 1: entry 13) with no reduction in the chemical yield, though the enantiomeric excess of the product was slightly reduced. Subsequent reduction of the amount of catalyst used back to 2 mol% (Table 1: entry 14) did give compound **4e**, all be it in reduced chemical yield and with a lower enantiomeric excess. Finally, allyl bromide reacted with substrate **3b** to give α-allyl leucine methyl ester **4f**, though again the reaction required 10 mol% of catalyst **1** and the enantiomeric excess of the product was very low (Table 1: entry 15).

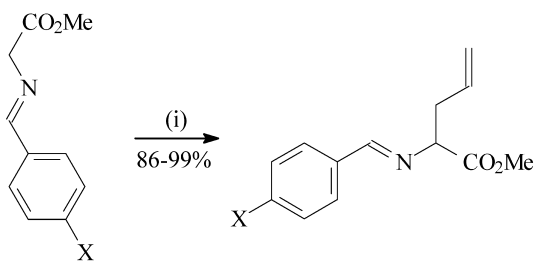
Phenylalanine derived substrate **3c** also branches at the γ-position. The initial studies using this substrate were carried out using allyl bromide as the alkylating agent (Table 1: entries 16–23). Despite numerous optimization attempts in which the catalyst concentration, alkylating agent concentration and reaction time were all varied, the

highest enantiomeric excess observed for product **4g** was 31%, and in a mediocre 40% yield. This enantiomeric excess was observed using 10 mol% of catalyst **1** (Table 1: entry 21), and use of a lower (Table 1: entry 16) or higher (Table 1: entries 22 and 23) concentration of catalyst **1** resulted in reduced enantioselectivity. The only other alkylating agent studied with substrate **3c** was *para*-nitrobenzyl bromide, and under the optimized conditions, this gave product **4h** with 34% enantiomeric excess (Table 1: entry 24) which is essentially identical to that observed using allyl bromide as the alkylating agent (Table 1: entry 21).

Valine derived substrate **3d** which is β-branched is amongst the most hindered possible substrates for this type of alkylation reaction. All attempts to react substrate **3d** with either allyl bromide (Table 1: entries 25 and 26) or benzyl bromide (Table 1: entry 27) were totally unsuccessful. It appears that substrate **3d** is too hindered to be a substrate for catalyst **1**.

The final unfunctionalized substrate that we have investigated is phenylglycine derivative **3e**. This substrate was of interest since although the sidechain branches at the β-position, the enolate of compound **3e** would be completely planar, unlike the enolates of compounds **3a**–**d**. Alkylation of substrate **3e** with allyl bromide (Table 1: entry 28) gave α-phenyl allylglycine with 48% enantiomeric excess. This enantioselectivity, whilst not comparable with that obtainable from aminobutyric acid derived substrate **31** (Table 1: entry 1), is significantly higher than that obtained from either leucine or phenylalanine derived substrates **3b** and **3c** (Table 1: entries 15 and 21). The alkylation of substrate **3e** by benzyl bromide was also investigated. In this case, the enantioselectivity was lower than that obtained for either substrate **3a** or **3b**, but the latter results are not strictly comparable due to the different amounts of catalyst used.

Substrates **3a**–**e** are all unfunctionalized but differ in their steric properties. It appears that the enantioselectivity of the alkylation of these substrates decreases as the substrate becomes more sterically hindered. We next decided to study more functionalized substrates to investigate the compatibility of the chemistry with functional groups. The first substrates chosen for this work were allylglycine derivatives **3f** and **3g**. Compounds **3f** and **3g** were prepared by the palladium catalysed allylation of glycine imines **6a** and **6b** as shown in Scheme 3.[30,31] This method has the advantage



6a: X = H
6b: X = Cl

3f: X = H
3g: X = Cl

Scheme 3. (i) $H_2C{=}CHCH_2OCO_2Me$/Pd(dppe) (5 mol%).

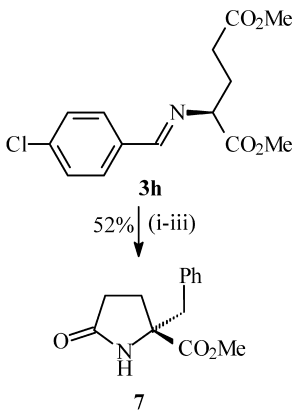
over a direct alkylation of the enolates of compounds **6a**,**b** in that no dialkylation occurs.

Imine **3f** was subsequently reacted with catalyst **1** and benzyl bromide according to Scheme 2 to give α-allyl-phenylalanine methyl ester **4k** in 66% yield and with 57% enantiomeric excess (Table 1: entry 30). Attempts to increase the enantioselectivity and/or chemical yield with this substrate by increasing the concentration of substrate or catalyst were unsuccessful (Table 1: entries 31 and 32). Optimal yields with all products derived from imines **3f** and **3g** were obtained by omitting the methanolic HCl treatment at the end of the alkylation reaction. Presumably, the products are sufficiently sterically hindered that ester hydrolysis does not occur on the reaction timescale and the methanolic HCl treatment reduces the isolated yield by inducing addition reactions to the alkene and/or alkyne units within products **4k**–**4n**. Product **4k** is constitutionally identical to product **4g** obtained by the allylation of phenylalanine derivative **3c**. However, analysis of the ^{1}H NMR spectra of the derived ureas **5g** and **5k** revealed that the major stereoisomer formed in each case was different. This implies that products **4g** and **4k** are enantiomeric, and this is consistent with the alkylation occurring enantioselectively on the *re*-face of the enolate. Further evidence for this hypothesis was obtained by hydrolysis of amino ester **4g** to give (+)-α-allyl-phenylalanine, which is known to correspond to the (*S*)-enantiomer of this amino acid.[32]

Use of *para*-nitrobenzyl bromide as the alkylating agent with substrate **3f** (Table 1: entry 33) gave α-*para*-nitrobenzyl-allylglycine **4l** with similar enantiomeric excess (47%) to that observed using benzyl bromide, though with a lower isolated yield. However, use of 1-bromo-2-butyne as the alkylating agent (Table 1: entry 34) gave α-but-2-ynyl-allylglycine **4m** with a much lower enantiomeric excess (25%) and with propargyl bromide as the alkylating agent, the enantioselectivity dropped still further (Table 1: entry 35). In this case, use of the *para*-chlorobenzylidene imine **3g** did not increase the enantioselectivity of the alkylation reaction (Table 1: entry 36). This result is consistent with our previous results on substrate **2** where propargyl bromide was found to give a product with lower enantiomeric excess than that observed using allylic or benzylic halides.[26,27]

Glutamic acid derivative **3h** was felt to be an interesting substrate for this chemistry since alkylated glutamic acid derivatives are known to be selective neurotransmitters.[33] In addition, since glutamic acid is branched only at the δ-carbon, it was expected to be a good substrate, and to lead to α-substituted derivatives with high enantiomeric excess. However, treatment of substrate **3h** with benzyl bromide in the presence of catalyst **1** (Table 1: entry 37) gave not the expected α-benzyl glutamic acid dimethyl ester, but α-benzyl-pyroglutamic acid methyl ester **7** as shown in Scheme 4. It appears that the alkylation chemistry works exactly as expected, but on work-up the α-substituted glutamic acid diester spontaneously cyclises to lactam **7**. Unfortunately, compound **7** failed to react with α-methyl benzylisocyanate, so we were unable to determine its enantiomeric excess.

To avoid the cyclisation problem encountered in the



Scheme 4. (i) **1** (2 mol%)/NaOH/BnBr; (ii) MeOH/AcCl; (iii) SiO_2.

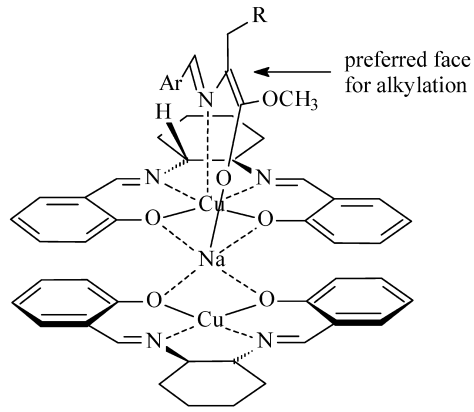
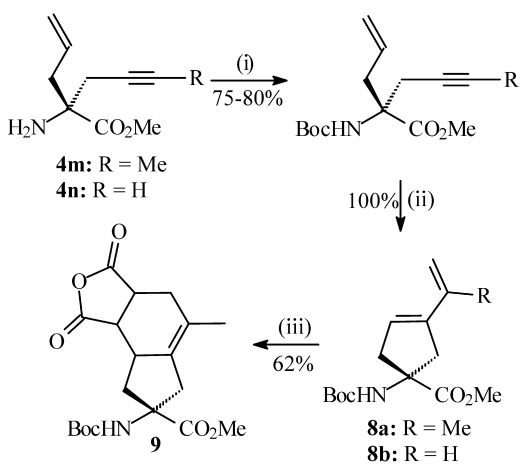


Figure 1.

synthesis of α-substituted glutamic acid derivatives, we turned to the lower homologue aspartic acid. Reaction of imine **3i** with allyl bromide gave α-allyl-aspartic acid dimethyl ester (**4o**) (Table 1: entry 38), and the corresponding reaction with benzyl bromide gave α-benzyl aspartic acid dimethyl ester (**4p**) (Table 1: entry 39). However, the enantiomeric excesses of products **4o/p** were disappointing (10–20%), possibly reflecting the fact that the sidechain of aspartic acid branches at the γ-carbon.

To demonstrate the utility of this methodology in the synthesis of complex amino acids, the further manipulation of adducts **4m** and **4n** was investigated. Thus, amino esters **4m** and **4n** were first protected with a Boc group, then treated with Grubbs' catalyst (5 mol%) under an ethene atmosphere to induce ring-closing ene–yne metathesis to give dienes **8a**,**b** as shown in Scheme 5. Subsequent Diels–Alder reaction of diene **8a** with maleic anhydride gave tricyclic amino acid derivative **9** as a 1:1 mixture of diastereomers.



Scheme 5. (i) Boc_2O; (ii) $(PCy_3)_2Ru(Cl)_2{=}CHPh$ (5 mol%) /$H_2C{=}CH_2$; (iii) maleic anhydride.

Our model for the alkylation of amino ester enolates catalysed by complex **1** is shown in Figure 1.[26,28] The enolate is coordinated to both the copper and sodium ions of a bimetallic complex and is held orthogonal to the plane of the salen ligand. Alkylation then occurs preferentially on the *re*-face of the enolate. This model works well for glycine and alanine substrates,[26] both of which are alkylated with high enantioselectivity. Other amino acid derived substrates are more complicated as an additional factor needs to be considered: rotation around the $C_\alpha-C_\beta$-bond of the enolate. Thus, the R-group shown in Figure 1 could be located over the *re*- (as shown) or *si*-face of the enolate. The former is more likely since the R-group will be repelled by the same features of the cyclohexane ring that direct alkylation to the *re*-face of the enolate. If the R-group is over the *re*-face of the enolate, then it will hinder the approach of the electrophile to the *re*-face and this will result in a lower enantioselectivity during the alkylation. The overall rate of reaction will also decrease as the size of the R-group increases. Thus, the model correctly predicts both the absolute configuration of the product, and the general relationship between the enantioselectivity of alkylation and the size of the amino acid sidechain.

Substrate **3e** derived from phenylglycine was included in this study specifically to probe the stereochemical model shown in Figure 1. Since the sidechain of this substrate consists of just a phenyl ring, the enolate of substrate **3e** should be completely planar and there should be no hindrance to alkylation on the preferred *re*-face of the enolate. Thus, substrate **3e** was expected to undergo highly enantioselective alkylation despite being a β-substituted amino acid. In the event, alkylation of enolate **3e** by allyl bromide (Table 1: entry 28) induced by catalyst **1** was not as highly enantioselective (48%) as the alkylation of the corresponding alanine[26,27] or aminobutyric acid derivatives (Table 1: entries 1 and 2) (70–80%). It was, however, considerably more enantioselective than the allylation of substrates **3b**,**c**,**i** (Table 1: entries 15, 21, 38) (17–30% ee). The reason for the lower than expected enantioselectivity observed with substrate **3e** is probably related to the highly acidic nature of the α-proton of this substrate. Control experiments have shown that substrates **3** undergo alkylation to give racemic products **4** under the reaction conditions, even in the absence of catalyst **1**. This uncatalysed process is expected to be particularly facile in the case of substrate **3e** which will lower the observed enantiomeric excess of the product, and account for the enantiomeric excess observed with this substrate being lower than would be predicted by the model shown in Figure 1.

3. Conclusions

Complex **1** has been shown to be a versatile catalyst for the asymmetric alkylation of enolates derived from a range of unhindered amino acids. Of the substrates studied, only the valine derivative failed to react, though for other substrates the enantioselectivity of the alkylation was found to diminish as the size of the sidechain increased.

Further work on the mechanism of the catalysis using complex **1** and the optimization of the catalyst for sterically hindered substrates is in progress and will be reported in due course.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 360 Spectrometer, (^{1}H 360 MHz and ^{13}C 90 MHz) The solvent for a particular spectrum is given in parentheses. Spectra were referenced to TMS and chemical-shift (δ) values, expressed in parts per million (ppm), are reported downfield of TMS. The multiplicity of signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of any of these. For ^{13}C NMR spectra, the peak assignments were made with the assistance of DEPT experiments. Infrared spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer, as a thin film between NaCl plates or as KBr disks. The characteristic absorption is reported as broad (br), strong (s), medium (m) or weak (w). Low and high resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea, or on a 4.7T Bruker Apex III FTMS within the chemistry department at King's College. The sample was ionised by electron ionisation (EI), chemical ionisation (CI) or electrospray ionization (ES). The major fragment ions are reported and only the molecular ions are assigned.

Optical rotations were recorded on a Perkin–Elmer 343 polarimeter in a thermostated cell of length 1 dm at 20 °C using the sodium D-line, and a suitable solvent that is reported along with the concentration (in g/100 ml). Melting points are uncorrected.

Chromatographic separations were performed with silica gel 60 (230–400 mesh) and thin-layer chromatography was performed on polyester backed silica sheets, both supplied by Merck.

4.1.1. Methyl *N*-*para*-chlorobenzylidene-(*R*,*S*)-2-aminobutyrate 3a. To a stirred suspension of methyl (*R*,*S*)-2-aminobutyrate hydrochloride (18.1 g, 118.2 mmol) in dichloromethane (50 ml), triethylamine (8.5 ml, 59.1 mmol), *para*-chlorobenzaldehyde (8.3 g, 59.1 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The crude product was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give imine **3a** (8.47 g, 60%) as a yellow oil. ν_{max} (film) 2970 (m), 2878 (w), 1738 (s), 1643 (m), 1596 (w) and 1573 cm^{-1} (w); δ_H ($CDCl_3$) 0.79 (3H, t J=7.4 Hz, CH_3CH$_2$), 1.7–1.85 (1H, m, CH$_2$), 1.9–2.0 (1H, m, CH$_2$), 3.61 (3H, s, OCH$_3$), 3.78 (1H, t J=5.5 Hz, CHCH$_2$), 7.24 (2H, d J=8.4 Hz, ArCH), 7.59 (2H, d J=8.5 Hz, ArCH), 8.11 (1H, s, CH=N); δ_C ($CDCl_3$) 9.48 (*C*H$_3$CH$_2$), 25.69 (CH$_2$), 51.12 (OCH$_3$), 73.73 (*C*HCH$_2$), 126.91 (ArCH), 126.97 (ArCH), 127.16 (ArC), 128.77 (ArC), 161.00 (N=CH), 171.81 (CO_2); *m*/*z* (CI, NH_3) 240 (MH^+, 80), 180 (100); [found: (ES) 240.0794 (MH^+, $C_{12}H_{15}NO_2{}^{35}Cl$ requires 240.0791)].

4.1.2. α-Ethyl-allylglycine methyl ester 4a. Imine **3a** (0.24 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (7.7 mg, 0.02 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and allyl bromide (14.5 mg, 1.2 mmol) were added to the mixture. The resulting solution was stirred overnight under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4a** (72.2 mg, 46%) as a colourless oil. $[\alpha]_D^{20}$=+1.6 (c=1.85, $CHCl_3$); ν_{max} (film) 3372 (m), 3012 (w), 2978 (m), 2882 (m), 1732 (s), 1596 (s) and 1492 cm^{-1} (m); δ_H ($CDCl_3$) 0.79 (3H, t J=7.5 Hz, CH_3CH$_2$), 1.4–1.6 (1H, m, CH_2CH$_3$), 1.54 (2H, br s, NH$_2$), 1.7–1.8 (1H, m, CH_2CH$_3$), 2.15 (1H, dd J=13.5, 8.4 Hz, CH_2CH=), 2.45 (1H, dd J=13.5, 6.4 Hz, CH_2CH=), 3.65 (3H, s, OCH$_3$), 5.0–5.1 (2H, m, =CH$_2$), 5.6–5.7 (1H, m, =C*H*); δ_C ($CDCl_3$) 8.68 (*C*H$_3$CH$_2$), 33.22 (CH$_3$*C*H$_2$), 44.36 (*C*H$_2$CH=), 52.46 (OCH$_3$), 61.61 (N*C*CO$_2$), 119.75 (=CH$_2$), 133.23 (=CH), 177.64 (CO_2); *m*/*z* (CI, NH_3) 158 (MH^+, 100); [found: (ES) 158.1183 (MH^+, $C_8H_{16}NO_2$ requires 158.1181)].

4.1.3. α-Ethyl-phenylalanine methyl ester 4b. Imine **3a** (0.24 g, 1.00 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (7.7 mg, 0.02 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and benzyl bromide (205 mg, 1.2 mmol) were added to the mixture. The resulting solution was stirred for 2 days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4b** (188 mg, 91%) as a yellow oil. $[\alpha]_D^{20}$=+20 (c=1.75, $CHCl_3$); ν_{max} (film) 3373 (m), 2968 (m), 2880 (w), 1732 (s), 1603 (m), 1495 (w) and 1454 cm^{-1} (m); δ_H ($CDCl_3$) 0.82 (3H, t J=7.5 Hz, CH_3CH$_2$), 1.46 (2H, br s, NH$_2$), 1.5–1.6 (1H, m, CH_2CH$_3$), 1.8–2.0 (1H, m, CH_2CH$_3$), 2.68 (1H, d J=13.2 Hz, CH$_2$Ph), 3.11 (1H, d J=13.2 Hz, CH$_2$Ph), 3.63 (3H, s, OCH$_3$), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 7.41 (*C*H$_3$CH$_2$), 32.21 (*C*H$_2$CH$_3$), 44.83 (CH$_2$Ph), 50.92 (OCH$_3$), 61.62 (N*C*CO$_2$), 125.90 (ArCH), 127.36 (ArCH), 128.85 (ArCH), 135.44 (ArC), 175.99 (CO_2); *m*/*z* (CI, NH_3) 208 (MH^+, 100); [found: (CI, NH_3) 208.1338 (MH^+, $C_{12}H_{18}NO_2$ requires 208.1337)].

4.1.4. α-Ethyl-*para*-nitrophenylalanine methyl ester 4c. Imine **3a** (0.24 g, 1.00 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (7.7 mg, 0.02 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and *para*-nitrobenzyl bromide (0.259 g, 1.2 mmol) were added to the mixture. The resulting solution was stirred for two days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added in a dropwise manner to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4c** (209 mg, 83%) as a yellow oil. $[\alpha]_D^{20}=+21$ ($c=3.65$, $CHCl_3$); ν_{max} (film) 3370 (m), 1732 (s), 1604 (m), and 1518 cm^{-1} (s); δ_H ($CDCl_3$) 0.83 (3H, t $J=7.5$ Hz, CH_3CH_2), 1.41 (2H, br s, NH_2), 1.5–1.6 (1H, m, CH_2CH_3), 1.8–2.0 (1H, m, CH_2CH_3), 2.81 (1H, d $J=13.0$ Hz, CH_2Ar), 3.17 (1H, d $J=13.0$ Hz, CH_2Ar), 3.64 (3H, s, OCH_3), 7.27 (2H, d $J=8.6$ Hz, ArCH), 8.06 (2H, d $J=8.5$ Hz, ArCH); δ_C ($CDCl_3$) 8.69 (CH_3CH_2), 33.59 (CH_2CH_3), 45.91 (CH_2Ar), 52.57 (OCH_3), 62.99 ($NCCO_2$), 123.77 (ArCH), 131.25 (ArCH), 144.94 (ArC), 147.38 (ArC), 176.67 (CO_2); *m/z* (CI, NH_3) 253 (MH^+, 20), 223 (50), 116 (100); [found: (CI, NH_3) 253.1190 (MH^+, $C_{12}H_{17}N_2O_4$ requires 253.1188)].

4.1.5. *N*-*para*-Chlorobenzylidene (*R*,*S*)-leucine methyl ester 3b. To a stirred suspension of (*R*,*S*)-leucine methyl ester hydrochloride (9.43 g, 52.1 mmol) in dichloromethane (190 ml), triethylamine (5.26 g, 52.1 mmol), *para*-chlorobenzaldehyde (7.32 g, 52.1 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The crude product was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give compound **3b** (9.06 g, 65%) as a yellow oil. ν_{max} (film) 2956 (s), 2871 (m), 1742 (s), 1642 (m), 1596 (w) and 1572 cm^{-1} (w); δ_H ($CDCl_3$) 0.80 (3H, d $J=6.6$ Hz, CH_3CH), 0.85 (3H, d $J=6.6$ Hz, CH_3CH), 1.4–1.5 (1H, m, $CHMe_2$), 1.73–1.75 (1H, m, $CHCH_2CH$), 1.76–1.78 (1H, m, $CHCH_2CH$), 3.64 (3H, s, OCH_3), 4.22 (1H, dd $J=8.3$, 6.1 Hz, $NCHCO_2$), 7.28 (2H, d $J=8.5$ Hz, ArCH), 7.63 (2H, d $J=8.5$ Hz, ArCH), 8.16 (1H, s, N=CH); δ_C ($CDCl_3$) 21.85 (CH_3CH), 23.47 (CH_3CH), 24.79 ($CHMe_2$), 42.43 ($CHCH_2CH$), 52.51 (OCH_3), 71.83 ($NCHCO_2$), 129.22 (ArCH), 130.09 (ArCH), 134.50 (ArC), 137.45 (ArC), 162.12 (N=CH), 173.06 (CO_2); *m/z* (CI, NH_3) 268 (MH^+, 100); [found: (ES) 268.1100 (MH^+, $C_{14}H_{19}NO_2{}^{35}Cl$ requires 268.1104)].

4.1.6. α-Benzyl-leucine methyl ester 4d.[34,35] Imine **3b** (0.267 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (38.5 mg, 0.10 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and benzyl bromide (0.14 ml, 1.2 mmol) were added to the mixture. The resulting solution was stirred for 7 days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The crude residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4d** (127 mg, 54%) as a colourless oil. δ_H ($CDCl_3$) 0.76 (3H, d $J=6.6$ Hz, CH_3CH), 0.89 (3H, d $J=6.6$ Hz, CH_3CH), 1.46 (2H, br s, NH_2), 1.55 (1H, dd $J=13.7$, 4.6 Hz, CH_2CH), 1.6–1.75 (1H, m, $CHMe_2$), 1.82 (1H, dd $J=13.7$, 4.6 Hz, CH_2CH), 2.64 (1H, d $J=13.1$ Hz, CH_2Ph), 3.09 (1H, d $J=13.1$ Hz, CH_2Ph), 3.61 (3H, s, OCH_3), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 24.28 (CH_3CH), 26.06 (CH_3CH), 26.45 ($CHMe_2$), 49.24 (CH_2), 50.73 (CH_2), 53.51 (OCH_3), 63.40 ($NCCO_2$), 128.71 (ArCH), 130.11 (ArCH), 131.61 (ArCH), 137.87 (ArC), 179.31 (CO_2); *m/z* (CI, NH_3) 236 (MH^+, 100).

4.1.7. α-*para*-Nitrobenzyl-leucine methyl ester 4e. Imine **3b** (0.267 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (38.5 mg, 0.10 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and *para*-nitrobenzyl bromide (0.259 g, 1.2 mmol) were added to the mixture. The resulting solution was stirred for 7 days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The crude residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4e** (176 mg, 63%) as a yellow oil. $[\alpha]_D^{20}=+2.7$ ($c=0.6$, $CHCl_3$); ν_{max} (film) 3390 (w), 2956 (s), 2872 (m), 1733 (s), 1605 (s) and 1521 cm^{-1} (s); δ_H ($CDCl_3$) 0.77 (3H, d $J=6.5$ Hz, CH_3CH), 0.90 (3H, d $J=6.5$ Hz, CH_3CH), 1.46 (2H, br s, NH_2), 1.60 (1H, dd $J=13.6$, 4.5 Hz, CH_2CH), 1.7–1.8 (1H, m, $CHMe_2$), 1.85 (1H, dd $J=13.6$, 8.0 Hz, CH_2CH), 2.82 (1H, d $J=13.0$ Hz, CH_2Ar), 3.17 (1H, d $J=13.0$ Hz, CH_2Ar), 3.63 (3H, s, OCH_3), 7.27 (2H, d $J=8.6$ Hz, ArCH), 8.07 (2H, d $J=8.6$ Hz, ArCH); δ_C ($CDCl_3$) 21.15 (CH_3CH), 22.88 (CH_3CH), 23.23 ($CHMe_2$), 45.83 (CH_2), 47.45 (CH_2), 50.66 (OCH_3), 60.32 ($NCCO_2$), 122.03 (ArCH), 130.20 (ArCH), 142.75 (ArC), 145.67 (ArC), 175.49 (CO_2); *m/z* (CI, NH_3) 281 (MH^+, 70), 251 (100); [found: (ES) 281.1501 (MH^+, $C_{14}H_{21}N_2O_4$ requires 281.1501)].

4.1.8. α-Allyl-leucine methyl ester 4f.[35] Imine **3b** (0.267 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (38.5 mg, 0.10 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and allyl bromide (145 mg, 1.2 mmol) were added to the mixture. The resulting solution was stirred overnight under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4f** (85 mg, 46%) as a colourless oil. δ_H ($CDCl_3$) 0.75 (3H, d $J=6.2$ Hz, CH_3CH), 0.87 (3H, d $J=6.3$ Hz, CH_3CH), 1.4–1.5 (1H, m, CH_2CHMe_2), 1.6–1.7 (1H, m, CH_2CHMe_2), 2.14 (1H, dd $J=13.5$, 8.6 Hz, CH_2CH=), 2.39 (2H, br s, NH_2), 2.48 (1H, dd $J=13.4$, 6.5 Hz, CH_2CH=), 2.9–3.0 (1H, m, $CHMe_2$), 3.64 (3H, s, OCH_3), 5.0–5.1 (2H, m, =CH_2), 5.5–5.6 (1H, m, =CH); *m/z* (CI, NH_3) 186 (MH^+, 100).

4.1.9. *N*-*para*-Chlorobenzylidene (*R*,*S*)-phenylalanine methyl ester 3c.[36] To a stirred suspension of (*R*,*S*)-phenylalanine methyl ester hydrochloride (3.00 g,

13.95 mmol) in dichloromethane (40 ml), triethylamine (1.28 g, 12.68 mmol), *para*-chlorobenzaldehyde (1.78 g, 12.68 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The residue was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give compound **3c** (3.82 g, 90%) as yellow solid. Mp 63–65 °C; δ_H ($CDCl_3$) 3.06 (1H, dd J=13.5, 9.0 Hz, CH_2Ph), 3.28 (1H, dd J=13.5, 4.9 Hz, CH_2Ph), 3.67 (3H, s, OCH_3), 4.08 (1H, dd J=9.0, 4.9 Hz, $NCHCO_2$), 7.0–7.2 (5H, m, ArCH), 7.27 (2H, d J=8.5 Hz, ArCH), 7.53 (2H, d J=8.5 Hz, ArCH), 7.76 (1H, s, CH=N); δ_C ($CDCl_3$) 40.74 (CH_2Ph), 53.34 (OCH_3), 75.93 ($NCHCO_2$), 127.66 (ArCH), 129.36 (ArCH), 129.86 (ArCH), 130.66 (ArCH), 130.76 (ArCH), 134.96 (ArC), 138.12 (ArC), 138.24 (ArC), 163.42 (N=CH), 172.98 (CO_2).

4.1.10. α-Allyl-phenylalanine methyl ester 4g.[37] Imine **3c** (0.301 g, 1.00 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (96.25 mg, 0.25 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and allyl bromide (0.145 g, 1.2 mmol) were added to the mixture. The resulting solution was stirred overnight under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The crude residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4g** (149 mg, 68%) as a colourless oil. ν_{max} (KBr) 3378 (w), 3030 (w), 2955 (w), 1738 (s), 1634 (m) and 1604 cm^{-1} (m); δ_H ($CDCl_3$) 1.48 (2H, br s, NH_2), 2.25 (1H, dd J=13.5, 8.5 Hz, CH_2CH=), 2.64 (1H, dd J=13.4, 6.4 Hz, CH_2CH=), 2.71 (1H, d J=13.2 Hz, CH_2Ph), 3.11 (1H, d J=13.2 Hz, CH_2Ph), 3.63 (3H, s, OCH_3), 5.08–5.09 (2H, m, CH_2=), 5.6–5.7 (1H, m, =CH), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 42.32 (CH_2), 43.79 (CH_2), 53.04 (OCH_3), 64.36 (NCCO_2), 121.98 (=CH_2), 128.07 (ArCH), 129.23 (ArCH), 130.55 (ArCH), 131.07 (=CH), 134.47 (ArC), 173.00 (CO_2); m/z (CI, NH_3) 220 (MH^+, 100); [found: (CI, NH_3) 220.1337 (MH^+, $C_{13}H_{17}NO_2$ requires 220.1337)].

4.1.11. Hydrolysis of 4g to α-Allyl-phenylalanine.[38,39] A sample of compound **4g** was refluxed overnight in 2 M hydrochloric acid. The solvent was evaporated as an azeotrope with toluene to leave α-allyl-phenylalanine as a white solid which was analysed without further purification. $[\alpha]_D^{25}$=+4.6 (c=1, 1 M HCl) $[\alpha]_D$=+16 (c=1, aqueous HCl) for (*S*)-enantiomer.[39] δ_H (CD_3OD) 2.66 (1H, dd J=14.5, 7.6 Hz, CH_2CH=), 2.86 (1H, dd J=14.5, 7.1 Hz, CH_2CH=), 3.16 (1H, d J=14.3 Hz, CH_2Ph), 3.35 (1H, d J=14.3 Hz, CH_2Ph), 5.3–5.4 (2H, m, =CH_2), 5.7–5.9 (1H, m, =CH), 7.2–7.4 (5H, m, ArCH).

4.1.12. α-(4-Nitrophenylmethyl)-phenylalanine methyl ester 4h. Imine **3c** (0.301 g, 1.00 mmol) was dissolved in dry toluene, then copper(salen) complex **1** (38.4 mg, 0.1 mmol), powdered NaOH (140 mg, 3.5 mmol) and 4-nitrobenzyl bromide (259.2 mg, 1.2 mmol) were added. The mixture was stirred overnight under an argon atmosphere at room temperature. Methanol and acetyl chloride were added and the mixture was stirred for 4 h. The solvents were then removed in vacuo. The residue was purified by column chromatography using ethyl acetate and ethanol (4:1) as eluent to give compound **4h** (210 mg, 67%) as light yellow oil. $[\alpha]_D^{20}$=+1.6 (c=0.6, $CHCl_3$); ν_{max} (KBr) 3028 (m), 2953 (m), 1951 (w), 1739 (s), 1603 (s) and 1520 cm^{-1} (s); δ_H ($CDCl_3$) 1.63 (2H, br s, NH_2), 2.79 (1H, d J=13.3 Hz, CH_2Ph), 2.88 (1H, d J=12.9 Hz, CH_2Ph), 3.29 (1H, d J=13.0 Hz, CH_2ArNO_2), 3.35 (1H, d J=13.0 Hz, CH_2ArNO_2), 3.59 (3H, s, OCH_3), 7.0–7.1 (2H, m, ArCH), 7.1–7.3 (3H, m, ArCH), 7.29 (2H, d J=8.6 Hz, ArCH), 8.07 (2H, d J=8.7 Hz, ArCH); δ_C ($CDCl_3$) 39.85 (CH_2), 41.03 (CH_2), 52.20 (OCH_3), 64.45 (NCCO_2), 123.07 (ArCH), 127.38 (ArCH), 128.17 (ArCH), 129.41 (ArCH), 130.1 (ArCH), 131.09 (ArC), 139.19 (ArC), 146.71 (ArC), 168.35 (CO_2); m/z (CI, NH_3) 315 (MH^+, 58), 285 (100); [found: (ES) 337.1141 (M+Na^+, $C_{17}H_{18}N_2O_4Na$ requires 337.1159)].

4.1.13. *N*-*para*-Chlorobenzylidene (*R*,*S*)-phenylglycine methyl ester 3e.[40] To a stirred suspension of (*R*,*S*)-phenylglycine methyl ester chloride (2.00 g, 9.92 mmol) in dichloromethane (28 ml), triethylamine (0.84 g, 8.27 mmol), *para*-chlorobenzaldehyde (1.16 g, 8.27 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The crude product was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give compound **3e** (1.09 g, 46%) as a yellow oil. δ_H ($CDCl_3$) 3.67 (3H, s, OCH_3), 5.13 (1H, s, NCH), 7.1–7.5 (7H, m, ArCH), 7.69 (2H, d J=8.5 Hz, ArCH), 8.22 (1H, s, CH=N).

4.1.14. α-Phenyl-allylglycine methyl ester 4i.[41] Imine **3e** (0.200 g, 0.70 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (5 mg, 0.014 mmol) was added. Finely ground sodium hydroxide (0.097 g, 2.4 mmol) was then added, followed by allyl bromide (101 mg, 0.83 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.3 ml) and acetyl chloride (0.3 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4i** (43 mg, 31%) as a colourless oil. ν_{max} (KBr) 3389 (w), 3320 (w), 3070 (w), 3025 (w), 2952 (m), 1732 (s), 1640 (m) and 1600 cm^{-1} (m); δ_H ($CDCl_3$) 1.97 (2H, br s, NH_2), 2.59 (1H, dd J=13.6, 7.8 Hz, CH_2CH=), 2.91 (1H, dd J=13.6, 6.7 Hz, CH_2CH=), 3.64 (3H, s, OCH_3), 5.0–5.1 (2H, m, =CH_2), 5.5–5.7 (1H, m, =CH), 7.2–7.5 (5H, m, ArCH); δ_C ($CDCl_3$) 45.05 (CH_2), 52.92 (OCH_3), 63.54 (NCCO_2), 120.38 (=CH_2), 125.79 (ArCH), 127.92 (ArCH), 128.83 (ArCH), 133.34 (=CH), 143.14 (ArC), 176.05 (CO_2); m/z (CI, NH_3) 206 (MH^+, 20), 164 (97), 145 (81), 104 (100); [found: (ES) 206.1168 (MH^+, $C_{12}H_{16}NO_2$ requires 206.1176)].

4.1.15. α-Phenyl-phenylalanine methyl ester 4j.[42] Imine **3e** (0.200 g, 0.70 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (5 mg, 0.014 mmol) was added. Finely

ground sodium hydroxide (0.097 g, 2.4 mmol) was then added, followed by benzyl bromide (143 mg, 0.83 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.3 ml) and acetyl chloride (0.3 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4j** (67 mg, 38%) as a colourless oil. δ_H ($CDCl_3$) 1.61 (2H, br s, NH_2), 3.08 (1H, d J=13.3 Hz, CH_2Ph), 3.57 (1H, d J=13.3 Hz, CH_2Ph), 3.66 (3H, s, OCH_3), 7.0–7.5 (10H, m, ArCH); δ_C ($CDCl_3$) 46.40 (CH_2), 52.84 (OCH_3), 64.88 ($NCCO_2$), 125.94 (ArCH), 127.39 (ArCH), 128.01 (ArCH), 128.68 (ArCH), 128.81 (ArCH), 130.83 (ArCH), 136.53 (ArC), 175.72 (CO_2); *m/z* (CI, NH_3) 256 (MH^+, 20), 196 (90), 165 (100), 104 (100); [found: (ES) 256.1323 (MH^+, $C_{16}H_{18}NO_2$ requires 256.1338)].

4.1.16. α-Allyl-phenylalanine methyl ester 4k.[37] Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added followed by benzyl bromide (0.26 ml, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4k** (249 mg, 69%). $[\alpha]_D^{20}=-47.0$ (c=0.3, $CHCl_3$); other data as reported for compound **4g**.

4.1.17. α-(4-Nitrophenylmethyl)-allylglycine methyl ester 4l.[43] Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added, followed by *para*-nitrobenzyl bromide (0.477 g, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4l** (365 mg, 75%). $[\alpha]_D^{20}=-62.6$ (c=0.3, $CHCl_3$); ν_{max} (KBr) 3367 (w), 3010 (w), 2957 (w), 1733 (s), 1604 (m) and 1519 cm^{-1} (s); δ_H ($CDCl_3$) 1.64 (2H, br s, NH_2), 2.26 (1H, dd J=13.0, 8.4 Hz, CH_2CH=), 2.6–2.7 (1H, m, CH_2CH=), 2.84 (1H, d J=12.9 Hz, CH_2Ar), 3.18 (1H, d J=12.8 Hz, CH_2Ar), 3.65 (3H, s, OCH_3), 5.1–5.2 (2H, m, CH=CH_2), 5.5–5.7 (1H, m CH=CH_2), 7.28 (2H, d J=8.2 Hz, ArCH), 8.07 (2H, d J=8.0 Hz, ArCH); δ_C ($CDCl_3$) 44.9 (CH_2CH=), 46.0 (CH_2Ar), 52.7 (CH_3), 64.4 ($NCCO_2$), 120.8 (CH_2=CH), 123.9 (ArCH), 131.6 (ArCH), 132.2 (CH=CH_2), 132.9 (ArC), 144.5 (ArC), 173.0 (CO_2); *m/z* (CI, NH_3) 265 (MH^+, 60), 235 (100); [found: (CI, NH_3) 265.1188 (MH^+, $C_{13}H_{17}N_2O_4$ requires 265.1185)].

4.1.18. α-But-2-ynyl-allylglycine methyl ester 4m from imine 3f. Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added, followed by 1-bromo-2-butyne (294 mg, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4m** (154 mg, 46%). ν_{max} (KBr) 3395 (w), 3063 (w), 2951 (w), 1733 (s), 1642 (s), 1601 (m) and 1581 cm^{-1} (m); δ_H ($CDCl_3$) 1.71 (3H, t J=2.5 Hz, C≡CCH_3), 1.85 (2H, br s, NH_2), 2.24 (1H, dd J=13.4, 8.1 Hz, CH_2–CH), 2.34 (1H, dq J=16.3, 2.5 Hz, CH_2–C≡CMe), 2.45 (1H, dd J=13.4, 6.7 Hz, CH_2–CH), 2.55 (1H, dq J=16.3, 2.5 Hz, CH_2–C≡CMe), 3.67 (3H, s, OCH_3), 5.0–5.1 (2H, m, CH=CH_2), 5.5–5.7 (1H, m, CH=CH_2); δ_C ($CDCl_3$) 2.5 (CH_3C≡C), 29.0 (CH_2C≡CMe), 42.6 (CH_2CH), 51.3 (OCH_3), 59.7 ($NCCO_2$), 72.9 (C≡CCH_3), 78.1 (C≡CCH_2), 118.5 (CH_2=CH), 131.4 (CH=CH_2), 174.9 (CO_2); *m/z* (CI, NH_3) 182 (MH^+, 100); [found: (CI, NH_3) 182.1181 (MH^+, $C_{10}H_{16}NO_2$ requires 182.1180)].

4.1.19. α-But-2-ynyl-allylglycine methyl ester 4m from imine 3g. Imine **3g** (0.4 g, 1.59 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (12 mg, 0.03 mmol) was added. Finely ground sodium hydroxide (0.222 g, 5.57 mmol) was then added, followed by 1-bromo-2-butyne (254 mg, 1.91 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4m** (124 mg, 44%). $[\alpha]_D^{20}=-27.3$ (c=0.3, $CHCl_3$); other data as reported for the same compound prepared from imine **3f**.

4.1.20. α-Propargyl-allylglycine methyl ester 4n. Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added, followed by propargyl bromide (263 mg, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4n** (150 mg, 49%). $[\alpha]_D^{20}=-22.7$ (c=0.3, $CHCl_3$); ν_{max} (KBr) 3301 (w), 2952 (w), 1736 (s), and 1641 cm^{-1} (m); δ_H ($CDCl_3$) 1.8–2.0 (2H, br, NH_2), 2.00 (1H, t J=2.8 Hz, H–C≡), 2.28 (1H, dd J=13.5, 8.2 Hz, CH_2–CH=), 2.41 (1H, dd J=16.5, 2.6 Hz, CH_2–C≡), 2.48 (1H, dd J=13.5, 6.7 Hz, CH_2–CH=), 2.62 (1H, dd J=16.5, 2.6 Hz, CH_2–C≡), 3.69 (3H, s, OCH_3), 5.0–5.2 (2H, m, CH=CH_2), 5.5–5.7 (1H, m, CH=CH_2); δ_C ($CDCl_3$) 29.9 (CH_2C≡), 43.8 (CH_2CH=), 52.9 (OCH_3), 60.8 ($NCCO_2$), 72.0 (C≡CH), 79.8 (C≡CCH_2), 120.3 (CH_2=CH), 132.4 (CH=CH_2), 174.8 (CO_2); *m/z* (CI, NH_3) 168 (MH^+, 100); [found: (CI, NH_3) 168.1019 (MH^+, $C_9H_{14}NO_2$ requires 168.1019)].

4.1.21. Dimethyl *N*-*para*-chlorobenzylidene (*R*,*S*)-glutamate 3h. To a suspension of dimethyl glutamate hydrochloride (10.0 g, 47.5 mmol) in dichloromethane (110 ml), was added triethylamine (4.7 ml, 33.8 mmol), *para*-chlorobenzaldehyde (5.53 g, 39.6 mmol) and magnesium sulphate (4.0 g). The reaction was stirred overnight, filtered, and

evaporated in vacuo. The residue was redissolved in dichloromethane (50 ml) and washed with water (3×50 ml). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to leave imine **3h** (6.5 g, 69%) as a white solid. Mp 62–63 °C; ν_{max} (KBr) 3004 (s), 2954 (m), 1743 (s), 1642 (s) and 1593 cm^{-1} (m); δ_H ($CDCl_3$) 2.1–2.5 (4H, m, CH_2CH_2), 3.67 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.09 (1H, dd J=7.5, 4.9 Hz, N*C*HCO$_2$), 7.41 (2H, d J=8.7 Hz, ArCH), 7.73 (2H, d J=8.5 Hz, ArCH), 8.27 (1H, s, HC=N); δ_C ($CDCl_3$) 28.67 (CH_2), 30.53 (CH_2), 52.08 (OCH_3), 52.74 (OCH_3), 72.04 (NCHCO$_2$), 129.32 (ArCH), 130.18 (ArCH), 138.12 (ArC), 138.21 (ArC), 163.36 (HC=N), 172.36 (CO_2), 174.58 (CO_2); *m/z* (EI) 299 (M^+(^{37}Cl), 23), 297 (M^+(^{35}Cl), 42), 266 (40), 238 (100), 224 (65), 178 (91); [found: (ES) 320.0636 (M(^{35}Cl)+Na^+, $C_{14}H_{16}NO_4{}^{35}ClNa$ requires 320.0662)].

4.1.22. α-Benzyl-pyroglutamic acid methyl ester 7.[44] Imine **3h** (0.635 g, 2.13 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (16 mg, 0.043 mmol) was added. Finely ground sodium hydroxide (0.298 g, 7.46 mmol) was then added, followed by benzyl bromide (437 mg, 2.56 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (4 ml) and acetyl chloride (1 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **7** (256 mg, 52%) as a colourless oil. ν_{max} (KBr) 3221 (br), 3025 (w), 2930 (m), 2859 (w), 1736 (s) and 1698 cm^{-1} (s); δ_H ($CDCl_3$) 2.0–2.5 (4H, m, CH_2CH_2), 2.85 (1H, d J=13.4 Hz, CH_2Ph), 3.18 (1H, d J=13.4 Hz, CH_2Ph), 3.64 (3H, s, OCH_3), 6.33 (1H, br s, NH), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 28.73 (CH_2), 29.53 (CH_2), 43.92 (CH_2), 51.64 (OCH_3), 65.42 (N*C*CO$_2$), 126.48 (ArCH), 127.68 (ArCH), 128.78 (ArCH), 133.75 (ArC), 172.63 (CO_2), 175.82 (NCO).

4.1.23. Dimethyl *N*-*para*-chlorobenzylidene (*R*,*S*)-aspartate 3i.[45] To a suspension of dimethyl aspartate hydrochloride (2.5 g, 12.8 mmol) in dichloromethane (35 ml), was added triethylamine (2.5 ml, 17.9 mmol), *para*-chlorobenzaldehyde (1.19 g, 8.4 mmol) and magnesium sulphate (2.0 g). The reaction was stirred overnight, filtered, and evaporated in vacuo. The residue was redissolved in dichloromethane (50 ml) and washed with water (3×50 ml). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to leave imine **3i** (2.0 g, 84%) as a yellow oil. δ_H ($CDCl_3$) 2.89 (1H, dd J=16.8, 7.8 Hz, CH_2CO_2Me), 3.17 (1H, dd J=16.8, 5.8 Hz, CH_2CO_2Me), 3.68 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.49 (1H, dd J=7.8, 5.8 Hz, NCHCO$_2$Me), 7.40 (2H, d J=8.5 Hz, ArCH), 7.72 (2H, d J=8.5 Hz, ArCH), 8.36 (1H, s, HC=N); *m/z* (EI) 285 (M^+(^{37}Cl), 10), 283 (M^+(^{35}Cl), 30), 226 (35), 224 (100); [found: (ES) 306.0488 (M(^{35}Cl)+Na^+, $C_{13}H_{14}NO_4{}^{35}ClNa$ requires 306.0505)].

4.1.24. α-Allyl-aspartic acid dimethyl ester 4o. Imine **3i** (0.200 g, 0.71 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (5.4 mg, 0.043 mmol) was added. Finely ground sodium hydroxide (0.298 g, 7.5 mmol) was then added, followed by allyl bromide (102 mg, 0.85 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.3 ml) and acetyl chloride (0.3 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4o** (35 mg, 25%) as a colourless oil. $[\alpha]_D^{20}$=+0.9 (c=0.8, $CHCl_3$); ν_{max} (KBr) 3384 (w), 3002 (w), 2954 (m) and 1736 cm^{-1} (s); δ_H ($CDCl_3$) 1.89 (2H, br s, NH_2), 2.23 (1H, dd J=13.2, 8.3 Hz, C*H*$_2$CH=), 2.3–2.4 (1H, m, C*H*$_2$CH=), 2.48 (1H, d J=16.7 Hz, CH_2CO_2Me), 2.91 (1H, d J=16.6 Hz, CH_2CO_2Me), 3.61 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 5.0–5.2 (2H, m, =CH_2), 5.5–5.7 (1H, m, =CH); δ_C ($CDCl_3$) 43.57 (CH_2), 44.87 (CH_2), 52.17 (OCH_3), 52.82 (OCH_3), 59.20 (N*C*CO$_2$), 120.52 (=CH_2), 131.88 (=CH), 172.23 (CO_2); *m/z* (EI) 202 (MH^+, 8), 160 (100), 142 (90), 128 (30); [found: (ES) 224.0891 (M+Na^+, $C_9H_{15}NO_4Na$ requires 224.0893)].

4.1.25. α-Benzyl-aspartic acid dimethyl ester 4p. Imine **3i** (0.222 g, 0.78 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (6 mg, 0.043 mmol) was added. Finely ground sodium hydroxide (0.298 g, 7.5 mmol) was then added, followed by benzyl bromide (161 mg, 0.94 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.5 ml) and acetyl chloride (0.4 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4p** (146 mg, 75%) as a colourless oil. $[\alpha]_D^{20}$=+0.7 (c=0.7, $CHCl_3$); ν_{max} (KBr) 3386 (w), 3056 (w), 2925 (m), 2852 (m) and 1736 cm^{-1} (s); δ_H ($CDCl_3$) 1.98 (2H, br s, NH_2), 2.51 (1H, d J=16.7 Hz, CH_2CO_2Me), 2.77 (1H, d J=13.2 Hz, CH_2Ph), 2.95 (1H, d J=13.2 Hz, CH_2Ph), 2.99 (1H, d J=16.7 Hz, CH_2CO_2Me), 3.60 (6H, s, 2× CO_2Me), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 43.73 (CH_2), 46.55 (CH_2), 52.15 (OCH_3), 52.62 (OCH_3), 60.47 (N*C*CO$_2$), 127.67 (ArCH), 128.81 (ArCH), 130.10 (ArCH), 135.48 (ArC), 172.16 (CO_2); *m/z* (EI) 252 (MH^+, 49), 192 (60), 160 (80), 100 (100); [found: (ES) 252.1222 (MH^+, $C_{13}H_{18}NO_4$ requires 252.1230)].

4.1.26. *N*-Boc-α-but-2-ynyl-allylglycine methyl ester. A solution of $(BOC)_2O$ (12 mg, 0.056 mmol) in *tert*-butanol (0.2 ml) was added dropwise at room temperature to a vigorously stirred solution of amine **4m** (10 mg, 0.055 mmol) in *tert*-butanol (0.5 ml). After the addition was complete, the reaction mixture was stirred at 30 °C for 3 h. The solvent was then evaporated in vacuo to leave a yellow oil which was purified by column chromatography on silica gel using EtOAc/hexane (4:1) as eluent to give *N*-Boc-α-but-2-ynyl-allylglycine methyl ester (12 mg, 80%) as a yellow oil. $[\alpha]_D^{20}$=+7 (c=0.6, $CHCl_3$); ν_{max} (KBr) 3565 (s), 3287 (s), 2902 (s) and 1704 cm^{-1} (m); δ_H ($CDCl_3$) 1.37 (9H, s, (CH_3)$_3$C), 1.70 (3H, t J=5.0 Hz, $CH_3C{\equiv}C$), 2.47 (1H, dd J=13.7, 6.9 Hz, CH_2–CH), 2.6–2.7 (1H, m, CH_2–C≡), 2.8–2.9 (1H, m, CH_2–CH), 2.9–3.0 (1H, m, CH_2–C≡), 3.69 (3H, s, OCH_3), 5.0–5.1 (2H,

m, CH═CH_2), 5.33 (1H, br s, NH), 5.5–5.7 (1H, m CH═CH_2); δ_C ($CDCl_3$) 2.6 (CH_3), 27.3 ((CH_3)$_3$C), 28.7 (CH_2C), 38.4 (CH_2CH), 51.7 (OCH_3), 61.4 ((CH_3)$_3$C), 72.6 (C≡CCH$_3$), 84.2 (C≡CCH$_2$), 118.4 (CH_2═CH), 130.1 (CH═CH_2), 153.2 (CONH), 171.7 (CO_2); *m/z* (CI, NH_3) 282 (MH^+, 54), 225 (100); [found: (CI, NH_3) 282.1698 (MH^+, $C_{15}H_{24}NO_4$ requires 282.1700)].

4.1.27. *N*-Boc-α-Propargyl-allylglycine methyl ester. A solution of $(BOC)_2O$ (40 mg, 0.181 mmol) in *tert*-butanol (0.5 ml) was added dropwise at room temperature to a vigorously stirred solution of amine **4n** (30 mg, 0.179 mmol) in *tert*-butanol (2 ml). After the addition was complete, the reaction mixture was stirred overnight at 30 °C. The solvent was then evaporated in vacuo to leave a yellow oil which was purified by column chromatography on silica gel using EtOAc/hexane (4:1) as eluent to give *N*-Boc-α-propargyl-allylglycine methyl ester (36 mg, 75%) as a yellow oil. $[\alpha]_D^{20}$=+4 (c=0.6, $CHCl_3$); ν_{max} (KBr) 3430 (s), 3305 (s), 2981 (s), 2123 (w), 1809 (s) and 1712 cm^{-1} (s); δ_H ($CDCl_3$) 1.37 (9H, s, (CH_3)$_3$C), 1.93 (1H, t J=2.5 Hz, H–C≡), 2.47 (1H, dd J=13.7, 7.3 Hz, CH_2–CH═), 2.7–2.8 (1H, m, CH_2–C≡), 2.8–2.9 (1H, m, CH_2–CH═), 3.0–3.1 (1H, m, CH_2–C≡), 3.71 (3H, s, OCH_3), 5.0–5.1 (2H, m, CH═CH_2), 5.35 (1H, br s, NH), 5.5–5.7 (1H, m, CH═CH_2); δ_C ($CDCl_3$) 25.9 (CH_2C≡), 27.8 ((CH_3)$_3$C), 40.0 (CH_2CH═), 53.2 (OCH_3), 62.4 ((CH_3)$_3$$C$), 71.4 (C≡$C$H), 85.6 (C≡$CCH_2$), 120.2 ($CH_2$═CH), 131.9 ($CH$═$CH_2$), 147.2 (OCONH), 172.8 (CO_2Me); *m/z* (CI, NH_3) 268 (MH^+, 93), 229 (100); [found: (CI, NH_3) 268.1539 (MH^+, $C_{14}H_{22}NO_4$ requires 268.1543)].

4.1.28. Diene 8a. *N*-Boc-α-but-2-ynyl-allylglycine methyl ester (7 mg, 0.025 mmol) was dissolved in dry dichloromethane (2.5 ml) and Grubbs' catalyst (1.0 mg, 5 mol%) was added to the solution. The reaction mixture was stirred overnight at room temperature under an ethene atmosphere. The solvent was removed in vacuo, the residue redissolved in dichloromethane and filtered through silica to remove the catalyst. The eluent was evaporated in vacuo to leave diene **8a** (10 mg, 100%) as a yellow oil. ν_{max} (KBr) 3364 (m), 2925 (s), 2854 (s), and 1715 cm^{-1} (s); δ_H ($CDCl_3$) 1.36 (9H, s, (CH_3)$_3$C), 1.85 (3H, s, CH_3C═), 2.6–2.7 (2H, m, CH_2), 3.1–3.2 (2H, m, CH_2), 3.69 (3H, s, OCH_3), 4.78 (1H, s, ═CH_2), 4.87 (1H, s, ═CH_2), 5.02 (1H, br s, NH), 5.57 (1H, s, CH═); δ_C ($CDCl_3$) 19.3 (CH_3), 27.3 ((CH_3)$_3$C), 34.6 (CH_2CH), 43.9 (CH_2C), 51.6 (OCH_3), 63.4 (NCCO_2), 84.2 ((CH_3)$_3$$C$), 112.4 ($CH_2$═CH), 122.5 (═$C$H), 138.0 ($C$═CH), 140.3 ($CH$═$CH_2$), 153.9 (CONH), 173.6 ($CO_2$); *m/z* (EI) 281 ($M^+$, 18), 207 (100); [found: (EI) 281.1622 (M^+, $C_{14}H_{22}NO_4$ requires 281.1628)].

4.1.29. Diene 8b. *N*-Boc-α-propargyl-allylglycine methyl ester (14 mg, 0.052 mmol) was dissolved in dry dichloromethane (5 ml) and Grubbs catalyst (2.1 mg, 5 mol%) was added to the solution. The reaction mixture was stirred overnight at room temperature under an ethene atmosphere. The solvent was removed in vacuo, the residue redissolved in dichloromethane and filtered through silica to remove the catalyst. The eluent was evaporated in vacuo to leave diene **8b** (14 mg, 100%) as a yellow oil. ν_{max} (KBr) 3372 (m), 2933 (s), and 1715 cm^{-1} (s); δ_H ($CDCl_3$) 1.37 (9H, s, (CH_3)$_3$C), 2.6–2.7 (2H, m, CH_2), 3.0–3.1 (2H, m, CH_2), 3.69 (3H, s, OCH_3), 4.9–5.1 (3H, m, ═CH_2 + ═HCCH_2), 5.55 (1H, br s, NH), 6.44 (1H, dd J=17.4, 10.8 Hz, H_2C═CH); δ_C ($CDCl_3$) 27.3 ((CH_3)$_3$C), 34.6 (CH_2CH═), 43.8 (CH_2C═), 51.6 (OCH_3), 63.2 (NCCO_2), 84.2 ((CH_3)$_3$$C$), 114.1 (═$CH_2$), 125.6 (═CH), 131.6 ($C$═CH), 145.7 (CH═), 154.2 (OCONH), 173.5 (CO_2Me); *m/z* (CI, NH_3) 268 (MH^+, 54), 229 (100); [found: (CI, NH_3) 268.1547 (MH^+, $C_{14}H_{22}NO_4$ requires 268.1543)].

4.1.30. Diels–Alder adduct 9. To a solution of diene **8a** (10 mg, 0.036 mmol) in ethyl acetate (2 ml) at room temperature was added maleic anhydride (8 mg, 0.078 mmol). The mixture was stirred at room temperature overnight. The solvent was then removed in vacuo and the residue was dissolved in dichloromethane and filtered twice through a pad of Celite, leaving product **9** (8 mg, 62%) as a 1:1 mixture of diastereomers. ν_{max} (KBr) 2929 (m), 2855 (w), 2254 (w), 1850 (w) and 1779 cm^{-1} (s); δ_H ($CDCl_3$) 1.37 (18H, s, 2× (CH_3)$_3$C), 1.6–1.7 (6H, m, 2× CH_3), 1.8–2.0 (4H, m, 2× CH_2), 2.2–2.3 (2H, m, 2× CH), 2.4–2.6 (4H, m, 2× CH_2), 2.6–2.7 (4H, m, 2× CH_2), 3.3–3.4 (4H, m, 4× CH), 3.68 and 3.65 (3H, 2× s, OCH_3), 4.7–4.8 and 5.0–5.1 (2H, 2× br s, NH); δ_C ($CDCl_3$) 16.9 (CH_3), 27.3 (C(CH_3)$_3$), 28.8 (COCH), 31.2 (COCH), 36.0 (CH_2), 38.2 (CH–C═), 42.4 (CH_2), 43.8 (CH_2), 51.6 (OCH_3), 63.2 (NCCO_2), 84.2 ($OCMe_3$), 133.6 (═CH), 142.2 (═C), 154.2 (OCONH), 167.7 (CO_2), 173.6 (CO_2); *m/z* (CI, NH_3) 397 (M+NH_4^+, 100), 380 (MH^+, 70); [found: (CI, NH_3) 397.1971 (M+NH_4^+, $C_{19}H_{29}N_2O_7$ requires 397.1969)].

4.2. Determination of enantiomeric excess

(*S*)-α-Methylbenzyl isocyanate (one or two drops) was added to an NMR sample of α,α-disubstituted amino acid methyl ester and left overnight to react completely with the amino ester. The diastereomeric excess and therefore enantiomeric excess was determined from the integration of the methylene or methyl ester region of the ^{1}H NMR spectrum of the resulting diastereomers.

Acknowledgements

The authors thank the EU for funding a Socrates exchange visit (V.T.) and for funding this project through the Descartes prize research grant. Mass spectra were recorded by the EPSRC national service at the University of Wales, Swansea.

References and notes

1. Nelson, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1583.
2. (a) O'Donnell, M. J.; Drew, M. D.; Cooper, J. T.; Delgado, F.; Zhou, C. *J. Am. Chem. Soc.* **2002**, *124*, 9348. (b) O'Donnell, M. J.; Delgado, F. *Tetrahedron* **2001**, *57*, 6641. (c) O'Donnell, M. J.; Delgado, F.; Pottorf, R. S. *Tetrahedron* **1999**, *55*, 6347. (d) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775. (e) O'Donnell, M. J.; Wu, Sh.; Hauffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (f) O'Donnell, M. J.; Bennet, W.; Wu, Sh. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

3. (a) Lygo, B.; Andrews, B. I. *Tetrahedron Lett.* **2003**, *44*, 4499. (b) Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015. (c) Lygo, B.; Humphreys, L. D. *Tetrahedron Lett.* **2002**, *43*, 6677. (d) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron* **2001**, *57*, 6447. (e) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403. (f) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391. (g) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1385. (h) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389. (i) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.
4. (a) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
5. For other work on the use of monomeric N-alkylated cinchona alkaloid derivatives as asymmetric phase transfer catalysts see: (a) Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611. (b) Jew, S.-s.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Lee, Y.-J.; Park, B.-s.; Kim, M. G.; Park, H.-g. *J. Org. Chem.* **2003**, *68*, 4514. (c) Mazón, P.; Chinchilla, R.; Nájera, C.; Guillena, G.; Kreiter, R.; Gebbink, R. J. M. K.; Koten, G. van *Tetrahedron: Asymmetry* **2002**, *13*, 2181. (d) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, J. I.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245. (e) Dehmlow, E. V.; Düttmann, S.; Neumann, B.; Stammler, H.-G. *Eur. J. Org. Chem.* **2002**, 2087.
6. For the alkylation of a non-amino acid derived enolate see: Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.
7. (a) O'Donnell, M. J.; Delgado, F.; Domínguez, E.; Blas, J. de.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821. (b) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 4257. (c) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.
8. Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synthesis* **2001**, 1742.
9. (a) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843. (b) Corey, E. J.; Zhang, F. Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931.
10. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289. (b) Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1*, 1287.
11. (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329. (c) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567.
12. For an application to alanine derived substrates see: Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671.
13. (a) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277. (b) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2003**, *14*, 1671.
14. (a) Kim, S.; Lee, J.; Lee, T.; Park, H.-g.; Kim, D. *Org. Lett.* **2003**, *5*, 2703. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497. (c) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927. (d) Park, H.-g.; Jeong, B.-s.; Yoo, M.-s.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem. Int. Ed.* **2002**, *41*, 3036. (e) Park, H.-g.; Jeong, B.-s.; Yoo, M.-s.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645.
15. Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 1515.
16. (a) Hashimoto, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1599. (b) Hashimoto, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3313. (c) Ooi, T.; Tayama, E.; Maruoka, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 579. (d) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (e) Ooi, T.; Uematsu, Y.; Maruoka, K. *Adv. Synth. Catal.* **2002**, *344*, 288. (f) Ooi, T.; Doda, K.; Maruoka, K. *Org. Lett.* **2001**, *3*, 1273. (g) Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716. (h) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. *Synlett* **2001**, 1185. (i) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (j) Ooi, T.; Tayama, E.; Doda, K.; Takeuchi, M.; Maruoka, K. *Synlett* **2000**, 1500. (k) Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339. (l) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.
17. (a) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (b) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4542.
18. Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022.
19. Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3796.
20. (a) Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629. (b) Mase, N.; Ohno, T.; Hoshikawa, N.; Ohishi, K.; Morimoto, H.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 4073. (c) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539. (d) Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535.
21. Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2832.
22. Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734.
23. (a) Belokon', Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmer, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851. (b) Belokon', Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Kagan, H. B. *Russ. Chem. Bull.* **1999**, *48*, 917. (c) Belokon', Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Singh, I.; Parmer, V. S.; Vyskocil, S.; Kagan, H. B. *J. Org. Chem.* **2000**, *65*, 7041.
24. (a) Belokon', Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Vyskocil, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1723. (b) Belokon', Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Larionov, O. V.; Harutyunyan, S. R.; Vyskocil, S.; North, M.; Kagan, H. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 1948.
25. Casas, J.; Nájera, C.; Sansano, J. M.; González, J.; Saá, J. M.; Vega, M. *Tetrahedron: Asymmetry* **2001**, *12*, 699.
26. (a) Belokon', Y. N.; Davies, R. G.; Fuentes, J. A.; North, M.; Parsons, T. *Tetrahedron Lett.* **2001**, *42*, 8093. (b) Belokon', Y. N.; North, M.; Churkina, T. D.; Ikonnikov, N. S.; Maleev, V. I. *Tetrahedron* **2001**, *57*, 2491. (c) Belokon', Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. I. *Tetrahedron Lett.* **1999**, *40*, 6105.
27. Belokon', Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245.
28. For a preliminary communication of some of the result in this paper see: Belokon', Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; Maleev, V.; North, M.; Pertosyan, A. *Tetrahedron Lett.* **2003**, *44*, 2045.
29. Tanaka, M.; Nishimura, S.; Oba, M.; Demizu, Y.; Kurihara, M.; Suemune, H. *Chem. Euro. J.* **2003**, *9*, 3082.
30. Werf, A. van der; Kellogg, R. M. *Tetrahedron Lett.* **1988**, *29*, 4981.

31. (a) Kingma, I. E.; Wiersma, M.; Baan, J. L. van der; Balt, S.; Bickelhaupt, F.; Bolster, M. W. G. de; Klumpp, G. W.; Spek, A. L. *J. Chem. Soc., Chem. Commun.* **1993**, 832. (b) Blaauw, R.; Kingma, I. E.; Laan, J. H.; Baan, J. L. van der; Balt, S.; Bolster, M. W. G. de; Klumpp, G. W.; Smeets, W. J. J.; Spek, A. L. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 1199.
32. Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.
33. Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron* **2001**, *57*, 9711.
34. Schöllkopf, U.; Tölle, R.; Egert, E.; Nieger, M. *Liebigs Ann. Chem.* **1987**, 399.
35. Schöllkopf, U.; Busse, U.; Kilger, R.; Lehr, U. *Synthesis* **1984**, 271.
36. (a) Gilbert, I.; Rees, D. C.; Richardson, R. S. *Tetrahedron Lett.* **1991**, *33*, 2277. (b) Chaari, M.; Lavergne, J.-P.; Viallefont, P. *Synth. Commun.* **1989**, *19*, 1211. (c) O'Donnell, M. J.; Bruder, W. A.; Daugherty, B. W.; Liu, D.; Wojciechowski, K. *Tetrahedron Lett.* **1984**, *25*, 3651. (d) Gilbert, I. H.; Rees, D. C.; Crockett, A. K.; Jones, R. C. F. *Tetrahedron* **1995**, *51*, 6315. (e) Goswami, L. N.; Srivastava, S.; Panday, S. K.; Dikshit, D. K. *Tetrahedron Lett.* **2001**, *42*, 7891.
37. (a) Hulst, R.; Vries, N. de K.; Feringa, B. L. *Angew. Chem.* **1992**, *104*, 1089. (b) Fuchi, N.; Doi, T.; Harada, T.; Urban, J.; Cao, B.; Kahn, M.; Takahashi, T. *Tetrahedron Lett.* **2001**, *42*, 1305.
38. (a) Zydowsky, T. M.; Lara, E. de; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5437. (b) Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Peters, P. J. H.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1113. (c) Achatz, O.; Grandl, A.; Wanner, K. T.; Eur, *J. Org. Chem.* **1999**, 1967.
39. Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460.
40. (a) Marquez, A.; Rodriguez, H.; Medina, J.; Cheung, K. K. *Syn. Commun.* **1993**, *23*, 1321. (b) Grigg, R.; Gunaratne, H. Q. N.; Kemp, J. *Tetrahedron* **1990**, *46*, 6467. (c) Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *J. Chem. Soc., Chem. Commun.* **1980**, 648.
41. Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236.
42. Chaari, M.; Lavergne, J.-P.; Viallefont, P. *Syn. Commun.* **1989**, *19*, 1211.
43. Fuchi, N.; Doi, T.; Harada, T.; Urban, J.; Cao, B.; Kahn, M.; Takahashi, T. *Tetrahedron Lett.* **2001**, *42*, 1305.
44. Gillan, T.; Mor, G.; Pepper, F. W.; Cohen, S. G. *Bioorg. Chem.* **1977**, *6*, 329.
45. O'Donnell, M. J.; Bennett, W. D.; Jacobsen, W. N.; Ma, Y.-a. *Tetrahedron Lett.* **1989**, *30*, 3913.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1863–1868
Tetrahedron

Novel synthesis of *meso*-tetraarylporphyrins using CF_3SO_2Cl under aerobic oxidation

Hashem Sharghi* and Alireza Hassani Nejad

Department of Chemistry, College of Science, Shiraz University, Adebiat Cross, Shiraz 71454, Iran

Received 27 September 2003; revised 12 November 2003; accepted 11 December 2003

Abstract—*meso*-Tetraarylporphyrins are synthesized from pyrrole and aryl aldehydes cleanly and efficiently in one pot at room temperature using equimolar amount of CF_3SO_2Cl in the presence of air as oxidant. By this novel method 5,10,15,20-tetraarylporphyrins can be prepared in excellent yields.

1. Introduction

The continuing progress in porphyrin chemistry in recent years has caused a growing interest for such compounds. The remarkably diverse photo-electro- and bio-chemical properties of the porphyrins continue to attract the attention of researchers even after well over a hundred years. Porphyrin research has gone from Hans Fischer's pioneering synthesis of hemin in the 1920s,[1] to their use as selective catalysts,[2–5] molecular electronic devices,[6] photodynamic therapy agents[7] and applications to materials chemistry.[8] Advances in porphyrin model systems are closely tied to methods for preparing synthetic porphyrins.

Over the past years, numerous advances in porphyrin synthetic methodology have been realized. These developments have advanced systematically through monopyrrole tetramerization,[9–13] dipyrromethene self-condensation in organic acid metals,[14] '2+2' *MacDonald* dipyrromethane syntheses[15] and '3+1' synthesis with a tripyrrane and a diformylpyrrole.[16] Most porphyrin syntheses proceed by tetramerization of monopyrrole. Tetraphenylporphyrin was first synthesized by *Rothemund*,[9] then *Adler-Longo* proposed a simplified synthesis for *meso*-tetraphenylporphyrin.[10] In this method a solution of aldehyde and pyrrole in a high-boiling acid solvent is heated at reflux in air, so that condensation and oxidation occur simultaneously. This method gives low yields of sensitive porphyrins, reflecting rather vigorous conditions, and intractable purification problems arise for porphyrins which do not readily crystallize or precipitate from the tar-laden propionic acid and a high percentage of tarry by-products are also formed.

Lindsey et al.[11] published results on studies of improved methods of some *meso*-tetraarylporphyrins and discussed a mechanistic interpretation of the reaction. Recent methods in the synthesis of tetraphenylporphyrins from tetramerization of mono pyrrole include the use of an oxidizing cosolvent,[17] Lewis acids,[18] and various clays as catalysts.[19] In these methods, there are intrinsic disadvantages in the requirement for the expensive high-potential quinone oxidant and in elaborate, costly purification procedures needed to isolate the porphyrin, and/or high-thermal conditions, so that the reaction fails completely with benzaldehydes bearing substituents in *ortho* positions and sensitive functional groups.

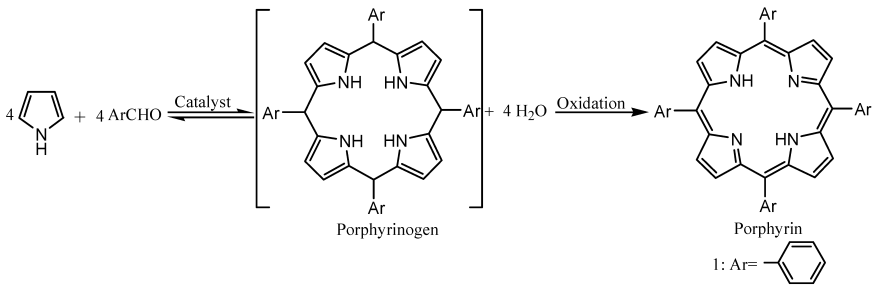
In this paper, we report a method for preparing porphyrins under mild conditions at room temperature. Pyrrole and benzaldehyde in the presence of CF_3SO_2Cl react to form tetraphenylporphyrin in one pot without the need of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant. The reaction conditions were optimized for benzaldehyde. Under these reaction conditions, tetraarylporphyrins are formed in 25–67% yields.

2. Result and discussion

The conversion of aldehydes and pyrroles to porphyrins is a multi-step process involving condensation (polymerization and cyclization) followed in timed sequence by oxidation. Porphyrins are known to be easily obtained by treatment of the precursor 'porphyrinogen' with oxidizing agents such as chloranil[11,18,19] or aerobic oxidation[10,20] (Scheme 1). The existence of this intermediate has been shown by *Dolphin*,[21] who isolated β-octamethyl-*meso*-tetraphenylporphyrinogen under *Adler-Longo* conditions.

Keywords: Porphyrin; Synthesis; Pyrrole.
* Corresponding author. Tel.: +98-711-2284822; fax: +98-711-2280926; e-mail address: shashem@chem.susc.ac.ir

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.030



Scheme 1. For Ar, see Table 2.

Therefore, the preparation of porphyrinogen by the pyrrole-aldehyde condensation is the important step in this synthesis. To synthesize *meso*-tetraarylporphyrins efficiently, it is necessary to select the specific conditions for the generation of the corresponding porphyrinogen, followed by appropriate oxidative workup.

Our efforts in this area have been largely directed toward the systematic investigation of best conditions for porphyrin synthesis. We have investigated the effects of numerous reaction parameters on the yield of tetraphenylporphyrin **1** obtained in a one-flask, room-temperature synthesis. Initially, a systematic study was undertaken with various catalysts, and it was found that CF_3SO_2Cl showed excellent activity for the condensation of pyrrole and benzaldehyde for the preparation of **1** (Table 1). In a typical trial reaction, 1 equiv. of CF_3SO_2Cl was added to a solution of benzaldehyde and pyrrole (1:1) in CH_2Cl_2 (10^{-2} M) under N_2 gas. After 1 h, the stoichiometric amount of DDQ (39 °C, 1 h) was then added to oxidize the porphyrinogen to porphyrin. The general workup involves concentration of the crude reaction mixture, followed by passing over a short chromatography column. The porphyrin product obtained in this manner is relatively pure.

Table 1. Reaction of pyrrole (10^{-2} M) and benzaldehyde (10^{-2} M) in the presence of 1 equiv. of various catalysts, at room temperature with DDQ as oxidant

Entry	Catalyst	Solvent	Time (h)	Yield (%) of **1**
1	—	CH_2Cl_2	6	0
2	Al_2O_3 (pH=7)[a]	CH_2Cl_2	3	5
3	Al_2O_3 (pH=4.5)[a]	CH_2Cl_2	3	12
4	CH_3SO_3H	CH_2Cl_2	3	10
5	Al_2O_3/CH_3SO_3H[b]	CH_2Cl_2	3	11
6	$MgSO_4$	CH_2Cl_2	4	9
7	CsCl	CH_2Cl_2	4	5
8	$Al(O_2CCH_3)_3$	CH_2Cl_2	3	8
9	$Al(O_2CCF_3)_3$	CH_2Cl_2	3	18
10	$AlCl_3$	CH_2Cl_2	3	20
11	$CaCl_2$	CH_2Cl_2	4	15
12	CaO	CH_2Cl_2	4	13
13	MgO	CH_2Cl_2	4	11
14	$(CF_3CO)_2O$	CH_2Cl_2	4	19
15	TsCl	CH_2Cl_2	3	25
16	$SOCl_2$	CH_2Cl_2	3	22
17	CH_3SO_2Cl	CH_2Cl_2	2.5	49
18	CF_3SO_2Cl	CH_2Cl_2	2	62
19	CF_3SO_2Cl	$CHCl_3$	3	58
20	CF_3SO_2Cl	CH_3CN	4	18
21	CF_3SO_2Cl	THF	5	7
22	CF_3SO_2Cl	CH_3COCH_3	5	Trace
23	CF_3SO_2Cl	C_6H_6	4	30
24	CF_3SO_2Cl	Et_2O	4	23

[a] 1 g for 1 mmol of reactants.
[b] Three drops of CH_3SO_3H was added to 1 g of Al_2O_3 for 1 mmol of reactants.

The results from Table 1 (entries 2–18) show the influence of the nature of catalyst on porphyrin synthesis and clearly indicate that CF_3SO_2Cl is the best catalyst for this condensation reaction. Several metal salts have been used as catalyst but metal insertion does not occur under these reaction conditions (Table 1 entries 6–11). The reactions were carried out in CH_2Cl_2, $CHCl_3$, CH_3CN, THF, CH_3COCH_3, C_6H_6 and Et_2O. As shown in Table 1 (entry 18), CH_2Cl_2 is the best solvent for porphyrin synthesis under these reaction conditions.

Porphyrin **1** yields as a function of reactant concentration are shown in Figure 1. The concentrations of benzaldehyde and pyrrole are critical determinants of the ultimate yield of porphyrin. The maximum yield of **1** is observed, when an equimolar amount of benzaldehyde and pyrrole concentrations of 10^{-2} M are used (Fig. 1). The yield declines markedly at concentrations 10-fold higher and 10-fold lower. This relies on the fact that pyrrole and benzaldehyde under acid catalysis will stabilise a balance with tetraphenylporphyrinogen. The dilution conditions are important to optimize formation of the porphyrinogen at the expense of open chain polypyrrylmethanes.

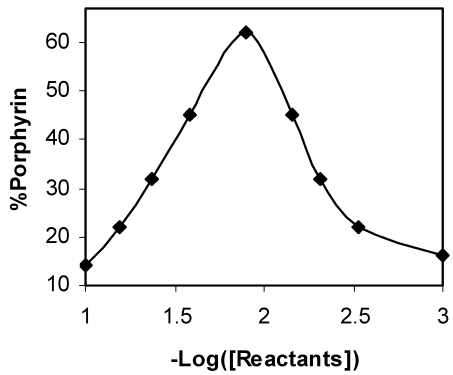


Figure 1. Dependence of porphyrin formation on concentration of reactants.

A milder and slower oxidant gave the best results for porphyrinogen oxidation.[17] Molecular oxygen is the oxidant in the *Adler*[10] and *Drain*[20] reactions. The specially demanding conditions for the oxidation of the *meso*-tetraarylporphyrinogens led us to check their behavior in aerobic oxidations. We found that, when the reaction time extended to 4 h, porphyrinogen, under aerobic oxidation, was converted to porphyrin, and DDQ or *para*-chloranil was

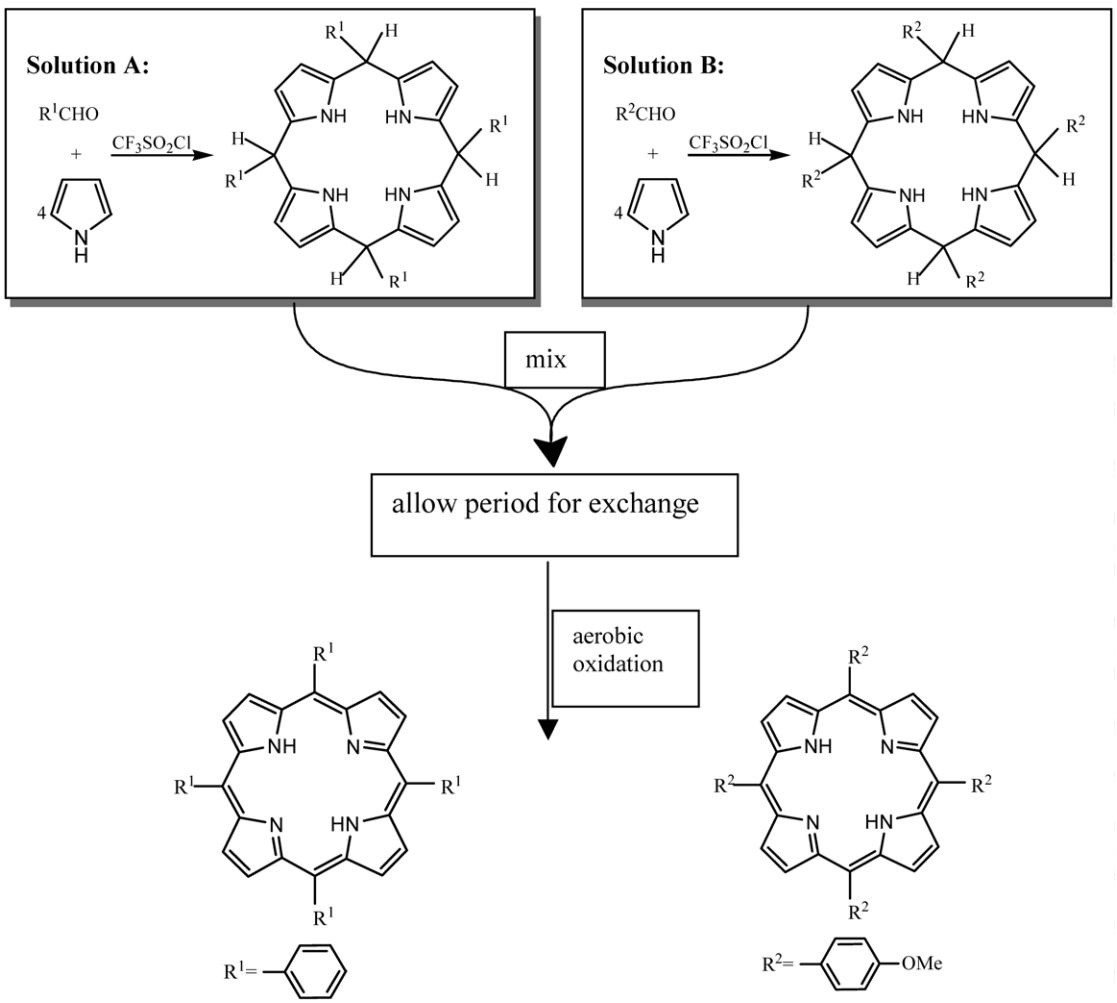
Table 2. Synthesis of *meso*-tetraarylporphyrins from pyrrole and aryl aldehydes in the presence of CF_3SO_2Cl, at room temperature with air as oxidant

Entry	Ar	Product	Reaction time (h)	Yield (%)
1	Ph	**1**	3	62
2	*p*-MeC_6H_4	**2**	3	60
3	*p*-$MeOC_6H_4$	**3**	3	67
4	*p*-ClC_6H_4	**4**	3	56
5	*p*-BrC_6H_4	**5**	3	64
6	*p*-CNC_6H_4	**6**	3.5	40
7	*p*-$NO_2C_6H_4$	**7**	4	34
8	*p*-IsopropylC_6H_4	**8**	3	60
9	*m*-MeC_6H_4	**9**	3	57
10	*m*-$MeOC_6H_4$	**10**	3	40
11	*m*-ClC_6H_4	**11**	3.5	41
12	*m*-$NO_2C_6H_4$	**12**	4	40
13	*o*-MeC_6H_4	**13**	3	40
14	*o*-ClC_6H_4	**14**	3	35
15	*o*-$NO_2C_6H_4$	**15**	4	27
16	Mesityl	**16**	4	25

not required. This avoids the requirement for expensive quinones, and simplifies workup.

In an effort to evaluate the range of applicability of our method, we also examined some other benzaldehydes having a wide variety of *ortho*, *meta* and *para* substituted, both electron-donating and withdrawing. The reaction conditions for benzaldehyde were applied to a set of sixteen aldehydes (Table 2). This synthetic procedure can be used for the synthesis of a large number of tetraarylporphyrins, with pyrrole and aryl aldehydes. Sterically hindered aldehydes such as 2,4,6-trimethylbenzaldehyde and 2-nitrobenzaldehyde can also be employed in the reaction (Table 2, entries 15, 16). A comparison of the reaction of aldehydes with pyrrole in the presence of CF_3SO_2Cl indicates that an increase in steric hindrance and the presence of electron withdrawing groups at the benzaldehyde results in a general decrease in the yield of porphyrin formation (for example, compare Table 2, entry *1* with entry *15*). All reactions were run under standard conditions: 10^{-2} M aldehyde and 10^{-2} M pyrrole with equimolar amount of CF_3SO_2Cl in CH_2Cl_2. The yields given in Table 2 reflect the ease with which pure material (one spot in TLC) could be obtained from a single chromatographic step. The porphyrins were identified by comparison with authentic samples prepared according to literature procedures.[11,12,19,20,22–24] The advantage of this method is that it allows the formation of porphyrins from sensitive aldehydes, in higher yields, with more facile purification.

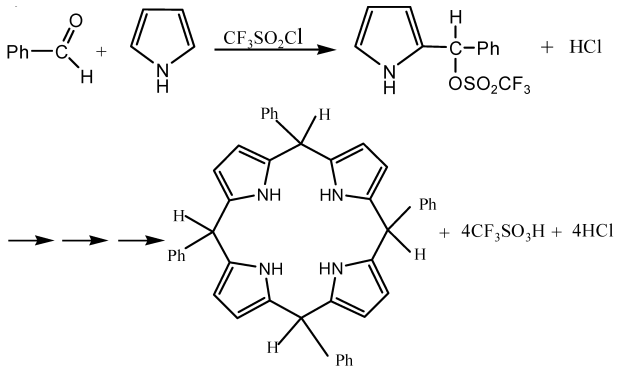
Previous workers have demonstrated that porphyrinogen formation is a reversible process, when aryl aldehydes are



Scheme 2. Porphyrinogen exchange experiment.

condensed with pyrrole.[11,22] We examined the porphyrinogen exchange according to Lindsey's procedure.[11b] The procedure is illustrated for one pair of aldehydes, benzaldehyde and *p*-methoxybenzaldehyde (two pairs of aryl aldehydes which reacted at similar rates and gave similar yields of porphyrin). Two solutions (**A** and **B**) were prepared and two aldehydes were condensed separately with pyrrole by addition of CF_3SO_2Cl under N_2 gas. When the porphyrinogen concentrations had reached a maximum (t_{max} 1 h) the solutions were mixed (Scheme 2). At a common time, 5 h after mixing, the distribution of products was analyzed. We only obtained two porphyrins, and scrambling was not detected.

The results indicate that in these conditions the condensation of monomers and cyclization of tetrapyrrolic oligomers are irreversible. The proposed mechanism for irreversibility condensation of pyrrole and aldehyde is shown in Scheme 3.



Scheme 3.

In this paper, we first present a survey of the effects of different catalysts in the reaction of pyrrole and benzaldehyde, focusing primarily on reactions at 0.01 M. Second, we examined the effects of solvent, reactant concentration, aerobic oxidation, and the reversibility of the pyrrole-aldehyde condensation under these conditions. Third, we reported the application of the best reaction conditions identified, for a variety of aldehydes. By this method porphyrinogen, under aerobic oxidation, was converted to porphyrin, and this oxidation system avoids application of organic oxidants. This procedure currently allows the preparation of a large variety of porphyrins in good-to-excellent yields from the corresponding aldehydes. The advantages of our method are high yield of porphyrins without need of man-made oxidant, ease of isolation and purification of the porphyrins obtained, and mild conditions for aldehydes bearing sensitive substituents.

3. Experimental

Dichloromethane and chloroform (Merck) were distilled from K_2CO_3. Pyrrole was distilled from calcium hydride, and stored samples were rejected when discoloration occurred. Benzaldehyde was distilled under reduced pressure. Substituted benzaldehydes and other chemical materials obtained from commercial sources (Aldrich, Fluka) were used as received. Elemental analyses were performed at the National Oil Co. of Iran, Tehran Research Center. IR spectra were recorded on Perkin–Elmer spectrometer. Proton NMR spectra were recorded on a Bruker Advance DPX FT 250 MHz instrument. UV/Vis. Spectra was obtained with an Ultrospec 3000 UV/Visible spectrometer.

3.1. General procedure for synthesis of *meso*-tetraarylporphyrins

A standard reaction was performed in a 150-ml, three-necked, round-bottomed flask fitted with a septum port, a reflux condenser, and a gas-inlet port. The inlet port consisted of a glass disk immersed in the solution, with nitrogen flow rates maintained at about 2 ml per min. The flask was charged with 100 ml of distilled CH_2Cl_2, benzaldehyde (0.1 ml, 1 mmol, 10^{-2} M), and pyrrole (0.07 ml, 1 mmol, 10^{-2} M). The resulting solution was magnetically stirred at room temperature. After stirring the solution for 5–10 min, an appropriate amount of CF_3SO_2Cl (0.1 ml, 1 mmol) was added via syringe. After 1 h, the yield of porphyrinogen was maximum, then the gas-inlet line was switched to filtered house air, and the mixture was aerated for 4 h (39 °C). During this time, the mixture became dark purple, and porphyrinogen under aerobic oxidation was converted to porphyrin. The solution was concentrated by rotary evaporation and chromatographed (silica gel; with CH_2Cl_2/petroleum ether 1:1) to give **1** in 62% yield.

3.1.1. 5,10,15,20-Tetraphenylporphyrin (1). Purple crystal; mp >300 °C; yield=62%; [Found: C, 85.72; H, 5.01; N, 8.93. $C_{44}H_{30}N_4$ requires C, 85.90; H, 4.92; N, 9.12%]; λ_{max} (benzene; log ε): 418 nm (5.68), 483 (3.53), 517 (4.27), 549 (3.91), 591 (3.72), 647 (3.57). δ_H (250 MHz, $CDCl_3$): −2.76 (br. *s* 2NH); 7.73 (*m*, 12 arom. H); 8.21 (*d*, 8H_o); 8.80 (*s*, 8H (pyrrole)). δ_C (62.9 MHz; $CDCl_3$) 120.5 (C(5), C(10), C(15), C(20)), 127.1, 128.1 (C(β) (pyrrole)); 134.9, 139.2, 142.6.

3.1.2. 5,10,15,20-Tetrakis(*p*-methylphenyl)porphyrin (2). Purple crystal; mp >300 °C; yield=60%; spectroscopic data identical to that reported in the literature.[19b]

3.1.3. 5,10,15,20-Tetrakis(*p*-methoxyphenyl)porphyrin (3). Purple crystal; mp >300 °C; yield=67%; spectroscopic data identical to that reported in the literature.[12]

3.1.4. 5,10,15,20-Tetrakis(*p*-chlorophenyl)porphyrin (4). Purple crystal; mp >300 °C; yield=56%; spectroscopic data identical to that reported in the literature.[19b]

3.1.5. 5,10,15,20-Tetrakis(*p*-bromophenyl)porphyrin (5). Purple crystal; mp >300 °C; yield=64%; [Found: C, 56.75; H, 2.78; N, 6.11. $C_{44}H_{26}Br_4N_4$ requires C, 56.80; H 2.81; N, 6.02%]; λ_{max} (benzene; log ε): 421 nm (5.71), 518 (4.40), 550 (3.99), 591 (3.76), 649 (3.54). δ_H (250 MHz, $CDCl_3$): −2.94 (br. *s* 2NH); 7.81 (*d*, 8H_m); 8.01 (*d*, 8H_o); 8.76 (*s*, 8H (pyrrole)). δ_C (62.9 MHz; $CDCl_3$): 118.1 (C(5), C(10), C(15), C(20)); 127.5, 131.6 (C(β) (pyrrole)); 133.9, 136.9, 139.9.

3.1.6. 5,10,15,20-Tetrakis(*p*-cyanophenyl)porphyrin (6). Purple crystal; mp >300 °C; yield=40%; spectroscopic data identical to that reported in the literature.[11b]

3.1.7. 5,10,15,20-Tetrakis(*p*-nitrophenyl)porphyrin (7). Purple crystal; mp >300 °C; yield=34%; spectroscopic data identical to that reported in the literature.[23]

3.1.8. 5,10,15,20-Tetrakis(*p*-isopropylphenyl)porphyrin (8). Purple crystal; mp >300 °C; yield=60%; [Found: C, 85.78; H, 6.61; N, 7.43. $C_{56}H_{54}N_4$ requires C, 85.93; H, 6.90; N, 7.16%]; λ_{max} (benzene; log ε): 420 nm (5.72), 489 (3.32), 518 (4.23), 520 (4.04), 599 (3.95), 652 (4.32). δ_H (250 MHz, $CDCl_3$): −2.74 (br. *s* 2NH); 1.40 (*d*, 24H, *J*=4.4 Hz, 8Me); 3.2 (*m*, 4CH); 7.55 (*d*, $8H_m$); 8.02 (*d*, $8H_o$); 8.83 (*s*, 8H (pyrrole)).

3.1.9. 5,10,15,20-Tetrakis(*m*-methylphenyl)porphyrin (9). Purple crystal; mp >300 °C; yield=57%; spectroscopic data identical to that reported in the literature.[23]

3.1.10. 5,10,15,20-Tetrakis(*m*-methoxyphenyl)porphyrin (10). Purple crystal; mp >300 °C; yield=40%; [Found: C, 78.37; H, 5.24; N, 7.65. $C_{48}H_{38}N_4O_4$ requires C, 78.45; H, 5.21; N, 7.62%]; λ_{max} (benzene; log ε): 418 (5.73), 518 (4.09), 550 (3.95), 589 (3.91), 650 (3.90). δ_H (250 MHz, $CDCl_3$): −2.79 (br. *s* 2NH); 3.97 (s, 12H, 4MeO); 7.33–7.77 (*m*, 16 arm. H); 8.46 (*s*, 8H (pyrrole)).

3.1.11. 5,10,15,20-Tetrakis(*m*-chlorophenyl)porphyrin (11). Purple crystal; mp >300 °C; yield=41%; spectroscopic data identical to that reported in the literature.[12]

3.1.12. 5,10,15,20-Tetrakis(*m*-nitrophenyl)porphyrin (12). Purple crystal; mp >300 °C; yield=40%; [Found: C, 66.38; H, 3.27; N, 14.22. $C_{44}H_{26}N_8O_8$ requires C, 66.50; H, 3.27; N, 14.10%]; λ_{max} (benzene; log ε): 418 nm (5.72), 480 (3.08), 515 (4.33), 550 (4.04), 591 (4.02), 646 (3.63). δ_H (250 MHz, $CDCl_3$): −2.96 (br. *s* 2NH); 8.13–8.70 (*m*, 16 arom. H); 8.93 (*s*, 8H (pyrrole)).

3.1.13. 5,10,15,20-Tetrakis(*o*-methylphenyl)porphyrin (13). Purple crystal; mp >300 °C; yield=40%; spectroscopic data identical to that reported in the literature.[19b]

3.1.14. 5,10,15,20-Tetrakis(*o*-chlorophenyl)porphyrin (14). Purple crystal; mp >300 °C; yield=35%; spectroscopic data identical to that reported in the literature.[19b]

3.1.15. 5,10,15,20-Tetrakis(*o*-nitrophenyl)porphyrin (15). Purple crystal; mp >300 °C; yield=27%; [Found: C, 66.53; H, 3.41; N, 14.06. $C_{44}H_{26}N_8O_8$ requires C, 66.50; H, 3.27; N, 14.10%]; λ_{max} (benzene; log ε): 422 nm (5.72), 518 (3.99), 550 (3.85), 588 (3.66), 650 (3.36). δ_H (250 MHz, $CDCl_3$): −2.95 (br. *s* 2NH); 7.54–8.27 (*m*, 16 arom. H); 8.64 (*s*, 8H (pyrrole)).

3.1.16. 5,10,15,20-Tetramesitylporphyrin (16). Purple crystal; mp >300 °C; yield=25%; spectroscopic data identical to that reported in the literature.[11c]

Acknowledgements

We would like to acknowledge the support of this work by Shiraz University Research Council and Professor N. Iranpoor for his helpful comments.

References and notes

1. For a remarkable book on porphrin history, chemistry and applications, see. In *The chemical and physical behavior of porphyrin compounds and related structures*. *Annales New York academy science*; Adler, A. D., Ed.;, 1973; Vol. 206.
2. For a review, (a) Mlodnicka, T. *J. Mol. Catal.* **1986**, *36*, 205. (b) Haslam, E. *Shikimic acid metabolism and metabolites*; Wiley: New York, 1993. (c) Wijesekera, T. P.; Dolphin, D. In *Metalloporphyrins in catalytic oxidations*; Sheldon, R. A., Ed.; Marcel Dekker: New York, 1994; pp 193–231.
3. Mansuy, D. *Coord. Chem. Rev.* **1993**, 129.
4. *Metalloporphyrin catalyzed oxidation*; Montanari, F., Cassela, L., Eds.; Kluwer: Dordrecht, 1994.
5. (a) Sharghi, H.; Naeimi, H. *J. Chem. Res. (S)* **1999**, 310. (b) Shamsipur, M.; Soleymanpour, A.; Akhond, M.; Sharghi, H.; Hasaninejad, A. R. *Sens. Actuators, B* **2003**, *89*, 9.
6. (a) Drain, C. M.; Lehn, J. M. *J. Chem. Soc. Chem. Commun.* **1994**, 2313. (b) Drain, C. M.; Russell, K. C.; Lehn, J. M. *J. Chem. Soc. Chem. Commun.* **1996**, 2337.
7. Hartley, J. A.; Forrow, S. M.; Souhami, R. L. *Cancer Res.* **1990**, *50*, 1936.
8. Kadish, K.; Smith, K.; Guilard, R. *The porphyrin handbook*; Academic: New York, 2000; Vol. 6. pp 43–131.
9. Rothemund, P. *J. Am. Chem. Soc.* **1939**, *61*, 2912.
10. (a) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Golldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1976**, *32*, 476. (b) Longo, F. R.; Finarelli, J. D.; Kim, J. *J. Heterocycl. Chem.* **1969**, *6*, 927. (c) Adler, A. R.; Longo, F. R.; Kampas, F.; Kim, J. *J. Inorg. Nucl. Chem.* **1970**, *32*, 2443.
11. (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969. (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827. (c) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828. (d) Wagner, R. W.; Breakwell, B. V.; Ruffing, J.; Lindsey, J. S. *Tetrahedron Lett.* **1991**, *32*, 1703. (e) Lindsey, J. S.; MacCrum, K. A.; Tyhonas, J. S.; Chuang, Y.-Y. *J. Org. Chem.* **1994**, *59*, 579. (f) Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427. (g) Wagner, R. W.; Johnson, T. E.; Lindsey, J. S. *Tetrahedron* **1997**, *53*, 6755. (h) Ravikanth, M.; Achim, C.; Tyhonas, J. S.; Münck, E.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **1997**, *1*, 385. (i) Li, F.; Yang, K.; Tyhonas, J. S.; MacCrum, K. A.; Lindsey, J. S. *Tetrahedron* **1997**, *53*, 12339. (j) Geier, G. R.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2002**, *6*, 159.
12. Johnstone, R. A.; Nunes, M. L.; Pereira, M. M.; Gonsalves, M. R.; Serra, A. C. *Heterocycles* **1996**, *43*, 1423.
13. Sharghi, H.; Hassani Nejad, A. R. *J. Chem. Res. (S)* **2003**, 87.
14. Fischer, H.; Friendrich, H.; Lamatsch, W.; Morgenroth, K. *Liebigs Ann. Chem.* **1928**, *466*, 147.
15. (a) Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384. (b) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245.
16. Boudif, A.; Momenteau, M. *J. Chem. Soc., Chem. Commun.* **1994**, 2069.
17. Rocha Gonsalves, A. M.; Varejao, J. M. M. *J. Heterocycl. Chem.* **1991**, *28*, 635.
18. Geier, G. R.; Cirigh, Y.; Li, F.; Haynes, D. M.; Lindsey, J. S. *Org. Lett.* **2000**, *2*, 1745.
19. (a) Shinoda, T.; Izumi, Y.; Onaka, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1801. (b) Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Tetrahedron Lett.* **1993**, *34*, 2625. (c) Laszlo, P.; Luchetti, J. *Chem. Lett.* **1993**, 449.

20. Drain, C. M.; Gong, X. *Chem. Commun.* **1997**, 2117.
21. Dolphin, D. *J. Heterocycl. Chem.* **1970**, *7*, 275.
22. Dimagno, G. S.; Williams, R. A. *J. Org. Chem.* **1994**, *59*, 6943.
23. Liama, E. F.; Sinisterra, V.; Campo, C.; Gradillas, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2611.
24. Mamardashuli, M. Zh.; Golubchikov, O. A. *Russ. Chem. Rev.* **2001**, *70*, 577.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1869–1873

Synthetic studies towards the benzophenone precursor for balanol

Mahesh L. Patil, Vishnu H. Deshpande, S. Ramlingam and Hanumant B. Borate*

Organic Chemistry Technology, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

Received 26 September 2003; revised 13 November 2003; accepted 11 December 2003

Abstract—Synthesis of 4-carboxy-2,6-dimethoxyphenyl 2′-carboxy-6′-methoxyphenyl ketone, an important precursor for balanol's benzophenone portion, has been achieved via a short and efficient route in three steps using *ortho*-lithiation as the key step. In another approach aromatization of 2-(2′-methoxy-6′-methylbenzoyl)-5-methyl-1,3-cyclohexanedione afforded benzophenone precursor 2,6-dimethoxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone along with the formation of substituted xanthone.

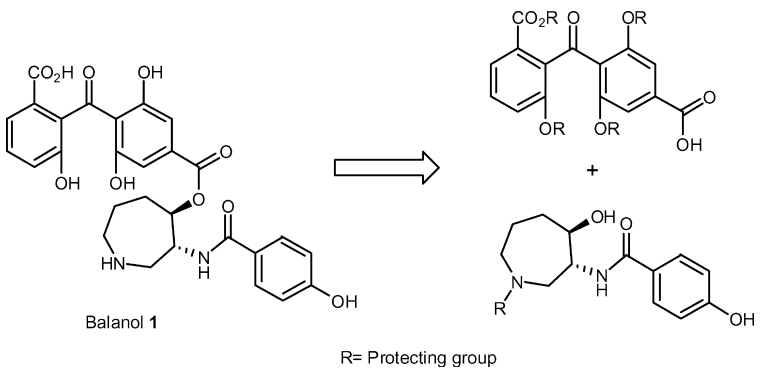
1. Introduction

Balanol (**1**), a novel protein kinase 'C' inhibitor, was isolated in 1993 by Kulanthaivel et al.[1] as an unusual metabolite produced by the fungus *Verticillium balanoides*. Balanol shows remarkable activity against cancer, HIV infection, rheumatoid arthritis, diabetes, central nervous system disorder etc. A wide range of biological activities associated with this compound has attracted researchers to undertake synthesis of balanol and its intermediates.[2]

The synthetic approaches mainly began with disconnection of balanol at its ester linkage to yield the hexahydroazepine and the benzophenone carboxylic acid. The retrosynthesis of balanol is as shown in Scheme 1. Total synthesis of balanol has been achieved by coupling the protected benzophenone domain and hexahydroazepine moiety by esterification using modified Mukaiyama procedure.

The structure–activity relationship studies[3] on balanol (**1**) proved the critical importance of the benzophenone portion for the efficacy of balanol. Any attempted change in this tetra-*ortho*-substituted benzophenone portion resulted in a decrease in its activity. Adams et al.[2c] used benzophenone precursor **2** in the total synthesis of balanol.

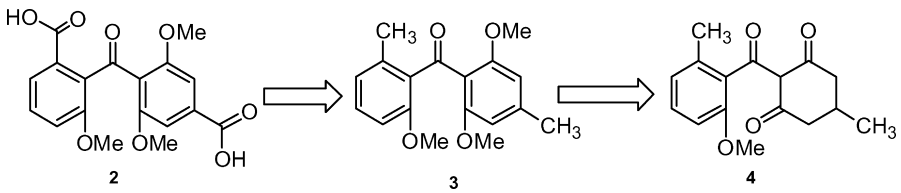
The steric hindrance, which makes the synthesis of this tetra-*ortho*-substituted benzophenone difficult, prompted us to undertake its synthesis. Earlier reports on the synthesis of balanol benzophenone precursors are based on the direct utilization of aromatic rings. We envisaged that use of alicyclic systems where the steric hindrance would be less compared to the aromatic systems and later aromatization of these alicyclic systems to the desired benzophenone portion would be a convenient route for the synthesis of this sterically hindered benzophenone portion.



Scheme 1. Retrosynthetic analysis for balanol (**1**).

Keywords: Balanol; Benzophenone; Dicarboxylic acid; Xanthone.
* Corresponding author. Tel.: +91-20-5893300; fax: +91-20-5893614; e-mail address: borate@dalton.ncl.res.in

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.029



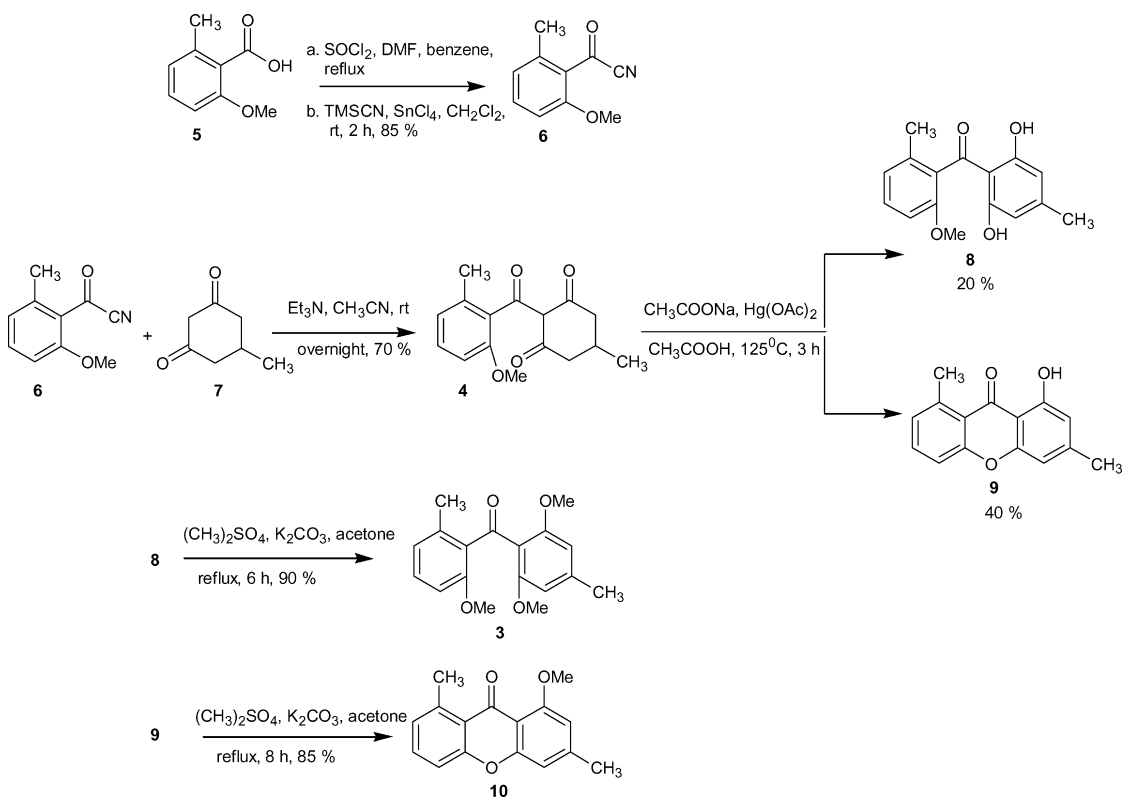
Scheme 2. Retrosynthetic analysis for the synthesis of benzophenone precursor **2**.

Retrosynthetic plan for benzophenone domain **2** (Scheme 2) suggested the triketone **4** as an important intermediate which on aromatization and oxidation would afford benzophenone precursor **3**. Our synthetic route started with synthesis of acyl cyanide **6** from carboxylic acid **5**.[4] Thus carboxylic acid **5** was converted into corresponding acid chloride followed by treatment with trimethylsilyl cyanide in the presence of catalytic stannic chloride to afford the acyl cyanide **6** in 85% yield. The synthesis of triketone **4** was achieved by the treatment of acyl cyanide **6** with 5-methylcyclohexane-1,3-dione (**7**) in presence of triethylamine to give the triketone **4** in 70% yield as shown in Scheme 3.[5,6]

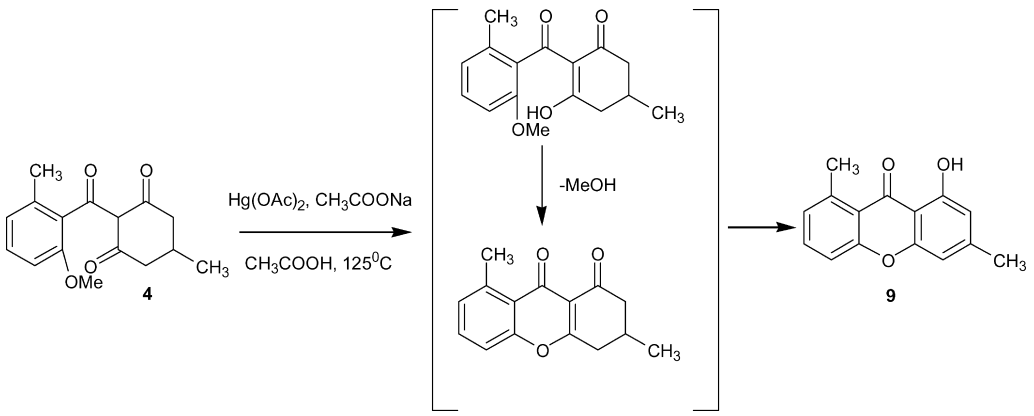
After successful synthesis of triketone **4**, our next aim was to convert compound **4** into the desired benzophenone **3**. Unfortunately the attempted aromatization of the compound **4** using I_2/MeOH,[7] DDQ in benzene or Pd/C failed to give the desired compound **3** and resulted either in the recovery of starting material or a complex reaction mixture. Finally aromatization of compound **4** was achieved using mercuric acetate and sodium acetate in acetic acid under the conditions reported by Oliver et al.[8] for the aromatization of 2-acyl-3-hydroxy-2-cyclohexane-1-ones. Aromatization of the triketone **4** under these conditions resulted in the formation of aromatized product **8** in 20% yield. Formation of compound **8** was confirmed by converting it into the known intermediate **3**, an important benzophenone precursor for balanol. Spectral data for compound **3** were identical to those reported by Adams et al.[2c]

Aromatization of triketone **4** in the presence of mercuric acetate and sodium acetate in acetic acid afforded only 20% of the required product **8** along with formation of xanthone **9**[9] in 40% yield. The ^{1}H NMR spectrum of xanthone **9** exhibited singlets at δ 2.41 and 2.89 for aromatic methyls, singlets at δ 6.55 and 6.65 each integrating for one proton and a singlet at δ 12.86 for chelated –OH group. This xanthone **9** was then methylated using dimethyl sulphate in the presence of potassium carbonate in refluxing acetone to give the corresponding methyl ether **10** whose ^{1}H NMR spectrum showed the presence of only one methoxy group at δ 4.01 confirming the assigned structure of xanthone **9**.

Probable reason for the formation of xanthone would be the loss of methanol during aromatization due to the presence of Lewis acidic mercuric acetate as shown in Scheme 4. Burger



Scheme 3. Synthesis of benzophenone precursor **3**.



Scheme 4. Formation of xanthone **9**.

and Montes[5] reported similar results of dehydration during the synthesis of the antibiotic pyoluteorin.

Thus aromatization of triketone **4** afforded the desired benzophenone **8**, the precursor for balanol, in 20% yield along with the formation of xanthone **9** in 40% yield. Though this reaction yielded the desired intermediate **8** in low yield, the formation of xanthone **9** in this reaction could be explored for the synthesis of substituted xanthones using appropriately substituted triketone **4**.

Low yield for aromatization of triketone **4** to the desired benzophenone **8** in the earlier approach prompted us to explore another route for the synthesis of benzophenone precursor **3** for balanol.

Hollinshead et al.[2b] reported two efficient syntheses of the benzophenone portion of balanol. The key step of this synthesis was the utilization of *ortho*-lithiation reactions to generate a carbinol, which was then oxidized to the benzophenone portion of balanol. We anticipated that coupling of aldehyde **12**, which can be easily prepared from 2,3-dimethylanisole, and commercially available 3,5-dimethoxytoluene under these conditions followed by oxidation would afford the desired benzophenone **2** easily and effectively. Accordingly, 3,5-dimethoxytoluene (**11**) was *ortho*-lithiated[10] using *n*-BuLi in the presence of TMEDA at 0 °C and coupled with the aldehyde **12** to afford alcohol **13** in 70% yield (Scheme 5). Further oxidation of the benzylic alcohol **13** to the desired intermediate **3** was carried out using MnO_2 in dichloromethane at room temperature in 90% yield. This compound showed spectroscopic data in good agreement with those reported by Adams et al.[2c]

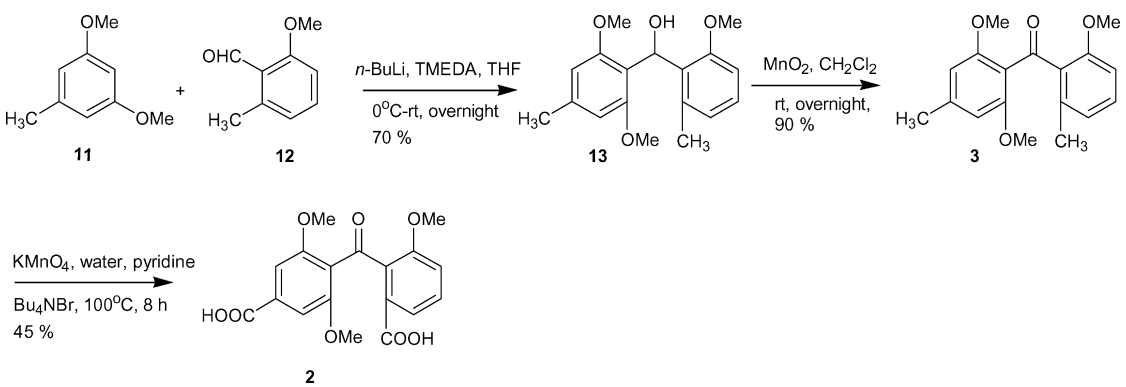
Oxidation of **3** to the dicarboxylic acid **2**, an important precursor for benzophenone portion of balanol (**1**), has been reported by Adams et al.[2c] Thus oxidation of the compound **3** using potassium permanganate and pyridine in the presence of phase transfer catalyst tetrabutylammonium bromide in water afforded the desired benzophenone precursor for balanol **2** in 45% yield.

Thus in conclusion we have achieved synthesis of an important intermediate **2** for balanol's benzophenone portion by using two different approaches. In the first approach we have developed a new method for the synthesis of benzophenone **3** starting with an alicyclic system followed by aromatization to give sterically hindered benzophenone **8** along with formation of xanthone **9**. This method would be useful for the synthesis of substituted xanthones. In another approach, an improved synthesis of dicarboxylic acid **3** has been achieved via a short and efficient route starting from commercially available chemicals in three steps using *ortho*-lithiation as the key step.

2. Experimental

2.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer in $CDCl_3$ containing TMS as an internal standard. Infrared spectra (ν_{max} in cm^{-1}) were



Scheme 5. Synthesis of benzophenone precursor **2**.

recorded as either nujol mull or in $CHCl_3$ on Perkin–Elmer Infrared 683 B or 160S FT-IR spectrometer with sodium chloride optics. All solvents and reagents were purified and dried by standard procedures. TLC was carried out on silica gel plates prepared by spreading the slurry (in CCl_4) and drying at room temperature. The plates were analyzed by keeping in iodine chamber. Column chromatography was performed on silica gel (60–120 mesh). Petroleum ether refers to the fraction boiling in the range of 60–80 °C.

2.1.1. 2-(2′-Methoxy-6′-methylbenzoyl)-5-methyl-1,3-cyclohexanedione (4). To a stirred solution of 2-methoxy-6-methylbenzoic acid (**5**) (498 mg, 3 mmol) in dry benzene (10 mL), thionyl chloride (0.43 mL, 6 mmol) and a drop of dimethylformamide were added. The resulting mixture was then refluxed for 6 h. After completion of the reaction (checked by paper chromatography), benzene was removed by distillation to leave the acid chloride as a brownish semisolid. IR (neat): 1800 cm^{-1} (acid chloride). Acid chloride obtained above was used for further reaction without purification. To a stirred solution of the acid chloride (554 mg, 3 mmol) and cyanotrimethylsilane (0.48 mL, 3.6 mmol) in dry dichloromethane (5 mL) under nitrogen atmosphere was added stannic chloride (0.2 mL) at room temperature. The stirring was continued for a further 2 h. After the reaction, the mixture was poured into ice-cold water (10 mL) and extracted with dichloromethane. The combined dichloromethane layer was washed with water (20 mL) followed by brine (20 mL) and dried over sodium sulphate. Evaporation of the solvent under reduced pressure afforded crude cyanide **6** as a brown oil (335 mg, 85%). IR ($CHCl_3$): 2150, 1680 cm^{-1}.

Triethylamine (1 mL) was added to a stirred solution of the above acyl cyanide **6** (472 mg, 2.7 mmol) and 5-methyl-cyclohexane-1,3-dione (**7**) (378 mg, 3 mmol) in dry acetonitrile (5 mL) at room temperature and stirring was continued overnight. After completion of the reaction, acetonitrile was evaporated and the mixture was poured into ice-cold 1 N HCl (10 mL). The reaction mixture was then extracted with dichloromethane and the combined organic layer was washed with water (20 mL) followed by brine (20 mL) and dried over sodium sulphate. Evaporation of the solvent and purification by column chromatography over silica gel (eluent 20% ethyl acetate in petroleum ether) afforded the triketone **4** (574 mg, 70%) as a pale yellow thick oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.12 (d, J=5.8 Hz, 3H), 2.10–2.88 (m including singlet for benzylic methyl at δ 2.17, 9H), 3.72 (s, 3H, $-OCH_3$), 6.65–6.90 (m, 2H, aromatic), 7.15–7.35 (m, 1H, aromatic). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.25, 21.05, 26.86, 41.09, 46.53, 55.97, 108.50, 114.79, 122.91, 130.04, 135.08, 155.96, 193.56 (C=O), 197.16 (C=O), 199.04 (C=O). Mass (*m*/*z*): 274 (M^+, 5), 259 (M−15, 8), 243 (90), 166 (50), 148 (100). Anal. calcd for $C_{16}H_{18}O_4$: C 70.06, H 6.60; found C 70.00, H 6.61.

2.2. Aromatization of triketone 4

The triketone **4** (274 mg, 1 mmol) was taken in glacial acetic acid (3 mL) in a round bottom flask attached with a short path condenser under argon atmosphere. To this were added mercuric acetate (956 mg, 3 mmol) and sodium acetate (246 mg, 3 mmol). The reaction mixture was heated at 120–125 °C so that the clear liquid turned to a voluminous precipitate that was again redissolved to give a brown coloured liquid with separation of mercury (2–3 h). The mixture was cooled and then 1 N HCl (5 mL) was added and allowed to boil for 30 min. Ethyl acetate was added after cooling and the mixture was filtered through a pad of Celite. The ethyl acetate layer was separated, washed with brine (10 mL), dried over sodium sulphate and concentrated in vacuo. TLC of the reaction mixture indicated the formation of two compounds. Evaporation of the solvent and purification by column chromatography over silica gel (eluent 10–20% ethyl acetate in petroleum ether) afforded the xanthone **9** (96 mg, 40%) and the required compound **8** (55 mg, 20%).

2.2.1. 2,6-Dihydroxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone (8). Pale yellow solid, mp 270–273 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.22 (s, 3H, Ar-CH_3), 2.25 (s, 3H, Ar-CH_3), 3.76 (s, 3H, −OMe), 6.26 (s, 2H, aromatic), 6.86 (d, J=8 Hz, 1H, aromatic), 6.92 (d, J=8 Hz, 1H, aromatic), 7.36 (t, J=8 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.71, 22.24, 56.02, 108.49, 109.45 (2C), 123.52 (2C), 128.59, 131.57 (2C), 136.02, 149.88 (2C), 155.68, 198.18 (C=O). Mass (*m*/*z*): 272 (M^+).

2.2.2. 1-Hydroxy-3,8-dimethyl-xanthen-9-one (9). Pale yellow solid, mp 146–149 °C (lit.[9] mp 149–151 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (s, 3H, Ar-CH_3), 2.89 (s, 3H, Ar-CH_3), 6.55 (s, 1H, aromatic), 6.65 (s, 1H, aromatic), 7.07 (d, J=8 Hz, 1H, aromatic), 7.25 (d, J=8 Hz, 1H, aromatic), 7.52 (t, J=8 Hz, 1H, aromatic), 12.86 (s, 1H, −OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.55, 23.30, 106.76, 107.50, 110.99, 115.79, 118.99, 126.67, 134.10, 141.66, 148.13, 155.36, 157.35, 161.61, 183.92 (C=O). Mass (*m*/*z*): 240 (M^+, 100), 222 (12), 211 (30).

2.3. 1-Methoxy-3,8-dimethyl-xanthen-9-one (10)

To the stirred solution of compound **9** (90 mg, 0.37 mmol) and potassium carbonate (76 mg, 0.55 mmol) in dry acetone (2 mL) was added dimethyl sulphate (52 mg, 0.40 mmol). The resulting reaction mixture was refluxed for 8 h. The acetone was then removed under reduced pressure and the residue was diluted with ice-cold water (5 mL) followed by extraction with ethyl acetate. The combined ethyl acetate layer was washed with water (5 mL), brine (5 mL) and dried over sodium sulphate. Evaporation of the solvent afforded the xanthone **10** as a white solid (81 mg, 85%), mp 169–171 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.45 (s, 3H, Ar-CH_3), 2.90 (s, 3H, Ar-CH_3), 4.01 (s, 3H, $-OCH_3$), 6.56 (s, 1H, aromatic), 6.81 (s, 1H, aromatic), 7.06 (d, J=7.2 Hz, 1H, aromatic), 7.24 (d, J=7.2 Hz, 1H, aromatic), 7.46 (t, J=7.2 Hz, 1H, aromatic). Mass (*m*/*z*): 254 (M^+, 100), 240 (70).

2.3.1. 2,6-Dimethoxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone (3). A mixture of the compound **8** (54 mg, 0.2 mmol) and dimethyl sulphate (0.05 mL, 0.55 mmol) and potassium carbonate (100 mg, 0.72 mmol) in dry acetone (5 mL) was refluxed for 6 h. The acetone was then evaporated under reduced pressure and the residue was diluted with water (5 mL), extracted with ethyl acetate and concentrated to give the benzophenone **3** as a white solid (54 mg, 90%), mp 133–135 °C (lit.[2c] mp 132–133 °C). IR

($CHCl_3$): 1675 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.32 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3), 3.58 (s, 3H, $-OCH_3$), 3.66 (s, 6H, 2× $-OCH_3$), 6.35 (s, 2H, aromatic), 6.68 (d, J=8 Hz, 1H, aromatic), 6.79 (d, J=8 Hz, 1H, aromatic), 7.17 (t, J=8 Hz, 1H, aromatic). Mass (*m/z*): 300 (M^+, 15), 269 (100). Anal. calcd for $C_{18}H_{20}O_4$: C 71.99, H 6.70; found C 72.23, H 6.90.

2.3.2. 1-{(2,6-Dimethoxy-4-methyl)phenyl}hydroxy-methyl-2′-methoxy-6′-methylbenzene (13). *n*-Butyllithium (1.5 mL of a 1.4 M solution in hexane, 2.1 mmol) was added dropwise to a stirred solution of 3,5-dimethoxytoluene (**11**) (304 mg, 2 mmol) and TMEDA (0.31 mL, 2.1 mmol) in anhydrous THF (5 mL) at room temperature under argon atmosphere. The mixture was stirred for 5 h whereupon it was added to a solution of the aldehyde **12** (345 mg, 2.3 mmol) in anhydrous THF (5 mL) at 0 °C. The resulting light yellow solution was stirred at 0 °C for 2 h and at room temperature overnight (the colour changes from light yellow to dark brown). The reaction mixture was then quenched with a saturated solution of ammonium chloride, ice-cold water (5 mL) was added and extracted with ethyl acetate. The ethyl acetate layer was washed with water (10 mL), brine (10 mL) and dried over sodium sulphate. Evaporation of the solvent and purification by column chromatography over silica gel (eluent 15% ethyl acetate in petroleum ether) afforded alcohol **13** (423 mg, 70%) as yellow solid; mp 125–128 °C. IR ($CHCl_3$): 1580, 3450 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.30 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 3.75 (s, 6H, 2× $-OCH_3$), 3.78 (s, 3H, $-OCH_3$), 5.80 (d, J=10 Hz, 1H, exchanges with D_2O, $-OH$), 6.37 (s, 2H, aromatic), 6.43 (d, J=8.2 Hz, 1H, aromatic), 6.75 (d, J=8.2 Hz, 1H, aromatic), 7.07 (t, J=8.2 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.96, 22.16, 56.16 (3C), 67.69, 105.99 (2C), 109.96, 117.13, 123.69, 127.36, 131.05, 137.61, 138.41, 158.40, 159.00 (2C). Mass (*m/z*): 302 (M^+, 25), 284 (85), 269 (60), 253 (40), 179 (100). Anal. calcd for $C_{18}H_{22}O_4$: C 71.50, H 7.32; found C 71.58, H 7.24.

2.3.3. 2,6-Dimethoxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone (3). Manganese dioxide (1.3 g, 15 mmol) was added in portions to a stirred solution of the alcohol **13** (302 mg, 1 mmol) in anhydrous dichloromethane at room temperature and mixture was stirred overnight. The catalyst was removed by filtration through Celite and the residue was washed with dichloromethane. The filtrate was evaporated to provide the benzophenone **3** (270 mg, 90%) as white crystals; mp 133–135 °C (lit.[2c] 132–133 °C). The spectral data were identical to the product obtained by methylation of compound **8**.

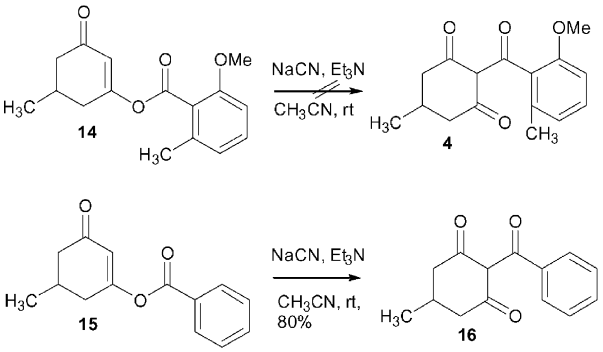
2.3.4. 4-Carboxy-2,6-dimethoxyphenyl 2′-carboxy-6′-methoxyphenyl ketone (2). To a stirred solution of potassium permanganate (284 mg, 1.8 mmol) in water (3 mL) and pyridine (1 mL), a solution of compound **3** (180 mg, 0.6 mmol) in pyridine (2 mL) was added followed by water (1 mL) and a pinch of tetrabutylammonium bromide. The mixture was then heated at 100 °C. After 1 h further quantities of potassium permanganate (in lots of 284 mg, 1.8 mmol) were added at intervals of 1 h until a total of 23.4 equiv. had been added. The reaction mixture was then filtered through Celite. The residue was washed with water (5 mL) and the filtrate was acidified with conc. HCl (5 mL). The aqueous solution was saturated with sodium chloride and extracted with ethyl acetate. The combined extracts were dried over sodium sulphate and evaporated to give dicarboxylic acid **2** as colourless solid (97 mg, 45%); mp 253–255 °C (lit.[2c] 253–256 °C). IR ($CHCl_3$): 1690, 3400 cm^{-1}. ^1H NMR (acetone d_6, 200 MHz): δ 3.76 (s, 3H, $-OCH_3$), 3.82 (s, 6H, 2× $-OCH_3$), 7.33 (d, J=8 Hz, 1H, aromatic), 7.38 (s, 2H, aromatic), 7.50 (d, J=8 Hz, 1H, aromatic), 7.57 (t, J=8 Hz, 1H, aromatic). Mass (*m/z*): 360 (M^+, 10), 342 (8), 315 (25), 299 (30), 285 (90), 209 (98), 195 (100). Anal. calcd for $C_{18}H_{16}O_8$: C 60.01, H 4.47; found C 60.07, H 4.60.

Acknowledgements

M.L.P. thanks CSIR, New Delhi for the award of senior research fellowship.

References and notes

1. Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452–6453.
2. (a) Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem. Eur. J.* **1995**, *1*, 454–456. (b) Hollinshead, S.; Nichols, J.; Wilson, J. *J. Org. Chem.* **1994**, *59*, 6703–6709. (c) Adams, C.; Fairway, S.; Hardy, C.; Hibbs, D.; Hursthouse, M.; Morley, A.; Sharp, B.; Vicker, N.; Warner, I. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2355–2362. (d) Miyabe, H.; Torieda, M.; Kiguchi, T.; Naito, T. *Synlett* **1997**, 580–582. (e) Denieul, M.-P.; Skrydstrup, T. *Tetrahedron Lett.* **1999**, *40*, 4901–4904. (f) Storm, J. P.; Andersson, C.-M. *Organic Lett.* **1999**, *1*, 1451–1453.
3. Lai, Y.-S.; Mendoza, J.; Jagdmann, G. E., Jr.; Menaldino, D.; Biggers, C.; Heerding, J.; Wilson, J.; Hall, S.; Jiang, J.; Janzen, W.; Ballas, L. *J. Med. Chem.* **1997**, *40*, 226–235.
4. Carter, S.; Wallace, T. *Synthesis* **1983**, 1000–1002.
5. Burger, U.; Montes, I. F. *Tetrahedron Lett.* **1996**, *37*, 1007–1010.
6. The cyanide catalyzed rearrangement of enol ester **14** under conditions reported by Burger and Montes[5] failed to give triketone **4**. However, when unsubstituted benzoate ester **15** was subjected to cyanide catalyzed rearrangement, it afforded triketone **16**



7. Mphahlele, M.; Modro, T. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2261–2264.
8. Oliver, J.; Wilzer, K.; Waters, R. *Synthesis* **1990**, 1117–1119.
9. Aghoramurthy, K.; Sarma, K. G.; Seshadri, T. R. *J. Sci. Ind. Res.* **1961**, *20B*, 437–440.
10. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1875–1886

Solid-phase peptide synthesis in water. Part 3: A water-soluble N-protecting group, 2-[phenyl(methyl)sulfonio]ethoxycarbonyl tetrafluoroborate, and its application to solid phase peptide synthesis in water☆

Keiko Hojo, Mitsuko Maeda and Koichi Kawasaki*

Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Ikawadani-cho, Nishi-ku, Kobe 651-2180, Japan

Received 26 September 2003; accepted 11 December 2003

Abstract—Chemical synthesis of peptides has been performed in various organic solvents, but the safe disposal of organic solvents is now an important environmental issue. Our aim is to be able to perform solid-phase peptide synthesis in water. For this, we have designed a new water-soluble N-protecting group, 2-[phenyl(methyl)sulfonio]ethoxycarbonyl (Pms), and have studied its introduction onto amino acids. Pms-amino acids were prepared by treating 2-(phenylthio)ethoxycarbonyl amino acids with methyl iodide in the presence of silver tetrafluoroborate. Because sulfur-containing amino acids, such as Met and Cys, were modified by the reaction, we designed a new reagent, 2-[phenyl(methyl)sulfonio]ethyl-4-nitrophenyl carbonate, to introduce the Pms group on amino acids. This reagent is a stable crystalline material and its introduction onto amino acids (including sulfur-containing amino acids) was successful. The solid-phase synthesis of Leu- and Met-enkephalin amides using Pms-protected amino acids was successfully achieved in water.

1. Introduction

Chemical synthesis of peptides has been performed in various organic solvents by both solid-phase and solution methods. Advances in HPLC accelerated the development of the solid-phase method, which in turn accelerated the development of combinatorial chemistry. The solid-phase method is now the principal method for peptide synthesis, but it requires a large amount of organic solvent. Because the safe disposal of organic solvent waste is an important environmental issue, a method for peptide synthesis in water using low toxic reagents would be desirable.

To perform the coupling reaction in water, protected amino acids that are soluble in water are needed. Various polar N-protecting groups that enhance solubility in polar solvents including water have been reported, including a methylsulfonylethoxycarbonyl group by Tesser and Balvert-Geers,[2] a 2-(triphenylphosphonio)ethoxycarbonyl group by Kunz,[3] and a 9-(2-sulfo)fluorenylmethoxycarbonyl group by Merrifield and Bach.[4] These protecting groups are removable under basic conditions by a β-elimination mechanism. Kunz also reported the use of 2-(methylthio)ethoxycarbonyl[5] and 2-(4-pyridyl)ethoxycarbonyl[6] as a two-step-protecting group (Zweistufen–Schutzgruppe), which is removable under mild basic conditions after its methylation or oxidation. In 1978, Kunz[7] reported preparation of a tripeptide, 2-[diphenyl(methyl)phosphonio]ethoxycarbonyl-Leu-Phe-Phe-O*t*Bu, by the solution method in water.

In previous papers, we reported the preparation of water-soluble active esters (4-trimethylammoniophenyl ester and sulfophenyl ester) and their application to peptide synthesis by the solution method.[8] Here, with the aim of achieving solid phase peptide synthesis in water, we have designed a new water-soluble N-protecting group. We designed the 2-[phenyl(methyl)sulfonio]ethoxycarbonyl tetrafluoroborate (Pms) group (Fig. 1) as a water-soluble and easily removable N-protecting group. Introduction of the Pms group onto amino acids with various reagents was studied, and Leu- and Met-enkephalin amides were synthesized by the solid-phase method in water to evaluate the utility of Pms-amino acids.

☆ See Ref. 1.

Keywords: 2-[Phenyl(methyl)sulfonio]ethoxycarbonyl group; Synthesis in water; Water-soluble protecting group; Peptide synthesis; Solid phase synthesis.

* Corresponding author. Tel.: +81-78-974-4794; fax: +81-78-974-5689; e-mail address: kawasaki@pharm.kobegakuin.ac.jp

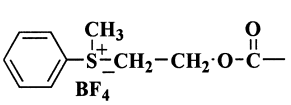


Figure 1. Structure of Pms group.

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.036

2. Results and discussion

Pms-amino acids were prepared according to Route 1, as shown in Scheme 1. 2-(Phenylthio)ethyl chloroformate **2** was prepared from 2-(phenylthio)ethanol **1** and phosgene (prepared from triphosgen[9]) in dichloromethane. Compound **2** was reacted with an amino acid to give 2-(phenylthio)ethoxycarbonyl (Pte) amino acid **3**, which was extracted by ethyl acetate from the reaction mixture and showed a single spot on TLC. Compound **3** was used without further purification and was treated with methyl iodide and silver tetrafluoroborate to give Pms-amino acid **4**. Pms-amino acids **4a–j** (Table 1) were synthesized by Route 1. These Pms-amino acids were obtained as amorphous materials and identified by time-of-flight mass spectrometry (Tof-MS) and NMR spectra (see Section 4). In the ^{1}H NMR spectra of Pms-amino acid **4**, the methyl proton adjacent to the sulfonium moiety showed a clear singlet at δ 3.30. The signals due to the methylene region of the Pms group appeared as highly complex multiplets at δ 4.00–4.40, which is much lower than this region in **3**.

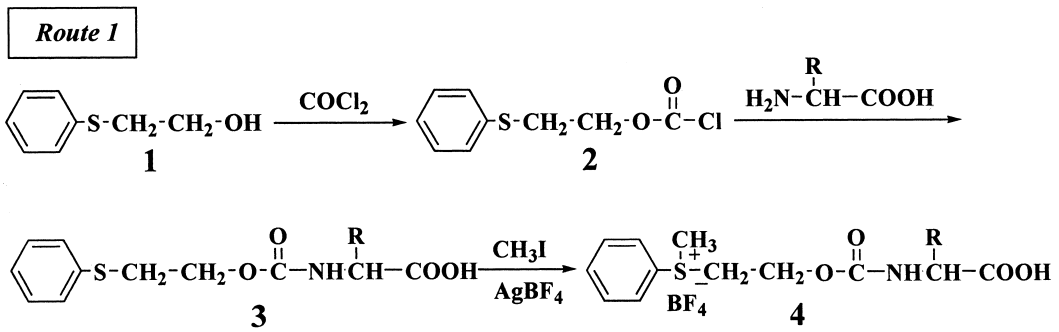
As expected, elimination of the Pms group from Pms-amino acids proceeded according to a base-promoted β-elimination mechanism. The electron-withdrawing sulfonium region of the Pms group renders hydrogens on the ethylene portion labile, and thus the hydrogens are susceptible to removal with weak bases to form the 2-[phenyl(methyl)-sulfonio]ethylene **5**. The mechanism of Pms elimination from a Pms-amino acid was studied by treating Pms-Phe-OH **4a** with a 5% aqueous solution of $NaHCO_3$ for 30 min. The reaction mixture was checked by HPLC and Tof-MS (Fig. 2). New peaks corresponding to 2-[phenyl(methyl)-sulfonio]ethylene **5** and its water adduct, 2-[phenyl (methyl)sulfonio]ethanol **6**, were detected by Tof-MS and HPLC, which verified that the Pms group was removed through a β-elimination mechanism.

Route 1 is an easy and efficient method by which to prepare Pms-amino acids; however, Pms sulfur-containing amino acids (Met and Cys) cannot be prepared, because the sulfurs of Met and Cys are converted to the onium salt by treatment with methyl iodide. In addition, it is not possible to prepare Pms-amino acids with an acid-labile group [such as *t*-butyl (*t*Bu) group, trityl (Trt) group and 2,2,5,7,8-pentamethyl-chroman-6-sulfonyl (Pmc) group] at their side chain could not be prepared by Route 1, because the acid labile group was cleaved by methylation procedure with methyl iodide and silver tetrafluoroborate. To overcome these limitations, we designed preparation Routes 2–5 using various *N*-Pms acylating agents, 2-[phenyl(methyl)sulfonio]ethyl chloroformate (Pms-Cl) **7**, 2-[phenyl(methyl)sulfonio]-ethoxycarbonylsuccinimide (Pms-OSu) **9**, 2-[phenyl(methyl) sulfonio]ethoxycarbonyl-5-norbornene-*endo*-2,3-dicarboximide (Pms-ONB) **11**, and 2-[phenyl(methyl)sulfonio]ethyl-4-nitrophenyl carbonate (Pms-ONp) **13**.[1b]

Pms-Cl **7** was prepared from phosgene[9] and the onium salt alcohol 2-[phenyl(methyl)sulfonio]ethanol **6**, which was converted from **1** by treatment with methyl iodide and silver tetrafluoroborate. The resulting Pms-Cl **7** was unstable even at low temperature, so it was used without purification to prepare Pms-amino acid (Route 2). Introduction of the Pms group onto Phe by using **7** at −10 °C in aqueous acetonitrile resulted in Pms-Phe-OH **4a** in low yield (27%) (Table 2). HPLC analysis of the reaction mixture showed major contaminant peaks of 2-[phenyl(methyl)sulfonio]ethanol **6** and its dehydrated product **5** (both might be derived from decomposition of **7**). These results indicate that **7** is so unstable that it decomposes readily before reaction in aqueous media such as aqueous acetonitrile. Thus, efficient Pms acylating agents with a more stable leaving group than chloride were required.

Because *N*-hydroxysuccinimide (HOSu) ester[10] is hydrophilic, has good reactivity and might be more stable than chloride, the preparation of Pms-OSu **9** was designed in two different ways, as shown in Scheme 2. In method A, the preparation of **9** from **7** and HOSu was attempted, but **9** could not be obtained because of the instability of **7**. In method B, **9** was prepared via Pte-OSu **8**, which was easily purified by column chromatography. Next, **8** was treated with methyl iodide and silver tetrafluoroborate to give **9**. Although crude **9** was obtained in over 90% purity, further purification was difficult because of its instability. The **9** was used without purification to react with Phe in aqueous acetonitrile to give Pms-Phe-OH **4a** in 68? yield. (Route 3).

Next, the *N*-hydroxy-5-norbornene-endo-2,3-dicarboximide (HONB)[11] carbonate (Pms-ONB) **11** (Fig. 3) was examined as an acylating agent (Route 4 in Scheme 3). Compound **11** was prepared via Pte-ONB **10** in the same way as the preparation of **9**. Compound **11** was obtained in over 90% purity but, like **9**, it could not be purified further without its decomposition. The crude **11** was reacted with Phe (Route 4) in aqueous acetonitrile to give Pms-Phe-OH **4a** in 66%



Scheme 1. Preparation of Pms-amino acid (Route 1).

Table 1. Analytical data for Pms amino acids

	Amino acid	MW.	Tof-Ms (*m/z*)	$[\alpha]_D^{24a}$	HPLC[b] room temperature (min)	Yield (%)
4a	Phe	360.45	360.4	−9.8	23.4	81[c]
4b	Gly	270.33	270.2	—	14.3[d]	73[c]
4c	Ala	284.35	284.4	−17.5	17.8[d]	63[c]
4d	Val	312.41	312.4	+5.7	16.7	73[c]
4e	Ile	326.43	326.5	+2.1	19.2	68[c]
4f	Leu	326.43	326.5	−9.8	20.4	72[c]
4g	Ser	300.35	300.3	+3.0	18.9[d]	56[c]
4h	Asp	328.36	328.6	+11.4	17.6	46[c]
4i	Pro	310.39	310.1	−19.2	20.1	69[c]
4j	Tyr	376.45	376.4	−2.3	12.2[d]	86[c]
14a	Met	344.47	344.3	−33.5	21.2	65[e]
14b	Cys(Acm)	387.50	387.6	−20.1	18.7	47[e]
14c	Cys(Trt)	558.73	558.9	+7.3	32.7[f]	68[e]
15a	Tyr(*t*Bu)	432.55	432.9	−3.8	24.7[f]	69,[e] 65[g]
15b	Ser(*t*Bu)	356.46	356.9	+2.1	22.8	61,[c] 86[g]
15c	Asp(O*t*Bu)	384.47	384.4	+12	24.6	49,[e] 50[g]
15d	Glu(O*t*Bu)	398.49	398.16	−5.8	28.1	62[e]
15e	Thr(*t*Bu)	370.48	370.3	+4.9	25.9	74[e]
15f	Asn(Trt)	569.69	570.0	−13.2	30.1[f]	69,[e] 61[g]
15g	Gln(Trt)	583.72	583.5	−9.2	30.7[f]	55,[e] 59[g]
15h	His(Trt)	592.23	592.3	−3.6	25.5[f]	72,[e] 42[g]
15i	Trp(Boc)	499.60	499.7	−4.3	36.5[f]	59,[e] 62[g]
15j	Arg(Pmc)	635.82	635.8	−7.3	40.9[f]	63,[e] 41[g]
15k	Lys(Boc)	441.53	442.3	−3.8	28.3	57,[e] 43[g]

[a] c=1.0, CH_3CN.
[b] Column, DAISOPAK SP-120-5-ODS-B (2.5×250 mm). Flow rate, 1 ml/min. Eluent, CH_3CN/H_2O containing 0.05% TFA. Gradient: 10/90–50/50 (40 min).
[c] Route 1.
[d] Gradient: 1/99–50/50 (49 min).
[e] Route 5.
[f] Gradient: 10/90–70/30 (30 min).
[g] Route 4.

Table 2. Yields and reaction times of Routes 1–5 for preparation of Pms-Phe-OH

	Route 1	Route 2, Pms-Cl	Route 3, Pms-Osu	Route 4, Pms-ONB	Route 5, Pms-Onp
Yield (%)	81	27	68	66	88
Reaction time	—	<5 min	4 h	4 h	>1 day

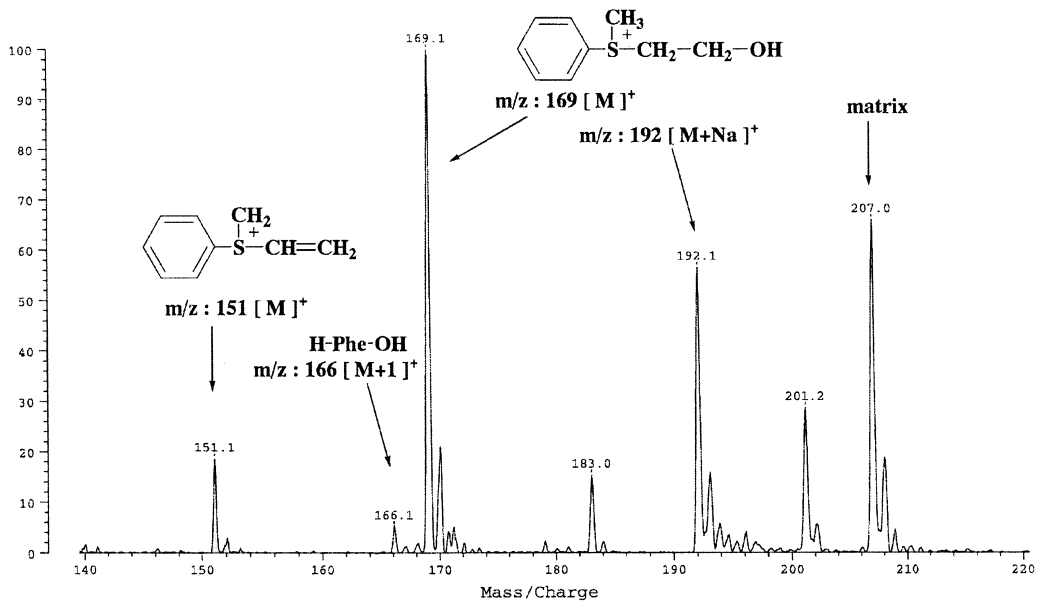
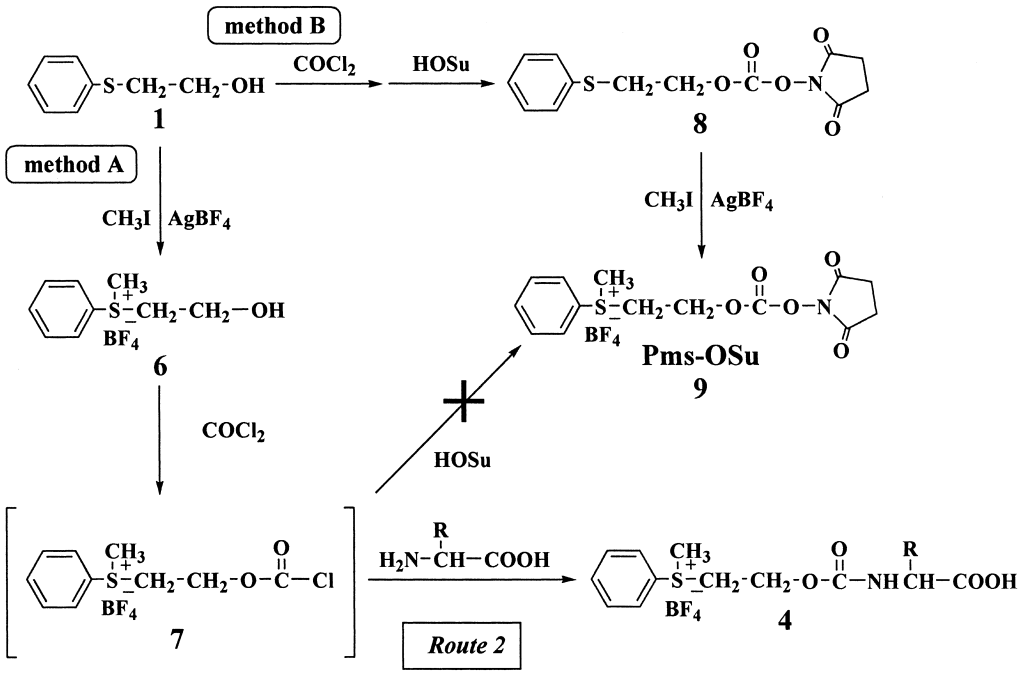


Figure 2. Tof-MS spectrum of the deprotection mixture of Pms-Phe-OH.



Scheme 2. Synthesis of Pms-OSu.

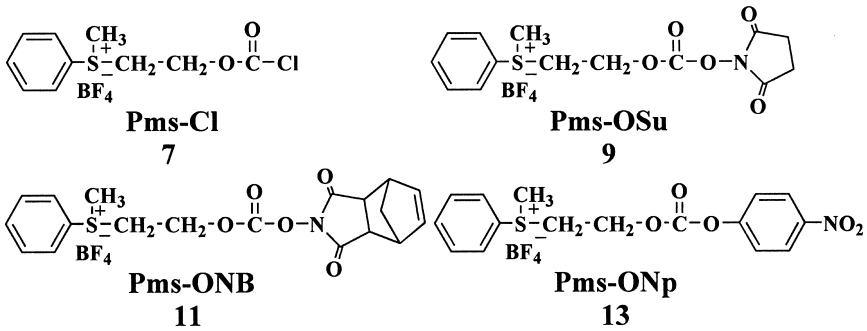
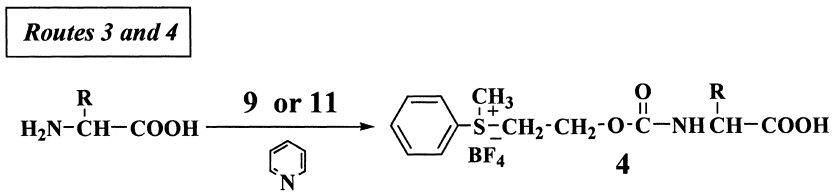


Figure 3. Reagents for preparing Pms-amino acids.

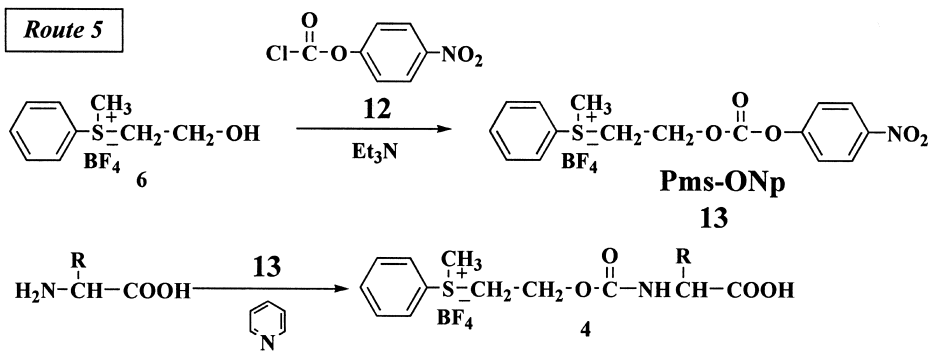


Scheme 3. Preparation of Pms-amino acid (Routes 3 and 4). Route 3: **9**, Pms-OSu. Route 4: **11**, Pms-ONB.

yield. Compound **11** has a high reactivity, similar to that of **9**.

Looking for a more stable acylating agent, we examined the Pms-4-nitrophenyl carbonate (Pms-ONp) **13** (Route 5 in Scheme 4). Compound **6** was reacted with 4-nitrophenyl chloroformate **12** at room temperature in acetonitrile to give **13** in 71% yield. Compound **13** was obtained as colorless crystal and could be stored for a few months in a refrigerator. Acylation of Phe with **13** in the presence of pyridine in aqueous acetonitrile (Route 5) was slow as compared to that with **9** and **11**. The acylation with **13** took more than 1 day at room temperature, while the acylation with **9** and **11** took 4 h at room temperature. However, the yield of **4a** was 88% by acylation with **13**, which was better than that obtained with either **9** (68%) or **11** (66%). Acylation of Phe with **7**, **9**, **11** and **13** (Routes 1–5) is summarized in Table 2. The three acylating agents **9**, **11** and **13**, but not **7**, gave a satisfactory coupling yield.

The procedure for introducing the Pms group onto sulfur-containing amino acids, such as Met, Cys(Trt) and



Scheme 4. Preparation of Pms-amino acid (Route 5).

Cys(Acm), was examined through Route 5. Pms-Met-OH **14a** was prepared using **13** in a mixture of aqueous 0.1% Triton X-100 solution and acetonitrile (1/1) in the presence of pyridine with a yield of 65% (Table 1). Pms-Cys(Acm)-OH **14b** and Pms-Cys(Trt)-OH **14c** were also prepared by the same procedure. The yields of **14b** and **14c** were 47 and 68%, respectively (Table 1). Whereas **14a** and **14b** were readily soluble, **14c** was sparingly soluble in water. Compound **14c** was soluble in aqueous organic solvents, such as 50% acetonitrile and 50% dimethylformamide (DMF), and also soluble in aqueous 5% Triton X-100 solution. Thus the hydrophobicity of the trityl group is greater than the hydrophilicity of the Pms group in **14c**.

Pms-amino acids with an acid-labile group [such as *t*-butyl (*t*Bu) group, trityl (Trt) group and 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) group] at their side chain could not be prepared by Route 1, **11** and **13** were used to prepare these Pms-amino acids (Schemes 3 and 4) and results were passable as shown in Table 1.

To evaluate Pms-amino acids, Leu-enkephalin amide (H-Tyr-Gly-Gly-Phe-Leu-NH_2) was synthesized by the solid-phase method in water. Before the synthesis, removal of the Pms group by various base treatments was examined using Pms-Phe-Leu-TentaGel resin. Because removal of the Pms group on Phe-Leu-TentaGel resin with base was slower than that on Phe itself, the Pms-Phe-Leu-TentaGel resin was preferentially used as the test compound. Hydrophobic or bulky sequence like Phe-Leu may have influence on removal of the Pms group in water. The resin was treated with various base solutions to remove the Pms group in water and then reacted with 9-fluorenylmethoxycarbonyl glycine (Fmoc-Gly-OH) with diisopropylcarbodiimide/1-hydroxybenzotriazole[12] in DMF until the resin gave a negative result in the Kaiser test[13] (ninhydrin test). The resulting Fmoc-Gly-Phe-Leu-TentaGel resin was treated with 20% piperidine/DMF to remove the Fmoc group. The resin was hydrolyzed, and the amino acids in the acid hydrolysate were analyzed. Removal of the Pms group from the Pms-Phe-Leu-TentaGel resin was calculated from the amino acid ratio of Gly and Phe in the acid hydrolysate. The Pms group was removable with mild bases, such as an aqueous solution of either 5% $NaHCO_3$ or 5% Na_2CO_3, as shown in Table 3. Treatment with an aqueous solution of 5% $NaHCO_3$ for 30 min was not strong enough to remove the Pms group completely, but a double treatment (30 min×2) gave a satisfactory result.

An important factor to consider in solid-phase synthesis is the swelling ability of the resin. To perform solid-phase synthesis in water, a resin is required to swell in water. However, the most common core resin, polystyrene resin, does not swell in polar solvents such as methanol and water. A poly(ethylene glycol)-grafted polystyrene resin, TentaGel resin,[14] has been reported as a resin designed to have increased swelling ability in both polar and non-polar solvents. This TentaGel resin was used for synthesis of Leu-enkephalin amide using a water-soluble carbodiimide [WSCD, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride[15]] as a coupling reagent in water. Because the introduction of Phe onto the resin and the subsequent coupling reaction for peptide synthesis was slow under the above conditions, an aqueous solution of 0.2% Triton X-100 was used as a solvent to increase the swelling ability of the resin and to increase the solubility of reactants. Furthermore, HOSu, which is soluble in water, was used as an additive to accelerate the coupling reactions.[16] Although the coupling reactions were accelerated under this condition, β-Ala was found in the acid hydrolysate of the synthetic Leu-enkephalin amide. Pure synthetic Leu-enkephalin amide could not be separated from by-products which contained β-Ala by HPLC. The amino acid ratios in the acid hydrolysate

Table 3. Deprotection studies on the Pms-Phe-Leu-TentaGel resin

Entry	Reagents	Time (min)	Yield (%)
1	5% $NaHCO_3/H_2O$	30	80
2	5% $NaHCO_3/H_2O$	30	96
3	0.01 mol/l $NaOH/H_2O$	1, 1, 1	100
4	0.01 mol/l $NaOH/H_2O$	3, 3, 3	100
5	0.005 mol/l $NaOH/EtOH-H_2O$ (1/1)	3, 3, 3	86
6	0.001 mol/l $NaOH/EtOH-H_2O$ (1/1)	3, 3, 3	77
7	2.5% $NaHCO_3/EtOH-H_2O$ (1/1)	3, 3, 3	81
8	2.5% $NaHCO_3/EtOH-H_2O$ (1/1)	5, 5, 5	100
9	2.5% $Na_2CO_3/EtOH-H_2O$ (1/1)	3, 3, 3	75
10	2.5% $Na_2CO_3/EtOH-H_2O$ (1/1)	5, 5, 5	100

Table 4. Synthetic protocol for the solid phase peptide synthesis in water

Step	Reagents	Time
1	H_2O	3 min×2
2	Aq. 5.0% $NaHCO_3$ or aq. 0.01 mol/l NaOH	30 min×2 or 3 min×2
3	H_2O	3 min×2
4	Aq. 0.2% Triton X	3 min×3
5	Pms-amino acid, WSCD, HONB, in aq. 0.2% Triton X	3 h
6	Aq. 0.2% Triton X	3 min×3

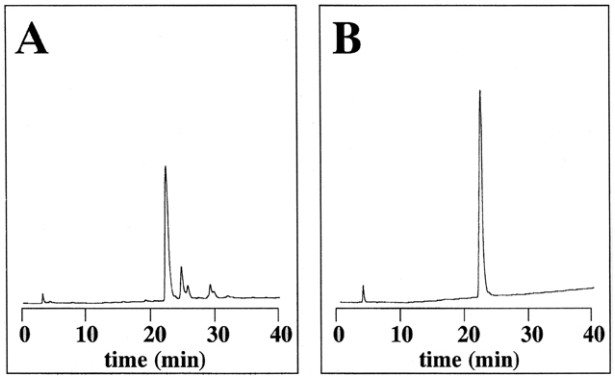


Figure 4. HPLC profiles of synthetic Leu-enkephalin amide. (A) Preparative HPLC Column, DAISOPAK SP-120-5-ODS-B (20×250 mm). Flow rate, 10 ml/min. Eluent, CH_3CN/H_2O containing 0.05% TFA. Gradient: 10/90–50/50 (40 min). (B) Analytical HPLC of the purified sample. Column, DAISOPAK SP-120-5-ODS-B (2.5×250 mm). Flow rate, 1 ml/min. Eluent, CH_3CN/H_2O containing 0.05% TFA. Gradient: 10/90–50/50 (40 min).

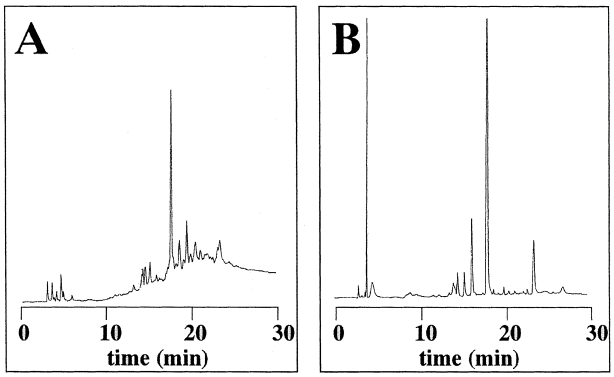


Figure 5. HPLC profile of synthetic crude Met-enkephalin amide. (A) Crude Met-enkephalin amide prepared on CLEAR resin. (B) Crude Met-enkephalin amide prepared on TentaGel resin. Column, DAISOPAK SP-120-5-ODS-B (2.5×250 mm). Flow rate, 1 ml/min. Eluent, CH_3CN/H_2O containing 0.05% TFA. Gradient: 10/90–50/50 (20 min).

of synthetic crude Leu-enkephalin separated by HPLC was; Tyr 0.82, Gly 1.92, Phe 1.06, β-Ala 4.69. Formation of β-Ala has been reported as a product of a side reaction (Lossen rearrangement reaction[17]) when HOSu is used as an additive. We did not examine this side reaction (Lossen rearrangement reaction) further, but it might occur more easily in aqueous media than in non-polar solvents.

Next, HONB,[11] which is also water-soluble, was used as an additive instead of HOSu and Leu-enkephalin was synthesized according to the protocol shown in Table 4. The Pms group was removed by treatment with an aqueous solution of 5% $NaHCO_3$ for 30 min, or by two lots of this treatment for Phe, because removal of the Pms group on Phe was slower than that on other Pms-amino acids, as described above. The synthetic Pms-Tyr-Gly-Gly-Phe-Leu-TentaGel resin was treated with an aqueous solution of 5% $NaHCO_3$ and then treated with trifluoroacetic acid (TFA) to cleave the peptide from the resin. The product was purified by HPLC on an ODS column. The HPLC profile of the synthetic Leu-enkephalin amide is shown in Figure 4. The retention time of the synthetic Leu-enkephalin amide was identical to that of Leu-enkephalin amide prepared by the Fmoc-based solid-phase method using organic solvents. The total yield calculated from the amino group content of the starting TentaGel resin was 61%.

In addition to the TentaGel resin, a cross-linked ethoxylate acrylate resin (CLEAR resin which has been also reported[18] to swell not only with organic solvents but also with water) was examined as a solid support for synthesis in water. Met-enkephalin amide was synthesized using CLEAR resin in water according to the same procedure (shown in Table 4) except for the base treatment. The Pms group was removed by two 3-min treatments with an aqueous solution of 0.01 mol/l NaOH, which yielded a more rapid and complete removal of the Pms group. The synthetic H-Tyr-Gly-Gly-Phe-Met-CLEAR-resin was treated with TFA to cleave the peptide from the resin, and then purified by HPLC on an ODS column. The crude HPLC profile of the synthetic Met-enkephalin amide is shown in Figure 5A. The yield calculated from amino group content of the starting CLEAR resin was 29%. Minor peaks were observed before and after the main peak of Met-enkephalin amide, which corresponded to that of Met-enkephalin amide prepared by the Fmoc-based solid-phase method using organic solvents. The early peaks contained deletion peptides (such as H-Tyr-Gly-Phe-Met-NH_2 and H-Gly-Gly-Phe-Met-NH_2) and oxidized peptide (such as H-Tyr-Gly-Gly-Phe-Met(O)-NH_2 and H-Tyr-Gly-Phe-Met(O)-NH_2), whereas the later peaks contained non-peptide compounds that probably derived from the used resin.

For comparison, Met-enkephalin amide was also synthesized in water using TentaGel resin, and the HPLC profile of the crude product is shown in Figure 5B. Again, minor peaks of deletion peptides (such as H-Tyr-Gly-Phe-Met-NH_2 and H-Gly-Gly-Phe-Met-NH_2) and oxidized peptides (such as H-Tyr-Gly-Gly-Phe-Met(O)-NH_2 and H-Tyr-Gly-Phe-Met(O)-NH_2) were observed before and after the main peak of Met-enkephalin amide. The yield of Met-enkephalin amide prepared on TentaGel resin was 32% and was just a little better than that of Met-enkephalin amide prepared on CLEAR resin (29%).

The yield of Leu-enkephalin and Met-enkephalin using TentaGel resin was 61 and 32%, respectively. Synthetic protocol for preparation of these 2 enkephalins was different (deprotection with 5% $NaHCO_3$ and 0.01 mol/l NaOH), but this difference might be mainly derived from properties of Leu and Met. The synthesis of both Met and Leu-enkephalin amide was performed under atmosphere (i.e. not under inert gas). Oxidation of Met during synthesis was observed in the profile of HPLC and might cause the lower yield.

3. Conclusion

Pms, a new water-soluble N-protecting group with high base lability and high polarity, has been developed and its application to solid-phase peptide synthesis in water has been evaluated. The derivative Pms-ONp was designed to prepare all types of Pms-amino acids including sulfur-containing amino acids. This reagent is a crystalline compound and can be kept stable in a refrigerator for a few months. Leu- and Met-enkephalin amides were successfully synthesized by the solid-phase method in

water using Pms-amino acids and, as such, this study may be the first to report the successful synthesis of peptides by the solid-phase method in water. In addition, we evaluated the potential of CLEAR resin and TentaGel resin for solid-phase synthesis in water. Future work should aim to develop a new resin that swells more than these two resins.

4. Experimental

Optical rotations were determined with an automatic polarimeter, model DIP-360 (Japan Spectroscopic Co.) Tof-Mass spectra were measured with a KRATOS-MALDI mass spectrometer (SiMADZU Co.) and ESI-Mass spectra were measured with a Waters ZQ2000 mass spectrometer. Reversed phase HPLC was performed using a Waters model 600 equipment with a DISOPAK column and gradient system of acetonitrile/water containing 0.05% TFA. Open column chromatography was performed on Silica gel 60 (BW-127ZH, Fuji Silicia Chemical Co.). Solvent system for ascending thin-layer chromatography on Silica gel G (type 60, Merck) is indicated as follows: R_f^1=$CHCl_3$–MeOH–H_2O (8/3/1, lower phase). ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer. 2-(phenylthio)ethanol and 4-nitorphenyl chloroformate were purchased from Tokyo Kasei Co., Ltd, Japan. HOSu, HONB and amino acid derivatives were purchased from Watanabe Chemical Industries, Ltd, Japan.

4.1. Route 1. Preparation of Pte-amino acids

4.1.1. Pte-Phe-OH (3a). To a solution of 2-(phenylthio)ethanol (4.4 ml, 30 mmol) and triphosgen (2.96 g, 10 mmol) in tetrahydrofuran (100 ml), Et_3N (4.18 ml, 30 mmol) in tetrahydrofuran (40 ml) was added dropwise at room temperature and the reaction mixture was stirred for 1.5 h. The mixture was filtered and the solvent was evaporated. The residue was dissolved in acetonitrile (30 ml) and added to a solution of Phe (4.95 g, 30 mmol) and Et_3N (4.18 ml, 30 mmol) in a mixture of acetonitrile and H_2O (1/1, 100 ml) at 0 °C. The mixture was stirred for 2 h at room temperature keeping its pH at 8 by addition of Et_3N and the solvent was removed in vacuo. The residue was dissolved in AcOEt and extracted with aqueous 5% $NaHCO_3$. The aqueous layer was acidified with 1.0 mol/l HCl, and the resulting precipitate was extracted with AcOEt. The extract was washed with saturated NaCl solution and concentrated in vacuo to leave an oily material. Yield 890 mg, 86%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.41 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 2H), 7.25 (m, 5H), 7.21 (t, J=7.4 Hz, 1H), 4.43 (dd, J=5, 14 Hz, 1H), 4.18 (t, J=6.9 Hz, 2H) 3.18 (t, J=6.9 Hz, 3H), 3.05 (m, 1H), 2.92 (m, 1H). R_f^1 0.60.

The following Pte-amino acids were prepared according to the procedure described above.

4.1.2. Pte-Gly-OH (3b). Colorless solid. Yield 78%. ^{1}H NMR (400 MHz, D_2O) δ 7.39 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 2H), 7.20 (t, J=7.4 Hz, 1H), 4.17 (t, J=6.9 Hz, 2H), 3.76 (s, 2H), 3.16 (t, J=6.9 Hz, 3H). R_f^1 0.20.

4.1.3. Pte-Ala-OH (3c). Oily material. Yield 70% ^{1}H NMR (400 MHz, CD_3CN) δ 7.40 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 2H), 7.20 (t, J=7.4 Hz, 1H), 4.30 (s, 1H), 4.17 (t, J=6.9 Hz, 2H), 3.16 (t, J=6.9 Hz, 2H), 1.37 (d, J=7.2 Hz, 3H) R_f^1 0.28.

4.1.4. Pte-Val-OH (3d). Oily material. Yield 82%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.39 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 2H), 7.19 (t, J=7.4 Hz, 1H), 4.19 (t, J=6.9 Hz, 2H), 4.06 (s, 1H), 3.16 (t, J=6.9 Hz, 3H), 2.16 (m, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.94 (d, J=6.8 Hz, 3H). R_f^1 0.51.

4.1.5. Pte-Ile-OH (3e). Oily material. Yield 76%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.39 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 2H), 7.19 (t, J=7.4 Hz, 1H), 4.18 (t, J=6.9 Hz, 2H), 4.08 (s, 1H), 3.16 (t, J=6.9 Hz, 2H), 1.87 (m, 1H), 1.52 (m, 1H), 1.25 (m, 1H), 0.95 (d, J=7.0 Hz, 3H), 0.92 (t, J=7.0 Hz, 3H). R_f^1 0.57.

4.1.6. Pte-Leu-OH (3f). Oily material. Yield 80%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.40 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 2H), 7.19 (t, J=7.4 Hz, 1H), 4.17 (t, J=6.9 Hz, 2H), 4.16 (s, 1H), 3.16 (t, J=6.9 Hz, 2H), 1.72 (m, 1H), 1.59 (m, 1H), 0.95 (d, J=5.3 Hz, 3H), 0.93 (t, J=5.3 Hz, 3H). R_f^1 0.56.

4.1.7. Pte-Ser-OH (3g). Oily material. Yield 65%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.40 (d, J=7.3 Hz, 2H), 7.28 (t, J=7.3 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 4.53 (br s, 1H), 4.20 (t, J=6.9 Hz, 2H), 3.89 (dd-like, 1H), 3.83 (dd-like, 1H), 3.16 (t, J=6.9 Hz, 2H). R_f^1 0.24.

4.1.8. Pte-Asp-OH (3h). Colorless solid. Yield 66%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.41 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 2H), 7.21 (t, J=7.4 Hz, 1H), 4.50 (s, 1H), 4.19 (t, J=6.9 Hz, 2H), 3.16 (t, J=6.9 Hz, 2H), 2.75 (m, 1H). R_f^1 0.12.

4.1.9. Pte-Pro-OH (3i). Colorless solid. Yield 78%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.39 (d, J=7.3 Hz, 2H), 7.30 (t, J=7.3 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 4.24 (m, 1H), 4.20 (m, 2H), 3.47 (m, 1H), 3.20 (m, 1H), 3.18 (t, J=6.9 Hz, 2H) 2.43 (m, 1H), 2.00 (m, 1H), 1.89 (m, 2H). R_f^1 0.51.

4.1.10. Pte-Tyr-OH (3j). Oily material. Yield 68%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.40 (d, J=7.4 Hz, 2H), 7.32 (t, J=7.4 Hz, 2H), 7.22 (t, J=7.4 Hz, 1H), 7.07 (d, J=8.6 Hz, 2H), 6.74 (d, J=8.6 Hz, 2H), 4.32 (m, 1H), 4.14 (t, J=6.9 Hz, 2H), 3.16 (t, J=6.9 Hz, 2H), 3.13 (m, 1H), 2.83 (m, 1H). R_f^1 0.34.

4.2. Preparation of Pms-amino acids

Yields, MS spectra data and rotations of synthetic Pms-amino acids are shown in Table 1.

4.2.1. Pms-Phe-OH (4a). To an acetonitrile (15 ml) solution of **3a** (400 mg, 1.15 mmol) and silver tetrafluoroborate (389 mg, 2.0 mmol), methyl iodide (0.8 ml, 2.0 mmol) was added and the mixture was refluxed overnight at 40 °C. After cooling, the yellow precipitates were filtered off and the solvent was removed in vacuo. The residue was purified by preparative HPLC. Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.95 (d, J=7.5 Hz, 2H), 7.81 (t, J=7.3 Hz, 1H), 7.71 (dd, J=7.5, 7.3 Hz, 2H), 7.25 (m, 5H), 4.45 (m, 1H), 4.39 (m, 1H), 4.20 (m, 1H), 3.99

(m, 2H), 3.34 (s, 3H), 3.23 (m, 1H), 2.91 (m, 1H). Anal. Calcd for $C_{19}H_{22}BF_4NO_4S\cdot 1/3TFA$: C, 48.68; H, 4.64; N, 2.89. Found: C, 48.62; H, 4.32; N, 2.89.

The following Pms-amino acids were prepared according to the procedure described above (Route 1).

4.2.2. Pms-Gly-OH (4b). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.95 (d, J=7.8 Hz, 2H), 7.82 (t, J=7.2 Hz, 1H), 7.72 (dd, J=7.8, 7.2 Hz, 2H), 4.52 (dt, J=13, 5.1 Hz, 1H), 4.32 (dt, J=13, 5.1 Hz, 1H), 4.00 (t, J=5.1 Hz, 2H), 3.74 (s, 1H), 3.31 (s, 3H). Anal. Calcd for $C_{12}H_{16}BF_4NO_4S\cdot 1/2TFA$: C, 37.70; H, 4.02; N, 3.38. Found: C, 37.92; H, 4.23; N, 3.36.

4.2.3. Pms-Ala-OH (4c). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J=7.8 Hz, 2H), 7.84 (t, J=7.2 Hz, 1H), 7.74 (dd, J=7.8, 7.2 Hz, 2H), 4.50 (m, 1H), 4.34 (m, 1H), 4.30 (m, 1H), 4.01 (m, 2H), 3.31 (s, 3H), 1.31 (m, 3H). Anal. Calcd for $C_{13}H_{18}BF_4NO_4S\cdot 1/2TFA\cdot CH_3CN$: C, 40.15; H, 4.49; N, 4.68. Found: C, 40.41; H, 4.22; N, 4.29.

4.2.4. Pms-Val-OH (4d). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.97 (d, J=7.5 Hz, 2H), 7.84 (t, J=7.3 Hz, 1H), 7.75 (dd, J=7.5, 7.3 Hz, 2H), 4.51 (m, 1H), 4.34 (m, 1H), 4.01 (t, J=5.2 Hz, 2H), 3.92 (m, 1H), 3.33 (s, 3H), 2.11 (m, 1H), 0.93 (d-like, 3H), 0.92 (d-like, 3H). Anal. Calcd for $C_{15}H_{22}NBF_4O_4S\cdot 2/5TFA$: C, 40.59; H, 4.69; N, 3.68. Found: C, 40.97; H, 4.21; N, 3.56.

4.2.5. Pms-Ile-OH (4e). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J=7.5 Hz, 2H), 7.83 (t, J=7.3 Hz, 1H), 7.73 (dd, J=7.5, 7.3 Hz, 2H), 4.54 (m, 1H), 4.34 (m, 1H), 4.01 (br s, 2H), 3.95 (m, 1H), 3.31 (s, 3H), 1.82 (m, 1H), 1.38 (dquint., J=14.0, 7.0 Hz, 1H), 1.17 (dquint., J=14.0, 7.0 Hz, 1H), 0.90 (3H, d, J=7.0 Hz, βC–CH_3), 0.89 (3H, t, J=7.0 Hz, γC–CH_3). Anal. Calcd for $C_{16}H_{24}BF_4NO_4S\cdot 2/3TFA$: C, 39.06; H, 4.40; N, 2.40. Found: C, 38.67; H, 4.20; N, 2.22.

4.2.6. Pms-Leu-OH (4f). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J=7.5 Hz, 2H), 7.83 (t, J=7.3 Hz, 1H), 7.73 (dd, J=7.5, 7.3 Hz, 2H), 4.54 (m, 1H), 4.34 (m, 1H), 4.01 (br s, 2H), 3.98 (m, 1H), 3.31 (s, 3H), 1.62 (m, 1H), 1.48 (m, 2H), 0.93 (d, J=5.5 Hz, 3H), 0.90 (t, J=5.5 Hz, 3H). Anal. Calcd for $C_{16}H_{24}BF_4NO_4S\cdot TFA$: C, 41.51; H, 4.68; N, 2.59. Found: C, 41.00; H, 4.78; N, 2.66.

4.2.7. Pms-Ser-OH (4g). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J=7.5 Hz, 2H), 7.83 (t, J=7.3 Hz, 1H), 7.73 (dd, J=7.5, 7.3 Hz, 2H), 4.54 (m, 1H), 4.34 (m, 1H), 4.22 (m, 1H), 4.01 (br s, 2H), 3.31 (s, 3H), 3.94 (m, 1H), 3.86 (m, 1H). Anal. Calcd for $C_{13}H_{18}BF_4NO_5S$: C, 40.33; H, 4.69; N, 3.62. Found: C41.01; H, 4.36; N, 3.59.

4.2.8. Pms-Asp-OH (4h). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J=7.7 Hz, 2H), 7.83 (t, J=7.5 Hz, 1H), 7.73 (dd, J=7.7, 7.5 Hz, 2H), 4.50 (m, 1H), 4.47 (m, 1H), 4.34 (m, 1H), 4.01 (br s, 2H), 3.32 (s, 3H), 2.78 (m, 2H). Anal. Calcd for $C_{14}H_{18}BF_4NO_6S\cdot 2/3TFA\cdot 1/2CH_3CN$: C, 35.94; H, 3.42; N, 3.40. Found: C, 35.63; H, 3.49; N, 3.46.

4.2.9. Pms-Pro-OH (4i). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J=7.5 Hz, 2H), 7.84 (t, J=7.3 Hz, 1H), 7.75 (dd, J=7.5, 7.3 Hz, 2H), 4.57 (m, 1H), 4.38 (m, 1H), 4.16 (m, 1H), 4.00 (m, 2H), 3.30 (s, 3H), 3.47–3.01 (m, 2H), 2.22 (m, 1H), 2.00 (m, 1H), 1.84 (m, 2H). Anal. Calcd for $C_{15}H_{20}BF_4NO_4S\cdot TFA$: C, 39.86; H, 4.33; N, 2.73. Found: C, 39.54; H, 4.10; N, 2.74.

4.2.10. Pms-Tyr-OH (4j). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.96 (d, J=7.5 Hz, 2H), 7.80 (t, J=7.3 Hz, 1H), 7.71 (dd, J=7.5, 7.3 Hz, 2H), 7.07 (d, J=8.4 Hz, 2H), 6.73 (d, J=8.4 Hz, 2H), 4.41 (m, 1H), 4.34 (m, 1H), 4.19 (m, 1H), 3.97 (m, 1H), 3.88 (m, 1H), 3.31 (s, 3H), 3.13 (m, 1H), 2.81 (m, 1H). Anal. Calcd for $C_{19}H_{22}BF_4NO_5S\cdot 1/2TFA$: C, 46.17; H, 4.36; N, 2.69. Found: C, 46.43; H, 4.52; N, 2.60.

4.3. Route 2

4.3.1. 2-[Phenyl(methyl)sulfonio]ethanol (6). To a solution of 2-(phenylthio)ethanol (1.34 ml, 10 mmol) and silver tetrafluoroborate (2.32 g, 12 mmol) in acetonitrile (60 ml), methyl iodide (1.24 ml, 20 mmol) was added and the mixture was stirred overnight at 40 °C. After cooling, the yellow precipitate was filtered off and the solvent was evaporated in vacuo. The residue was flash chromatographed on silica gel, eluted with CH_3Cl–MeOH–H_2O (8/3/1, lower phase). The collected fractions were combined and concentrated in vacuo to leave a colorless oil. Yield 2.26 g, 88%. ^{1}H NMR (400 MHz, D_2O) δ 7.97 (dd-like, J=8.0, 1.7 Hz, 2H), 7.84 (tt, J=7.5, 1.7 Hz, 1H), 7.75 (dd-like, J=8.0, 7.5 Hz, 2H), 4.03 (m, 1H), 4.34 (m, 1H), 3.90 (m, 2H), 3.82 (s, 3H), 3.78 (m, 1H), 3.31 (s, 3H). Tof-MS m/z 169.14 (M^+, $C_9H_{13}OS$ requires 169.26).

4.3.2. Pms-Phe-OH (4a). To a suspension of **6** (513 mg, 2.0 mmol) and triphosgen (394 mg, 1.33 mmol) in dichloromethane (30 ml), Et_3N (0.56 ml, 4.0 mmol) in dichloromethane (10 ml) was added dropwise at −10 °C, and the mixture was stirred at −10 °C for 1.5 h. After evaporation of the solvent in vacuo at 10 °C, the residue was dissolved in acetonitrile (15 ml), and this solution was added to a solution of Phe (330 mg, 2.0 mmol) and Et_3N (0.35 ml, 2.5 mmol) in a mixture of acetonitrile and water (1/1, 50 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and the solvent was removed in vacuo. The product was purified by preparative HPLC. Yield: 241 mg. The product was identified with Pms-Phe-OH prepared through Route 1 by NMR and Mass spectra.

4.4. Route 3

4.4.1. Pte-OSu (8). To a solution of 2-(phenylthio)ethanol (1.34 ml, 10 mmol) and triphosgen (1.96 g, 6.6 mmol) in tetrahydrofuran (40 ml), Et_3N (2.79 ml, 20 mmol) in tetrahydrofuran (15 ml) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and the mixture was filtered. The solvent was evaporated off in vacuo and the residue was dissolved in acetonitrile (15 ml). The solution was added to a solution of HOSu (1.15 g, 10 mmol) and Et_3N (1.39 ml, 10 mmol) in a mixture of acetonitrile (30 ml) at 0 °C, and the mixture was stirred at room temperature for 3 h keeping its pH at 8. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel, using hexane–ethyl acetate

(2/1) as an eluate. The collected fractions were combined and concentrated in vacuo to leave a colorless oil. Yield. 2.12 g, 72%. ^{1}H NMR (400 MHz) δ (CD_3CN): 7.42 (d, J=7.1 Hz, 2H), 7.34 (dd, J=7.3, 7.1 Hz, 2H), 7.25 (dd, J=7.3 Hz, 1H), 4.43 (t, J=6.5 Hz, 2H), 3.27 (t, J=6.5 Hz, 2H), 2.76 (s, 4H). ESI-MS m/z 313.2[$(M+NH_4)^+$, $C_{13}H_{13}NO_5{\cdot}NH_4$ requires 313.3]. R_f [(hexane–ethyl acetate (2/1)] 0.38.

4.4.2. Pms-OSu (9). To an acetonitrile solution (15 ml) of **8** (295 mg, 1.0 mmol) and silver tetrafluoroborate (232 mg, 1.2 mmol), methyl iodide (1.24 ml, 20 mmol) was added, and the mixture was stirred overnight at 40 °C. After cooling, the yellow precipitate was filtered off and the solvent was removed in vacuo to leave a colorless oil. Yield 384 mg, 97%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.96 (d, J=7.5 Hz, 2H), 7.84 (t, J=7.4 Hz, 1H), 7.74 (dd, J=7.5, 7.4 Hz, 2H), 4.73 (m, 1H), 4.49 (m, 1H), 4.04 (m, 1H), 3.93 (m, 1H), 3.29 (s, 3H), 2.76 (s, 4H). Tof-MS m/z 310.41 (M^+, $C_{14}H_{16}NO_5S$ requires 310.35).

4.4.3. Pms-Phe-OH (4a). To a solution of Phe (83 mg, 0.5 mmol) and pyridine (40.43 ml, 0.5 mmol) in aqueous 0.1% Triton X-100 solution–acetonitrile (1/1, 20 ml), **9** [prepared from **8** (146 mg, 0.5 mmol)] in acetonitrile (10 ml) was added at 0 °C, and the mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo, the product was purified by preparative HPLC to give a colorless oil. The product was identified with Pms-Phe-OH prepared through Route 1 by NMR and Mass spectra.

4.5. Route 4

4.5.1. Pte-ONB (10). To a solution of 2-(phenylthio)ethanol (1.34 ml, 10 mmol) and triphosgen (1.96 g, 6.6 mmol) in tetrahydrofuran (40 ml), Et_3N (2.79 ml, 20 mmol) in tetrahydrofuran (15 ml) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and filtered. The solvent was removed filtrate in vacuo and the residue was dissolved in acetonitrile (15 ml) and added to a solution of HONB (1.79 g, 10 mmol) and Et_3N (1.39 ml, 10 mmol) in acetonitrile (30 ml) at 0 °C. The reaction mixture was stirred at room temperature for 3 h keeping it pH at 8. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel using hexane–ethyl acetate (2/1) as an eluate. The collected fractions were combined and concentrated in vacuo to leave a colorless solid. Yield 2.72 g, 76%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.42 (d, J=7.1 Hz, 2H), 7.34 (dd, J=7.3, 7.1 Hz, 2H), 7.25 (dd, J=7.3 Hz, 1H), 6.18 (s, 2H), 4.36 (t, J=6.5 Hz, 2H), 3.45 (d-like, 2H), 3.30 (d-like, 2H) 3.18 (t, J=6.5 Hz, 2H), 1.78 (dd, J=9.0, 1.6 Hz, 1H), 1.52 (dd, J=9.0, 1.6 Hz, 1H). ESI-MS m/z 377.3 [$(M+NH_4)^+$, $C_{18}H_{17}NO_5S{\cdot}NH_4$ requires 377.3]. R_f [hexane–AcOEt (2/1)] 0.45.

4.5.2. Pms-ONB (11). To a solution of **10** (359 mg, 1.0 mmol) and silver tetrafluoroborate (232 mg, 1.2 mmol) in acetonitrile (15 ml), methyl iodide (1.24 ml, 20 mmol) was added and the mixture was stirred overnight at 40 °C. The resulting yellow precipitate was removed by filtration and the solvent was evaporated in vacuo to leave a colorless oil. Yield 450 mg, 98%. ^{1}H NMR (400 MHz, CD_3CN) δ 7.96 (d, J=7.5 Hz, 2H), 7.84 (t, J=7.4 Hz, 1H), 7.74 (dd, J=7.5, 7.4 Hz, 2H), 6.18 (s, 2H), 4.73 (m, 1H), 4.49 (m, 1H), 4.04 (m, 1H), 3.93 (m, 1H), 3.45 (d-like, 2H), 3.30 (d-like, 2H), 3.29 (s, 3H), 1.78 (dd, J=9.0, 1.6 Hz, 1H), 1.52 (dd, J=9.0, 1.6 Hz, 1H). Tof-MS m/z 374.5 (M^+, $C_{19}H_{20}NO_5S$ requires 374.43).

4.5.3. Pms-Phe-OH (4a). To a solution of Phe (83 mg, 0.5 mmol) and pyridine (40.43 ml, 0.5 mmol) in aqueous 0.1% Triton X-100 solution–acetonitrile (1/1, 20 ml), **11** [prepared from **10** (179 mg, 0.5 mmol)] in acetonitrile (10 ml) was added at 0 °C and the mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo and the residue was purified by preparative HPLC to give a colorless oil. The product was identified with Pms-Phe-OH prepared through Route 1 by NMR and Mass spectra.

The following Pms-amino acids were prepared from Pms-ONB and a corresponding amino acid according to the procedure described above (Route 4).

4.5.4. Pms-Tyr(*t*Bu)-OH (15a). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J=7.6 Hz, 2H), 7.80 (t, J=7.6 Hz, 1H), 7.69 (dd, J=7.5, 7.3 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 6.93 (d, J=8.4 Hz, 2H), 4.35 (m, 1H), 4.34 (m, 1H), 4.13 (m, 1H), 3.80 (m, 1H), 3.72 (m, 1H), 3.18 (s, 3H), 3.14 (m, 1H), 2.89 (m, 1H), 1.29 (s, 9H). Anal. Calcd for $C_{23}H_{30}BF_4NO_5S{\cdot}$TFA: C, 47.41; H, 4.93; N, 2.21. Found: C, 47.85; H, 4.54; N, 2.40.

4.5.5. Pms-Ser(*t*Bu)-OH (15b). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.96 (d, J=7.7 Hz, 2H), 7.84 (t, J=7.4 Hz, 1H), 7.72 (dd, J=7.7, 7.4 Hz, 2H), 4.54 (m, 1H), 4.34 (m, 1H), 4.28 (br m, 1H), 4.02 (br s, 2H), 3.77 (m, 1H), 3.68 (m, 1H), 3.32 (s, 3H), 1.19 (s, 9H). Anal. Calcd for $C_{17}H_{26}BF_4NO_5S{\cdot}1/2$TFA: C, 43.21; H, 5.34; N, 2.80. Found: C, 43.35; H, 4.86; N, 2.66.

4.5.6. Pms-Asp(O*t*Bu)-OH (15c). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.96 (d, J=7.7 Hz, 2H), 7.84 (t, J=7.5 Hz, 1H), 7.72 (dd, J=7.7, 7.5 Hz, 2H), 4.53 (m, 1H), 4.45 (br m, 1H), 4.34 (m, 1H), 4.01 (br s, 2H), 3.32 (s, 3H), 2.79 (d, J=5.5 Hz, 2H) 1.44 (s, 9H). Anal. Calcd for $C_{18}H_{26}BF_4NO_6S{\cdot}1/2$TFA: C, 43.20; H, 5.06; N, 2.65. Found: C, 43.89; H, 4.78; N, 2.65.

4.5.7. Pms-Glu(O*t*Bu)-OH (15d). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.92 (d, J=7.7 Hz, 2H), 7.82 (t, J=7.5 Hz, 1H), 7.72 (dd, J=7.7, 7.5 Hz, 2H), 4.43 (m, 1H), 4.21 (m, 1H), 4.11 (m, 1H), 3.87 (m, 1H), 3.78 (m, 1H), 3.23 (s, 3H), 2.29 (m, 2H), 2.07 (m, 1H), 1.86 (m, 1H), 1.43 (s, 9H). Anal. Calcd for $C_{19}H_{28}BF_4NO_6S{\cdot}1/5$TFA: C, 45.86; H, 5.59; N, 2.76. Found: C, 46.15; H, 5.38; N, 2.63.

4.5.8. Pms-Thr(*t*Bu)-OH (15e). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.96 (d, J=7.7 Hz, 2H), 7.84 (t, J=7.5 Hz, 1H), 7.72 (dd, J=7.7, 7.5 Hz, 2H), 4.46 (m, 1H), 4.23 (m, 1H), 4.22 (br m, 1H), 4.22 (m, 2H), 4.07 (m, 1H), 3.89 (m, 1H), 3.80 (m, 1H), 3.23 (s, 3H), 1.16 (s, 12H). Anal. Calcd for $C_{18}H_{28}BF_4NO_5S{\cdot}1/2$TFA: C, 44.37; H, 5.59; N, 2.72. Found: C, 44.35; H, 5.36; N, 2.51.

4.5.9. Pms-Asn(Trt)-OH (15f). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J=7.7 Hz, 2H), 7.74 (t, J=7.5 Hz, 1H), 7.72 (br s, 1H), 7.63 (dd, J=7.7, 7.5 Hz, 2H), 7.24 (m, 15H), 4.37 (m, 1H), 4.18 (m, 1H), 4.05 (m, 1H), 3.82 (m, 1H), 3.74 (m, 1H), 3.20 (s, 3H), 2.88 (m, 1H), 2.77 (m, 1H). Anal. Calcd for $C_{34}H_{35}BF_4N_2O_5S$·1/3TFA·CH_3CN: C, 57.38; H, 4.95; N, 5.63. Found: C, 57.74; H, 4.91; N, 6.08.

4.5.10. Pms-Gln(Trt)-OH (15g). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J=7.7 Hz, 2H), 7.77 (t, J=7.5 Hz, 1H), 7.66 (dd, J=7.7, 7.5 Hz, 2H), 7.54 (br s, 1H), 7.25 (m, 15H), 4.37 (m, 1H), 4.18 (m, 1H), 4.05 (m, 1H), 3.79 (m, 1H), 3.74 (m, 1H), 3.20 (s, 3H), 2.42 (m, 2H), 2.11 (m, 1H), 1.81 (m, 1H). Anal. Calcd for $C_{33}H_{33}BF_4N_2O_5S$·2/3TFA·1/3CH_3CN·1/3H_2O: C, 56.43; H, 4.91; N, 4.27. Found: C, 56.26; H, 4.67; N, 4.42.

4.5.11. Pms-His(Trt)-OH (15h). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 8.34 (s, 1H), 7.87 (d, J=7.7 Hz, 2H), 7.79 (m, 1H), 7.70 (dd, J=7.7, 7.5 Hz, 2H), 7.43–7.15 (m, 15H), 7.08 (s, 1H), 4.44 (m, 1H), 4.34 (m, 1H), 4.18 (m, 1H), 3.87 (m, 1H), 3.75 (m, 1H), 3.29 (d, J=14.7, 4.3 Hz), 3.21 (s, 3H), 3.06 (dd, J=14.7, 9.0 Hz, 1H). Anal. Calcd for $C_{35}H_{34}BF_4N_3O_4S$·2TFA·H_2O: C, 50.61; H, 4.14; N, 4.54. Found: C, 50.47; H, 3.82; N, 4.41.

4.5.12. Pms-Trp(Boc)-OH (15i). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 8.09 (d, J=8.3 Hz, 1H), 7.84–7.72 (m, 3H), 7.67–7.61 (m, 3H), 7.53 (d-like, 1H), 7.33 (t-like, 1H), 7.26 (t-like, 1H), 4.49 (m, 1H), 4.35 (m, 1H), 4.14 (m, 1H), 3.78 (m, 1H), 3.71 (m, 1H), 3.32 (m, 1H), 3.15 (m, 1H), 3.12 (m, 1H), 1.63 (s, 9H). Anal. Calcd for $C_{26}H_{31}BF_4N_2O_6S$·1/2TFA: C, 51.29; H, 5.06; N, 4.49. Found: C, 51.24; H, 5.04; N, 4.21.

4.5.13. Pms-Arg(Pmc)-OH (15j). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.92 (d, J=7.7 Hz, 2H), 7.78 (t, J=7.1 Hz, 1H), 7.70 (dd, J=7.7, 7.1 Hz, 2H), 6.21 (br s, 1H), 4.43 (m, 1H), 4.21 (m, 1H), 4.04 (br m, 1H), 3.87 (m, 1H), 3.79 (m, 1H), 3.59 (m, 1H), 3.23 (s, 3H), 2.65 (t, J=6.8 Hz, 2H), 2.52 (s, 3H), 1.82 (t, J=6.8 Hz, 2H), 1.78 (br m, 1H), 1.62 (br m, 1H), 1.58 (br m, 2H), 1.30 (s, 6H). Anal. Calcd for $C_{30}H_{43}BF_4N_4O_7S_2$·TFA·1/2$CH_3CN$: C, 46.24; H, 5.35; N, 7.35. Found: C, 46.49; H, 5.17; N, 7.30.

4.5.14. Pms-Lys(Boc)-OH (15k). Amorphous material. ^{1}H NMR (400 MHz, CD_3CN) δ 7.93 (d, J=7.7 Hz, 2H), 7.82 (t, J=7.5 Hz, 1H), 7.72 (dd, J=7.7, 7.5 Hz, 2H), 4.43 (m, 1H), 4.21 (m, 1H), 4.06 (m, 1H), 3.81 (m, 1H), 3.24 (s, 3H), 3.02 (t-like, 2H), 1.79 (br m, 2H), 1.67 (br m, 2H), 1.39 (s, 11H). Anal. Calcd for $C_{21}H_{33}BF_4N_2O_6S$·4/3TFA: C, 42.11; H, 5.13; N, 4.71. Found: C, 42.11; H, 5.13; N, 4.75.

4.6. Route 5

4.6.1. Pms-ONp (13). To a solution of **6** (256 mg, 1.0 mmol) in acetonitrile (15 ml, a solution of 4-nitrophenyl chloroformate (402 mg, 2.0 mmol) in acetonitrile (10 ml) and a solution of Et_3N (279 μl, 2.0 mmol) in acetonitrile (10 ml) were added alternately at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and concentrated in vacuo, and the residue was washed with water and crystallized from ether-hexane to give colorless crystal. Yield 298 mg, 71%. Mp 140 °C (decomp.). ^{1}H NMR (400 MHz, D_2O) δ 8.31 (dd, J=9.4 Hz, 2H), 7.98 (d, J=7.5 Hz, 2H), 7.86 (t, J=7.3 Hz, 1H), 7.75 (dd, J=7.5, 7.3 Hz, 2H), 7.43 (dd, J=9.4 Hz, 2H), 4.67 (m, 1H), 4.45 (m, 1H), 4.04 (m, 1H), 3.95 (m, 1H), 3.29 (s, 3H). Tof-MS m/z 334.5 (M^+, $C_{16}H_{16}NO_5S$ requires 334.37). Anal. Calcd for $C_{16}H_{16}BF_4NO_5S$: C, 45.63; H, 3.83; N, 3.33. Found: C, 45.68; H, 3.91; N, 3.39.

4.6.2. Pms-Phe-OH (4a). To a solution of Phe (83 mg, 0.5 mmol) and pyridine (40.4 μl, 0.5 mmol) in aqueous 0.1% Triton X-100 solution–acetonitrile (1/1, 20 ml), **13** (211 mg, 0.5 mmol) in acetonitrile (10 ml) was added at 0 °C, and the mixture was stirred at room temperature for 4 h. After removal of the solvent, the residue was dissolved in water and washed with AcOEt. The aqueous layer was concentrated in vacuo and the residue was purified by preparative HPLC to give a colorless oil. The product was identified by NMR and Mass spectra with Pms-Phe-OH prepared through Route 1.

The following Pms-amino acids were prepared from Pms-ONp and a corresponding amino acid according to the procedure described above.

4.6.3. Pms-Met-OH (14a). Amorphous material. ^{1}H NMR (400 MHz, D_2O) δ 7.98 (d, J=7.7 Hz, 2H), 7.85 (t, J=7.5 Hz, 1H), 7.75 (dd, J=7.7, 7.5 Hz, 2H), 4.52 (m, 1H), 4.34 (m, 1H), 4.34 (m, 1H), 4.01 (m, 2H), 3.32 (s, 3H), 2.91 (m, 2H), 2.21 (s, 3H). Anal. Calcd $C_{14}H_{19}BF_4NO_4S_2$·TFA: C, 37.44; H, 4.25; N, 2.57. Found: C, 37.71; H, 4.43; N, 2.60.

4.6.4. Pms-Cys(Acm)-OH (14b). Amorphous powder. ^{1}H NMR (400 MHz, D_2O) δ 7.94 (d, J=7.5 Hz, 2H), 7.80 (t, J=7.5 Hz, 1H), 7.72 (t, J=7.5 Hz, 2H), 4.52 (m, 1H), 4.34 (m, 1H), 4.34, 4.27 (ABq, J=14 Hz, 1H), 4.31 (m, 1H), 4.00 (m, 2H), 3.31 (s, 3H), 2.92 (dd, J=14, 4.7 Hz, 1H), 2.88 (dd, J=14, 4.7 Hz, 1H), 1.99 (s, 3H). Anal. Calcd for $C_{16}H_{23}BF_4N_2O_5S_2$·1/2TFA: C, 38.43; H, 4.46; N, 5.27. Found: C, 38.39; H, 4.21; N, 4.98.

4.6.5. Pms-Cys(Trt)-OH (14c). Amorphous powder. ^{1}H NMR (400 MHz, CD_2CN) δ 7.87 (d, J=7.5 Hz, 2H), 7.75 (t, J=7.5 Hz, 1H), 7.65 (t, J=7.5 Hz, 2H), 7.26–7.39 (m, 15H), 4.40 (m, 1H), 20 (m, 1H), 3.94 (m, 1H), 3.85 (br d, J=14 Hz, 1H), 3.75 (br d, J=14 Hz, 1H), 3.19 (s, 3H), 2.64 (dd like, 1H), 2.54 (dd like, 1H) Anal. Calcd for $C_{32}H_{32}BF_4NO_4S_2$: C, 59.54; H, 5.00; N, 2.17. Found: C, 59.79; H, 4.77; N, 1.88.

4.7. Examination in deprotection rate of Pms group on Pms-Phe-Leu-TentaGel resin with various bases in water

Pms-Phe-OH (89.4 mg, 0.2 mmol) and the H-Leu-TentaGel resin (192 mg, 50 μmol) was reacted with WSCD (38.2 mg, 0.2 mmol) in a presence of HONB (35.8 mg, 0.2 mmol) in aqueous 0.2% Triton X solution. The resulting Pms-Phe-Leu-TentaGel resin was washed with DMF and dichloromethane and dried in vacuo. Yield 210 mg (98%). Amino acid ratio in an acid hydrolysate: Phe 1.00, Leu 0.96. The resin (10 mg each) was treated with various base solutions

(aqueous 5% $NaHCO_3$, aqueous 0.01 mol/l NaOH, 0.005 mol/l NaOH in 50% aqueous EtOH, 2.5% $NaHCO_3$ in aqueous 50% EtOH, 2.5% Na_2CO_3 in aqueous 50% EtOH). After base treatment, the resin was washed with H_2O and DMF. Then Fmoc-Gly-OH (3.0 mg, 10 μmol) was coupled on the resin with diisopropylcarbodiimide (1.6 μl, 10 μmol) and HOBt (1.4 mg, 10 μmol) in DMF until the resin gave negative Kaiser test. The resulting resin was washed with DMF and dichloromethane, and dried in vacuo. After removal of the Fmoc group with 20% piperidine/DMF, the resin was hydrolyzed and Gly, Phe and Leu contents in the hydrolysate were analyzed. Each deprotection yield was calculated from the amino acid ratio of Gly and Leu. Results are summarized in Table 3.

4.7.1. Synthesis of Leu-enkephalin amide on TentaGel resin in water. The Fmoc-Rink amide-TentaGel resin (100 mg, 25 μmol) was swelled with dichloromethane and DMF, and then Fmoc group on the resin was removed by treatment with 20% piperidine/DMF. After washed with DMF and H_2O, the resin was swelled with aqueous 0.2% Triton X-100 solution. The synthesis was carried out according to the protocol shown in Table 4. Pms-Leu-OH 41.3 mg (0.1 mmol), Pms-Phe-OH 44.7 mg (0.1 mmol), Pms-Gly-OH 35.7 mg (0.1 mmol), and Pms-Tyr-OH 46.3 mg (0.1 mmol) were coupled in turn with WSCD 19.1 mg (MW: 191.7, 0.1 mmol) and HONB 17.9 mg (0.1 mmol). Deprotection was carried out with an aqueous solution of 5.0% $NaHCO_3$. After completion of the synthetic reaction, the peptide resin (H-Tyr-Gly-Gly-Phe-Leu-TentaGel resin) was washed with H_2O, DMF and dichloromethane, and dried in vacuo. Yield: 107.5 mg, 97%. The whole resin was treated with TFA–thioanisole–ethanedithiol (94/3/3, 15 ml) for 2 h at room temperature. The resin was removed by filtration and the TFA was removed in vacuo to leave a yellowish oil. The residue was dissolved in water, washed with ether, and lyophilized. The crude product was purified by HPLC to give an amorphous powder. Yield (based on amino group content of the resin): Yield 10.3 mg, 61%. $[\alpha]_D^{24}=+8.2°$ (c=0.2, H_2O). Tof-MS m/z 555.0 [$(M+1)^+$, $C_{28}H_{39}N_6O_6$ requires 555.64]. Amino acid ratios in an acid hydrolysate: Tyr 0.99, Gly 2.00, Phe 0.96, Leu 0.98 (average recovery: 83%).

4.7.2. Synthesis of Leu-enkepharin amide by the Fmoc strategy. The Fmoc group on the Rinkamide resin (100 mg, 60 μmol) was removed by treatment with 20% piperidine/DMF. Synthesis was carried out according to a general Fmoc strategy[19] Fmoc-Leu-OH 63.6 mg (0.18 mmol), Fmoc-Phe-OH 69.7 mg (0.18 mmol), Fmoc-Gly-OH 53.5 mg (0.18 mmol), and Fmoc-Tyr(*t*Bu)-OH 82.7 mg (0.18 mmol) were coupled in turn by diisopropylcarbodiimide (0.18 mmol) and 1-hydroxybenzotriazole 24.3 mg (0.18 mmol). Deprotection of Fmoc group was carried out with 20% piperidine/DMF. After completion of the synthetic reaction, the peptide resin (H-Tyr(*t*Bu)-Gly-Gly-Phe-Leu-Rinkamide resin was washed with DMF and dichloromethane, and dried in vacuo. Yield 123 mg, 99%. The whole resin was treated with TFA–thioanisole–ethanedithiol (94/3/3, 15 ml) for 2 h at room temperature. The resin was filtered off, and the TFA was removed in vacuo to leave a yellowish oil. The residue was dissolved in water, washed with ether, and lyophilized. The crude product was purified by HPLC to give a white amorphous powder. Yield 34 mg (based on amino group content of the resin), 86%. $[\alpha]_D^{24}=+9.0°$ (c=0.2, H_2O). Tof-MS m/z 555.3 [$(M+1)^+$, $C_{28}H_{39}N_6O_6$ requires 555.64]. Amino acid ratios in an acid hydrolysate: Tyr 0.97, Gly 2.00, Phe 0.98, Leu, 1.01 (average recovery 97%).

4.7.3. Synthesis of Met-enkephalin amide on CLEAR resin in water. CLEAR resin (86 mg, 25 μmol) was swelled with dichloromethane and DMF and Fmoc group on the resin was removed with 20% piperidine/DMF. After washing with DMF and H_2O, the resin was swelled with aqueous 0.2% Triton X-100 solution. Synthetic reaction was carried out according to the protocol shown in Table 4. Pms-Met-OH 41.3 mg (0.1 mmol), Pms-Phe-OH 44.7 mg (0.1 mmol), Pms-Gly-OH 35.7 mg (0.1 mmol), and Pms-Tyr-OH 46.3 mg (0.1 mmol) were coupled in turn by WSCD 19.1 mg (0.1 mmol) and HONB 17.9 mg (0.1 mmol). Deprotection was carried out by treatment (twice) with an aqueous solution of 0.01 mol/l NaOH for 3 min. After completion of the synthetic reaction, the peptide resin (H-Tyr-Gly-Gly-Phe-Met-CLEAR resin) was washed with H_2O, DMF and dichloromethane, and dried in vacuo. Yield 92 mg, 86%. The whole resin was treated with TFA–thioanisole–ethanedithiol (94/3/3, 15 ml) for 2 h at room temperature. The resin was filtered off and the TFA was removed in vacuo to leave a yellowish oil. The residue was dissolved in water, washed with ether, and lyophilized. The crude product was purified by HPLC to give an amorphous powder. Yield (based on amino group content of the resin): Yield 4.9 mg, 29%. $[\alpha]_D^{24}=+6.7°$ (c=0.8, 20% CH_3CN/H_2O). Tof-MS m/z: 573.7 [$(M+1)^+$, $C_{27}H_{36}N_6O_6S$ requires 573.68]. Amino acid ratios in an acid hydrolysate: Tyr 1.01, Gly 2.00, Phe 0.93; Met 0.95 (average recovery: 94%).

4.7.4. Synthesis of Met-enkephalin amide on TentaGel resin in water. Performed in the same manner as described in Section 4.7.1. Yield (based on amino group content of the resin): yield 5.8 mg, 32% (amorphous powder). $[\alpha]_D^{24}=+7.1°$ (c=0.8, 20% CH_3CN/H_2O). Tof-MS m/z 573.4 [$(M+1)^+$, $C_{27}H_{36}N_6O_6S$ requires 573.68]. Amino acid ratios in an acid hydrolysate: Tyr 0.99, Gly 2.00, Phe 0.96, Met 0.98 (average recovery 92%).

References and notes

1. Preliminary communications were reported on: (a) Hojo, K.; Maeda, M.; Kawasaki, K. *J. Pept. Sci.* **2001**, *7*, 615–618. (b) Hojo, K.; Maeda, M.; Takahara, Y.; Yamamoto, S.; Kawasaki, K. *Tetrahedron Lett.* **2003**, *44*, 2849–2851.
2. Tesser, G. I.; Balvert-Geers, I. C. *Int. J. Pept. Protein Res.* **1975**, *7*, 295–305.
3. Kunz, H. *Chem. Ber.* **1976**, *109*, 2670–2683.
4. Merrifield, R. B.; Bach, A. F. *J. Org. Chem.* **1978**, *43*, 4808–4816.
5. Kunz, H. *Chem. Ber.* **1976**, *109*, 3693–3706.
6. Kunz, H.; Birnbach, S. *Tetrahedron Lett.* **1984**, *25*, 3567–3570.
7. Kunz, H. *Angew. Chem. Int.* **1978**, *17*, 67–68.
8. (a) Tsuji, T.; Okusada, S.; Maeda, M.; Kawasaki, K. *Chem.*

Pharm. Bull. **1986**, *34*, 2214–2217. (b) Kawasaki, K.; Tsuji, T.; Maeda, M.; Matsumoto, T.; Hirase, K. *Chem. Pharm. Bull.* **1987**, *35*, 1044–1048.
9. (a) Eckert, H.; Forster, B. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 894–895. (b) Livius, C.; Pietro, D.; Alfonso, N.; Vitomir, S. *Synthesis* **1996**, 553–576.
10. Raquet, A. *Can. J. Chem.* **1976**, *54*, 733–733. Raquet, A. *Can. J. Chem.* **1982**, *60*, 976–980.
11. (a) Fujino, M.; Kobayashi, S.; Obayashi, M.; Fukuda, T.; Shinagawa, S.; Nishimura, O. *Chem. Pharm. Bull.* **1974**, *22*, 1857–1863. (b) Kitada, C.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 585–590.
12. Konig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788–798.
13. Kaiser, E.; Colescitti, R. L.; Bossinger, C. D.; Cook, R. I. *Anal. Biochem.* **1970**, *34*, 595–598.
14. (a) Bayer, E.; Rapp, W. In *Chemistry of peptides and proteins*; Volter, E., Bayer, E., Ovchinikov, Y. A., Ivanov, V. T., Eds.; Walter de Gryyter: Berlin, 1986; pp 3–8. (b) Bayer, E. *Angew. Chem. Int, Ed. Engl.* **1991**, *30*, 113–129.
15. Sheehan, J. C.; Cruickshank, P. A.; Boshrt, G. L. *J. Org. Chem.* **1983**, *26*, 2525–2528.
16. (a) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839–1842. (b) Zimmerman, J. E.; Anderson, G. W. *J. Am. Chem. Soc.* **1967**, *89*, 7151–7152.
17. Gross, H.; Bilk, L. *Tetrahedron* **1968**, *24*, 6935–6939.
18. Kempe, M.; Barany, G. *J. Am. Chem. Soc.* **1996**, *118*, 7083–7093.
19. Fields, G.; Noble, R. L. *Int. J. Pept. Protein Res.* **1990**, *35*, 161–214.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 1887–1893

Synthesis of [3,4,8-$^{13}C_3$]daidzein

Mark F. Oldfield, Lirong Chen and Nigel P. Botting*

School of Chemistry, University of St Andrews, St Andrews, Fife KY16 9ST, Scotland, UK

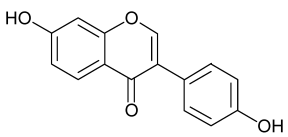
Received 22 September 2003; revised 24 November 2003; accepted 11 December 2003

Abstract—The biological effects of the soy isoflavones have attracted considerable interest in recent years leading to numerous studies on dietary intake and epidemiology. Such studies require accurate and reproducible analytical methods. Herein we report the first synthesis of a multiply ^{13}C-labelled daidzein derivative, [3,4,8-$^{13}C_3$]daidzein, which has been employed as an internal standard in LC-MS and GC-MS analysis. The synthesis includes an improved three-step method for the synthesis of [2-^{13}C]resorcinol as one building block.

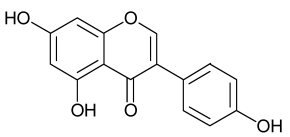
1. Introduction

The impact of phytoestrogens on human health is currently a subject of major interest.[1,2] In particular the soy isoflavones, including daidzein **1** and genistein **2**, have attracted considerable attention.[3,4] The soy isoflavones are present at significant levels in soya beans and soy products. They thus feature heavily in the diet particularly in Japan and Asia, where they have been associated with a low incidence of hormone dependent cancers.[5] These compounds have also been implicated in the prevention of cardiovascular disease,[6] lessening the symptoms of the menopause[7] and protection against osteoporosis.[8]

In order to understand the significance of the biological effects of phytoestrogens, analytical chemistry has had a key role to play. Accurate analysis has been important in attempts to establish the exposure of the population to the soy isoflavones through their diet and also in epidemiological studies to investigate the associations between isoflavone exposure and disease.



1



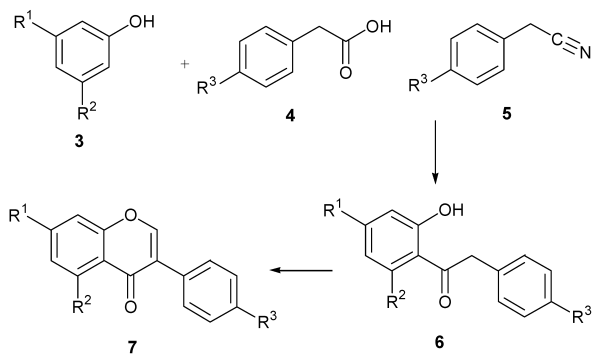
2

A number of analytical methods have been used to quantify the low levels of phytoestrogens found in food and biological fluids. HPLC has been employed with UV detection, but this suffers from poor selectivity and low sensitivity.[9] Time-resolved fluoroimmunoassay (TR-FIA) methods have been developed for both daidzein and genistein.[10] These are undoubtedly rapid methods with high sensitivity but can suffer from a lack of specificity.[11] However, by far the most widely used technique has been mass spectrometry due to its inherent sensitivity and selectivity. GC-MS has been used extensively for the quantification of isoflavones in urine, even though it requires complex purification procedures and derivatisation of the analytes.[12–14] More recently LC-MS procedures have become more popular as these can be carried out without derivatisation and often with little or no purification of the sample prior to analysis, allowing the use of smaller samples.[15–18]

An important aspect of any quantitative analytical procedure is the nature of the internal standard. The optimum internal standard for LC-MS and GC-MS is a pure, stable, isotopically labelled analogue of the analyte, which must have a large enough mass difference to nullify the effect of natural abundance heavy isotopes in the analyte. This mass difference will depend on the molecular weight of the analyte. For isoflavone type structures a minimum of three extra mass units is required. Initially a number of deuterated standards were used for the analysis of isoflavones.[18] These were prepared using acid, or base, catalysed exchange methods to incorporate the deuterium atoms into the phenol rings.[19–21] The problem with these deuterated isoflavones is that they are always a mixture of species with varying numbers of deuteriums incorporated into the isoflavone, which is an inevitable consequence of the exchange procedures employed. This produces a range of molecular ions and complicates the analysis procedure unnecessarily. More significantly it has been shown that under the analysis conditions back exchange occurs and the deuteriums are slowly replaced by hydrogen.[22,23] This results in a reduction of the amount of internal standard present and, also, an apparent increase in the amount of the phytoestrogen being analysed.

Keywords: Daidzein; Isoflavones; Phytoestrogens; ^{13}C-labelling.
* Corresponding author. Tel.: +44-1334-463856; fax: +44-1334-463808; e-mail address: npb@st-andrews.ac.uk

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.033



Scheme 1.

Due to the inherent problems with deuterated internal standards the aim of this work was to synthesise daidzein with three ^{13}C atoms incorporated into the carbon framework of the molecule for use as an internal standard. Using commercially available starting materials with 99% incorporation of ^{13}C, it should be possible to obtain the final product with 99% ^{13}C at the corresponding position in the phytoestrogen molecule. Thus with three ^{13}C atoms one major signal three mass units bigger than the unlabelled compound will be observed. This is in contrast to the variable levels of deuterium incorporation obtained through exchange procedures, which give an envelope of signals. Also the ^{13}C standards will be chemically stable and the ^{13}C atoms will not exchange back out from the molecule during the analysis procedures. We had previously prepared both daidzein and genistein labelled with a single ^{13}C-atom at the 4-position[24,25] and these compounds have been employed in metabolic studies on menopausal women.[26] This previous synthetic strategy was used as a suitable starting point.

2. Results and discussion

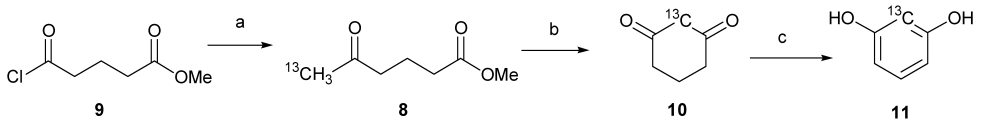
The general synthetic route towards the isoflavonoid phytoestrogens (Scheme 1) involves the condensation of an appropriate phenol **3** with either a substituted phenylacetic acid[24,25,27] **4** or a benzyl nitrile **5**.[24,25,28–30] This gives a deoxybenzoin **6** which then undergoes formylation and finally cyclisation to give the isoflavonoid **7**.[24,25,30,31] The synthesis presents various opportunities for the incorporation of ^{13}C atoms. However, the obvious strategy of putting put one ^{13}C atom into the 2-position in the formylation step at the end of the synthesis had already been shown to be unsuitable.[24] It was thus decided to incorporate one ^{13}C atom into the resorcinol and two into the side chain of the phenylacetic acid.

A previous literature procedure was discovered for the synthesis of [2-^{13}C]resorcinol[32] involving the synthesis of methyl 5-oxo-[6-^{13}C]hexanoate **8**, cyclisation via an intramolecular Claisen condensation and finally aromatisation to give the desired product. Firstly, methyl 4-(chloroformyl)butyrate **9** was converted into a mixed anhydride by reaction with 2-methoxybenzoic acid[33] and then reacted with [^{13}C]methyl magnesium iodide to give **8** in a low 30% yield. This step was thus modified and the methyl 4-(chloroformyl)butyrate **9** was reacted directly with a cuprate derived from [^{13}C]methyl iodide, giving the product in a much better 57% yield (Scheme 2).

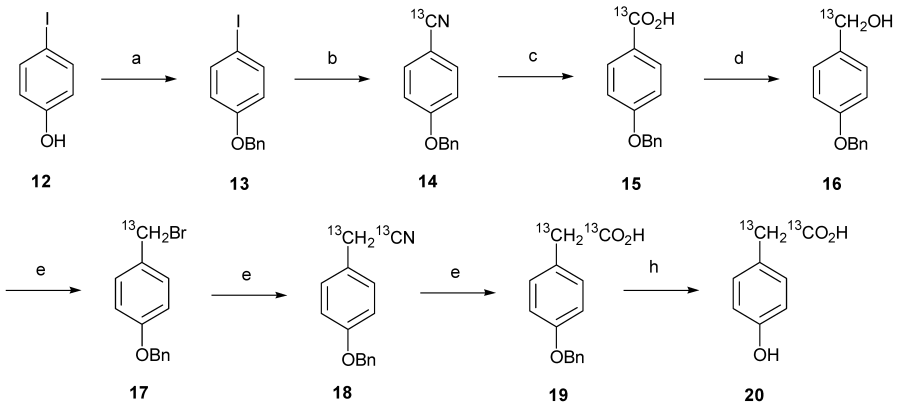
The cyclisation to [2-^{13}C]cyclohexane-1,3-dione **10** was previously[32] carried out in DMF with sodium methoxide in 61% yield, but we obtained a better 86% yield by using carefully dried potassium ^{t}butoxide in THF. Dehydrogenation was achieved using a palladium on charcoal catalyst in refluxing xylene at 137–140 °C giving [2-^{13}C]resorcinol **11** in 49% yield. A lower temperature was employed for this reaction compared to the 190 °C in refluxing triglyme previously reported.[32] The yields were comparable for the two procedures, but the lower temperature produced a cleaner more easily purified product. The spectral data for the [2-^{13}C]resorcinol were identical to the literature data.[32] The ^{13}C atom was clearly observed as an enhanced signal at 103.8 ppm in the ^{13}C NMR spectrum. This represents a much improved synthesis of [2-^{13}C]resorcinol in 24% yield over the three steps.

It was then necessary to incorporate two ^{13}C-atoms into the phenylacetic acid fragment and it was envisaged that these could both be derived from ^{13}C-labelled potassium cyanide, a very cheap source of ^{13}C atoms. In our previous work potassium [^{13}C]cyanide was reacted with a suitably protected benzyl bromide to give a single labelled precursor.[25] Therefore incorporation of two ^{13}C atoms required a ^{13}C-labelled benzyl bromide, which could be synthesised via an aromatic cyanation using another mole of potassium [^{13}C]cyanide and a suitably substituted aryl halide, followed by functional group transformations.

4-Iodophenol **12** was used as the starting material and the hydroxyl group was first protected as the benzyl ether **13** (Scheme 3). A large number of procedures are available for aromatic cyanation[34] but our choice was restricted by the requirement for ^{13}C-labelled cyanide, of which only the sodium and potassium salts are commercially available. Thus all the copper(I) cyanide methods were ruled out and instead a procedure employing potassium cyanide and a palladium(II) acetate catalyst in DMF under basic conditions (calcium hydroxide) was identified.[35] Only a limited range of aryl iodides had been examined under these conditions but we found that 4-benzyloxy-1-iodobenzene **13** reacted smoothly with unlabelled potassium cyanide to give the desired product. The reaction conditions were then optimised and using K^{13}CN the purified ^{13}C-labelled nitrile was obtained in 70% yield. The ^{13}C atom was clearly identified by the enhanced signal in the ^{13}C NMR spectrum at 119.6 ppm. The nitrile **14** was then hydrolysed under



Scheme 2. (a) $H_3^{13}CI$, Li, CuI, Et_2O, (57%); (b) KO^{t}Bu, THF then aq. HCl (86%); (c) 10% Pd/C, xylene, reflux (49%).



Scheme 3. (a) BnBr, K_2CO_3, acetone (90%); (b) $K^{13}CN$, $Pd(OAc)_2$, $Ca(OH)_2$, DMF (70%); (c) 2 N NaOH, MeOH (83%); (d) $LiAlH_4$, THF (93%); (e) PBr_3, Et_2O (93%); (f) $K^{13}CN$, 18-crown-6, MeCN (80%); (g) 2 M aq. NaOH, reflux (98%); (h) H_2, 10% Pd/C, EtOAc (96%).

alkaline conditions, sodium hydroxide in methanol, to give the acid **15** in 83% yield and reduced to the alcohol **16** in 93% yield using lithium aluminium hydride in THF.

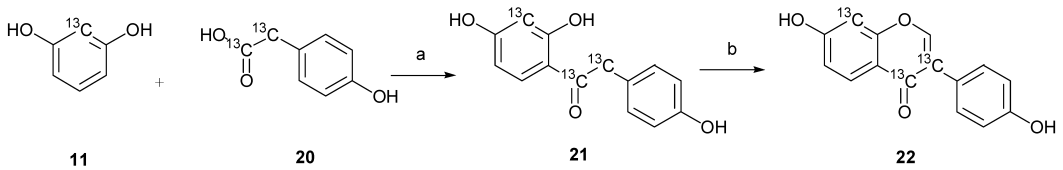
A number of procedures were examined for the conversion of the alcohol to the bromide **17** including trimethylsilyl bromide and carbon tetrabromide with triphenylphosphine. However, the best yield was obtained using phosphorus tribromide. The bromide was found to be reasonably unstable due to the 4-substituent and so was used without purification in the next step.

Reaction of the benzyl bromide **17** with a second mole of $K^{13}CN$ in acetonitrile, using 18-crown-6 to aid solubility, effected nucleophilic displacement to give the benzyl nitrile with **18** two ^{13}C-atoms, observed at 118.6 and 23.2 ppm in the ^{13}C NMR spectrum. Alkaline hydrolysis to the carboxylic acid, **19** was followed by hydrogenation to remove the benzyl ether and provide the precursor **20** for the synthesis of [3,4,8-$^{13}C_3$]daidzein (Scheme 3).

With the two ^{13}C-labelled building blocks prepared, the [3,4,8-$^{13}C_3$]daidzein was synthesised using adaptations of our previous methods (Scheme 4).[25] Condensation of the [2-^{13}C]resorcinol **11** and the phenylacetic acid **20** was carried out in neat boron trifluoride etherate, giving the deoxybenzoin intermediate **21** in 55% yield. The formylation/cyclisation step was achieved using dimethylformamide dimethylacetal in THF. In our previous work this had been carried out at reflux in 60% yield.[24,25] However, the step was carefully optimised by varying the temperature, time of reaction and solvent (THF, diethyl ether and DMF) and it was found that the yield increased as the reaction temperature was decreased, giving an optimum yield of 80% after stirring at room temperature in THF for 3 h. The crude product from this reaction was found to be much cleaner than from reactions at higher temperature and readily purified by simple crystallisation, whereas HPLC was required to clean up the products from the higher temperature reactions. This represents the best reported yield for this procedure in the synthesis of daidzein and we have found it to be more reproducible than many of the published methods.[25,30,31]

The [3,4,8-$^{13}C_3$]daidzein **22** was found to be identical to daidzein in all respects except for the expected increase in mass and NMR spectroscopic data. The three ^{13}C atoms were observed at 178.8 ppm, for the carbonyl at C-4, 126.0 ppm for C-3 and 103.5 ppm for C-8, with the expected coupling between C-3 and C-4 (J=54 Hz). The effect of the ^{13}C incorporation was also evident on the ^1H NMR spectrum, for example 8-H exhibited a 162 Hz coupling with the attached ^{13}C atom. The purity of the compound was confirmed by reverse phase HPLC (Kingsorb 3μ C18 Column (150×4.6 mm)) giving a retention time of 8 min 40 s with a mobile phase of acetonitrile:water (1:1) and a 0.3 mL min^{-1} flow rate. This gave a single peak at the identical retention time to unlabelled daidzein. Furthermore, the UV spectrum was measured giving a λ_{max} (EtOH) of 262 nm and ε= 23,894 $dm^3\ mol^{-1}\ cm^{-1}$, compared with literature value[36] of ε=24,739 $dm^3\ mol^{-1}\ cm^{-1}$, implying 96% purity within experimental error.

The compound has since been used as an internal standard in both GC-MS[37] and LC-MS[22,38] using isotope dilution methods. To be used over an extended dynamic range the isotopically labelled internal standard must have no significant mass overlap with the unlabelled analyte. This is obviously complicated by the natural abundance distribution of carbon, hydrogen and oxygen. When isotope distributions are taken into consideration the predicted mass intensity pattern for daidzein examined by negative electrospray ionisation is 253 (100%):254 (18%):255(3%). For quantitative analysis selective ion monitoring (SIM) is used at 253 for optimal instrumental sensitivity, so the



Scheme 4. (a) $BF_3{\cdot}Et_2O$ (55%); (b) $DMF{\cdot}(OMe)_2$, DMF (80%).

daidzein internal standard must not give any significant signal at this mass. When the isotopic purity of the [3,4,8-$^{13}C_3$]daidzein was examined by LC-MS, the major signal was observed, as expected, at 256 along with a signal of 4% relative intensity at 255 for daidzein molecules having only two ^{13}C atoms.[22] However, there were no discernible ions due to molecules with zero or one ^{13}C per molecule, thus comfortably meeting the criteria for use as an internal standard for isotope dilution mass spectrometry. Recent isoflavone analysis by GC-MS[37] demonstrated improved linearity over a range of concentrations due to the use of the ^{13}C-labelled internal standards, along with lower limits of detection. Quality control was also improved with lower intra- and interassay coefficients of variation (CV) for isoflavones where a ^{13}C-labelled standard was available.

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Gemini 2000 (^1H 300 MHz, ^{13}C 75.45 MHz) or a Bruker Avance 300 (^1H 300 MHz, ^{13}C 75.45 MHz) spectrometer chemical shifts (δ) in ppm are given relative to Me_4Si, coupling constants (J) in Hz. Elemental analyses were carried out in the departmental microanalytical laboratory. IR spectra were recorded on a Perkin–Elmer series 1420 FT IR spectrophotometer. The samples were prepared as Nujol mulls or thin films between sodium chloride discs and recorded in cm^{-1}. EI and CI mass spectra were recorded on a VG Autospec. Electrospray mass spectra recorded on Micromass LC-T UV spectra were recorded on a Kontron Uvikon 930 spectrometer. Melting points were recorded on an electrothermal melting point apparatus and are uncorrected. Analytical TLC was carried out on Merck 5785 Kieselgel $60F_{254}$ fluorescent plates. Flash chromatography was performed according to the procedure of Still[39] using silica gel of 35–70 μ particle size. DMF was distilled from magnesium sulfate. Diethyl ether and tetrahydrofuran were distilled from sodium metal and benzophenone.

3.1.1. Methyl 5-oxo-[6-^{13}C]hexanoate (8).[32] Under the protection of a nitrogen atmosphere, lithium pieces (489 mg, 70.4 mmol) were added to dry diethyl ether (70 mL). ^{13}C-Methyl iodide (1.8 mL, 4.104 g, 28.91 mmol) was then introduced and the reaction mixture stirred at room temperature for 1 h, then cooled to 0 °C and copper iodide (3.352 g, 17.6 mmol) was added. After 0.5 h stirring at 0 °C, the resulting lithium dimethylcuprate was cooled to −20 °C. Precooled methyl 4-chloroformyl butyrate (2 mL, 2.386 g, 14.5 mmol) was then added dropwise with vigorous stirring. The reaction mixture was maintained at −20 °C for 1 h, then room temperature overnight. The reaction was quenched with saturated ammonium chloride (45 mL) and filtered to remove the copper residue. The filtrate was extracted with diethyl ether (3×20 mL), washed with brine (20 mL) and dried ($MgSO_4$). Further purification was carried out by column chromatography, eluting with petroleum ether (40–60 °C)/ethyl acetate (1:1) to give a colourless oil (1.19 g, 57%); ν_{max} (nujol)/cm^{-1} 1725 (C=O); δ_H (300 MHz, $CDCl_3$) 3.64 (3H, s, $-OCH_3$), 2.48 (2H, t, J=7.2 Hz, CH_2-3), 2.31 (2H, t, J=7.2 Hz, CH_2-4), 2.11 (3H, d, J=127 Hz, CH_2-6), 1.86 (2H, quin, J=7.2 Hz, CH_2-2); δ_C (75.45 MHz, $CDCl_3$) 202 (d, $J_{5,6}$=45 Hz, *C*-5), 174.4 (*C*-1), 52.0 (OCH_3), 42.9 (d, $J_{4,6}$=22 Hz, *C*-4) 33.4 (*C*-2), 30.2 (enhanced, *C*-6), 26.4 (*C*-6); *m/z* (ES^+) 168 [$(M+Na)^+$, 100%]; (EI) 145 (M^+, 15%), 114 (40, $[M-OCH_3]^+$), 86 (30, $[M-COOCH_3]^+$), 44 (100, CH_3CO^+).

3.1.2. [2-^{13}C]Cyclohexane-1,3-dione (10). To the solution of methyl 5-oxo-[6-^{13}C]hexanoate **8** (758 mg, 5.22 mmol) in dry THF (100 mL), was added potassium ^{t}butoxide (2.345 g, 20.9 mmol). The mixture was heated under reflux for 6 h, then the THF was removed at reduced pressure. The residue was dissolved in water (20 mL), acidified to pH 1 with concentrated hydrochloric acid, extracted with ethyl acetate (6×20 mL) and dried ($MgSO_4$). After removal of the solvent at reduced pressure, the desired product was obtained as a pale yellow solid (510 mg, 86%) mp 102–103 °C (lit.[32] 103–104 °C); ν_{max} (nujol)/cm^{-1} 2480, 1627, 1600, 1180; δ_H (300 MHz, $CDCl_3$) 3.36 (2H, d, J=130 Hz, CH_2-2), 2.55 (4H, t, J=6.7 Hz, CH_2-4 and 6), 2.0–1.8 (2H, m, CH_2-5); δ_C (75.45 MHz, $CDCl_3$) 58.8 (enhanced, *C*-1); *m/z* (EI) 113 (M^+, 50%), 85 (50, $[M-CO]^+$).

3.1.3. [2-^{13}C]Resorcinol (11). To a flask containing [2-^{13}C]cyclohexane-1,3-dione **10** (500 mg, 4.42 mmol) and xylene (75 mL), palladium on carbon (10%, 2.5 g) was added. The mixture was heated under reflux for 3 h, then the palladium catalyst was filtered off through celite. The reaction mixture was extracted with aqueous sodium hydroxide (20%, 4×20 mL). The combined aqueous layers were cooled to 0 °C, acidified to pH 2 with concentrated hydrochloric acid, and extracted with diethyl ether (3×25 mL). After removal of the solvent at reduced pressure, red oil was obtained. Further purification was carried out by column chromatography on silica, eluting with diethyl ether/petroleum ether (40–60 °C) (2:1) to give the desired product as a white solid (238 mg, 49%) mp 105–108 °C (lit.[32] 108–109 °C); ν_{max} (nujol)/cm^{-1} 3240 (OH), 1615, 966; δ_H (300 MHz, acetone-d_6) 8.04 (2H, s, $-OH$), 6.84 (1H, dt, J=8.1, 1.4 Hz, *H*-5), 6.21 (1H, dt, $J_{C,H}$=156, $J_{2,4}=J_{2,6}$=2.3 Hz, *H*-2), 6.26–6.1 (2H, m, *H*-4 and 6); δ_C (75.45 MHz, acetone-d_6) 103.8 (enhanced, *C*-2); *m/z* (CI) 112.0480 (MH^+, $^{12}C_5{}^{13}CH_6O_2$ requires 112.0484).

3.1.4. 4-Benzyloxyiodobenzene (13). To a solution of 4-iodophenol (10 g, 45.5 mmol) in acetone (250 mL) were added potassium carbonate (30.273 g, 227.3 mmol) and benzyl bromide (4.5 mL, 6.471 g, 37.9 mmol). The mixture was heated under reflux for 6 h, then cooled and filtered to remove the solid. The solvent was evaporated at reduced pressure and the crude product dissolved in diethyl ether (50 mL), washed with water (3×20 mL) and dried ($MgSO_4$). Further purification was carried out by column chromatography, eluting with ethyl acetate/petroleum ether (40–60 °C) (1:10) to give the product as white crystals (11.1 g, 94%) mp 60–62 °C (lit.[40] 62–63 °C) (found: C, 50.51; H, 3.58, $C_{13}H_{11}IO$ requires C, 50.35; H, 3.58%); ν_{max} (nujol)/cm^{-1} 1600, 1119, 972; δ_H (300 MHz, $CDCl_3$) 7.57 (2H, d, $J_{2,3}=J_{5,6}$=8.9 Hz, *H*-2, 6), 7.54–7.32 (5H, m, *H*-2′ to H-6′), 6.76 (2H, d, $J_{2,3}=J_{5,6}$=8.9 Hz, *H*-3, 5), 5.04 (2H, s, OCH_2); δ_C (75.45 MHz, $CDCl_3$) 159.0 (*C*-4), 138.6 (*C*-2 and 6), 136.9 (*C*-1′), 129.0 (*C*-3′ and 5′), 128.5 (*C*-4′), 127.8

(*C*-2′ and 6′), 117.7 (*C*-3 and 5), 83.4 (*C*-1), 70.4 (*C*-7); *m/z* (CI) 311 (MH^+, 35%), 310 (23, M^+), 184 (97, $[M-I]^+$), 91 (58, $C_7H_7^+$).

3.1.5. 4-Benzyloxybenzo[^{13}C]nitrile (14). To a solution of 4-benzyloxyiodobenzene **13** (20.04 g, 64.62 mmol) in dry DMF (250 mL) were added calcium hydroxide (2.33 g, 31.5 mmol), potassium [^{13}C]-cyanide (4.30 g, 65 mmol) and palladium acetate (2.25 g, 10.0 mmol). Under a nitrogen atmosphere, the mixture was heated at reflux for 4 h, then the DMF was removed under reduced pressure. The crude product was extracted with diethyl ether (3×50 mL). The combined organic extracts were then washed with water (3×50 mL) and dried ($MgSO_4$). Further purification was carried out by column chromatography, eluted with ethyl acetate/petroleum ether (40–60 °C) (3:10). After removal of the solvent, a white solid was obtained (9.52 g, 70%) mp 96–99 °C; (found: C, 80.31; H, 5.05; N, 6.99. $^{12}C_{13}{}^{13}CH_{11}NO$ requires C, 80.45; H, 5.27; N, 6.66%); ν_{max} (KBr)/cm^{-1} 2169 (CN); δ_H (300 MHz, $CDCl_3$) 7.60 (2H, dd, $J_{2,3}$=$J_{5,6}$=9.0 Hz, $J_{C,H}$=5.0 Hz, *H*-2 and 6), 7.43–7.34 (5H, m, *H*-2′ and 6′), 7.03 (2H, d, $J_{2,3}$=$J_{5,6}$=9.0 Hz, *H*-3 and 5), 5.12 (2H, s, OCH_2); δ_C (75.45 MHz, $CDCl_3$) 162.3 (*C*-4), 136.1 (*C*-1′), 134.0 (*C*-2 and 6), 129.2 (*C*-3′ and 5′), 128.8 (*C*-4′), 127.9 (*C*-2′ and 6′), 119.6 (enhanced ^{13}CN), 116.0 (*C*-3 and 5), 104.6 (d, $J_{C,C}$=83 Hz, *C*-1), 70.7 (*C*-7); *m/z* (CI) 211 (MH^+, 100%), 91 (10, $C_7H_7^+$).

3.1.6. 4-Benzyloxy[*carboxy*-^{13}C]benzoic acid (15). 4-Benzyloxybenzo[^{13}C]nitrile **14** (8.53 g, 40.6 mmol) was mixed with sodium hydroxide (2 N, 500 mL) and methanol (50 mL). The reaction was followed by TLC (silica, ethyl acetate/methanol (50:1)) and heated under reflux until the starting material had disappeared. The resulting mixture was cooled and adjusted to pH 1 with concentrated hydrochloric acid. The solid that precipitated was collected, then heated to reflux with sodium hydroxide (2 N, 500 mL) for another 8 h. The resulting mixture was then cooled and adjusted to pH 1 with concentrated hydrochloric acid again, extracted with diethyl ether/methanol (6:1). The organic layers were combined, washed with brine (2×50 mL), dried ($MgSO_4$) and the solvent removed at reduced pressure to give the product as white crystals (7.74 g, 83%) mp 192–196 °C; (found: C, 73.58; H, 5.08. $^{12}C_{13}{}^{13}CH_{12}O_3$ requires C, 73.78; H, 5.28%); ν_{max} (nujol)/cm^{-1} 1648 (CO_2H), 1601, 972; δ_H (300 MHz, CDCl) 7.94 (2H, dd, $J_{2,3}$=$J_{5,6}$=9.0 Hz, $J_{C,H}$=3.9 Hz, *H*-2 and 6), 7.38–7.24 (5H, m, *H*-2′ and 6′), 6.92 (2H, d, $J_{2,3}$=$J_{5,6}$=9.0 Hz, *H*-3 and 5), 5.04 (2H, s, OCH_2); δ_C (75.45 MHz, $CDCl_3$) 168.9 (enhanced, ^{13}COOH), 162.7 (*C*-4), 136.7 (*C*-1′), 132.2 (*C*-2 and 6), 129.0 (*C*-3′ and 5′), 128.5 (*C*-4′), 127.8 (*C*-2′ and 6′), 123.7 (d, $J_{C,C}$=74 Hz, *C*-1), 114.7 (*C*-3 and 5), 70.4 (*C*-7); *m/z* (EI) 229 (M^+, 10%), 91 (100, $C_7H_7^+$).

3.1.7. 4-Benzyloxy[*methylene*-^{13}C]benzyl alcohol (16). Under the protection of a nitrogen atmosphere, 4-benzyloxy[*carboxy*-^{13}C]benzoic acid **15** (3.50 g, 15.27 mmol) in dry THF (50 mL) was added dropwise to a suspension of lithium aluminium hydride (2.277 g, 60 mmol) in dry THF (60 mL). The mixture was stirred at room temperature overnight, then sulfuric acid (10%, 150 mL) was added carefully to quench the reaction. The resulting mixture was extracted with diethyl ether (4×50 mL), washed with water (3×30 mL) and dried ($MgSO_4$). After removal of the solvent at reduced pressure the desired product was obtained as a pale white solid (3.0 g, 93%); mp 94–96 °C (lit.[41] 94–96 °C); ν_{max} (nujol)/cm^{-1} 3424 (OH), 1601, 972; δ_H (300 MHz, $CDCl_3$) 7.38–7.18 (7H, m, *H*-2′ to 6′, *H*-2 and 6), 6.89 (2H, d, $J_{2',3'}$=$J_{5',6'}$=8.5 Hz, *H*-3 and 5), 5.00 (2H, s, OCH_2), 4.54 (2H, d, $J_{C,H}$=143 Hz, $^{13}CH_2O$); δ_C (75.45 MHz, $CDCl_3$) 158.8 (*C*-4), 137.3 (*C*-1′), 133.7 (d, *J*=48 Hz, *C*-1), 129.1 (*C*-2 and 6), 129.0 (*C*-3′ and 5′), 128.4 (*C*-4′), 127.8 (*C*-2′ and 6′), 115.3 (*C*-3 and 5), 70.4 (C-7), 65.5 (enhanced, $^{13}CH_2O$); *m/z* (EI) 215 (M^+, 25%), 91 (100, $C_7H_7^+$).

3.1.8. 4-Benzyloxy[*methylene*-^{13}C]benzyl bromide (17). To a solution of 4-benzyloxy[*methylene*-^{13}C]benzyl alcohol **16** (2.50 g, 11.61 mmol) in dry diethyl ether (50 mL) was added phosphorus tribromide (3.3 mL, 34.83 mmol). The reaction mixture was stirred at room temperature overnight. The pale yellow solution formed was then poured into ice water (200 mL), extracted with diethyl ether (5×30 mL) and dried ($MgSO_4$). After removal of the solvent at reduced pressure a white solid was obtained (3.02 g, 93%) and this product was employed in next step immediately without further purification. δ_H (300 MHz, $CDCl_3$) 7.37–7.23 (7H, m, *H*-2′ to 6′, *H*-2 and 6), 6.86 (2H, d, $J_{2',3'}$=$J_{5',6'}$=8.6 Hz, *H*-3 and 5), 4.99 (2H, s, OCH_2), 4.43 (2H, d, $J_{C,H}$=153 Hz, $^{13}CH_2Br$); *m/z* (EI) 277/279 (M^+, 5%), 198 (50, $[M-Br]^+$), 91 (100, $C_7H_7^+$).

3.1.9. 4′-Benzyloxy[1,2-$^{13}C_2$]phenylacetonitrile (18). 4′-Benzyloxy[*methylene*-^{13}C]benzyl bromide **17** (2.80 g, 10.06 mmol) was dissolved in acetonitrile (120 mL) then 18-crown-6 (2.66 g, 10.06 mmol) and potassium ^{13}C-cyanide (666 mg, 10.06 mmol) were added. The mixture was heated under reflux for 4 h, then cooled, and the solvent was removed to give a pale white residue, which was then extracted with diethyl ether (3×30 mL). The combined ether layers were washed with water (2×30 mL), dried ($MgSO_4$) and the solvent removed at reduced pressure. Purification by column chromatography on silica, eluting with petroleum ether (40–60 °C)/ethyl acetate (10:3 to 2:1) gave the desired product as a white solid (1.82 g, 80%); mp 66–69 °C; (found: C, 80.46; H, 5.82; N, 6.15. $^{12}C_{13}{}^{13}C_2H_{13}NO$ requires C, 80.86; H, 5.82; N, 6.22%); ν_{max} (nujol)/cm^{-1} 2192 (CN); δ_H(300 MHz, $CDCl_3$) 7.46–7.21 (H, m, *H*-2′ to 6′, *H*-2 and 6), 6.98 (2H, d, $J_{2',3'}$=$J_{5',6'}$=8.7 Hz, *H*-3 and 5), 5.08 (2H, s, OCH_2), 3.69 (2H, dd, $J_{C,H}$=136, 10.6 Hz, $^{13}CH_2{}^{13}CN$); δ_C (75.45 MHz, $CDCl_3$) 158.9 (*C*-4), 137.0 (*C*-1′), 129.5 (*C*-2 and 6), 129.0 (*C*-3′ and 5′), 128.5 (*C*-4′), 127.8 (*C*-2′ and 6′), 122.4 (d, $J_{2,1'}$=42 Hz, *C*-1), 118.6 (enhanced d, $J_{1,2}$=58 Hz, ^{13}CN), 115.9 (*C*-3 and 5), 70.5 (*C*-7), 23.2 (enhanced d, $J_{1,2}$=58 Hz, $^{13}CH_2$); *m/z* (EI) 225 (M^+, 10%), 91 (100, $C_7H_7^+$).

3.1.10. 4′-Benzyloxy[1,2-$^{13}C_2$]phenylacetic acid (19). 4′-Benzyloxy[1,2-$^{13}C_2$]phenylacetonitrile **18** (1.666 g, 7.40 mmol) was dissolved in aqueous sodium hydroxide (2 N, 90 mL) and heated to reflux for 6 h, then cooled and adjusted pH to 1 with concentrated hydrochloric acid. The precipitate formed was collected by filtration, washed with plenty of water and then diethyl ether. After drying under vacuum, the desired product was obtained as a white solid (1.77 g, 98%) mp 120–122 °C; (lit.[42] 120–122 °C) ν_{max}

(nujol)/cm^{-1} 1654 (CO_2H), 1600, 970; δ_H (300 MHz, $CDCl_3$) 7.37–7.21 (5H, m, *H*-2′ and 6′), 7.12 (2H, m, *H*-2, 6), 6.86 (2H, d, $J_{2',3'}=J_{5',6'}=8.7$ Hz, *H*-3 and 5), 4.97 (2H, s, OCH_2), 3.49 (2H, dd, $J_{C,H}=129$, 7.7 Hz, $^{13}CH_2$); δ_C (75.45 MHz, $CDCl_3$) 177.2 (enhanced d, $J_{1,2}=56$ Hz, ^{13}COOH), 158.4 (*C*-4), 137.3 (*C*-1′), 130.8 (*C*-2 and 6), 129.0 (*C*-3′ and 5′), 128.4 (*C*-4′), 127.9 (*C*-2′ and 6′), 126.2 (d, $J=48$ Hz, *C*-1), 115.3 (C3, 5), 70.4 (*C*-7), 40.5 (enhanced d, $J_{1,2}=56$ Hz, $^{13}CH_2$); *m*/*z* (EI) 244 (M^+, 15%), 91 (100, $C_7H_7^+$).

3.1.11. 4′-Hydroxy[1,2-$^{13}C_2$]phenylacetic acid (20). 4′-Benzyloxy[1,2-$^{13}C_2$]phenylacetic acid **19** (300 mg, 1.23 mmol) was dissolved in ethyl acetate (12 mL). After flushing with nitrogen, palladium on carbon (10%, 100 mg) was added. The mixture was stirred under a hydrogen atmosphere at room temperature overnight. The mixture was then filtered through celite, and the solvent removed at reduced pressure to give the product as a pale white solid (181 mg, 96%) mp 149–151 °C (lit.[42] 149–152 °C); (found: C, 63.29; H, 5.15. $^{12}C_6{}^{13}C_2H_8O_3$ requires C, 63.63; H, 5.23%); ν_{max} (nujol)/cm^{-1} 3395 (OH), 1654 (CO_2H); δ_H (300 MHz, $CDCl_3$, ppm) 7.03 (2H, dd, $J_{2',3'}=J_{5',6'}=8.4$ Hz, $J_{C,H}=4.2$ Hz, *H*-2′ and 6′), 6.70 (2H, d, $J_{2',3'}=J_{5',6'}=8.4$ Hz, *H*-3 and 5), 3.42 (2H, dd, $J_{C,H}=129$, 7.6 Hz, $^{13}CH_2$); δ_C (75.45 MHz, $CDCl_3$) 175.0 (enhanced, d, $J_{1,2}=55$ Hz, ^{13}COOH), 156.1 (*C*-4′), 130.5 (*C*-2′ and 6′), 125.5 (d, $J_{2,1'}=42$ Hz, *C*-1′), 115.6 (*C*-3′ and 5′), 40.5 (enhanced d, $J_{1,2}=55$ Hz, $^{13}CH_2$); *m*/*z* (ES^+) 177 ($[M+Na]^+$, 100%); *m*/*z* (ES^-) 153 [$(M-H)^-$, 65%].

3.1.12. [1,2,3′-$^{13}C_3$]-1-(2′,4′-Dihydroxyphenyl)-2-(4″-hydroxyphenyl)ethanone (21). To [2-^{13}C]resorcinol **11** (100 mg, 0.9 mmol) and 4′-hydroxy[1,2-$^{13}C_2$]phenylacetic acid **20** (139 mg, 0.9 mmol) was added boron trifluoride diethyl etherate (5 mL) under a nitrogen atmosphere. The mixture was heated at 70–80 °C for 3 h, then cooled, and poured into saturated sodium acetate (50 mL) and basified with saturated sodium hydrogen carbonate (40 mL). The mixture was then extracted with diethyl ether (4×20 mL), the organic layers combined and concentrated at reduced pressure to yield a pink gum. This crude product was purified by column chromatography on silica, eluting with dichloromethane/ethyl acetate (4:1) to give the desired product as a white solid (114 mg, 55%) mp 186–188 °C (lit.[30] 188–190 °C); ν_{max} (nujol)/cm^{-1} 3395 (OH), 1610 (C=O); δ_H (300 MHz, CD_3OD) 7.74 (1H, ddd, $J_{5',6'}=8.9$ Hz, $J_{C,H}=4.0$, $J_{3',6'}=1.2$ Hz, *H*-6′), 7.00 (2H, dd, $J_{2'',3''}=J_{5'',6''}=8.2$ Hz, $J_{2,2''}=J_{2,6''}=4.1$ Hz, *H*-2″ and 6″), 6.62 (2H, d, $J_{2'',3''}=J_{5'',6''}=8.2$ Hz, *H*-3″ and 5″); 6.14 (1H, dd, $J_{C,H}=160$ Hz, $J_{3',6'}=1.2$, *H*-3′), 6.18–6.32 (1H, m, *H*-5′), 4.01 (2H, dd, $J_{C,H}=128$, 6.0 Hz, CH_2-2); δ_C (75.45 MHz, CD_3OD) 203.2 (enhanced, d, $J_{1,2}=44$ Hz, *C*-1), 102.5 (enhanced, *C*-3′), 43.5 (enhanced, d, $J_{1,2}=44$ Hz, *C*-2); *m*/*z* (ES^-) 246.0764 ([$(M-H)^-$], $^{12}C_{11}{}^{13}C_3H_{12}O_4$ ES^- requires 246.0760).

3.1.13. [3,4,8-$^{13}C_3$]Daidzein (22). Under the protection of a nitrogen atmosphere, the deoxybenzoin **21** (80 mg, 0.35 mmol) was dissolved in dry DMF (3 mL). Then DMF dimethyl acetal (0.9 mL, 0.807 g, 6.77 mmol) was introduced dropwise. The mixture was stirred at room temperature for 3 h, and then poured into aqueous hydrochloric acid (1 M, 70 mL) and stirred for a further 2 h. The suspension formed was left at room temperature overnight. The precipitate was then collected by filtration, washed with water (3×5 mL), then diethyl ether (3×2 mL) and dried under vacuum. Further recrystallisation of the product from methanol gave the pure product as white solid (72 mg, 80%) mp 221 °C (lit.[31] 212–214 °C); λ_{max} (EtOH)/nm 262 (ε/23894 dm^3 mol^{-1} cm^{-1}, lit.[36] 24,739); ν_{max} (nujol)/cm^{-1} 3360 (OH), 1735 (C=O); δ_H (300 MHz, d^6-acetone) 9.6 (1H, s, 7-O*H*), 8.4 (1H, s, 4′-O*H*), 8.06 (1H, ddd, $J_{5,6}=8.8$ Hz, $J_{4,5}=3.8$ Hz ($^{13}C-^1H$ coupling), $J_{5,8}=1.3$ Hz, *H*-5), 8.14 (1H, t, $J_{2,3}=J_{2,4}=6.4$ Hz ($^{13}C-^1H$ couplings), *H*-2), 7.48 (2H, dd, $J_{2',3'}=J_{5',6'}=8.6$ Hz, $J_{3,2'}=J_{3,6'}=3.5$ Hz ($^{13}C-^1H$ coupling), 2′ and *H*-6′), 7.0 (1H, m, *H*-6), 6.9 (1H, dt, $J=162$ Hz ($^{13}C-^1H$ coupling), $J_{6,8}=1.9$ Hz, *H*-8), 6.89 (2H, d, $J_{2',3'}=J_{5',6'}=8.6$ Hz, *H*-3′ and 5′); δ_C (75.45 MHz, d^6-acetone) 178.8 (d, enhanced, $J_{3,4}=54$ Hz, *C*-4), 126.0 (d, enhanced, $J_{3,4}=54$ Hz, *C*-3), 103.5 (enhanced, *C*-8); *m*/*z* (CI) 258.0750 (MH^+, $^{12}C_{12}{}^{13}C_3H_{11}O_4$ requires 258.0758).

Acknowledgements

This work was funded by the FSA under contracts T05001 and T05023. We would also like to thank Dr. Don Clarke at the Central Science Laboratory, York and Dr. Philip Grace at the MRC Dunn Human Nutrition Unit for their analytical support.

References and notes

1. Cassidy, A. *Proc. Nutr. Soc.* **1996**, *55*, 399–417.
2. Setchell, K. D. R. *Am. J. Clin. Nutr.* **1998**, *68*, 1333S–1346S.
3. Barnes, S. *Proc. Soc. Exp. Biol. Med.* **1998**, *217*, 386–392.
4. Dixon, R. A.; Ferreira, D. *Phytochemistry* **2002**, *16*, 205–211.
5. Barnes, S.; Peterson, T. G. *Proc. Soc. Exp. Biol. Med.* **1995**, *208*, 103–108. Adlercreutz, H. *Lancet Oncol.* **2002**, *3*, 364–373. Morrisey, C.; Watson, R. W. G. *Curr. Drug Targets* **2003**, *4*, 231–241.
6. Anthony, M. S. *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 1245–1247.
7. Greenwood, S.; Barnes, S.; Clarkson, T. B.; Eden, J.; Helferich, W. G.; Messina, M.; Setchell, K. D. R. *Menopause* **2000**, *7*, 215–229. Stark, A.; Madar, Z. J. *Pediatr. Endocrinol. Metab.* **2002**, *15*, 561–572.
8. Anderson, J. J. B.; Garner, S. C. *Nutr. Res.* **1997**, *17*, 1617–1632. Yamaguchi, M. *J. Health Sci.* **2002**, *48*, 209–222.
9. Franke, A. A.; Custer, L. J.; Wang, W.; Shi, C. Y. *Proc. Soc. Exp. Biol. Med.* **1998**, *217*, 263–273.
10. Wang, G. J.; Lapcík, O.; Hampl, R.; Uehara, M.; Al-Maharik, N.; Stumpf, K.; Mikola, H.; Wähälä, K.; Adlercreutz, H. *Steroids* **2000**, *65*, 339–348.
11. Stumpf, K.; Uehara, M.; Nurmi, T.; Adlercreutz, H. *Anal. Biochem.* **2000**, *284*, 153–157.
12. Setchell, K. D. R.; Lawson, A. M.; McLaughlin, L. M.; Patel, S.; Kirk, D. N.; Axelson, M. *Biomed. Mass Spectrom.* **1983**, *10*, 227–235.
13. Adlercreutz, H.; van der Wildt, J.; Kinzel, J.; Attalla, H.; Wähälä, K.; Mäkelä, T.; Hase, T.; Fotsis, T. J. *Steroid Biochem. Mol. Biol.* **1995**, *52*, 97–103.

14. Morton, M. S.; Wilcox, G.; Wahlqvist, M. L.; Griffiths, K. *J. Endocrinol.* **1994**, *142*, 251–259.
15. Barnes, S.; Coward, L.; Kirk, M.; Sfakianos, J. *Proc. Soc. Exp. Biol. Med.* **1998**, *217*, 254–262.
16. Franke, A. A.; Custer, L. J.; Wilkens, L. R.; Le Marchand, L.; Nomura, A. M.; Goodman, M. T.; Kolonel, L. N. *J. Chromatogr. B* **2002**, *777*, 45–59.
17. Twaddle, N. C.; Churchwell, M. I.; Doerge, D. R. *J. Chromatogr. B* **2002**, *777*, 139–145.
18. Doerge, D. R.; Churchwell, M. I.; Delclos, K. B. *Rapid Commun. Mass Spectrom.* **2000**, *14*, 673–678.
19. Mazur, W.; Fotsis, T.; Wähälä, K.; Ojala, S.; Salakka, A.; Adlercreutz, H. *Anal. Biochem.* **1996**, *233*, 169–180.
20. Wähälä, K.; Hase, T.; Aldercreutz, H. *Proc. Soc. Exp. Biol. Med.* **1995**, *208*, 27–32.
21. Wähälä, K.; Rasku, S. *Tetrahedron Lett.* **1997**, *38*, 7287–7290.
22. Clarke, D. B.; Lloyd, A. S.; Oldfield, M. F.; Botting, N. P.; Needs, P. W.; Wiseman, H. *Anal. Chem.* **2002**, *309*, 158–172.
23. Wähälä, K.; Rasku, S.; Parikka, K. *J. Chromatogr. B* **2002**, *777*, 111–122.
24. Whalley, J. L.; Bond, T. J.; Botting, N. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2569–2572.
25. Whalley, J. L.; Oldfield, M. F.; Botting, N. P. *Tetrahedron* **2000**, *56*, 455–460.
26. Setchell, K. D. R.; Faughnan, M. S.; Avades, T.; Zimmer-Nechemias, L.; Wolfe, B. E.; Brashear, T.; Desai, P.; Oldfield, M. F.; Botting, N. P.; Cassidy, A. *Am. J. Clin. Nutr.* **2003**, *77*, 411–419.
27. Hase, T.; Wähälä, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005–3008.
28. Chadderton, J.; Baker, W.; Harborne, J. B.; Ollis, W. D. *J. Chem. Soc.* **1953**, 1853–1860.
29. Pelter, A.; Ward, R. S.; Whalley, J. L. *Synthesis* **1998**, 1793–1802.
30. Cheng, Y. C.; Nair, M. G.; Santell, R. C.; Helferich, W. G. *J. Agric. Food Chem.* **1994**, *42*, 1869–1871.
31. Pelter, A.; Foot, S. *Synthesis* **1976**, 326.
32. Boyce, S. D.; Barefoot, A. C.; Hornig, J. F. *J. Labelled Compd. Radiopharm.* **1983**, *20*, 243–256.
33. Terasawa, T.; Okada, T. *Tetrahedron* **1977**, *35*, 595–598.
34. Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779–794.
35. Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn* **1975**, *48*, 3298–3301.
36. Wiseman, H.; Casey, K.; Clarke, D. B.; Barnes, K. A.; Bowey, E. *J. Agric. Food Chem.* **2002**, *50*, 1404–1410.
37. Grace, P. B.; Taylor, J. I.; Botting, N. P.; Fryatt, T.; Oldfield, M. F.; Bingham, S. A. *Anal. Biochem.* **2003**, *315*, 114–121.
38. Grace, P. B.; Taylor, J. I.; Botting, N. P.; Fryatt, T.; Oldfield, M. F.; Al-Maharik, N.; Bingham, S. A. *Rapid Commun. Mass Spectrom.* **2003**, *17*, 1350–1357.
39. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
40. Kipping, F. B.; Wren, J. J. *J. Chem. Soc.* **1957**, 3246–3250.
41. Szajnman, S. H.; Yan, W.; Bailey, B. N.; Docampo, R.; Elhalem, E.; Rodriguez, J. B. *J. Med. Chem.* **2000**, *43*, 1826–1840.
42. Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806–817.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1895–1902
Tetrahedron

From calixfurans to heterocyclophanes containing isopyrazole units

Grazia Cafeo,[a] Domenico Garozzo,[b] Franz H. Kohnke,[a,*] Sebastiano Pappalardo,[c] Melchiorre F. Parisi,[a] Rosetta Pistone Nascone[a] and David J. Williams[d]

[a]*Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, 98166 Messina, Italy*
[b]*CNR ICTP Catania, Viale Regina Margherita 6, 95123 Catania, Italy*
[c]*Dipartimento di Scienze Chimiche, Università di Catania, Viale A. Doria 6, 95125 Catania, Italy*
[d]*Department of Chemistry, Imperial College, South Kensington, London SW7 2AZ, UK*

Received 17 September 2003; revised 18 November 2003; accepted 11 December 2003

Abstract—Cyclic poly-1,4-diketones **2**, obtained by the oxidation of the furan units present in calix[4]furan **1a** and calix[6]furan **1c** have been converted into the novel heterocyclophanes **4a** and **4c** containing four and six isopyrazole units, respectively. Solution studies have demonstrated the ability of **4a** and **4c** to act as ligands for transition metals. The crystal structures of **4a** and the coordination compound formed by **4c** with 2 equiv. of *cis*-$PtCl_2(DMSO)_2$ have been determined. In the solid state **4c** is shown to bind aromatic substrates within its cavity.

1. Introduction

Macrocycles containing aromatic units have been a topic of active research for many years.[1] The aromatic units, being rigid building blocks, allow the design and synthesis of molecular cavities having defined spatial characteristics,[2] and also serve as binding sites for hosts capable of interacting with their π-electron systems.[3] Benzo rings have been the most frequently used aromatic subunits, as for example in the calixarenes.[1a,b,f] However, heterocyclic rings are also of equal interest for the construction of cyclophane-type molecular receptors because the presence of hetero-atoms provides a means for the incorporation of specific stereoelectronic characteristics within the macrocyclic structure.[4]

As part of our ongoing research on the synthesis of heterocalixarenes, we have developed effective methods for the preparation of calix[*n*]furans (n=4–12)[5] and explored the conversion of their furan units into other aromatic systems such as naphthalene[6] and pyrrole.[7a,b]

The conversion of calix[6]furan **1c** to calix[6]pyrrole **3c** is based on the use of **1c** as the precursor of the cyclic polyketone **2c**,[8] which is subjected to the Paal–Knorr reaction with $AcONH_4$ to give **3c**[7a,b] (Scheme 1). This result encouraged us to investigate the use of polyketones **2a-c** for the synthesis of macrorings containing heterocyclic units other than pyrrole.

With this goal in mind, we reacted polyketones **2a-c** with hydrazine hydrate (Scheme 1). In principle, these reactions can lead to the formation of macrocycles containing either isopyrazole[9] (**4a-c**) or dihydropyridazine[10] units (**5a-c**), since the pair of nucleophilic nitrogen atoms of hydrazine have the potential to react with pairs of carbonyl units placed in either 1,3- or 1,4- relative positions within the polyketonic macroring. Both types of heterocyclic units are interesting components for the construction of hetero-cyclophanes because of their potential ability to bind a number of metal cations and also molecules capable of forming hydrogen bonds with the nitrogen atoms.[11,12]

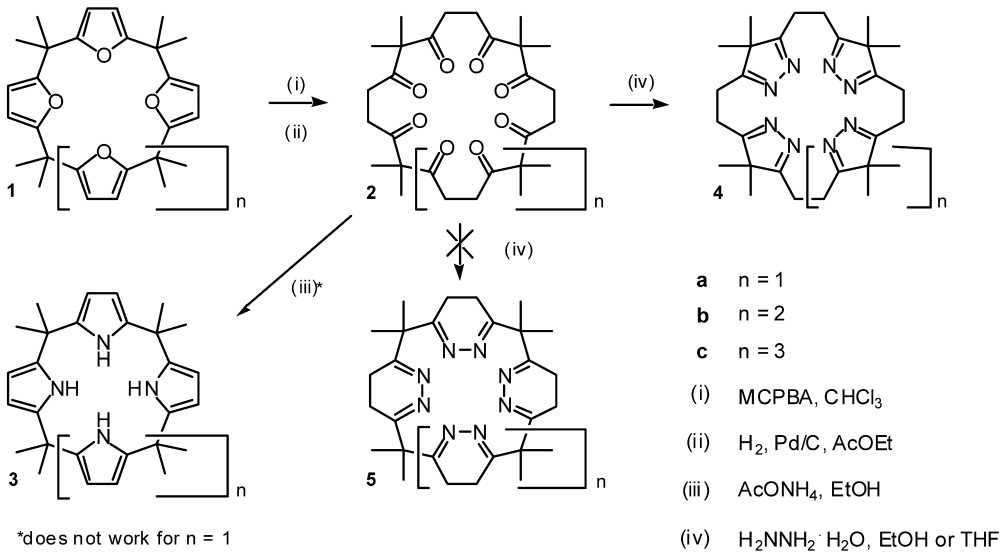
2. Results and discussion

Treatment of **2a** and **2c** with hydrazine hydrate in either EtOH, or THF gave the isopyrazole-based macrocycles **4a** and **4c**, which were easily isolated (35 and 45% yield, respectively) by column chromatography (SiO_2, DCM/MeOH 95:5). However, decaketone **2b** gave a complex mixture and no evidence for the formation of **4b**. Moreover, none of these reactions produced detectable amounts of **5a-c**.

The ^1H NMR spectrum of **4a** (300 MHz, $CDCl_3$, 20 °C)

Keywords: Macrocycles; N ligands; Isopyrazole; Metal coordination; X-ray structure.
* Corresponding author. Tel.: +39-090-6765171; fax: +39-090-393895; e-mail address: franz@unime.it

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.028



Scheme 1.

contains a broad signal (centred at δ 2.93) for the methylene protons which indicates a slow conformational mobility of the macrocycle on the NMR time-scale in this solvent and at this temperature; however, these methylene resonances appear as a sharp singlet at δ 2.84 in CD_3CN. The ^1H NMR spectrum of **4c** in $CDCl_3$ shows a sharp singlet for the methylene protons (δ 2.95) and a spectrum consistent with a time-averaged D_{6h} symmetry in solution. The ^{13}C NMR spectra of **4a** and **4c** are almost identical and each shows four resonances (consistent with D_{4h} and D_{6h} time-averaged symmetries, respectively, in solution).

Macrocycles **4a** and **4c** gave single crystals from toluene. The X-ray structure of **4a** (Fig. 1) shows the molecule to adopt a conformation with an alternating 'up/down' orientation of the isopyrazole units and approximate S_4 symmetry. The plane formed by the centroids of the bridging ethylidene units is planar to within 0.16 Å. Rings A, B, C, and D are inclined by 71, 77, 68, and 58°, respectively, to this plane, with in each case their N–N bonds being canted towards the macroring centre. The

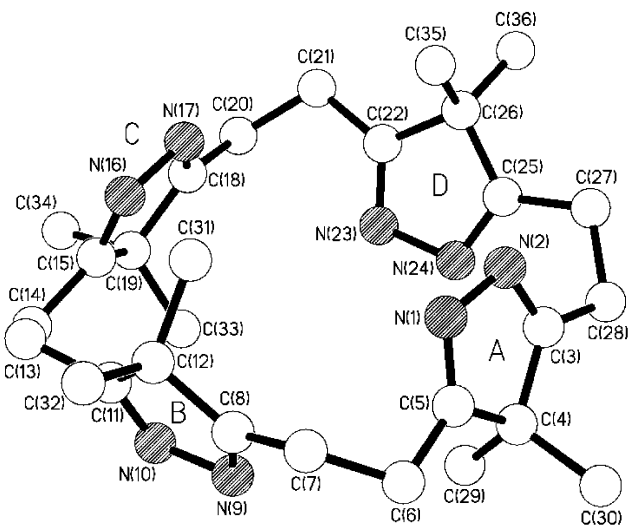


Figure 1. The X-ray structure of **4a**.

ethylidene units adopt *gauche* conformations with torsional twist angles of 68, −70, 65, and −65° about C(6)–C(7), C(13)–C(14), C(20)–C(21), and C(27)–C(28), respectively. The *trans*-annular centroid–centroid separations of the diametrically opposite isopyrazole units are 6.4 and 6.5 Å, respectively.

Within the isopyrazole rings there is a distinct pattern of bond localisation with the C=N and N–N bonds having average lengths of 1.283(2) and 1.459(2) Å, respectively. A comparison of these distances with literature values is not possible as to the best of our knowledge **4a** (and the following related structures) represent the first crystallographically characterised examples of molecules containing the isopyrazole unit (vide infra).

The structure also contains an included molecule of water of solvation and though this molecule is disordered there is evidence that it is involved in H-bonding with N(9) in one molecule and N(17) of another. There is a stacking of centrosymmetrically related N(23)-containing isopyrazole units (centroid–centroid separation of 3.62 Å and mean interplanar separation of 3.31 Å). There is an analogous approach between the N(9)-containing pairs of rings, though here the centroid···centroid separation is much larger at 4.34 Å.

The X-ray structure of **4c** (Fig. 2) shows that this molecule also adopts a conformation having an alternating up/down orientation of the isopyrazole units. The overall molecular geometry is here rectangular, with the long sides containing two isopyrazole units and the shorter ones a single isopyrazole ring. The overall molecular dimensions are ca. 8.0×12.0 Å, corresponding to the separations of C(20) and C(20A) and of the centroids of the two isopyrazole rings (B and B′) occupying the 'short sides', respectively.

The molecule is centrosymmetric and the centres of the six ethylidene linkages are coplanar to within 0.10 Å. Rings A, B, and C are inclined by 76, 66, and 80°, respectively, to this plane with in each case their nitrogen atoms being oriented towards the macroring centre. The ethylidene units adopt

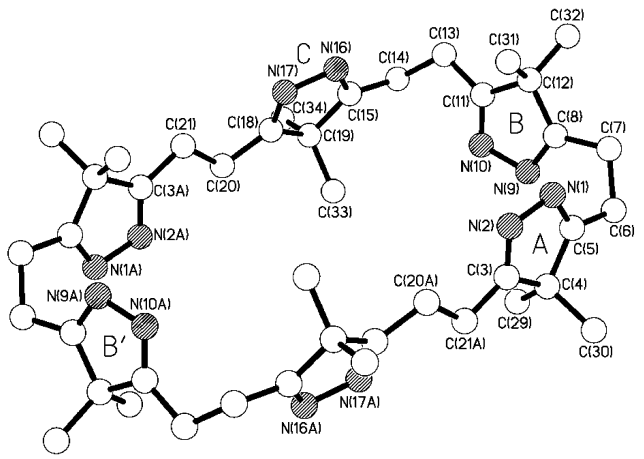


Figure 2. The X-ray structure of **4c**.

conformations with torsional twist angles of −66, 86, −166° about C(6)–C(7), C(13)–C(14), C(20)–C(21), respectively. A toluene molecule is trapped within the macrocycle cavity and exhibits an in-plane *p*-xylene-simulating disorder about the crystallographic centre of symmetry. Adventitious water molecules (two) are sited over the periphery of the macrocycle and are hydrogen-bonded to N(16) and N(16A), geometry: O···N 2.96, H···N 2.08 Å, O–H···N 166°. The other proton of the water molecule forms an intermolecular hydrogen bond to N(1) with geometry: O···N 2.95, H···N 2.05 Å, O–H···N 175°. The stacking of isopyrazole units observed in **4a** is not present in this structure, the separation of the centroids of the N(9)-containing rings of symmetry related molecules being 4.56 Å and too long for any significant interaction.

The observation of the trapping of toluene within the cavity of **4c** led us to expect that this macrocycle would also be able to include *p*-xylene. The X-ray analysis of single crystals of **4c** obtained from *p*-xylene confirmed this hypothesis. The structure (Fig. 3) is isomorphous with that obtained from toluene and the *p*-xylene molecule is ordered about the crystallographic inversion centre. The conformation of the macrocycle is only slightly perturbed, having overall dimensions of ca. 7.9×12.1 Å. The centres of the six linking ethylidene groups are coplanar to within 0.08 Å and rings A, B and C are inclined by 75, 59, and 82°, respectively, to this plane; the torsional twists about the CH_2–CH_2 bonds are −65, 83, and −168°. The bonding within the isopyrazole units in **4c**·*p*-xylene does not differ significantly from that observed in **4a**.

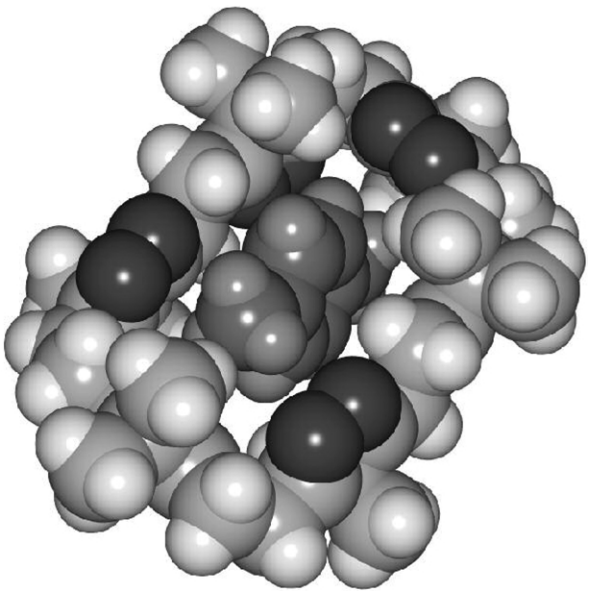


Figure 3. Space-filling representation of the solid-state structure of **4c**·*p*-xylene.

As in **4c**·$2H_2O$·$PhCH_3$ there are two included water molecules that are hydrogen-bonded intramolecularly to N(16) and intermolecularly to N(1); the hydrogen-bonding geometries [O···N, H···N (Å), O–H···N (°)] are 2.96, 2.07, 170 and 2.99, 2.11, 167, respectively. The small contraction in the width of the macrocyclic cavity compared with **4c**·$2H_2O$·$PhCH_3$ is interesting and may reflect an enhanced binding of *p*-xylene relative to toluene. An analysis of host–guest contacts reveals an overlap between the isopyrazole N(17)=C(18) bond and the *p*-xylene π-system; the distance of N(17) from the plane of the *p*-xylyl ring is 3.47 Å. This interaction is consistent with the electron-rich character of the *p*-xylyl unit and the π-electron deficient nature of the diene residue in isopyrazoles.[13] This binding is supplemented by a C–H···π interaction between one of the hydrogen atoms in each *p*-xylene methyl group and one of the C=N bonds in rings B and B′; the H···bond–centroid distance is 2.89 Å and the C–H···π angle is 161°.

We were unable, however, to observe any relevant complexation induced shifts in the ^{1}H NMR spectra of **4c** in $CDCl_3$, CD_2Cl_2 and CD_3CN upon addition of either toluene or *p*-xylene.

Pyrazole-based ligands have been widely studied for their ability to form coordination compounds with transition metals.[11] However, in almost all cases, the pyrazole unit in these ligands is 'aromatic' and in a deprotonated (pyrazolato) form. Indeed, to the best of our knowledge and prior to this study, only very few coordination compounds of isopyrazoles have been reported[14] and none of these have been crystallographically characterised.

Thus we decided to test the ability for **4a** and **4c** to form coordination compounds with selected transition metal ions. We treated methanolic solutions of both **4a** and **4c** with $Cu(ClO_4)_2$ (1:2 and 1:3 molar ratios, respectively). This led to an immediate change in colour (from almost colourless to dark blue), followed by the formation of dark precipitates which were insoluble in common solvents (including water, and DMSO). An attempt to confirm the nature of metal complexation of the ligand by IR spectroscopy was hindered by the fact that the characteristic absorptions associated with the C=N stretch were obscured by the perchlorate counterion. For this reason, we did not pursue the study of these precipitates any further.

Subsequently we treated **4a** and **4c** with *cis*-$PtCl_2(DMSO)_2$ or *cis*-$PtMe_2(DMSO)_2$. These platinum compounds[15] were chosen because their coordinated DMSO molecules are easily replaced by nitrogen-based ligands.[16]

The ^{1}H NMR spectrum of **4a** and $PtCl_2(DMSO)_2$ ($CDCl_3$, 1:1 ratio, 5×10^{-3} M) revealed, within a few minutes of mixing, the almost predominant formation of stoichiometric coordination compounds between $PtCl_2$ and the macrocycle—as confirmed by the appearance of the typical resonance for 'free' DMSO (δ 2.62, compared to δ 3.53 for Pt-coordinated DMSO).[16b] The displacement of DMSO from the Pt centre appears to be the prevailing process until 2 mol of $PtCl_2(DMSO)_2$ are added. Further addition of $PtCl_2(DMSO)_2$ does not produce quantitative displacement of DMSO from the Pt centre. Changes in the spectrum of **4a** upon addition of $PtCl_2(DMSO)_2$ include the appearance of novel and complex sets of resonances for the macrocycle methyl groups, which point to the likely existence of a mixture of coordination compounds having not only various stoichiometries, but also different regio- and stereochemistries. A very similar behaviour is also observed in CD_3CN.

Further evidence for the formation of various coordination compounds was obtained by the positive ESI-MS spectrum[17] of a mixture of **4a** and $PtCl_2(DMSO)_2$ (1:2 in CH_3CN, recorded within minutes after mixing); the significant peaks and the related assignments are listed in Table 1.

Table 1. Data for the positive ESI-MS spectrum of the reaction mixture formed by **4a** with $PtCl_2(DMSO)_2$ (1:2) in CH_3CN

m/z[a]	[Assignment]	Rel. int. (%)
489	$[M+H]^+$	100
511	$[M+Na]^+$	33
516[b]	$[2M+Fe]^{++}$	60
527	$[M+K]^+$	28
797	$[M+H+PtCl(DMSO)]^+$	22
977	$[2M+H]^+$	5
1063	$[M+PtCl_2PtCl(DMSO]^+$	52
1141	$[M+PtCl_2PtCl(DMSO)_2]^+$	7
1485	$[M+PtCl_2PtCl_2(DMSO)PtCl(DMSO)_2]^+$	4

[a] The *m/z* values indicated relate to the most abundant peak within the isotopic pattern calculated for the given composition.
[b] The presence of iron is presumed to be due to interactions with the metal components of the injection device.

When **4a** was treated with 1 equiv. of *cis*-$PtMe_2(DMSO)_2$ in $CDCl_3$, the most significant resonances observed in the ^{1}H NMR spectrum were at δ 0.56 for the Pt coordinated Me units ^2J (PtCH) 86 Hz, at δ 1.11, 1.15, and 1.35 ppm (2:1:1 intensity ratio, respectively) for the macrocycle methyl units, and a set of multiplets centred at 2.91, 3.22, and 3.51 ppm (1:2:1 intensity ratio, respectively) for the methylene groups. There were no resonances for Pt coordinated DMSO molecules, and only those for the free DMSO molecules were present.

These data are consistent with the prevalent formation of a 1:1 complex [(**4a**)$PtMe_2$] in which two nitrogen atoms of two different but adjacent isopyrazole units are coordinated to the metal centre in a way similar to that observed in the solid state for the larger analogue **4c** (vide infra).

The addition of 2 equiv. of *cis*-$PtMe_2(DMSO)_2$ produced changes in the spectra consistent with the dominant formation of a coordination compound with composition [Me_2Pt(**4a**)$PtMe_2$]. Apart from the Pt–Me resonances (δ 0.55, ^2J (PtCH) 86 Hz) there were only two signals for the methyl groups of the macrocycle (δ 1.14 and 1.34, 1:1 ratio) and two multiplets for the methylene protons (centred at δ 3.21 and 3.50 ppm, 1:1 ratio). These data suggest the predominant formation of the coordination compound shown in Fig. 4 (we exclude a *syn*-geometry for the $PtMe_2$ units because of unfavourable steric interactions).

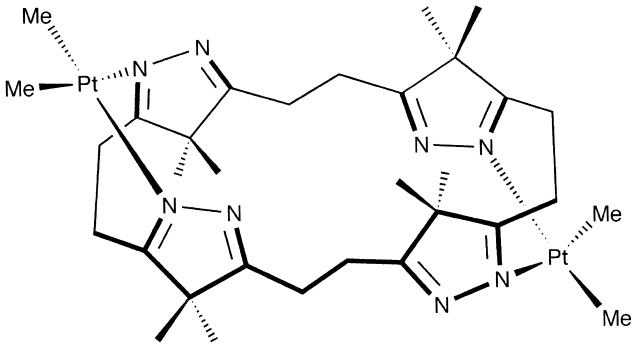


Figure 4. Schematic representation of the 1:2 complex formed between **4a** and $PtMe_2$.

The reaction mixtures of **4c** with either $PtCl_2(DMSO)_2$ or $PtMe_2(DMSO)_2$ (various stoichiometric proportions in $CDCl_3$) gave complex ^{1}H NMR spectra. However, it was evident that the nitrogen units of **4c** are capable of replacing either one or both of the DMSO ligands at the Pt centre (free DMSO molecules are formed) whereas the singlets observed for the methyl and methylene protons in the non-coordinated macrocycle give rise to multiple signals. The positive ESI-MS spectrum of the reaction mixture of **4c** with $PtCl_2(DMSO)_2$ (1:2 in CH_3CN) shows a much more complex set of peaks. Initial attempts to interpret these patterns in terms of simple stoichiometric coordination ratios was not possible. Alternative scenarios invoking the formation of mixed platinum complexes wherein some of the chloride ligands are replaced by acetonitrile gave a better (but not perfect) fit with the observed mass spectrum.

The $CDCl_3$ solution of **4c** with 2 equiv. of $PtCl_2(DMSO)_2$ gave very small colourless crystals suitable for X-ray analysis. The structure revealed that these crystals were the

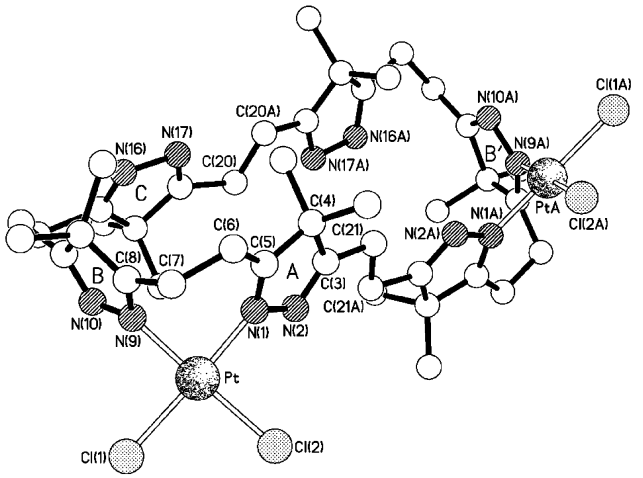


Figure 5. The X-ray structure of the [Cl_2Pt(**4c**)$PtCl_2$].

C_2 symmetric bis-platinum complex [Cl_2Pt(**4c**)$PtCl_2$] illustrated in Figure 5.

As was postulated for **4a**, the platinum atoms are coordinated to nitrogen atoms of adjacent pairs of isopyrazole rings. The platinum atoms are localised on one side of the molecule bridging between the isopyrazole rings positioned at the corners of the rectangular shaped macrocycle and lie one 'above' and one 'below' the mean plane of the macrocycle. This mode of coordination produces a helical twist of the macroring of ca. 45° about the axis joining the centroids of B and B′ isopyrazole units (Fig. 5). The macrocycle has a conformation with a 'down/down/up/down/up/up' pattern for the N–N bonds compared with the regularly alternating up/down arrangement seen in both **4a** and **4c**·toluene/*p*-xylene. The conformation and overall dimensions of the macrocycle (ca. 4.5×9.7 Å) are very different in the complex compared with those in the toluene and xylene adducts, exhibiting a contraction in both the length and breadth but retaining an *anti* geometry for the ethylidene linkages in the two 'long' sides. Most noticeable is the substantial reduction in the breadth, the macrocycle being effectively self-filling. Another feature that emerges from this structure is that once the first two $PtCl_2$ ligands have been coordinated in the geometry observed, the conformation of the macrocycle is constrained such that only one further $PtCl_2$ unit can in principle be coordinated after flipping of one of the remaining pair of non-coordinated isopyrazole rings.

The structure is heavily solvated with chloroform molecules, some of which are ordered, but many that are not and which could not be resolved. The poor quality of the crystals, their instability (two different crystals had to be used for the limited resolution data collection) and their tendency to desolvate spontaneously on removal from solution resulted in relatively large errors in the derived bond lengths and angles. The Pt–Cl and Pt–N distances (av. 2.298(6) and 1.96(2) Å, respectively) are unexceptional and comparable with those seen in for example a dinuclear complex of platinum with 4,4′-dipyrazolylmethane.[18] An analysis of the geometries of the isopyrazole rings is, however, not meaningful because of the large estimated standard deviations in their bond lengths. An analysis of the packing of the molecules revealed no important inter-complex interactions but did show the presence of a network of large channels that extend through the crystal in the *c* direction (Fig. 6).

3. Conclusions

The isopyrazole-containing macrocycles described here are easily obtained in satisfactory yields from the appropriate calixfuran precursors. These macrocycles have been shown to form coordination compounds with platinum complexes and are likely to coordinate other transition metals as well. The larger 'hexameric' macrocycle **4c** is also capable of complexing aromatic substrates by inclusion, though this property has only been proven in the solid state. The diene components of the isopyrazole units are also capable of undergoing cycloadditions, thereby offering a further means to manipulate these macrocyclic systems synthetically. We are currently exploring the use of these compounds for the selective extraction of metal ions from aqueous into organic phases.

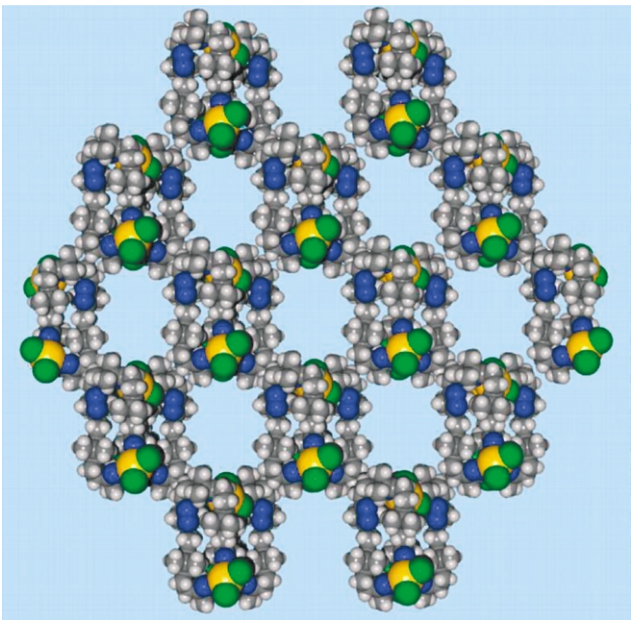


Figure 6. Space-filling representation of the packing in the solid state of molecules of [Cl_2Pt(**4c**)$PtCl_2$] showing the honeycomb pattern of channels that extend in the crystallographic *c* direction.

4. Experimental

4.1. General methods and instrumentation

All chemicals were standard reagent grade and were used without further purification. All air-sensitive and/or moisture sensitive reactions were conducted under a dry argon atmosphere. Thin layer chromatography (TLC) was conducted on Merck SiO_2 60 F254 plastic plates. Compounds were visualised with iodine, vanillin, or by examination under UV light. Column chromatography was conducted on Aldrich Silica gel 230–400 mesh, 60 Å. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 at 300 and 75 MHz, respectively, using the residual proton resonances of the solvents ($CDCl_3$, CD_3CN and CD_2Cl_2) as δ reference. Electron impact mass spectra (EI-MS) were measured on a Finnigan Mat 90 spectrometer operated by Dr Marcello Saitta. Electrospray ionisation mass spectra (ESI-MS) were recorded on a Mariner™ (PerSeptive Biosystems) electrospray ionisation-time of flight (ESI-TOF) mass spectrometer using the following conditions: spray tip potential, 4000 V; nozzle potential, 85 V; detector voltage 2200 V; nozzle temperature 140 °C. The samples, dissolved in CH_3CN at a concentration of about 10^{-6} M, were introduced at a flow rate of 7 mL/min. IR spectra were recorded on a Mattson Genesis II FT-IR spectrometer in mineral oil mull using NaCl disks. Melting points were determined on a Kofler hot stage apparatus, and are not corrected.

The syntheses for compounds **1**, **2**, and **3** have been reported elsewhere.[5a,7,8]

Table 2. Crystal data, data collection and refinement parameters[a]

Data	**4a**	**4c**	**4c**	$[Cl_2Pt(\mathbf{4c})PtCl_2]$
Formula	$C_{28}H_{40}N_8$	$C_{42}H_{60}N_{12}$	$C_{42}H_{60}N_{12}$	$C_{42}H_{60}N_{12}Cl_4Pt_2$
Solvent	$C_7H_8{\cdot}H_2O$	$C_7H_8{\cdot}2(H_2O)$	$C_8H_{10}{\cdot}2(H_2O)$	$10(CHCl_3)$
Formula weight	598.8	861.2	875.2	2458.7
Colour, habit	Colourless prisms	Pale yellow rhombs	Pale yellow rhombs	Colourless needles
Crystal size (mm)	0.80×0.40×0.20	0.52×0.48×0.12	0.77×0.67×0.07	0.83×0.03×0.03
Lattice type	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group, number	$P\bar{1}$, 2	$P2_1/c$, 14	$P2_1/c$, 14	$C2/c$, 15
T (K)	193	183	183	183
Cell dimensions				
a (Å)	10.337(1)	14.727(1)	15.070(2)	29.659(4)
b (Å)	10.493(1)	14.816(2)	14.591(2)	23.380(4)
c (Å)	16.871(1)	11.512(2)	11.487(1)	15.940(2)
α (°)	101.15(1)	—	—	—
β (°)	95.87(1)	105.87(1)	105.50(1)	95.11(1)
γ (°)	99.01(1)	—	—	—
V (Å^3)	1751.7(2)	2416.2(5)	2434.0(4)	11009(3)
Z	2	2[b]	2[b]	4[c]
D_c (g cm^{-3})	1.135	1.184	1.194	1.483
$F(000)$	648	932	948	4800
Radiation used	Cu Kα	Cu Kα	Cu Kα	Cu Kα
μ (mm^{-1})	0.56	0.59	0.59	12.56
θ range (°)	2.7–63.0	4.3–64.0	4.3–60.0	3.6–55.0
No. of unique refln.				
Measured	5613	3701	3606	6953
Observed, $\lvert F_o\rvert>4\sigma(\lvert F_o\rvert)$	4731	3033	2933	3409
No. of variables	438	329	299	535
R_1[d]	0.039	0.047	0.061	0.084
wR_2[e]	0.094	0.116	0.154	0.189
Weights a, b[f]	0.040, 0.448	0.056, 0.703	0.083, 0.473	0.075, 12.463
Largest difference peak, hole (e Å^{-3})	0.17, −0.17	0.21, −0.15	0.50, −0.43	1.80, −1.30

[a] Details in common: graphite monochromated radiation, ω-scans, Siemens P4 diffractometer, rotating anode source, refinement based on F^2.
[b] The molecule has crystallographic C_i symmetry.
[c] The molecule has crystallographic C_2 symmetry.
[d] $R_1=\sum||F_o|-|F_c||/\sum|F_o|$.
[e] $wR_2=\sqrt{\{\sum[w(F_o^2-F_c^2)^2]/\sum[w(F_o^2)^2]\}}$.
[f] $w^{-1}=\sigma^2(F_o^2)+(aP)^2+bP$.

4.1.1. Macrocycle 4a. $N_2H_4{\cdot}H_2O$ (573 mg, 0.55 mL, 11.40 mmol) was added to a solution of octaketone **2a** (960 mg, 1.90 mmol) in THF (50 mL) and the mixture was refluxed for 4 h. After removal of the solvent at reduced pressure, the crude product was subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) to give a major fraction which was crystallized from toluene: 330 mg, 35%, mp 262–264 °C; ^{1}H NMR (CD_3CN) δ: 1.06 (s, 24H, CH_3), 2.84 (s, 16H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 19.7 (CH_3), 21.9 (CH_2), 60.0 [$C(CH_3)_2$], 181.6 (C═N); EI-MS: 489 $(M+1)^+$; selected IR absorptions: 1637 (w), 1577 (m) cm^{-1}. Anal. Calcd for $C_{28}H_{40}N_8{\cdot}C_7H_8{\cdot}H_2O$: C, 70.20; H, 8.42. Found: C, 70.02; H, 8.39.

4.1.2. Macrocycle 4c. $N_2H_4{\cdot}H_2O$ (90 mg, 1.78 mmol) was added to a suspension of dodecaketone **2c** (150 mg, 0.20 mmol) in THF (10 mL) and the mixture was refluxed for 4 h. After removal of the solvent at reduced pressure, the crude product was subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) to give a major fraction which was crystallized from toluene: 60 mg, 41%; mp>260 °C from *p*-xylene; ^{1}H NMR ($CDCl_3$) δ: 1.12 (s, 36H, CH_3), 2.92 (s, 24H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 20.2 (CH_3), 22.0 (CH_2), 60.1 [$C(CH_3)_2$], 182.0 (C═N); EI-MS: 733 $(M+1)^+$; selected IR absorptions: 1630 (w), 1570 (m) cm^{-1}. Anal. Calcd for $C_{42}H_{60}N_{12}{\cdot}C_7H_8{\cdot}2H_2O$: C, 68.34; H, 8.43. Found: C, 68.38; H, 8.31.

A summary of the crystal data, data collection, and refinement parameters for the structures reported in this paper is given in Table 2. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Cryatallography Data Centre as supplementary publication numbers CCDC 214699-214702. 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].

Acknowledgements

This work was supported by the MURST/MIUR, Messina and Catania Universities in Italy. We thank Professor S. Lanza and Professor L. Monsù Scolaro at Messina University for helpful discussions and for supplying the platinum complexes *cis*-$PtMe_2(DMSO)_2$ and *cis*-$PtCl_2$-$(DMSO)_2$.

References and notes

1. (a) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 2001. (b) Gutsche, C. D. In *Calixarenes revisited,*

monographs in supramolecular chemistry; Stoddart, J. F., Ed.; RSC: London, 1998. (c) *Cyclophanes. Topics in current chemistry*; Weber, E., Ed.; Springer: Berlin, 1994; Vol. 172. (d) *Macrocycles. Topics in current chemistry*; Weber, E., Vögtle, F., Eds. 1991; Vol. 161. Springer-Verlag: Berlin, Germany. (e) Diederich, F. In *Cyclophanes, monographs in supramolecular chemistry*; Stoddart, J. F., Ed.; RSC: Cambridge, UK, 1991. (f) Gutsche, C. D. In *Calixarenes, monographs in supramolecular chemistry*; Stoddart, J. F., Ed.; RSC: Cambridge, UK, 1989. (g) *Cyclophanes I. Topics in current chemistry*; Rossa, L., Vögtle, F., Boekelheide, V., Tabushi, I., Yamamura, K., Eds.; Springer: Berlin, 1983; Vol. 113. (h) *Cyclophanes II. Topics in current chemistry*; Vögtle, F., Ed.; Springer: Berlin, 1983; Vol. 115. (i) *Cyclo-phanes, and cyclophanes II, organic chemistry*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic: New York, 1983; Vol. 45.

2. (a) Rudkevich, D. A. *Bull. Chem. Soc. Jpn* **2002**, *75*, 393–413. (b) Holman, K. T.; Pivovar, A. M.; Swift, J. A.; Ward, M. D. *Acc. Chem. Res.* **2001**, *34*, 107–118. (c) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 1018–1033.
3. (a) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1210–1250. (b) Carver, F. J.; Hunter, C. A.; Livingstone, D. J.; McCabe, J. F.; Seward, E. M. *Chem. Eur. J.* **2002**, *8*, 2847–2859. (c) Aschi, M.; Mazza, F.; Di Nolab, A. *J. Mol. Struct. (THEOCHEM)* **2002**, *587*, 177–188. (d) Adams, H.; Jimenez Blanco, J.-L.; Chessari, G.; Hunter, C. A.; Low, C. M. R.; Sanderson, J. M.; Vinter, J. G. *Chem. Eur. J.* **2001**, *7*, 3494–3503. (e) Takahashi, O.; Kohno, Y.; Iwasaki, S.; Saito, K.; Iwaoka, M.; Tomoda, S.; Umezawa, Y.; Tsuboyama, S.; Nishio, M. *Bull. Chem. Soc. Jpn* **2001**, *74*, 2421–2430. (f) Takahashi, H.; Tsuboyama, S.; Umezawa, Y.; Honda, K.; Nishio, M. *Tetrahedron* **2000**, *56*, 6185–6191. (g) Gokel, G. W.; De Wall, S. L.; Meadows, E. S. *Eur. J. Org. Chem.* **2000**, 2967–2978. (h) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.
4. (a) Vysotsky, M.; Saadioui, M.; Böhemer, V. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 2001; pp 250–265. (b) Alcalde, E.; Ayala, C.; Dinares, I.; Mesquida, N.; Sánchez-Ferrando, F. *J. Org. Chem.* **2001**, *66*, 2281–2290. (c) Islyaikin, M. K.; Danilova, E. A.; Yagodarova, L. D.; Rodrìguez-Morgade, M. S.; Torres, T. *Org. Lett.* **2001**, *3*, 2153–2156. (d) Kumar, S.; Hundal, G.; Paul, D.; Hundal, M. S.; Singh, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2295–2301. (e) Kumar, S.; Paul, D.; Hundal, G.; Hundal, M. S.; Singh, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1037–1043. (f) Scheytza, H.; Reissig, H.-U.; Rademacher, O. *Tetrahedron* **1999**, *55*, 4709–4720. (g) Scheytza, H.; Rademacher, O.; Reißig, H.-U. *Eur. J. Org. Chem.* **1999**, 2373–2381. (h) Král, V.; Gale, P. A.; Anzenbacher, P., Jr.; Jursìkova, K.; Lynch, V. M.; Sessler, J. L. *Chem. Commun.* **1998**, 9–10. (i) Trepte, J.; Czugler, M.; Gloe, K.; Weber, E. *Chem. Commun.* **1997**, 1461–1462. (j) König, B.; Rödel, M.; Dix, I.; Jones, P. *J. Chem. Res. (S)* **1997**, 69. (k) Weber, E.; Trepte, J.; Gloe, K.; Piel, M.; Czugler, M.; Kravtosov, V. C.; Simonov, Y. A.; Lipkowski, J.; Ganin, E. V. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2359–2366. (l) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 661–662. (m) König, B.; Rödel, M.; Bubenitschek, P. *J. Org. Chem.* **1995**, *60*, 7406–7410. (n) Musau, R. M.; Whiting, A. *J. Chem. Soc., Perkin Trans.1* **1994**, 2881–2888. (o) Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513–597.
5. (a) Kohnke, F. H.; La Torre, G. L.; Parisi, M. F.; Menzer, S.; Williams, D. J. *Tetrahedron Lett.* **1996**, *37*, 4593–4596. (b) Kohnke, F. H. Unpublished results. For a related example see: (c) Bénéteau, V.; Meth-Cohn, O.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3297–3304.
6. Cafeo, G.; Giannetto, M.; Kohnke, F. H.; La Torre, G. L.; Parisi, M. F.; Menzer, S.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1999**, *5*, 356–368.
7. (a) Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; Parisi, M. F.; Pistone Nascone, R.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **2002**, *8*, 3148–3156. (b) Cafeo, G.; Kohnke, F. H.; Parisi, M. F.; Pistone Nascone, R.; La Torre, G. L.; Williams, D. J. *Org. Lett.* **2002**, *4*, 2695–2697. (c) For conversions of furan units into isothiazoles see: Guillard, J.; Meth-Cohn, O.; Rees, C. W.; White, A. J. P.; Williams, D. *J. Chem. Commun.* **2002**, 232–233.
8. Williams, P. D.; Le Goff, E. *J. Org. Chem.* **1981**, *46*, 4143–4147.
9. (a) Adam, W.; Harrer, H. M.; Nau, W. M.; Peters, K. *J. Org. Chem.* **1994**, *59*, 3786–3797. (b) Sammers, M. P.; Katritzky, A. R. *Adv. Heterocyclc. Chem.* **1983**, *34*, 53–78. (c) Gree, R.; Park, H.; Paquette, L. A. *J. Am. Chem. Soc.* **1980**, *102*, 4397–4403. (d) Stetter, H.; Jonas, F. *Chem. Ber.* **1981**, *114*, 564–580. (e) Bramley, R. K.; Grigg, R.; Guilford, G.; Milner, P. *Tetrahedron* **1973**, *29*, 4159–4167. (f) Evnin, A. B.; Arnold, D. R.; Katritzky, L. A.; Strom, E. *J. Am. Chem. Soc.* **1970**, *92*, 6218–6231.
10. Nicolau, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 766–768.
11. Pyrazole units (but rarely isopyrazole, vide infra) have been extensively investigated as components of transition-metal ligands: (a) Krämer, R. I.; Fritsky, O.; Pritzkow, H.; Kovbasyuk, L. A. *J. Chem. Soc., Dalton Trans.* **2002**, 1307–1314. (b) Mukherjee, R. *Coord. Chem. Rev.* **2000**, *203*, 151–218. (c) Bode, R. H.; Bol, J. E.; Driessen, W. L.; Hulsbergen, F. B.; Reedijk, J. A.; Spek, L. *Inorg. Chem.* **1999**, *38*, 1239–1243. (d) Bol, J. E.; Maase, B.; Gonesh, G.; Driessen, W. L.; Goubitz, K.; Reedijk, J. *Heterocycles* **1997**, *45*, 1477–1492. (e) Sadimenko, P. A.; Basson, S. S. *Coord. Chem. Rev.* **1996**, *147*, 247–297. (f) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943–980. (g) Trofimenko, S. *Chem. Rev.* **1972**, *72*, 497–509.
12. Brooker, S. *Eur. J. Inorg. Chem.* **2002**, *10*, 2535–2547, and references therein.
13. The diene unit in isopyrazole is known to behave as an electron deficient diene in Diels–Alder cycloadditions: (a) Adam, W.; Harrer, H. M.; Nau, W. M.; Peters, K. *J. Org. Chem.* **1994**, *59*, 3786–3797. (b) Beck, K.; Hünig, S. *Chem. Ber.* **1987**, *120*, 477–483. (c) Beck, K.; Hünig, S.; Klärner, F.-G.; Kraft, P.; Artschwager-Perl, U. *Chem. Ber.* **1987**, *120*, 2041–2051. (d) Beck, K.; Hoehn, A.; Hünig, S.; Prokschy, F. *Chem. Ber.* **1984**, *117*, 517–533.
14. Tom, D.; Heindirk, R.; Ingo, W.; Brehm, H. P. Z. *Anorg. Allg. Chem.* **1970**, *379*, 169–182.
15. (a) Price, J. H.; Williamson, A. N.; Schramm, R. F.; Wayland, B. B. *Inorg. Chem.* **1972**, *11*, 1280–1284. (b) Eaborn, C.; Kundu, K.; Pidcock, A. *J. Chem. Soc., Dalton Trans. 4* **1981**, 933–938.
16. (a) Gemma, C.; Amparo, L.; Concepcion, M.; Virtudes, M. E. *Helv. Chim. Acta* **1999**, *82*, 1025–1037. (b) Romeo, R.; Monsù Scolaro, L.; Nastasi, N.; Arena, G. *Inorg. Chem.* **1996**, *35*, 5087–5096, and references therein. (c) Annibale, G.; Bonivento, M.; Cattalini, L.; Tobe, M. L. *J. Chem. Soc.,*

Dalton Trans. **1992**, 3433–3438. (d) Lanza, S.; Monsù Scolaro, L.; Rosace, G. *Inorg. Chim. Acta* **1994**, *227*, 63–69.
17. For recent examples of ESI MS spectra of Pt Complexes with nitrogen-based ligands see: (a) Styles, M. L.; O'Hair, R. A.; McFadyen, W. D.; Tannous, L.; Holmes, R. J.; Gable, R. W. *J. Chem. Soc., Dalton Trans.* **2000**, 93–99. (b) Canty, A. J.; Traill, P. R.; Colton, R.; Thomas, I. M. *Inorg. Chim. Acta* **1993**, *210*, 91–97.
18. Broomhead, J. A.; Rendina, L. M.; Sterns, M. *Inorg. Chem.* **1992**, *31*, 1880–1889.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1903–1911
Tetrahedron

New fluorescent probes for testing combinatorial catalysts with phosphodiesterase and esterase activities

Francisco Caturla,* Juan Enjo, M. Carmen Bernabeu and Stephanie Le Serre

Fachbereich Chemie der Philipps-Universität Marburg, D-35032 Marburg, Germany

Received 17 April 2003; revised 11 December 2003; accepted 11 December 2003

Abstract—Combinatorial development of new catalysts with phosphodiesterase and esterase activities requires specific fluorescent probes for rapid visual detection of hydrolytic activity. Such fluorescent probes have been synthesized with special attention to solubility in water and stability towards spontaneous hydrolysis at a given pH. The probes reported here include compound **5** based on a fluorescein fluorophore, compound **12** for FRET-detection of phosphodiester hydrolysis and compound **25** based on a quinolinium fluorophore.

1. Introduction

Combinatorial chemistry[1] has a major impact on catalyst discovery and optimization.[2] However, the application of combinatorial techniques to this subject requires new high throughput screening methods to monitor a large number of reactions in a quick and simple way.[2a–g,3] While pursuing combinatorial approaches to the development of molecular catalysts for the hydrolysis of phosphodiesters and carboxylic esters, we became interested in the preparation and characterization of novel substrate probes that would allow to monitor hydrolysis reactions, by means of appearance of fluorescence. Our goal was to provide substrates that allow rapid qualitative visual screening of compound libraries for catalytic activity in phosphodiester and carboxylic ester hydrolyses. We were certainly led by known fluorescent probes for enzyme assays, but we did not intend to use these substrates for that purpose.

To design these substrates, we focused on the excellent fluorescent properties of fluorescein,[4] which possesses a relatively high absorptivity and excellent quantum yield. Fluorescein esters have been used previously as fluorescent probes to determine esterase activities. Guilbaut and Kramer[5] reported a study of the hydrolysis of various fluorescein esters by lipases. Also, *p*-guanidinobenzoic acid esters of fluorescein have been used as active site titrants of serine proteases[6] and water insoluble fluorescein monoesters, for example, 3′- or 6′-laureates or myristates, have been used for medicinal applications, determining the activity of pancreas enzymes, lipases or of chymotrypsin in blood, duodenal fluid, or urine.[7] Moreover, the use of fluorescein in the preparation of fluorogenic substrates to continuously monitor the activity of the enzyme phosphatidylinositide-specific phospholipase C has been previously described[8] and Scheigetz and co-workers[9] have prepared 3′,6′-fluorescein diphosphate and different fluorescein monophosphates for highly sensitive and continuous protein tyrosine phosphatase assays.

We therefore wanted to synthesize non-fluorescent esters of fluorescein, which upon hydrolysis liberate the fluorescent fluorescein molecule. Fluorescent probes of that nature could be used in concentrations of up to 10^{-3} M, which is necessary to ensure a reasonable reaction rate on reaction with a catalyst which is present in even lower concentration. If one aims at fluorescent probes which could be used at much lower concentration, one can turn to FRET-based systems,[10] see for instance the system described by Berkessel and co-workers.[11] This methodology requires the presence of a fluorophore and a quencher group linked through an ester or phosphodiester bond. Upon irradiation, a rapid energy transfer occurs between these two parts and the phosphodiester does not fluoresce. When hydrolysis occurs, the fluorophore and the quencher are separated and the internal quenching is disrupted with the consequence that fluorescence can be observed. In the design of our catalytic systems, we tried to emulate nature using aqueous media. Therefore, the fluorescent probes of interest to us should be soluble in water over a broad concentration range and should be stable towards spontaneous hydrolysis at a given pH.

Keywords: Combinatorial catalysis; Fluorescence; Ester hydrolysis; Phosphodiester hydrolysis.
* Corresponding author at present address: Almirall Prodesfarma, Dpto. de Química Médica, Treball 2-4, 08960 Sant Just Desvern, Spain. Tel.: +34-93-291-35-83; fax: +34-93-312-86-35;
e-mail address: jfcaturl@almirall.es

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.032

2. Results and discussion

2.1. Phosphodiester probes

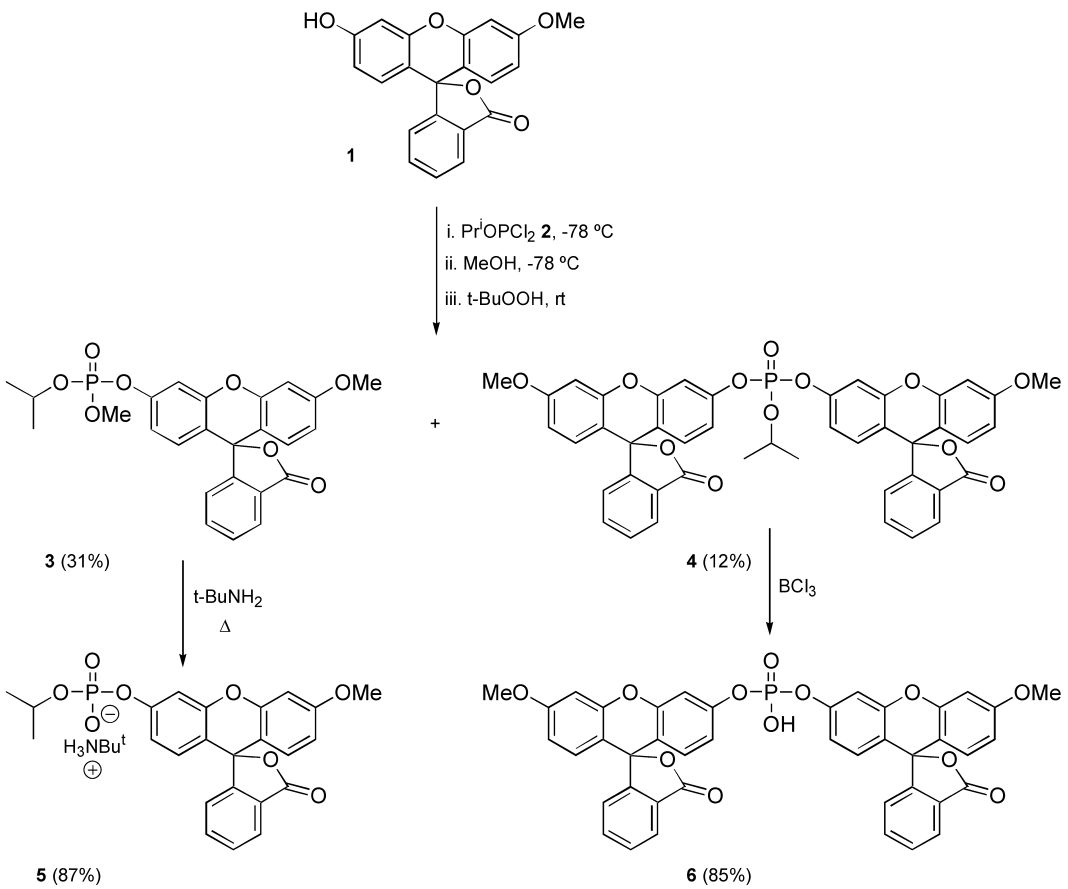
Taking into consideration the wide importance of the phosphodiester linker in nature, we wanted to prepare fluorogenic substrates to continuously monitor phosphodiesterase activity of artificial catalysts. We therefore targeted phosphodiesters of fluorescein. For their preparation, we used the dichloridite procedure previously developed for the synthesis of oligonucleotides.[12] In this vein, dichloridite **2** was reacted sequentially at −78 °C with methyl-fluorescein **1** and MeOH (Scheme 1). In situ oxidation at rt with *t*-BuOOH gave a mixture of two products that could be separated by column chromatography: the phosphate **3** in 31% yield, and the product **4** resulting from the coupling of two molecules of methyl-fluorescein **1** to dichloridite **2** in 12% yield (Scheme 1). Product **3** was subsequently demethylated by treatment with *t*-$BuNH_2$ under reflux, affording phosphodiester **5** in 87% yield after crystallization. The isopropyl group present in phosphate **4** was cleaved by treatment with BCl_3 to give the corresponding phosphodiester **6** in 85% yield (Scheme 1).

For the preparation of a FRET-based system, we aimed at one which would quickly detect phosphodiesterase activity of potential catalysts by using a fluorophore, which could be excited by a simple UV-lamp ($\lambda_{abs}\approx360$ nm) and which would produce a visible fluorescence ($\lambda_{em}>500$ nm) upon hydrolysis of the phosphodiester bond. We therefore modified the Berkessel system and focused on compound **12** shown in Scheme 2. We envisaged that compound **12** would be a suitable substrate, which allows to detect hydrolysis by simple visual observation of fluorescence avoiding the use of spectrophotometers. The synthesis of **12** started with the separate preparation of both the fluorophore **7** and the quencher **10** following procedures described in the literature (Scheme 2).[13,14] For the combination of these two parts, the phosphoramidite coupling method developed by Beaucage and Caruthers[15] for the synthesis of oligonucleotides was used. Thus, fluorophore **7** was reacted with phosphoramidite **8** to afford compound **9** in 61% yield (Scheme 2). Afterwards, compound **9** could be coupled with the azo-derivative **10** in the presence of tetrazole, and the crude product was oxidized in situ with *t*-BuOOH to give the phosphate **11** in 64% yield. The last step was the cleavage of the methyl ester group in **11** using Me_3SiBr[16] to form the desired phosphodiester **12** (Scheme 2).

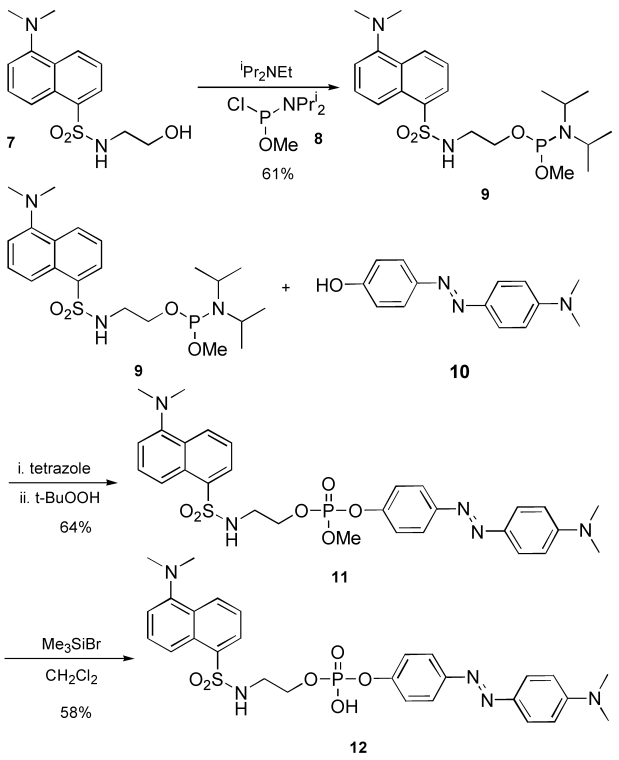
2.2. Carboxylic ester probes

Aiming at water soluble fluorescent probes capable of indicating hydrolysis of carboxylic esters, the attachment of polyol units to fluorescein derivatives was envisioned as a method to increase solubility in water. This could be done either through a polyol moiety bound via the phenolic hydroxyl group to fluorescein or by a polyol group bound via a carboxyl link to the fluorescein core.

Regarding the first approach, our synthetic targets were

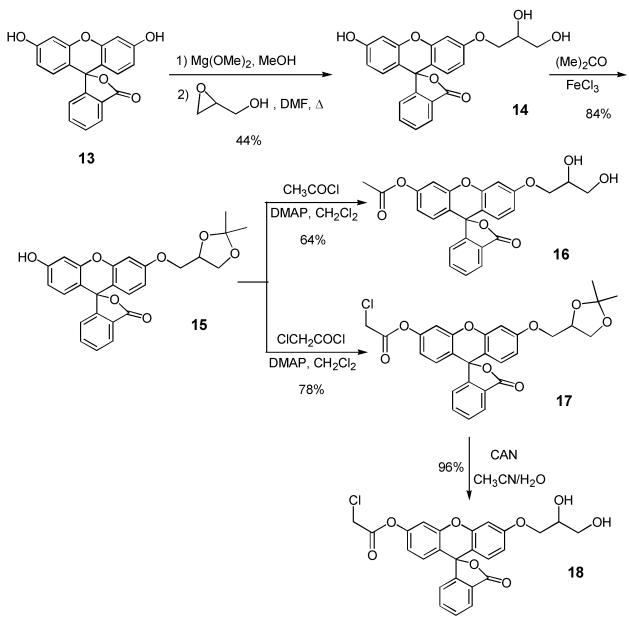


Scheme 1.



Scheme 2.

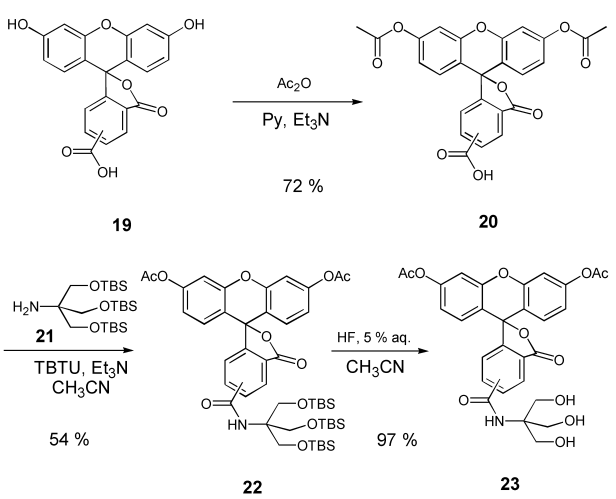
compounds **16** and **18**, having a diol moiety to increase solubility in water (Scheme 3). These compounds were prepared starting from commercially available fluorescein **13** in the following way: the magnesium salt of fluorescein was reacted with glycidol to afford diol **14** in 44% yield. After protection of the diol function as a ketal, the phenolic hydroxyl group of **15** was reacted with acetyl chloride, affording ester **16** directly in 64% yield (Scheme 3), as ketal deprotection took place during the work-up. Likewise compound **15** was treated with chloroacetyl chloride to give compound **17** in 78% yield. After purification by flash chromatography ketal deprotection was achieved under essentially neutral conditions with cerium ammonium nitrate[17] in 96% yield (Scheme 3).



Scheme 3.

Unfortunately, despite the presence of a diol group, did the solubility in water of neither **16** nor **18** exceed 10^{-5} M.

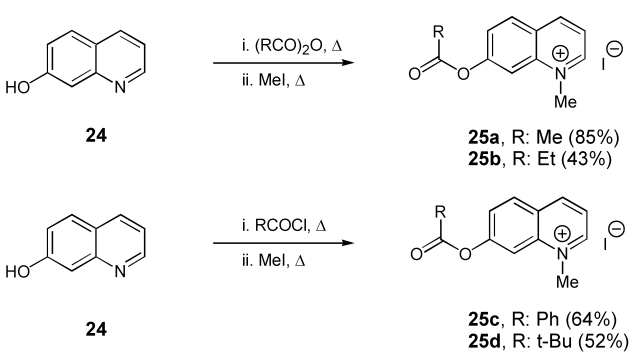
In order to test other possibilities, we turned to carboxyfluorescein **19** to introduce a polyol unit attached via the pendant carboxyl group. Thus, acetylcarboxyfluorescein **20** was coupled to the triethanolamine derivative **21** using *O*-benzotriazolyl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate in 54% yield and the *tert*-butyldimethylsilyl groups of intermediate **22** were removed by treatment with 5% aq. HF, yielding compound **23** in 97% yield (Scheme 4).



Scheme 4.

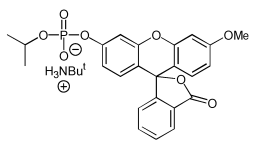
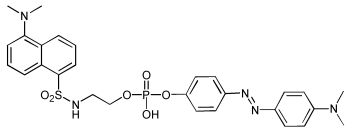
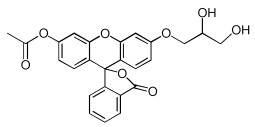
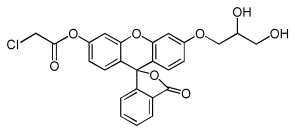
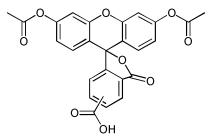
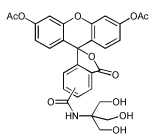
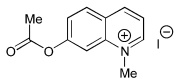
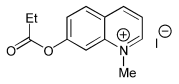
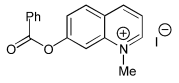
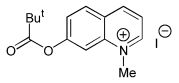
However, again the solubility of compound **23** in water did not exceed 10^{-5} M. Likewise, the solubility of diacetylcarboxyfluorescein **20**, a potential candidate, was also around 10^{-5} M.

Due to the difficulties to increase the water solubility of fluorescein derivatives, we were intrigued by a study of Menger and co-workers[18] who tested the activity of some esterases like acetylcholinesterase and chymotrypsin, using carboxylic esters derived from 7-hydroxyquinoline **24**. The synthesis of compounds **25** was achieved by acylating 7-hydroxyquinoline **24** with an anhydride or an acid chloride and treating the resulting esters with MeI (Scheme 5).



Scheme 5.

Table 1. Qualitative characterization of fluorescent probes

	Fluorescent probes	Solubility	Stability	Enzymatic assay[a]	Outcome[b]
5		$>10^{-3}$ M, pH=8.8[c]	1 d, 10^{-3} M, pH=8.8[c]	PDI[d] 10 min, 10^{-3} M, pH=8.8[c]	Green fluorescence
12		10^{-5} M, pH=8.8[c]	6 h, 10^{-5} M, pH=8.8[c]	PDI,[d] 10 min, 10^{-6} M, pH=8.8[c]	Green fluorescence
16		10^{-5} M, pH=7.0[e]	6 h, 10^{-5} M, pH=7.0[e]	PPL,[f] 10 min, 10^{-5} M, pH=7.0[e]	Green fluorescence
18		10^{-5} M, pH=7.0[e]	2 h, 10^{-5} M, pH=7.0[e]	PPL,[f] 10 min, 10^{-5} M, pH=7.0[e]	Green fluorescence
20		10^{-5} M, pH=8.8[c]	2 d, 10^{-5} M, pH=8.8[c]	PPL,[f] 10 min, 10^{-5} M, pH=8.8[c]	Green fluorescence
23		10^{-5} M, pH=8.8[c]	1 d, 10^{-5} M, pH=8.8[c]	—[g]	—[g]
25a[h]		$>10^{-2}$ M, pH=7.0[e]	2 h, 10^{-3} M, pH=7.0[e]	—[g]	—[g]
25b[h]		$>10^{-2}$ M, pH=7.0[e]	3 h, 10^{-3} M, pH=7.0[e]	PPL,[f] 20 min, 10^{-3} M, pH=7.0[e]	Green fluorescence
25c[i]		$>10^{-2}$ M, pH=7.0[e]	24 h, 10^{-3} M, pH=7.0[e]	PPL,[f] 120 min, 10^{-3} M, pH=7.0[e]	Green fluorescence
25d[i]		$>10^{-2}$ M, pH=7.0[e]	30 h, 10^{-3} M, pH=7.0[e]	PPL,[f] 240 min, 10^{-3} M, pH=7.0[e]	Green fluorescence

[a] All enzymatic assays were done taking 1 mL of a stock solution of the corresponding fluorescent probe in the buffer and concentration quoted and adding the enzyme as solid.
[b] The estimated visual detection threshold of all the probes is below 10^{-6} M.
[c] 0.1 M AMPSO buffer {3-[(1,1-dimethyl-2-hydroxyethyl)amino]-2-hydroxypropanesulfonic acid}.
[d] Phosphodiesterase I (EC 3.1.4.1, type IV from crotalus atrox crude dried venom): 10 mg, 0.1 units.
[e] 0.1 M HEPES buffer [*N*-(2-hydroxyethyl)piperazine-*N*′-(2-ethanesulfonic acid)].
[f] Porcine pancreas lipase (EC 3.1.1.3. type II, crude): 4 mg, 50 units.
[g] Compound not tested because of a lack of enough material.
[h] A 10^{-3} M solution of this compound in water shows a blue color.
[i] A 10^{-3} M solution of this compound in water shows a violet color.

The water solubility of this class of fluorescent probes was in all cases, larger than 10^{-2} M providing a set of compounds which should allow easy visual detection of ester hydrolysis when exposed to potential catalysts.

3. Testing

In order to characterize the new fluorescent probes in a qualitative manner, these were first subjected to stability

tests at pH 7 or 8.8. Lacking active synthetic catalysts at this stage of our work we tested the viability of our probes by subjecting them to cleavage by phosphodiesterase I or porcine pancreas lipase under buffered conditions. The results reported in Table 1 reflect the appearance of color as determined by the naked eye.

As we can see from the table, the fluorescein derived phosphodiester **5** showed good solubility in water ($>10^{-3}$ M) and is stable in aqueous pH 8.8 buffer safely over one day. Phosphodiester **6** was not tested because of a lack of enough material. In the case of the phosphodiester **12**, its solubility in water was only around 10^{-5} M, but higher concentrations are anyhow not tolerated if the FRET technique is to be applied to monitor ester hydrolysis.

Turning to the carboxylic esters **16** and **18**, they showed a low solubility in water (10^{-5} M as maximum) and also low stability towards spontaneous hydrolysis.

The problem of insufficient stability was overcome with compounds **20** and **23** derived from carboxyfluorescein **19**, stability in the buffer system extended to around 2 d for compound **20**. The solubility of compounds **20** and **23** in water is still low (10^{-5} M). The triol moiety therefore did not contribute too much to increase the solubility in water. Nevertheless the strong green fluorescence emitted by the fluorophore can easily be detected, once the carboxylic ester is hydrolyzed.

In the case of the quinolinium derivatives shown in Table 1, the solubility was not a problem, being higher than 10^{-2} M. The stability to spontaneous hydrolysis ranges from 2 h, for compound **25a**, to 30 h in the case of compound **25d**. Therefore, compounds **25a** and **25b** are too labile to be considered useful fluorescent probes.

In summary, the best fluorescent probe for monitoring the cleavage of phosphodiesters is compound **5**. Regarding fluorescent probes for cleavage of carboxylic esters, the best candidates are compound **20**, derived from carboxyfluorescein **19** and the quinolinium derivatives **25c** and **25d**, showing good solubility in water and a useful stability against spontaneous hydrolysis.

4. Experimental

4.1. General

All temperatures quoted are not corrected. Reactions were carried out under dry nitrogen or argon. ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX-200 and AC-300 spectrometers. Spectra were recorded for ca. 0.2 mM solutions in $CDCl_3$ (99% d), which was also used as an internal standard. Coupling constants are quoted in Hz. Flash chromatography was run using silica gel Si 60 (40–63 μm, E. Merck AG, Darmstadt). Electron impact (EI, 70 eV) mass spectra were recorded on a Varian CH 7A instrument.

4.2. 3′-(Isopropoxy(methoxy)phosphoryl(-6′-methoxy-spiro(isobenzo-furan-1(3*H*)-9′(9′*H*)-xanthen(-3-one (3) and isopropylbis{6′-methoxy-spiro[isobenzofuran-1(3*H*)-9′(9′*H*)-xanthen]-3-one-3′-yl}phosphate (4)

Pyridine (1 mmol, 81 μL) was added via syringe to a solution of Pr^iOPCl_2 **2**[19] (0.265 mmol, 43 mg) in dry THF (0.35 mL) maintained at −78 °C in a small flask equipped with a septum cover. To the solution was added methylfluorescein (0.24 mmol, 83 mg) dissolved in 0.65 mL of dry THF. After a total of 10 min, methanol (0.19 mmol) was added (via syringe). The solution was maintained for 15 min at −78 °C. The reaction mixture was warmed to rt and to it was added a solution of *t*-BuOOH in CH_2Cl_2 (7 M, 125 μL). After 2 h at rt, H_2O was added and the aqueous phase was extracted with $CHCl_3$ (3×15 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford a residue which was purified by flash chromatography (eluent: CH_2Cl_2/EtOAc: 93/7), yielding phosphates **3** and **4** with the yield mentioned in the text. Compound **3**. R_f=0.36 ($CHCl_3$/EtOAc: 9/1). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.38 (m, 6H), 3.84 (s, 3H), 3.86 (d, *J*=14.0 Hz, 3H), 4.79 (m, 1H), 6.64–6.79 (m, 5H), 7.19 (m, 2H), 7.66 (m, 2H), and 8.03 (d, *J*=7.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.6, 54.7, 54.9, 55.6, 74.3, 74.4, 82.5, 100.9, 108.5, 111.0, 112.0, 115.8, 116.0, 124.0, 125.1, 126.6, 129.0, 129.4, 129.9, 135.1, 152.1, 152.3, 153.1, 161.5, and 169.3. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−5.98. HR-MS: $C_{24}H_{20}PO_8-CH_3$ requires 467.0896; found 467.0903. Compound **4**. R_f=0.57 ($CHCl_3$/EtOAc: 9/1). Mp 97–99 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.41 (m, 6H), 3.83 (s, 6H), 4.94 (m, 1H), 6.64–7.00 (m, 10H), 7.17 (m, 4H), 7.65 (m, 4H), and 8.03 (d, *J*=7.0 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.5, 25.8, 55.6, 75.8, 82.3, 100.9, 108.7, 110.9, 112.1, 115.8, 116.5, 123.9, 125.1, 126.5, 129.0, 129.6, 129.9, 135.2, 151.6, 152.1, 152.2, 153.0, 161.5, and 169.2. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−13.10. *m/z* 360 (M^+−436, 8%). HR-MS: $C_{20}H_{10}PO_5$ requires 360.0188; found 360.0981.

4.3. *tert*-Butylammonium isopropyl-{6′-methoxy-spiro-(isobenzofuran-1(3*H*)-9′(9′*H*)-xanthen(-3-one-3′-yl}phosphate (5)

A solution of phosphate **3** (230 mg) in *t*-$BuNH_2$ (140 mL) was heated at reflux for 8 h. The solvent was removed at reduced pressure affording a solid which was recrystallized from EtOAc/hexane to afford 200 mg of pure phosphodiester **5** (87%). R_f=0.27 ($CHCl_3$/MeOH: 9/1). Mp 205–206 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.20 (d, *J*= 6.2 Hz, 6H), 1.31 (s, 9H), 3.83 (s, 3H), 4.50 (m, 1H), 6.58–7.24 (m, 7H), 7.63 (m, 2H), and 8.01 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=23.9, 27.7, 51.4, 55.6, 70.5, 83.0, 100.9, 107.7, 107.8, 111.1, 111.7, 113.6, 116.0, 116.1, 123.8, 125.0, 126.8, 128.7, 129.0, 129.7, 135.0, 151.9, 152.5, 153.2, 154.7, 154.8, 161.4, and 169.4. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−6.23. *m/z* 466 ($M^+-H_3N^+Bu^t$-1, 2%). HR-MS: $C_{24}H_{20}O_8P$ requires 467.0894; found 467.1537.

4.4. Bis{6′-methoxy-spiro[isobenzofuran-1(3*H*)-9′(9′*H*)-xanthen]-3-one-3′-yl}phosphate (6)

To a solution of phosphate **4** (48 mg, 0.06 mmol) in dry CH_2Cl_2 (4 mL) was added with stirring a 1 M solution of

BCl_3 in heptane at −10 °C. The stirring was continued under N_2 for 45 min at the same temperature, and then 1 M HCl was added. The resulting mixture was extracted with EtOAc (3×15 mL). The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated to afford 38 mg (85% yield) of phosphodiester **6**, essentially pure. R_f=0.24 ($CHCl_3$/MeOH: 85/15). Mp 198–200 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.69 (s, 6H), 6.50–7.11 (m, 14H), 7.51 (m, 4H), 7.90 (m, 2H), and 8.60 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=55.7, 100.7, 108.6, 111.2, 111.2, 112.6, 116.2, 116.5, 124.3, 125.4, 126.6, 129.0, 129.4, 129.9, 135.0, 152.2, 152.6, 162.1, and 169.1. ^{31}P NMR (81 MHz, $CDCl_3$): δ=−12.20. *m/z* 360 (M^+−395, 66%). HR-MS: $C_{20}H_{10}PO_5$ requires 360.0188; found 360.0981.

4.5. *N*-[2-(Diisopropylamino-methoxyphosphoxy)ethyl]-5-dimethylamino-1-naphthalenesulfonamide (9)

Chloro(diisopropylamino)methoxyphosphine **8** (268 mg, 1.35 mmol) was added to a solution of compound **7** (200 mg, 0.679 mmol) in CH_2Cl_2 (3 mL), containing diisopropylethylamine (473 μL, 2.7 mmol). The mixture was stirred for 35 min at rt. The resulting solution was diluted with CH_2Cl_2 (50 mL) and washed with 5% aq. $NaHCO_3$ (2×25 mL), brine (820 mL), dried ($MgSO_4$), filtered and concentrated. The crude phosphoramidite was purified by chromatography (5 g of silica gel, prewashed with a mixture of pentane/EtOAc/Et_3N: 50/50/1). The product was eluted with the same mixture and evaporation of appropriate fractions gave the phosphoramidite as a yellow oil (71% yield). R_f=0.53 (pentane/EtOAc/Et_3N: 50/50/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (d, *J*=6.8 Hz, 6H), 2.78 (s, 6H), 2.99 (t, *J*=5.83 Hz, 2H), 3.16 (d, *J*=12.8 Hz, 3H), 3.39–3.48 (m, 4H), 6.56 (t, *J*=9.8 Hz, 1H), 7.16 (m, 1H), 7.47–7.55 (m, 2H), and 8.11–8.48 (m, 2H). ^{31}P NMR (81 MHz, CDCl3) δ=149.5. ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.0, 43.2, 45.3 (d, *J*=13.5 Hz), 50.5 (d, *J*=10.06 Hz), 62.5 (d, *J*=17.1 Hz), 115.4, 119.2, 123.5, 128.6, 129.7, 130.0, 130.3, 130.4, 135.1, 137.0.

4.6. 2-(5-Dimethylamino-1-naphthalenesulfonyl-amide)ethoxy-4-(4-dimethyl-aminophenylazo)-phenyl-methylphosphate (11)

A solution of phosphoramidite **9** (196 mg, 0.43 mmol) in dry and acid free CH_2Cl_2 (2 mL) was added to a solution of the azo-compound **10** (103 mg, 0.43 mmol) in CH_2Cl_2 (1 mL) containing tetrazole (1.9 mL, 0.45 M in CH_3CN). The mixture was stirred for 2 h and then *t*-BuOOH (3 M solution in isooctane, 430 μL) was added and this mixture was stirred for an additional hour. The resulting solution was diluted with CH_2Cl_2 (30 mL) and washed with 5% aq. $NaHCO_3$ (2×15 mL), brine (20 mL), and dried ($MgSO_4$). The solution was filtered and evaporated under vacuum and the residue was chromatographed (silica flash, 5 g, CH_2Cl_2/EtOAc: 10/1 and 7/3). Evaporation of appropriate fractions gave the phosphotriester **11** as an oil (64% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.74 (s, 6H), 2.97 (s, 6H), 3.36 (dd, *J*=5.5, 5.4 Hz, 2H), 3.65 (d, *J*=11.4 Hz, 3H), 4.03 (ddd, *J*=9.2, 5.6 Hz, 2H), 6.73 (d, *J*=9.2 Hz, 1H), 7.16 (m, 4H), 7.43–7.47 (m, 2H), 7.69 (t *J*=9.2 Hz, 4H), 8.12 (dd, *J*=7.3, 1.3 Hz, 1H), 8.26 (d, *J*=8.3 Hz, 1H), 8.44 (d, *J*=8.6 Hz, 1H). ^{31}P NMR (81 MHz, CDCl3) δ=−4.36. ^{13}C NMR (50 MHz, $CDCl_3$): δ=40.7, 43.8, 55.6 (d, *J*= 6.0 Hz), 67.7 (d, *J*=6.0 Hz), 111.8, 115.7, 119.1, 120.6, 120.7, 123.5, 124.0, 125.4, 128.9, 129.8, 129.9, 130.3, 131.0, 135.0, 143.8, 151.2 (d, *J*=7.0 Hz), and 152.9.

4.7. 2-(5-Dimethylamino-1-naphthalenesulfonyl-amide)ethoxy-4-(4-dimethylaminophenylazo)-phenyl-phosphate (12)

To a solution of phosphate **11** (84 mg, 0.14 mmol) in CH_2Cl_2 (4 mL), was added Me_3SiBr (38.2 μL, 0.28 mmol). The solution was stirred for 3 h at rt and then evaporated under vacuum (30 °C). The residue was dissolved in acetone (6.1 mL) followed by addition of water (1.15 mL). The solution was stirred for 30 min at rt and then evaporated in vacuo to give a residue that was dissolved in $CHCl_3$ (50 mL), washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated to yield a crude phosphodiester which was purified by chromatography (silica flash, 5 g, Et_2O, $CHCl_3$/MeOH: 10/1). Concentration of the appropriate fractions gave phosphodiester **12** as a red solid (34% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.76 (s, 6H), 2.87 (s, 6H), 2.87 (m, 2H), 4.02 (ddd, *J*=9.2, 5.6 Hz, 2H), 6.51 (m, 2H), 6.75 (m, 1H), 6.80 (d, *J*=9.2 Hz, 1H), 7.36 (t, *J*=9.0 Hz, 2H), 7.74 (m, 5H), 8.20 (d, *J*=7.3 Hz, 1H), 8.37 (d, *J*=7.4 Hz, 1H), 8.40 (d, *J*=8.6 Hz, 1H). ^{31}P NMR (81 MHz, $CDCl_3$) δ=−3.68. ^{13}C NMR (50 MHz, $CDCl_3$): δ=40.1, 40.4, 42.3, 62.4 (d, *J*=9.4 Hz), 118.8, 120.0, 121.8, 122.5, 122.8, 123.2, 123.8, 124.7, 125.4, 126.0, 135.6, 136.6, 140.1, 142.2, 148.1, 153.7 (d, *J*=10.1 Hz), and 154.1.

4.8. 3′-Hydroxy-6′-(2,3-dihydroxypropoxy)spiro-(isobenzofuran-1(3*H*)-9′(9′*H*)-xanthen(-3-one (14)

Fluorescein **13** (332 mg, 1 mmol) was added in small portions under stirring at rt to a methanol solution of $Mg(OCH_3)_2$ (0.25 M, 8 mL). After stirring for 40 min the solvents were evaporated to dryness in vacuum. The resulting solid was powdered and added to a solution of glycidol (271 μL, 4 mmol) in DMF (8 mL). The mixture was stirred at 120 °C for 16 h. The resulting solution was diluted with 1 M HCl to pH=2 and extracted by continuous extraction with CH_2Cl_2 during 1 d. The organic layer was dried ($MgSO_4$) and evaporated to give a residue which was purified by flash chromatography ($CHCl_3$/MeOH: 85/15) on silica gel, affording 179 mg (44%) of compound **14** as a yellow solid (mixture of diastereomers). R_f=0.25 ($CHCl_3$/CH_3OH: 85/15). ^{1}H NMR (300 MHz, CD_3OD): δ=3.52–3.74 (m, 2H), 3.89–4.02 (m, 3H), 4.78 (broad s, 2H), 6.39–6.25 (m, 5H), 6.74 (d, *J*=2.2 Hz, 1H), 7.04 (m, 1H, ArH), 7.59 (m, 2H), and 7.86 (m, 1H). ^{13}C NMR (75 MHz, CD_4OD): δ=61.1, 63.3, 69.9, 70.8, 78.6, 80.2, 85.5, 101.9, 102.9, 110.4, 110.7, 112.2, 112.9, 124.4, 124.6, 125.0, 125.1, 127.2, 127.5, 129.2, 129.3, 129.4, 130.3, 135.7, 135.8, 153.1, 153.3, 153.5, 160.3, 160.5, 161.4, 170.8, and 170.9. *m/z* 406 (M^+, 1%). HR-MS: $C_{23}H_{18}O_7$ requires 406.1053; found 406.1052.

4.9. 6′-Hydroxy-3′-(2,2-dimethyl-1,3-dioxolan-4-yl-methoxy)spiro(isobenzo-furan-1(3*H*),9′(9′*H*)-xanthen(-3-one (15)

Anhydrous $FeCl_3$ (33 mg, 0.20 mmol) was added at rt to a

solution of compound **14** (100 mg, 0.25 mmol) in dry acetone (13 mL), stirring the mixture at 36 °C. After 2 h, evaporation of solvent left a residue, which was purified by flash chromatography ($CHCl_3$/MeOH: 95/5) to afford the ketal **15** as a yellow solid (94 mg, 84%, mixture of diastereomers). R_f=0.20 ($CHCl_3$/CH_3OH: 95/5). ^1H NMR (300 MHz, $CDCl_3$): δ=1.41, 1.47 (2 s, 6H), 3.90 (dd, J=8.3, 5.8 Hz, 1H), 3.97 (dd, J=9.6, 5.7 Hz, 1H), 4.06 (dd, J=9.6, 5.4 Hz, 1H), 4.17 (m, 1H), 4.50 (m, 1H), 6.60–6.76 (m, 6H), 7.17 (d, J=7.2 Hz, 1H), 7.64 (m, 2H), and 8.02 (d, J=6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.3, 26.7, 66.6, 69.0, 73.8, 84.5, 101.6, 103.1, 110.0, 110.7, 111.5, 111.9, 112.5, 124.0, 125.0, 126.7, 129.1, 129.2, 129.7, 135.1, 152.4, 153.1, 158.3, 160.2, and 170.1. m/z 446 (M^+, 2%), and 431 (M^+-15, 12%). HR-MS: $C_{26}H_{22}O_7$ requires 446.1366; found 446.1372.

4.10. 6′-Acetoxy-3′-(2,3-dihydroxypropoxy)spiro-(isobenzo-furan-1(3*H*),9′(9′*H*)-xanthen(-3-one (16)

A solution of ketal **15** (118 mg, 0.26 mmol), acetyl chloride (21 μL, 0.29 mmol) and an excess of 4-dimethylamino-pyridine (DMAP) in dry CH_2Cl_2 (4 mL) was heated under reflux for 3 h. Then, one more portion of acetyl chloride (21 μL, 0.29 mmol) was added, and the mixture was refluxed for 4 h and kept overnight at rt H_2O was added, the phases were separated and the aqueous layer was extracted with $CHCl_3$ (3×15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuum to give a residue which was purified by silica flash chroma-tography eluting with $CHCl_3$/MeOH: 95/5 to give the ester **16** (72 mg, 64%) as a mixture of diastereomers. R_f=0.20 ($CHCl_3$/CH_3OH: 95/5). ^1H NMR (300 MHz, $CDCl_3$): δ=1.67 (broad s, 1H), 2.31 (s, 3H), 2.67 (m, 1H), 4.06 (m, 2H), 4.14–4.34 (m, 3H), 6.58–6.83 (m, 5H), 7.08 (m, 1H), 7.17 (m, 1H), 7.66 (m, 2H), and 8.03 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.1, 65.2, 68.4, 69.1, 84.5, 101.7, 110.3, 112.2, 116.7, 117.5, 124.0, 125.1, 126.5, 129.0, 129.1, 129.9, 135.1, 151.8, 152.0, 152.2, 153.0, 160.1, 168.8, and 171.1. m/z 446 (M^+-2, 4%). $C_{25}H_{20}O_8$: requires C, 66.96; H, 4.50; found C, 66.85; H, 4.66.

4.11. 6′-(2-Chloroacetoxy)-3′-(2,2-dimethyl-1,3-dioxo-lan-4-yl-methoxy)spiro-(isobenzofuran-1(3*H*),9′(9′*H*)-xanthen(-3-one (17)

A solution of compound **15** (64 mg, 0.14 mmol), chloro-acetyl chloride (13 μL, 0.16 mmol) and an excess of 4-dimethylaminopyridine (DMAP) in dry CH_2Cl_2 (3 mL) was heated under reflux for 6 h. The volatile components were removed under reduced pressure and the residue was purified by flash chromatography (pentane/EtOAc: 1/1) on silica gel to give the ester **17** as almost colorless solid (57 mg, 78%, mixture of diastereomers). R_f=0.38 ($CHCl_3$/CH_3OH: 10/1). ^1H NMR (3×00 MHz, $CDCl_3$): δ=1.41, 1.47 (2s, 6H), 3.90 (dd, J=8.3, 6.0 Hz, 1H), 3.98 (dd, J=9.6, 5.8 Hz, 1H), 4.08 (dd, J=9.6, 5.5 Hz, 1H), 4.18 (dd, J=8.3, 6.7 Hz, 1H), 4.32 (s, 2H), 4.49 (q, J= 5.8 Hz, 1H), 6.61–6.84 (m, 5H), 7.10–7.20 (m, 2H), 7.67 (m, 2H), and 8.04 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.3, 26.7, 40.7, 66.6, 69.1, 73.7, 82.2, 101.6, 109.9, 110.0, 111.3, 112.3, 116.9, 117.3, 123.9, 125.2, 126.4, 129.1, 129.3, 129.9, 135.2, 151.3, 151.8, 152.0, 152.9, 160.4, 165.4, and 169.2. m/z 521 (M^+-1, 2%), and 523 (M^+, 2%). HR-MS: $C_{28}H_{22}ClO_8$ requires 521.1003; found 521.0989.

4.12. 6′-(2-Chloroacetoxy)-3′-(2,3-dihydroxypropoxy)-spiro-(isobenzofuran-1(3*H*),9′(9′*H*)-xanthen(-3-one (18)

A solution of CAN (123 mg, 0.22 mmol) in 6 mL of H_2O was added at 70 °C under inert atmosphere to a stirred solution of the protected ester **17** (45 mg, 0.09 mmol) in 3 mL of CH_3CN. The mixture was stirred at 70 °C during 5 min. Then, H_2O was added (15 mL) and this mixture was extracted with $CHCl_3$ (3×15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure affording 40 mg of pure product **18** (96%) as mixture of diastereomers. R_f=0.32 (pentane/EtOAc: 1/4). ^1H NMR (500 MHz, $CDCl_3$): δ= 2.04, 2.61 (2 broad s, 2H), 3.75 (dd, J=11.4, 5.4 Hz, 1H), 3.85 (dd, J=11.4, 3.8 Hz, 1H), 4.05–4.16 (m, 3H, CH_2), 4.31 (s, 2H), 6.62–6.84 (m, 5H), 7.12–7.17 (m, 2H), 7.67 (m, 2H), and 8.03 (d, J=7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=40.8, 63.5, 69.4, 70.2, 82.1, 101.7, 110.0, 111.5, 112.3, 117.0, 117.4, 123.9, 125.2, 126.4, 129.2, 130.0, 135.2, 151.4, 151.8, 152.1, 152.9, 160.3, 165.4, and 169.2. m/z 439 (M^+-44, <1%).

4.13. 3′,6′-Diacetyl-5(6)-carboxyspiro-(isobenzofuran-1(3*H*),9′(9′*H*)-xanthen(-3-one (20)

Acetic anhydride (1.08 g, 10.58 mmol) was added dropwise to a solution of carboxyfluorescein (2.00 g, 5.31 mmol) in dry pyridine (25 mL) and dry Et_3N (14 mL). The yellow solution was stirred for 36 h and then $HCCl_3$ (30 mL) was added, washed with HCl 10% (4 x 20 mL) and dried (Na_2SO_4). The residue was crystallized in EtOAc–pentane to obtain the desired diacetyl carboxyfluorescein **20** (1.75 g, 71%) as a white solid.

The observed spectral data were in accord with those reported in literature.[20]

4.14. 3′,6′-Diacetyl-5(6)-{tris[(*tert*-butyldimethyl)-silyl-oxymethyl]methylcarbamoyl}spiro-(isobenzo-furan-1(3*H*),9′(9′*H*)-xanthen(-3-one (22)

To a solution of compound **20** (200 mg, 0.43 mmol), amine 24 (202 mg, 0.43 mmol), and triethylamine (0.13 mL, 0.93 mmol) in dry acetonitrile (10 mL) was added TBTU (167 mg, 0.52 mmol). After stirring at rt for 25 min, brine (20 mL) was added and the aqueous layer extracted with EtOAc (3×15 mL). Organic layers were washed succes-sively with HCl 10% (20 mL), water (20 mL), $NaHCO_3$ 5% (2×25 mL), and water (20 mL), and dried with Na_2SO_4. Solvent was removed to obtain a yellow foam which was purified by silica gel flash chromatography (Et_2O/pentane: 1/1) affording fluorescein derivative **22** as a white foam (210 mg, 54%). ^1H NMR (200 MHz, $CDCl_3$, mixture of two compounds) δ=−0.03 (s, $18H_B$), 0.07 (s, $18H_A$), 0.78 (s, $27H_B$), 0.89 (s, $27H_A$), 2.32 (s, $6H_A$+$6H_B$), 3.88 (s, $6H_B$), 3.98 (s, $6H_A$), 6.28 (s, $1H_B$), 6.77 (s, $4H_A$+$4H_B$), 7.07 (s, $2H_A$+$2H_B$), 7.20 (m, $1H_A$), 7.36 (s, $1H_B$), 7.95 (d, J= 4.2 Hz, $1H_B$), 8.05 (m, $1H_A$+$1H_B$), 8.29 (s, $1H_A$). m/z 890 (M^+-Me, 52%), 848 ($MH^+-Me-Ac$, 100%), 806 ($MH^+-Me-2Ac$, 4%).

4.15. 3′,6′-Diacetyl-5(6)-[tris[(hydroxymethyl)methylcarbamoyl]spiro-(isobenzofuran-1(3*H*),9′(9′*H*)-xanthen(-3-one (23)

To a solution of fluorescein derivative **22** (100 mg, 0.11 mmol) in acetonitrile (2 mL) was added 1 mL of a solution of HF 5% (acetonitrile/water). Ten minutes later, CH_2Cl_2 (10 mL) and water (10 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and organic layers were washed with brine (2×10 mL), and dried with Na_2SO_4. Solvent was removed to obtain fluoresceintriol **23** as a white solid (60 mg, 97%). ^{1}H NMR (200 MHz, $CDCl_3$, mixture of two compounds) δ= 2.19 (s, $6H_A$+$6H_B$), 3.60 (s, $6H_B$), 3.68 (s, $6H_A$), 6.60 (m, $3H_A$+$4H_B$), 6.98 (m, $2H_A$+$2H_B$), 7.15 (d, J=4.0 Hz, $1H_A$), 7.24 (s, $1H_B$), 7.42 (s, $1H_A$), 7.56 (s, $1H_B$), 7.95 (m, $1H_A$), 8.08 (d, J=4.2 Hz, $1H_B$), 8.39 (s, $1H_A$). *m/z* 564 (MH^+, 8%).

4.16. 7-Acetoxy-*N*-methylquinolinium iodide (25a)

A solution of 7-hydroxyquinoline **24** (60 mg, 0.41 mmol) in acetic anhydride (3 mL, 31.8 mmol) was stirred for 40 h at 37 °C. Methyl iodide (1.50 mL, 24.09 mmol) was added and the mixture was stirred at 50 °C for 24 h. A solid was formed. Ethyl ether was added to ensure complete precipitation, and the solution was filtered. The crude solid was crystallized three times from methanol–ethyl ether to obtain 115 mg (85%) of yellow crystals. Mp 202–203 °C (decomp.). ^{1}H NMR (200 MHz, $CDCl_3$) δ=2.43 (s, 3H), 4.73 (s, 3H), 7.74 (dd, J=9.0, 2.0 Hz, 1H), 8.09 (dd, J=8.3, 5.8 Hz, 1H), 8.17 (d, J=1.5 Hz, 1H), 8.33 (d, J= 9.0 Hz, 1H), 9.18 (d, J=8.3 Hz, 1H), 9.94 (d, J=6.0 Hz, 1H). ^{13}C NMR (50 MHz, MeOH-d_4) δ=21.11, 46.59, 112.20, 122.63, 127.36, 129.19, 133.35, 141.39, 148.50, 151.57, 157.77, 170.06. m/z 187 (M^+−Me, 5%), 160 (MH^+−Ac, 7%), 145 (MH^+−Me−Ac, 100%), 142 (M^+−AcOH, 43%). HR-MS: $C_{11}H_9NO_2$ requires 187.0633; found 187.0637.

4.17. 7-Propionyloxy-*N*-methylquinolinium iodide (25b)

A mixture of 7-hydroxyquinoline **24** (48 mg, 0.33 mmol) in propionic anhydride (3 mL, 23.4 mmol) was stirred at 40 °C for 48 h. Methyl iodide (1.50 mL, 24.09 mmol) was added and the mixture was stirred at reflux for 24 h. Ethyl ether was added and the yellow precipitate was filtered. The crude solid was crystallized twice from methanol–ethyl ether to obtain 47 mg (43%) of dark yellow crystals. Mp 159–160 °C (decomp.). ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.30 (t, J=7.6 Hz, 3H), 2.75 (q, J=7.5 Hz, 2H), 4.80 (s, 3H), 7.73 (dd, J=9.0, 2.0 Hz, 1H), 8.10 (dd, J=8.3, 5.7 Hz, 1H), 8.22 (d, J=1.5 Hz, 1H), 8.42 (d, J=9.0 Hz, 1H), 9.04 (d, J=8.3 Hz, 1H), 10.16 (d, J=5.7 Hz, 1H). ^{13}C NMR (50 MHz, MeOH-d_4) δ=9.12, 28.51, 46.65, 112.16, 122.61, 127.36, 129.16, 133.35, 141.41, 148.49, 151.55, 157.89, 173.59. *m/z* 201 (M^+−Me, 12%), 159 (M^+−EtCO, 11%), 145 (MH^+−Me−EtCO, 100%), 142 (M^+−$EtCO_2H$, 52%), 57 ($EtCO^+$, 30%), 29 (Et^+, 49%). HR-MS: $C_{12}H_{11}NO_2$ requires 201.0790; found. 201.0784.

4.18. *N*-Methyl-7-benzoyloxyquinolinium iodide (25c)

A mixture of 7-hydroxyquinoline **24** (50 mg, 0.34 mmol) and benzoyl chloride (0.24 mL, 2.06 mmol) in dry CH_2Cl_2 (2 mL) was heated at reflux for 29 h. Water (5 mL) was added, the aqueous layer extracted with CH_2Cl_2 (3×5 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (1×15 mL) and dried (Na_2SO_4). The crude was solved in dry CH_2Cl_2 (5 mL) and methyl iodide (1.00 mL, 16.06 mmol) was added. The mixture was stirred at 50 °C for 24 h and a solid was formed. Ethyl ether was added to ensure complete precipitation, and the solution was filtered. The crude solid was crystallized twice from methanol–ethyl ether to obtain 85 mg (64%) of yellow crystals. Mp 213–214 °C (decomp.). ^{1}H NMR (200 MHz, $CDCl_3$) δ=4.87 (s, 3H), 7.59 (tt, J=7.5, 1.5 Hz, 2H), 7.74 (tt, J=7.5, 1.5 Hz, 1H), 7.93 (dd, J=9.0, 2.0 Hz, 1H), 8.16 (dd, J=8.3, 5.8 Hz, 1H), 8.25 (t, J=1.8 Hz, 2H), 8.28 (dd, J=2.0, 1.0 Hz, 1H), 8.40 (d, J=8.8 Hz, 1H), 9.06 (dm, J=8.0 Hz, 1H), 10.46 (dm, J=5.7 Hz, 1H). ^{13}C NMR (50 MHz, MeOH-d_4) δ= 46.55, 112.37, 122.73, 127.43, 129.37, 129.77, 130.14, 131.49, 133.49, 135.73, 141.49, 148.59, 151.64, 158.02, 165.71. *m/z* 249 (M^+−Me, 8%), 142 (M^+−$PhCO_2H$, 26%), 105 ($PhCO^+$, 100%), 77 (Ph^+, 34%). HR-MS: $C_{16}H_{11}NO_2$ requires 249.0790; found 249.0789.

4.19. 7-(*tert*-Butylcarbonyloxy)-*N*-methylquinolinium iodide (25d)

A mixture of 7-hydroxyquinoline **24** (50 mg, 0.34 mmol) and pivaloyl chloride (0.26 mL, 2.13 mmol) in dry CH_2Cl_2 (2 mL) was heated at reflux for 29 h. Water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with sat. $NaHCO_3$ (1×15 mL), dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (5 mL) and methyl iodide (1.00 mL, 16.06 mmol) was added. Upon stirring the mixture at 50 °C for 24 h a solid formed. Ethyl ether was added to ensure complete precipitation, and the solution was filtered. The crude material was crystallized twice from methanol–ethyl ether to obtain 66 mg (52%) of yellow crystals. Mp 180–181 °C (Decomp.). ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.44 (s, 9H), 4.84 (s, 3H), 7.72 (dd, J=9.0, 2.0 Hz, 1H), 8.10 (s, 1H), 8.14 (dd, J=8.3, 5.8 Hz, 1H), 8.35 (dd, J=9.0, 1.5 Hz, 1H), 9.08 (dm, J=8.0 Hz, 1H), 10.35 (dm, J=6.2 Hz, 1H). ^{13}C NMR (50 MHz, MeOH-d_4) δ=27.22, 40.32, 111.87, 122.45, 127.08, 129.04, 133.24, 141.27, 148.33, 151.37, 158.03, 177.34. *m/z* 244 (M^+, 0.5%), 229 (M^+−Me, 11%), 186 (M^+−Me−^{t}BuH, 1%), 159 (M^+−^{t}BuCO, 6%), 145 (MH^+−^{t}$BuCO_2$, 94%), 142 (M^+−^{t}$BuCO_2H$, 60%), 57 (^{t}Bu^+, 100%). HR-MS: $C_{14}H_{15}NO_2$ requires 229.1103; found 229.1105.

Acknowledgements

We thank Professor Dr. R. W. Hoffmann for his continuous support and advice during the realization of this work. This work has been supported by the European Commission through the TMR network ERB FMRX CT-960011.

References and notes

1. (a) Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, *97*,

411. (b) In *Combinatorial chemistry*; Wilson, S. R., Czarnik, A. W., Eds.; Wiley: New York, 1997. (c) In *Combinatorial peptide and nonpeptide libraries*; Jung, G., Ed.; VCH: New York, 1996. (d) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* **1996**, *35*, 2288.

2. (a) Dahmen, S.; Bräse, S. *Synthesis* **2001**, 1431. (b) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885. (c) Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 313. (d) Reetz, M. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 284. (e) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2494. (f) De Muynck, H.; Madder, A.; Farcy, N.; De Clercq, P. J.; Pérez-Payán, M. N.; Öhberg, L. M.; Davis, A. P. *Angew. Chem. Int. Ed.* **2000**, *39*, 145. (g) Berkessel, A.; Riedl, R. *J. Comb. Chem.* **2000**, *2*, 215. (h) Müller, M.; Mathers, T. W.; Davis, A. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 3813. (i) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422.
3. (a) Bein, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 323. (b) Berkessel, A.; Hérault, D. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 102. (c) Cooper, A. C.; McAlexander, L. H.; Lee, D.-H.; Torres, M. T.; Crabtree, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 9971. (d) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (e) Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522. (f) Taylor, S. J.; Morken, J. P. *Science* **1998**, *280*, 267. (g) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (h) Badalassi, F.; Wahler, D.; Klein, G.; Crotti, P.; Reymond, J.-L. *Angew. Chem. Int. Ed.* **2000**, *39*, 4067. (i) Wahler, D.; Badalassi, F.; Crotti, P.; Reymond, J.-L. *Angew. Chem. Int. Ed.* **2001**, *40*, 4457.
4. Haugland, R. P. Handbook of fluorescent probes and research chemicals. Molecular Probes, 1996; pp 19 and 552.
5. Guilbaut, G. G.; Kramer, D. N. *Anal. Biochem.* **1966**, *14*, 28.
6. Melhado, L. L.; Peltz, S. W.; Leytus, S. P.; Mangel, W. F. *J. Am. Chem. Soc.* **1982**, *104*, 7299.
7. Meyer-Bertenrath, J.; Kaffarnik, H.; Rey, H. G.; Michal, G.; Busch, E. W. Ger. Offen. DE1945663, 1971.
8. Rukavishnikov, A.; Smith, M. P.; Birell, G. B.; Keana, J. F. W.; Griffith, O. H. *Tetrahedron Lett.* **1998**, *39*, 6637.
9. (a) Huang, Z.; Wang, Q.; Ly, H. D.; Gorvindarajan, A.; Scheigetz, J.; Zamboni, R.; Desmarais, S.; Ramachandran, C. *J. Biomol. Screening* **1999**, *4*(6), 327. (b) Wang, Q.; Scheigetz, J.; Gilbert, M.; Snider, J.; Ramachandran, C. *Biochim. Biophys. Acta* **1999**(1431), 14. (c) Scheigetz, J.; Roy, B. *Synth. Commun.* **2000**, *30*(8), 1437.
10. (a) Brand, L.; Witholt, B. *Meth. Enzymol.* **1967**, *11*, 776. (b) Steinberg, I. Z. *Annu. Rev. Biochem.* **1971**, *40*, 83. (c) Styer, L. *Annu. Rev. Biochem.* **1978**, *40*, 819. (d) Fairclough, R. H.; Cantor, C. R. *Meth. Enzymol.* **1978**, *48*, 347. (e) Cheng, H. C. *Topics in fluorescent Spectroscopy*; Plenum: New York, 1991; Vol. 2. p 127.
11. Berkessel, A.; Riedl, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 1481.
12. Ogilvie, K. K.; Theriault, N. Y.; Seifert, J.-M.; Pon, R. T.; Nemer, M. J. *Can. J. Chem.* **1980**, *58*, 2686.
13. Kondo, H.; Takar, K.; Kuroki, R.; Tada, A.; Fukumoto, K.; Sunamoto, J. *Bull. Chem. Soc. Jpn* **1984**, *57*, 2957.
14. Hewitt, H. J.; Thomas, W. *J. Chem. Soc.* **1909**, *95*, 1292.
15. Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859.
16. (a) Mckenna, C. E.; Higa, M. T.; Cheung, N. H.; Mckenna, M. C. *Tetrahedron Lett.* **1977**, *18*, 155. (b) Mckenna, C. E.; Schmidhauser, *J. Chem. Soc. Chem. Commun.* **1979**, 739.
17. (a) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799. (b) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett.* **1999**, *40*, 5613.
18. Menger, F. M.; Nelson, K. H.; Guo, Y. *Chem. Commun.* **1998**, 2001.
19. (a) Zwierzak, A.; Koziara, A. *Tetrahedron* **1967**, *23*, 2243. (b) Jouko, V.; Heikki, N.; Esko, P. *Synth. Commun.* **1992**, *22*, 271. (c) Lloyd, J. R.; Lowther, N.; Hall, C. D. *J. Chem. Soc. Perkin Trans. 2* **1995**, 245.
20. Chen, C. S.; Poenie, M. *J. Biol. Chem.* **1993**, *268*, 15812.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1913–1920
Tetrahedron

A convenient method for the preparation of α-vinylfurans by phosphine-initiated reactions of various substituted enynes bearing a carbonyl group with aldehydes

Hirofumi Kuroda,* Emi Hanaki, Hironori Izawa, Michiko Kano and Hiromi Itahashi

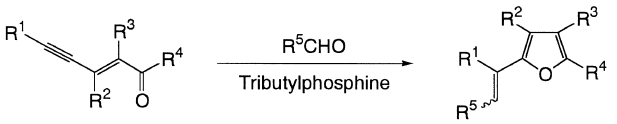
Department of Chemical and Biochemical Engineering, Toyama National College of Technology, 13 Hongo-machi, Toyama-shi, Toyama 939-8630, Japan

Received 14 July 2003; accepted 9 December 2003

Abstract—α-Vinylfurans were obtained by phosphine-initiated cyclization of various enynes bearing a carbonyl group at the ene end in the presence of various aldehydes, in moderate to high yields. The reaction may consist of 1,6-addition of phosphine to the enynes, ring closure, and Wittig reaction between the ylid resulting from cyclization and an aldehyde. Thus, various aldehydes were able to be used in the reaction. The reaction was influenced greatly by the substituents at the acetylene position (R^1) and the α-position of the carbonyl group (R^3).

1. Introduction

The development of cyclization reactions is of vital importance in organic chemistry, so that the cyclic systems found in naturally occurring products can be constructed. A number of cyclic systems containing one oxygen atom are present in nature (e.g., hydrofuran, furan, pyran ring). Furan rings, one example of five-membered heterocycles, are found in a lot of naturally occurring products.[1] The furan ring is not only present as key structural units in naturally occurring products, but is also important in the pharmaceutical industry.[2] Therefore, there has been interest in the synthesis of polysubstituted furans, and a number of useful synthetic methods for furans have been reported, by many synthetic chemists.[3] The Paal–Knorr method,[4] the Feist–Benary method,[5] etc. are known as long-standing methods for furan ring construction. Conjugated enynols are useful and important key intermediates for direct furan ring construction.[6] In our previous communication,[7] we described a novel synthetic method for the preparation of α-vinylfurans in high yields by a phosphine-initiated reaction of the simple 2-penten-4-yn-1-one system with benzaldehyde in dichloromethane. Kim et al. have reported furan ring construction by reaction of alkynic acetal, aldehyde and phosphine.[8] Trialkylphosphines are mild, useful reagents in various organic reactions,[9] including the addition of alcohols to acetylenes having electron-withdrawing groups,[10] isomerization of ynones, ynoates, and ynamides to the corresponding (2*E*, 3*E*)-diene[11] and polyenes.[12] Trost et al. have reported phosphine-catalyzed cyclization of ω-hydroxylynoates to the corresponding tetrahydrofuran or tetrahydropyran derivatives.[13] Herein, we wish to describe in detail the preparation of multi-substituted enynes (**1A**–**C**) and phosphine-initiated furan ring construction with a vinyl group at the α-position, by reaction of the various enynes (**1**) in the presence of various aldehydes (Scheme 1).



1 2

R^1	R^2	R^3	R^4	
Bu	H	H	Ph	Aa
Bu	H	H	Me	Ab
Ph	H	H	Ph	Ac
Ph	H	H	Me	Ad

R^1	R^2	R^3	R^4	
Bu	Bu	H	Me	Ba
Bu	Ph	H	Me	Bb
Bu	H	Et	Ph	Ca
Bu	H	Ph	Ph	Cb

Scheme 1.

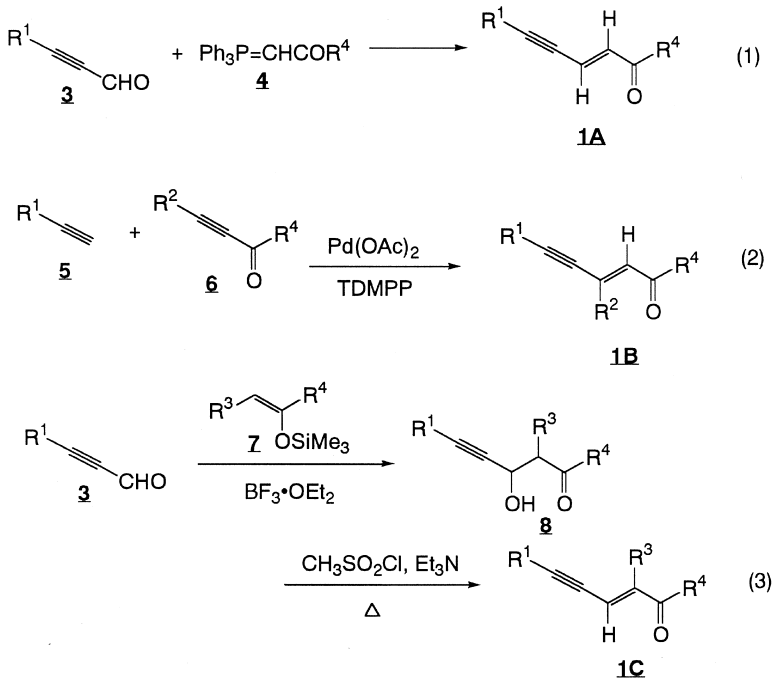
2. Results and discussions

2.1. Preparation of various enynes (1)

The synthesis of enynes (**1Aa**–**1Ad**; R^2=R^3=H) with disubstituted olefinic moieties was carried out by the reaction of ynals (**3**) with Wittig reagent (**4**) (Y. 69–82%) (Eq. 1 in Scheme 2). The enynes (**1Ba** and **1Bb**; R^3=H) with

Keywords: Cyclization; Vinyl furans; Enynes; Phosphine; Wittig reaction.
* Corresponding author. Tel./fax: +81-76-493-5464;
e-mail address: kuroda@toyama-nct.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.034



Scheme 2.

trisubstituted olefinic moieties were prepared by the procedure reported by Trost et al. from terminal alkynes (**5**) and ynones (**6**), in 87 and 40% yields, respectively (Eq. 2 in Scheme 2).[14] The enynes (**1Ca** and **1Cb**; R^2=H) with trisubstituted olefinic moieties were synthesized in two steps by acidic aldol reaction of ynal (**3**) with silyl enol ether (**7**), followed by dehydration of the aldol products in 69 and 64% yields (two steps), respectively (Eq. 3 in Scheme 2). As mentioned above, the three types of enynes (**1A**–**1C**) were prepared conveniently by modification of the known methods.

2.2. Phosphine-initiated cyclization of 1

The tributylphosphine-initiated (Bu_3P; 1 equiv.) cyclization of **1** in the presence of a stoichiometric amount of benzaldehyde was tried by using **1Aa** in CH_2Cl_2 for 6 h at room temperature, to obtain α-vinylfuran (**2Aa**) in 83% yield. **1Aa** was almost entirely consumed within 1 h under these conditions, as shown by GC analysis, and it was found that the reaction proceeded very smoothly under the mild conditions. From the NMR, IR, and MS spectra, the compound obtained was determined to be **2Aa**, containing an α-vinyl furan skeleton. **2Aa** contained a small amount of geometrical isomer† (*E*:*Z*=90:10) and an NOE experiment was carried out to determine the geometry of the major isomer in **2Aa**. The geometry of the major product was determined to be the *E*-isomer because no effect was observed between the olefinic proton of the vinyl group and the proton at the allylic position in the experiment (Fig. 1).

Furthermore, the reaction was carried out in the presence of stoichiometric amounts of triphenylphosphine or triethylamine instead of tributylphosphine. Although the corresponding furan (**2Aa**) was obtained in 73% yield after 6 h in the presence of triphenylphosphine, in the case of triethylamine the reaction did not proceed, and mostly **1Aa** was recovered. Moreover, when the amount of tributylphosphine was reduced to a 0.5 stoichiometric equiv., the yield was reduced approximately by half. These results may suggest the mechanism shown in Scheme 3. The reaction may be initiated by 1,6-addition of phosphine to **1**, followed by cyclization to yield the ylid (**8**) as an intermediate, and then Wittig reaction of **9** with an aldehyde may take place to give the furan (**2**) which has a double bond at the α-position. It is known that ylids stabilized by an aromatic ring, such as **9**, generally give an *E*-isomer as the major product.[15] Thus, the *E*-isomer might be obtained as the major product in this reaction. The reaction might not proceed in the presence of triethylamine due to prevention of the generation of **9**. Furthermore, the reaction might be stoichiometric with regard to the amount

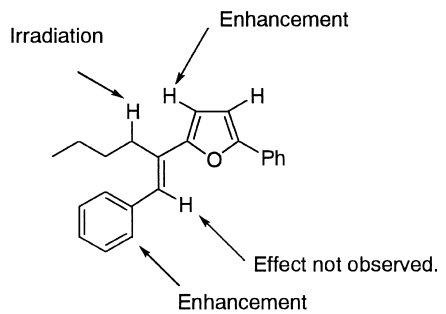
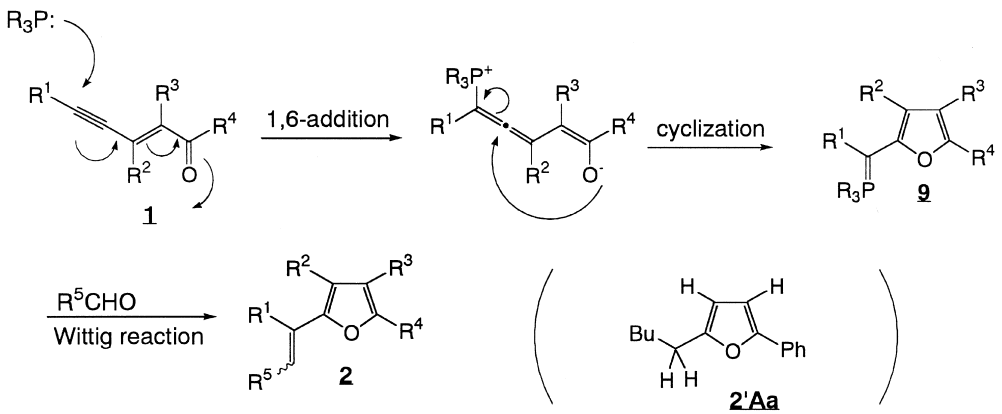


Figure 1. DNOE experiment for **2Aa**.

† We were not able to separate the isomers because their physical properties were almost identical, the products were slightly unstable at rt in air, and the amount of minor isomer in the mixture was very small. We presumed the minor product was a geometric isomer of the major product because **2′Aa** containing no double bonds was obtained as a single product in the reaction of **1Aa** with water in the presence of tributylphosphine and the found value almost agreed with the calculated value in the elemental analysis of the mixture of major and minor products, as described below.



Scheme 3.

of phosphine because the phosphine was converted to the corresponding phosphine oxide as shown in the suggested reaction mechanism. Therefore, the yield might decrease if the amount of phosphine is reduced. To detect the formation of the ylid (**9**), **1Aa** in CH_2Cl_2 was treated with tributylphosphine (1 equiv.) in the presence of water (5 equiv.) without aldehyde. The furan (**2′Aa**) containing no double bonds at the α-position was then obtained as a single product after hydrolysis[16] of the ylid, in 58% yield. **2′Aa** was not obtained when **1Aa** was treated with tributylphosphine without water and aldehyde. These results may suggest formation of the ylid (**9**) in the reaction process.

The reaction of various substituted enynes (**1A**–**1C**) was carried out in CH_2Cl_2 at room temperature (Table 2). The influence of substituents R^1 and R^4 was examined by using **1Aa**–**1Ad** (runs 1–4). When R^1=alkyl groups (i.e., **1Aa** and **1Ab**; runs 1 and 2), **2Aa** and **2Ab** were obtained in 83 and 56% yields, respectively. On the other hand, when R^1=aromatic (i.e., **1Ac** and **1Ad**; runs 3 and 4), the reaction gave a complex mixture containing only a small amount of the corresponding furan. From these results, it was found that the yields were markedly influenced by R^1 rather than by R^4. In the cases of **1Ac** and **1Ad**, **8** stabilized by two aromatic rings might be generated as the intermediate, based on the mechanism described above. Generally, such an ylid is too inert to react with aldehyde.[17] Therefore, the corresponding furans might not be obtained in the reactions with **1Ac** and **1Ad**. Furthermore, the reaction was investigated by using enynes (**1B** and **1C**) with trisubstituted olefinic moieties to examine the influence of R^2 and R^3 in this reaction. In the case of enynes (**1Ba** and **1Bc**; runs 5 and 6), the yield was not influenced by the type of substituent on the double bond. In contrast to this result, the substituent R^3 greatly affected the yield. In the case of R^3=alkyl group (i.e., **1Ca**), although **1Ca** was almost entirely consumed, the corresponding furan was not obtained, due to unknown side-reactions (run 7). When the reaction was retried by using triphenylphosphine, as a milder initiator than tributylphosphine, **1Ca** was almost exclusively recovered. This result may be attributable to the stability of the enolate in the suggested reaction mechanism. Thus, in the case of R^3=alkyl group, the enolate might become unstable due to the electron-donating effect of the alkyl substituent, compared with the case of R^3=H. When **1Cb** (R^3=phenyl group) was used as substrate, the reaction proceeded smoothly to give the corresponding furan in good yield (run 8). The phenyl group might stabilize the enolate by the resonance effect. These results suggest that the substituent R^3 may be important for control of the stability of the enolate. Although all the substituents (R^1–R^4) in the enynes (**1**) were effective for obtaining α-vinylfurans (**2**) as mentioned above, the substituents were not so effective for geometrical selectivity.‡ The α-vinylfurans (**2**) were obtained regardless of the kind of substituents, with high geometrical selectivity (runs 1, 2, 5, 6, and 8) (Table 1).

Table 1. Synthesis of furans from various enynes (**1**) and benzaldehyde[a]

Run	R^1	R^2	R^3	R^4		Yield[b]/%	*E*:*Z*[c]
1	Bu	H	H	Ph	Aa	83	90:10
2	Bu	H	H	Me	Ab	56	>99 (E)
3	Ph	H	H	Ph	Ac	0	
4	Ph	H	H	Me	Ad	0	
5	Bu	Bu	H	Me	Ba	64	91:9
6	Bu	Ph	H	Me	Bb	63	93:7
7	Bu	H	Et	Ph	Ca	0	
8	Bu	H	Ph	Ph	Cb	70	90:10

[a] The reaction of **1** with benzaldehyde (1 equiv.) was carried out at room temperature for 5 h in the presence of tributylphosphine (1 equiv.).
[b] Isolated yield (SiO_2, ethyl acetate and hexane eluent).
[c] Determined by ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$).

Table 2. Synthesis of furans from **1Aa** and various carbonyl compounds[a]

Run	Carbonyl compounds	Yield[b]/%	*E*:*Z*[c]
1	PhCHO	83	90:10
2	EtCHO	92	80:20
3	*trans*-PhCH=CHCHO	90	79:21
4	*p*-$MeOC_6H_4CHO$	89	92:8
5	*p*-$MeC_6H_4COCH_3$	0	

[a] The reaction of **1** with various carbonyl compounds (1 equiv.) was carried out at room temperature for 5 h in the presence of tributylphosphine (1 equiv.).
[b] Isolated yield (SiO_2, ethyl acetate and hexane eluent).
[c] Determined by ^{1}H NMR spectroscopy (400 MHz).

The reaction of **1Aa** with various carbonyl compounds was also examined on the basis of the suggested reaction mechanism (Scheme 3). Although ketones were not suitable, various aldehydes were able to be used in this reaction. Furthermore, the aldehyde substituents (R^5) had a

‡ Although attempts to separate the isomers were unsuccessful, we presumed the major isomer of all obtained α-vinylfurans was the *E*-form, from the suggested mechanism mentioned above.

greater affect on the geometry of α-vinylfurans (**2**) than the substituents (R^1–R^4) in the enynes (**1**).‡ (Table 2)

3. Conclusion

In this paper we described a novel phosphine-initiated cyclization of enynes bearing a carbonyl group at the ene end, in the presence of aldehydes, to obtain α-vinylfurans. Although the reaction was influenced by some substituents in the enyne compounds, the furans were obtained easily with high geometrical selectivity in moderate to high yields. We believe this reaction could become an important and convenient method for the synthesis of compounds containing α-vinylfuran skeletons, which are currently being investigated in detail.

4. Experimental

4.1. Materials and instruments

Tetrahydrofuran (THF), diethyl ether and benzene were dried over sodium benzophenone ketyl and distilled under nitrogen. Dichloromethane, dimethylformamide (DMF) and triethyl amine were dried over calcium hydride and then purified by distillation. Tributylphosphine and all aldehydes were purified by distillation. Triphenylphosphine was purified by recrystallization from ethyl acetate and dried in vacuo. Other commercially available chemicals were used without purification.

Infrared (IR) spectra were obtained with a JASCO FT/IR 8000 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on JNM-FX90 or AL400 spectrometers, in $CDCl_3$ (using tetramethylsilane as an internal standard). MS spectra were measured with a JMS-AX500 mass spectrometer. Elemental analysis was carried out by using Yanagimoto MT-5.

4.2. Synthesis of enynes

Enynes (**1A**, R^2=R^3=H) with disubstituted olefinic moieties were synthesized by Wittig reaction of the corresponding ynals (**3**) with phosphoranes (**4**).

The ynals were prepared from terminal acetylenes and DMF by modification of the method described in literature.[18]

4.2.1. 2-Heptynal (3a). *n*-Butyllithium (1.54 M in hexane, 39.6 mL, 61.0 mmol) was added dropwise to a solution of 1-hexyne (5.00 g, 61.0 mmol) in diethyl ether (40 mL) at −70 °C under nitrogen. After 30 min, dried DMF (6.68 g, 91.5 mmol) was added, and then the temperature of the mixture was allowed to rise to room temperature, and stirring was continued for 30 min. The mixture was poured into ice water and acidified slightly with conc. hydrochloric acid. The mixture was then neutralized with sodium hydrogen carbonate until a pH between 6 and 7 was reached. The organic layer was separated and the aqueous layer was extracted four times with 25 mL of ethyl acetate. The combined organic solution was dried over magnesium sulfate. After evaporation of the solvents, the residue was purified by vacuum distillation to give 2-heptynal (5.19 g, 47.2 mmol, 86%: colorless oil, bp_{14} 58–60 °C); IR (neat) 2959, 3310, 2961, 2872, 2282, 2202, 1670, 1138 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 0.93 (t, *J*=6.4 Hz, 3H, CH_3CH_2–), 1.14–1.89 (m, 4H, –CH_2–), 2.42 (t, *J*=6.4 Hz, 2H, $CH_2C{\equiv}C$–), 9.18 (s, 1H, –CHO).

4.2.2. Phenyl-2-propynal (3b). Similarly, phenyl-2-propynal (**3b**) (colorless oil, R_f=0.45 on TLC; SiO_2, hexane/ethyl acetate=4/1) was synthesized and then purified by column chromatography on silica gel (hexane/ethyl acetate=20/1). Yield 97%; IR (neat) 3301, 2984, 2856, 2239, 2189, 1736, 1661, 1489 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 7.1–7.8 (5H, Ph–), 9.41 (s, 1H, –CHO).

Phosphoranes were prepared from corresponding α-haloketones and triphenylphosphine in two steps by modification of the method described in the literature.[19]

4.2.3. Phenylcarbonylmethylenetriphenylphosphorane (4a). A solution of α-bromoacetophenone (4.53 g, 22.8 mmol) in benzene (15 mL) was added dropwise to a solution of triphenylphosphine (5.96 g, 22.8 mmol) in benzene (15 mL) under nitrogen. The mixture was stirred overnight and the resulting phosphonium salt was filtered. The precipitate was washed with benzene and collected to dry in vacuo. The dried phosphonium salt was suspended in a mixture of water (250 mL) and methanol (250 mL), and the mixture was stirred for 1 h. Aqueous sodium hydroxide (2.00 M) was added to the mixture until a pH between 7 and 8 was reached. The mixture was then stirred vigorously for 1 h. The phosphorane precipitate was filtered and washed water. After drying in vacuo, the phosphorane was recrystallized from ethyl acetate and dried under vacuum to obtain 7.39 g (19.1 mmol, yield 89%, white crystal) of pure product; IR (neat) 3051, 2361, 1971, 1896, 1824, 1774, 1588, 1522 cm^{-1}. ^{1}H NMR (90 MHz, δ, ppm) 4.44 (bd, *J*=24.3 Hz, 1H, P=C*H*–), 7.22–8.14 (20H, Ph).

4.2.4. Methylcarbonylmethylenetriphenylphosphorane (4b). Similarly, methylcarbonylmethylenetriphenylphosphorane (**4b**) was obtained from triphenylphosphine and bromoacetone in 69% yield as a white crystal; IR (neat) 3049, 2990, 2912, 1572, 1535, 1481, 1437 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 2.09 (d, *J*=1.9 Hz, 3H, CH_3), 3.29–4.06 (br, 1H, P=C*H*–), 7.32–7.84 (15H, Ph).

4.2.5. *trans*-1-Phenyl-2-nonen-4-yn-1-one (1Aa). 2-Heptynal (1.00 g, 9.09 mmol) was added slowly to a mixture of phenylcarbonylmethylenetriphenylphosphorane (3.45 g, 9.09 mmol) in CH_2Cl_2 (56 mL). The mixture was stirred at room temperature for 5 h and then concentrated by using an evaporator. Hexane (100 mL) was added to the mixture, and the triphenylphosphine oxide crystals were filtered. The filtrate was concentrated by using an evaporator, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=100/1) to obtain the enyne (**1Aa**, 1.53 g, 7.20 mmol) in 79% yield (pale yellow oil, R_f=0.63 on TLC: SiO_2, hexane/ethyl acetate=4/1); IR (neat) 2959, 2934, 2872, 2210, 1660, 1591, 1448, 1290 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 0.93 (t, *J*=6.6 Hz, 3H, CH_3–), 1.24–1.57 (m, 4H, –CH_2–), 2.42 (dt, *J*=2.3, 6.8 Hz, 2H, –$CH_2C{\equiv}$,

6.68 (dt, J=15.6, 2.3 Hz, 1H, ≡CC*H*═), 7.29 (d, J=15.6 Hz, 1H, ═C*H*CO–), 7.44–7.58 (m, 3H, Ph), 7.89–8.00 (m, 2H, Ph).

Similarly, other **1A** were synthesized from their corresponding ynals and phosphoranes.

4.2.6. *trans*-3-Decen-5-yn-2-one (1Ab). Yield 82%, colorless oil, R_f=0.53 on TLC (SiO_2, hexane/ethyl acetate=4/1); IR (neat) 2961, 2936, 2872, 2213, 1693, 1674, 1595, 1356 cm^{-1}; ^1H NMR (90 MHz, δ, ppm) 0.93 (t, J=7.2 Hz, 3H, CH_3–), 1.26–1.74 (m, 4H, –CH_2–), 2.25 (s, 3H, CH_3CO), 2.24 (t, J=7.2 Hz, 2H, ≡CCH_2–), 6.36 (d, J=18.0 Hz, 1H, ═C*H*CO–), 6.55 (dt, J=18.0, 2.3 Hz, 1H, ≡CC*H*═).

4.2.7. *trans*-1,5-Diphenyl-2-penten-4-yn-1-one (1Ac). Yield 69%, pale yellow solid, mp 46 °C, R_f=0.72 on TLC (SiO_2, hexane/ethyl acetate=4/1); IR (neat) 3063, 2191, 1661, 1597, 1580, 1337, 1308, 1254, 1211 cm^{-1}; ^1H NMR (90 MHz, δ, ppm) 7.01 (d, J=16.2 Hz, 1H, –C*H*═CHCO–), 7.20–7.80 (9H, ═C*H*CO–, Ph), 7.80–8.10 (m, 2H, Ph).

4.2.8. *trans*-6-Phenyl-3-hexen-5-yn-2-one (1Ad). Yield 75%, pale yellow solid, mp 104 °C, R_f=0.38 on TLC (SiO_2, hexane/ethyl acetate=4/1); IR (neat) 3038, 3015, 2195, 1657, 1590, 1489, 1445, 1363 cm^{-1}; ^1H NMR (90 MHz, δ, ppm) 2.24 (s, 3H, CH_3CO–), 6.28 (d, J=16.1 Hz, 1H, ≡CC*H*═), 6.49 (d, J=16.1 Hz, 1H, ═C*H*CO–), 7.20–7.56 (m, 5H, Ph).

Enynes (**1B**) with trisubstituted olefinic moieties were prepared by the palladium-catalyzed cross coupling reaction of ynones with terminal alkynes described in the literature.[14] The ynones used in the cross coupling reaction were prepared as follows:[20]

4.2.9. 3-Octyn-2-one (6a). *n*-Butyllithium (1.54 M in hexane, 39.6 mL, 61.0 mmol) was added dropwise to a solution of 1-hexyne (5.00 g, 61.0 mmol) in THF (60 mL) at −70 °C. After 30 min, acetic anhydride (12.4 g, 122 mmol) was added to the mixture over 30 min and the mixture was then stirred for an additional 20 min. The temperature was then allowed to rise to 0 °C, and aqueous ammonium chloride (3 M, 100 mL) was poured into the mixture, followed by dropwise addition of concentrated aqueous ammonia, over 30 min. The mixture was extracted four times with 25 mL of ethyl acetate. The combined organic solution was washed twice with 50 mL of saturated aqueous ammonium chloride solution and then dried over magnesium sulfate. After solvent evaporation, the residue was purified by vacuum distillation to give 3-octyn-2-one (4.60 g, 37.1 mmol, yield 68%: colorless oil, bp_{22} 71–77 °C); IR (neat) 3335, 2961, 2212, 1678, 1466, 1625, 1300, 1234 cm^{-1}; ^1H NMR (90 MHz, δ, ppm) 0.93 (t, J=7.4 Hz, 3H, CH_3CH$_2$–), 1.14–1.89 (m, 4H, –CH_2–), 2.32 (s, 3H, CH_3CO–), 2.36 (t, J=7.4 Hz, 2H, –CH_2C≡C–).

4.2.10. 4-Phenyl-3-butyn-2-one (6b). *n*-Butyllithium (1.54 M in hexane, 31.8 mL, 49.0 mmol) was added dropwise to a solution of ethynylbenzene (5.00 g, 49.0 mmol) in THF (28 mL), at −30 °C. After 30 min, a solution of zinc chloride (6.69 g, 49 mmol) in THF (18 mL) was added dropwise to the mixture. The temperature of the mixture was allowed to rise to 0 °C. After 30 min, acetylchloride (3.85 g, 49.0 mmol) was added. The mixture was stirred at 0 °C for 5 h and then poured into saturated aqueous ammonium chloride. The mixture was extracted four times with 25 mL of ethyl acetate and then dried over magnesium sulfate. After evaporation of the solvents, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate=100/1) to give 4-phenyl-3-butyn-2-one (4.70 g, 32.6 mmol, 67% yield, pale yellow oil, R_f=0.48 on TLC; SiO_2, hexane/ethyl acetate=4/1); IR (neat) 2202, 1674, 1359, 1280, 1157, 978, 758, 690 cm^{-1}; ^1H NMR (90 MHz, δ, ppm) 2.44 (s, 3H, CH_3–), 7.25 (5H, Ph–).

4.2.11. (3*E*)-4-Butyl-3-decen-5-yn-2-one (1Ba). Tris (2,6-dimethoxyphenyl)phosphine (0.092 g, 0.261 mmol) was added to a suspension of palladium (II) acetate (0.035 g, 0.156 mmol) in benzene (9 mL). After 5 min, **6a** (1.00 g, 8.06 mmol) was added, and the mixture was stirred for 10 min. 1-Hexyne (0.661 g, 8.06 mmol) was then added slowly to the mixture, and the stirring was continued for 24 h. The mixture was subsequently concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate=100/1) to obtain **1Ba** (1.45 g, 7.03 mmol) (colorless oil, R_f=0.63 on TLC; SiO_2, hexane/ethyl acetate=4/1) in 87% yield; IR (neat) 2932, 2872, 2214, 1682, 1590, 1356, 1169 cm^{-1}; ^1H NMR (90 MHz, δ, ppm) 0.94 (t, J=7.6 Hz, 6H, CH_3–) 1.36–1.58 (8H, –CH_2–), 2.17 (s, 3H, CH_3CO–), 2.36 (t, J=6.4 Hz, –CH_2CH═), 2.69 (t, J=7.62 Hz, 2H, –CH$_2$C≡), 6.34 (s, 1H, ═C*H*CO–).

4.2.12. (3*E*)-4-phenyl-3-decen-5-yn-2-one (1Bb). Similarly, (3*E*)-4-phenyl-3-decen-5-yn-2-one (**1Bb**) (pale yellow oil, R_f=0.63 on TLC; SiO_2, hexane/ethyl acetate=4/1) was prepared by the palladium catalyzed reaction (reaction time: 4 h) of **6b** and 1-hexyne in 40% yield; IR (neat) 2959, 2231, 1685, 1657, 1361, 1259, 763, 692 cm^{-1}; ^1H NMR (90 MHz, δ, ppm) 0.96 (t, J=6.6 Hz, 6H, CH_3–) 1.36–1.66 (4H, –CH_2–), 2.56 (s, 3H, CH_3CO–), 2.58 (t, J=6.6 Hz, 2H, –CH$_2$C≡), 6.71 (s, 1H, ═C*H*CO–), 7.34 (m, 5H, Ph–).

Enynes (**1C**) with trisubstituted olefinic moieties were synthesized from 2-heptynal (**3a**) and silyl enol ethers (**7**) in two steps. The silyl enol ethers were prepared as follows, by modification of the method described in the literature:[21]

4.2.13. 1-phenyl-1-trimethylsiloxy-1-butene (7a). Butyllithium (1.54 M in hexane, 21.9 mL, 33.7 mmol) was added slowly at 0 °C to a solution of diisopropylamine (3.40 g, 33.7 mmol) and THF (150 mL). After 10 min, 1-phenyl-1-butanone (5.00 g, 33.7 mmol) was added slowly to the solution at −78 °C. The mixture was stirred for a further 30 min, and then chlorotrimethylsilane (4.39 g, 40.5 mmol) was added at the same temperature. The solution was allowed to warm slowly from −78 °C to room temperature. After 12 h, the solvent had almost evaporated completely, and hexane was added. The resulting precipitate was removed and the obtained filtrate was evaporated, and purified by distillation to obtain **7a** (colorless oil, bp_7 75–80 °C) (7.01 g, 31.9 mmol, 95% yield); IR (neat) 2963, 1649, 1446, 1342, 1251, 1074, 843 cm^{-1}; ^1H NMR

(90 MHz, δ, ppm) 0.13 (s, 9H, CH_3Si–), 1.04 (t, J=7.4 Hz, 3H, CH_3–), 2.22 (q, J=7.4 Hz, 2H, –CH_2C═), 5.23 (t, J=7.2 Hz, 1H, –CH═), 7.22–7.44 (m, 5H, Ph–).

4.2.14. 1,2-Diphenyl-1-trimethylsiloxyethene (7b). Colorless oil, bp_7 125–140 °C) was prepared similarly in 48% yield; IR (neat) 2959, 1630, 1448, 1350, 1253, 1066, 897, 846 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 0.13 (s, 9H, CH_3Si–), 6.29 (s, 1H, –CH═), 7.15–7.88 (m, 10H, Ph–).

4.2.15. 2-Ethyl-1-phenyl-2-nonen-4-yn-1-one (1Ca). 1Ca was synthesized via 2-ethyl-3-hydroxy-1-phenyl-4-nonyn-1-one. 2-Ethyl-3-hydroxy-1-phenyl-4-nonyn-1-one (**8a**): Trifluoroborone diethyl ether complex (1.97 g, 13.9 mmol) was added dropwise at −78 °C to a solution of **3a** (1.00 g, 9.09 mmol) and **7a** (2.00 g, 9.09 mmol) in CH_2Cl_2 (25 mL). After 1 h, the mixture was poured into cold water (100 mL), and neutralized with sodium bicarbonate until a pH of 7 was attained. After separation of the organic layer, the aqueous phase was extracted four times with 25 mL of ethyl acetate. The combined organic phase was dried over magnesium sulfate. After solvent evaporation, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate=20/1) to give **8a** (2.15 g, 8.33 mmol) (pale yellow oil, R_f=0.10 and 0.20 on TLC; SiO_2, hexane/ethyl acetate=4/1) as a diastereo mixture (The diastereo ratio was estimated from the ^{1}H NMR spectrum as 1:1.5) in 92% yield; IR (neat) 3443, 2963, 2229, 1676, 1448, 1205, 1028, 704 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 0.78 (t, J=7.0 Hz, 3H, CH_3–), 0.91 (t, J=7.0 Hz, 3H, CH_3–), 1.17–1.80 (m, –CH_2–, 4H), 2.86 (br, 1H, –OH) (this peak may be attributable to the minor diastereoisomer), 3.20 (br, 1H, –OH), 3.68 (q, J=6.6 Hz, 1H, –CH(Et)CO–), 4.64 (br, 1H, –CH(OH)–), 7.00–8.00 (m, 5H, Ph–). Methanesulfonyl chloride (0.177 g, 1.55 mmol) and then triethylamine (0.157 g, 1.55 mmol) were added at 0 °C to a solution of **8a** (diastereo mixture) (0.400 g 1.55 mmol) in CH_2Cl_2 (1.5 mL). This mixture was refluxed for 3 h and then poured into saturated aqueous ammonium chloride (25 mL). After separation of the organic layer, the aqueous phase was extracted four times with 15 mL portions of ethyl acetate. The combined organic phase was dried over magnesium sulfate. After evaporation of the solvents, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate=20/1) to give **1Ca** (0.280 g, 1.17 mmol) (pale yellow oil, R_f=0.58 on TLC; SiO_2, hexane/ethyl acetate=4/1) as a single isomer in 75.2% yield; IR (neat) 2963, 2208, 1774, 1649, 1597, 1250, 1057, 880, 720 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 0.96 (t, J=7.9 Hz, 3H, CH_3–), 1.12 (t, J=7.9 Hz, 3H, CH_3–), 1.32–1.90 (m, –CH_2–, 4H), 2.48 (t, J=7.8 Hz, 2H, –CH_2C≡), 3.76 (q, J=7.9 Hz, 2H, –CH_2C═), 6.10 (s, 1H, –CH═), 7.28–7.76 (m, 5H, Ph–).

4.2.16. 1,2-Diphenyl-2-nonen-4-yn-1-one (1Cb). Similarly, 1,2-diphenyl-2-nonen-4-yn-1-one (**1Cb**) was prepared as a single isomer via 3-hydroxy-1,2-diphenyl-4-nonyn-1-one (**8b**) in two steps. **8b** (pale yellow oil, R_f=0.33 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained as a mixture of diastereoisomers (1:1.7) in 81% yield; IR (neat) 3458, 2959, 2231, 1678, 1450, 1205, 1047, 700 cm^{-1}; ^{1}H NMR (400 MHz, δ, ppm) 0.81 (t, J=7.3 Hz, 3H, CH_3–), 1.32–1.60 (m, –CH_2–, 4H), 2.12 (t, J=6.8 Hz, 2H, –CH_2C≡), 2.80 (br, 1H, –OH), 4.80 (d, J=6.3 Hz, 1H, –CHPh–), 5.12 (d, J=6.3 Hz, 1H, –CH(OH)–), 7.00–8.00 (m, 10H, Ph–). 0.82 (t, J=7.3 Hz, 3H, CH_3–), 1.32–1.60 (m, –CH_2–, 4H), 2.13 (t, J=6.8 Hz, 2H, –CH_2C≡), 3.15 (br, 1H, –OH), 4.80 (d, J=7.8 Hz, 1H, –CHPh–), 5.06 (d, J=7.8 Hz, 1H, –CH(OH)–), 7.00–8.00 (m, 10H, Ph–). **1Cb** (pale yellow oil, R_f=0.48 on TLC; SiO_2, hexane/ethyl acetate=4/1); IR (neat) 2959, 2208, 1657, 1591, 1259, 1068, 731, 696 cm^{-1}; ^{1}H NMR (90 MHz, δ, ppm) 0.88 (t, J=7.7 Hz, 3H, CH_3–), 1.11–1.69 (m, 4H, –CH_2–), 2.34 (dt, J=2.6, 7.7 Hz, 2H, –CH_2C≡), 6.30 (t, J=2.6 Hz, 1H, –CH═), 7.11–8.09 (m, 10H, Ph–).

4.2.17. Phosphine-initiated cyclization of 1. 2-(1-Butyl-2-phenylethenyl)-5-phenylfuran (2Aa). Tributylphosphine (190 mg, 0.943 mmol) was added at room temperature to a solution of **1Aa** (200 mg, 0.943 mmol) and benzaldehyde (100 mg, 0.943 mmol) in CH_2Cl_2 (1.9 mL). After stirring for 5 h, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=200/1) to give 236 mg (83%) of **2Aa** as a mixture of geometric isomers; colorless oil, R_f=0.63 on TLC (hexane/ethyl acetate=4/1); IR (neat) 3059, 2957, 1685, 1599, 1483, 1468, 1449, 1024, 785, 758, 692 cm^{-1}; ^{1}H NMR (400 MHz, δ, ppm) 0.95 (t, J=7.3 Hz, 3H, CH_3–), 1.44 (m, 2H, CH_3CH_2–), 1.66 (m, 2H, –CH_2C$H_2$$CH_2$–), 2.53 (t, J=7.6 Hz, 2H, –CH_2-furan; minor isomer), 2.61 (t, J=8.3 Hz, 2H, –$CH_2$$CH_2CH_2$–), 6.23 (d J=3.6 Hz, 1H, furan-H; minor isomer), 6.45 (d, J=3.4 Hz, 1H, furan-H), 6.56 (d J=3.6 Hz, 1H, furan-H; minor isomer), 6.68 (d, J=3.4 Hz, 1H, furan-H) 7.19 (s, 1H, –CH═), 7.20–7.75 (m, 10H, Ph),; ^{13}C NMR (100 MHz, δ, ppm; major isomer) 13.9 (CH_3), 23.0 (–CH_2–), 28.2 (–CH_2–), 32.0 (–CH_2–), 107.0 (CH in furan ring), 108.6 (CH in furan ring), 123.7 (Ph), 124.2 (═*C*HPh), 126.6 (Ph), 127.3 (Ph), 128.3 (Ph), 128.7 (Ph), 128.8 (Ph), 130.8 (Ph), 131.6 (Ph), 137.5 (>*C*═CHPh), 153.0 (O–C in furan ring), 155.2 (O–C in furan ring). MS (EI, *m*/*z*) 302 (M^+). Anal. Calcd for $C_{22}H_{22}O$: C 87.38, H 7.33. Found: C 87.41, H 7.65.

Similarly, the cyclization was carried out by using various enynes and aldehydes in the presence of tributylphosphine.

4.2.18. 2-(1-Butyl-2-phenylethenyl)-5-methylfuran (2Ab). 2-(1-Butyl-2-phenylethenyl)-5-methylfuran (**2Ab**) (pale yellow oil, R_f=0.75 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained in 56% yield; IR (neat) 2957, 2930, 2870, 1701, 1653, 1599, 1456 cm^{-1}; ^{1}H NMR (400 MHz, δ, ppm) 0.93 (t, J=7.4 Hz, 3H, CH_3–), 1.41 (m, 2H, –CH_2–), 1.63 (m, 2H, –CH_2–), 2.34 (d, J=0.8 Hz, 3H, CH_3-furan), 2.53 (t, J=8.2 Hz, 2H, –CH_2C═), 6.00 (dq, J=3.2, 0.8 Hz, 1H, furan-H), 6.26 (d, J=3.2 Hz, 1H, furan-H) 7.01 (s, 1H, –CH═), 7.20–7.50 (m, 5H, Ph); ^{13}C NMR (100 MHz, δ, ppm) 13.8 (CH_3), 13.9 (CH_3), 22.9 (–CH_2–), 28.1 (–CH_2–), 31.9 (–CH_2–), 107.1 (CH in furan ring), 107.2 (CH in furan ring), 122.4 (═*C*HPh), 126.0 (Ph), 127.9 (Ph), 128.4 (Ph), 131.4 (Ph), 137.4 (>*C*═CHPh), 150.5 (O–*C* in furan ring), 153.7 (O–*C* in furan ring). MS (EI, *m*/*z*) 240 (M^+). Anal. Calcd for $C_{17}H_{20}O$: C 84.96, H 8.39. Found: C 84.60, H 8.52.

4.2.19. 2-(1-Butyl-2-phenylethenyl)-3-butyl-5-methylfuran (2Ba). Pale yellow oil, R_f=0.63 on TLC; SiO_2,

hexane/ethyl acetate=4/1) was obtained as a mixture of geometric isomers in 64% yield; IR (neat) 2957, 2860, 1616, 1458, 1259, 750, 698 cm^{-1}; ^1H NMR (400 MHz, δ, ppm) 0.74 (t, J=7.1 Hz, 3H, CH_3-; minor isomer), 0.84 (t, J=7.2 Hz, 3H, CH_3-), 0.92 (t, J=7.6 Hz, 3H, CH_3-), 1.20–1.60 (m, 8H, $-CH_2-$), 1.80 (t, J=7.6 Hz, 2H, $-CH_2$-furan; minor isomer), 2.28 (s, 3H, CH_3-Furan), 2.51 (t, J=7.6 Hz, 2H, CH_2-furan), 2.61 (t, J=7.6 Hz, 2H, $-CH_2C=$), 5.80 (s, 1H, furan-H; minor isomer), 5.92 (s, 1H, furan-H), 6.46 (s, 1H, $-CH=$; minor isomer), 6.62 (s, 1H, $-CH=$), 6.46 (s, 1H, $-CH=$; minor isomer), 7.20–7.50 (m, 5H, Ph),; ^{13}C NMR (100 MHz, δ, ppm) 13.6 (CH_3), 13.9 (CH_3), 14.0 (CH_2), 22.5 (CH_2), 22.7 (CH_2), 25.7 (CH_2), 28.7 (CH_2), 31.4 (CH_2), 32.5 (CH_2), 109.0 (CH in furan ring), 122.8 (Bu–C in furan), 126.0 (Ph), 126.1 (PhCH=), 127.9 (Ph), 128.4 (Ph), 133.7 (Ph), 137.6 (>C=CHPh), 148.9 (O–C in furan ring), 149.4 (O–C in furan ring). MS (EI, m/z) 296 (M^+). Anal. Calcd for $C_{21}H_{28}O$: C 85.08, H 9.52. Found: C 85.03, H 9.71.

4.2.20. 2-(1-Butyl-2-phenylethenyl)-5-methyl-3-phenylfuran (2Bb). Pale yellow oil, R_f=0.68 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained as a mixture of geometric isomers in 63% yield; IR (neat) 3026, 2926, 1740, 1601, 1444, 1126, 956, 763 cm^{-1}; ^1H NMR (400 MHz, δ, ppm) 0.84 (t, J=7.2 Hz, 3H, CH_3-), 1.26 (m, 2H, $-CH_2-$), 1.51 (m, 2H, $-CH_2-$), 2.33 (d, J=0.8 Hz, 3H, CH_3-furan), 2.39 (d, J=0.8 Hz, 3H, CH_3-furan), 2.42 (t, J=8.0 Hz, 2H, $-CH_2C=$; minor isomer), 2.58 (t, J=8.0 Hz, 2H, $CH_2C=$), 6.16 (q, J=0.8 Hz, 1H, furan-H), 6.24 (q, J=0.8 Hz, 1H, furan-H, minor isomer), 6.58 (s, 1H, $-CH=$; minor isomer), 6.77 (s, 1H, $-CH=$), 7.20–7.50 (m, 10H, Ph); ^{13}C NMR (100 MHz, δ, ppm; major isomer) 13.8 (CH_3), 13.9 (CH_3), 22.8 (CH_2), 28.6 (CH_2), 31.5 (CH_2), 109.6 (CH in furan ring), 123.3 (Ph–C in furan), 126.4 (=CHPh), 126.5 (Ph), 128.0 (Ph), 128.1 (Ph), 128.4 (Ph), 128.5 (Ph), 133.1 (Ph), 135.0 (Ph), 137.4 (>C=CHPh), 149.1 (O–C in furan ring), 150.2 (O–C in furan ring). MS (EI, m/z) 316 (M^+). Anal. Calcd for $C_{23}H_{24}O$: C 87.30, H 7.64. Found: C 86.86, H 7.87.

4.2.21. 2-(1-Butyl-2-phenylethenyl)-4,5-diphenylfuran (2Cb). Pale yellow oil, R_f=0.60 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained as a mixture of geometric isomers in 70% yield; IR (neat) 2959, 2870, 1703, 1599, 1446, 1147, 763, 696 cm^{-1}; ^1H NMR (400 MHz, δ, ppm) 0.88 (t, J=7.6 Hz, 3H, CH_3-), 1.38 (m, 2H, $-CH_2-$), 1.63 (m, 2H, $-CH_2-$), 2.47 (t, J=7.6 Hz, 2H, $-CH_2C=$; minor isomer), 2.56 (t, J=8.2 Hz, 2H, $-CH_2C=$), 6.24 (s, 1H, furan-H; minor isomer), 6.47 (s, 1H, furan-H), 7.14 (s, 1H, $-CH=$), 7.10–7.55 (m, 15H, Ph); ^{13}C NMR (100 MHz, δ, ppm) 14.0 (CH_3), 23.2 (CH_2), 28.4 (CH_2), 32.1 (CH_2), 110.7 (CH in furan ring), 124.2 (Ph–C in furan), 124.5 (=CHPh), 126.0 (Ph), 126.5 (Ph), 127.1 (Ph), 127.3 (Ph), 128.2 (Ph), 128.3 (Ph), 128.5 (Ph), 128.6 (Ph), 128.7 (Ph), 130.9 (Ph), 131.2 (Ph), 134.2 (Ph), 137.3 (>C=CHPh), 147.3 (O–C in furan ring), 154.1 (O–C in furan ring). MS (EI, m/z) 378 (M^+). Anal. Calcd for $C_{28}H_{26}O$: C 88.85, H 6.92. Found: C 88.64, H 7.14.

4.2.21. 2-Pentyl-5-phenylfuran (2′Aa). Colorless oil, R_f=0.63 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained in 58% yield; IR (neat) 2957, 2930, 2870, 1738, 1685, 1599, 1483, 1024, 785, 758 cm^{-1}; ^1H NMR (400 MHz, δ, ppm) 0.91 (t, J=7.0 Hz, 3H, CH_3-), 1.37 (m, 4H, $-CH_2-$), 1.69 (m, 2H, $-CH_2-$), 2.67 (t, J=7.6 Hz, 2H, $-CH_2$-furan), 6.05 (d, J=3.20 Hz, 1H, furan-H), 6.54 (d, J=3.2 Hz, 1H, furan-H), 7.21 (m, 1H, –Ph), 7.34 (m, 2H, Ph), 7.62 (m, 2H, Ph); ^{13}C NMR (100 MHz, δ, ppm) 14.2 (CH_3), 22.6 (CH_2), 27.9 (CH_2), 28.3 (CH_2), 31.5 (CH_2), 105.5 (CH in furan ring), 106.7 (CH in furan ring), 123.2 (Ph), 126.5 (Ph), 128.4 (Ph), 131.1 (Ph), 151.9 (O–C in furan ring), 156.2 (O–C in furan ring). MS (EI, m/z) 214 (M^+). Anal. Calcd for $C_{15}H_{18}O$: C 84.07, H 8.47. Found: C 84.00, H 8.60.

4.2.22. 2-(1-Butyl-2-ethylethenyl)-5-phenylfuran. Pale yellow oil, R_f=0.73 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained as a mixture of geometric isomers in 92% yield; IR (neat) 2959, 2932, 1606, 1523, 1485, 1458, 1024, 783, 758, 688 cm^{-1}; ^1H NMR (400 MHz, δ, ppm) 0.94 (t, J=7.2 Hz, 3H, CH_3-), 0.96 (t, J=7.2 Hz, 3H; minor isomer), 1.09 (t, J=7.6 Hz, 3H, CH_3-), 1.12 (t, J=7.6 Hz, 2H, CH_3-; minor isomer), 1.39 (m, 2H, $-CH_2-$), 1.49 (m, 2H, $-CH_2-$), 1.74 (quint, J=7.6 Hz, 2H, $CH_3CH_2CH=$; minor isomer), 2.24 (quint, J=7.6 Hz, 2H, $CH_3CH_2CH=$), 2.38 (t, J=7.2 Hz, 2H, $-CH_2CH_2C=$), 2.50 (t, J=7.2 Hz, 2H, $-CH_2CH_2C=$; minor isomer), 5.45 (t, J=7.2 Hz, 1H, $-CH=$; minor isomer), 6.15 (t, J=7.6 Hz, 1H, $-CH=$), 6.26 (d, J=3.2 Hz, 1H, furan-H), 6.34 (d, J=3.6 Hz, 1H, furan-H; minor isomer), 6.63 (d, J=3.2 Hz, 1H, furan-H), 6.67 (d, J=3.6 Hz, 1H, furan-H; minor isomer), 7.10–7.80 (m, 5H, Ph); ^{13}C NMR (100 MHz, δ, ppm; major isomer) 14.0 (CH_3), 14.3 (CH_3), 21.2 (CH_2), 22.8 (CH_2), 27.6 (CH_2), 31.8 (CH_2), 106.2 (CH in furan ring), 106.4 (CH in furan ring), 123.2 (Ph), 126.6 (=CHPh), 127.5 (Ph), 128.3 (Ph), 128.9 (Ph), 130.7 (>C=CHPh), 151.8 (O–C in furan ring), 154.9 (O–C in furan ring). MS (EI, m/z) 254 (M^+). Anal. Calcd for $C_{18}H_{22}O$: C 84.99, H 8.72. Found: C 84.72, H 8.79.

4.2.23. 2-(1-Butyl-4-phenyl-1,3-butadienyl)-5-phenylfuran. Pale yellow oil, R_f=0.73 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained as a mixture of geometric isomers in 90% yield; IR (neat) 3032, 2957, 2932, 1606, 1532, 1506, 1250, 1176, 1035, 758, 690 cm^{-1}; ^1H NMR (400 MHz, δ, ppm) 0.94 (t, J=7.2 Hz, 3H, CH_3-; minor isomer), 0.97 (t, J=7.6 Hz, 3H, CH_3-), 1.44 (m, 2H, $-CH_2-$), 1.61 (m, 2H, $-CH_2-$), 2.46 (t, J=7.6 Hz, 2H, $-CH_2CH_2C=$; minor isomer), 2.60 (t, J=7.2 Hz, 2H, $-CH_2CH_2C=$), 6.21 (d, J=11.6 Hz, 1H, PhCH=CHCH=; minor isomer), 6.44 (d, J=3.6 Hz, 1H, furan-H), 6.49 (d, J=3.6 Hz, 1H, furan-H; minor isomer), 6.64 (d, J=15.6 Hz, 1H, PhCH=CH–; minor isomer), 6.68 (d, J=3.20 Hz, 1H, furan-H), 6.72 (d, J=3.6 Hz, 1H, furan-H; minor isomer), 6.73 (d, J=15.2 Hz, 1H, PhCH=CH–), 6.95 (d, J=11.6 Hz, 1H, PhCH=CHCH=), 7.16 (dd, J=11.6, 15.6 Hz, 1H, PhCH=CH–), 7.20–7.80 (m, 10H, Ph) 7.96 (dd, J=11.6, 15.6 Hz, 1H, PhCH=CH–; minor isomer); ^{13}C NMR (100 MHz, δ, ppm; major isomer) 13.9 (CH_3). 22.8 (CH_2), 28.0 (CH_2), 32.3 (CH_2), 107.0 (CH in furan ring), 108.5 (CH in furan ring), 123.4 (Ph), 123.8 (PhCH=CH–CH=), 124.6 (PhCH=CH–), 126.0 (Ph), 127.0 (Ph), 127.0 (Ph), 128.3 (Ph), 130.4 (=CH–CH=C<), 130.7 (Ph), 132.6 (PhCH=CH–), 137.5 (Ph), 152.8 (O–C in furan ring), 154.7 (O–C in furan ring). MS (EI, m/z) 328 (M^+). Anal.

Calcd for $C_{24}H_{24}O$: C 87.76, H 7.37. Found: C 87.34, H 7.53.

4.2.24. 2-[1-Butyl-2-(*p*-methoxyphenyl)ethenyl]-5-phenylfuran. Pale yellow oil, R_f=0.70 on TLC; SiO_2, hexane/ethyl acetate=4/1) was obtained as a mixture of geometric isomers in 89% yield; IR (neat) 2957, 29.32, 1606, 1524, 1506, 1464, 1250, 1176, 758 cm^{-1}; ^1H NMR (400 MHz, δ, ppm) 0.88 (t, J=6.8 Hz, 3H, CH_3–; minor isomer), 0.96 (t, J=7.2 Hz, 3H, CH_3–), 1.45 (m, 2H, –CH_2–), 1.66 (m, 2H, –CH_2–), 2.51 (t, J=8.0 Hz, 2H, –CH$_2$CH_2CH=; minor isomer), 2.60 (t, J=8.0 Hz, 2H, –CH$_2$CH_2CH=), 3.80 (s, 3H, CH_3O–; minor isomer), 3.82 (s, 3H, CH_3O–), 6.24 (d, J=3.6 Hz, 1H, furan-H; minor isomer), 6.42 (d, J=3.6 Hz, 1H, furan-H), 6.57 (d, J=3.6 Hz, 1H, furan-H; minor isomer), 6.68 (d, J=3.6 Hz, 1H, furan-H), 6.91 (m, 2H, MeOPh–; minor isomer), 6.92 (m, 2H, MeOPh–), 7.13 (s, 1H, –CH=), 7.20–7.80 (m, 7H, Ph, MeOPh–); ^{13}C NMR (100 MHz, δ, ppm) 13.9 (CH_3), 23.0 (CH_2), 28.2 (CH_2), 31.8 (CH_2), 55.1 (CH_3O), 106.7 (CH in furan ring), 107.7 (CH in furan ring), 113.1 (p-MeC_6H_4–), 123.3 (Ph), 123.5 (Ph), 126.8 (–CH=), 128.3 (Ph), 129.7 (p-MeOC_6H_4–), 129.8 (p-MeOC_6H_4–, Ph), 130.5 (>C=CH–), 152.4 (O–C in furan ring), 155.1 (O–C in furan ring), 158.0 (p-MeC_6H_4–),. MS (EI, m/z) 332 (M^+). Anal. Calcd for $C_{23}H_{24}O_2$: C 83.10, H 7.28. Found: C 82.98, H 7.52.

Acknowledgements

We are grateful to Dr. Shin Ono Ms. Yukiko Hoshino at Toyama Univ. for performing the elemental analysis.

References and notes

1. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
2. Nakanishi, K. *Natural products chemistry*; Kodan-sha: Tokyo, 1974.
3. Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955.
4. Konfeld, E. C.; Jones, R. G. *J. Org. Chem.* **1954**, *19*, 1671.
5. Rinkes, I. *J. Rec. Trav. Chim.* **1931**, *50*, 1127.
6. (a) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc. Chem. Commun.* **1994**, 493. (b) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089. (c) Kucukbay, H.; Cetinkaya, B.; Guesmi, S.; Dixneuf, P. H. *Organometallics* **1996**, *51*, 2423. (d) Marshall, J. A.; Bennet, C. E. *J. Org. Chem.* **1994**, *59*, 6110.
7. Kuroda, H.; Hanaki, E.; Kawakami, M. *Tetrahedron Lett.* **1999**, *40*, 3753.
8. Kim, S.; Kim, Y. G. *Synlett* **1991**, *32*, 869.
9. Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.
10. Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241.
11. (a) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7993. (b) Guo, C.; Lu, X. *J. Chem. Soc. Perkin Trans.* **1993**, 1921.
12. Rychnovsky, A. D.; Kim, *J. Org. Chem.* **1994**, *59*, 2659.
13. (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819.
14. Trost, B. M.; Sorum, T.; Chan, C.; Harms, A. E.; Ruther, G. *J. Am. Chem. Soc.* **1997**, *119*, 698.
15. (a) Wittig, G.; Schöllkipf, U. *Chem. Ber.* **1954**, *87*, 1318. (b) Drefahl, G.; Lorenz, D.; Schnitt, G. *J. Prakt. Chem.* **1964**, *23*, 143. (c) Johnes, M. E.; Trippett, S. *J. Chem. Soc. C* **1966**, 1090. (d) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.
16. Hoffman, H.; Diehr, H. *J. Chem. Ber.* **1965**, *98*, 363.
17. Ramirez, F.; Lery, S. *J. Am. Chem. Soc.* **1957**, *79*, 6167.
18. Brandsma, L. *Preparative acetylenic chemistry*, 2nd ed.; Elsevier, 1988; p 102.
19. Ramirez, F.; Deshowitz, S. *J. Org. Chem.* **1957**, *22*, 41.
20. Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier, 1988; p. 104.
21. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 3324.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1921–1929
Tetrahedron

Electron transfer reactions of organic sulfoxides with photochemically generated ruthenium(III)–polypyridyl complexes

Muniyandi Ganesan,[a] Veluchamy Kamaraj Sivasubramanian,[a] Seenivasan Rajagopal[b,*] and Ramasamy Ramaraj[b,*]

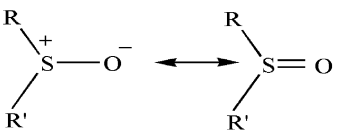
[a]*Department of Chemistry, Vivekananda College, Thiruvedagam West, Madurai 625 217, India*
[b]*School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India*

Received 22 August 2003; revised 7 November 2003; accepted 4 December 2003

Abstract—The electron transfer (ET) reaction of aryl methyl sulfoxides with ruthenium(III)–polypyridine complexes is sensitive to the change of substituent in the aryl moiety of $ArS(O)CH_3$ and ligand of Ru(III) complex. The detection of sulfoxide radical cation as the transient by conventional flash photolysis confirms ET in the rate-controlling step. The successful application of Marcus cross relation of ET leads to the evaluation of self-exchange rate constant of $ArS^+(O)CH_3/ArS(O)CH_3$ as 4.0×10^5 M^{-1} s^{-1} similar to organic sulfides. Comparison with the reactivity of iron(III)–polypyridyl complexes points out that both reactivity and ρ values are higher with Ru(III) complexes.

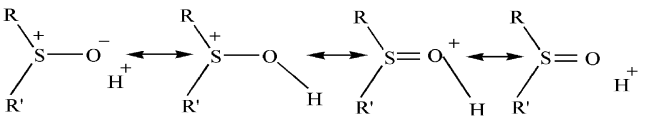
1. Introduction

The sulfoxide functional group is involved in different biological activities[1–3] and chiral sulfoxides are of considerable importance as synthetic intermediates[4] and ligands for asymmetric synthesis.[5] Organic sulfoxides are biphilic substrates and they may act as either electrophiles or nucleophiles depending on the nature of oxidant.[1,2,5] The X-ray spectroscopy and MO calculations indicate that the sulfoxide may be represented as a resonance hybrid of two cannonical forms, Eq. 1.[1,3]



(1)

The S–O bond distance of 1.492 Å is lengthened in the presence of proton and in this case single bond becomes more important, reducing the bond order. The protonated sulfoxide may be represented as given in Eq. 2.[3]



(2)

The presence of polarized S–O bond and weakening of the S–O bond by protonation make sulfoxide a weaker nucleophile compared to organic sulfides particularly at high $[H^+]$. When these substrates, organic sulfides and sulfoxides, undergo redox reactions with electrophiles or electron transfer (ET) reactions with electron acceptors, it is expected that sulfoxides are less reactive and reaction constant (ρ) values are always smaller with aryl methyl sulfoxides compared to the corresponding sulfides.[1,2,6–10] To get an idea of the reactivity of these biologically important substrates, organic sulfides and sulfoxides, we have initiated a systematic study on the kinetics and mechanism of oxidation of these substrates with several electrophilic oxo(salen)metal complexes[11–15] and iron(III)–polypyridyl complexes.[16,17]

Both organic sulfides and sulfoxides behave as nucleophiles towards oxo(salen)manganese(V)[11,12] and oxo(salen)iron[14,15] complexes. With oxo(salen)iron complexes the reactivity and reaction constant values are smaller for sulfoxides compared to sulfides. On the other hand, with oxo(salen)-manganese complexes, though the reactivity of sulfoxides is slightly less, interestingly the ρ value is higher with sulfoxides compared to sulfides. This is explained in terms of the Hammond postulate that sulfides proceed via the

Keywords: Electron transfer reactions; Organic sulfoxides; Ruthenium(III)–polypyridyl complexes.
* Corresponding authors. Tel.: +91-452-2458246; fax: +91-452-2459139; e-mail address: seenirajan@yahoo.com

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.009

reaction with an early transition state and sulfoxides with a late transition state. Organic sulfoxides behave differently with oxo(salen)chromium(V) complexes and they act as a donor ligand and bind with metal center with appreciable binding constant (K=100 M^{-1}).[13b] These interesting observations obtained in this laboratory and by other workers[7–19] led us to conclude that the presence of polarized S–O bond in sulfoxides makes these substrates behave differently from sulfides depending on the nature of the oxidant. Recently, we have reported our results on the ET reactions of organic sulfides with powerful one electron oxidants, Ru(III)–polypyridyl complexes, generated photochemically from Ru(II) complexes using molecular oxygen as oxidant.[20] Because of the unique behavior of organic sulfoxides with the different metal ions, we wanted to check the reactivity of organic sulfoxides towards these Ru(III) complexes (see Chart 1 for the structure of Ru(III) complexes (**I**–**V**)). The study of the reactivity of Ru(III) ion with organic sulfoxides is significant because several Ru(III)–sulfoxide complexes have recently been tried as anti-tumor agents.[21] Though organic sulfoxides have less reactivity (reactivity differs by more than two orders) as electron donors towards Ru(III) complexes (**I**–**V**), a comparable ρ value is obtained compared to organic sulfides. The ET nature of the titled reaction is confirmed from the transient absorption spectrum of sulfoxide radical cation recorded using conventional flash photolysis technique. Since the self-exchange rates for the redox couple Ru^{3+}/Ru^{2+} and the redox potentials of the reactants used in the titled reaction are available we utilized this ET reaction to estimate the self-exchange rate of $ArS^{+}(O)Me/ArS(O)Me$. The interesting spectral, kinetic and mechanistic details of the ET reaction of organic sulfoxides with five Ru(III)–polypyridyl complexes (**I**–**V**) are presented in this article.

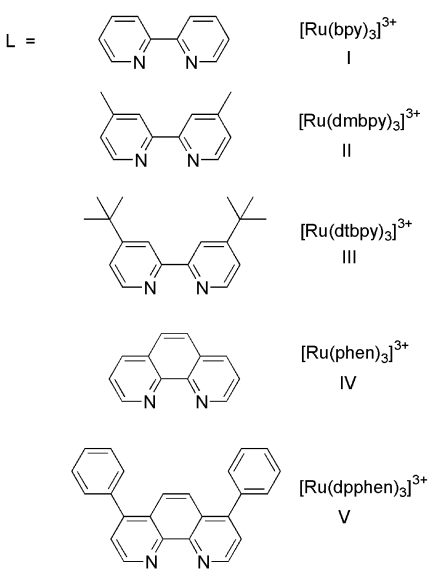


Chart 1. Structures of NN in $[Ru(NN)_3]^{3+}$.

2. Results and discussion

The structure of ligands and abbreviation of $[Ru(NN)_3]^{3+}$ complexes used in the present study are shown in Chart 1.

The kinetics of oxidation of six organic sulfoxides with five $[Ru(NN)_3]^{3+}$ complexes (**I**–**V**) have been studied by spectrophotometric technique under pseudo first-order condition by monitoring the increase in the absorbance of Ru(II) complex formed during the course of reaction. A sample run to show the change in the O.D. with time is given in Figure 1.

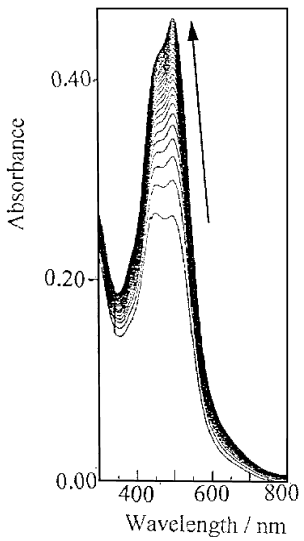


Figure 1. The absorption spectral changes for the reaction between $[Ru(bpy)_3]^{3+}$ and methyl phenyl sulfoxide at 20 s time intervals.

The linear log OD of $[Ru(bpy)_3]^{2+}$, formed from the reaction between $[Ru(bpy)_3]^{3+}$ and methyl phenyl sulfoxide (MPSO), versus time plot and constant k_1 value at different concentration of $[Ru(NN)_3]^{3+}$ indicate that the reaction is first-order in Ru(III). The kinetic data observed at different [sulfoxide] but at constant [Ru(III)] of complexes (**I**–**V**) show that the reaction is first-order in sulfoxide also (Fig. 2).

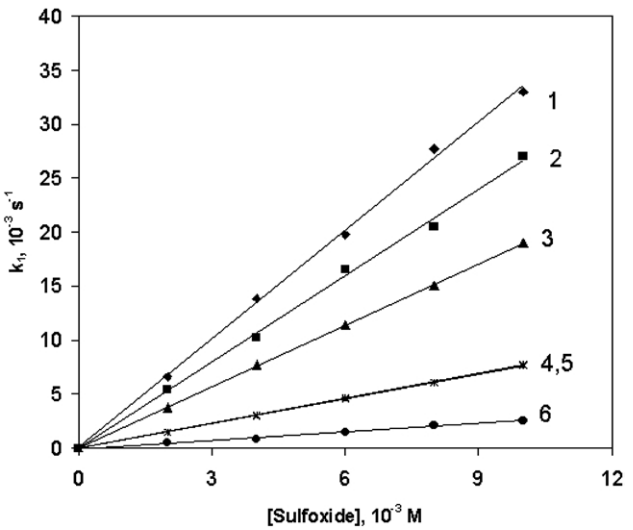


Figure 2. Plots of k_1 versus [sulfoxide] for the oxidation of aryl methyl sulfoxides by $[Ru(dtbpy)_3]^{3+}$ in aqueous CH_3CN (50% v/v) at 298 K. The numbers refer to the sulfoxides given in Table 2.

In order to understand the influence of other parameters on the rate of the reaction, the kinetics of the reaction has been followed at different solvent composition and the results are collected in Table 1.

Table 1. Effect of varying solvent composition on the reaction of $[Ru(NN)_3]^{3+}$ with methyl phenyl sulfoxide (MPSO) at 298 K

Solvent composition, CH_3CN-H_2O (v/v)	MPSO	
	$[Ru(bpy)_3]^{3+}$, k_2 ($M^{-1}\,s^{-1}$)	$[Ru(phen)_3]^{3+}$, k_2 ($M^{-1}\,s^{-1}$)
80:20	1.26	1.37
70:30	1.70	1.74
60:40	1.94	2.00
50:50	2.37	2.45
40:60	3.71	3.49
20:80	5.63	4.92

The increase in water content in the CH_3CN–water mixture favors the reaction which may be attributed to charge development on the substrate in the transition state. The reaction is highly sensitive to the change of substituent in the phenyl ring of $X-C_6H_4S(O)Me$ and the observed data are collected in Table 2. The data given in Table 2 show that introduction of electron-donating groups in the phenyl ring of $C_6H_5S(O)Me$ facilitates the reaction and electron-withdrawing groups inhibit the reaction. Application of the Hammett equation[22] for the analysis of kinetic data points out that a good correlation is obtained between log k_2 and Hammett σ values (Fig. 3) and the reaction constant values (ρ) are also collected in Table 2.

Though there is a substantial variation in the reactivity with the change of Ru(III) complex, surprisingly the ρ value remains almost constant (Table 2). These results support the postulation of ET in the rate-determining step. To check the importance of resonance interaction of the substitutent with the reaction site we tried the correlation of log k_2 with Brown–Okamoto's σ^+ values[23] but there is no improvement in the correlation ($\rho^+=-0.65$, $r=-0.941$). It is worthwhile to recall that better correlation with σ^+ and low ρ^+ value have been taken as kinetic evidence for the operation of ET mechanism in the oxidation of organic sulfoxides.[24] As Ru(III) is a well established one electron oxidant and the formation of sulfoxide radical cation is confirmed from flash photolysis study (vide infra), the postulation of better correlation of log k_2 with σ^+ is not a necessary condition for the operation of an ET mechanism.

The ET reaction of $[Ru(NN)_3]^{3+}$ with organic sulfoxides has been studied in four different temperatures and the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation evaluated from kinetic data. The rate constants obtained at four temperatures and the thermodynamic data are collected in Table 3. The values of $\Delta G^{\ddagger}$ calculated from these $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values using the equation $\Delta G^{\ddagger}=\Delta H^{\ddagger}-T\Delta S^{\ddagger}$ have also been given in Table 2. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ collected in Table 3 show that the change in $\Delta H^{\ddagger}$ with the change of substituent in the aryl moiety of ArS(O)Me is mainly responsible for the change in the reactivity because there is little change in $\Delta S^{\ddagger}$ values, i.e., the reaction is enthalpy controlled. Further, the values of $\Delta G^{\ddagger}$ collected in Table 2 are in accordance with the reactivity of different sulfoxides conforming the operation of an ET mechanism for all substrates.

Table 2. Second order (k_2, $M^{-1}\,s^{-1}$) rate constant values for the oxidation of *p*-$XC_6H_4S(O)Me$ by $[Ru(NN)_3]^{3+}$ in aqueous CH_3CN (50% v/v) at 298 K

Sl. no.	X=	Oxidation potential, E° versus SCE (V)	k_2 ($M^{-1}\,s^{-1}$)											
			$[Ru(bpy)_3]^{3+}$ (1.02 V) (I)			$[Ru(dmbpy)_3]^{3+}$ (0.86 V) (II)		$[Ru(dtbpy)_3]^{3+}$ (0.87 V) (III)		$[Ru(phen)_3]^{3+}$ (1.02 V) (IV)			$[Ru(dpphen)_3]^{3+}$ (0.96 V) (V)	
			Obs	Calcd	$\Delta G^{\neq}$, k (cal mol^{-1})	Obs	Calcd	Obs	Calcd	Obs	Calcd	$\Delta G^{\neq}$, k (cal mol^{-1})	Obs	Calcd
1.	OMe	1.51	4.21±0.12	905.0	16.6	1.41±0.04	40.0	0.80±0.05	49.0	5.20±0.21	905.0	16.5	3.37±0.17	282
2.	Me	1.62	3.22±0.08	106.0	16.8	1.09±0.05	4.72	0.61±0.03	5.66	4.21±0.14	106.0	16.6	2.62±0.11	33.1
3.	H	1.73	2.30±0.07	12.5	17.0	0.76±0.04	0.55	0.45±0.01	0.67	2.81±0.08	12.5	16.8	1.90±0.10	3.89
4.	Br	1.81	0.84±0.03	0.83	17.5	0.27±0.01	0.12	0.14±0.01	0.14	0.92±0.04	0.83	17.5	0.74±0.04	0.82
5.	Cl	1.81	0.82±0.03	0.83	17.6	0.25±0.01	0.11	0.16±0.01	0.14	0.82±0.03	0.83	17.6	0.73±0.04	0.82
6.	NO_2	—	0.26±0.01	—	18.3	0.08±0.01	—	0.05±0.01	—	0.35±0.02	—	18.1	0.23±0.01	—
			$r=-0.986$			$r=-0.986$		$r=-0.989$		$r=-0.968$			$r=-0.989$	
			$\rho=-1.16+0.10$			$\rho=-1.21+0.10$		$\rho=-1.17+0.12$		$\rho=-1.17+0.15$			$\rho=-1.13+0.08$	

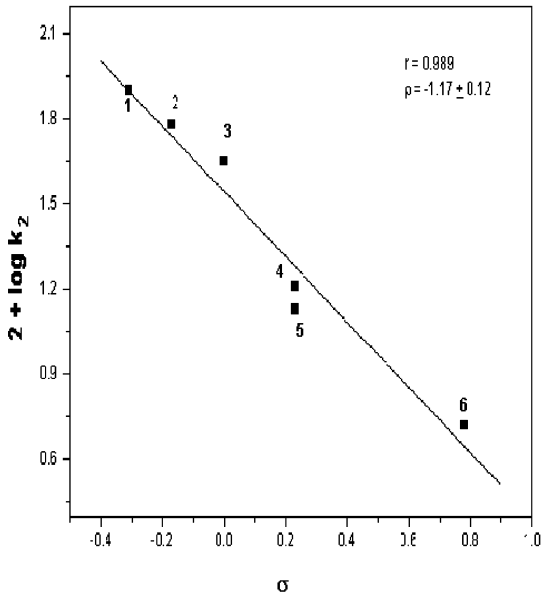


Figure 3. Hammett plot for the oxidation of aryl methyl sulfoxides by $[Ru(dtbpy)_3]^{3+}$ in aqueous CH_3CN (50% v/v) at 298 K. The numbers refer to the sulfoxides given in Table 2.

2.1. Formation of sulfoxide radical cation

Ruthenium(III) complexes (**I**–**V**), $[Ru(NN)_3]^{3+}$, are one-electron oxidants and the proposal of ET mechanism can be confirmed if the short lived transient radical, formed during the course of the reaction, is identified by time resolved technique. In the titled reaction, the progress of the reaction is followed by monitoring the increase in the concentration of Ru(II) complex formed as the product which supports the ET nature of the reaction. To confirm it further we have decided to record the transient absorption spectrum of sulfoxide radical cation. Though the transient absorption spectrum of sulfide radical cation has been recorded previously by generating them using pulse radiolysis and flash photolysis techniques by many workers,[23–25] as far as we know no attempt has been made to record the absorption spectrum of the sulfoxide radical cation. This is understandable because X-ray spectroscopy, MO calculations and other physical measurements show that the S–O band in organic sulfoxide is polarized with a net positive charge localized on the sulfur atom (Eq. 1).[3,5] Thus compared to sulfide it will be difficult to remove an electron from the positively charged sulfur of organic sulfoxides. In order to ascertain the formation of the sulfoxide radical cation we attempted the flash photolysis study of the reaction between $[Ru(NN)_3]^{3+}$ complex and organic sulfoxides. The experiment is designed as follows: the reaction mixture consisting of $[Ru(phen)_3]^{2+}$ and methyl phenyl sulfoxide (MPSO), taken in aqueous CH_3CN (50% v/v) and 4.5 M H_2SO_4, is purged with molecular oxygen for 20 min.

Then the reaction mixture is irradiated with flash of light and the absorption spectrum of the reaction solution is monitored at different time intervals. The spectra shown in Figure 4 show two strong absorptions at 300–350 and 500–550 nm. Comparing these data with the spectral data obtained for the sulfide radical cation by Baciocchi et al.,[25,26] Yokoi et al.,[27] and others[28] and from our recent study[20] we feel it reasonable that the peaks at 300–350 and 500–550 nm may be attributed to the sulfoxide radical cation. The absorption spectrum and the lifetime of this transient are not affected by the presence of oxygen. To get a clear picture of the different transients formed during the course of the reaction, a detailed study using a facility with high time resolution is required. At this stage we take the peaks at 300–350 and 500–550 nm to be due to the formation of sulfoxide radical cation.

Thus from the conventional flash photolysis study we are able to record the absorption spectrum of the transient, sulfoxide radical cation which supports the postulation of ET mechanism for the titled reaction. However, it is important to mention that though we are able to get spectral evidence for the formation of sulfoxide radical cation the bands are weak compared to the transients formed from organic sulfide. The transient spectrum of sulfide radical cation recorded under similar reaction conditions is shown in Figure 5.

In the present study, it is possible to record the transient spectrum of sulfoxide radical cation with millisecond (ms) time resolution because the species is stable at high $[H^+]$. The stabilization of this type of radical ion at high $[H^+]$ has already been established.[29]

It is known that molecular oxygen reacts with the excited state Ru(II) complex, $^*[Ru(NN)_3]^{2+}$ to produce Ru(III) as shown in Eqs. 3–7 (vide supra) Scheme 1.

$$[Ru(NN)_3]^{2+} + h\nu \rightarrow {}^*[Ru(NN)_3]^{2+} \quad (3)$$

$${}^*[Ru(NN)_3]^{2+} + O_2 \rightarrow [Ru(NN)_3^{2+}\cdots O_2]^* \quad (4)$$

$$[Ru(NN)_3^{2+}\cdots O_2]^* \xrightarrow[\text{Transfer}]{\text{Electron}} [Ru(NN)_3]^{3+}\cdots O_2^{\cdot -}] \quad (5)$$

$$[Ru(NN)_3^{3+}\cdots O_2^{\cdot -}] + H^+ \rightarrow [Ru(NN)_3]^{3+} + HO_2^{\cdot} \quad (6)$$

$$2HO_2^{\cdot} \rightarrow H_2O_2 + O_2 \quad (7)$$

Scheme 1.

Table 3. Second order rate constants for the oxidation of sulfoxides (p-$XC_6H_4SOCH_3$) by $[Ru(phen)_3]^{3+}$ in aqueous acetonitrile (50% (v/v)) at four different temperatures and activation parameters, enthalpy ($\Delta H^{\#}$) and entropy ($\Delta S^{\#}$) of activation

No.	X=	k_2 (M^{-1} s^{-1})				$\Delta H^{\#}$ (kcal mol^{-1})	$-\Delta S^{\#}$ (cal K^{-1} mol^{-1})
		293 K	298 K	303 K	313 K		
1	OMe	4.49	5.18	6.06	7.92	4.5	40.1
2	Me	3.74	4.30	5.08	6.76	4.8	39.7
3	H	2.25	2.86	3.73	4.89	6.4	35.1
4	Br	0.66	0.80	1.01	1.48	5.8	39.3
5	Cl	0.75	0.96	1.16	1.56	6.6	36.7
6	NO_2	0.24	0.34	0.46	0.68	8.5	32.3

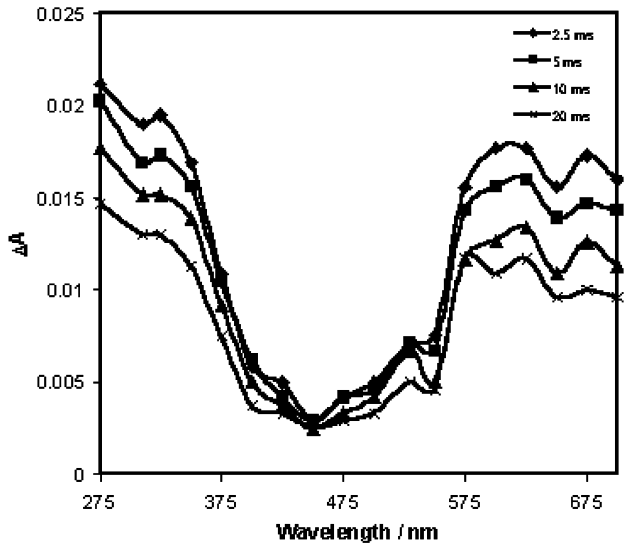


Figure 4. The absorption spectra of transients at different time intervals formed from the reaction of $[Ru(phen)_3]^{3+}$ with MPSO in oxygen-saturated aqueous CH_3CN (50% v/v) solution at 298 K by flash photolysis experiment.

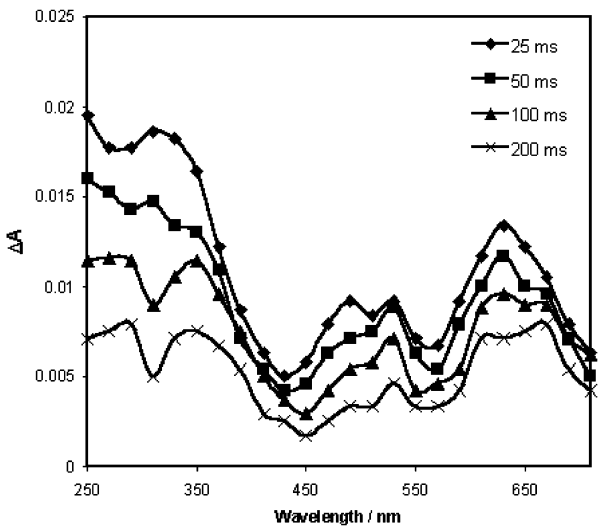


Figure 5. The absorption spectra of transients at different time intervals formed from the reaction of $[Ru(bpy)_3]^{3+}$ with MPS in oxygen-saturated aqueous CH_3CN (50% v/v) at 298 K.

It is important to mention that apart from ET quenching, $^*[Ru(NN)_3]^{2+}$ is also quenched by energy transfer mechanism to produce singlet oxygen. As the present reaction is concerned with the reaction of $[Ru(NN)_3]^{3+}$ with ArS(O)Me, the role of $^1O_2$ is not discussed here. The oxygenation of organic sulfur compounds with $^1O_2$ has been extensively studied. It is known that at high $[H^+]$ both $^1O_2$ and $[Ru(NN)_3]^{3+}$ contribute equally for the oxidation of organic substrates. The H_2O_2 oxidation of organic sulfoxides with H_2O_2 has been extensively studied but the reaction is slow. Thus the major part of the redox reaction takes place between $[Ru(NN)_3]^{3+}$ and ArS(O)Me particularly at $[H^+]$.

2.2. Mechanism of the $[Ru(NN)_3]^{3+}$ oxidation of organic sulfoxides

The formation of Ru(II) as one of the products of the reaction and sulfoxide radical cation as a transient are strongly in favor of ET from sulfoxide to Ru(III) in the rate determining step. The additional support for the ET mechanism comes from the substituent effect study, i.e., electron-donating substituents facilitate the reaction and electron-withdrawing groups retard the rate of reaction. The reaction constant (ρ) value is around −1.20 (Table 2). To account for the above spectral and kinetic results the mechanism shown in Scheme 2 has been proposed. Equations 8–12 are given in Scheme 2.

$$ArS(O)Me + [Ru(NN)_3]^{3+} \xrightarrow{k} ArS^{+\cdot}(O)Me + [Ru(NN)_3]^{2+} \quad (8)$$

$$ArS^{+\cdot}(O)Me + H_2O \xrightarrow{\text{fast}} ArS(OH)(O)Me + H^+ \quad (9)$$

$$ArS(OH)(O)Me + [Ru(NN)_3]^{3+} \xrightarrow{\text{fast}} ArS^{+}(OH)(O)Me + [Ru(NN)_3]^{2+} \quad (10)$$

$$ArS(OH)(O)Me + [Ru(NN)_3]^{3+} \xrightarrow{\text{fast}} ArS^{+}(OH)(O)Me + {}^*[Ru(NN)_3]^{2+} \quad (11)$$

$$ArS^{+}(OH)(O)Me \xrightarrow{\text{fast}} ArS(O_2)Me + H^+ \quad (12)$$

Scheme 2.

Generally the outer sphere oxidants, $[Ru(NN)_3]^{3+}$, undergo reaction with electron donors by second order kinetics with rate limiting ET to generate organic radical ion. In the presence of strong oxidants like $[Ru(NN)_3]^{3+}$, the driving force for back ET is diminished resulting in the long lifetimes of the radical cation. Consequently, the sulfoxide radical cation may undergo other types of reaction, either fragmentation or reaction with $[Ru(NN)_3]^{3+}$ or solvent in competition with back ET.[25,30] Jenks and co-workers have established that the photolysis of aromatic sulfoxides leads to α-cleavage as the predominant primary photochemical process.[31] The formation of sulfone as the major product of the reaction helps us to conclude that the major portion of sulfoxide radical cation is consumed by the solvent, water, though fragmentation and back ET may be competing processes. The formation of sulfone from sulfoxide radical cation may be shown as three-step process (Eqs. 9–12). Further, a good agreement between the experimentally observed second-order rate constants and the values calculated by Marcus theory (vide infra) also support the proposed mechanism (Scheme 2). The reaction between $[Ru(NN)_3]^{3+}$ and ArS(O)(OH)Me is fast and leads to the formation of Ru(II) complex in the excited state ($^*[Ru(NN)_3]^{2+}$) (Eq. 11) which is supported from the peak observed at 600 nm in the transient spectrum (Fig. 4). However, it is well known that when $[Ru(bpy)_3]^{3+}$ captures electrons from radicals or powerful electron donors the product $[Ru(bpy)_3]^{2+}$ is formed in the excited state.[32–35] The mechanism proposed here is similar to the one postulated for the $[Ru(NN)_3]^{3+}$ oxidation of organic sulfides.[20]

2.3. Application of Marcus cross-reaction relation

In the past half-century, great progress has been achieved in understanding both the kinetics and thermodynamics of ET

reactions (Eq. 13) by applying the Marcus cross-relation.

$$red_1 + ox_2 \rightleftharpoons ox_1 + red_2 \quad (13)$$

For ET reactions, like Eq. 13, the value of k_{12} is given by activated complex theory as Eq. 14

$$k_{12} = Z_{12} \exp(-\Delta G^{\#}_{12}/RT) \quad (14)$$

Where Z_{12} is the preexponential term and $\Delta G^{\ddagger}_{12}$ is the free energy of activation. According to Marcus theory, reactions like Eq. 13 can be described using the cross-relation given in Eqs. 15a and 15b.

$$k_{12} = (k_{11}k_{22}K_{12}f_{12})^{1/2} \quad (15a)$$

$$\ln f_{12} = [\ln(K_{12})]^2/[4 \ln k_{11}k_{22}/Z^2] \quad (15b)$$

The self-exchange rate constants, k_{11} and k_{22} and the equilibrium constant K_{12} are the principal parameters determining k_{12}. The term Z is the preexponential factor which is often taken as 10^{11} M^{-1} s^{-1}. The more general form of Eqs. 15a and 15b including work terms, has successfully been applied to a variety of inorganic, organic, organometallic and biochemical reactions.[33,36–42] The fundamental assumption in deriving Eqs. 15a and 15b was that averaging the activation barriers for self-exchange reactions produced the proper activation barrier for the cross-reactions.[30] Recently, it has been established that the great majority of ET reactions are non-adiabatic.[43] The rate constant of non-adiabatic ET is given by Eq. 16.

$$k_{12}\left(4\pi^3/h^2\lambda k_B T\right)^{1/2} V^2 \exp\left[-\frac{(\Delta G^{o} + \lambda)^2}{4\lambda k_B T}\right] \quad (16)$$

In Eq. 16, V is the electronic coupling matrix element, λ, the reorganization energy and ΔG^{o}, the free energy change for ET. The reorganization energy of ET(λ) is the energy required to structurally reorganize the donor, acceptor and their solvation spheres upon ET. Despite the predictions of modern theory by Bixon and Jortner,[43] Nelson et al.,[30,44] have applied Eqs. 15a and 15b successfully for the calculation of rate constants, k_{12}, for 141 reactions having couples of a wide range of structural types. Since Eqs. 15a and 15b is successful in accounting for ET reactions for couples having a wide range of structural types including heteroatom-substituted aromatics we have applied this equation to the titled reaction and to get the self-exchange rate of SO^+/SO. The value of self-exchange rate of $[Ru(NN)_3]^{3+}/[Ru(NN)_3]^{2+}$ is known from previous studies of Sutin et al.[37] as 4×10^8 M^{-1} s^{-1}. The high self-exchange rates observed with $[M(NN)_3]^{3+/2+}$ (M=Fe, Ru and Os) complexes is accounted for by Sutin et al. and others.[37,42c] In the divalent state there is relatively strong mixing of metal d and ligand π^* orbitals so that significant metal electron density exists on the ligands. The back-bonding interaction has the effect of shortening the metal(II)–nitrogen bonds so that inner-shell reorganization barrier to ET is lowered. Sutin and co-workers[37] pointed out another reason for large self-exchange rates of $[M(NN)_3]^{3+}$. The space-filling models of the tris(2,2′-bipyridine) or tris(1,10-phenanthroline) metal complexes show the favorable 'stacked' overlap of a pyridine ring in one complex with one pyridine in another complex. This contact may offer an especially facile pathway for the self-exchange reaction.

In Eqs. 15a and 15b the value of K_{12} is calculated from the redox potentials of the couples $[Ru(NN)_3]^{3+}/[Ru(NN)_3]^{2+}$ and SO^+/SO using Eqs. 17 and 18.

$$\Delta G^0 = nF(E^0_{SO^+/SO} - E^0_{Ru^{3+}/Ru^{2+}}) \quad (17)$$

$$K_{12} = \exp(-\Delta G^{o}/RT) \quad (18)$$

On taking logarithm Eq. 15a becomes Eq. 18.

$$\log k_{12} - 0.5 \log k_{11} - 0.5 \log f_{12} = 0.5 \log k_{22} + 0.5 \log K_{12} \quad (19)$$

The value of k_{22} for SO^+/SO can be estimated from an iterative procedure, i.e., a value of k_{22} is guessed and plugged into Eq. 16 to calculate f. With the calculated value of log f, plots of left hand side of Eq. 16 versus log K_{12} are made and from mean least-square calculations, the intercept and slope of such plots are determined. From the intercept a new estimated value of k_{22} is obtained and this is then used to calculate a new log f. The entire iterative process was repeated until successive estimates of k_{22} differed by less than 10%. The final results give k_{22}=4.0×10^5 M^{-1} s^{-1} if we use all five Ru(III) complexes (**I**–**V**) as the oxidant and a sample plot is shown in Figure 6.

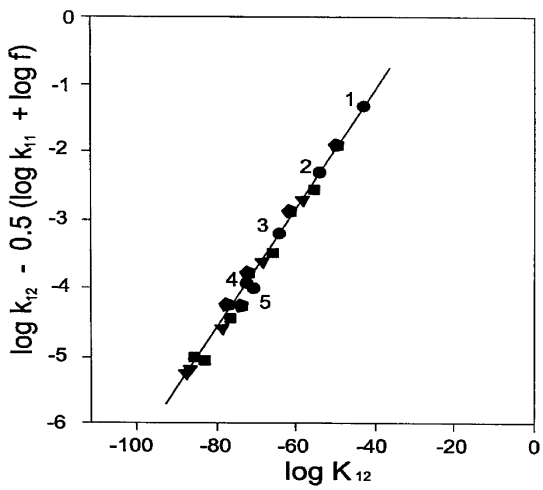


Figure 6. Plot of log $k_{12}-0.5(\log k_{11}+\log f)$ versus log K_{12}. The numbers refer to the sulfoxides given in Table 2. $[Ru(bpy)_3]^{3+}$ and $[Ru(phen)_3]^{3+}$ (●), $[Ru(dmbpy)_3]^{3+}$ (▲) $[Ru(dtpby)_3]^{3+}$ (■) and $[Ru(dpphen)_3]^{3+}$ (◆).

It is pertinent to point out that similar treatment to oxidation of organic sulfides has given the same value of k_{22} for sulfides.[20] After calculating the value of k_{22}, it is then used to get the values of rate constant for ET, k_{12}, from organic sulfoxides to $[Ru(NN)_3]^{3+}$ and the values are collected in Table 2. These calculated values are in fair agreement with the experimental values, supporting our arguments presented above. A difference of 1–2 orders is observed between the experimental and the calculated values for sulfoxides carrying electron-donating groups in the phenyl ring. The solvation of the reactants and transients plays an important role in deciding the reactivity and course of the reaction particularly when polar solvents are used in reactions involving charge development. The presence of electron-donating and withdrawing groups leads to different solvation energy. Recently it has been established that

p-$OCH_3C_6H_4S^{\cdot}$ involves a solvation energy of 42 kJ mol^{-1} and p-$NO_2C_6H_5S^{\cdot}$ −96 kJ mol^{-1} in CH_3CN.[45] Thus, in order to account for the dynamics of ET reactions it is essential to include the solvation energy in the calculation. Thus we presume that if the solvation energy was also included the agreement between the experimental and calculated values would be better.

2.4. Comparison of the reactivity of $[Ru(NN)_3]^{3+}$ with $[Fe(NN)_3]^{3+}$

Recently, iron(III)–polypyridyl complexes have been used in this laboratory as one-electron oxidants for the oxidation of organic sulfides and sulfoxides.[16,17] Compared to Fe(III), Ru(III) complexes are better electron acceptors and undergo facile one-ET reactions with a variety of organic, inorganic and biological substrates. The reduction potentials of $[Ru(bpy)_3]^{3+}$ and $[Fe(bpy)_3]^{3+}$ are 1.02 and 0.76 V versus SCE, respectively. It was interesting to compare the reactivity of these metal–polypyridyl complexes towards the same substrate, organic sulfoxides. The second-order rate constants for the ET reaction of $[Ru(bpy)_3]^{3+}$ and $[Fe(bpy)_3]^{3+}$ with MPSO under similar conditions are 2.3 and 0.27 $M^{-1}\,s^{-1}$, respectively. The ΔG° values for the reactions of $[Ru(bpy)_3]^{3+}$ and $[Fe(bpy)_3]^{3+}$ with MPSO are 0.70 and 0.90 eV, respectively. This comparison points out that the reactivity of these metal complexes is in accordance with the driving force of the reaction. The reaction constant (ρ^+) values for the reaction of $[Ru(bpy)_3]^{3+}$ and $[Fe(bpy)_3]^{3+}$ with X–$C_6H_4S(O)Me$ are −1.2 and −0.8, respectively. These rate (k) and reaction constant (ρ) data point out that for Ru(III) complexes the rate as well as the ρ values are higher compared to those of Fe(III) complexes.

This comparison leads us to conclude that reactions proceeding through an ET mechanism do not obey the reactivity–selectivity principle (RSP). It is interesting to recall that though aromatic sulfides have more reactivity by two orders magnitude compared to sulfoxides towards the same oxidant $[Ru(NN)_3]^{3+}$, they have a similar ρ value. On the other hand, these substrates have ρ values of ~3.2 and 0.8, respectively, towards $[Fe(NN)_3]^{3+}$. All these results strengthen our conclusion that though all reactions proceed through a similar ET mechanism, RSP is not successful for these ET reactions. To provide an explanation for this behavior, it is useful to take at the nature of the transition state of this ET reaction. In order to achieve selectivity in a chemical reaction the transition state should have definite structure.[46,47] For the reactions proceeding through outer-sphere ET mechanism the implicit assumption is that little interaction exists between the electron donor and acceptor in the transition state.[48–50] On the other hand, for the S_N2 transition state the most dominant interaction exists between the donor highest occupied molecular orbital (HOMO) and the acceptor lowest unoccupied molecular orbital (LUMO). It is interesting to mention that reactions of organic sulfides and sulfoxides with oxo(salen)metal complexes obey RSP and these reactions proceed through the nucleophilic attack of sulfur of the substrate on the oxygen center of the oxidant. The failure of RSP in the ET reactions led us to presume that these reactions might be of the unbound, outer-sphere type involving weakly bound transition states.

Further it is important to note the difference in self-exchange rate constant obtained for these organic sulfur compounds at different $[H^+]$. The self-exchange rate is $1.0\times10^7\ M^{-1}\,s^{-1}$ at 0.5 mH^+ but the value is $4.0\times10^5\ M^{-1}\,s^{-1}$ at 4.5 $[H^+]$. Thus at high $[H^+]$ the self-exchange rate is small because the radical cation is more stabilized at high $[H^+]$.

In conclusion the ET reaction between organic sulfoxides and Ru(III) complexes is established by observation of absorption spectrum of transient sulfoxide radical cation at high $[H^+]$. The Marcus cross relation is applied successfully to estimate the self-exchange rate constant of sulfoxide radical cation/sulfoxide redox couple. This conclusion on the metal ion oxidation of biologically important organic sulfides and sulfoxides is of importance because the oxidation of proteins and lipids by a single ET process has been associated with the onset of several diseases.[49,50]

3. Experimental

3.1. Materials

The $[Ru(NN)_3]^{2+}$ complexes (NN=2,2′-bipyridine (bpy), 4,4′-dimethyl-2,2′-dipyridine (dmbpy), 4,4′-di-*tert*-2,2′-bipyridine (dtbpy), 1,10-phenanthroline (phen) and 4,7-diphenyl-1,10-phenanthroline (dpphen)) were synthesized by known procedures.[51–53] The Ru(III) complexes needed for the titled reaction were prepared by adopting the procedure described below.[54,55] The steady-state photolysis of $[Ru(NN)_3]^{2+}$ in 4.5 M H_2SO_4 using a 500 W tungsten–halogen lamp led to the formation of corresponding Ru(III) complex. The light beam was made parallel by using a planoconvex lens. The infrared (IR) and ultraviolet (UV) radiations were cut-off by passing the light beam through a 5 cm quartz cell filled with water and pyrex glass filter. It was observed that the color of the solution readily changed from orange-yellow to green during irradiation. The formation of $[Ru(NN)_3]^{3+}$ complexes was confirmed by recording the absorption spectrum of the irradiated solution. $[Ru(NN)_3]^{3+}$ complexes showed peaks around 420–430 and 650–670 nm.

Methyl phenyl sulfoxide and methyl p-tolyl sulfoxide (Aldrich) were used as received. The other aryl methyl sulfoxides used in this study were prepared from the corresponding sulfides according to the literature procedures.[56,57] All the sulfoxides were purified by vacuum distillation/recrystallization from suitable solvents. The physical constants of the sulfoxides were found to agree with literature values. The GC analyses of each sulfoxide showed the presence of a single entity, and no impurity peak appeared in the ^1H NMR spectra. Acetonitrile (GR, E. Merck) was refluxed over P_2O_5 for 5 h and then distilled.[58] All other reagents were of AnalaR grade or used after purification. The kinetic study of the reaction was performed after confirming the purity of the reactants and solvents used in the system.

3.2. Conventional flash kinetic spectrometer

Flash photolysis experiments were carried out using an

applied photophysics UK KN-020 series model flash kinetic spectrometer. It consists of two LR-16, xenon filled flash lamps with an electrode separation of 140 mm, an overall length of 205 mm and a bore diameter of 10 mm. The sample cell was made of quartz with an outer jacket. The cell has an inner diameter of 10 mm and an optical path length of 105 mm. The cell was placed between the flash lamps in the middle and the lamps were fired at 10 kV using a 200 J, 1 μF capacitor bank. A 12 V, 100 W quartz-iodine lamp (Phillips, Holland) operated by a power supply unit (Model 415/01) was used as the light source for the monitoring beam. The detecting system consisted of a Hamamatsu R-928 photomultiplier tube with a spectral sensitivity from 190 to 900 nm. The output signal from the PMT was fed into an International Electronics India, digital storage oscilloscope and hard copies of the traces were obtained using an EPSON-LX80 printer.

3.3. Kinetic measurements

The absorption spectra of $[Ru(NN)_3]^{2+}$ and $[Ru(NN)_3]^{3+}$ complexes were obtained using a JASCO model 7800 UV–Vis spectrophotometer. The reaction between the photo-generated $[Ru(NN)_3]^{3+}$ and sulfoxide was monitored by following the increase in absorbance of $[Ru(NN)_3]^{2+}$ (λ_{max}=450 nm) at definite time intervals at 298 K. The reaction was followed up to 50% conversion. The kinetic study was carried out in aqueous CH_3CN (50% v/v) under pseudo first-order condition. The pseudo first-order rate constant (k_1) for each kinetic run was evaluated from the slope of linear plot of log OD versus time by the method of least squares. The linearity of each fit is confirmed from the values of correlation co-efficient (r) and standard deviations (s). The second-order rate constant (k_2) is evaluated from the relation $k_2=k_1/(\text{sulfoxide})$. The thermodynamic parameters, the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\neq}$) of activation, were evaluated by the least-squares method from the linear plot of log k_2/T versus $1/T$.

3.4. Product analysis

A sample of 0.5 mM substrate (ArSOMe) was added to a 0.5 mM solution of $[Ru(NN)_3]^{3+}$ complex in 5 ml of aqueous CH_3CN (50% v/v). The solution was stirred at 298 K for ~90 min or more depending upon the nature of sulfoxide and complex. The products of the reaction were extracted with chloroform and dried and the solvent was removed. Then the resulting residue was analyzed by IR spectroscopy and GC. The IR spectrum of the product (sulfone) was found to have stretching frequency in the characteristic region 1100–1150 cm^{-1}. The GC analysis (Model GC17A Schimadzu) of the product also indicated the formation of sulfone as the major product under the present experimental conditions.

Acknowledgements

The authors thank Professor P. Natarajan and Dr. P. Ramamurthy, National Centre for Ultrafast Processes, University of Madras for their help to record transient spectrum using flash photolysis technique.

References and notes

1. Oae, S. Organic sulfur chemistry: structure and mechanism; CRC: Boca Raton, FL, 1991.
2. (a) Clarke, M. J.; Zhu, F.; Frasca, D. R. *Chem. Rev.* **1999**, *99*, 2511. (b) Lipponer, K. G.; Vogel, E.; Keppler, B. K. *Metal-Based Drugs* **1996**, *3*, 243.
3. Calligaris, M.; Carugo, O. *Coord. Chem. Rev.* **1996**, *153*, 83.
4. (a) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717. (b) Colonna, S.; Gaggero, N.; Richelmi, C.; Pasta, P. *Trends Biotech.* **1999**, *17*, 163. (c) Posner, G. H. In *The chemistry of sulfones and sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: Chichester, England, 1988; p 823 Chapter 16.
5. (a) Hiroi, K.; Suzuki, Y. *Tetrahedron Lett.* **1998**, *39*, 6499. (b) Tokunoh, R.; Sodeoka, M.; Aoe, K.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 8035.
6. (a) Davies, J. A. *Adv. Inorg. Chem. Radiochem.* **1981**, *24*, 115. (b) Ianelli, S.; Musatti, A.; Nardelli, M.; Benassi, R.; Folli, U.; Taddei, F. *J. Chem. Soc. Perkin Trans. 2* **1992**, 49.
7. (a) Srinivasan, C.; Chellamani, A.; Rajagopal, S. *J. Org. Chem.* **1985**, *50*, 1201. (b) Balaiah, V.; Satayanarayana, P. V. V. *Indian J. Chem.* **1978**, *16A*, 966. (c) Srinivasan, C.; Venkatasamy, R.; Rajagopal, S. *Indian J. Chem.* **1981**, *20A*, 505.
8. (a) Di Furia, F.; Modena, G. *Pure Appl. Chem.* **1982**, *54*, 1853. (b) Curci, R.; Modena, G. *Tetrahedron* **1966**, *22*, 1227. (c) Curci, R.; Giovine, A.; Modena, G. *Tetrahedron* **1966**, *22*, 1235. (d) Curci, R.; Di Fura, F.; Modena, G. *J. Chem. Soc. Perkin Trans. 2* **1978**, 603.
9. Murray, R. W.; Jeyaraman, R.; Pillay, M. K. *J. Org. Chem.* **1987**, *52*, 746.
10. Acquaze, J. H.; Miller, J. G.; Takeuchi, K. *J. Inorg. Chem.* **1993**, *32*, 160.
11. (a) Chellamani, A.; Alhaji, N. M. I.; Rajagopal, S.; Sevvel, R.; Srinivasan, C. *Tetrahedron* **1995**, *51*, 12677. (b) Chellamani, A.; Alhaji, N. M. J.; Rajagopal, S. *J. Chem. Soc. Perkin Trans. 2* **1997**, 299.
12. Chellamani, A.; Kulandaipandi, P.; Rajagopal, S. *J. Org. Chem.* **1999**, *64*, 2232.
13. (a) Sevvel, R.; Rajagopal, S.; Srinivasan, C.; Alhaji, N. M. I.; Chellamani, A. *J. Org. Chem.* **2000**, *65*, 3334. (b) Venkataramanan, N. S.; Premsingh, S.; Rajagopal, S.; Pitchumani, K. *J. Org. Chem.* **2003**, *68*, 7460.
14. Sivasubramanian, V. K.; Ganesan, M.; Rajagopal, S.; Ramaraj, R. *J. Org. Chem.* **2002**, *67*, 1506.
15. Sivasubramanian, V. K. PhD Thesis, Madurai Kamaraj University, 2002..
16. Balakumar, S.; Thanasekaran, S.; Rajagopal, S.; Ramaraj, R. *Tetrahedron* **1995**, *51*, 4801.
17. John Adaikalasamy, K.; Venkataramanan, N. S.; Rajagopal, S. *Tetrahedron* **2003**, *59*, 3613.
18. Oae, S.; Asada, K.; Yoshimura, T. *Tetrahedron Lett.* **1983**, *24*, 1265.
19. Lahti, D. W.; Espenson, J. H. *Inorg. Chem.* **1999**, *38*, 5230.
20. Ganesan, M. PhD Thesis, Madurai Kamaraj University, 2002.
21. (a) Sadler, P. J.; Guo, Z. *Pure Appl. Chem.* **1998**, *70*, 863. (b) In *Metabolism of sulfur functional groups. Sulfur containing drugs and related organic compounds, chemistry, bio-chemistry and toxicology*; Damani, L. A., Ed.; Ellis Howard: Chichester, UK, 1989; Vol. I. Part B. (c) Mestroni, G.; Alessio, E.; Sava, G.; Pacor, P.; Coluccio, M. In *Metal complexes in cancer chemotherapy*; Keppler, B. K., Ed.; VCH: Weinheim, 1994; p 159.

22. March, J. Advanced organic chemistry; 4th ed. Wiley: New York, 1992; p 278.
23. Brown, H. C.; Okamota, K. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
24. Oae, S.; Watanabe, Y.; Fujimori, K. *Tetrahedron Lett.* **1982**, *23*, 1189.
25. (a) Baciocchi, E.; Ioele, M.; Lanzalunga, O.; Malandrucco, M.; Steenken, *J. Am. Chem. Soc.* **1996**, *118*, 8973. (b) Ioele, M.; Steenken, S.; Baciocchi, E. *J. Phys. Chem. A* **1997**, *101*, 2979. (c) Baciocchi, E.; Biethi, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243.
26. Giacco, T. D.; Elisei, F. Lan Zalunga. *O. Phys. Chem. Chem. Phys.* **2000**, *2*, 1701.
27. Yokoi, H.; Hatta, A.; Ishiguro, K.; Sawaki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12728.
28. (a) Schoneich, C.; Asmus, K. D.; Bonifacic, M. *J. Chem. Soc,. Faraday Trans.* **1995**, *91*, 1923. (b) Chaudhri, S. A.; Mohan, H.; Anklam, E.; Asmus, K. D. *J. Chem. Soc. Perkin Trans. 2* **1996**, 383. (c) Adam, W.; Arguello, J. E.; Penenorg, A. B. *J. Org. Chem.* **1998**, *63*, 3905. (d) Engman, L.; Lind, J.; Merenyi, G. *J. Phys. Chem.* **1994**, *98*, 3174.
29. (a) Gawandi, V. B.; Mohan, H.; Mittal, J. P. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1425. (b) Gawandi, V. B.; Mohan, H.; Mittal, J. P. *Chem. Phys. Lett.* **1999**, *314*, 451. (c) Gawandi, V. B.; Mohan, H.; Mittal, J. P. *J. Phys. Chem. A* **2000**, *104*, 11877.
30. Nelsen, S. F.; Pladziewicz, J. R. *Acc. Chem. Res.* **2002**, *35*, 247.
31. Darmanyan, A. P.; Gregory, D. D.; Guo, Y.; Jenks, W. S. *J. Phys. Chem. A* **1997**, *101*, 6855.
32. Kanoufi, F.; Zu, Y.; Bard, A. J. *J. Phys. Chem. B* **2001**, *105*, 210.
33. Ghosh, P. K.; Brunschwig, B. S.; Chou, M.; Creutz, C.; Sutin, N. *J. Am. Chem. Soc.* **1984**, *106*, 4772.
34. Kapturkiewicz, A.; Szrebowaty, P.; Angulo, G.; Grampp, G. *J. Phys. Chem. A* **2002**, *106*, 1678.
35. Szrebowaty, P.; Kapturkiewicz, A. *Chem. Phys. Lett.* **2000**, *328*, 160.
36. (a) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966. (b) Marcus, R. A. *Discuss. Faraday Soc.* **1960**, *29*, 21. (c) Marcus, R. A. *J. Chem. Phys.* **1963**, *853*, 2889. (d) Marcus, R. A.; Sutin, N. *Inorg. Chem.* **1975**, *14*, 213. (e) Marcus, R. A. *Angew. Chem. Int. Ed.* **1993**, *32*, 1111.
37. (a) Chou, M.; Creutz, C.; Sutin, N. *J. Am. Chem. Soc.* **1977**, *99*, 5615. (b) Brown, G. W.; Sutin, N. *J. Am. Chem. Soc.* **1979**, *101*, 883. (c) Macartney, D. H.; Sutin, N. *Inorg. Chem.* **1985**, *24*, 3403.
38. (a) Marcus, R. A.; Sutin, N. *Biochim. Biophys. Acta* **1985**, *811*, 265. (b) Sutin, N. *Prog. Inorg. Chem.* **1983**, *30*, 441.
39. (a) Wherland, S. *Coord. Chem. Rev*. **1993**, *123*, 169. (b) Brunschwig, B. S.; Sutin, N. *Coord. Chem. Rev.* **1999**, *187*, 233. (c) In *Electron transfer in chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, 2001.
40. (a) Eberson, L. *Electron transfer reactions in organic chemistry*; Springer: Heidelberg, 1987. (b) In *Electron transfer in inorganic, organic and biological systems. Advances in chemistry series*; Bolton, J. R., Mataga, N., Mc Lendon, G., Eds.; ACS: Washington, DC, 1991; Vol. 228.
41. (a) Barbara, P. F.; Meyer, T. J.; Ratner, M. A. *J. Phys. Chem.* **1996**, *100*, 13148. (b) Gray, H. B.; Winkler, J. R. *Ann. Rev. Biochem.* **1996**, *65*, 537.
42. (a) Fukuzumi, S.; Nakanishi, I.; Tanaka, K. *J. Phys. Chem. A* **1999**, *103*, 11212. (b) Fukuzumi, S.; Nakanishi, I.; Tanaka, K.; Suenobu, T.; Tabard, A.; Guilard, R.; Caemelbecke, E. V.; Kadish, K. M. *J. Am. Chem. Soc.* **1999**, *121*, 785. (c) Roth, J. P.; Lovell, S.; Mayer, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 5486.
43. Bixon, M.; Jortner, J. *Adv. Chem. Phys.* **1999**, *106*, 35.
44. Nelsen, S. F.; Trieber, D. A., II; Nagy, M. A.; Konradsson, A.; Halfen, D. T.; Splan, K. A.; Pladziewicz, J. R. *J. Am. Chem. Soc.* **2000**, *122*, 5940, and references cited therein.
45. (a) Larsen, A. G.; Holm, A. H.; Roberson, M.; Daasbjerg, K. *J. Am. Chem. Soc.* **2001**, *123*, 1723. (b) Brinck, T.; Carlqvist, P.; Holm, A. H.; Daasbjerg, K. *J. Phys. Chem. A* **2002**, *106*, 8827.
46. Tolbert, L. M.; Bedlek, J.; Terapane, M.; Kowalik, J. *J. Am. Chem. Soc.* **1997**, *119*, 2291.
47. Zipse, H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1697.
48. (a) Shaik, S.; Shurki, A. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 587. (b) Bakken, V.; Danovich, D.; Shaik, S.; Schlegel, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 130.
49. (a) Rauk, A.; Armstrong, D. A.; Fairlic, D. P. *J. Am. Chem. Soc.* **2000**, *122*, 9761. (b) Rauk, A. *Can. Chem. News.* **2001**, *53*, 20.
50. Lai, S.; Lepage, C. J.; Lee, D. G. *Inorg. Chem.* **2002**, *41*, 1954.
51. Skarada, V.; Cook, M. J.; Lewis, A. P.; Mc Anliffe, G. S. G.; Thomson, A. J.; Robbins, D. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1309.
52. Kawamnishi, S.; Kitamura, N.; Tazuke, S. *Inorg. Chem.* **1989**, *28*, 2968.
53. (a) Kitamura, N.; Rajagopal, S.; Tazuke, S. *J. Phys. Chem.* **1987**, *91*, 3767. (b) Rajendran, T.; Thanasekaran, P.; Rajagopal, S.; Allen Gnanaraj, G.; Srinivasan, C.; Ramamoorthy, P.; Venkatachalapathy, B.; Manimaran, B.; Lu, K. L. *Phys. Chem. Chem. Phys.* **2001**, *3*, 2063.
54. Zhang, X.; Rodgers, M. A. *J. Phys. Chem.* **1995**, *99*, 12797.
55. Das, A.; Joshi, V.; Kotkar, D.; Pathak, V. S.; Swayambunathan, V.; Kamat, P. V.; Ghosh, P. K. *J. Phys. Chem. A* **2001**, *105*, 6945.
56. Suthakaran, R.; Subramanain, P.; Srinivasan, C. *Proc. Indian Acad. Sci. (Chem. Sci.)* **1986**, *97*, 555.
57. Suthakaran, R.; Srinivasan, C.; Rajagopal, S. *Tetrahedron* **2001**, *47*, 1369.
58. Perrin, D. D.; Arrmago, A. L. F.; Perrin, D. R. *Purification of laboratory chemicals*, 2nd ed.; Pergamon: New York, 1980.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1931–1939
Tetrahedron

O-Trimethylsilylenol ethers as versatile building blocks in a modular preparation of polyenic backbone

Beata W. Domagalska,[a] Ludwik Syper[b] and Kazimiera A. Wilk[a,*]

[a]*Institute of Organic and Polymer Technology, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland*
[b]*Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland*

Received 14 August 2003; revised 7 November 2003; accepted 4 December 2003

Abstract—Versatility and synthetic potential of 1-(trimethylsilyloxy)-1,3-butadiene, 1-(trimethylsilyloxy)penta-1,3-diene, and their methyl substituted derivatives have been demonstrated in a modular synthetic methodology of stereodefined π-conjugated unsymmetrical, symmetrical two-dimensional, and octupolar polyenal structure.

1. Introduction

The conjugated polyenic backbone is an important structural unit in macrolide antibiotics and various classes of natural products (e g., retinoic acids, chrysophysarin A).[1] It has also been shown that conjugated polyenes can be used as model compounds for a variety of applications including electron transfer,[2] light harvesting,[3] nonlinear optics,[4,5] and conductivity[2] and are potentially useful compounds for electronic and non-linear optical materials.[6] Thus, it is not surprising that considerable efforts have been made to search for stereoselective methods of synthesis of such conjugated systems.

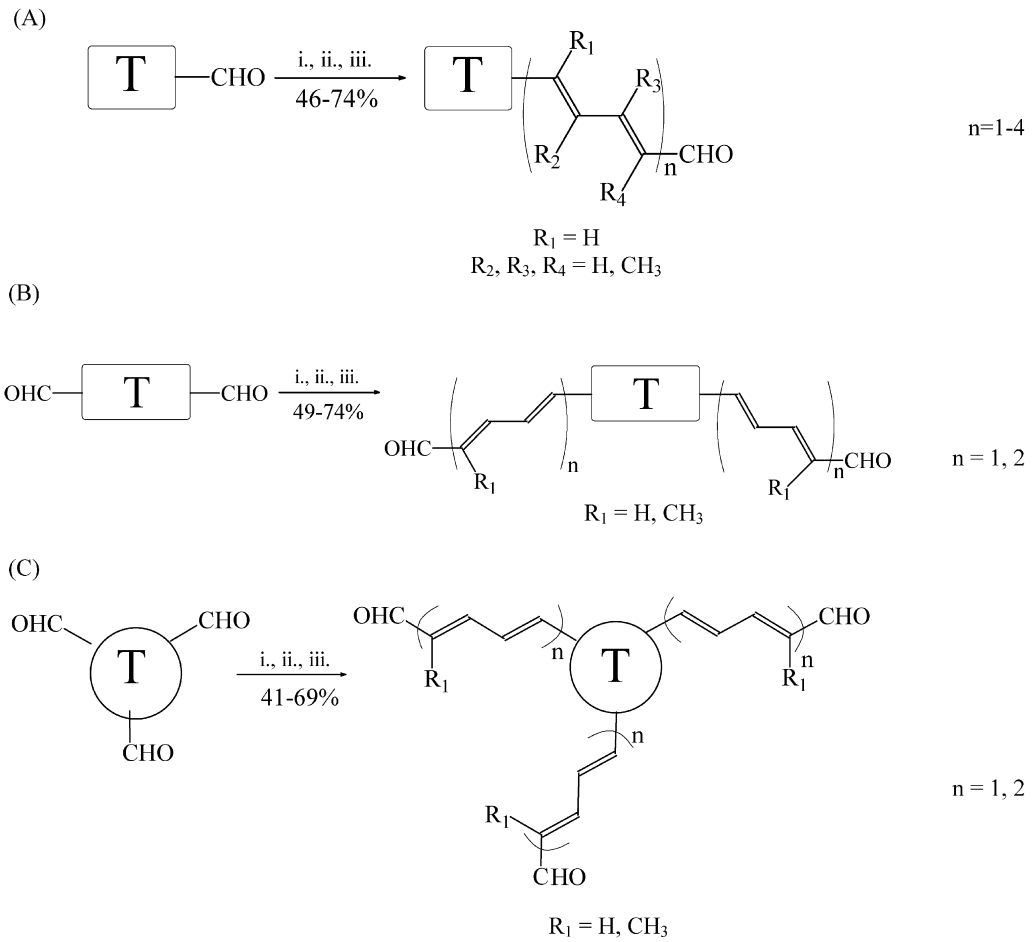
In the literature, the most common strategy of double-bond formation in the conjugated system is the Wittig reaction or one of its variants (Wittig–Horner, WH; Horner–Wadsworth–Emmons, HWE).[7] A site of unsaturation in the conjugated structure can also be generated by means of, for example, ring opening metathesis oligomerization,[8] retro-Diels–Alder reaction,[9] transition-metal-catalyzed reaction,[10] homocoupling reaction of unsaturated silanes[11] or allylboration reaction[12] and hydrozirconation-cross-coupling.[13] Knoevenagel condensation affords a possibility for incorporation of double bond, and donor or acceptor entity at one time and is commonly used to prepare conjugated polyenes with various functional groups.[14,15]

In our previous studies dealing with the synthesis of stereodefined (pure *all*-E) π-conjugated polyenes[16] we have devised new methodology for the synthesis of a polyenic backbone starting from 5,5-diethoxypenta-2-enal as a template and using 1-(trimethylsilyloxy)-1,3-butadiene as a building block. This modular method was successfully applied to the synthesis of linear, unsymmetrical amphiphilic conjugated *all*-E polyenals (ω,ω′-(*p*-alkoxyphenyl)-polyenals)[16] containing up to eight double bonds.

The main purpose of the present contribution is to illustrate the versatility and the efficient synthetic potential of *O*-trimethylsilylenol ethers (1-(trimethylsilyloxy)-1,3-butadiene **8**, 1-(trimethylsilyloxy)penta-1,3-diene **4** and their methyl substituted derivatives **5**–**7**) for the stereoselective preparation of unsymmetrical as well as symmetrical and octupolar conjugated polyenals with and without the methyl groups in the polyenic backbone. We generalize the modular method by use of 1-(trimethylsilyloxy)penta-1,3-diene **4**, 3-methyl-1-(trimethylsilyloxy)-1,3-butadiene **5**, 2-methyl-1-(trimethylsilyloxy)-1,3-butadiene **6**, 2-methyl-1-(trimethylsilyloxy)penta-1,3-diene **7** as building blocks and new templates (4-hexyloxy-3-methoxybenzaldehyde **1**(**0**), 3-(4-hexyloxy-3-methoxyphenyl)propenal **1**(**1**), 2-methoxy-5-methyl-isophtalaldehyde **2**, and 2,4,6-trimethoxy-1,3,5-benzenetricarbaldehyde **3**). These building blocks lead to new conjugated polyenes with an angular methyl group — very important class of carotenoid-type polyenes. We are also interested in the synthesis of symmetrical two-dimensional conjugated polyenals and octupolar structures. The use of template with two reactive carbonyl moieties (**2**) leads to new symmetrical, conjugated polyenals — precursors of acceptor or donor substituted polyenes which represent an approach to a molecular wire.[17] The new octupolar structures that are of particular interest in the field of nonlinear optics due to their potentially large two

Keywords: *O*-Trimethylsilyl enol ethers; Unsymmetrical conjugated polyenes; Symmetrical conjugated polyenes; Octupolar conjugated polyenes.
* Corresponding author. Tel.: +48-71-3202828; fax.: +48-71-3203678; e-mail address: kazimiera.wilk@pwr.wroc.pl

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.008



i. $(EtO)_3CH$, EtOH, PPTS or CSA,r.t.; ii. O-trimethylsilylenol ether, $ZnCl_2$, Et_2O, 5 °C

iii. Py·HBr, acetone/H_2O

Scheme 1. The general synthetic approach for (A) unsymmetrical carotenoid-type polyenals, (B) symmetrical conjugated polyenals and (C) octupolar conjugated polyenals. Templates T and silyl enol ethers are presented in Table 1.

or three-dimensional quadratic nonlinearities can be obtained from the template with three reactive carbonyl moieties.

2. Results and discussion

Scheme 1 presents the synthetic approach for unsymmetrical carotenoid-type structures (A), as well as symmetrical (B) and octupolar (C) conjugated polyenals. Thus, in this modular synthesis, which involves reactive silyl enol ethers **4**–**8** as building blocks, and aldehyde comprising conjugation in its structure (**1**(**0**), **1**(**1**), **2**, **3**) as templates, a series of conjugated polyenals presented in Table 1 are obtained.

Each particular step of the designed iterative process, independent of the applied template, involves three steps. The first one — the slowest reaction step in the whole modular approach (reaction (i) in Scheme 1) — denotes the acetalization of the respective template (aldehyde comprising conjugation in its structure) with triethyl orthoformate in the presence of pyridinium *p*-toluenesulfonate (PPTS) or camphorsulfonic acid (CSA). In the case of PPTS, as the catalyst at 25 °C, the first step has been completed within 154 h for template **3** (see Table 2). Increasing temperature up to 50 °C makes the reaction time shorter (130 h), but unfortunately, the yield was diminished (Table 2). It is worth noting that CSA catalyzes the studied reaction effectively at 25 °C; tenfold reaction time decrease, high yield (see Table 2).

The second step (reaction (ii) in Scheme 1) represents the reaction of the nucleophilic building block to the above mentioned acetal in the presence of catalytic amounts of $ZnCl_2$, giving rise to δ-ethoxy-α,β-unsaturated aldehydes. The use of silyl enol ethers **4**–**8**, indicated in the first paragraph, made it possible to achieve in one step the carbon chain elongation of up to four atoms. Then, the **4**–**7** silyl enol ethers led, additionally to the methyl group introduction in the polyenic backbone and, furthermore, to the carotenoid-like structures **8**–**11**, **14**, **16** and polyenals **12**. The building block **8** is commercially available and the rest of used silyl enol ethers are easy to obtain from appropriate aldehydes according to method described in the literature.[18] In order to complete the synthesis of conjugated polyenals,

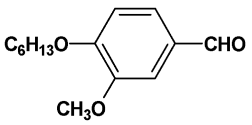
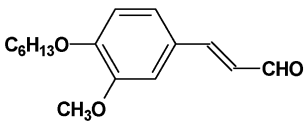
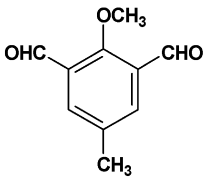
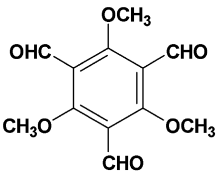
Table 1. Templates **1**–**3** and building blocks **4**–**6** leading to polyenals **8**–**16** by modular synthesis

Template	Building block	Product
m = 0, or 1 **1(m)**	**4**	for m=0, **8(n);** n = 1-4
	5	for m=0, **9(n);** n = 1-4
	6	for m=1, **10(n);** n = 1-4
		for m=0, **11(n);** n = 1-4
	7	for m=0, **12(n)**
2	**8**	13(**n**); n = 1, 2
	6	14(**n**); n = 1, 2
3	**8**	15(**n**), n = 1, 2
	6	16(**n**); n = 1, 2

water or/and ethanol are to be eliminated, double bonds shifted and the acetal moiety hydrolyzed in a cascade of four simultaneous reactions. The intermediates are carbocations, which are stable because of their allylic character.[11] The mentioned process carried out in the presence of pyridinium hydrobromide[12] (reaction (iii) Scheme 1) gave thermodynamically stable pure *all*-E isomers comprising two, three, four, five, six, seven and eight double bonds in one conjugated chain. The overall yields for the given series of conjugated polyenes **8**–**11**, **12**, **13**, **14**, **15** and **16** ranged between 53–75%, 43–62%, 51–74%, 49–72%, 41–69% and 40–67%, respectively.

All synthesized polyenals **8**–**16** were purified by medium pressure column chromatography (MPLC) or/and radial chromatography in darkness under N_2 and identified

Table 2. Experimental conditions of template **1**–**3** acetalization

Template	Catalyst	T (°C)	t[a] (h)	Yield[b]
	PPTS[c]	25	9	90
	CSA[d]	25	0.5	93
1(0)				
	PPTS[c]	25	18	94
	CSA[d]	25	1.5	96
1(1)				
	PPTS[c]	25	35	89
	PPTS[c]	50	8.5	85
	CSA[d]	25	2.5	93
2				
	PPTS[c]	25	154	87
	PPTS[c]	50	130	85
	CSA[d]	25	10	90
3				

[a] The progress of reaction was followed by TLC on silica gel with ethyl acetate/hexane (v/v, 3:1) as eluent.
[b] Isolated.
[c] Pyridinium *p*-toluenesulfonate.
[d] Camphorsulfonic acid.

unambiguously by NMR. The structure and stereochemistry of conjugated polyenals **8**–**16** were studied by NMR spectroscopy using one- (^{1}H, ^{13}C) and two-dimensional spectra (^{1}H–^{1}H and ^{1}H–^{13}C correlated spectroscopy—COSY). At 300 MHz these two methods allowed identification of almost all protons of the studied polyenic chains and determination of the coupling constants $J_{CH=CH}$ (14.1–15.4 Hz) and J_{CH-CH} (10.1–11.2 Hz) which are characteristic for *all*-E structures.[13] The stereochemical homogeneity of all obtained aldehyde structures was evidenced by the presence of a single doublet (at about 9.6 ppm) corresponding to the CHO. As in other *all*-E polyenes described in the literature the UV–vis spectra of compounds **8**–**16** are characterized by an intense, structureless and broad absorption band in the visible and ultraviolet region.[15,19] The $\pi-\pi^*$ transition is responsible for the first absorption band.[15,19] Symmetry of the first absorption band and lack of the additional bands in the longer wavelength region of the spectra evidence the existence of *all*-E isomer in the $CHCl_3$ solution. The IR spectrum in KBr of all studied compounds is very complex but detailed analysis confirms the structure and *all*-E configuration for the new polyenals **8**–**15**. The IR spectrum of all polyenals has absorption band between 1665 and 1685 cm^{-1} indicating the presence of long conjudated system (C=C–C=C and C=C–C=O). We do not observe any bands between 1400 and 1420 cm^{-1} and 660 and 730 cm^{-1} what confirms the absence of *Z* isomer. All spectroscopic analysis indicate *all*-E configuration for the studied compounds.

3. Conclusion

Summing up, we have described the use of *O*-trimethylsilyl enol ethers as versatile building blocks in modular synthesis of unsymmetrical, symmetrical and octupolar conjugated polyenals containing long polyenic backbones. In spite of difficulties with purity of conjugated polyenes MPLC and radial chromatography proved effective purification methods (purity was confirmed by elemental analysis, ESI-MS, NMR and UV–vis spectroscopy). Thus, obtained and purified derivatives, identified by NMR, UV–vis and IR spectroscopy, represent in ground state only one *all*-E isomer.

The unsymmetrical polyenals are convenient reagents for the synthesis of push–pull structures.[15,20] Push–pull polyenes as well as symmetrical and octupolar polyenals and their derivatives play important role as: molecular wires, novel NLO materials or electroluminescent material for light-emitting diodes.[21–23]

4. Experimental

4.1. General methods and materials

Starting materials were of the highest commercial quality and were used without further purification. All reactions were carried out under a protective atmosphere of N_2 gas using oven-dried glassware. Mps were determined on a Kofler block and are uncorrected. Elemental analyses were carried out with a Perkin–Elmer 2400 CHN analyzer (Norwalk, CT). Chromatographic purification was accomplished by medium pressure column chromatography (MPLC, Büchi Labortechnik AG, silica gel, flow rate 20 mL min^{-1}, eluent—hexane/ethyl acetate, 3:1) or/and radial chromatography (Chromatotron, Harrison Research Inc., N_2, 60 rpm, 2 mm layer of Silica Gel 60 GF254, flow rate 6 mL min^{-1}, eluent — hexane/ethyl acetate, 4:1). Electrospray ionization (ESI) spectra were obtained with a Finnigan TSQ-700 mass spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AMX-300 spectrometer (Karlsruhe, Germany). ^{1}H chemical shifts (at 300.13 MHz) are referenced in $CDCl_3$ to residual protons of $CDCl_3$ (7.24 ppm). The UV–Vis absorption spectra of freshly prepared solutions of all obtained polyenes were measured in CH_3Cl at room temperature using UV–Vis Unicam (Thermo Spectronic) spectrophotometer. IR spectra were obtained on FT-IR Nexus (Thermo Nicolet) spectrophotometer.

4.2. General procedure for the preparation of unsymmetrical conjugated polyenals 8(n)-12(n)

A mixture of appropriate aldehyde (template **1**(**m**), or polyenal **8**(**n**)–**12**(**n**) (22 mmol), $CH(OEt)_3$ (10 mL, 60 mmol) and catalyst (PPTS or CSA, 100 mg) in anhyd Et_2O (10 mL) was stirred at rt for 16–120 h (reaction

progress was controlled by TLC analysis). Then the mixture was poured into 5% aq ammonium hydroxide solution (50 mL) and the aqueous layer was extracted with Et_2O (4×80 mL). The combined organic layers were washed with brine, dried with K_2CO_3 and the solvent was evaporated under reduced pressure. The appropriate silyl enol ether (**4**, **5**, **6**, or **7**) (36 mmol) in anhyd Et_2O (20 mL) was then added dropwise to a well-stirred, ice-cooled solution of bis-acetal and $ZnCl_2$ (1.0 g, 7.34 mmol) in anhyd Et_2O (20 mL). After 36 h stirring at 5 °C, the reaction mixture was poured into the ice–water (100 mL). The organic phase was shaken with sat. aq $NaHCO_3$ and water, dried with $MgSO_4$ and the solvent was removed in vacuo. The obtained brown oil was added to a solution of a pyridine hydrobromide (0.10 g, 0.31 mmol) in acetone containing 0.2 mL of water. The mixture was stirred at 40 °C for 20–46 h, then poured into cold water (25 mL) and extracted with anhyd Et_2O (2×25 mL). The organic phase was washed with cold water, dried with $MgSO_4$ and evaporated. The residue was purified by medium pressure column chromatography or radial chromatography (hexane/EtOAc, 3:1 v/v).

4.2.1. (2*E*,4*E*)-5-(4-Hexyloxy-3-methoxyphenyl)-4-methyl-penta-2,4-dienal (8(1)). Brown solid, mp 30–35 °C, yield 75%. Anal. Calcd for $C_{19}H_{26}O_3$ (302.4): C, 75.46; H, 8.67. Found: C, 75.26; H, 8.85. ESI-MS: MH^+=303.2. ν_{max} (KBr) 2940, 2851, 1668, 1591, 1507, 1470, 1395, 1310, 1249, 1180, 1028, 968, 850, 795, 640 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.40 (1H, d, *J*=8.1 Hz, C*H*O), 7.20 (1H, d, *J*=15.0 Hz, C*H*=CHCHO), 6.82 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.80 (1H, s, ArC*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.65 (1H, d, *J*=3.0 Hz), 6.20 (1H, dd, *J*=8.0, 15.1 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (3H, s, CH=C*Me*), 1.30–1.80 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz, *Me*(CH_2)$_4$). λ_{max}($CHCl_3$)=354 nm, ε=2.8×10^5.

4.2.2. (2*E*,4*E*,6*E*,8*E*)-9-(4-Hexyloxy-3-methoxyphenyl)-4,8-dimethyl-nona-2,4,6,8-tetraenal (8(2)). Brown solid, mp 49–54 °C, yield 67%. Anal. Calcd for $C_{24}H_{32}O_3$ (368.5): C, 78.22; H, 8.75. Found: C, 78.0; H 8.9. ESI-MS: MH^+=369.22. ν_{max} (KBr) 3020, 2949, 2860, 1730, 1640, 1620, 1600, 1537, 1510, 1250, 1180, 1024, 975, 835, 795, 645, 645 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.42 (1H, d, *J*=8.1 Hz, C*H*O), 6.98 (1H, d, *J*=15.0 Hz, C*H*=CHCHO), 6.82 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.80 (1H, s, ArC*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.70 (1H, dd, *J*=14.9, 7.9 Hz, MeCCH=C*H*), 6.66 (1H, d, *J*=14.9 Hz, MeCC*H*=CH), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.44 (1H, d, *J*=7.9 Hz, C*H*=C(Me)), 6.22 (1H, dd, *J*=14.9, 8.1 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (6H, s, 2×C*Me*), 1.30–1.80 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz, *Me*(CH_2)$_4$). λ_{max}($CHCl_3$)=394 nm, ε=4.2×10^5.

4.2.3. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-13-(4-Hexyloxy-3-methoxyphenyl)-4,8,12-trimethyl-trideca-2,4,6,8,10, 12-heksaenal (8(3)). Brown solid, mp 62–68 °C, yield 60%. Anal. Calcd for $C_{29}H_{38}O_3$ (434.61): C, 80.14; H, 8.81. Found: C, 79.9; H, 8.9. ESI-MS: MH^+=435.3. ν_{max} (KBr) 3025, 2960, 2937, 2853, 1677, 1586, 1508, 1470, 1390, 1302, 1290, 1254, 1240, 1175, 1150, 1120, 1010, 990, 920, 855, 795, 650, 625 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.40 (1H, d, *J*=8.1 Hz, C*H*O), 6.82 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.80 (1H, s, ArC*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.73–6.78 (2H, m, ((Me)CCH=C*H*CH=)$_2$), 6.71 (1H, dd, *J*=14.9, 7.9 Hz, MeCCH=C*H*), 6.70 (1H, d, *J*=15.0 Hz, C*H*=CHCHO), 6.66 (1H, d, *J*=14.9 Hz, MeCC*H*=CH), 6.65 (1H, d, *J*=3.0 Hz), 6.44 (2H, 2×d, *J*=7.9 Hz, (C*H*=C(Me)CH=CH)$_2$), 6.22 (1H, dd, *J*=14.9, 8.1 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (9H, s, 3×CH=C*Me*), 1.30–1.80 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz, *Me*(CH_2)$_4$). λ_{max}($CHCl_3$)=422 nm, ε=4.9×10^5.

4.2.4. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-17-(4-Hexyloxy-3-methoxyphenyl)-4,8,12,16-tetramethyl-heptadeca-2,4,6,8,10,12,14,16-octaenal (8(4)). Brown solid, mp 79–84 °C, yield 54%. Anal. Calcd for $C_{34}H_{44}O_3$ (500.72): C, 81.56; H, 8.86. Found: C, 81.3; H, 9.0. ESI-MS: MH^+=501.4. ν_{max} (KBr) 3020, 2935, 2855, 1665, 1590, 1510, 1465, 1395, 1300, 1267, 1465, 1260, 1140, 1120, 1030, 970, 850, 645 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.40 (1H, d, *J*=8.0 Hz, C*H*O), 6.98 (1H, d, *J*=15.0 Hz, C*H*=CHCHO), 6.82 (1H, dd, *J*=9.0, 3.0 Hz, Ar*H*), 6.80 (1H, s, ArC*H*), 6.73–6.78 (4H, m, (C*H*CH=C(Me)CH)$_3$+Ar*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.60 (3H, 3×d, *J*=14.9 Hz, (C*H*=CHCH=CMe)$_3$), 6.42 (3H, 3×d, *J*=7.9 Hz, (C*H*=C(Me)CH=CH)$_3$), 6.22 (1H, dd, *J*=8.1, 14.9 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (12H, s, 4×CH=C*Me*), 1.30–1.80 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz, *Me*(CH_2)$_4$). λ_{max}($CHCl_3$)=445 nm, ε=5.7×10^5.

4.2.5. (2*E*,4*E*)-5-(4-Hexyloxy-3-methoxyphenyl)-3-methyl-penta-2,4-dienal (9(1)). Brown solid, mp 32–36 °C, yield 74%. Anal. Calcd for $C_{19}H_{26}O_3$ (302.41): C, 75.46; H, 8.67. Found: C, 75.2; H, 8.9. ESI-MS: MH^+=303.2. ν_{max} (KBr) 2950, 2862, 1663, 1590, 1508, 1470, 1395, 1305, 1250, 1150, 1025, 965, 850, 642 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.42 (1H, d, *J*=8.0 Hz, C*H*O), 6.82 (1H, dd, *J*=8.7, 3.0 Hz), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.70 (1H, d, *J*=15.1 Hz, ArC*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.63 (1H, d, *J*=15.4 Hz, ArCH=C*H*), 6.32 (1H, d, *J*=8.0 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.88 (3H, s, CH=C*Me*), 1.30–1.80 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz, *Me*(CH_2)$_4$). λ_{max}($CHCl_3$)=345 nm, ε=2.5×10^5.

4.2.6. (2*E*,4*E*,6*E*,8*E*)-9-(4-Hexyloxy-3-methoxyphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenal (9(2)). Brown solid, mp 49–54 °C, yield 68%. Anal. Calcd for $C_{24}H_{32}O_3$ (368.52): C, 78.22; H, 8.75. Found: C, 78.0; H, 8.9. ESI-MS: MH^+=369.2. ν_{max} (KBr) 2930, 2890, 1670, 1638, 1620, 1510, 1470, 1380, 1253, 1135, 999, 836, 792, 645 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.45 (1H, d, *J*=8.0 Hz, C*H*O), 6.82 (1H, dd, *J*=8.9, 3.0 Hz), 6.77 (1H, d, *J*=8.6 Hz), 6.75 (1H, dd, *J*=9.0, 14.8 Hz, C*H*=CHC(Me)), 6.71 (1H, d, *J*=15.3 Hz, ArC*H*), 6.65 (1H, d, *J*=3.0 Hz), 6.64 (1H, d, *J*=8.9 Hz, MeC=C*H*CH), 6.63 (1H, d, *J*=15.0 Hz, ArCH=C*H*), 6.41 (1H, d, *J*=15.0 Hz, C*H*C(Me)=CHCHO), 6.32 (1H, d, *J*=7.9 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (6H, s, 2×CH=C*Me*), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz, *Me*(CH_2)$_4$). λ_{max}($CHCl_3$)=384 nm, ε=4.0×10^5.

4.2.7. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-13-(4-Hexyloxy-3-methoxyphenyl)-3,7,11-trimethyl-trideca-2,4,6,8,10, 12-heksaenal (9(3)). Brown solid, mp 62–66 °C, yield 59%. Anal. Calcd for $C_{29}H_{38}O_3$ (434.62): C, 80.14; H, 8.81. Found: C, 79.9; H, 9.0. ESI-MS: MH^+=435.3. ν_{max} (KBr) 3020, 2950, 2931, 2860, 1675, 1585, 1510, 1465, 1390, 1305, 1292, 1253, 1170, 1135, 1015, 998, 920, 855, 645 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.45 (1H, d, *J*=8.0 Hz, C*H*O), 6.82 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.76 (1H, d, *J*=8.7 Hz, Ar*H*), 6.72 (2H, dd, *J*=14.8, 9.0 Hz, C*H*=CHC(Me)), 6.70 (1H, d, *J*=15.3 Hz, ArC*H*), 6.65 (3H, m, (C(Me)=C*H*CH=CH)$_2$+Ar*H*), 6.64 (1H, d, *J*=15.0 Hz, ArCH=C*H*), 6.41 (2H, m, (C(Me)=C*H*CH=C*H*)$_2$), 6.30 (1H, d, *J*=7.9 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (9H, s, 3×CH=C*Me*), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=415 nm, ε=5.1×10^5.

4.2.8. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-17-(4-Hexyloxy-3-methoxyphenyl)-3,7,11,14-tetramethyl-heptadeca-2,4,6,8,10,12,14,16-octaenal (9(4)). Brown solid, mp 80–85 °C, yield 55%. Anal. Calcd for $C_{34}H_{44}O_3$ (500.72): C, 81.56; H, 8.86. Found: C, 81.3; H, 9.0. ESI-MS: MH^+=501.3. ν_{max} (KBr) 3025, 2940, 2852, 1665, 1589, 1511, 1463, 1380, 1310, 1290, 1230, 1175, 1130, 1015, 998, 850, 795, 650 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.42 (1H, d, *J*=8.0 Hz, C*H*O), 6.82 (1H, dd, *J*=8.9, 2.9 Hz, Ar*H*), 6.76 (4H, m, (C*H*=CHC(Me)=CH)$_3$+Ar*H*), 6.70 (1H, d, *J*=15.3 Hz, ArCH), 6.66 (3H, m, (C*H*CH=CHCMe)$_3$), 6.65 (1H, d, *J*=2.98 Hz, Ar*H*), 6.63 (1H, d, *J*=15.0 Hz, ArCH=C*H*), 6.41 (3H, m, (C(Me)=C*H*CH=C*H*)$_3$), 6.32 (1H, d, *J*=8.0 Hz, C*H*CHO), 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (12H, s, 4×CH=C*Me*), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=438 nm, ε=5.9×10^5.

4.2.9. (2*E*,4*E*,6*E*)-7-(4-Hexyloxy-3-methoxyphenyl)-2-methyl-hepta-2,4,6-trienal (10(1)). Brown solid, mp 40–45 °C, yield 70%. Anal. Calcd for $C_{21}H_{28}O_3$ (328.45): C, 76.79; H, 8.59. Found: C, 75.12; H, 8.69. ESI-MS: MH^+=329.2. ν_{max} (KBr) 3000, 2930, 2860, 1720, 1660, 1604, 1512, 1465, 1270, 1031, 1020, 995, 845, 800, 645 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.43 (1H, s, C*H*O), 6.92 (1H, d, *J*=11.0 Hz, C*H*C(CH_3)CHO), 6.82 (dd, 1H, *J*=8.9, 3.0 Hz, Ar*H*), 6.80 (1H, dd, *J*=10.1, 15.0 Hz, ArCH=C*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.70 (1H, d, *J*=14.7 Hz, ArC*H*=CH), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.60 (2H, dd, *J*=15.0, 9.2 Hz, CH=C*H*) 3.97 (2H, t, *J*=6.54 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (3H, s, CH=C*Me*), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=369 nm, ε=2.4×10^5.

4.2.10. (2*E*,4*E*,6*E*,8*E*,10*E*)-11-(4-Hexyloxy-3-methoxyphenyl)-2,6-dimethyl-undeca-2,4,6,8,10-pentaenal (10(2)). Brown solid, mp 58–63 °C, yield 63%. Anal. Calcd for $C_{26}H_{34}O_3$ (394.55): C, 79.15; H, 8.69. Found: C, 78.9; H, 8.8. ESI-MS: MH^+=395.2. ν_{max} (KBr) 2999, 2930, 2859, 1720, 1659, 1600, 1510, 1465, 1270, 1250, 1175, 1140, 1029, 969, 845, 645 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.40 (s, 1H, C*H*O), 6.90 (1H, d, *J*=11.0 Hz, C*H*C(CH_3)-CHO), 6.82 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.79 (1H, dd, *J*=14.9, 9.8 Hz, ArC*H*=CH), 6.76 (1H, dd, *J*=14.8, 10.1 Hz, ArCH=C*H*), 6.76 (d, 1H, *J*=8.6 Hz, Ar*H*), 6.71 (1H, d, *J*=14.7 Hz, ArC*H*), 6.66 (1H, d, *J*=15.0 Hz, C(Me)C*H*), 6.65 (1H, d, *J*=3.0 Hz), 6.59 (2H, m, CH=CHC*H*=C*H*), 6.30 (1H, d, *J*=9.2 Hz, C*H*=CMe), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (6H, s, (CH=CHCH=C*Me*)$_2$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=415 nm, ε=2.8×10^5.

4.2.11. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*)-15-(4-Hexyloxy-3-methoxyphenyl)-2,6,10-trimethyl-pentadeca-2,4,6,8,10, 12,14-heptaenal (10(3)). Brown solid, mp 70–74 °C, yield 59%. Anal. Calcd for $C_{31}H_{40}O_3$ (460.65): C, 80.83; H, 8.75. Found: C, 81.1; H, 9.0. ESI-MS: MH^+=461.3. ν_{max} (KBr) 3005, 2935, 2850, 1670, 1600, 1511, 1466, 1268, 1178, 1138, 1030, 835, 795, 650 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (1H, s, C*H*O), 6.90 (1H, d, *J*=10.2 Hz, C*H*C(CH_3)-CHO), 6.82 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.79 (1H, dd, *J*=14.9, 9.8 Hz, ArC*H*=CH), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.76 (2H, m, (CH=C*H*CH=CMe)$_2$), 6.71 (1H, d, *J*=14.7 Hz, ArC*H*=CH), 6.65 (1H, d, *J*=2.9 Hz), 6.63 (2H, m, (C*H*=CHCH=CMe)$_2$), 6.59 (1H, dd, *J*=15.9, 9.0 Hz, CH=CHC*H*=CH), 6.58 (dd, 1H, *J*=14.9, 9.7 Hz, CH=CHCH=C*H*), 6.41 (2H, m, (C*H*=C(Me)CH=CH)$_2$), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (6H, s, (CH=CHCH=C*Me*)$_2$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=452 nm, ε=3.4×10^5.

4.2.12. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*,18*E*)-19-(4-Hexyloxy-3-methoxyphenyl)-2,6,10,14-tetramethylheptadeca-2,4,6,8,10,12,14,16,18-nonaenal (10(4)). Brown solid, mp 87–91 °C, yield 53%. Anal. Calcd for $C_{36}H_{46}O_3$ (526.75): C, 82.09; H, 8.80. Found: C, 81.7; H, 9.0. ESI-MS: MH^+=527.3. ν_{max} (KBr) 3029, 2952, 2856, 1662, 1587, 1510, 1471, 1365, 1137, 991, 863, 790, 742, 640 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.43 (1H, s, C*H*O), 6.91 (1H, d, *J*=10.2 Hz, C*H*C(CH_3)CHO), 6.82 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.79 (1H, dd, *J*=14.9, 9.8 Hz, ArC*H*=CH), 6.73–6.77 (4H, m, (CH=C*H*CH=CMe)$_3$+Ar*H*), 6.71 (1H, d, *J*=14.7 Hz, ArC*H*=CH), 6.62–6.66 (4H, m, (C*H*=CHCH=CMe)$_3$+Ar*H*), 6.59 (2H, m, CH=CHC*H*=C*H*), 6.40 (3H, m, (C*H*=C(Me)CH=CH)$_3$), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (12H, s, (CH=CHCH=C*Me*)$_2$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=467 nm, ε=4.0×10^5.

4.2.13. (2*E*,4*E*)-5-(4-Hexyloxy-3-methoxyphenyl)-2-methyl-penta-2,4-dienal (11(1)). Brown solid, mp 35–39 °C, yield 71%. Anal. Calcd for $C_{19}H_{26}O_3$ (302.41): H, 8.67; C, 75.46. Found: H, 8.7; C, 75.4. ESI-MS: MH^+=303.2. ν_{max} (KBr) 3030, 2950, 2860, 1670, 1590, 1511, 1475, 1265, 1135, 990, 860, 789, 745, 650 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.40 (1H, s, C*H*O), 6.90 (1H, d, *J*=10.8 Hz, C*H*=C(CH_3)CHO), 6.81 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.79 (1H, dd, *J*=14.7, 10.7 Hz, ArCH=C*H*), 6.76 (1H, d, *J*=8.6 Hz, ArH), 6.70 (1H, d, *J*=14.5 Hz, ArC*H*), 6.65 (1H, d, *J*=3.0 Hz), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.91 (3H, s, C*Me*), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=354 nm, ε=1.1×10^5.

4.2.14. (2*E*,4*E*,6*E*,8*E*)-9-(4-Hexyloxy-3-methoxyphenyl)-2,6-dimethylnona-2,4,6,8-tetraenal (11(2)). Brown solid,

mp 50–54 °C, yield 65%. Anal. Calcd for $C_{24}H_{32}O_3$ (368.51): H, 8.75; C, 78.22. Found: H, 8.80; C, 78.18. ESI-MS: MH^+=369.3. ν_{max} (KBr) 3025, 2955, 2855, 1670, 1588, 1510, 1471, 1265, 1137, 991, 864, 791, 640 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (1H, s, C*H*O), 6.90 (1H, d, *J*= 10.3 Hz, C*H*=C(CH_3)CHO), 6.81 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.79 (1H, dd, *J*=10.1, 14.5 Hz, ArCH=C*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.79 (1H, dd, *J*=14.0, 10.1 Hz, ArCH=C*H*), 6.71 (1H, d, *J*=14.8 Hz, ArC*H*), 6.65 (1H, d, *J*=2.98 Hz, Ar*H*), 6.61 (1H, d, *J*=10.2 Hz, ArCH=CHC*H*), 6.30 (d, 1H, *J*=14.3 Hz, C(Me)C*H*), 3.97 (2H, t, *J*=6.6 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (6H, s, (CH=CHCH=C(*Me*))$_2$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$) 410 nm, ε=1.7×10^5.

4.2.15. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-13-(4-Hexyloxy-3-methoxyphenyl)-2,6,10-trimethyl-trideca-2,4,6,8,10,12-heksaenal (11(3)). Brown solid, mp 69–73 °C, yield 58%. Anal. Calcd for $C_{29}H_{38}O_3$ (434.62): H, 8.81; C, 80.14. Found: H, 8.9; C, 80.1. ESI-MS: MH^+=435.3. ν_{max} (KBr) 3022, 2960, 2920, 2870, 1668, 1588, 1509, 1470, 1264, 1137, 990, 862, 879, 740, 640 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 ((1H, s, C*H*O), 6.89 (1H, d, *J*=10.2 Hz, C*H*=CMe-CHO), 6.81, (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.79 (1H, dd, *J*=10.1, 14.0 Hz, ArCH=C*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.70–6.73 (3H, m, (CH=C*H*CHCMe)$_2$+ArC*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.63 (2H, m, (C*H*=CHCHCMe)$_2$), 6.61 (1H, d, *J*=10.2 Hz, ArCH=CHC*H*), 6.30 (d, 1H, *J*=9.8 Hz, (C*H*=CHC*H*CMe)$_2$), 3.97 (2H, t, *J*= 6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (9H, s, (CH=CHCH=C(*Me*))$_3$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=442 nm, ε=2.1×10^5.

4.2.16. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-17-(4-Hexyloxy-3-methoxyphenyl)-2,6,10,14-tetramethylheptadeca-2,4,6,8,10,12,14,16-octaenal (11(4)). Brown solid, mp 87–93 °C, yield 54%. Anal. Calcd for $C_{34}H_{44}O_3$ (500.72): H, 8.86; C, 81.56. Found: H, 8.9; C, 81.5. ESI-MS: MH^+= 501,3. ν_{max} (KBr) 3025, 2955, 2950, 2860, 1672, 1587, 1510, 1472, 1265, 1140, 1125, 1030, 990, 860, 792, 742 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (1H, s, C*H*O), 6.90 (1H, d, *J*=10.2 Hz, C*H*=CMeCHO), 6.81, (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.79 (1H, dd, *J*=10.1, 14.0 Hz, ArCH=C*H*), 6.74–6.77 (4H, m, Ar*H*+(CH=C*H*CHCMe)$_3$CHO), 6.71 (1H, d, *J*=14.8 Hz, ArC*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.63 (3H, m, (C*H*=CHCHCMe)$_3$), 6.41 (3H, m, (C*H*=CMeCH=CH)$_3$), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (12H, s, (CH=CHCH=C(*Me*))$_4$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz). λ_{max}($CHCl_3$)=458 nm, ε=2.5×10^5.

4.2.17. (2*E*,4*E*)-5-(4-Hexyloxy-3-methoxyphenyl)-2,4-dimethyl-penta-2,4-dienal (12(1)). Brown solid, yield 62%. Anal. Calcd for $C_{20}H_{28}O_3$ (316.44): H, 8.92; C, 75.91. Found: H, 9.0; C, 75.7. ESI-MS: MH^+=317.3. ν_{max} (KBr) 2980, 2930, 2850, 1668, 1637, 1510, 1466, 1377, 1253, 1135, 999 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.40 (1H, s, C*H*O), 7.23 (1H, s, C*H*=CMeCHO), 6.81, (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.39 (1H, s, ArC*H*), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.90 (6H, s, CH=C*Me*)$_2$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz).

4.2.18. (2*E*,4*E*,6*E*,8*E*)-9-(4-Hexyloxy-3-methoxyphenyl)-2,4,6,8-tetramethylnona-2,4,6,8-tetraenal (12(2)). Brown solid, yield 55%. Anal. Calcd for $C_{26}H_{36}O_3$ (396.57): H, 9.15; C, 78.75. Found: H, 9.35; C, 78.62. ESI-MS: MH^+=397.3. ν_{max} (KBr) 3010, 2985, 2933, 2860, 1668, 1625, 1510, 1460, 1340, 1255, 1140, 998 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (1H, s, C*H*O), 7.20 (1H, s, C*H*=CMeCHO), 6.81 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.40 (1H, s, ArC*H*), 6.31 (2H, s, (C*H*CMe)$_2$), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.91 (12H, s, CH=C*Me*)$_4$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz).

4.2.19. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-13-(4-Hexyloxy-3-methoxyphenyl)-2,4,6,8,10,12-hexamethyltrideca-2,4,6,8,10,12-heksaenal (12(3)). Brown solid, yield 46%. Anal. Calcd for $C_{32}H_{44}O_3$ (476.70): H, 9.30; C, 80.63. Found: H, 9.55; C, 80.98. ESI-MS: MH^+=477.3. ν_{max} (KBr) 3025, 2965, 2935, 2857, 1670, 1596, 1511, 1468, 1360, 1254, 1240, 1175, 1150, 1010, 990, 855 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (1H, s, C*H*O), 7.20 (1H, s, C*H*=CMeCHO), 6.81 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.40 (1H, s, ArC*H*), 6.30 (4H, s, (C*H*CMe)$_4$), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.91 (18H, s, (CH=C*Me*)$_6$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz).

4.2.20. (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-17-(4-Hexyloxy-3-methoxyphenyl)-2,4,6,8,10,12,14,16-octamethylheptadeca-2,4,6,8,10,12,14,16-octaenal (12(4)). Brown solid, yield 63%. Anal. Calcd for $C_{38}H_{52}O_3$ (556.83): H, 9.41; C, 81.97. Found: H, 9.7; C, 81.8. ESI-MS: MH^+=557.4. ν_{max} (KBr) 3023, 2985, 2964, 2937, 2855, 1672, 1599, 1510, 1465, 1366, 1250, 1180, 1145, 1009, 995, 858 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (1H, s, C*H*O), 7.19 (1H, s, C*H*=CMeCHO), 6.81 (1H, dd, *J*=8.9, 3.0 Hz, Ar*H*), 6.76 (1H, d, *J*=8.6 Hz, Ar*H*), 6.65 (1H, d, *J*=3.0 Hz, Ar*H*), 6.40 (1H, s, ArC*H*), 6.30 (6H, s, (C*H*CMe)$_6$), 3.97 (2H, t, *J*=6.5 Hz, CH_2O), 3.89 (3H, s, O*Me*), 1.91 (24H, s, (CH=C*Me*)$_6$), 1.30–1.79 (8H, m, Me(CH_2)$_4$), 0.90 (3H, t, *J*=6.9 Hz).

4.3. General procedure for the preparation of symmetrical conjugated polyenals 13(n)–14(n)

Symmetrical conjugated polyenes **13**(**n**)–**14**(**n**) were obtained according to the procedure in Section 4.2 using 120 mmol of $CH(OEt)_3$ (20 mL) in the first step and 22 mmol of template **2** and 72 mmol of appropriate ether **6** or **8** in the second step of synthesis.

4.3.1. 5-[2-Methoxy-5-methyl-3-(5-oxo-penta-1,3-dienyl)-phenyl]-penta-2,4-dienal (13(2)). Brown solid, mp 42–45 °C, yield 74%. Anal. Calcd for $C_{18}H_{18}O_3$ (382.1): H, 6.43; C, 76.56. Found: H, 6.7; C, 76.2. ESI-MS: MH^+= 383.3. ν_{max} (KBr) 3010, 2973, 2930, 1689, 1475, 1470, 1396, 1234, 1095, 1002, 877 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.50 (2H, d, *J*=8.0 Hz, 2×C*H*O), 7.8 (2H, s, *H*Ar*H*), 7.25 (2H, dd, *J*=14.8, 10.6 Hz, 2×C*H*=CHCHO), 6.93 (2H, d, *J*=15.2 Hz, *H*CArC*H*), 6.79 (2H, dd, *J*=10.4, 15.1 Hz, 2×CH=C*H*), 6.2 (2H, dd, *J*=8.1, 14.8 Hz, 2×C*H*CHO), 4.01 (3H, s, OCH_3), 2.40 (3H, s, Ar*Me*). λ_{max}($CHCl_3$)=316 nm, ε=1.3×10^5.

4.3.2. 9-[2-Methoxy-5-methyl-3-(9-oxo-nona-1,3,5,7-teraenyl)-phenyl]-nona-2,4,6,8-tetraenal (13(4)). Brown solid, yield 51%. Anal. Calcd for $C_{26}H_{26}O_3$ (386.19): H, 6.79; C, 80.79. Found: H, 7.0; C, 80.5. ESI-MS: MH^+=387.5. ν_{max} (KBr) 3025, 2970, 2932, 1690, 1472, 1470, 1400, 1235, 1170, 1002, 875 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.51 (2H, d, J=8.1 Hz, 2×C*H*O), 7.8 (2H, s, *H*Ar*H*), 7.18 (2H, dd, J=15.1, 11.3 Hz, 2×C*H*=CHCHO), 6.93 (2H, d, J=15.0 Hz, *H*CArC*H*), 6.79 (2H, dd, J=15.2, 10.8 Hz, 2×CH=C*H*), 6.45–6.70 (8H, m, 2×(C*H*=C*H*)$_2$), 6.1 (2H, dd, J=8.1, 15.0 Hz, 2×C*H*CHO), 3.90 (3H, s, OCH_3), 2.40 (3H, s, Ar*Me*). λ_{max}($CHCl_3$)=362 nm, ε=2.2×10^5.

4.3.3. 5-[2-Methoxy-5-methyl-3-(4-methyl-5-oxo-penta-1,3-dienyl)-phenyl]-2-methyl-penta-2,4-dienal (14(1)). Brown solid, yield 72%. Anal. Calcd for $C_{20}H_{22}O_3$ (310.39): H, 7.14; C, 77.39. Found: H, 7.3; C, 77.4. ESI-MS: MH^+=311.1. ν_{max} (KBr) 3030, 2970, 2861, 2756, 1690, 1477, 1396, 1235, 1170, 1090, 870 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (2H, s, 2×C*H*O), 7.8 (2H, s, *H*Ar*H*), 6.91 (2H, d, J=10.5 Hz, C*H*=CMeCHO), 6.75 (2H, dd, J=10.5, 14.5 Hz, *H*C=HCArCH=C*H*), 6.71 (2H, d, J=13.5 Hz, *H*CArC*H*), 3.90 (3H, s, OCH_3), 2.40 (3H, s, Ar*Me*), 1.90 (6H, s, 2×C*Me*CHO). λ_{max}($CHCl_3$)=337 nm, ε=1.5×10^5.

4.3.4. 9-[3-(4,8-Dimethyl-9-oxo-nona-1,3,5,7-tetraenyl)-2-methoxy-5-methyl-phenyl]-2,6-dimethyl-nona-2,4,6,8-tetraenal (14(2)). Brown solid, yield 49%. Anal. Calcd for $C_{30}H_{34}O_3$ (442.60): H, 7.74; C, 81.41. Found: H, 7.88; C, 81.12. ESI-MS: MH^+=443.2. ν_{max} (KBr) 2975, 2932, 2856, 1690, 1625, 1475, 1470, 1396, 1233, 1100, 875 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.41 (2H, s, 2×C*H*O), 7.60 (2H, s, *H*Ar*H*), 6.90 (2H, d, J=10.0 Hz, C*H*=CMeCHO), 6.79 (2H, dd, J=10.5, 14.5 Hz, *H*C=HCArCH=C*H*), 6.76 (2H, dd, J=14.1, 10.1 Hz, 2×C*H*CH=C(Me)CHO), 6.71 (2H, d, J=14.8 Hz, *H*CArC*H*), 6.61 (2H, d, J=10.2 Hz, *H*CHC=HCArCH=CHC*H*), 6.30 (2H, d, J=14.3 Hz, 2×CMeC*H*), 3.90 (3H, s, OCH_3), 2.40 (3H, s, Ar*Me*), 1.90 (12H, s, 4×C*Me*). λ_{max}($CHCl_3$)=382 nm, ε=2.5×10^5.

4.4. General procedure for the preparation of symmetrical conjugated polyenals 15(n), 16(n)

Octupolar conjugated polyenes were obtained according to procedure described in Section 4.2 using 180 mmol of $CH(OEt)_3$ (30 mL) to acetalization reaction and 22 mmol of template **3** and 108 mmol of appropriate ether **6** or **8** in the second step of reaction.

4.4.1. 5-[2,4,6-Trimethoxy-3,5-bis-(5-oxo-penta-1,3-dienyl)-phenyl]-penta-2,4-dienal (15(2)). Brown solid, mp 98–102 °C, yield 69%. Anal. Calcd for $C_{24}H_{24}O_6$ (408.15): H, 5.93; C, 70.56. Found: H, 6.0; C, 70.5. ESI-MS: MH^+=409.1. ν_{max} (KBr) 3029, 2954, 2856, 1705, 1637, 1510, 1467, 1132, 975, 870 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.50 (3H, d, J=8.0 Hz, 3×C*H*O), 7.19 (3H, dd, J=14.8, 10.6 Hz, 3×C*H*=CHCHO), 6.93 (3H, d, J=15.2 Hz, Ar(C*H*)$_3$), 6.79 (3H, dd, J=10.4, 15.1 Hz, 3×CH=C*H*), 6.2 (3H, dd, J=8.1, 14.8 Hz, 3×C*H*CHO), 4.03 (9H, s, 3×OCH_3). λ_{max}($CHCl_3$) 331 nm, ε=3.4×10^5.

4.4.2. 9-[2,4,6-Trimethoxy-3,5-bis-(9-oxo-nona-1,3,5,7-tetraenyl)-phenyl]-nona-2,4,6,8-tetraenal (15(4)). Brown solid, mp 135–139 °C, yield 41%. Anal. Calcd for $C_{36}H_{36}O_6$ (564.2): H, 6.43; C, 76.56. Found: H, 6.5; C, 76.4. ESI-MS: MH^+=565.7. ν_{max} (KBr) 2980, 2935, 2850, 1860, 1688, 1626, 1590, 1475, 1399, 1235, 1100, 1025, 880, 640 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.51 (3H, d, J=8.1 Hz, 3×C*H*O), 7.18 (3H, dd, J=15.1, 11.3 Hz, 3×C*H*=CHCHO), 6.92 (3H, d, J=15.0 Hz, Ar(C*H*)$_3$), 6.80 (3H, dd, J=10.8, 15.2 Hz, 3×CH=C*H*), 6.45–6.70 (m, 12H), 6.1 (3H, dd, J=8.1, 15.0 Hz, 3×C*H*CHO), 3.90 (9H, s, 3×OCH_3).

4.4.3. 2-Methyl-5-[2,4,6-trimethoxy-3,5-bis-(4-methyl-5-oxo-penta-1,3-dienyl)-phenyl]-penta-2,4-dienal (16(1)). Brown solid, yield 67%. Anal. Calcd for $C_{27}H_{30}O_6$ (450.2): H, 6.72; C, 71.97. Found: H, 6.9; C, 71.8. ESI-MS: MH^+=451.5. ν_{max} (KBr) 2935, 2890, 1850, 1670, 1630, 1510, 1472, 1380, 1240, 1135, 889, 645 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.50 (3H, s, 3×C*H*O), 6.90 (3H, d, J=10.8 Hz, 3×C*H*=CMe), 6.79 (3H, dd, J=10.7, 14.7 Hz, CH=C*H*), 6.70 (3H, d, J=14.5 Hz, Ar(C*H*)$_3$), 4.01 (9H, s, 3×OCH_3), 1.91 (9H, s, 3×C*Me*). λ_{max}($CHCl_3$)=324 nm, ε=1.9×10^5.

4.4.4. 9-[3,5-Bis-(4,8-dimethyl-9-oxo-nona-1,3,5,7-tetraenyl)-2,4,6-trimethoxy-phenyl]-2,6-dimethyl-nona-2,4,6,8-tetraenal 16(2). Brown solid, yield 40%. Anal. Calcd for $C_{42}H_{48}O_6$ (648.3): H, 7.46; C, 77.74. Found: H, 7.6; C, 77.6. ESI-MS: MH^+=649.8. ν_{max} (KBr) 3020, 2940, 2839, 1680, 1580, 1476, 1390, 1310, 1230, 1170, 1015, 798, 650 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.44 (3H, s, 3×C*H*O), 6.90 (3H, d, J=10.2 Hz, 3×C*H*=CMe), 6.79 (3H, dd, J=10.1, 14.5 Hz, 3×CH=C*H*), 6.76 (3H, dd, J=14.1, 10.2 Hz, 3×C*H*CH=C(Me)CHO), 6.71 (3H, d, J=14.8 Hz, Ar(C*H*)$_3$), 6.61 (3H, d, J=10.2 Hz, 3×C*H*=CHMe), 6.30 (3H, d, J=14.3 Hz, MeC=C*H*), 4.01 (9H, s, 3×OCH_3), 1.90 (18H, s, 6×C*Me*).

Acknowledgements

Supports of this work by the State Committee of Scientific Research (Grant No. 7 T09A 063 20) and the Faculty of Chemistry (Wrocław University of Technology) are gratefully acknowledged. We thank the Laboratory of Materials Science (Institute of Physical and Theoretical Chemistry, Wrocław University of Technology) for the use of their FT-IR Nexus (Thermo Nicolet) and UV–Vis Unicam (Thermo Spectronic) spectrophotometers.

References and notes

1. (a) Eisenbarth, S.; Steffan, B. *Tetrahedron* **2000**, *56*, 363–365. (b) Rychnovsky, S. D. *Chem. Rev* **1995**, *95*, 2021–2040.
2. Spangler, C. W. *J. Mater. Chem.* **1999**, *9*, 2013–2020.
3. Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **1993**, *26*, 198–205.
4. Szymusiak, H.; Zieliński, R.; Domagalska, B. W.; Wilk, K. A. *Comput. Chem.* **2000**, *24*, 369–380.
5. Domagalska, B. W.; Wilk, K. A.; Szymusiak, H.; Zieliński, R. *Comput. Chem.* **2000**, *24*, 359–367.

6. Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1350–1377.
7. (a) Alain, V.; Blanchard-Desce, M.; Ledoux-Rak, J.; Zyss, J. *Chem. Commun.* **2000**, 353–354. (b) Effenberger, F.; Heid, S.; Merkle, R.; Zimmermann, P. *Synthesis* **1995**, *9*, 1115. (c) Mladenova, M.; Ventelon, L.; Blanchard-Desce, M. *Tetrahedron Lett.* **1999**, *40*, 6923–6926.
8. Bunning, T. J.; Natarajan, L. V.; Schmitt, M. G.; Epling, B. L.; Crane, R. L. *Appl. Opt.* **1991**, *30*, 4341–4349.
9. Knoll, K.; Schrock, R. R. *J. Am. Chem. Soc.* **1989**, *111*, 7989–8004.
10. Babudri, F.; Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron* **1998**, *54*, 1085–1094.
11. Babudri, F.; Cicciomessere, A. R.; Farinola, G. M.; Fiandanese, V.; Marchese, G.; Musio, R.; Naso, F.; Sciacovelli, O. *J. Org. Chem.* **1997**, *62*, 3291–3298.
12. Hoffmann, R.; Schäfer, F.; Haeberlin, E.; Rohde, T.; Köber, K. *Synthesis* **2000**, 2060.
13. Zeng, F.; Negishi, E. *Org. Lett.* **2002**, *4*, 703–706.
14. De Lucas, A. J.; Martin, N.; Sanchez, L.; Seoane, C.; Andreu, R.; Garin, J.; Orduna, J.; Alcala, R.; Villacampa, B. *Tetrahedron* **1998**, *54*, 4655–4662.
15. Domagalska, B. W.; Wilk, K. A.; Wysocki, S. *Phys. Chem. Chem. Phys.* **2003**, *5*, 696–702.
16. Domagalska, B. W.; Syper, L.; Wilk, K. A. *Synthesis* **2001**, *16*, 2463–2469.
17. Arrhenius, T. S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 5355–5359.
18. (a) Iqbal, J.; Khan, M. A. *Synth. Commun.* **1989**, *19*, 515–521. (b) Gaonac'h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045–4048. (c) Riehokainene, E.; Mikerin, J. E.; Slobodyan, N.; Severin, S. E. *Tetrahedron* **1998**, *54*, 10161–10166. (d) Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841–846.
19. Blanchard-Desce, M.; Runser, C.; Fort, A.; Barzoukas, M.; Lehn, J.-M.; Bloy, O.; Alain, V. *Chem. Phys.* **1995**, *199*, 253–261.
20. Plaza, P.; Laovge, D.; Martin, M. M.; Alain, V.; Blanchard-Desce, M.; Thompson, W. H.; Hynes, J. *J. Phys. Chem. A* **2000**, *104*, 2396.
21. Larsson, S.; Braga, M. *Chem. Phys.* **1993**, *176*, 367–375.
22. Luo, E.-T.; Tao, Y.-T.; Ko, S.-L.; Chuen, C.-H.; Chen, H. *J. Mater. Chem.* **2002**, *12*, 47–52.
23. Andraud, C.; Zabulon, T.; Collet, A.; Zyss, *J. Chem. Phys.* **1999**, *245*, 243–261.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1941–1949
Tetrahedron

Michael reaction of indoles with 3-(2′-nitrovinyl)indole under solvent-free conditions and in solution. An efficient synthesis of 2,2-bis(indolyl)nitroethanes and studies on their reduction

Manas Chakrabarty,[a,*] Ramkrishna Basak,[a] Nandita Ghosh[a] and Yoshihiro Harigaya[b]

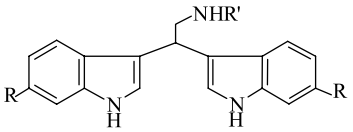
[a]*Department of Chemistry, Bose Institute, 93/1, A.P.C. Road, Kolkata 700009, India*
[b]*School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan*

Received 29 July 2003; revised 7 November 2003; accepted 4 December 2003

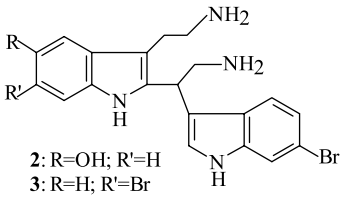
Abstract—Michael reaction of 3-(2′-nitrovinyl)indole with eight 3-unsubstituted indoles on TLC-grade silica gel furnished unsymmetrical bis(indolyl)nitroethanes in 7–12 min under microwave irradiation and in 8–14 h at rt. In contrast, the *p*-TsOH-catalysed reaction of the nitrovinylindole with the 3-unsubstituted and two 3-substituted indoles in solution under reflux furnished both unsymmetrical and symmetrical bis(indolyl)nitroethanes, the latter resulting from novel tandem Michael addition–elimination–Michael addition reactions. The synthesis of a 2′,3″-bis(indolyl)nitroethane, the precursor core structure of two bioactive marine metabolites, and the reduction of 2,2-bis(3′-indolyl)nitroethane to the corresponding ethylamine, isolated as its *N*-acetyl derivative, have been achieved. Significantly, attempted hydrolysis of three nitronates, derived from the corresponding bis(indolyl)nitroethanes, with buffered aqueous $TiCl_3$ has led to the first isolation of oximes (*syn*/*anti*-mixture) as the only products.

1. Introduction

Bis(indolyl)alkanes, -alkylamines, -alkanols, -alkanals and -alkanoic acids, often with bromo and hydroxy substituents in the benzenoid rings, constitute a small group of bisindoles of synthetic as well as natural origins (both terrestrial and marine). Some of these compounds are reported to be significantly bioactive as, for example, coronary dilator,[1] plant hormone,[2a,b] hallucinogen,[3] antibacterial,[4] DNA-damaging,[5] antiserotonin activity, strong affinity for somatostatin and neuropeptide Y receptors in recepter-binding assays[6] and anticarcinogen.[7a,b] In our recent review on this class of compounds,[8] we stated that bioactive 2,2-bis(indolyl)ethylamines (BIEAs), earlier reported to be only of synthetic origin,[1] have recently been reported from marine sources as well, for example, the BIEAs **1** from a tunicate[9] and **2** and **3** from a sponge.[6]



1: R=Br; R'=H
4: R=H; R'=COPh



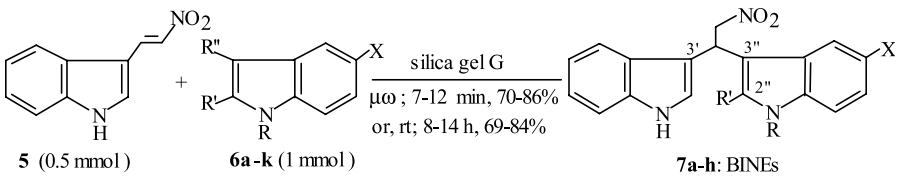
2: R=OH; R'=H
3: R=H; R'=Br

Although a BIEA (**4**) was first synthesised by the reaction of 3-indolylmagnesium iodide with benzamidoacetaldehyde,[10] the first general synthesis of BIEAs, only symmetrical ones, involved mainly the acid-catalysed reaction of indoles with *N*,*N*-dialkylaminoalkanals or their diethylacetals.[1] The second synthesis of BIEAs comprised the reaction of indoles with nitrones or 3-indolylhydroxylamines using trimethylsilyl chloride as an activator.[11a,b] But both these routes often required long reaction periods (up to 60 h) and furnished BIEAs in very low (e.g., 7%) or wide ranging yields (31–92%). We, therefore, intended to synthesise 2,2-bis(indolyl)nitroethanes (BINEs) which, upon subsequent reduction, should furnish BIEAs.

In this context, our attention was drawn to the fact that, although the Michael addition of nucleophilic indoles to nitroolefins has been well studied,[12a–c] the use of 3-(2′-nitrovinyl)indole (**5**) as a Michael acceptor in its reaction

Keywords: 3-(2′-Nitrovinyl)indole; Indoles; Michael reaction; Bis(indolyl)nitroethanes; Reduction; Oximes (*syn*/*anti*-).
* Corresponding author. Tel.: +91-33-2350-2402; fax: +91-33-2350-6790; e-mail address: chakmanas@yahoo.co.in

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.021



Scheme 1.

Table 1. Reaction of **5** with **6** on TLC-grade silica gel (5 g)

Indoles (**6**)					BINEs (**7**)			
Sl. No.	R	R′	R″	X	μω		rt	
					Time (min)	Yield (%)	Time (h)	Yield (%)
6a	H	H	H	H	10	86	14	82
6b	Me	H	H	H	9	85	9	84
6c	Me	H	H	Br	9	73	10	72
6d	Et	H	H	H	8.5	71	8	70
6e	^{i}Pr	H	H	H	9	75	9.5	72
6f	H	Me	H	H	7	70	8	69
6g	H	H	H	Br	10	83	9	82
6h	Me	Me	H	H	12	78	11	76
6i[a]	H	H	Me	H	—	—	—	—
6j[a]	Me	H	Me	H	—	—	—	—
6k[a]	Ac	H	H	H	—	—	—	—

[a] No reaction occurred.

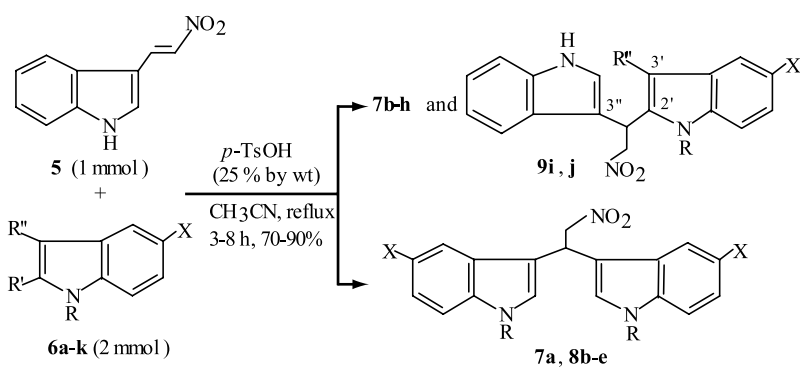
with indoles as nucleophiles has never been reported. We, therefore, developed an efficient synthesis of BINEs by the Michael reaction of **5** with 3-unsubstituted indoles (**6a**–**f**) on TLC-grade silica gel (acting as a mild acidic catalyst) under microwave irradiation or at rt to furnish in high yields the BINEs **7a**–**f**,[13] all but one (**7a**) of which were unsymmetrical. We have now extended this reaction to other substrates and have overcome the failures encountered in some cases by carrying out the Michael reaction in conventional solution phase in the presence of a protic acid catalyst to furnish both unsymmetrical and symmetrical BINEs, the latter resulting from novel tandem reactions. We applied our solution phase protocol for the synthesis of a 2′,3″-BIEA which forms the precursor to the core structure of two naturally occurring bioactive BIEAs. Further, as originally targeted, a BINE was successfully reduced to the corresponding BIEA. Moreover, while trying to convert some of the BINEs to the respective bis(indolyl)alkanals with aqueous $TiCl_3$, the respective oximes were isolated as the only products for the first time. The significance of these observations and the results are presented in this report.

2. Results and discussion

In our preliminary communication,[13] we reported that when **5**,[14] prepared by Henry reaction of 3-formylindole, was allowed to react with indole (**6a**) and the 3-unsubstituted indoles (**6b**–**f**) on TLC-grade silica gel, only the unsymmetrical BINEs (**7b**–**f**; also **7a**, which is clearly a symmetrical BINE) were formed in high yields, expeditiously (7–12 min) under microwave irradiation and in a much longer period (8–14 h) at rt. The reaction with **5** has now been extended to 5-bromoindole (**6g**), 1,2-dimethylindole (**6h**), skatole (**6i**), 1-methylskatole (**6j**) and 1-acetylindole (**6k**). 1-Acetylindole (**6k**) failed to react obviously due to its lack of nucleophilicity. Surprisingly, however, both the 3-methylindoles (**6i**,**j**) also met with failure, which is rather baffling. The results are shown in Scheme 1, Table 1.

In order to account for this failure, we reasoned that silica gel is not acidic enough to bring about the desired Michael addition of **6i** and **6j** at their less nucleophilic site, C-2, to **5**. To overcome this difficulty, the reaction of **5** with **6a**–**k** in general was studied in acetonitrile solution under reflux using *para*-toluene sulfonic acid (*p*-TsOH; 25% by wt) as the catalyst. As expected, except **6k** which failed to react this time too, all other indoles furnished unsymmetrical BINEs (**7b**–**h**,**9i**,**9j**). But surprisingly, the 1-alkylindoles **6b**–**e** additionally furnished the symmetrical bis(1-alkylindolyl)nitroethanes **8b**–**e** (Scheme 2, Table 2), whose formation must involve tandem reactions.

Regarding the formation of **8b**–**e**, we envisaged that the corresponding unsymmetrical BINEs **7b**–**e** were the initial reaction products in these cases too. Once formed, these BINEs underwent acid-catalysed elimination of an indole



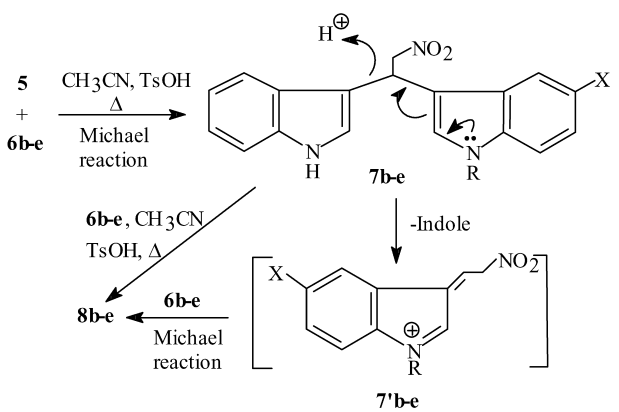
Scheme 2.

Table 2. Reaction of **5** with **6** in CH_3CN solution using *p*-TsOH

Indoles (**6**)					BINEs				
Sl. No.	R	R′	R″	X	Time (h)	Yield (%)			
						7	**8**	**9**	Overall
6a	H	H	H	H	8	84	—	—	84
6b	Me	H	H	H	5	63	27	—	90
6c	Me	H	H	Br	6	56	20	—	76
6d	Et	H	H	H	4	51	22	—	73
6e	^{i}Pr	H	H	H	4	52	26	—	78
6f	H	Me	H	H	6	70	—	—	70
6g	H	H	H	Br	7	81	—	—	81
6h	Me	Me	H	H	5	78	—	—	78
6i	H	H	Me	H	4	—	—	82	82
6j	Me	H	Me	H	3	—	—	80	80
6k[a]	Ac	H	H	H	—	—	—	—	—

[a] No reaction occurred.

molecule, resulting in the indoleninium cations **7′b–e**. Michael addition of 1-alkylindoles (**6b–e**) to **7′b–e** soon after their formation lead to the rearranged symmetrical BINEs **8b–e**. Since only the 1-alkylindoles **6b–e** furnished the rearranged BINEs **8b–e**, the increased electron density at the indolic nitrogen, arising from 1-alkylation, may be considered to have triggered the elimination of indole molecules to form the crucial indoleinium compounds **7′b–e**. This mechanistic proposition of tandem Michael addition–elimination–Michael addition received support from the slow formation of the respective BINEs (**8b–e**) in 15–30% yields when each of **7b–e** was separately refluxed with the corresponding alkylindole (**6b–e**) in solution under similar conditions (CH_3CN, *p*-TsOH, △) (Scheme 3).



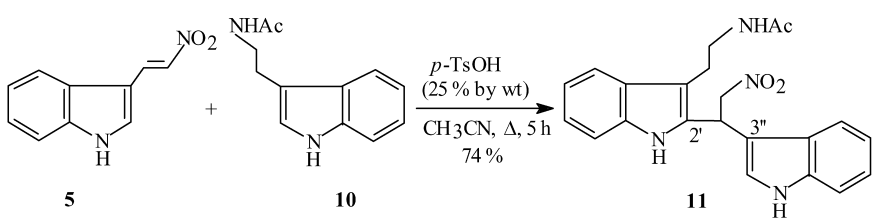
Scheme 3.

It is not clear to us as to why a similar product of tandem reactions was not formed from the reaction of 1,2-dimethylindole (**6h**), although the initial Michael addition product **7h** was formed in comparable yield.

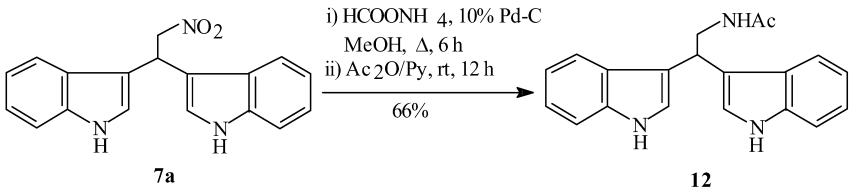
Our methodology could be well utilised for the synthesis of the BINE **11**, which can be reduced to the core BIEA structure of the marine metabolites **2** and **3**. Thus, when **5** was treated with *N*-acetyltryptamine (**10**) in the solution phase (CH_3CN, *p*-TsOH, △), the 2′,3″-BINE **11** was obtained in high yield (Scheme 4).

Since various types of BINEs could now be easily and efficiently prepared by our method, it only remained to be seen if the BINEs could be reduced to the corresponding BIEAs, the original target molecules. We, therefore, attempted the reduction of the representative BINE **7a**, the simplest member of the group, by some of the reagents reported for this purpose,[15a] viz. $LiAlH_4$, $NiCl_2{\cdot}6H_2O$/$NaBH_4$, Zn/HCl, H_2/Pd–C (1 atm), NiB_2/$NH_2NH_2.H_2O$,[16] In/NH_4Cl.[17] But none of these reagents worked. We, therefore, tried another method, viz. transfer hydrogenation using HCO_2NH_4/Pd–C under reflux[18a,b] (Scheme 5), when **7a** was smoothly reduced to the corresponding amine, isolated as its *N*-acetyl derivative (**12**).

In order to widen the utility of the present synthesis, the conversion of the BINEs into the corresponding 2,2-bis(indolyl)alkanals was aimed at because the latter can be converted into the corresponding alkanols and alkanoic acids which are natural products. The obvious choice, the Nef reaction,[19] could not be employed since it involves the use of sulfuric acid. Although the conversion of nitroalkanes

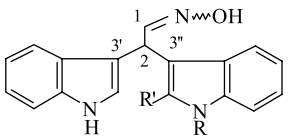


Scheme 4.



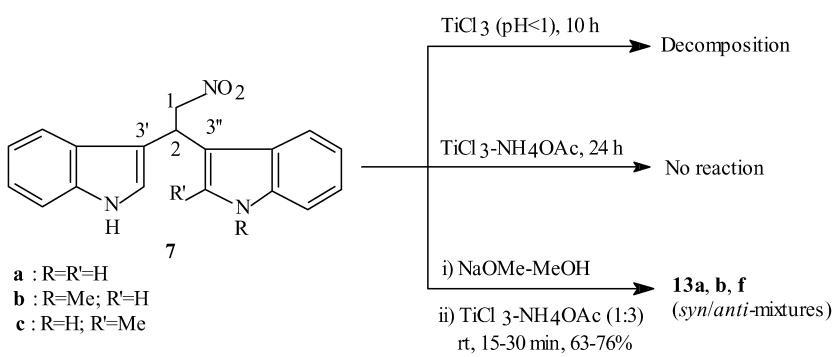
Scheme 5.

to aldehydes or ketones has been reported to be accomplished by several other reagents,[15b] we opted for McMurry's method of using aqueous $TiCl_3$ in buffered or unbuffered media on the nitroalkanes or the nitronates derived therefrom.[20a,b] Accordingly, when the BINE **7a** was treated with aqueous $TiCl_3$ (pH<1) at rt under nitrogen atmosphere and later in the presence of ammonium acetate, it caused decomposition and no change, respectively. However, when the nitronate derived (NaOMe/MeOH) from **7a** was treated with aqueous $TiCl_3$ in a buffered medium (pH~5–6) in methanol under nitrogen atmosphere at rt, the reaction was complete (TLC) within 30 min. Contrary to our expectation, the product was identified as the corresponding aldoxime **13a** (a mixture of the *syn*- and *anti*-isomers: 2:1; ^{1}H NMR) and no aldehyde could be isolated even after repeated trials. An attempt to drive the reaction towards the formation of the alkanal by stirring the reaction mixture for a longer period (2 h) led only to decomposition. In order to test the generality of this observation, we carried out the reaction with two more substrates, viz. **7b** and **7f**. In each case, a mixture of the *syn*- and *anti*-isomers of the corresponding aldoxime (**13b**,**f**) was obtained (Scheme 6; Table 3). Attempts were made to separate the two isomeric products in all three cases, but only the *anti*-isomer of **13a** could be isolated in 20% yield, i.e. with 80% recovery.



a : R=R'=H
b : R=Me; R'=H
c : R=H; R'=Me

The configurations of the *syn*- and the *anti*-isomers of the oximes were ascertained from their ^{1}H NMR spectroscopic data. A survey of the literature[21a–c] revealed that the aldehydic proton of alkenyl or aryl aldoximes appears downfield in the *syn*-isomers compared to their chemical shifts in the *anti*-isomers. Based on the chemical shift of the aldehydic proton of the pure *anti*-isomer of **13a**, it was noted that the C*H*=N appears at δ 7.23, 7.16 and 7.28 for the *anti*-isomers and δ 7.82, 7.79 and 7.91 for the *syn*-isomers of **13a**,**b** and **f**, respectively. A perusal of the ^{13}C NMR chemical shifts of the isomers of **13a**,**b**,**f** revealed that in each case the two isomers can be very well differentiated also from the chemical shifts of the Ar_2CH carbons. Thus, the Ar_2CH appears at around δ 29 for the *anti*-isomers and around δ 35 for the *syn*-isomers (vide Section 4).



a : R=R'=H
b : R=Me; R'=H
c : R=H; R'=Me

Scheme 6.

Table 3. Reaction of BINEs (**7**) with buffered aqueous $TiCl_3$

BINEs (**7**)	Oximes (**13**)		
	Time (min)	*syn*/*anti* (^{1}H NMR)	Overall yield (%)
7a	30	2:1	76
7b	15	2:1	63
7f	25	3:2	72

The formation of the oximes was indeed surprising and significant too. In view of an earlier report on the reduction of oximes by aqueous $TiCl_3$ to the imines and their subsequent hydrolysis to the carbonyl compounds,[22] McMurry suggested[20] that the conversion of primary and secondary nitroalkanes to the aldehydes and ketones, respectively by titanium(III) proceeds through the intermediacy of the oximes. But, to our knowledge, no oxime has yet been reported to be isolated from such a reduction. Thus, the isolation of the oximes **13a**,**b** and **f** is significant because

it constitutes the first direct evidence in support of the intermediacy of the oximes in McMurry's conversion of nitroalkanes, BINEs in this case, by aqueous $TiCl_3$. The failure to isolate any bis(indolyl)acetaldehyde from these reactions is probably due to the instability of the corresponding oximes under the reaction conditions.

3. Conclusions

A novel Michael reaction of 3-(2′-nitrovinyl)indole (**5**) with 3-unsubstituted indoles (**6a**–**h**) furnished only the addition products (BINEs **7a**–**h**, all but **7a** of which are unsymmetrical) using dry reaction conditions on TLC-grade silica gel, but both **7a**–**e** and symmetrical BINEs (**8b**–**e**) were obtained when the reactions were carried out in acetonitrile solution in presence of *p*-TsOH. A new sequence of tandem Michael addition–elimination–Michael addition reactions has been proposed for the formation of **8b**–**e**. This methodology has also been employed for the preparation of a 2′,3″-BINE (**11**), thereby opening a new avenue to the synthesis of naturally occurring BIEAs, for example, **2** and **3**, which would, of course, require a subsequent reduction. Further, the BINE **7a** was efficiently reduced by transfer hydrogenation (HCO_2NH_4, Pd–C) to the corresponding BIEA **12**, which thus provides access to a general synthesis of both symmetrical and unsymmetrical BIEAs. Finally, treatment of three BINEs (**7a**,**b**,**f**) with buffered aqueous $TiCl_3$ afforded the corresponding oximes (**13a**,**b**,**f**; *syn*- and *anti*-mixtures), which constitutes the first evidence in support of the previously predicted[20] intermediacy of oximes in the $TiCl_3$-mediated conversion of primary nitroalkanes to alkanals.

4. Experimental

4.1. General

Solvents were dried and purified using standard techniques. The glass apparatus for the anhydrous reactions were dried in an oven and assembled hot before use. Melting points (in Celcius) were determined on a Toshniwal apparatus and are uncorrected. IR spectra were recorded on a Nicolet Impact 410 and Nicolet Magnus 750 Series II spectrophotometer, LR EI-MS in a AEI MS 30 and LR EI-MS as well as HR MS, both EI and FAB (*m*-nitrobenzyl alcohol as liquid matrix), on JEOL JMS-AX505HA and JEOL JMS-700 MStation mass spectrometers and ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra, both 1D and 2D including DEPT-135, on a Bruker DRX 500 NMR spectrometer. Individual ^1H and ^{13}C NMR assignments, wherever made, are based on HMQC and HMBC spectral analyses. Silica gel G (Merck, India) was used for carrying out the dry reactions as well as for TLCs, both analytical and preparative, and silica gel (60–120 mesh; Qualigens, India) was used for column chromatography (CC). Elemental analyses were performed in a Dr. Hans Hoesli Analyser (Type A1; No. 1058).

4.2. General procedure for the synthesis of BINEs

Under microwave irradiation. A solution of **5** (0.5 mmol) and an 3-unsubstituted indole (**6a**–**h**; 1 mmol) in EtOAc (5 mL) was adsorbed on silica gel G (5 g) and the solvent was allowed to evaporate off at rt. The resulting dry mass was irradiated with microwave (BPL-SANYO, domestic multimode oven, 800 W, 50% power). When **5** was consumed (TLC), the reaction mixture was allowed to cool down to rt, the organic matter leached with EtOAc (3×25 mL), filtered through a bed of celite and the residue obtained by removal of solvent from the filtrate was purified by prep. TLC or CC to furnish the BINEs **7a**–**h**.

At rt. The reactants adsorbed on silica gel G as above was left at rt until **5** was consumed. The products were isolated as above and identified by comparison (mp, mmp, co-TLC) with samples obtained from the microwave-assisted experiments.

4.2.1. 2,2-Bis(3′-indolyl)nitroethane (7a). Brown solid; yield: μω, 86%; rt, 82%; mp 64–66 °C (pet. ether–CH_2Cl_2); IR (KBr) 3414, 1548, 1378, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.08 (2H, d, J=8 Hz), 5.49 (1H, t, J=8 Hz), 7.03 (2H, d, J=2 Hz), 7.09 and 7.20 (2H, t each, J=7.5 Hz), 7.35 and 7.59 (2H, d each, J=8 Hz), 8.01 (2H, br s); ^{13}C NMR: δ 34.2 (Ar_2CH), 79.5 (CH_2NO_2), 111.8 (2×), 119.4 (2×), 120.2 (2×), 122.7 (2×), 122.9 (2×) (all Ar–CH), 114.7 (2×), 126.5 (2×), 136.9 (2×) (all Ar–C); MS: *m*/*z* (%) 305 (M^+, 18), 258 (35), 257 (23), 245 (50), 243 (37), 142 (27), 130 (97), 115 (100), 89 (86), 77 (52). Anal. calcd for $C_{18}H_{15}N_3O_2$: C, 70.82; H, 4.91; N, 13.77. Found C, 70.74; H, 4.93; N, 13.74.

4.2.2. 2-(3′-Indolyl)-2-(1″-methyl-3″-indolyl)nitroethane (7b). Orange crystals; yield: μω, 85%; rt, 84%; mp 174 °C (pet. ether–$CHCl_3$); IR (KBR), ^1H and ^{13}C NMR ($CDCl_3$) and EI–MS data have earlier been reported by us.[13]

4.2.3. 2-(3′-Indolyl)-2-(5″-bromo-1″-methyl-3″-indolyl)-nitroethane (7c). Waxy; yield: μω, 73%; rt, 72%; IR ($CHCl_3$) 3429, 1560, 1381, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.65 (3H, s, NCH_3), 4.98 (1H, dd, J=8, 6.25 Hz, CH_AH_B-NO_2), 5.04 (1H, dd, J=7.5, 6.25 Hz, $CH_AH_BNO_2$), 5.38 (1H, dd, J=8, 7.5 Hz, Ar_2CH), 6.89 (1H, s, H-2″), 6.99 (1H, d, J=2 Hz, H-2′), 7.08 (1H, t, J=7.5 Hz, H-5′), 7.12 (1H, d, J=9 Hz, H-7″) 7.18 (1H, t, J=7.5 Hz, H-6′), 7.27 (1H, dd, J=9, 2 Hz, H-6″), 7.33 (1H, d, J=8 Hz, H-7′), 7.54 (1H, d, J=8 Hz, H-4′), 7.66 (1H, d, J=2 Hz, H-4″), 8.05 (1H, br s, NH); ^{13}C NMR: δ 33.3 (NCH_3), 34.0 (Ar_2CH), 79.4 (CH_2NO_2), 111.5 (CH-7″), 111.9 (CH-7′), 113.2 (CH-5″), 119.2 (CH-4″), 120.3 (CH-5′), 121.9 (CH-4″), 122.6 (CH-2′), 123.0 (CH-6′), 125.3 (CH-6″), 128.5 (CH-2″); 112.6 (C-3″), 114.4 (C-3′), 126.4 (C-3′a), 128.6 (C-3″a), 136.4 (C-7″a), 137.0 (C-7′a); MS: *m*/*z* (%) 399 (22), 397 (M^+, 21), 352 (44), 350 (33), 339 (100), 337 (95), 257 (45). Anal. calcd for $C_{19}H_{16}N_3O_2Br$: C, 57.28; H, 4.02; N, 10.55. Found C, 57.20; H, 4.01; N, 10.59.

4.2.4. 2-(3′-Indolyl)-2-(1″-ethyl-3″-indolyl)nitroethane (7d). Brown crystals; yield: μω, 71%; rt, 70%; mp 135–136 °C (pet. ether–CH_2Cl_2); IR (KBr) 3400, 1541, 1379, 758, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (3H, t, J=7.0 Hz, NCH_2CH_3), 4.09 (2H, dq, J=3, 7 Hz, NCH_2), 5.09 (2H, d, J=7.75 Hz, CH_2NO_2), 5.50 (1H, t, J=7.75 Hz, Ar_2CH), 6.97 (1H, s, H-2″), 7.03 (1H, d, J=2 Hz, H-2′), 7.10 (1H, t,

J=7.5 Hz, H-5″), 7.11 (1H, t, J=7.5 Hz, H-5′) 7.21 (1H, t, J=7.5 Hz, H-6′), 7.24 (1H, t, J=7.5 Hz, H-6″), 7.34 (2H, d, J=8.0 Hz, H-7′, 7″), 7.61 (2H, d, J=8 Hz, H-4′, 4″), 8.06 (1H, br s, NH); ^{13}C NMR: δ 15.8 (CH_3), 34.2 (Ar_2CH), 41.3 (NCH_2), 79.7 (CH_2NO_2), 110.0 (CH-7″), 111.8 (CH-7′), 119.4 and 119.5 (CH-4′, 4″), 119.6 (CH-5″), 120.1 (CH-5′), 122.2 (CH-6″), 122.80 and 122.84 (CH-2′, 6′), 125.7 (CH-2″); 113.1 (C-3″), 114.8 (C-3′), 126.6 (C-3′a), 127.1 (C-3″a), 136.8 (C-7″a), 137.0 (C-7′a); MS: m/z (%) 333 (M^+, 24), 286 (36), 273 (96), 272 (80), 271 (100), 256 (41), 243 (32). Anal. calcd for $C_{20}H_{19}N_3O_2$: C, 72.07; H, 5.70; N, 12.61. Found C, 72.18; H, 5.73; N, 12.56.

4.2.5. 2-(3′-Indolyl)-2-(1″-isopropyl-3″-indolyl)nitroethane (7e). Reddish brown crystals; yield: μω, 75%; rt, 72%; mp 142 °C (pet. ether–EtOAc); IR (KBr) 3406, 1537, 1377, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.46 and 1.49 (3H, d each, J=7 Hz, NCHMe_2), 4.63 (1H, septet, J=7 Hz, NCHMe$_2$), 5.10 (2H, d, J=7.5 Hz, CH_2NO_2), 5.51 (1H, t, J=7.5 Hz, H-2), 7.04 (1H, d, J=2 Hz, H-2′), 7.094 (1H, t, J=8 Hz, H-5″), 7.097 (1H, s, H-2″), 7.11 (1H, t, J=8 Hz, H-5′), 7.21 (1H, t, J=8 Hz, H-6′) 7.22 (1H, t, J=8 Hz, H-6″), 7.35 (1H, d, J=8 Hz, H-7′), 7.38 (1H, d, J=8 Hz, H-7″), 7.60 (1H, d, J=7.5 Hz, H-4″), 7.61 (1H, d, J=7.5 Hz, H-4′), 8.02 (1H, br s, NH); ^{13}C NMR: δ 23.10 and 23.14 (NCHMe_2), 34.4 (Ar_2CH), 79.7 (CH_2NO_2), 47.5 (NCHMe$_2$), 110.2 (CH-7″), 111.8 (CH-7′), 119.4 (CH-4′), 119.61 (CH-4″), 119.67 (CH-5″), 120.1 (CH-5′), 122.1 (CH-6″), 122.3 (CH-2″), 122.83 (CH-6′), 122.85 (CH-2′); 113.1 (C-3″), 114.9 (C-3′), 126.6 (C-3′a), 127.1 (C-3″a), 136.6 (C-7″a), 137.0 (C-7′a). MS: m/z (%) 347 (M^+, 50), 300 (44), 287 (100), 257 (29), 243 (61). Anal. calcd for $C_{21}H_{21}N_3O_2$: C, 72.62; H, 6.05; N, 12.10. Found C, 72.50; H, 6.03; N, 12.14.

4.2.6. 2-(3′-Indolyl)-2-(2″-methyl-3″-indolyl)nitroethane (7f). Orange crystals; yield: μω: 70%; rt, 69%; mp 207–208 °C (pet. ether–EtOAc); IR (KBr) 3413, 1550, 1378, 747 cm^{-1}; ^{1}H NMR (d_6-DMSO): δ 2.43 (3H, s, CH_3), 5.22 (1H, dd, J=9.5, 6.5 Hz), 5.31 (1H, dd, J=12.5, 9.5 Hz), 5.44 (1H, dd, J=12.5, 6.5 Hz), 6.82, 6.92 and 7.0 (1H, t each, J=7.5 Hz), 6.86 (1H, d, J=7.5 Hz), 7.19, 7.30 and 7.48 (1H, d each, J=8 Hz), 7.27 (1H, t, J=8 Hz), 7.42 (1H, d, J=2 Hz), 10.82 and 10.93 (1H, br s each); ^{13}C NMR: δ 12.4 (CH_3), 33.3 (Ar_2CH), 79.3 (CH_2NO_2), 111.4, 112.3, 119.11, 119.14, 119.15, 119.3, 120.8, 122.0, 122.7 (all Ar–CH), 108.8, 114.1, 127.2, 127.5, 133.4, 136.1, 137.1 (all Ar–C); MS: m/z (%) 319 (M^+, 24), 272 (33), 259 (76), 257 (100), 256 (57), 243 (27). Anal. calcd for $C_{19}H_{17}N_3O_2$: C, 71.47; H, 5.33; N, 13.16. Found C, 71.60; H, 5.30; N, 13.21.

4.2.7. 2-(3′-Indolyl)-2-(5″-bromo-3″-indolyl)nitroethane (7g). Reddish brown solid; yield: μω, 83%; rt, 82%; mp 86–88 °C (pet. ether–CH_2Cl_2); IR (nujol) 3405, 1544, 1376, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.01 (1H, dd, J=12.5, 8.3 Hz), 5.06 (1H, dd, J=12.5, 7.5 Hz), 5.40 (1H, t, J=7.5 Hz), 6.98 and 7.03 (1H, d each, J=2 Hz), 7.09 (1H, t, J=7.5 Hz), 7.19 (1H, d, J=8.5 Hz), 7.199 (1H, t, J=8.5 Hz), 7.25 (1H, dd, J=8.5, 1.5 Hz), 7.35 and 7.55 (1H, d each, J=8 Hz), 7.67 (1H, d, J=1.2 Hz), 8.11 and 8.17 (1H, br s each); ^{13}C NMR: δ 34.0 (Ar_2CH), 79.3 (CH_2NO_2), 111.9, 113.3, 119.2, 120.3, 121.9, 122.7, 123.0, 123.9, 125.8 (all Ar–CH), 113.5, 114.21, 114.27, 126.3, 128.2, 135.6, 137.0 (all Ar–C). Anal. calcd for $C_{18}H_{14}N_3O_2Br$: C, 56.25; H, 3.64; N, 10.94. Found C, 56.35; H, 3.61; N, 10.90.

4.2.8. 2-(3′-Indolyl)-2-(1″,2″-dimethyl-3″-indolyl)nitroethane (7h). Dark brown solid; yield: μω, 78%; rt, 76%; mp 128–130 °C (pet. ether–EtOAc); IR (nujol) 3409, 1546, 1374, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.41 (3H, s, CH_3), 3.63 (3H, s, NCH_3), 5.10 (1H, dd, J=12, 9.5 Hz), 5.23 (1H, dd, J=12.5, 6 Hz), 5.45 (1H, dd, J=9, 6 Hz), 7.01, 7.13 and 7.17 (1H, t each, J=7.5 Hz), 7.05 (1H, s), 7.07 (1H, t, J=8 Hz), 7.25 and 7.32 (1H, d each, J=8 Hz), 7.52 and 7.53 (1H, d each, J=7.5 Hz), 8.0 (1H, br s); ^{13}C NMR: δ 10.8 (2″-CH_3), 30.0, 34.1, 79.0 (CH_2NO_2), 109.4, 111.7, 119.17, 119.19, 119.4, 120.2, 121.1, 122.4, 122.8 (all Ar–CH), 108.2, 114.9, 126.5, 126.8, 134.8, 136.8, 137.4 (all Ar–C); MS: m/z (%) 333 (M^+, 38), 287 (9), 273 (100), 170 (25), 160 (29), 148 (31), 145 (23); HR EI-MS: calcd for $C_{20}H_{19}N_3O_2$ 333.1496. Found 333.1487.

4.3. General procedure for the synthesis of BINEs in solution phase

To a solution of **5** (1 mmol) and the indoles (**6a–k**,**10**, 2 mmol) in CH_3CN (10 mL) containing p-TsOH (25% by wt) was refluxed until **5** was consumed. The solution was poured into satd. aq. $NaHCO_3$ and extracted with EtOAc (3×25 mL). The pooled solvent phase was washed, dried (Na_2SO_4), solvent distilled off and the resulting residue purified by prep. TLC to furnish the BINEs (**7a–h**, **8b–e**, **9i–j** and **11**), as shown in Table 2.

4.3.1. 2,2-Bis(1′-methyl-3′-indolyl)nitroethane (8b). Ochre yellow flakes; yield: 27%; mp 165–166 °C (pet. ether–$CHCl_3$); IR (KBr) 1546, 1377, 1332, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.69 (6H, s, 2×NCH_3), 5.04 (2H, d, J=7.5 Hz, CH_2NO_2), 5.47 (1H, t, J=7.5 Hz, Ar_2CH), 6.89 (2H, s, H-2′), 7.09 and 7.22 (2H, t each, J=7.5 Hz, H-5′ and -6′, respectively), 7.29 and 7.59 (2H, d each, J=8 Hz, H-7′ and -4′, respectively); ^{13}C NMR: δ 33.2 (2×; NCH_3), 34.1 (Ar_2CH), 79.7 (CH_2NO_2), 109.9 (2×; CH-7′), 119.5 (2×; CH-4′), 119.7 (2×; CH-5′), 122.4 (2×; CH-6′), 127.4 (2×; CH-2′); 113.2 (2×; C-3′) 127.0 (2×; C-3′a), 137.7 (2×; C-7′a); MS: m/z (%) 333 (M^+, 28), 290 (22), 288 (32), 276 (54), 275 (100), 273 (27), 259 (34). Anal. calcd for $C_{20}H_{19}N_3O_2$: C, 72.07; H, 5.70; N, 12.61. Found C, 72.18; H, 5.68; N, 12.56.

4.3.2. 2,2-Bis(5′-bromo-1′-methyl-3′-indolyl)nitroethane (8c). Orange solid; yield: 20%; mp 76–78 °C (pet. ether–CH_2Cl_2); IR (nujol) 1560, 1381, 804 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.69 (6H, s, 2×NCH_3), 4.98 (2H, d, J=8 Hz, CH_2NO_2), 5.32 (1H, t, J=8 Hz, Ar_2CH), 6.88 (2H, s, H-2′), 7.15 (2H, d, J=9 Hz, H-7′), 7.29 (2H, dd, J=9, 1.75 Hz, H-6′), 7.65 (2H, d, J=2 Hz, H-4′); ^{13}C NMR: δ 33.4 (2×; NCH_3), 33.7 (Ar_2CH), 79.3 (CH_2NO_2), 111.5 (2×; CH-7′), 113.2 (2×; CH-5′), 121.8 (2×; CH-4′), 125.4 (2×; CH-6′), 128.41 (2×; CH-2′); 112.4 (2×; C-3′), 128.47 (2×; C-3′a), 136.5 (2×; C-7′a); MS: m/z (%) 493 (6), 491(11), 489 (M^+, 6), 446 (8), 444 (12), 442 (7), 433 (18), 431 (37), 429 (21), 223 (29), 142 (61), 128 (77), 115 (100). Anal. calcd for $C_{20}H_{17}N_3O_2Br_2$: C, 48.88; H, 3.46; N, 8.55. Found C, 48.98; H, 3.48; N, 8.52.

4.3.3. 2,2-Bis(1′-ethyl-3′-indolyl)nitroethane (8d). Orange granular crystals; yield: 22%; mp 146 °C (pet. ether–$CHCl_3$); IR (KBr) 1546, 1375, 748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (6H, t, J=7.5 Hz, 2×CH_3), 4.09 (4H, dq, J=2, 7.0 Hz, NCH_2), 5.06 (2H, d, J=8 Hz, CH_2NO_2), 5.47 (1H, t, J=7.5 Hz, Ar_2CH), 6.96 (2H, s, H-2′), 7.08 (2H, t, J=7.5 Hz, H-5′), 7.21 (2H, t, J=7.5 Hz, H-6′), 7.32 (2H, d, J=8.5 Hz, H-7′), 7.59 (2H, d, J=8 Hz, H-4′); ^{13}C NMR: δ 15.8 (2×; CH_3), 34.3 (Ar_2CH), 41.3 (2×; NCH_2), 79.3 (CH_2NO_2), 110.0 (2×; CH-7′), 119.62 and 119.65 (2×; CH-4′, 5′), 122.2 (2×; CH-6′), 125.7 (2×; CH-2′); 113.2 (2×; C-3′) 127.2 (2×; C-3′a), 136.8 (2×; C-7′a); MS: m/z (%) 361 (M^+, 23), 314 (24), 301 (100), 271 (16), 256 (16), 130 (35), 115 (19). Anal. calcd for $C_{22}H_{23}N_3O_2$: C, 73.13; H, 6.37; N, 11.63. Found C, 73.20; H, 6.40; N, 11.60.

4.3.4. 2,2-Bis(1′-isopropyl-3′-indolyl)nitroethane (8e). Yellowish brown flakes; yield: 26%; mp 138 °C (pet. ether–$CHCl_3$); IR (KBr) 1545, 1375, 742 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 and 1.47 (6H, dd each, J=6.5, 1.5 Hz, 2×NCH*Me*$_2$), 4.612 and 4.616 (1H, septet each, J=6.5 Hz, NC*H*Me_2), 5.07 (2H, dd, J=7.5, 2.5 Hz, CH_2NO_2), 5.47 (1H, td, J=7.5, 2.5 Hz, Ar_2CH), 7.06 (2H, t, J=7 Hz, H-5′), 7.07 (2H, d, J=2.5 Hz, H-2′), 7.19 (2H, t, J=7 Hz, H-6′), 7.35 (2H, d, J=8 Hz, H-7′), 7.57 (2H, dd, J=7.5, 1.5 Hz, H-4′); ^{13}C NMR: δ 23.11 and 23.16 (2×; NCH*Me*$_2$), 34.6 (Ar_2CH), 79.9 (CH_2NO_2), 47.5 (2×; N*C*HMe_2), 110.2 (2×; CH-7′), 119.61 and 119.65 (2×; CH-4′, 5′), 122.0 and 122.4 (2×; CH-2′, 6′); 113.3 (2×; C-3′), 127.2 (2×; C-3′a), 136.6 (2×; C-7′a); MS: m/z (%) 389 (M^+, 24), 342 (25), 330 (55), 329 (100), 246 (43), 244 (49). Anal. calcd for $C_{24}H_{27}N_3O_2$: C, 74.03; H, 6.94; N, 10.79. Found C, 74.21; H, 6.92; N, 10.83.

4.3.5. 2-(3′-Methyl-2′-indolyl)-2-(3″-indolyl)nitroethane (9i). Brown crystals; yield: 82%; mp 98–100 °C (pet. ether–$CHCl_3$); IR (KBr) 3410, 1550, 1376, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.42 (3H, s, CH_3), 4.88 (1H, dd, J=12.5, 7 Hz, C$H_AH_BNO_2$), 5.06 (1H, dd, J=12.5, 7.5 Hz, CH_AH_B-NO_2), 5.49 (1H, t, J=7.5 Hz, Ar_2CH), 7.03 (1H, t, J=7.5 Hz, H-5″), 7.06–7.15 (4H, m, H-2″, 5′, 6′, 7′), 7.18 (1H, t, J=7.5 Hz, H-6″), 7.33 (1H, d, J=8 Hz, H-7″), 7.36 (1H, d, J=8 Hz, H-4″), 7.53–7.54 (1H, m, H-4′) 7.67 (1H, br s, H-1′), 8.11 (1H, br s, H-1″); ^{13}C NMR: δ 9.0 (CH_3), 34.2 (Ar_2CH), 78.3 (CH_2NO_2), 111.9 (CH-7″), 111.2, 119.8, 121.8, 122.4 (CH-2″, 5′, 6′, 7′), 119.0 (CH-4′), 119.2 (CH-4″), 120.7 (CH-5″), 123.4 (CH-6″); 109.2 (C-3′), 112.4 (C-3″), 126.4 (C-3′a), 129.7 (C-3′a), 131.3 (C-2′), 135.9 (C-7′a), 136.9 (C-7″a); MS: m/z (%) 319 (M^+, 13), 272 (8), 259 (32), 257 (31), 243 (8), 130 (87), 117 (100). Anal. calcd for $C_{19}H_{17}N_3O_2$: C, 71.47; H, 5.33; N, 13.16. Found C, 71.40; H, 5.31; N, 13.11.

4.3.6. 2-(1′,3′-Dimethyl-2′-indolyl)-2-(3″-indolyl)nitroethane (9j). Yellowish brown solid; yield: 80%; mp 82–84 °C (pet. ether–CH_2Cl_2); IR (nujol) 3396, 1546, 1374, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.37 (3H, s, CH_3), 3.61 (3H, s, NCH_3), 5.06 (1H, dd, J=13, 9 Hz), 5.22 (1H, dd, J=13, 7 Hz), 5.60 (1H, dd, J_1=J_2=7.5 Hz), 6.90 (1H, d, J=1 Hz), 7.03 and 7.18 (1H, t each, J=7.5 Hz), 7.10 (1H, td, J=7, 2 Hz), 7.20 (1H, d, J=7 Hz), 7.21 (1H, td, J=7.5, 0.75 Hz), 7.30, 7.32 and 7.55 (1H, d each, J=7.5 Hz), 8.07 (1H, d, J=2.5 Hz); ^{13}C NMR: δ 9.9 (3′-CH_3), 30.5 (1′-CH_3), 33.9 (Ar_2CH), 77.9 (CH_2NO_2), 109.4, 111.8, 119.0, 119.08, 119.4, 120.6, 122.2, 122.4, 123.2 (all Ar–CH), 109.1, 122.5, 126.3, 128.8, 132.3, 137.0, 137.4 (all Ar–C); MS: m/z (%) 333 (M^+, 73), 304 (100), 289 (94), 273 (66), 257 (18), 160 (41), 149 (43), 144 (60), 130 (34); HR EI-MS: calcd for $C_{20}H_{19}N_3O_2$ 333.1492. Found 333.1485.

4.3.7. 2-{3′-(β-Acetamidoethyl)-2′-indolyl}-2-(3″-indolyl)nitroethane (11). Orange solid; yield: 74%; mp 128–132 °C (pet. ether–EtOAc); IR (KBr) 3403, 3273, 1648, 1549, 1374, 745 cm^{-1}; ^1H NMR (d_6-DMSO): δ 1.75 (3H, s), 2.88–2.92 (2H, m), 3.12–3.16 and 3.21–3.27 (1H, m each), 5.29–5.35 (2H, m), 5.38–5.45 (1H, m), 6.94, 6.95, 7.02 and 7.05 (1H, t each, J=7.5 Hz), 7.27, 7.33, 7.39 and 7.54 (1H, d each, J=8 Hz), 7.46 (1H, d, J=7.5 Hz), 7.95 (1H, t, J=5.5 Hz), 10.92 and 11.08 (1H, br s each); ^{13}C NMR: δ 23.5 and 25.3 (CH_2CH_2), 79.1 (CH_2NO_2), 33.3 (Ar_2CH), 111.8, 112.4, 118.9, 119.0, 119.3, 119.7, 121.8, 122.2, 123.7 (all Ar–CH), 109.7, 112.6, 126.7, 128.5, 134.3, 136.5, 136.8, 170 (all Ar–C); MS: m/z (%) 390 (M^+, 1), 344 (50), 343 (35), 329 (35), 286 (47), 271 (63), 270 (40), 257 (100), 187 (4), 156 (11), 143 (12), 130 (32). Anal. calcd for $C_{22}H_{22}N_4O_3$: C, 67.69; H, 5.64; N, 14.35. Found C, 67.60; H, 5.62; N, 14.40.

4.4. Reduction of the BINE 7a

To a stirred solution of **7a** (319 mg, 1 mmol) in dry MeOH (20 mL), was added 10% Pd/C (60 mg) at rt, followed by anhydrous HCO_2NH_4 (315 mg, 5 mmol) in a single portion under nitrogen atmosphere. The resulting mixture was heated to 60 °C for 1 h. After the completion of the reaction (TLC), the catalyst was removed by filtration through a celite bed, washed with methanol, the pooled filtrates concentrated and poured into water, extracted with EtOAc (3×20 mL) and dried (Na_2SO_4). The solvent on evaporation furnished a residue which was dissolved in pyridine (1 mL) and Ac_2O (2 mL) and kept overnight. The reaction mixture was poured into excess water and washed successively with 2 M aq. HCl, satd. aq. $NaHCO_3$ and extracted with EtOAc (3×20 mL) and dried (Na_2SO_4). The removal of the solvent furnished **12** as a brown solid (209 mg; 66%), mp. 116–118 °C (pet. ether–CH_2Cl_2). All data of **12** were in agreement with those reported earlier for it from our laboratory.[23]

4.5. General procedure for the reduction of the nitronates, derived from 7a,b,f by aqueous $TiCl_3$ at pH 5–6

The BINE (**7a**,**b**,**f**) (1 mmol) was dissolved in dry methanol (20 mL) and treated with NaOMe (1.1 equiv.) and stirred for 1 h. A buffered $TiCl_3$–NH_4OAc solution, prepared by adding NH_4OAc (0.95 g, 12 mmol) in water (3 mL) to 15% aqueous $TiCl_3$ (3 mL, 4.5 mmol), was then added rapidly to the above solution at rt under nitrogen atmosphere. After the indicated period (Table 3), the reaction mixture was poured into water and extracted with EtOAc (3×20 mL). The organic extracts were combined, washed with aq. $NaHCO_3$, dried (Na_2SO_4) and the solvent distilled off. The resulting residue was purified by prep. TLC to furnish the oximes **13a**,**b** and **f**, each a mixture of the *syn*- and *anti*-isomers. For **13b** and **13f**, the designatory letters mj and mn stand for the major and the minor isomers, respectively.

4.5.1. 2,2-Bis(3′-indolyl)ethanaloxime (13a; *syn/anti*-mixture). *anti*-Isomer (pure). Dark brown solid; yield: 20%; mp 226–228 °C (pet. ether–EtOAc); IR (nujol) 3454, 3412, 3400, 3193, 1614, 918, 745 cm^{-1}; ^1H NMR (d_6-DMSO): δ 6.06 (1H, d, J=8 Hz, Ar_2CH), 6.91 and 7.04 (2H, t each, J=7.5 Hz), 7.14 (2H, s), 7.23 (1H, d, J=8 Hz, CH=N), 7.34 (2H, d, J=8 Hz), 7.49 (2H, d, J=7.5 Hz), 10.89 (2H, s, 2×NH), 10.95 (1H, s, =NOH); ^{13}C NMR: δ 29.9 (Ar_2CH), 112.3 (2×), 119.1 (2×), 119.7 (2×), 121.8 (2×), 123.7 (2×) (all Ar–CH), 151.7 (CH=N), 115.0 (2×), 127.2 (2×), 137.2 (2×) (all Ar–C); MS: *m/z* (%) 289 (M^+, 44), 272 (100), 271 (59), 245 (87), 243 (50); HR EI-MS: calcd for $C_{18}H_{15}N_3O$ 289.1215. Found 289.1212.

syn-Isomer (^1H NMR assignments ascertained by subtraction of data of pure *anti*-isomer from those of the *syn/anti*-mixture). Yield: 76%; *syn/anti*=2:1; IR (KBr) 3406, 1618, 742 cm^{-1}; ^1H NMR (d_6-DMSO): δ 5.24 (1H, d, J=8 Hz, Ar_2CH), 6.88 and 7.01 (2H, t each, J=7.5 Hz), 7.11 (2H, s), 7.31 (2H, d, J=8 Hz), 7.46 (2H, d, J=7.5 Hz), 7.82 (1H, d, J=7.5 Hz, CH=N), 10.42 (1H, br s, =NOH), 10.82–10.95 (2H, m, 2×NH); ^{13}C NMR: δ 35.8 (Ar_2CH), 112.3 (2×), 119.1(2×), 119.8 (2×), 121.8 (2×), 123.75 (2×) (all Ar–CH), 151.6 (CH=N), 115.4 (2×), 127.1 (2×), 137.3 (2×) (all Ar–C); MS: *m/z* (%) 289 (M^+, 29), 272 (100), 245 (68), 243 (70).

4.5.2. 2-(3′-Indolyl)-2-(1″-methyl-3″-indolyl)ethanaloxime (13b; *syn/anti*-mixture). Yield: 62%; *syn*:*anti*=2:1; IR ($CHCl_3$) 3474, 3413, 1613, 769 cm^{-1}; ^1H NMR (d_6-DMSO): δ 3.67 (3H mj+3H mn, s, 2×NMe), 5.24 (mj) and 6.02 (mn) (1H, d each, J=8 Hz, 2×Ar_2CH), 6.88 and 6.92 (1H mj+1H mn, t each, J=7 Hz), 7.01 (1H mj+1H mn, t, J=7 Hz), 7.04–7.11 (1H mj+1H mn, m), 7.07 (1H mj+1H mn, s), 7.13 (1H mj+1H mn, s), 7.16 (mn) and 7.79 (mj) (1H, d each, J=8 Hz, 2×CH=N), 7.31 and 7.33 (1H mj+1H mn, d each, J=9 Hz), 7.45 (1H mj+1H mn, d, J=9 Hz), 7.47 (1H mj+1H mn, d, J=8.5 Hz), 10.43 (mj) and 10.92 (mn) (1H, s each, 2×NH), 10.86 (mn) and 10.88 (mj) (1H, s each, 2×=NOH); ^{13}C NMR: δ 29.7 (mn) and 35.6 (mj) (2×Ar_2CH), 33.1 (2×; NMe), 110.5 (mj+mn), 112.3 (mj+mn), 119.21 (mn), 119.23 (mj), 119.28 (mn), 119.3 (mj), 119.6 (mn), 119.7 (mj), 119.9 (mn), 120.0 (mj), 121.91 (mn), 121.92 (mj), 122.0 (mj+mn), 123.73 (mn), 123.77 (mj), 128.11 (mn) and 128.13 (mj) (all Ar–CH), 151.5 (mj) and 151.6 (mn) (2×CH=N), 114.4 (mn), 114.7 (mj) and 115.2 (mj+mn), 127.1 (mj), 127.2 (mn), 127.5 (mj) and 127.6 (mn), 137.2 (mn), 137.3 (mj), 137.70 (mn) and 137.74 (mj) (all Ar–C); MS: *m/z* (%) 303 (M^+, 82), 286 (100), 285 (63), 259 (100), 257 (88), 245 (44); HR FAB-MS: calcd for $C_{19}H_{17}N_3O$ 303.1372. Found 303.1350.

4.5.3. 2-(3′-Indolyl)-2-(2″-methyl-3″-indolyl)ethanaloxime (13f; *syn/anti*-mixture). Yield: 72%; *syn/anti*=3:2; IR (nujol) 3396, 3283, 1619, 744 cm^{-1}; ^1H NMR (d_6-DMSO): δ 2.33 (mj) and 2.37 (mn) (3H, s each, 2×NMe), 5.21 (mj) and 5.94 (mn) (1H, d each, J=7.5 Hz, 2×Ar_2CH), 6.77–6.87 (2H mj+2H mn, m), 6.91 and 6.93 (1H mj+1H mn, t each, J=7 Hz), 7.0 (1H mj+1H mn, t, J=7.5 Hz), 7.04 (mj) and 7.06 (mn) (1H, s each), 7.15–7.27 (2H mj+2H mn, m), 7.28 (1H mn, d, J=9 Hz, CH=N), 7.30 (1H mj+1H mn), 7.34 (mj) and 7.36 (mn) (2H, t each, J=7.5 Hz), 7.91 (1H mj, d, J=8 Hz, CH=N), 10.47 (1H mj), 10.78 (1H mn), 10.80 (1H mn), 10.82 (2H mj) and 10.91 (1H mn) (s each, 4×NH+2×OH); ^{13}C NMR: δ 12.6 (2×; CH_3), 29.6 and 35.3 (2×Ar_2CH), 111.4 (2×), 112.2 (2×), 119.0 (2×), 119.1 (2×), 119.3 (2×), 119.4, 119.6, 120.7, 120.8, 121.8 (2×), 123.2, 123.4 (all Ar–CH), 151.2 and 151.4 (2×CH=N), 110.3 (2×), 115.3 (2×), 127.4 (2×), 128.0, 128.1, 132.6, 132.7, 136.1 (2×), 137.2 (2×) (all Ar–C); MS: *m/z* (%) 303 (M^+, 29), 286 (49), 285 (31), 270 (23), 259 (61), 258 (71), 257 (100), 243 (28), 130 (43); HR EI-MS: calcd for $C_{19}H_{17}N_3O$ 303.1372. Found 303.1379.

Acknowledgements

The authors express their sincere thanks to the Director, Bose Institute for providing laboratory facilities, Mr. J. Chatterjee, R.S.I.C., Mr. P. Dey, Microanalytical Laboratory and Mr. B. Majumdar, NMR Facilities, Bose Institute for recording the spectra and the C.S.I.R., Govt. of India for providing fellowships (R.B., N.G.).

References and notes

1. Julia, M.; Tilly, G. *Bull. Chem. Soc. Fr.* **1965**, 2175.
2. (a) Greenberg, J. B. PhD Dissertation, Yale University, New Haven, Connecticut, 1958. (b) Jones, A.; Galston, A. W. *J. Exp. Bot.* **1969**, *20*, 257.
3. Porter, J. K.; Bacon, C. W.; Robbins, J. D.; Himmelsbach, D. S.; Higman, H. C. *J. Agric. Food Chem.* **1977**, *25*, 88.
4. Bell, R.; Carmeli, S.; Sar, N. *J. Nat. Prod.* **1994**, *57*, 1587.
5. Osawa, T.; Namiki, M. *Tetrahedron Lett.* **1983**, *24*, 4719.
6. Bifulco, G.; Bruno, I.; Riccio, R.; Lavayre, J.; Bourdy, G. *J. Nat. Prod.* **1995**, *58*, 1254.
7. (a) Ge, X.; Yannai, S.; Rennert, G.; Gruener, N.; Fares, F. A. *Biochem. Biophys. Res. Commun.* **1996**, *228*, 153. (b) McDougal, A.; Gupta, M. S.; Ramamoorthy, K.; Sun, G.; Safe, S. H. *Cancer Lett.* **2000**, *151*, 169.
8. Chakrabarty, M.; Basak, R.; Harigaya, Y. *Heterocycles* **2001**, *55*, 2431.
9. Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564.
10. Ames, D. E.; Bowman, R. E.; Evans, D. D.; Jones, W. A. *J. Chem. Soc.* **1956**, 1984.
11. (a) Denis, J.-N.; Mauger, H.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 8515. (b) Chalaye-Mauger, H.; Denis, J.-N.; Averbuch-Pouchot, M.-T.; Vallée, Y. *Tetrahedron* **2000**, *56*, 791.
12. (a) Noland, W. E.; Hartman, P. J. *J. Chem. Soc.* **1954**, *76*, 3227. (b) Noland, W. E.; Christensen, G. M.; Sauer, G. L.; Dutton, G. G. S. *J. Chem. Soc.* **1955**, *77*, 456. (c) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110.
13. Chakrabarty, M.; Basak, R.; Ghosh, N. *Tetrahedron Lett.* **2001**, *42*, 3913.
14. Young, E. H. P. *J. Chem. Soc.* **1958**, 3493.
15. March, J. *Advanced organic chemistry*; 4th ed. Wiley: New York, 1992; see pp (a) 886 and (b) 1216.
16. Lloyd, D. H.; Nichols, D. E. *J. Org. Chem.* **1986**, *51*, 4294.
17. Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc. Perkin Trans. 1* **2001**, 955.

18. (a) Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415. (b) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1986**, 133.
19. Pinnick, H. W. *Org. React.* **1990**, *38*, 655.
20. (a) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367. (b) McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281.
21. (a) Danilenko, V. M.; Tishkov, A. A.; Ioffe, S. L.; Lyapkalo, I. M.; Strelenko, Y. A.; Tartakovsky, V. A. *Synthesis* **2002**, 635. (b) Makarenkova, L. M.; Bliznets, I. V.; Ioffe, S. L.; Strelenko, Yu. A.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2000**, *49*, 1261. (c) Silverstein, R. M.; Webster, F. X. *Spectrometric identification of organic compounds*; 6th ed. Wiley: New York, 1998; see pp 210 and 233.
22. Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, 195.
23. Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Synth. Commun.* **2004**, *34*, 409.