ASYMMETRIC α-ALKYLATION REACTIONS

THESIS

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MASTER OF SCIENCE

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by

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And finally, thank you to my God, who continually stirs in me a delight and enthusiasm for chemistry. I would not dare to do this without Him!

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LIST OF ABBREVIATIONS

acac	acetyl acetonate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*t*-butoxycarbonyl
CBZ	carbobenzyloxy
CDI	carbonyldiimidazole
COSY	^{1}H - ^{1}H shift-correlated spectroscopy
DMF	dimethylformamide
DNA	deoxyribonucleic acid
EtOAc	ethyl acetate
HMPT	hexamethylphosphorous triamide
HETCOR	^{1}H - ^{13}C shift-correlated spectroscopy
HPLC	high performance liquid chromatography
IR	infrared
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilylamide
MCPBA	*m*-chloroperbenzoic acid
NHMDS	sodium hexamethyldisilylamide
NMR	nuclear magnetic resonance
PTSA	*p*-toluenesulfonic acid
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride

ABSTRACT

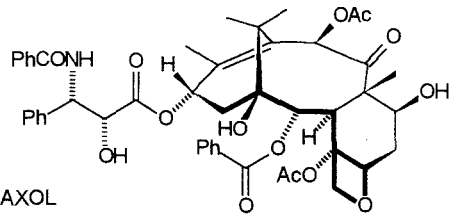
A novel camphor-derived hydroxy ketal **138** has been developed as a chiral auxiliary, and used to prepare a series of six carboxylic esters of increasing steric bulk. The α-benzylation of this series of esters was achieved with diastereoselectivities of 59 - 83% d.e. and in 39 - 48% material yield. These results compared very favourably with those obtained in earlier studies using a regioisomeric analogue as the chiral auxiliary. Computer modelling studies of the putative enolate intermediate has provided some insight into the possible mode of electrophilic attack at the α-carbon and the roles of the ketal protecting group and the lithium cation in these asymmetric transformations.

In a related investigation, based on earlier work, a camphor-derived imino lactone has provided convenient access to α-alkyl α-amino acids, the imino lactone serving as a masked glycine equivalent. Using straight chain primary alkyl iodides [RI; R = Me, Et, Pr, Bu, $CH_3(CH_2)_4$ and $CH_3(CH_2)_5$], alkylation of the potassium enolate of the camphor-derived imino lactone was effected with 54 - 89% d.e. and in 54 - 87% material yield. Four novel alkylated derivatives were synthesised using isopropyl iodide, *sec*-butyl iodide and allyl iodide, the latter reagent resulting in both the monoallylated and diallylated products. While very good diastereoselectivities were achieved (83 - 88% d.e.) in these reactions, the material yields from reaction with the secondary alkyl iodides were low (31 - 35%) due, presumably, to their decreased electrophilicity. Computer modelling studies of the enolate were carried out and support the hypothesis of *endo* attack by the electrophile on the enolate intermediate. These studies also indicate the possibility of coordination of the postassium cation to the endocyclic ester oxygen, thus effectively anchoring the bulky cation away from the reaction site.

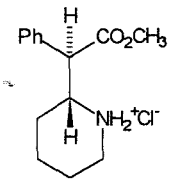
INTRODUCTION

1.1 The Importance of Asymmetric Synthesis

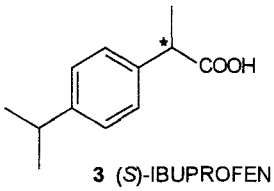
The importance of chirality in chemistry cannot be underestimated. Far from being an academic curiosity, it has enormous significance in the pharmaceutical and food industries, and more recently, in advanced materials such as liquid crystals. Chiral compounds form up to 28% of the world pharmaceuticals market.[1] Examples of well-known chiral drugs include: taxol **1** (an anti-cancer drug); ritalin [(2*R*,3*R*)-methylphenidate] **2**; (*S*)-ibuprofen **3**, the structures shown



1 TAXOL

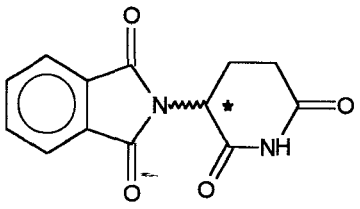


2 *(2R,3R)*- methylphenidate
RITALIN

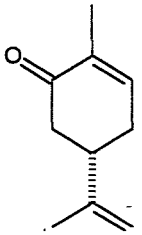


3 (*S*)-IBUPROFEN

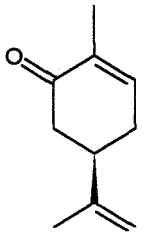
reflecting the stereochemistry of the active isomer in each case. Ritalin **2** and (*S*)-ibuprofen **3** are patented drugs, which were previously sold as racemic mixtures. This means that in any preparation using racemic material, the inactive isomer is wasted. Considering the enormous amount of money spent in producing such pharmaceuticals, it makes economic sense to produce only the active isomer if it is at all possible. In some cases, the enantiomer may be harmful to the body since each isomer has its own distinct interaction with the chiral receptors in the body. An example of this behaviour is the well-documented thalidomide (**4**) tragedy.[2]



4 THALIDOMIDE



(+) **-5**



(-) **-5**

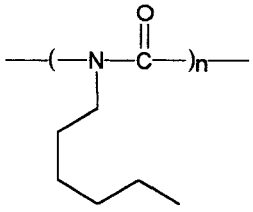
Less serious, is our ability to distinguish the taste of the enantiomers (+)- and (-)- carvone **5**, which are responsible for the flavours of caraway and spearmint respectively.[3] This is only one

of many examples of how chirality affects the food industry. In both pharmaceuticals and food, the effects of chirality are the result of chiral interactions with the inherently chiral biological receptors.

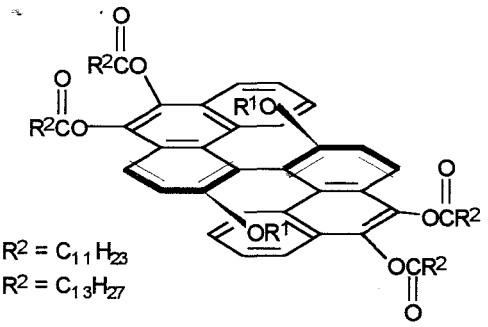
Also of interest is the interplay between chirality and the liquid crystalline state. In fact, the first liquid crystal discovered was chiral. The optical purity of a liquid crystal can be shown to confer upon it special properties such as colour changes and molecular recognition.[4] The colour changes result from the crystalline nature of the substance, giving rise to Bragg reflection of visible light.[5] The most well-known use of liquid crystals, especially chiral liquid crystals, is therefore in display technology. Chirality in liquid crystal systems is achieved in two main ways:

(I) by doping an achiral or racemic mixture with a small amount of a chiral material;[6] and

(ii) by starting with a chiral compound exhibiting liquid crystal behaviour.[7]



6 PHIC



7a: $R^1 = C_{12}H_{25}$, $R^2 = C_{11}H_{23}$
7b: $R^1 = C_{14}H_{29}$, $R^2 = C_{13}H_{27}$

An example of the first approach has been investigated by Green *et al.*[6] Poly(*n*-hexyl isocyanate) (PHIC) **6** exists as dynamically interconverting racemic helices. The addition of a small amount of dopant (small chiral molecules such as camphor and cholestane) shifts this equilibrium in the direction of one of the enantiomeric helices, thus conferring new and useful properties. The second approach may be illustrated by both naturally occurring compounds (e.g. chiral poly-peptides, polysaccharides and DNA), and synthetic molecules. For example, Yamamura *et al.*[7] have synthesised a series of 4,4'-biphenanthryl-derived liquid crystal mesogens **7** having the necessary molecular assembly potential.

1.2 Development Stages of Asymmetric Synthesis

Asymmetry in synthesis can be achieved in a number of ways. These can be broadly classified into four generations.[8] While these have increased in sophistication with each generation, time has in no way decreased the usefulness of any of these approaches.

(I) First generation: substrate-controlled methods

In this approach the chiral starting material is taken from the pool of naturally occurring chiral molecules, *viz.* the "chiral pool". The starting material is then modified and the introduction of any further chirality is influenced by the stereochemistry of the starting material.

(ii) Second generation: auxiliary controlled methods

A chiral molecule can be attached to the substrate, thus creating a chiral environment. When a reaction is performed under such conditions some measure of stereocontrol is expected. The chiral auxiliary can then be removed (and, ideally, recycled) to afford the chiral product.

(iii) Third generation: reagent-controlled methods

In this approach a chiral reagent influences the stereochemical outcome of the reaction.

(iv) Fourth generation: catalyst-controlled methods

In this method, the asymmetric induction is achieved by means of a chiral catalyst.

The first approach is likely to be the most expensive since the chiral material is used up in the synthesis. The second approach is expected to be much less expensive since, in principle, recycling of the chiral auxiliary should be possible; however stoichiometric amounts of the chiral auxiliary must be used in each synthesis. With reagent-controlled methods, the attachment and removal of a chiral auxiliary is no longer necessary, although the reagent is usually used in stoichiometric or greater proportions. The final methodology may be conceived to be the ideal since very small amounts of the chiral catalyst may be necessary and recycling may be possible.

Camphor has been used in asymmetric synthesis almost since the beginning of research in this field. (+)-Camphor **8** occurs naturally in high enantiomeric purity and, in addition, lends itself to

transformation by means of skeletal rearrangements, ready functionalisation at C(3), C(5), C(8), C(9) and C(10) and cleavage of C(1)/C(2) and C(2)/C(3) bonds.[9] For these reasons it finds use at all levels of asymmetric synthesis as illustrated by the following survey.

(i) Substrate-controlled methods

This approach requires the selection of appropriate starting materials from the chiral pool. While there are many thousands of chiral molecules in nature, there are relatively few which are available in the quantity and purity exhibited by (+)-camphor.[10] Consequently, it has been widely used as a substrate in various syntheses of chiral natural products and other useful synthetic targets. One example is the synthesis of the secondary metabolite vitamin D_3 **9**, reported by Stevens and co-workers.[11] Since the isolation of this metabolite is difficult and limited in success, it has been imperative to develop an efficient total synthesis. A retro-synthetic analysis revealed the following intermediate targets (Figure 1):-

a. elaboration of the acyclic side chain,

b. the A ring

c. A suitable hydrindane derivative for the attachment of (a) and (b).

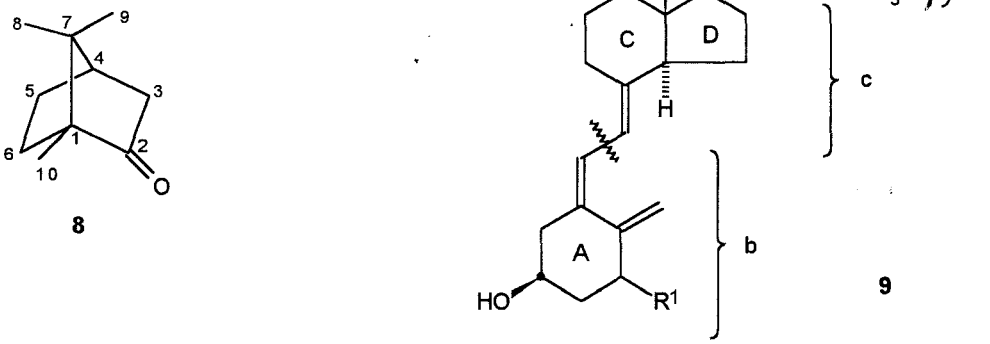
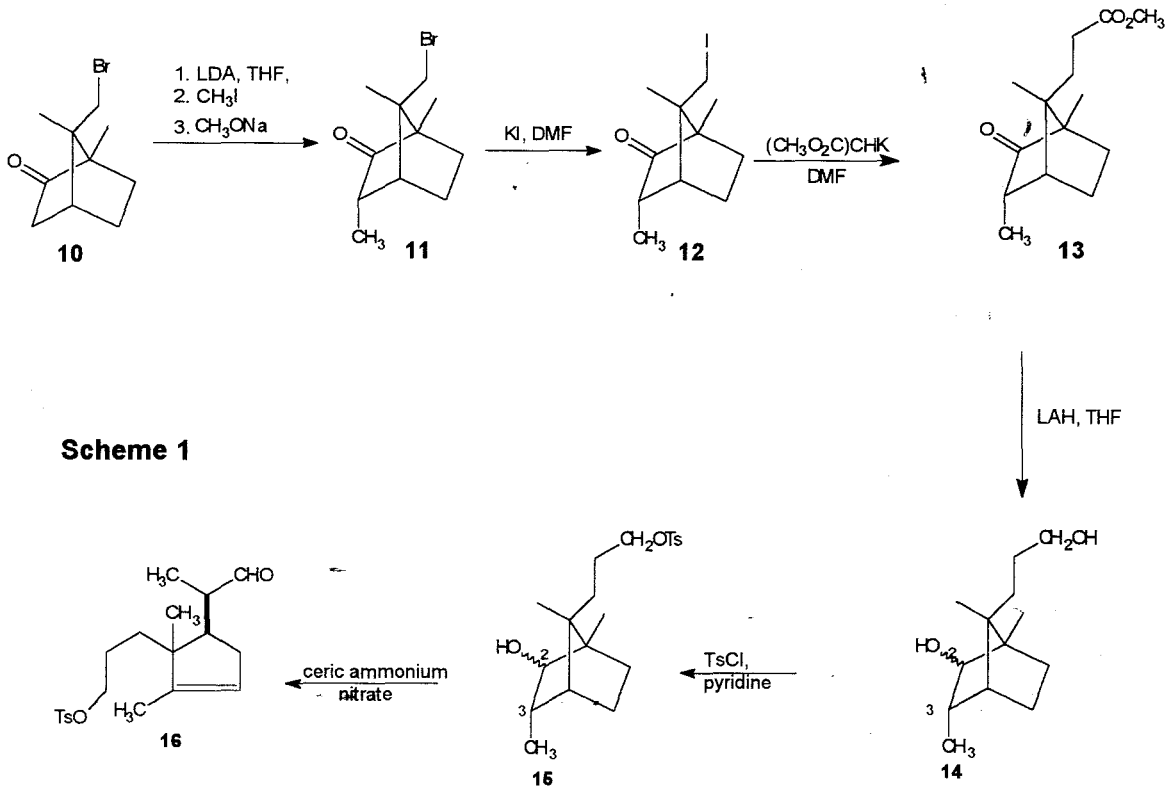


Figure 1. Disconnections proposed for the synthesis of Vitamin D_3

Since all three fragments incorporate at least one chiral centre, it was deemed important to synthesize each one in its enantiomerically pure form in order to avoid a complex mixture of diastereomers. Of particular concern were the acyclic chiral centre at C(20) (steroid numbering)

and the two contiguous cyclic chiral centres, and (+)-camphor was therefore chosen for the stereospecific synthesis of the hydrindane (CD) fragment.

Previous work [11] converting (-)-9-bromocamphor into a tricyclic steroid intermediate, revealed that C(20) would be derived from C(3) of camphor. Stevens and co-workers concluded that if (+)-9-bromocamphor were to be used then the three chiral centres C(13), C(14) and C(20) would have the correct absolute stereochemistry. Treatment of (+)-9-bromocamphor **10** with LDA in THF at -78°C followed by quenching with methyl iodide, provided a 1:2 mixture of the *endo* and *exo* products (Scheme 1), *endo* alkylation being necessary to provide the correct stereochemistry in the product. However, treatment of this mixture with sodium methoxide in methanol permitted isomerization affording the pure endo isomer **11**. Homologation of **11** to **13** was accomplished in good overall yields, while reduction of ketoester **13** with $LiAlH_4$ yielded a 1:1 mixture of the *endo* and *exo* diols **14** in 91% yield. The mixture was treated with *p*-toluenesulfonyl chloride and the resulting *p*-toluenesulfonate esters were cleaved with ceric ammonium nitrate in aqueous acetonitrile to afford the aldehyde **16** in 82% yield. Thus, using camphor, a route was established which ensures the proper relative and absolute stereochemistry at the three contiguous asymmetric centres. The desired hydrindane was then obtained *via* a multi-step sequence from this point.

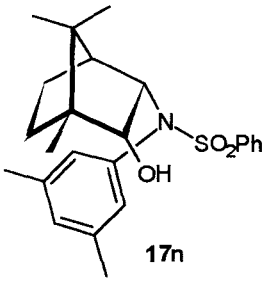


Scheme 1

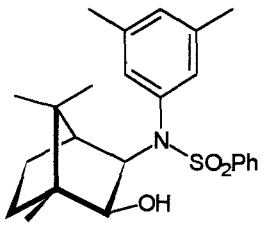
Another example which illustrates the use of camphor as a chiral starting material is its use as a starting material for the synthesis of taxol **1** and related *cis*-tricyclo[9.3.1.$0^{3,8}$]pentadecanones.[12]

(ii) Auxiliary controlled methods

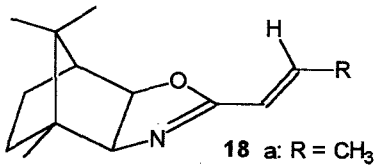
Due to the inherent rigidity of its bicyclic skeleton, camphor has also found extensive use as a chiral auxiliary;[10] prochiral fragments can be attached by various means to carbons 2,3 and 10. Chiral induction is mainly steric in origin but there are cases where electronic effects have been of equal importance. Successful camphor-derived chiral auxiliaries include the "concave" alcohols **17n** and **17x** used in the synthesis of 6-substituted 2-oxo-cyclohexanecarboxylates,[13] while the camphor derived α,β-unsaturated oxazolines **18a, b,** and **c** have found use in asymmetric Diels-Alder reactions.[14]



17n



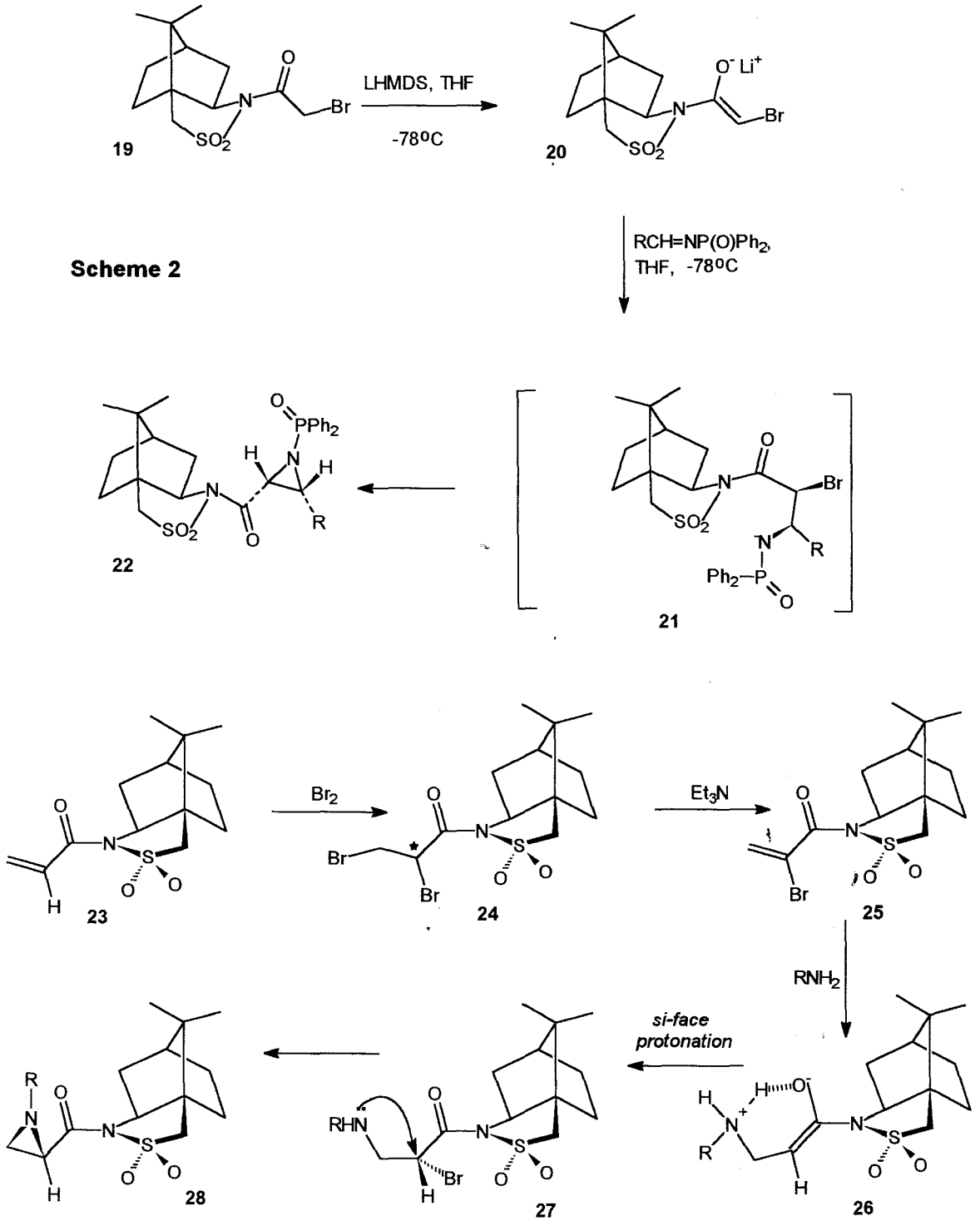
17x



18 a: R = CH_3
b: R = H
c: R = SO_2Ph

Camphor sultams are an important class of camphor-derived chiral auxiliaries.[15,16,17] One of these is bromoacylcamphorsultam **19**, the enolate of which is used in the aza-Darzens reaction with *N*-(diphenylphosphinyl)aryl- and *tert*-butyl methanamines (Scheme 2),[18] while the *N*-acylbornane-sultams (e.g. **23**) developed by Oppolzer *et al.*[19] have enjoyed wide application.

Philip Garner and his co-workers have used Oppolzer's camphor-derived sultam as a chiral auxiliary in the synthesis of aziridine-2-carboxylates (Scheme 3),[20] which are useful building blocks in the asymmetric synthesis of modified amino acids and related compounds. Starting from the readily accessible *N*-acrolyl camphorsultam **23**, bromination, followed by α-elimination of the dibromo product **24**, gives the α,β-unsaturated intermediate **25**. Conjugate addition of benzylamine is followed by *si*-face proton transfer and spontaneous ring closure *via* an internal S_N2 mechanism to give **28**. Removal of the chiral auxiliary may be effected non-destructively using methanolic magnesium methoxide to afford the *N*-substituted aziridine ester.



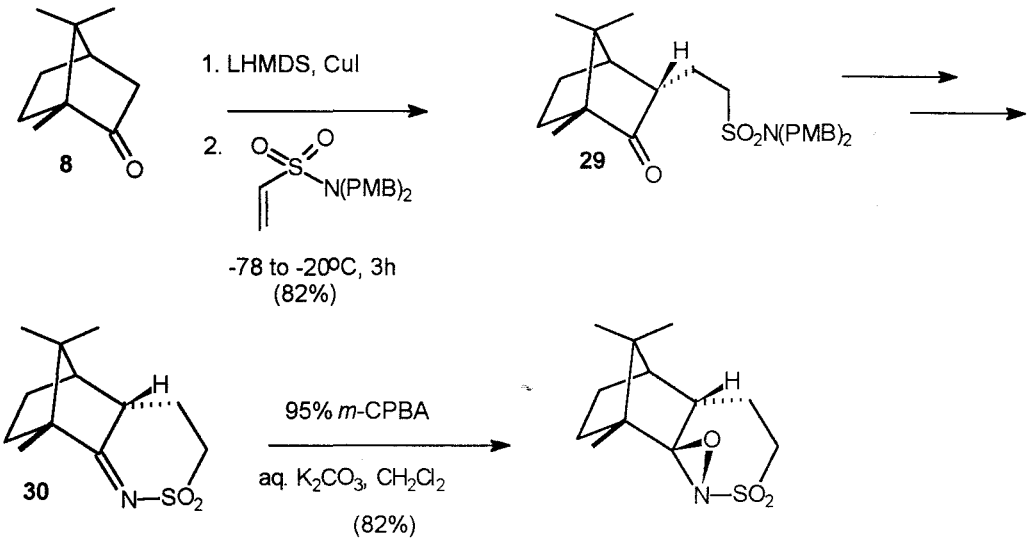
Scheme 2

Scheme 3: series **a**: R = Bn (86%); **b**: *p*-C_6H_4OMe (89%); **c**: R=H (60%)

(iii) Reagent-controlled methods

Exo-Camphorylsulfonyloxaziridine is a non-metallic chiral reagent which has been used effectively

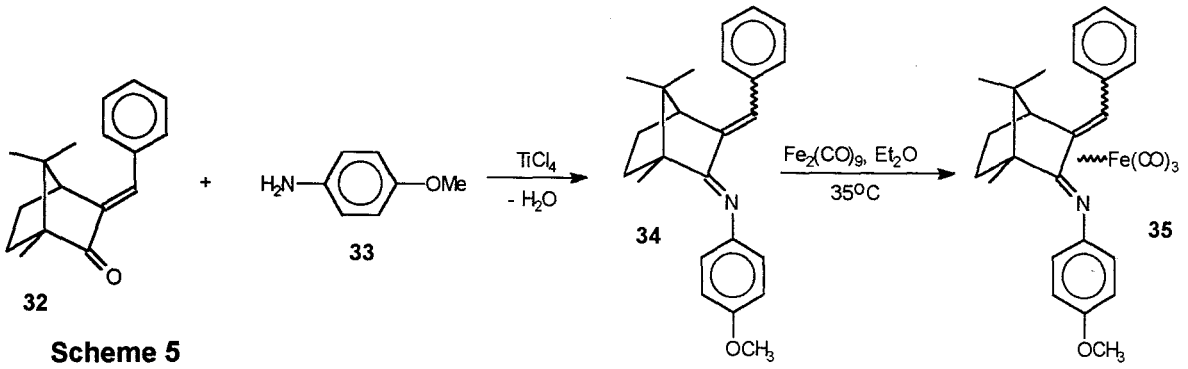
as a chiral oxidizing agent[21] in the asymmetric synthesis of sulfoxides, selenoxides, and α-hydroxy carbonyl compounds. The reagent is synthesized in a four-step process (Scheme 4) from (+)-camphor and such oxidations are carried out by treating the sulfides with one equivalent of the oxaziridine **31** for 2 - 4 hours in carbon tetrachloride at room temperature.



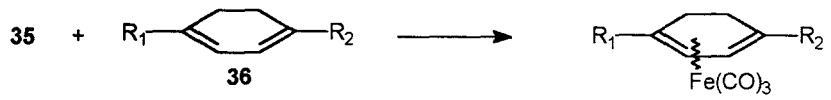
Scheme 4: PMB = *p*-methoxybenzyl

Although there are some asymmetric reagents which are solely organic, most contain a metal ion or ions. Those that have been used as chiral reagents include such diverse metals as tellurium,[22] magnesium, lithium, aluminium,[23] copper,[24] lanthanides,[25] and iron.[26] The value of metal ions in asymmetric synthesis derives from their ability to chelate with different parts of the reacting molecules, thus forming a rigid transition state complex.[27] This may be illustrated by the application of a chiral 1-aza-1,3-butadiene tricarbonyliron complex **35** which has been used for the enantioselective complexation of 1,3-dienes.[26]

The ligand **34** may be synthesised by condensation of 3-benzylidenecamphor with *p*-anisidine (Scheme 5), the stereoisomeric imines **34** being obtained in a *Z*:*E* ratio of 2:1. Separation of the stereoisomers was apparently unnecessary for the success of the complexation studies. Complexation of the 1-aza-1,3-butadiene **34** with nonacarbonyldiiron was carried out in diethyl ether under reflux. Due to its low stability and air sensitivity the exact structure of the complex



Scheme 5



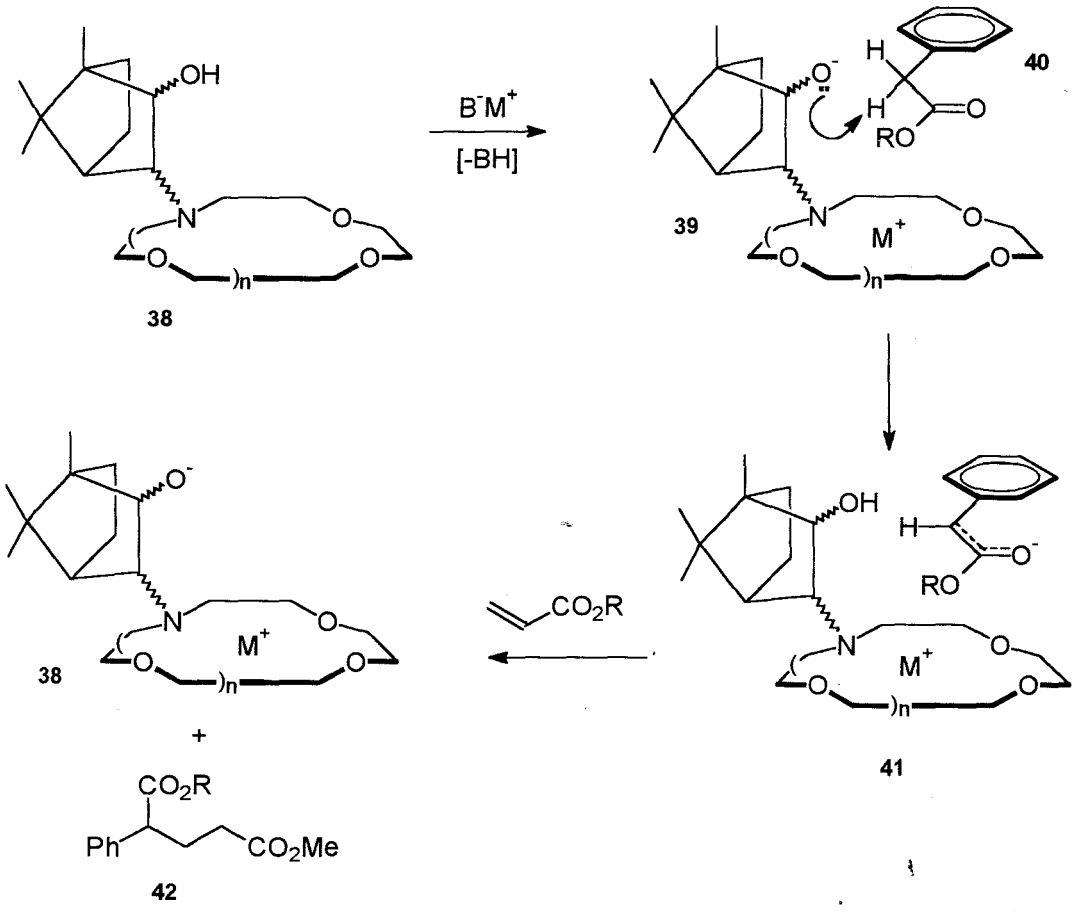
Scheme 6

35 was not elucidated. However, when heated in aromatic solvents with the appropriate dienes **36** (Scheme 6) the resulting complexes were stable and readily characterised. The enantioselectivities obtained ranged from 15% to 64% e.e. [26]

(iv) Catalytic methods

Catalytic methods are favoured due to the potential for recycling the catalyst and the relatively small amounts of chiral material required. Compounds such as BINAP[23] and modifications thereof are well known chiral catalysts. Of particular importance in the present context is the development of camphor-derived crown ether catalysts. Most crown ethers now in use as catalysts were first developed for their molecular recognition capability, and it is this property which lends itself to the development of chiral crown ethers as catalysts. One such series of chiral catalysts is based on (+)-camphor,[28] and an application is outlined in Scheme 7. Upon deprotonation of the hydroxyl group in the chiral crown ether **38** by an alkaline base, a stable complex **39** is formed between the crown ether and the metal, with the alkoxide group pointing to the centre of the cavity. The efficiency of these complexes as asymmetric bases to catalyse the Michael addition of phenylacetate esters to acrylate esters was examined, and it was found that, using the different crown ethers (n = 1, 2, 3) and acrylate esters (R = Me, *t*-Bu), enantiomeric excesses of up to 83% were achieved.[28] Stereoselectivity was observed to depend on the choice of crown ether, the

of crown ether, the temperature and the counterion of the alkaline base used. As expected, kinetic control (i.e. reaction at low temperature) led to higher enantioselectivity.

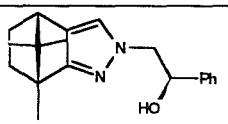
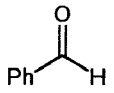
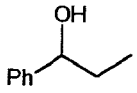
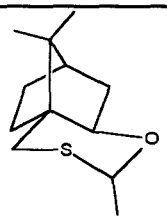
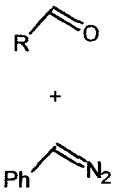
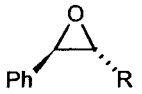
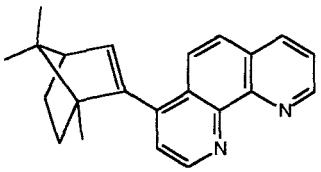
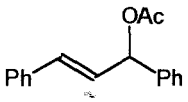
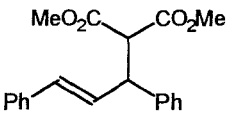


Scheme 7

The camphor-derived lanthanide complex, tris-{3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato}europium [Eu(hfc)$_3$], is well-known for its use as a chiral shift reagent in NMR spectroscopy. This is, however, not its only application. Danishefsky has conducted experiments in which [Eu(hfc)$_3$] is used as a Lewis acid to catalyze the cyclocondensation of heterodienophiles with aldehydes,[29] as well as using it in the total synthesis of the antibiotic vineomycinone B_2 methyl ester.[30]

A recent review[31] of asymmetric catalysis cites several camphor-derived catalysts, which are capable of excellent stereocontrol. These are summarized in Table 1.

Table 1. Camphor-derived ligands in asymmetric catalysis[31]

Ligands	Catalyst	Substrate	Product	Stereocontrol achieved
	Et_2Zn			up to 93% ee
	$Cu(acac)_2$			up to 93% ee
	Pd^0			up to 92% ee

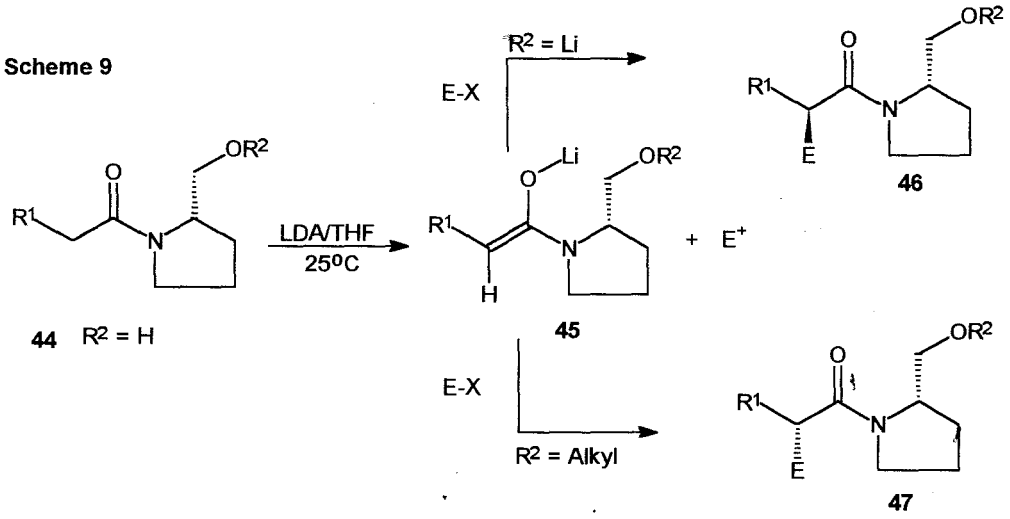
1.3 Synthesis of Chiral Carboxylic acids and esters

Chiral carboxylic acids are important building blocks for the synthesis of new materials, including natural products, non-steroidal anti-inflammatories and ferro-electric liquid crystals.[32] A number of methods for the synthesis of these important compounds have been reported,[33] and these concentrate on applications of α- and β-alkylation, hydrogenation, halogenation and hydroxylation reactions. Of these the first two have particular relevance to our own work on the formation of α-alkylated products.

The asymmetric α-alkylation of carboxylic acids and their derivatives ranks among the most important synthetic transformations in organic chemistry today. Of particular interest are methods which enable differentiation between the enantiotopic faces of prochiral enolates in alkylation reactions, leading to enantio-pure or enantio-enriched products. A number of such approaches have been reported, and these deal almost exclusively with the use of chiral auxiliaries. The use of (*R*)- and (*S*)-2-methoxymethylpyrrolidine (RAMP and SAMP) has been pioneered by Enders and coworkers,[34] while Sonnet[35] and Evans [36] described independently and simultaneously the use of this versatile chiral auxiliary in the α-alkylation of carboxylic acids. Evans, however, is probably

better known for his work on prolinol-derived amides.[36] Alkylation of the chiral amide enolates **45** derived from (-)-prolinol have been shown to proceed in high diastereomeric purity (Scheme 9). One design criterion relevant to the selection of prolinol as a suitable chiral auxiliary, centred on the incorporation of the hydroxy group proximal to the amide carbonyl. This was expected to perform a crucial role, *via* enolate chelation, in establishing an enantiotopic bias in the alkylation reaction. Treatment of the amide **44** with two equivalents of LDA in THF at or below room temperature, affords the *Z*-enolate **45** with ≥ 97% stereoselectivity, subsequent alkylation occurring at the *re*-face of the enolate to give the alkylated products **46a-c**. Use of the alkoxy derivative **44** (R^2 = Me), however, resulted in inversion of stereochemistry, with the electrophile attacking from the *si*-face of the enolate, thus illustrating the effect of chelation control in the lithium enolate.

Scheme 9



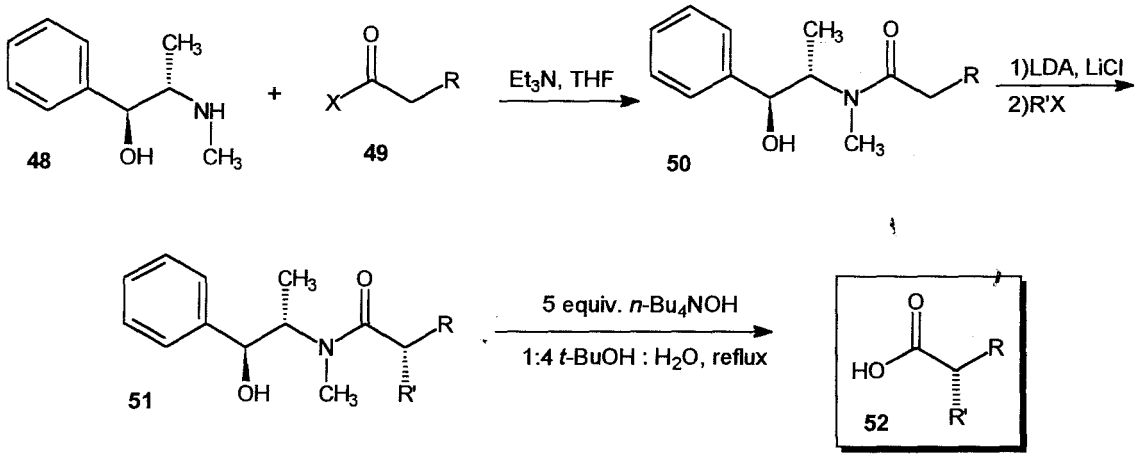
46	Electrophile	R1	%d.e.	Yield
a	CH_3CH_2I	CH_3	84%	98%
b	*n*-C_4H_9I	CH_3	88%	99%
c	$PhCH_2Br$	CH_3	76%	75%

Myers *et al.*[37] have investigated the use of pseudoephedrine **48** as an auxiliary for the asymmetric alkylation of a range of carboxylic acids (Scheme 10). This inexpensive amino alcohol is a non-conventional acyclic auxiliary, which has proved to be highly effective for the alkylation of a variety of *N*-acyl derivatives (**50**), the enolates being sufficiently reactive to be alkylated in good yields (80 - 99%) by a range of electrophiles, including β-branched primary alkyl iodides. Many

of the products are crystalline, facilitating diastereomeric enrichment by crystallisation. Typically, recrystallisation gives products of $\geq 99\%$ d.e. and excellent yield. Mild hydrolysis then affords the auxiliary and the corresponding α-alkylated carboxylic acid in high yields without any evidence of racemisation.

The stereoselectivity in these reactions (*ca.* 94 - 99% d.e.) is, of course, determined by the chirality of the pseudoephedrine. In every case examined so far, the major product arises from electrophilic attack on the *Z*-enolate (*i.e.* with the R^1 group *syn* to the oxygen) from the same face as the *C*-methyl group in pseudoephedrine.[37] The basis for selectivity could not be established by means of physical evidence, such as a crystal structure of the enolate, but a parallel has been drawn with the prolinol analogues discussed previously. A reactive conformer, as shown in Figure 2, has been invoked. In this model, the lithium alkoxide and the solvent molecules associated with the lithium cation, are proposed to block the β-face of the *Z*-enolate, thus forcing the alkyl halide to approach from the α-face.

Scheme 10



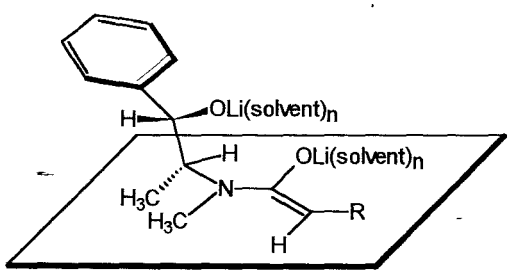
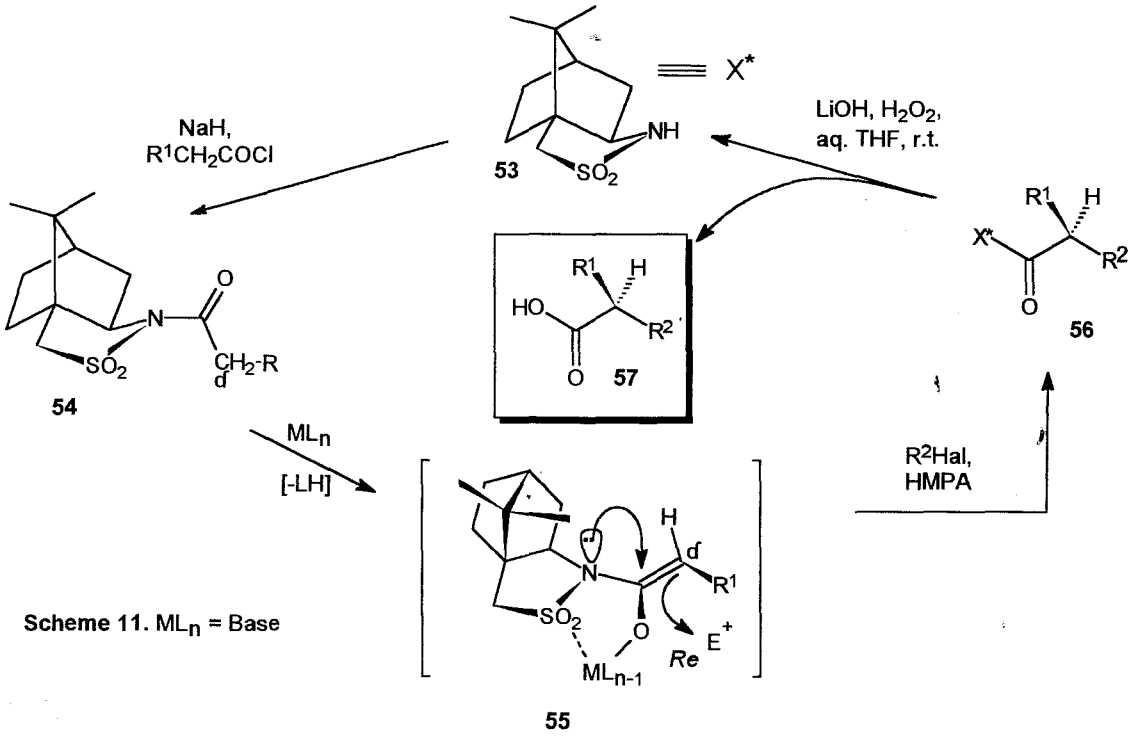


Figure 2: Proposed transition state

A discussion of the synthesis of enantiomerically pure carboxylic acids would be incomplete without mentioning Oppolzer's *N*-acyl camphorsultams.[38] Acyl sultams **54** are readily accessible from the relatively inexpensive auxiliary **53** (Scheme 11). When treated with BuLi or NHMDS, followed by a suitable alkyl halide (e.g. benzyl bromide or an alkyl iodide) the acyl sultams react smoothly to give the α-alkylated products **56** in high yield, typically, with high diastereoselectivity. In general, the diastereomeric products **56** can be separated by flash chromatography or crystallisation. The enantiomerically pure carboxylic acid is readily obtained by hydrogen peroxide-assisted saponification. The observed stereoselectivity of α-alkylation is, once again, consistent with formation of a chelated *Z*-enolate **55** which is alkylated preferentially from the bottom face, *i.e.* opposite to the nitrogen lone pair. Oppolzer's *N*-acyl camphorsultam has also been used in the palladium-catalysed cyclopropanation of α,β-unsaturated carboxylic acids.[39]

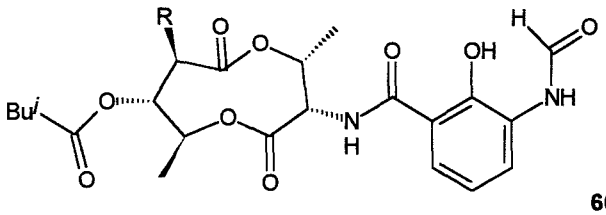


Scheme 11. ML_n = Base

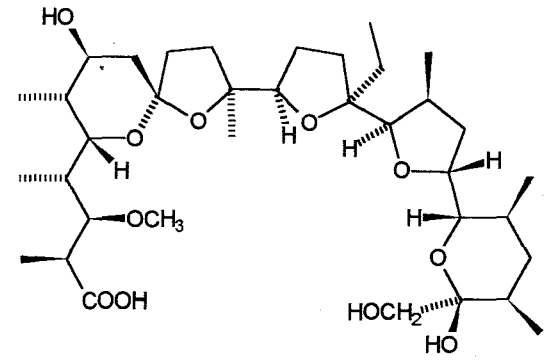
α-Alkylated carboxylic acids may also be obtained by the reduction of unsaturated carboxylic acids. This has been achieved both by using an achiral catalyst on an auxiliary-linked substrate [40] and by using a chiral catalyst on an achiral substrate.[32] An interesting application of a chiral tin hydride as a hydrogen transfer reagent permits the stereoselective trapping of prochiral *C*-centred

radicals to give chiral carboxylic acids in > 25% e.e.[41] Resolution methods, including preferential crystallisation [42] and chiral HPLC[43] have also been used to obtain stereochemically pure chiral carboxylic acids.

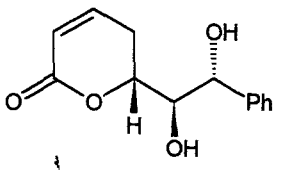
The synthesis of biologically active molecules, both cyclic and acyclic, containing numerous chiral centres requires access to a variety of simple chiral building blocks in high optical purity. As we have already shown, chiral carboxylic acids are readily accessible and may be readily converted into a myriad other functionalities due to the reactivity of the carboxyl group. Many of these products are then useful intermediates in natural product synthesis. Among the most useful of these conversions is the lactonisation of γ- and δ-hydroxy carboxylic acids. Chiral lactones, such as the Prelog-Djerassi lactone,[44] form important sub-units of several natural products including antimycins A_1 and A_3 (**58** and **59**) isolated from *Streptomyces*;[45] (+)-goniodiol **61**, isolated from *Goniothalamus sesquipedalis*, and shown to have potent cytotoxic activity;[46] and monensin **60**, a polyether antibiotic.[47] Chiral carboxylic acids can also be converted to amides, alcohols and even aldehydes, thus providing access to a wider range of synthetic opportunities.



58 antimycin A_1 : R = hexyl
59 antimycin A_3 : R = butyl



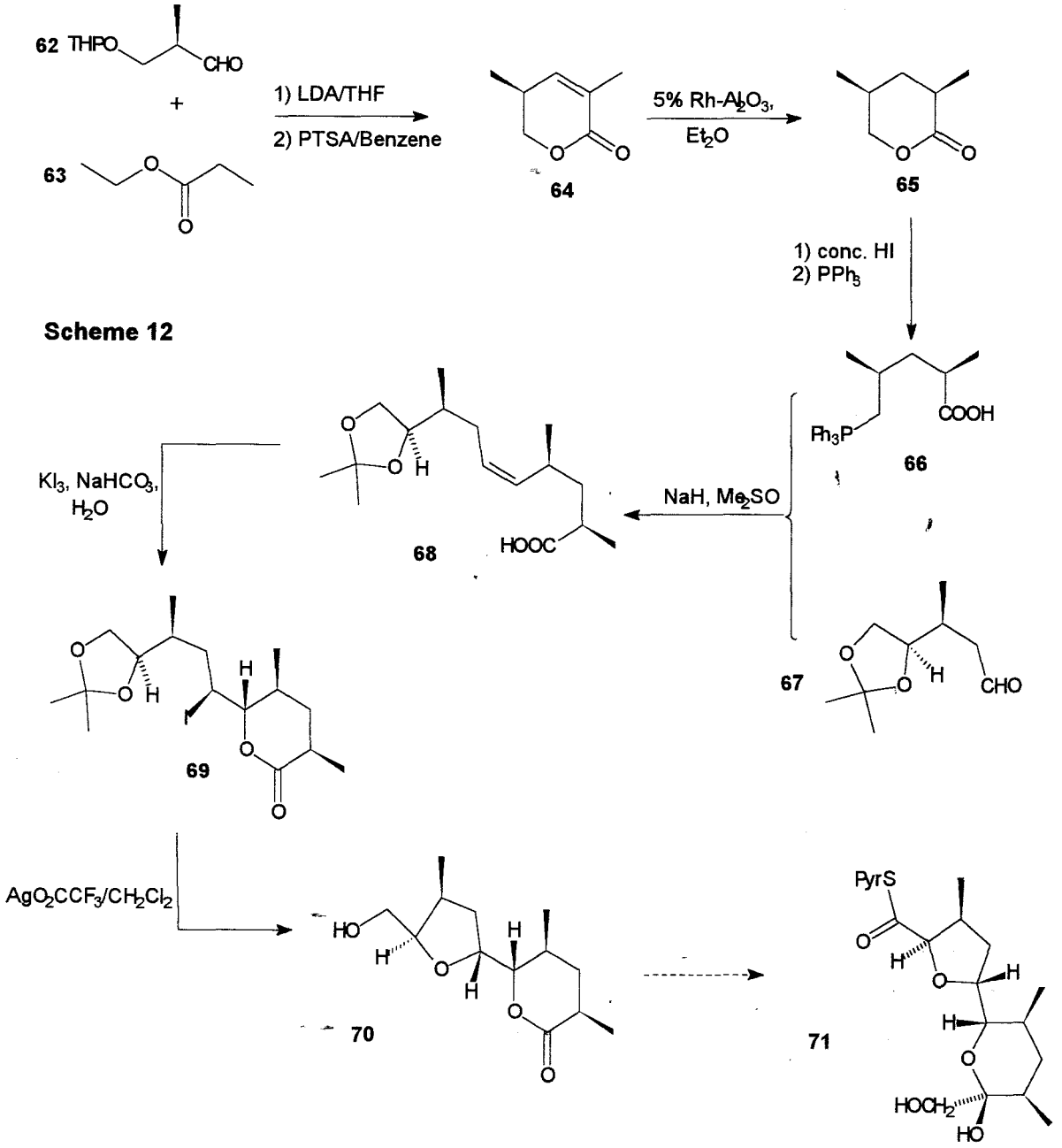
60 monensin



61 (+)-goniodiol

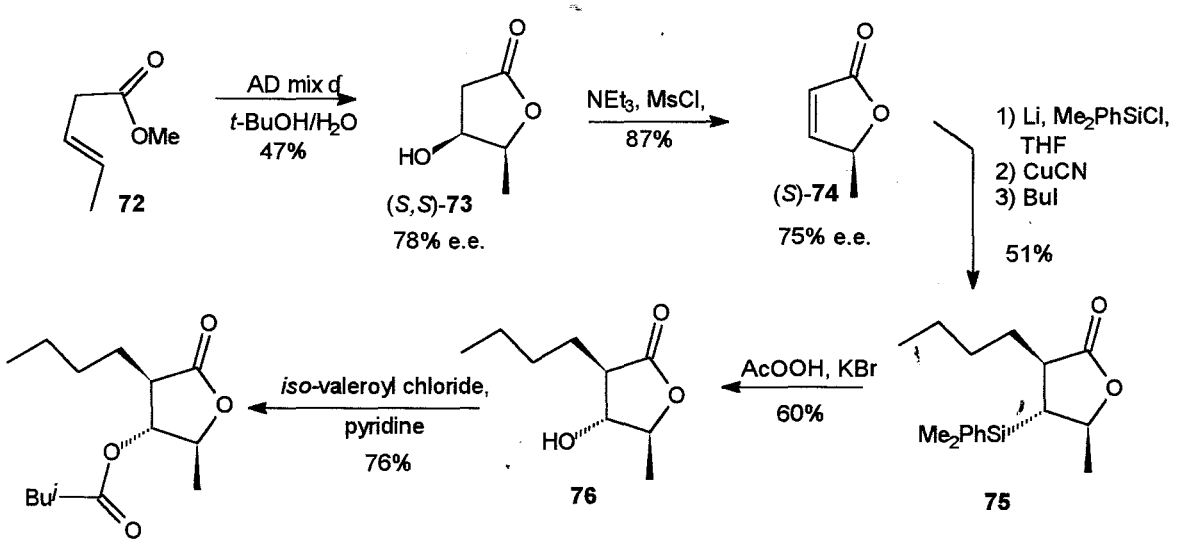
α-Alkylated carboxylic acids have found direct use in natural product synthesis. Clark Still *et al.*[47] have made use of an acid derived from a chiral aldehyde in the stereospecific synthesis of monensin (Scheme 12). The tetrahydropyranyl ether **62** of (*R*)-β-hydroxybutyraldehyde was

added to the lithium enolate of ethyl propanoate **63** to give an aldol. Cyclisation, followed by catalytic reduction of the resulting unsaturated lactone **64** was achieved with 5% rhodium on alumina to give dimethyl valerolactone **65** quantitatively, the 8:1 *cis-trans* mixture being readily separated by selective crystallisation. The valerolactone **65** was converted to the phosphonium salt in order to provide a linkage to the separately prepared **67** *via* a Wittig reaction. Iodolactonisation of the cis-olefin **68** thus formed provided access to the intermediate **69**, which was treated with silver trifluoroacetate to afford the tetrahydrofuran moiety **70**. Jones oxidation and conversion to the thiopyridyl ester **71** completed the construction of one of the three major optically active fragments of monensin.



Scheme 12

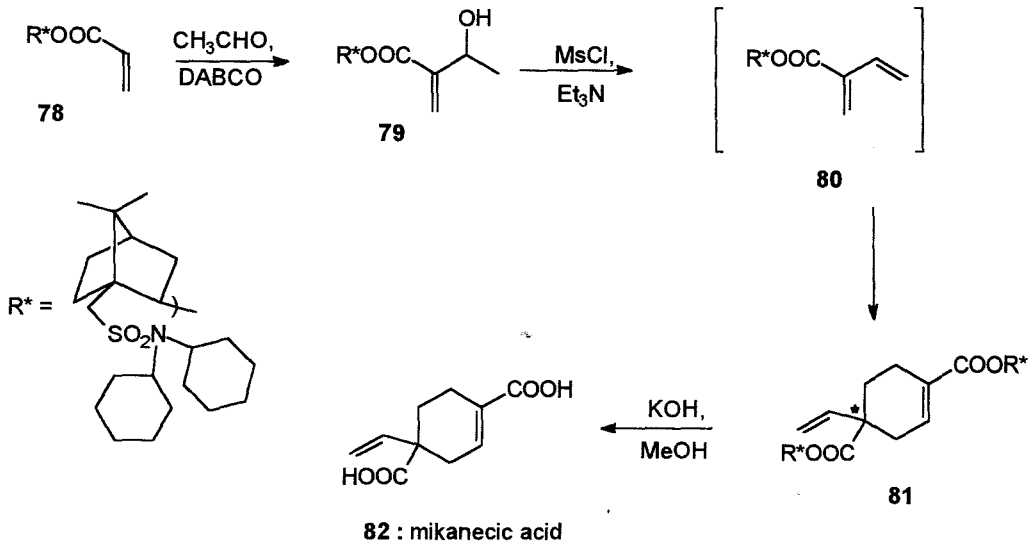
Another useful application of α-chiral carboxylic acids is in the synthesis of (+)-blastmycinone **77** performed by Berkenbusch and Brückner (Scheme 13).[45] (+)-Blastmycinone is a hydrolysis product of the antimycins **58** and **59**, secondary metabolites of *Streptomyces* bacteria which show potent activity as fungicides, insecticides and ichthyotoxins.[45] The key starting material was the achiral unsaturated ester **72**, which was converted to the lactone **73** following enzymatic dihydroxylation using the enzyme, AD mix α. Dehydration to the α,β-unsaturated lactone **74** was followed by silylation and subsequent alkylation to provide the *trans,trans*-trisubstituted lactone **75**. The stereocontrol in these transformations was governed by the stereochemistry of the methyl group in the lactone **74**, since the silyl group must enter *trans* to the methyl and the new alkyl substituent must enter *trans* to the silyl group. The silyl group was then removed by treatment with peracetic acid and the resulting alcohol **76** esterified with isovaleryl chloride, to provide the required target **77**.



Scheme 13

In the above examples, the required chirality was introduced in different ways. In the first, a readily available chiral molecule **62** (Scheme 12) was elaborated and converted into the chiral carboxylic acid **66**; in the second, a biological catalyst (enzyme) was used to induce chirality (Scheme 13). The final example to be cited illustrates the use of a chiral auxiliary to induce chirality in a carboxylic acid. Mikanecic acid is a terpene dicarboxylic acid obtained by alkaline hydrolysis of the mikanoidine alkaloid obtained from *Senecio mikanioides*.[48] The challenging part

of its synthesis is the construction of a chiral vinylic quaternary centre. Basavaiah and co-workers [48] approached this challenge by way of the Baylis-Hillman reaction (Scheme 14). By coupling acetaldehyde with the camphor-derived chiral acrylate **78**, followed by dehydration, they produced the novel chiral 1,3-butadiene-2-carboxylate **80**. This intermediate undergoes a spontaneous Diels-Alder reaction to provide, after hydrolysis of the auxiliaries, the desired, optically active (+)-mikanecic acid **82**.



Scheme 14

Chiral carboxylic acids thus constitute a significant group of sub-units used in the synthesis of natural products. There is still much research to be done in order to produce these valuable synthons more efficiently and in greater optical purity.

1.4 Synthesis of Chiral α-Amino Acids

Currently more than 700 naturally occurring α-amino acids are known, but only a small fraction of these are those incorporated into proteins. Many of them exhibit a wide range of bioactivities or form important building blocks for other natural products. These factors begin to account for the vast array of literature on the synthesis of α-amino acids. Diverse preparative methods have been employed, including neutral reactions, such as the catalytic reduction of dehydroamino acids, [49, 50] and hydrazonolactones;[51] nucleophilic reactions, exemplified by organometallic additions to glyoxylic imines;[52] and electrophilic reactions. The latter are the most conventional and, since they are most relevant to the present study, will be the focus of this review.

It is important to add, at this point, that asymmetric synthesis is not the only method in general use for obtaining chiral α-amino acids. Resolution methods with increasing sophistication and general applicability, are continually being developed. Methods for resolution include:- chiral HPLC,[53] phase transport/extraction,[54] and crystallisation.[55] Kożbiał and colleagues, [54] for example, have used a lipophilic chiral crown ether containing a D-mannopyranoside unit in phase transfer, extraction and chromatographic experiments to separate amino acids with different levels of success.

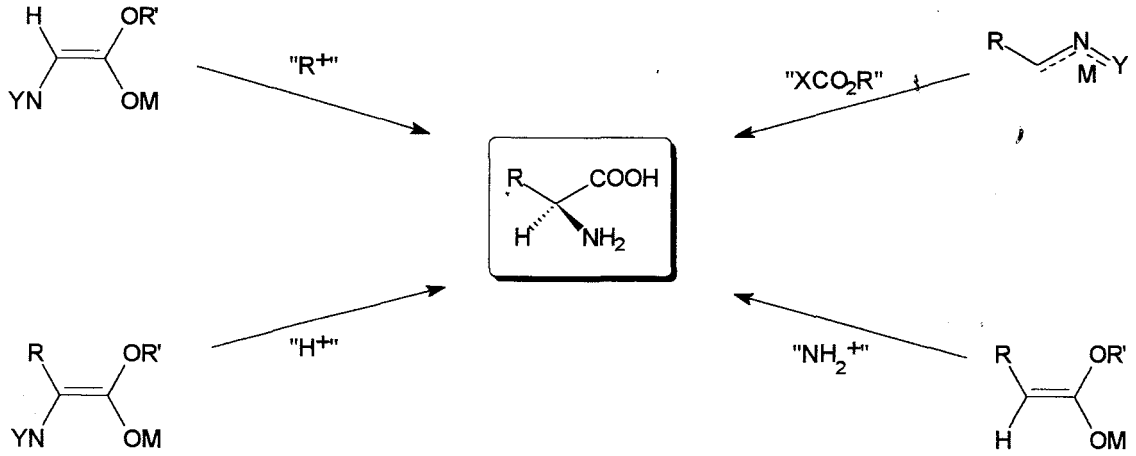


Figure 3. Electrophilic synthesis of α-amino acids.[56]

Electrophilic reactions used in the synthesis of amino acids include alkylation, amination, carboxylation, and protonation; these approaches are summarised in Figure 3. Much research has been directed at applying each of these processes to the synthesis of enantiomerically enriched α-

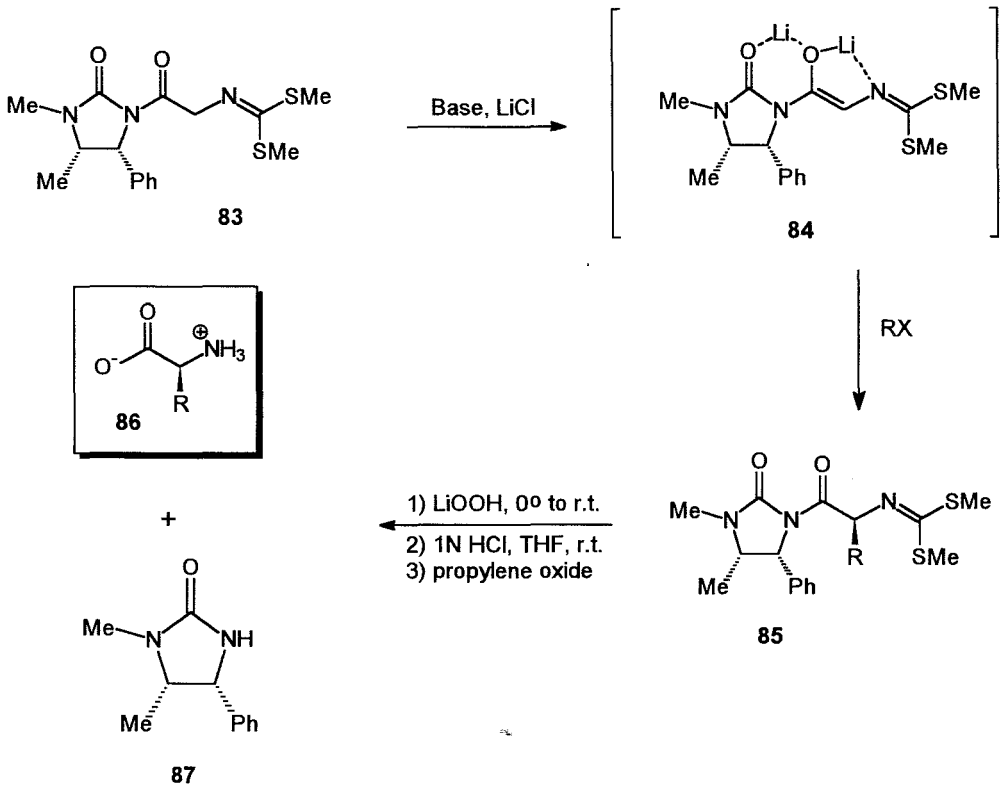
amino acids. In the following examples, attention will be given to the origin of the asymmetric induction and the generality of each method.

1.4.1 Alkylation reactions

Among the most thoroughly studied alkylation reactions in this field is the alkylation of glycine enolate derivatives. In most cases, these reactions, are carried out using chiral auxiliaries. A well-known example is the application of Oppolzer's sultam-derived glycine equivalent.[57, 58] Almost total stereo-control has been achieved, using this versatile auxiliary. Owing to its effectiveness, the sultam **53** has also been used in the synthesis of enantiopure, deuterium-labelled amino acids for application in peptide studies.[59]

A more recent example of the auxiliary approach to the asymmetric synthesis of amino acids is the use of (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one **87** (Scheme 17).[60] Treatment of either (+)- or (-)-ephedrinium chloride with urea, followed by protection of the amine group as the bis(methylthio)methylene imine affords the reaction substrate **83**. The best conditions for alkylation involve the use of LHMDS or potassium *tert*-butoxide (KOBu^t) as base, THF as solvent and six equivalents of lithium chloride. Lithium chloride seems to be a vital additive - probably due to its ability to chelate with the enolate **84** and so to change the degree of aggregation; it can also act as a Lewis acid, thus activating the electrophile. The fact that it also changes the polarity of the solution is not insignificant. Stereocontrol is achieved as a result of the chirality of the auxiliary and the rigidity of the enolate chelate **84**, the alkyl group attacking *anti* to the phenyl group of the ephedrine moiety. While the method has been carried out with various alkyl groups, the best results were obtained with allyl iodide (96% d.e.; 86% yield).

A related auxiliary (3,6-dihydro-2H-1,4-oxazin-2-one) has been used by the same group in the stereoselective synthesis of α,α-disubstituted proline derivatives,[61] while Ferey *et al.*[62] have obtained similar products in reactions of a borane-(*S*)-*N*-benzylproline ester adduct with alkyl halides.

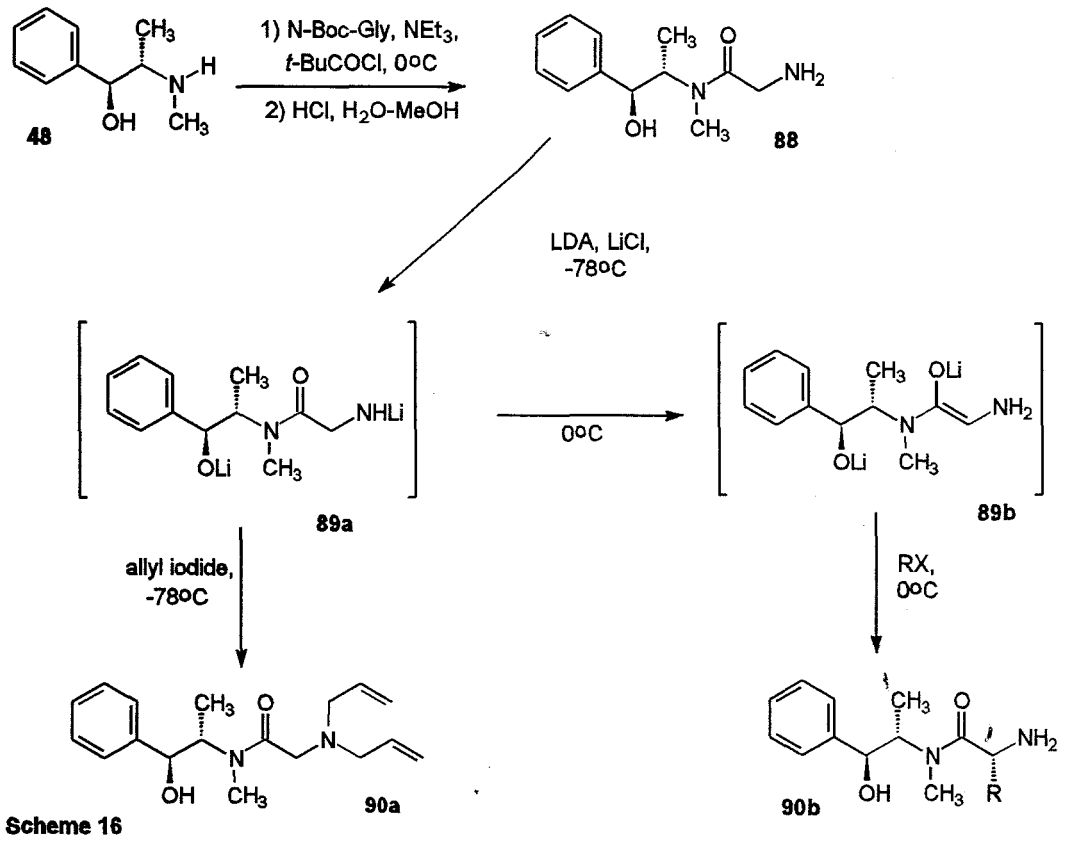


Scheme 15

Another group which has made a valuable contribution to the study of asymmetric α-alkylation reactions is that of Myers.[63] They have devised an auxiliary-based method which is possibly even more economical than a catalytic method. The auxiliary used was pseudoephedrine **48**, either enantiomer of which is available at a low cost. Further advantages of the approach are that many of the initial products are crystalline and can be readily hydrolysed without significant racemization and, remarkably, no protection of the free amine group is required! The substrate is prepared by selective *N*-acylation of pseudoephidrine **48** with the mixed anhydride derived from *N*-Boc-glycine and pivaloyl chloride in the presence of triethylamine in dichloromethane at 0°C (Scheme 16). The *N*-Boc-glycinamide, thus produced in 88% yield, is deprotected in acidic methanol to give the solid glycinamide **88**. It is possible to carry out this sequence in one reaction vessel, but since the glycinamide is highly hygroscopic the success of the reaction requires completely anhydrous conditions.

There are three acidic groups in the substrate molecule **88**, which make the stoichiometry of the base crucial. The dianion **89a** is generated using LDA (1.95 equivalents) at -78°C. Alkylation at this temperature, affords the *N*-alkyl product **90a** but, if the reaction mixture is warmed to 0°C

prior to alkylation, equilibration to enolate **89b** results in formation of the α-alkylated product **90b** in 75 - 97% d.e.. Since the products are typically crystalline, further enrichment is possible by recrystallisation. Not only are the yields moderate to high (50 - 92%) in this approach, but the conditions can be applied to a wide scope of alkyl halides. Even relatively unreactive alkyl halides [*e.g.* $(CH_3)_3SiCH_2Br$] may be made to react. Since the enolate **89b** is stable even at 23 °C, it is possible to allow these reactions to proceed at room temperature thus increasing reactivity.



Scheme 16

In most alkylation reactions, asymmetric induction is a function of the steric congestion caused by the substituents on the auxiliary and the rigidity of the system, which is often enhanced by chelation of the enolate.

1.4.2 Amination reactions

Amination of the α-carbon of a prochiral (or chiral) carboxylic acid provides a popular route to chiral amino acids. It comes as no surprise that Oppolzer's versatile sultam **53** has been found to

be useful in this reaction.[64, 65] The nitrogen source used in these reactions is 1-chloro-1-nitroso-cyclohexane, and the reaction gives excellent stereocontrol and very good yields.

α-Amino acids can also be synthesised *via* α-hydrazino acids. This has been demonstrated by a number of research groups [66, 67, 68] (Scheme 17), the approaches differing only in the auxiliaries used and the focus of each study. These differences are summarised in Table 2. In each case, the carboxylic acid is esterified and the enolate **92** generated, the enolate being trapped with TMSCl in route A.[68] In all three routes the enolate is then reacted with the diazo-formate, in what is the asymmetric step; in all three cases, di-*tert*-butylazodicarboxylate (DBAD) was found to be the most effective source of nitrogen. Hydrolysis to remove the auxiliary and protecting groups, followed by catalytic hydrogenation affords the corresponding amino acids **95**. Stereocontrol is attributed to the rigid structure of the enolate systems. While the chiral auxiliaries used in approaches B and C are fairly rigid, rigidity in enolate intermediate in approach A is established by chelation with titanium tetrachloride.

Scheme 17

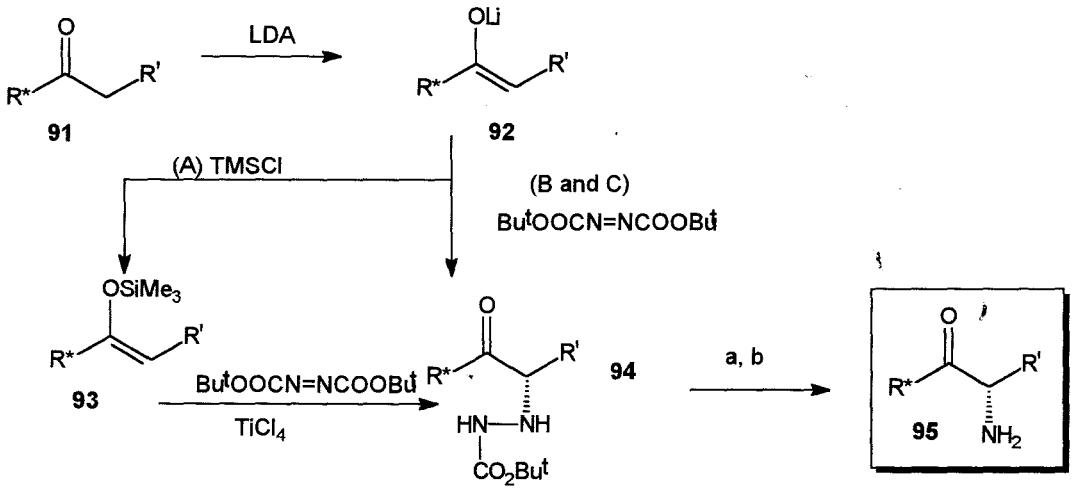
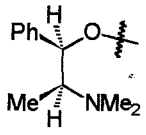
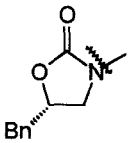
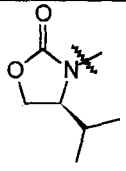
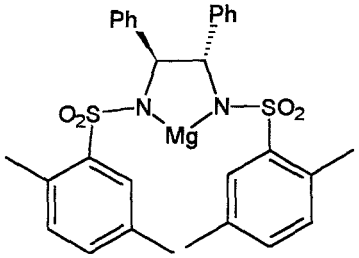


Table 2. Summary of differences between routes A, B, and C

		A	B	C
Reagents	a	1.CF_3CO_2H 2.LiOH	1.LiOH 2.CF_3CO_2H	1.LiSH 2.AcOOH 3.Pd/C,H_2
	b	PtO_2/H_2	Raney Ni/H_2	Raney Ni/H_2
Auxiliary, R*				
R' = Bn	Yield %	81	82	81
	% e.e. **95**	91	>99	66

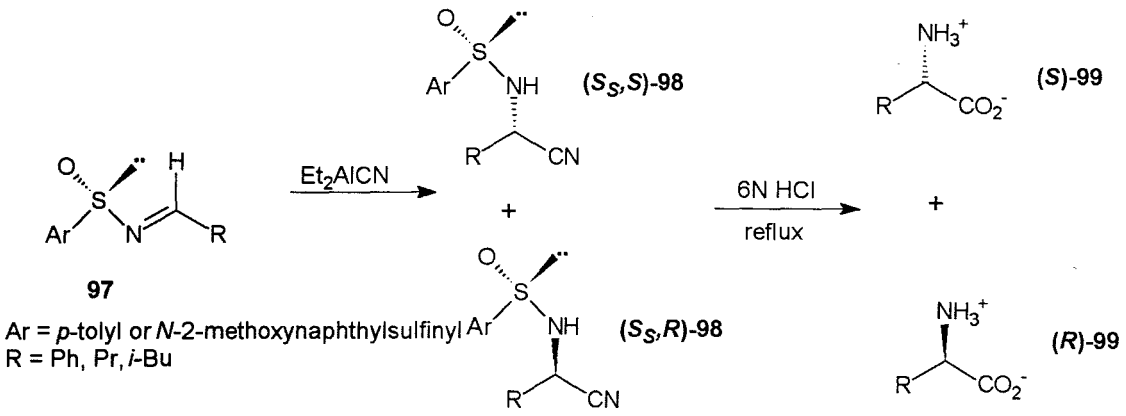
The above examples all require stoichiometric amounts of the chiral inducing agent. However, Evans and Nelson [69] have investigated the use of a chiral base **96** which is able to catalyse the amination reactions outlined above. The chiral base is a magnesium-(*S,S*)-bis(sulfonamide) complex, and its use has resulted in improvements in both chemical yield and enantiomeric excess.



96

1.4.3 Carboxylation reactions

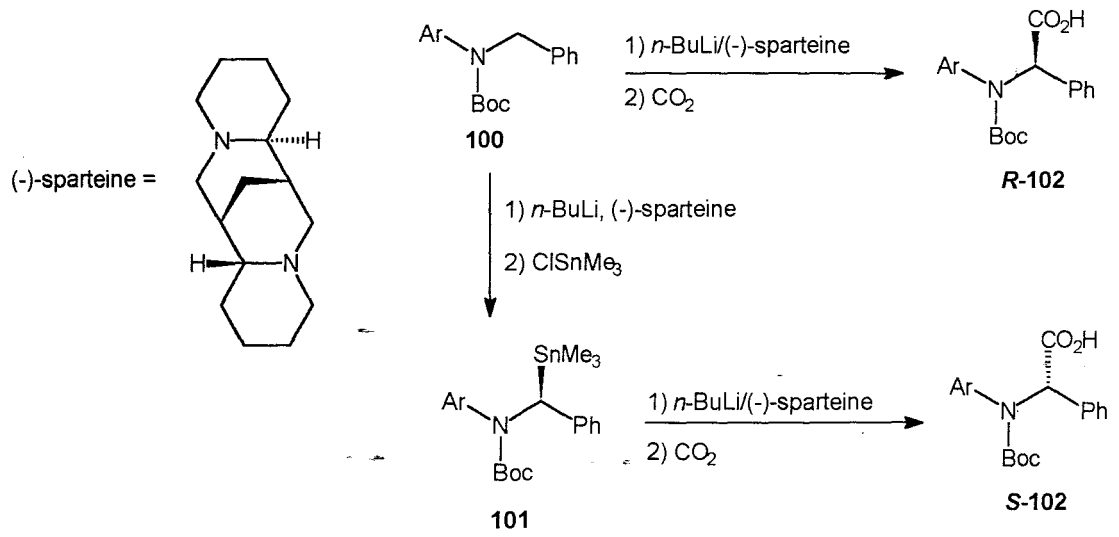
The well-known Strecker synthesis is the basis of the carboxylation of aminals to give amino acids. Typically, this involves reaction of an aldehyde or ketone with NaCN and NH_4Cl to form the α-amino nitrile and since the nitrile group is readily hydrolysed to the acid, this is a convenient method for the preparation of α-amino acids.[70] This reaction has been modified by Davis and coworkers to include asymmetric control.[71] Diethylaluminium cyanide was found to add stereoselectively to chiral sulfinimines **97** under mild conditions (typically -78°C to -40°C) (Scheme 18). Use of *N*-2-methoxy-1-naphthylsulfinyl as the auxiliary gave > 60% d.e., and the diastereomeric products *R*- and *S*-**98** were easily separated by standard chromatographic methods. Removal of the auxiliaries and hydrolysis of the nitriles may be achieved under mildly acidic conditions to give, after work-up and purification, the (*S*)-amino acids **99** in >95% e.e. and 71 - 81% yield. The product stereochemistry was determined by correlation with authentic samples, and is consistent with association of the Et_2AlCN with the sulfinyl oxygen to form a tetra-co-ordinated species, followed by intramolecular transfer of cyanide through a six-membered chair-like transition state. While the system has not been applied exhaustively to the synthesis of α-amino acids, it appears to be at least applicable to those bearing a simple alkyl or aryl group on the α-carbon.



Scheme 18

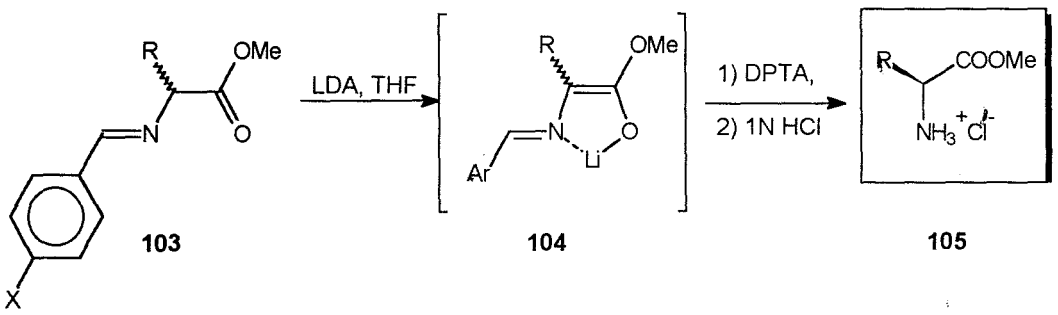
A transmetallation approach, based on an asymmetric deprotonation-electrophilic substitution sequence, shows particular promise.[72] Treatment of aryl amines with butyllithium and (-)-sparteine as a chiral base system (Scheme 19), followed by direct quenching of the imine with carbon dioxide, affords amino acid (*R*)-**102** in up to 92% e.e. and 93% yield. Alternatively, reaction of the imine intermediate with trimethyltin chloride, followed by a further deprotonation and quenching with carbon dioxide, furnishes the enantiomer (*S*)-**102** in slightly decreased yield and enantiomeric excess. While this method is efficient, it has so far only been effective for the synthesis of aryl substituted amino acids, such as phenylglycine. The basis for asymmetric induction, in this case, is not fully understood.

Scheme 19



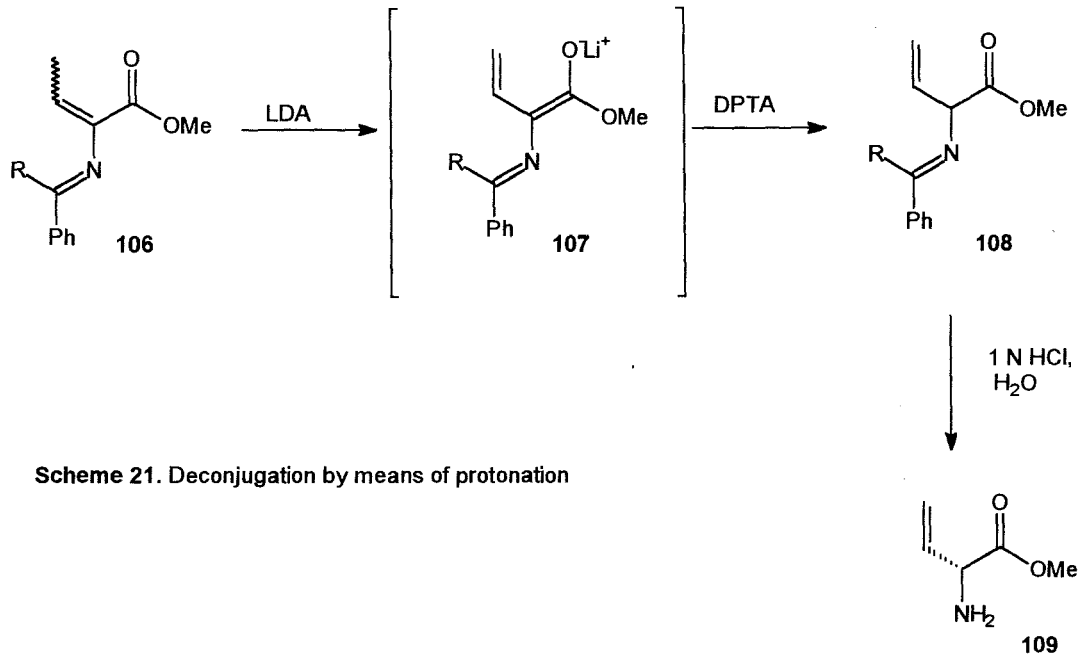
1.4.4 Protonation Reactions

In the approach used by Duhamel and coworkers,[56] a prochiral nucleophilic substrate (lithium enolate) is reacted with an achiral electrophile (proton source) bearing a chiral leaving group, which is responsible for the sense of asymmetric induction. Enantioselective protonation has been employed in two distinct ways, *viz.*, in deracemization and in deconjugation. In deracemization, the chiral proton carrier and the nature of the substituents on the prochiral substrate determine the stereochemistry of the product. This is illustrated by the transformations outlined in Scheme 20. The aldimine methyl esters **103** were deprotonated with LDA, and the resulting enolates **104** protonated using (2*R*,3*R*)-*O*,*O*′-dipivaloyltartaric acid (DPTA), followed by acid hydrolysis to give the chiral products **105**. Interestingly, a small decrease in selectivity was detected (56% → 44% e.e.) when the steric bulk of the substituent, R, was increased (R = Me → R = *t*-Bu). The reaction always favours the (*S*)-isomer, and decreasing the temperature increases enantioselectivity to as much as 70% e.e.. The rigidity of the chelated enolate **104** is considered to be an important factor in the stereoselectivity of this reaction. The method has been applied successfully to a number of different substrates, mainly α-amino acids having an α-alkyl substituent at the α-carbon.



Scheme 20. Deracemisation by means of protonation

Deconjugation experiments were carried out under very similar conditions on conjugated ester **108** (Scheme 21). The stereocontrol was found to be strongly dependent on temperature of enolization. It is clear that this type of reaction does have limited application, but it provides valuable access to β,γ-unsaturated amino acids **109**.



Scheme 21. Deconjugation by means of protonation

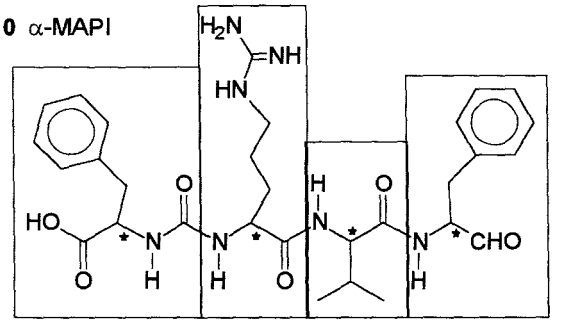
Many other methods appear in the literature for the synthesis of enantiomerically enriched α-amino acids, but time and space preclude review of every available approach.

1.5 Chiral α-Amino Acids in Natural Product Synthesis

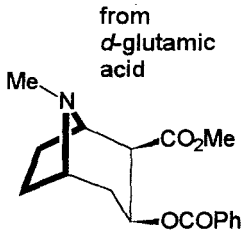
Several natural products contain sub-units which are derived from amino acids. Peptides constitute one obvious class. The tetrapeptide, α-MAPI (microbial alkaline proteinase inhibitor) **110**, which contains phenylalanine, arginine, and valine residues,[73] is produced by *Streptomyces nigrescens* and is known to inhibit HIV-I protease. Another example of an HIV-I protease inhibitor is the binaphthol derivative **111**, which, while not a natural product, contains two valine residues.[74]

Another class of natural products which depends on amino acids as biosynthetic precursors are the alkaloids. Two examples from this class which have appeared in the recent literature are (-)-cocaine **112**[75] and manzamine A **113**.[76] The former is extracted from the leaves of *Erythroxylon coca* and was recently synthesised in several steps from L-glutamic acid. The latter, a marine alkaloid having unique structural features and interesting biological activity, was synthesised from pyroglutamic acid.

110 α-MAPI



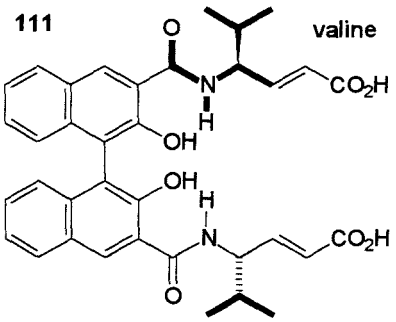
phenylalanine arginine valine phenylalanine



from *d*-glutamic acid

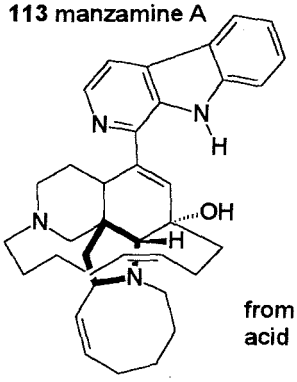
112 (-)-cocaine

111



valine

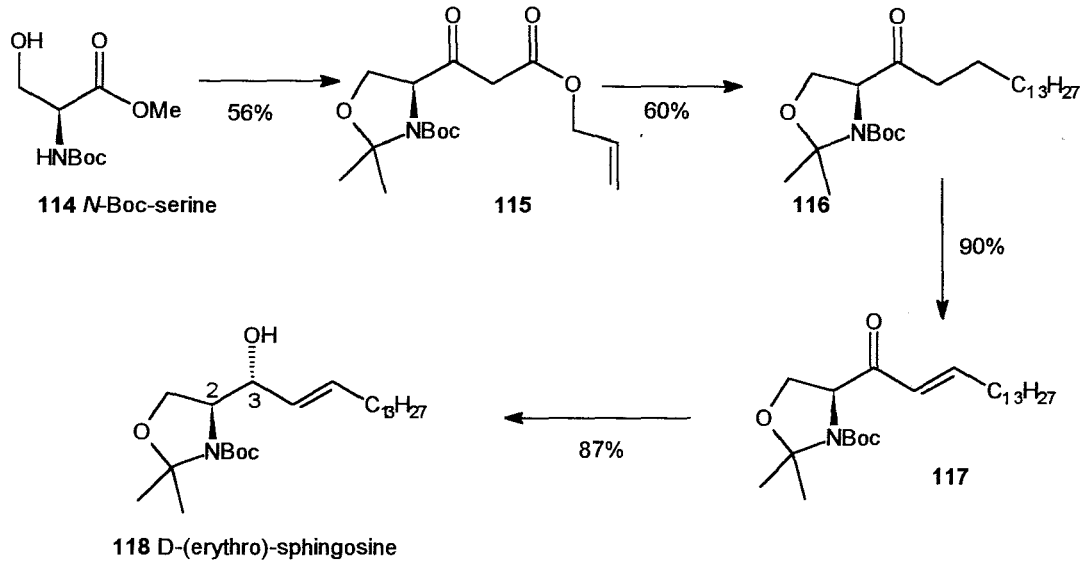
113 manzamine A



from pyroglutamic acid

The following two multistep syntheses exemplify the use of relatively simple amino acid precursors. The first of these is the recently reported[77] synthesis of sphingosine **118**, the core structure of most sphingolipids. The two most important issues in the synthesis of sphingosine involves establishing the stereochemistry at C(2) and C(3) and attaching the functionally diverse tail groups by a *trans* double bond to form the many different sphingolipid derivatives that have been found. It is interesting to note that all four stereoisomers arising from different configurations at C(2) and C(3) are known and have different degrees of bioactivity. The D-*erythro* isomer is by far the most widespread and was the focus of the following synthesis. Commercially available L-(*N*-Boc)-serine methyl ester **114** was cyclised to an oxazolidine intermediate which was converted to the β-keto ester **115** by reaction with the lithium enolate of allyl acetate (Scheme 22). This white crystalline β-keto ester, obtained in good yield after recrystallisation from hexane, was then alkylated with tetradecyl triflate; subsequent treatment with a Pd(0) catalyst at room temperature efficiently removed the allyl ester group and effected decarboxylation to give the ketone **116**. Reaction of the TMS-enol ether of the ketone **116** with $Pd(OAc)_2$ afforded the *trans*-3-ketosphingosine **117**. Within the limits of NMR detection, none

of the *cis*-isomer was detected. Finally, reduction with $NaBH_4$-$CeCl_3$ gave the known D-*erythro*-sphingosine derivative **118**.

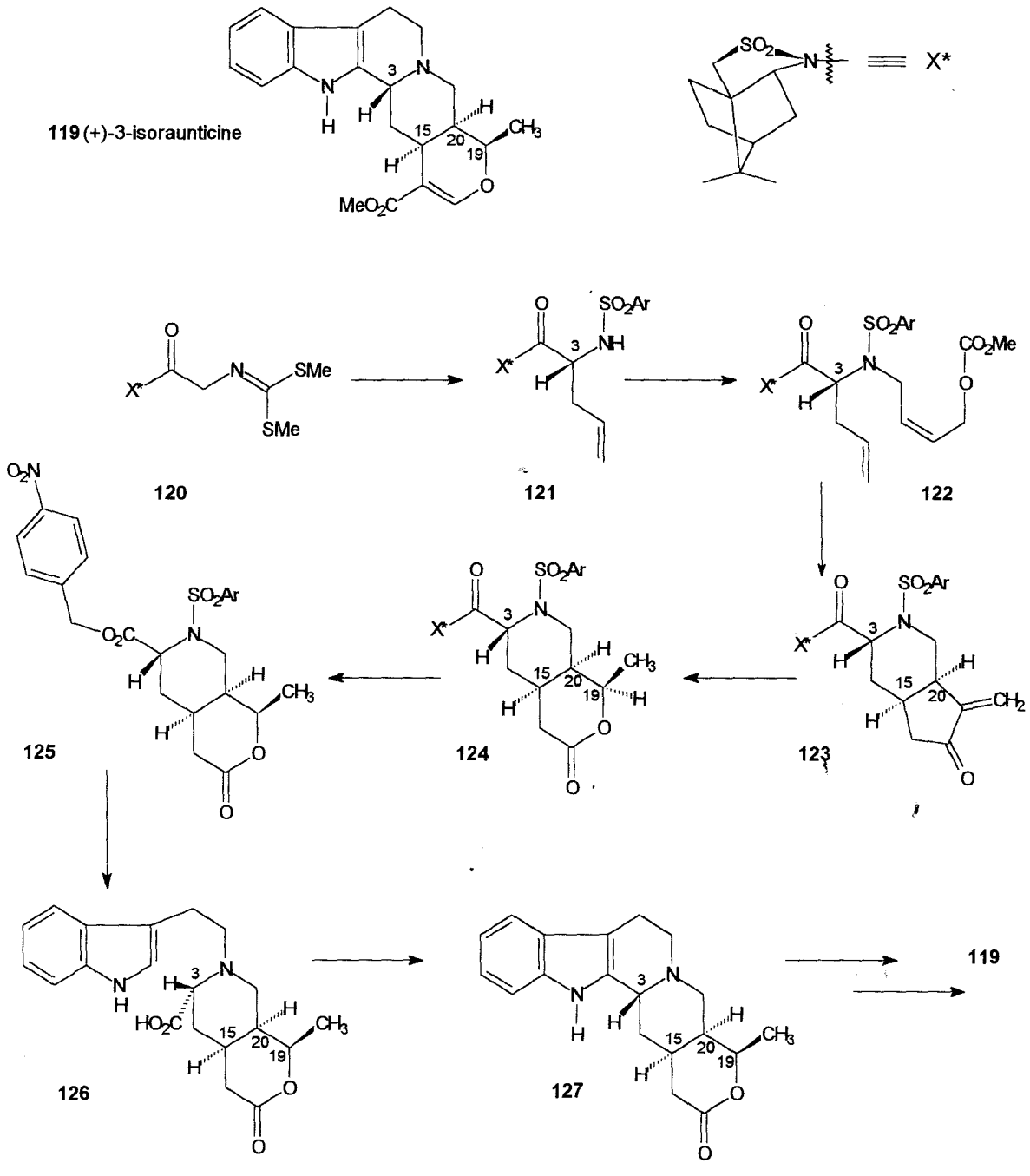


Scheme 22

The second example is the synthesis of (+)-3-isorauniticine **119** reported by Oppolzer *et al.*[78] This heteroyohimbine alkaloid was synthesised from glycine. The stereochemistry was introduced by auxiliary-mediated allylation of the camphor sultam-derived glycine equivalent **120** under phase transfer conditions (Scheme 23). *N*-alkylation of the mesitylenesulfonamide intermediate **121** with (*Z*)-1-bromo-4-[(methoxycarbonyl)oxy]-3-butene furnished the dienylcarbonate **122**, which was subjected to Pd(0)-catalysed carbonylation-cyclisation in acetic acid to afford the bicyclic system **123**. These transformations established stereochemistry at C(3), C(15) and C(20), while catalytic hydrogenation of the methylene group, gave the correct stereochemistry at C(19). Baeyer-Villiger oxidation afforded the lactone **124**. The sultam and sulfonamide protecting groups were removed and the tryptophan group was introduced in four steps. Decarboxylative cyclisation of the acid **126** gave the pentacyclic lactone **127**, formylation and rearrangement of which gave the required alkaloid **119**. This 14-step sequence highlights the value of sultam-directed alkylation of amino acid derivatives.

The value of enantiomerically pure α-amino acids in natural product synthesis is clearly apparent,

as is the need for simpler and more practical ways to make these valuable synthons in high enantiomeric purity.



Scheme 23 Synthesis of (+)-3-isoraunticine

1.6 Previous Work by the Rhodes Research Group and Aims of the Present Investigation

The study of camphor as a chiral auxiliary has been an area of intense research in these laboratories for over a decade.[79 - 83] Most recently, research has concentrated on the following, with particular reference to conformational studies of the various substrates and, hence, the origin of the stereocontrol achieved.

(i) The synthesis of novel camphor-derived diols **128** and their evaluation as chiral cyclic acetals in auxiliary-mediated asymmetric reactions. In fact, total sterocontrol (as detected by NMR spectroscopy) was achieved in cyclopropanation reactions in alkene acetals of the diol **128b**.[82]

(ii) The synthesis of auxiliaries **129**, **130** and **137** and their application in α-alkylation reactions of camphor-derived esters.[81] Moderate stereocontrol was achieved in these reactions.

(iii) The synthesis and evaluation of the camphor-derived imino lactones **131** and **132** as precursors for the synthesis of α-amino acids.[83] The diasteroselectivity in reactions of compound **131** was reported to range from 43% to >99% d.e.

(iv) The application of novel camphor-derived acrylate esters **133** [81] and **134** [83] in Balylis-Hillman reactions.

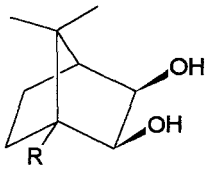
(v) Asymmetric induction achieved using other auxiliaries has also been examined, such as pinane and tartrate derivatives.[82]

In the light of previous work by this research group, the potential of camphor-derived auxiliaries in the synthesis of chiral carboxylic and amino acids was clear. It was decided to explore the application of such systems with the following objectives.

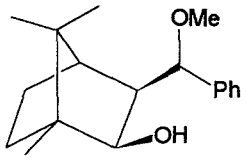
(i) The development of the novel camphor-derived hydroxy-ketal **138** and an evaluation of its potential as a chiral auxiliary in the α-benzylation of a series of esters.

(ii) The extension of the application of the previously developed imino lactone.

(iii) The application of CERIUS^2 molecular modelling package[84] to probe the origin of stereocontrol.



128a : R = CH_3
128b : R = CH_2SO_3Ph



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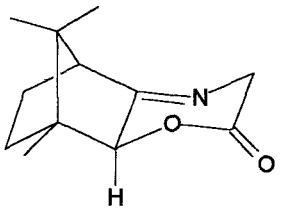
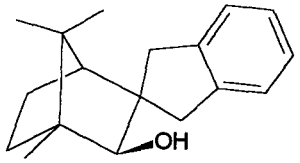


131



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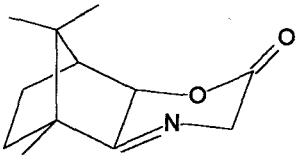
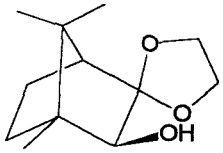
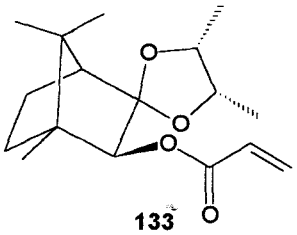


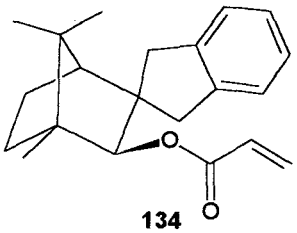
132



137



133



134

2. DISCUSSION

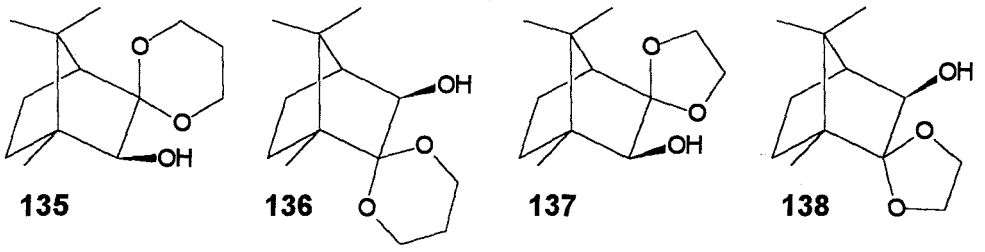
In the discussion which follows, attention will be given to: - the synthesis and benzylation of a series of novel camphor-derived esters (Section 2.1); and to the confirmation and extension of an earlier study [83] on the application of a camphor-derived glycine equivalent in the asymmetric synthesis of α-amino acids (Section 2.2).

2.1 Asymmetric α-Benzylation of Camphor-derived Esters

An important aspect of asymmetric enolate reactions relates to the presence of an attached chiral centre, which would render the two faces of the enolate diastereotopic.[85] Ground-breaking work in the early 1980's by Helmchen *et al.*[86, 87] revealed that esters attached to C(2) of a camphor skeleton having a bulky blocking group at C(3) could be alkylated with a high degree of stereoselectivity. The function of the blocking group is to increase order in the system, through non-bonded interactions and/or steric constraints, resulting in a restriction of flexibility without which chirality transfer is frequently minimal.[88]

This approach has been used in our research group by Ravindran [80] and Evans.[81] Ravindran, in particular, investigated the alkylation of a series of esters [89] prepared from each of the camphor-derived chiral auxiliaries **135**, **136**, and **137**. A design feature in these compounds was the introduction of a ketal moiety as a blocking group with the potential to participate in chelation of the enolate counterion.[36] Benzylation of carboxylic esters derived from these chiral alcohols was achieved with varying degrees of diastereocontrol (6 -58% d.e.), [89] the most efficient auxiliary proving to be the 3-hydroxy compound **136**. The 3-hydroxy compound **138** was required to complete this set of auxiliaries and, in the present study, the preparation of this alcohol and the benzylation of selected ester derivatives was investigated. The original three auxiliaries were accessed by $LiAlH_4$ reduction of the corresponding ketones which, in turn, were obtained by ketalisation of camphorquinone **139** (Scheme 24). The challenge was thus to obtain compound **138**, the regioisomer of **137**, and assess its value as a chiral auxiliary relative to its three predecessors (**135**, **136**, and **137**).

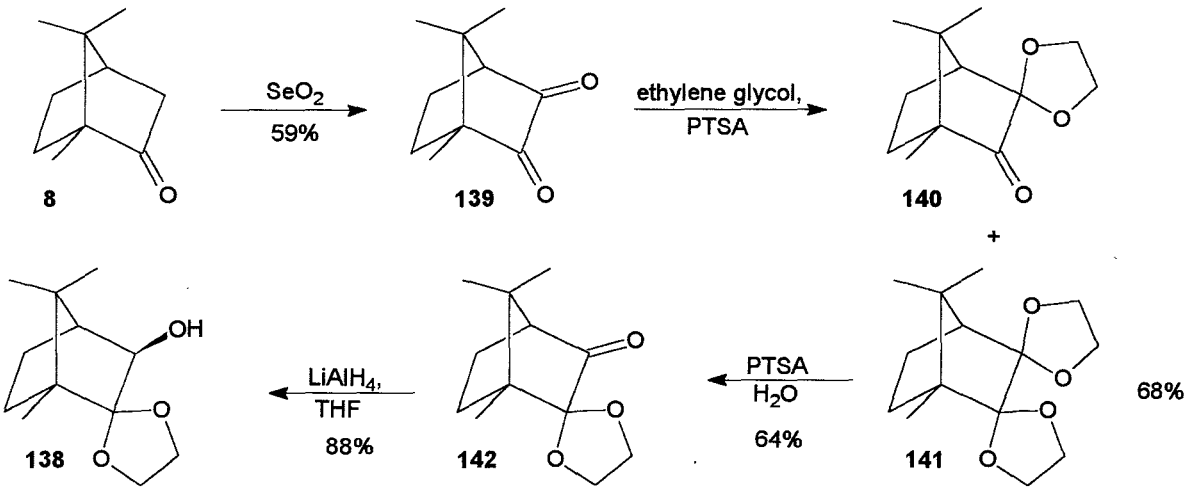
In Ravindran's study [89] it had been observed that the auxiliary displaying the greatest asymmetric induction was hydroxy ketal **136** which contains a six-membered dioxane ring at C(2) (58% d.e. for benzylation of the *t*-butylacetate ester). [89] The stereocontrol was attributed to buttressing of the flexible dioxane ring by the 10-methyl group and effective blocking of the *re*-face of the ester enolate by the buttressed dioxane ring. The dioxolane derivative **137** was the next most effective (47% d.e. for benzylation of the *t*-butylacetate ester), [89] the five membered ring providing protection of the *si*-face of the enolate even without the buttressing effect of the 10-methyl group. In contrast, the dioxane analogue **135** was the least effective (<17% d.e.), presumably due to the fact that the six-membered ring can adopt either of two chair conformations - one bending towards the enolate moiety, the other away from it. It was hoped that the five-membered cyclic ketal, when placed at C(2), would provide stereocontrol comparable with, if not better, than that observed in the α-benzylation of esters of the hydroxy ketal **136**.



135 **136** **137** **138**

2.1.1 Synthesis of Chiral Auxiliary 138

Many derivatives of camphor, functionalised at C(2) and C(3), have been used as chiral auxiliaries in the last two decades. [10] Functionalisation is readily achieved by selenium dioxide oxidation of (+)-camphor **8** to give camphorquinone **139** (Scheme 24) and, following the protocol developed by Ravindran[80] for the protection of the 3-carbonyl group, the diketal **141** was obtained as the minor product in 13% yield. However, by increasing the reaction time from one day to five days and using between five and ten equivalents of ethylene glycol, it became possible to produce the diketal **141** in up to 68% material yield. In experiments in which shorter reaction times were used (*e.g.* 12 hours), the diketal was produced in a much lower yield but, significantly, the desired camphorquinone monoketal **142** was detected; the concentration, however, was too low to make isolation viable. It thus seems that even when initial ketalisation involves the 2-carbonyl group, subsequent ketalisation of the less-hindered 3-carbonyl group proceeds readily to give the diketal **141**.



Scheme 24: Synthesis of chiral auxiliary **138.**

The reversibility of the ketalisation reactions necessitated the use of a Dean-Stark apparatus to collect the azeotropically distilled water and so drive the equilibrium towards the product. Interestingly, the reversibility also provided the means by which the required monoketal **142** was obtained. Removal of the ketal group at C(3) was effected by boiling an aqueous solution of the diketal **141** under reflux with an equimolar quantity of *p*-toluenesulfonic acid. Just as the first position to be protected is the less hindered C(3), so it is also the first position to be deprotected and, in fact, the monoketal **142** was the only product isolated. Stereoselective reduction of the monoketal **142** with $LiAlH_4$ gave the required 3-*exo*-hydroxy ketal **138** in very good yield (88%). The 3-*exo*-hydroxy ketal **138** was characterised by NMR, IR and mass spectroscopic methods; Figure 4 illustrates the assignment of the proton signals in the ^1H NMR spectrum. A major difference between the two regioisomers **137** and **138** is the proximity of the hydroxyl group in the latter to the 4-H nucleus. However, the steric constraints of the bicyclic skeleton result in an almost perpendicular relationship between the two nuclei which, in turn, gives rise to a coupling constant which is too small to be resolved at 400 MHz field. It is therefore difficult to differentiate between **137** and **138** on the basis of the ^1H NMR data alone. In the COSY spectrum (Figure 5), however, it is possible to detect this very small coupling. The assignment was confirmed by a comparison of the calculated[90] and experimental ^{13}C NMR spectra. The calculated values (Table 4, columns I and II) differ significantly from the experimental values (columns IV and V) in both **137** and **138**; however, analysis of the change in chemical shift for corresponding nuclei (columns III and VI) show the same pattern of change for both the experimental and calculated spectra.

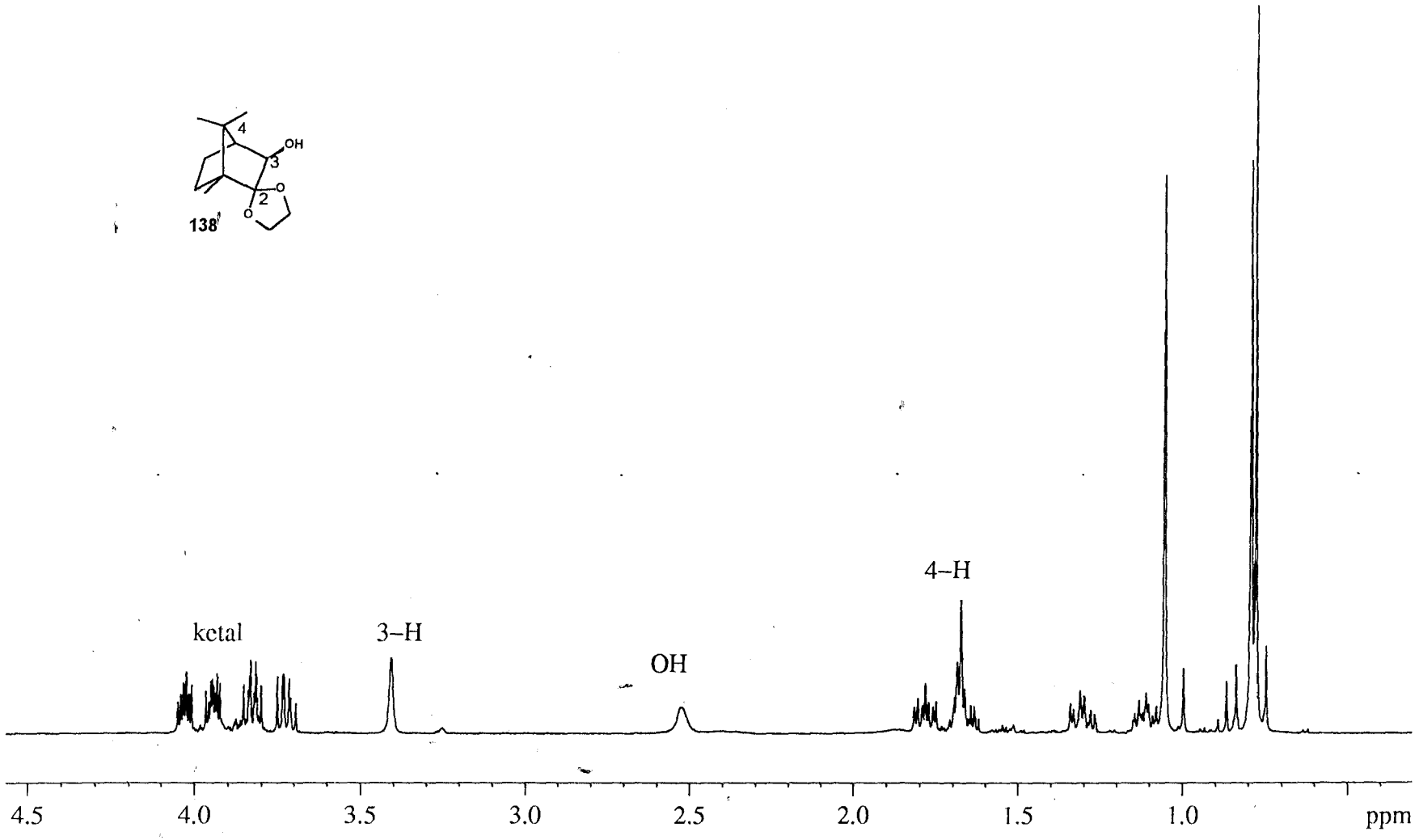


Figure 4. 400 MHz ^{1}H NMR spectrum of the auxiliary **138** in $CDCl_3$.

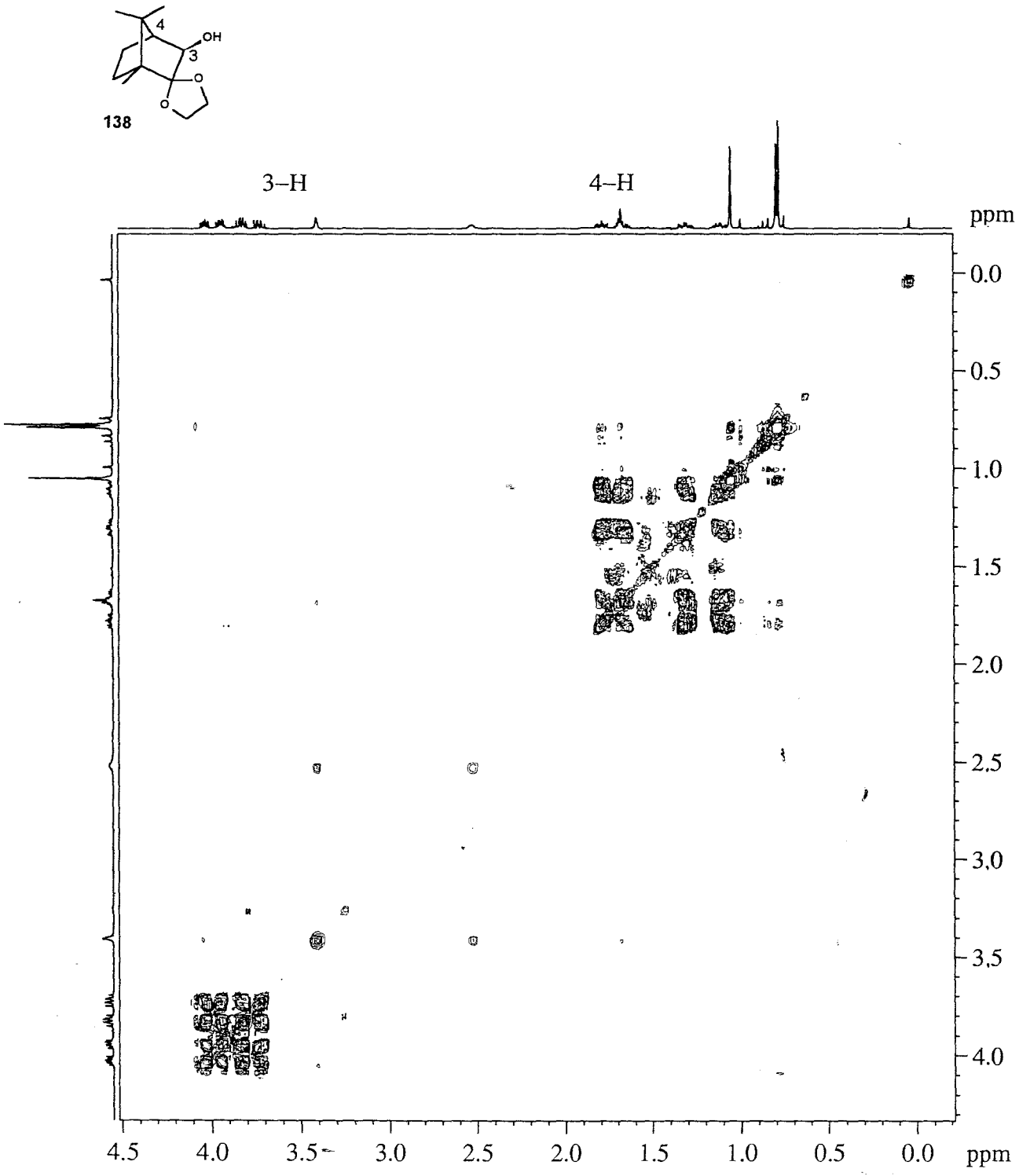


Figure 5. COSY spectrum of the chiral auxiliary **138** in $CDCl_3$, showing coupling between the 4-H and the 3-*endo*-H nuclei.

Table 4. Comparison of calculated[90] and experimental ^{13}C NMR data for the regioisomeric hydroxy compounds **137** and **138**.

	Calculated values			Experimental values		
	I (138)	**II (137)**	**III (Δδ)**	**IV (138)**	**V (137)[a]**	**VI (Δδ)**
C-1	52.9	44.2	8.7	51.8	49.6	2.2
C-2	121.9	112.0[b]	9.9	116.9	115.2[b]	1.7
C-3	73.5	83.9[b]	-10.4	83.0	85.5[b]	-2.5
C-4	39.6	48.8	-9.2	51.6	52.6	-1.0
C-5	16.7	10.8	5.9	24.5	21.2	3.3
C-6	21.2	27.1	-5.9	29.1	33.4	-4.3
C-7	32.1	32.1	0	47.7	47.5	0.2
C-8	20.0	20.0	0	21.1	21.0	0.1
C-9	20.0	20.0	0	21.6	20.7	0.9
C-10	7.6	13.5	-5.9	9.3	10.8	-1.5
C-ketal	71.8	71.5	0.3	63.9	63.5	0.4
C-ketal	71.8	71.5	0.3	66.5	65.6	0.9

[a] For synthesis of **137** refer to Section 2.2.1.

[b] To simplify analysis, the numbering of C(2) and C(3) have been reversed for compound **137**.

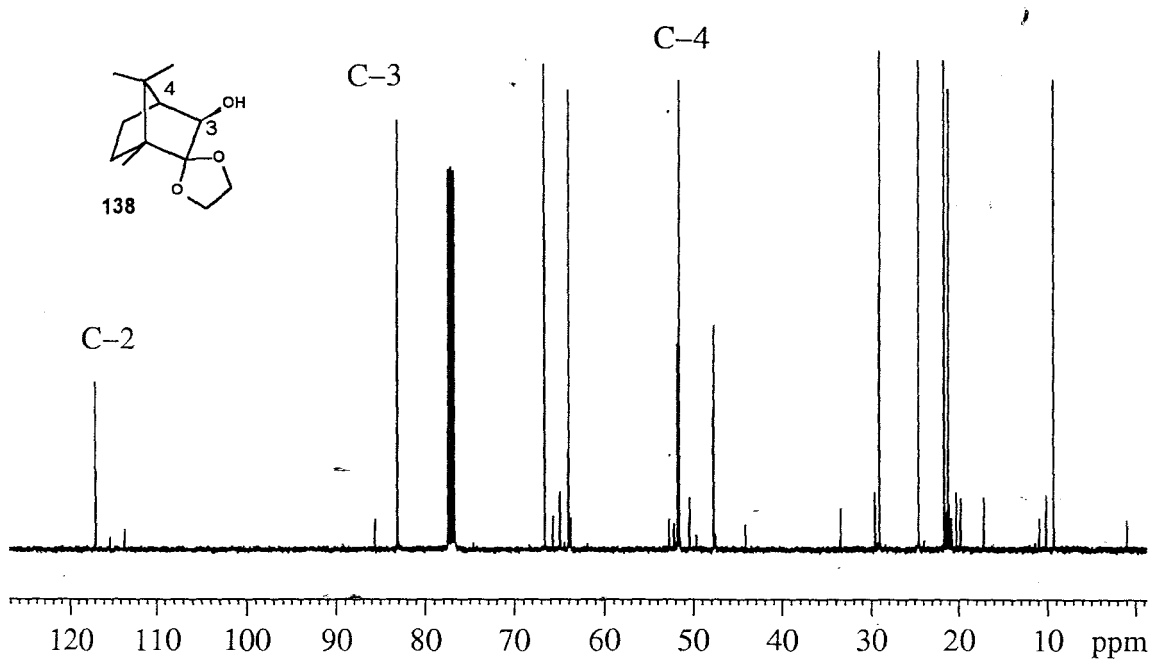
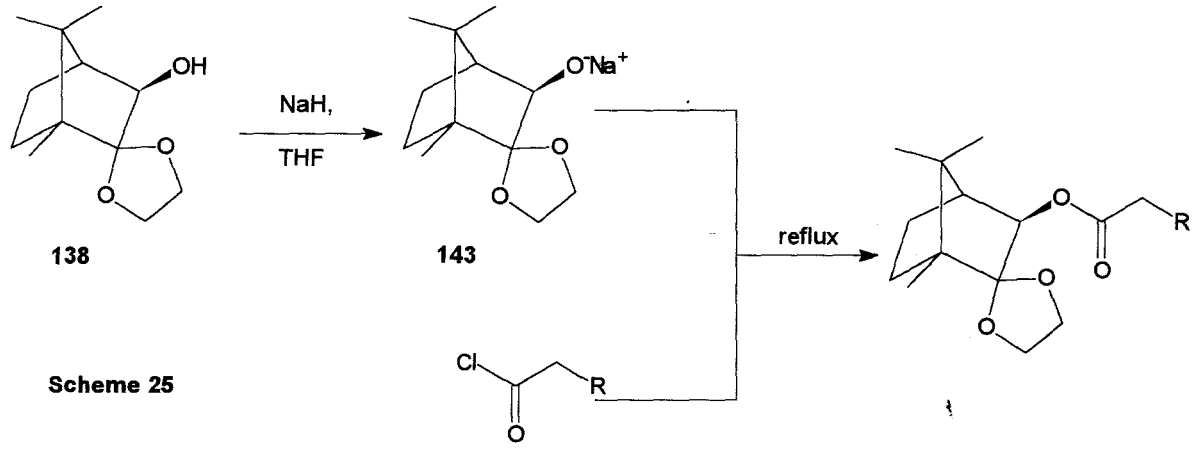


Figure 6. 100 MHz ^{13}C NMR spectrum of the chiral auxiliary **138** in $CDCl_3$.

2.1.2 α-Benzylation of Camphor-derived Ester Substrates

The target esters were obtained by reacting the sodium hydride-generated alkoxide **143** with the corresponding acid chlorides **144** - **149** (Scheme 25), which were used as supplied by Aldrich. The auxiliary **138** was used as the limiting reagent in all cases since it is the more expensive to produce, and more easily weighed (thus giving an accurate assessment of the yield). In addition, the acids (produced by hydrolysis of excess acid chloride during work-up) are more easily removed from the crude reaction mixture by washing with $NaHCO_3$ than excess auxiliary would have been. The target esters **150** - **155** were selected to illustrate the effect of the substituents (R) [CH_3; CH_3CH_2; $(CH_3)_2CH$; $(CH_3)_3C$;[91] Ph and OPh] on asymmetric induction during subsequent α-benzylation.



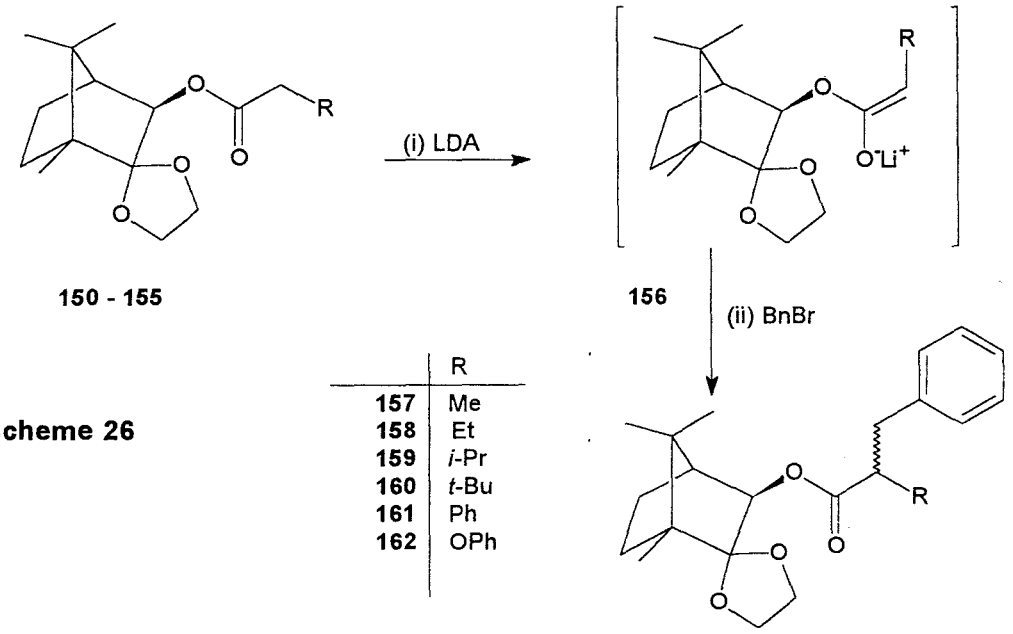
138 **143**

Scheme 25

	R
144	Me
145	Et
146	*i*-Pr
147	*t*-Bu
148	Ph
149	OPh

	R	Yield/%
150	Me	63
151	Et	60
152	*i*-Pr	53
153	*t*-Bu	80
154	Ph	27
155	OPh	39

The enolate intermediates **156** were generated at -78°C using the sterically hindered, non-nucleophilic base, LDA (Scheme 26), which is the most widely used kinetically selective base.[92] After one hour, enolization was deemed to be complete and the enolate was quenched with benzyl bromide. While the material yields for these reactions were moderate (Table 4) the stereocontrol achieved ranged from moderate (*ca.* 60% d.e.) to very good (>80% d.e.). The diastereomeric excesses (% d.e.) were calculated from the relative integrals of the signals corresponding to the



150 - 155 **156**

	R
157	Me
158	Et
159	*i*-Pr
160	*t*-Bu
161	Ph
162	OPh

Scheme 26

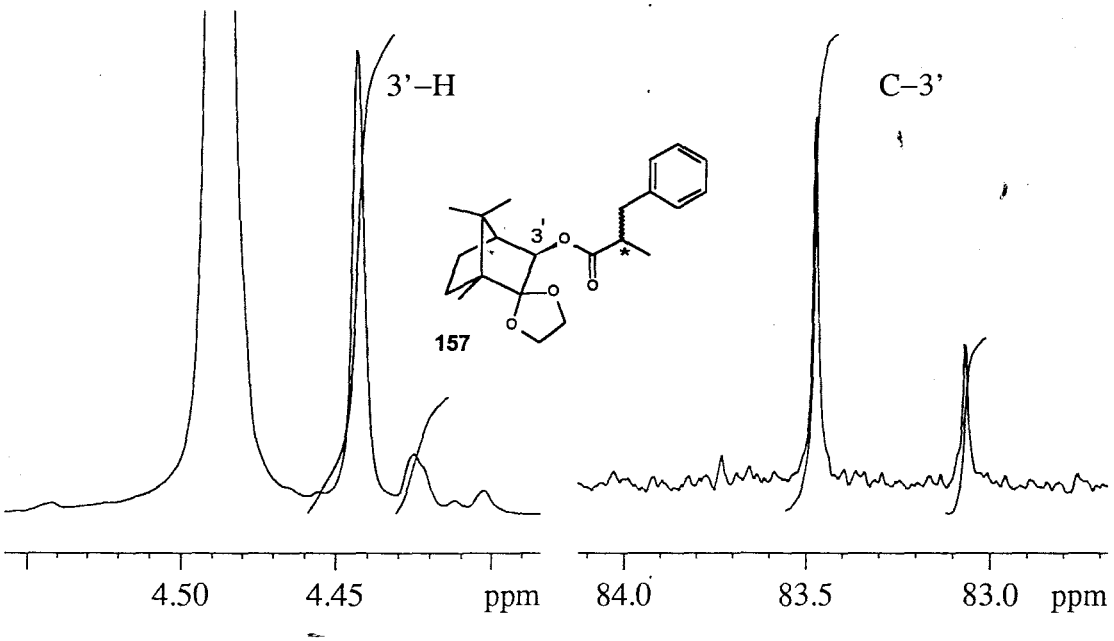
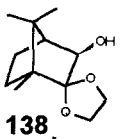
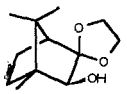


Figure 7. Partial 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra showing the 3'-H and C-3' signals for the diastereomers **157**.

3'-H nuclei in the ^{1}H NMR spectra (Figure 7) as well as from the relative integrals of the signals corresponding to the C-3' nuclei in the ^{13}C NMR spectra (assuming that the T_1 relaxation times for diastereomers are the same thus allowing direct comparison of ^{13}C signal intensities [93]). The lower estimates of the stereocontrol obtained using ^{13}C NMR data are attributed to the effect of baseline noise on the signals corresponding to the minor stereoisomer. However, use of the ^{13}C NMR data was necessary in the case of ester **162**, since resolution of the 3'-H signals was not possible in this case.

From a comparison of the diastereoselectivities for the corresponding products obtained using the regioisomeric auxiliary **137** [94] (Table 5) with those obtained using auxiliary **138**, it appears that the initial hypothesis was correct, the latter products exhibiting significantly higher optical purity. Due to the buttressing effect of the 10-methyl group on the ketal ring, as well as the inherent rigidity of the five-membered ring, the protection of the *re*-face in the enolates **156** is more effective than for the corresponding systems using auxiliary **137**. Somewhat surprisingly, increasing the steric bulk of the R substituent (**R** = Me → Et → Pr^i → Bu^t; Scheme 26) does not appear to influence stereocontrol significantly. While changing the substituents from methyl **157** to ethyl **158** results in an increase of 23% in the stereocontrol, the trend is not sustained with the introduction of an isopropyl (**159**) or *tert*-butyl (**160**) group.

Table 5. Data for the asymmetric α-benzylation of esters derived from chiral auxiliaries **137** and **138**.

	 **138**			 **137**
R	Product	Yield/%[a]	%d.e.[b]	%d.e.[c]	%d.e.[d]
Me	**157**	39	59.5	51	16
Et	**158**	46	83.0	54	28
i-Pr	**159**	46	82.4	75	23
t-Bu	**160**	47	59.3	59	47
Ph	**161**	44	59.5	59	38
OPh	**162**	48	-[e]	43	-

[a] Product yield was determined after preliminary purification, prior to HPLC.
[b] Diastereomeric excess calculated from the integrals of the 3'-H signals in the ^{1}H NMR spectra.
[c] Diastereomeric excess calculated from the integrals of the C-3' signals in the ^{13}C NMR spectra.
[d] For corresponding products using the auxiliary **137**.
[e] Resolution of the 3'-H signals was not possible in this case.

HPLC analysis of the α-benzylated products revealed that the diastereomers typically exhibited very similar retention times [as illustrated by the poorly resolved peaks in the chromatogram (Figure 8)], thus precluding their separation by this means.

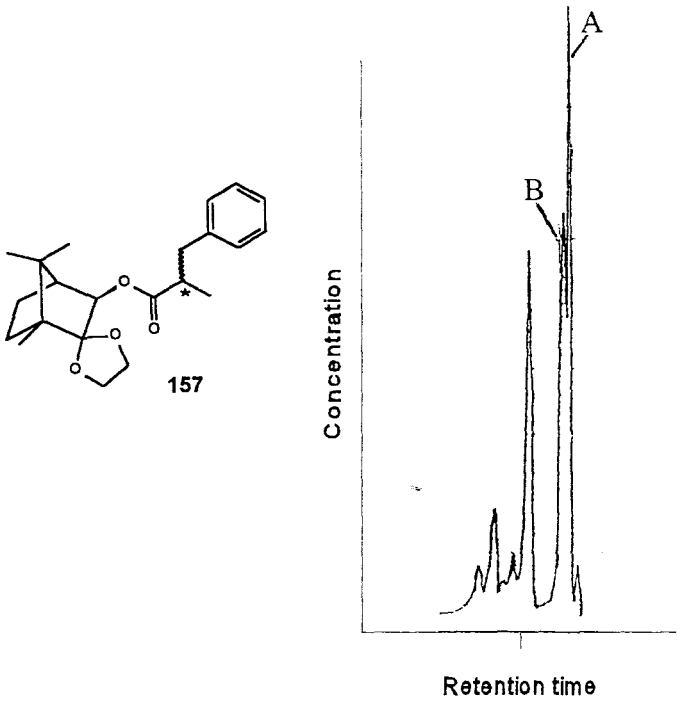


Figure 8. Representative HPLC trace showing the diastereomeric components A and B of the benzylated product **157**; elution with ethyl acetate - hexane (5:95).

Interestingly, although benzylation of the phenoxyacetic ester of **137** was found to be impossible in a previous study,[94] α-benzylation of the C(3)-ester analogue **155** was achieved in the present investigation. The formation of the α-benzylated product **162** is clearly evident from a comparison of the ^{1}H NMR spectra of the substrate and product (Figure 9), the most notable difference being the replacement of the 2-methylene singlet at 4.60 ppm in the ^{1}H NMR spectrum of the substrate **155** by two multiplets at 4.79 ppm and 4.84 ppm (each signal corresponding to one diastereomer) in the spectrum of the product **162**. The stereocontrol achieved in this case (43% d.e.) is somewhat lower than for the phenyl analogue (59% d.e.). It is not clear whether this reflects an electronic effect due to the oxygen spacer or the greater distance of the phenyl ring from the reactive site.

When addressing the issue of enolate π-facial selectivity in reactions with electrophiles, enolate geometry as well as steric and stereoelectronic effects in the transition states must be considered. Enolate geometry is, of course, of primary concern in reactions of acyclic enolates and, in this regard, a study of the enolate esters of the chiral alcohol **132** revealed a 98:2 preponderance of the *E*-enolate.[95] In the systems examined here, a preference for the *E*-enolate is also presumed (Figure 10a). In the absence of chelation effects, it may be expected that:-

(i) the planar enolate moiety lies quasi-parallel to the C(2)-ketal group;

(ii) the enolate oxygen is *endo*-oriented to obviate unfavourable steric interaction with the 9-methyl group; and

(iii) as a consequence, electrophilic attack is favoured "from the back" at the less sterically hindered *si*-face of the enolate.

However, when using LDA, the lithium cation may coordinate with the oxygen atoms of the ketal moiety,resulting in a quasi-perpendicular orientation of the enolate and ketal fragments (Figure 10c). Under these circumstances, attack at the *si*-face is still expected, but from the less hindered *endo*-face (*i.e.* "from the bottom"). This possibility is supported by the reversal in stereochemistry observed when a non-chelating xylyl group was used as a blocking group at C(3) instead of a dioxane blocking group,[81] and when a xylyl group was substituted for a thioketal moiety.[95] These observations may be rationalised by assuming that the polar *O*-metal bond points *away* from the hydrophobic xylyl moiety but *towards* the ketal oxygen, thus exposing opposite faces of the enolate to electrophilic attack. Helmchen *et al.*[95] have also encountered a reversal of stereochemistry in the α-benzylation of chiral propanoate systems on adding hexamethyl-phosphorous triamide (HMPT), which is known to be involved in chelation with the counterion of the enolate;[96] HMPT is also presumed to affect the relative preference for the *E*- or *Z*-lithium enolates. These observations demonstrate the importance of groups capable of shielding one face of the enolate as well as complexing with the counterion, since high diastereoselectivities can be achieved due to the increased conformational rigidity.[97]

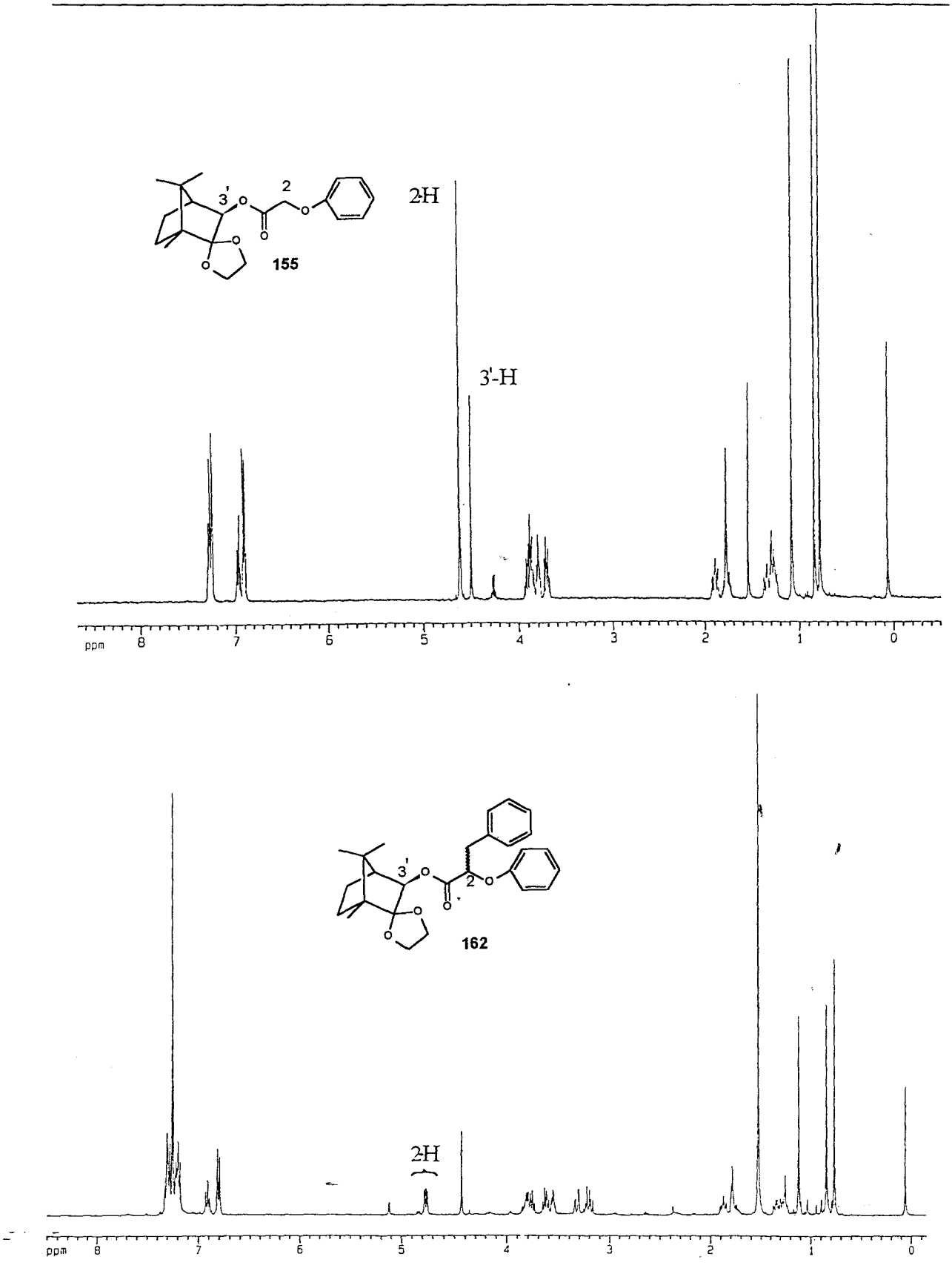


Figure 9: 400 MHz ^{1}H NMR spectra of the ester **155** and the α-benzylated product **162** in $CDCl_3$

In order to gain a better understanding of this system, molecular modelling studies were carried out under two sets of conditions. In the first, the geometry of the enolate was constrained in a quasi-parallel arrangement with the ketal ring at C-2 (Figure 10a,b). In this arrangement, the *re*-face of the enolate is partially shielded by the ketal blocking group and attack by the electrophile is preferentially from the *si*-face. When the energy minimization is carried out without geometric constraints, an interesting situation arises; the lithium cation appears to coordinate with the *exo*-oxygen of the ketal as well as with the ester (alkoxy) and the enolate oxygens (Figure 10c, d). Measurements of the corresponding Li-O distances are detailed in Table 5, and compared with the Li-O bond length found in a crystalline lithium diethyl ether complex.[98] The very small difference between the solid-state Li-O bond length and the calculated Li-O separation for the ketal-*exo*-oxygen suggests that this interaction could be significant. The separation calculated for the enolate oxygen is shorter than the solid-state Li-O bond since it is, in fact, a covalent bond. While the orientation of the ester moiety is quasi-perpendicular to the ketal ring (Figure 10c,d) the *si*-face is still exposed to preferential attack, but now due to protection of the *re*-face by the 9-methyl group. In addition to the good stereocontrol achieved in this investigation, it has also been possible to gain a better understanding of the mechanism of stereocontrol.

Table 5. Comparison of experimental and calculated Li-O distances in the $Li(OEt_2)_2$ complex and the enolate **160**.

Li-O interaction	Li-O $[Li(OEt_2)_2]$[98]	Li-ketal-*exo*-*O*	Li-alkoxy-*O*	Li-enolate-*O*
Separation/Å	1.901	1.931	2.049	1.872

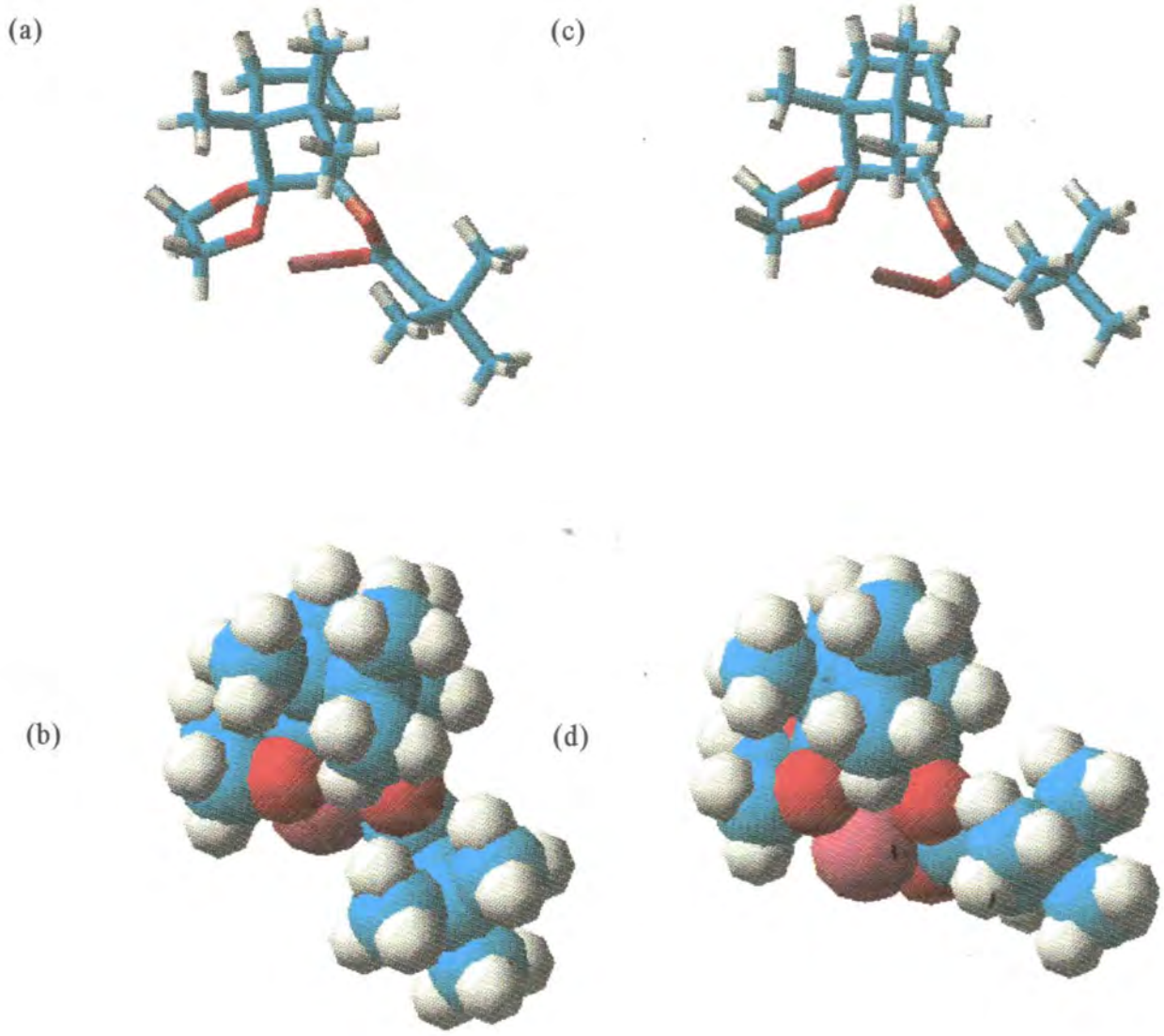


Figure 10. Computer models of the lithium enolate structure of ester **153** showing:- (a) stick; and (b) spacefilling structures for the constrained model; and (c) stick; and (d) spacefilling structures modelled without constraints.

2.2 Asymmetric Synthesis of α-Alkyl-α-Amino Acids

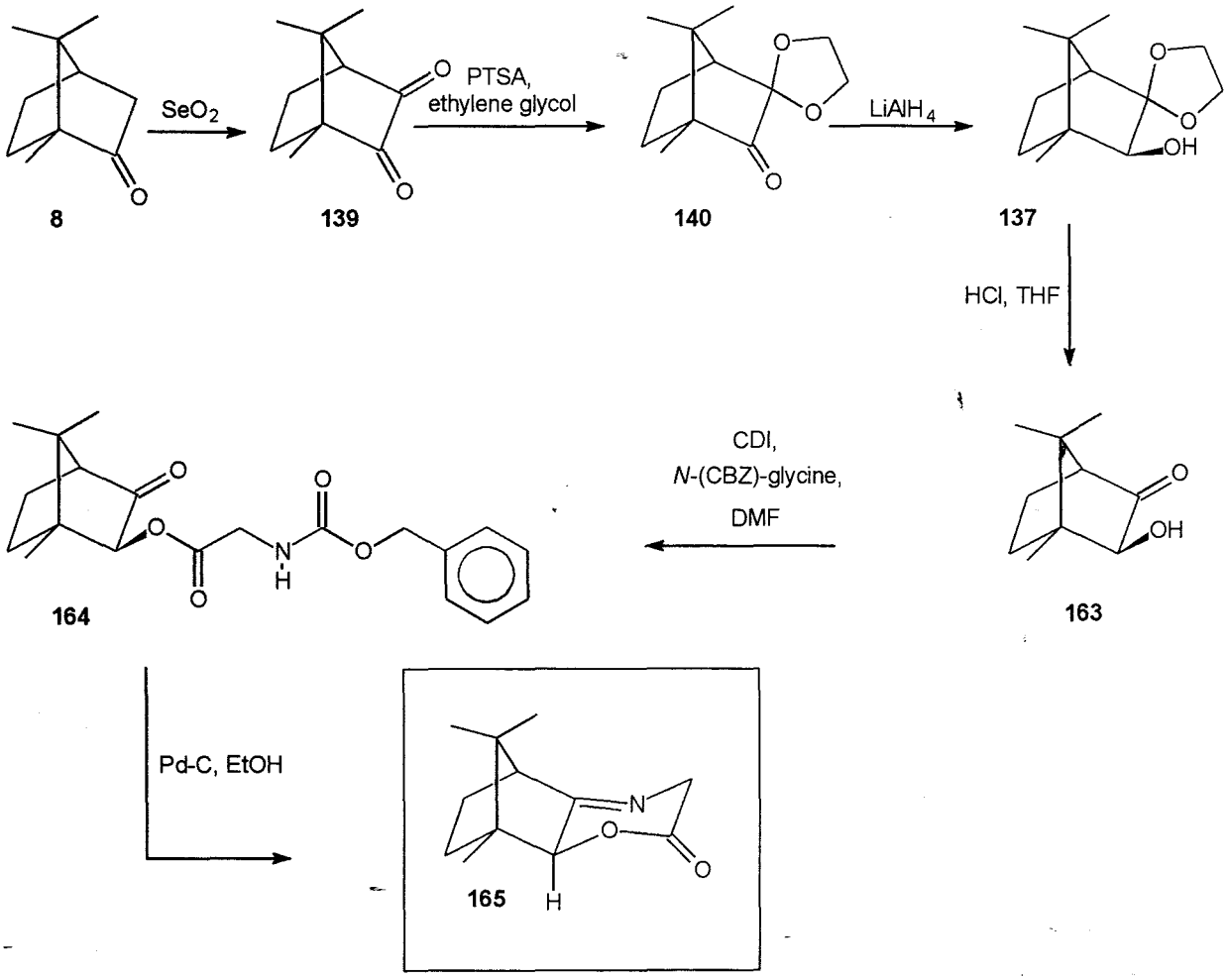
Of particular importance in the synthesis of chiral α-amino acids are those methods which employ glycine derivatives attached to simple chiral auxiliaries.[63] While many acyclic systems have been used with great success, as discussed previously, the use of cyclic substrates greatly simplifies the problems of stereocontrol in asymmetric reactions. Not only is the geometry of the enolate fixed, but there is no freedom of rotation for the prochiral fragment.

2.2.1 Synthesis of 3-Imino Lactone Precursor

Access to camphor-derived imino lactones with considerable potential as platforms for the synthesis of chiral α-amino acids has been developed in our laboratories. In the present study, attention has been given to confirming and extending these earlier results. The 3-imino lactone **165** {10,11,11-trimethyl-2-oxa-5-azatricyclo[4.4.$0^{1,6}$.$1^{7,10}$]undec-5-en-2-one} was synthesised in six steps from (+)-camphor **8** as outlined in Scheme 27. Functionality was introduced at C(3) by selenium dioxide oxidation of (+)-camphor **8**, and protection of the resulting carbonyl group was effected by acid catalysed ketalisation with ethylene glycol to afford the monoketal **140** as the major product. Reduction using $LiAlH_4$ gave the 2-*exo*-alcohol **137**, which was then deprotected by refluxing with aqueous hydrochloric acid in THF to afford the crystalline auxiliary, 2-*exo*-hydroxybornan-3-one **163**. The signal assignments for the ^1H and ^{13}C NMR spectra of the chiral auxiliary **163** are shown in Figure 11; of particular significance are the signals corresponding to the 2- and 4-H nuclei which show significant shifts compared to the ketal-protected precursor **137**. The 2-H nucleus gives rise to a signal in the ^1H NMR spectrum which has shifted from δ 3.22 (in the precursor **137**) to 3.50 ppm (in the product), and the 4-H nucleus to a signal which has shifted from δ 1.61 to 2.16 ppm. These downfield shifts, due to the change in functional group at C-3 from ketal to carbonyl, are similarly reflected in the ^{13}C NMR spectrum (Figure 11b) with the appearance of a signal at δ 171 ppm due to the 3-carbonyl carbon and the signal at δ 58.5 ppm corresponding to the deshielded C-4 nucleus.

N-carbobenzyloxyglycine [*N*-(CBZ)-glycine] was attached to the auxiliary **163** using the coupling agent CDI, to give the *N*-(CBZ)-ester **164** in 61% material yield. This ester was characterised by

1-D and 2-D NMR techniques. In the ^{1}H NMR spectrum of **164** (Figure 12), the diastereotopic glycine 2'-methylene protons resonate as a multiplet at δ 4.04 ppm, reflecting the chiral environment; the benzylic methylene protons, however, resonate as a singlet at δ 5.11 ppm, since they are distant from, and thus unaffected by, the chiral auxiliary. Hydrogenolysis of the glycine ester **164** in ethanol over 10% palladium on carbon effected removal of the *N*-CBZ protecting group, which was followed by spontaneous cyclisation to give the 3-imino lactone **165** in 43% yield. The ^{1}H NMR signals were unambiguously assigned (as shown in Figure 13), by comparison with previous studies. Interestingly, the diastereotopic lactone methylene protons were clearly separated (resonating at δ 3.84 and 4.43 ppm) as a result of the different electronic environments experienced on the *endo*- and *exo*-faces of the chiral imino lactone. The 2-H nucleus is strongly deshielded by the adjacent lactone group and, as a result, resonates at δ 4.23 ppm.



Scheme 27: Synthesis of 3-imino lactone **165**.

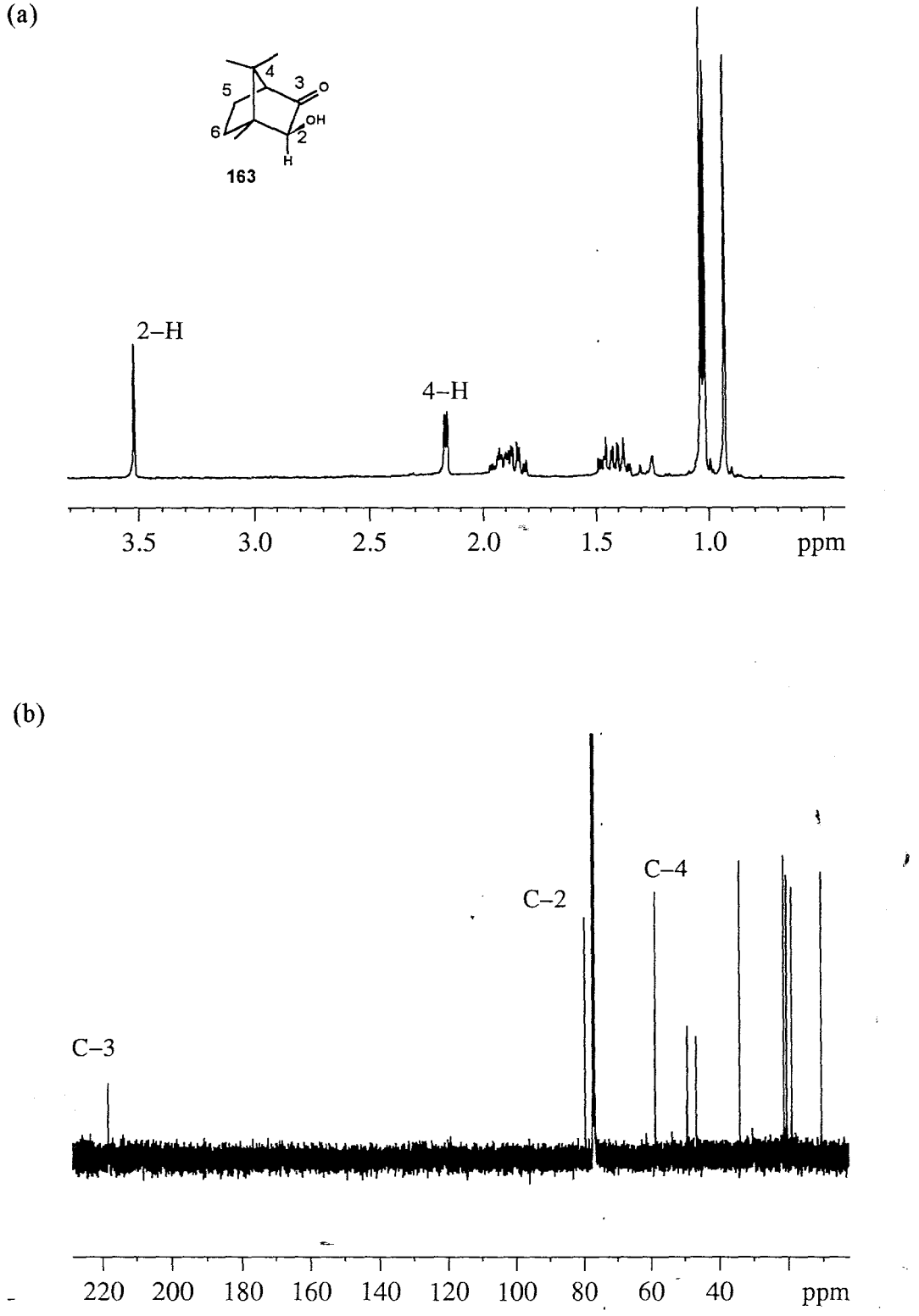


Figure 11. (a) 400 MHz ^{1}H-NMR and (b) 100 MHz ^{13}C-NMR spectra of 2-*exo*-hydroxy-3-bornanone **163** in $CDCl_3$.

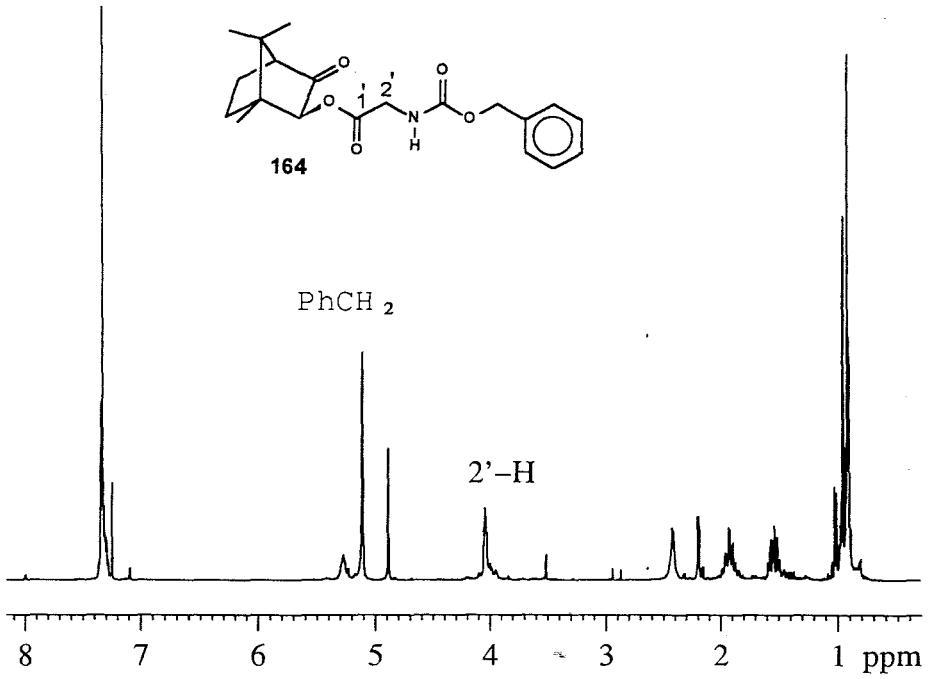


Figure 12. ^{1}H NMR spectrum of the *N*-(CBZ)-glycine ester **164** in $CDCl_3$.

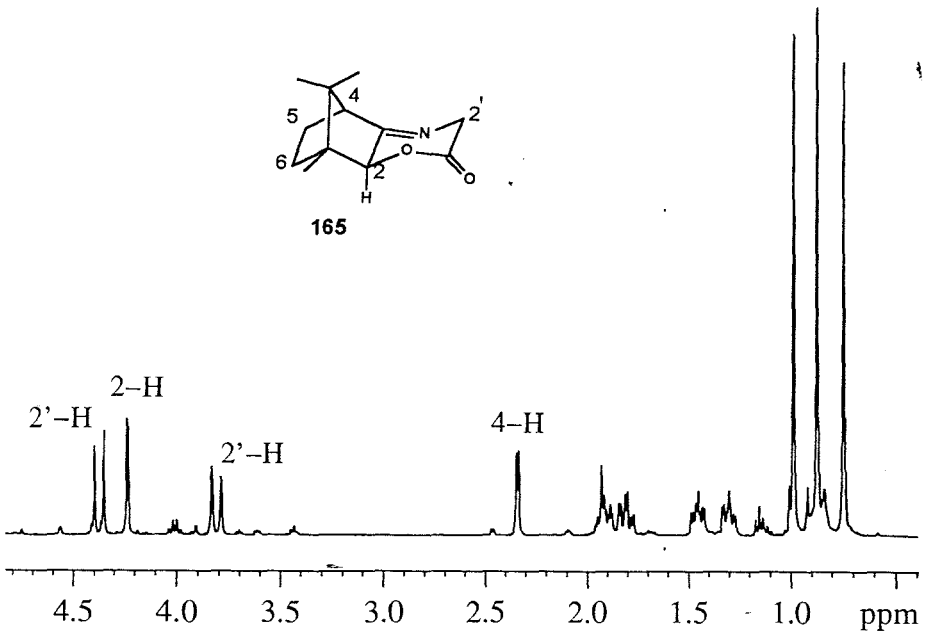
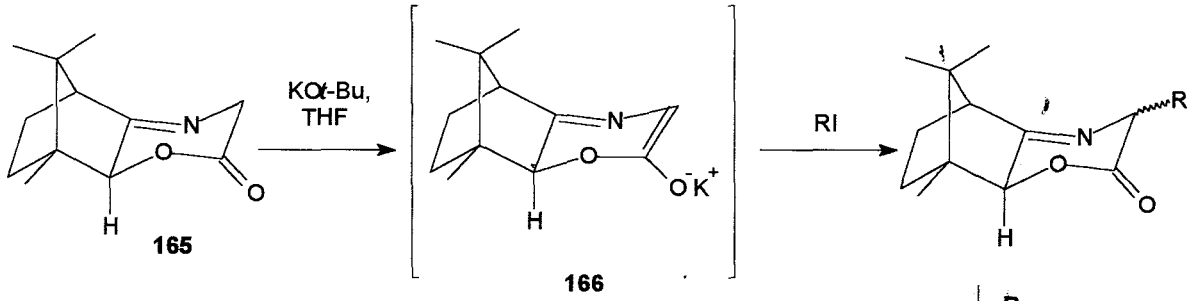


Figure 13. ^{1}H NMR spectrum of 3-imino lactone **165** in $CDCl_3$.

2.2.2 Alkylation studies

The next phase involved preparation and alkylation of the 3-imino lactone enolate **166** (Scheme 28). El Achqar *et al.*[99] had previously identified KOBu^t as a suitable base for the deprotonation of an α-pinene-derived imino lactone and this base was successfully used by Matjila;[83] consequently, a similar protocol was followed in the present study. Thus, the enolate **166** was formed by treating the imino lactone **165** with KOBu^t in THF under anhydrous conditions at -78°C (Scheme 28). After a delay of 45 minutes to ensure complete enolisation, a dilute solution of the alkyl iodide in dry THF was added. The low temperature was maintained for a further three hours before the mixture was allowed to warm to room temperature. ^{1}H NMR analysis of the crude reaction mixtures permitted the determination of the stereocontrol in each reaction, comparison of the 2-H signals for the diastereomeric compounds (illustrated for product **167** in Figure 14) affording the relative proportions of the *endo*- and *exo*-products in each case. The alkylation was achieved using three classes of alkyl iodides, *viz.*, primary alkyl iodides; secondary alkyl iodides; and allyl iodide. The results of these asymmetric alkylation reactions are summarised in Tables 6 and 7.



165 **166**

Scheme 28

	R
167	Me
168	Et
169	Pr
170	Bu
171	$CH_3(CH_2)_4$
172	$CH_3(CH_2)_5$
173	*i*-Pr
174	*sec*-Bu
175	CH_2=$CHCH_2$

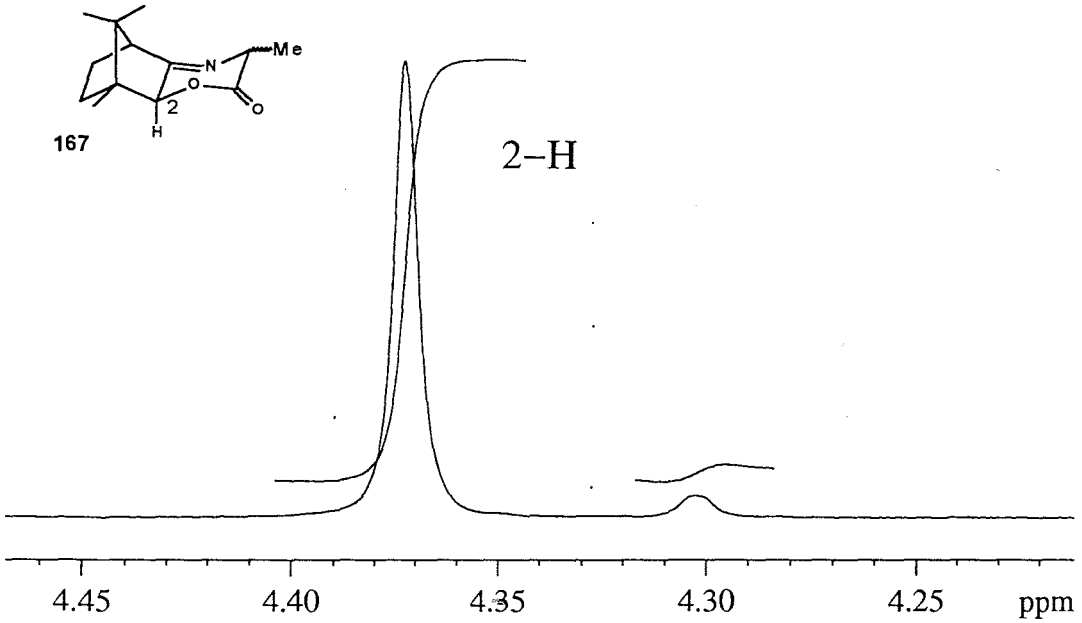


Figure 14. Partial 400 MHz ^{1}H NMR spectrum of the alkylated product **167**, showing integration of peaks corresponding to the diastereomeric components.

2.2.2.1 Reactions with primary alkyl iodides

The potassium enolate **166** was reacted with six primary alkyl iodides, RI [R = Me, Et, Pr, Bu, $CH_3(CH_2)_4$ and $CH_3(CH_2)_5$; Scheme 28]; the material yields and diastereoselectivities are summarised in Table 6. The material yields are typically good, ranging from 54 - 87%, and are comparable with those obtained by Matjila.[83] Somewhat surprisingly, however, while excellent stereocontrol was observed for R = Me (89% d.e.; entry 1), the level of stereocontrol appeared to decrease as the length of the alkyl group was increased, reaching a minimum for R = Bu (54% d.e.; entry 4). This trend is opposite to that reported by Matjila [83] (see Table 6) and, at first sight, difficult to rationalise. During the course of our investigation, however, it became apparent that diastereocontrol is affected adversely by the age of the imino lactone precursor **165**. This is well illustrated by a comparison of the ^{13}C NMR spectra of the α-butylated imino lactone **170** (Figure 15b) with those of the 3-imino lactone **165** and the ester **164** (Figures 15c and a respectively). Particular attention is drawn to the signals corresponding to carbons 2, 3, and 4 for each system, which are indicated as A/A', B/B', and C/C' respectively. The signals indicated as B and B' in

Figure 15b correspond to similar signals in Figure 15a and c respectively, similarly for the signal indicated as A/A' and C/C'. The significance of this comparison is that signals A, B and C correspond to an open-chain structure, signal B reflecting a carbonyl at C-3, while the signals A', B' and C' correspond to a closed-chain structure where signal B' reflects an imine group at C-3. These data suggest a degradation pathway involving fission of the imine bond and consequent opening of the imino lactone ring. This would inevitably affect the stereocontrol achieved in the alkylation reactions, and the lower stereoselectivities achieved in Table 6 may thus be due to partial degradation of the imino lactone precursor **165**. This hypothesis is further supported by the recovery of a small proportion of the chiral auxiliary **163** during HPLC purification of the crude alkylation products. It is proposed that prompt use of the imino lactone precursor would obviate this problem. On the positive side, the ease with which the imino lactone **165** degrades suggests that isolation of the α-alkylated amino acid and recovery of the auxiliary by hydrolysis of the α-imino lactone should be a trivial matter. An experiment carried out on the α-pentylated imino lactone **171** by Matjila[83] has shown that the α-amino acid and the auxiliary are, indeed, recoverable quantitatively and without racemisation following acid hydrolysis. In all cases, alkylation is expected to be favoured at the less-hindered, *endo*-face of the enolate **166**, resulting in preferential formation of the corresponding (*R*)-α-amino acids.

Table 6. Data for the alkylation of the potassium enolate **166** using primary alkyl iodides RI (see Scheme 28).

Entry	Product	R	Yield[a] /%	% d.e.[b]	% d.e.[c]
1	**167**	Me	84	89	43
2	**168**	Et	72	69	60
3	**169**	Pr	69	61	70
4	**170**	Bu	75	54	>99
5	**171**	$CH_3(CH_2)_4$	73	60	>99
6	**172**	$CH_3(CH_2)_5$	83	81	>99

[a] The reactions in this series were essentially complete, thus the crude yields were considered an adequate assessment of the chemical transformation and are reported here.
[b] Determined from ^1H NMR spectroscopy.
[c] Reported by Matjila (see ref. 83).

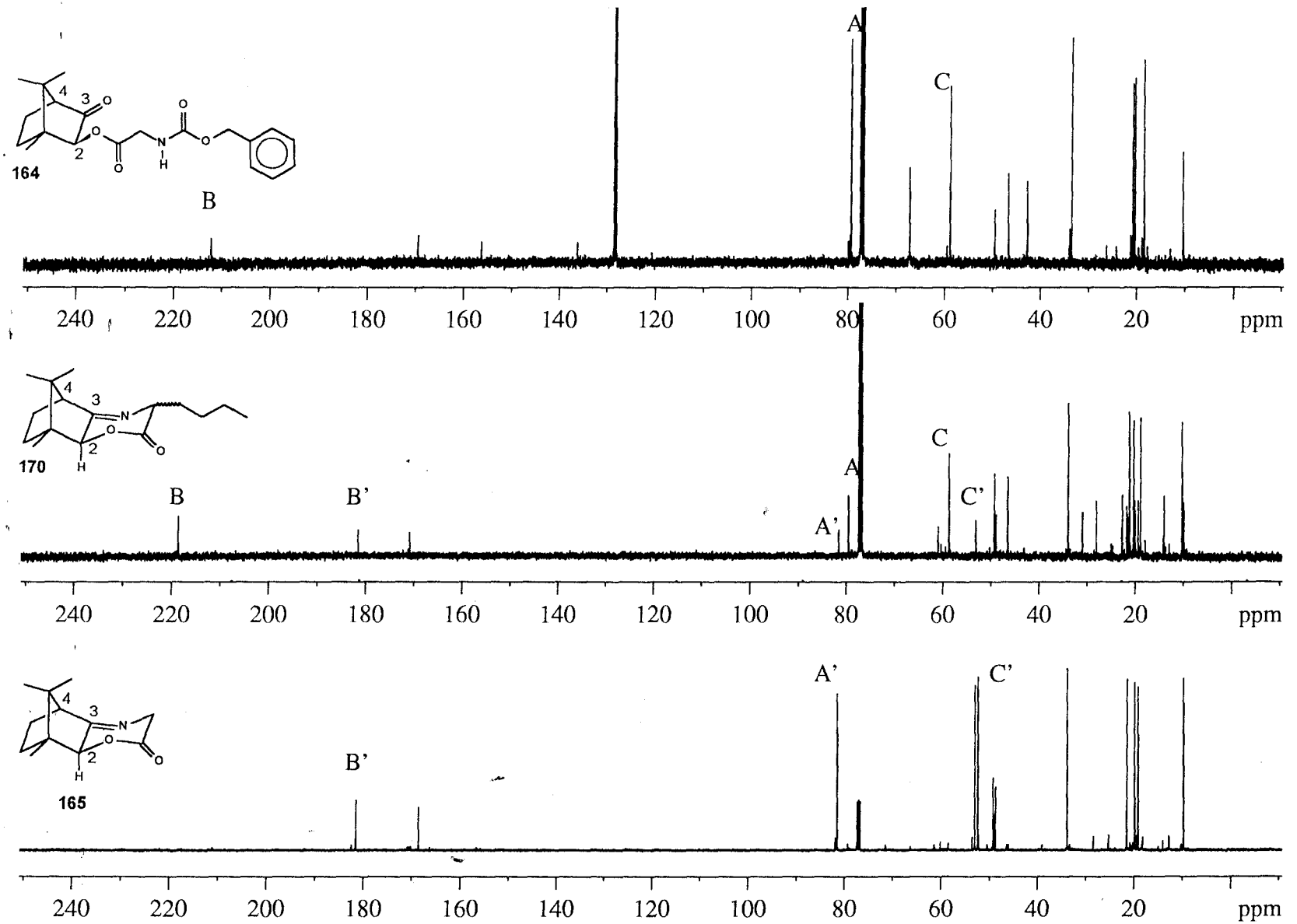


Figure 15. Comparison of 100 MHz ^{13}C NMR spectra of **164**, **170** and **165** respectively (in $CDCl_3$). A/A', B/B' and C/C' indicating C(2), C(3) and C(4) respectively.

2.2.2.2 Reactions with secondary alkyl iodides

In a further extension of the previous work, two secondary alkyl iodides were included in the series of alkylating agents, *viz.*, isopropyl iodide and *sec*-butyl iodide. Although secondary alkyl iodides are typically less reactive than primary alkyl iodides, the alkylation proceeded smoothly, albeit in lower yields, to give the corresponding α-alkyl imino lactones **173** and **174** (Scheme 28). These compounds are of particular interest since their hydrolysis products would be the enantiomers of the natural amino acids, (*S*)-isoleucine and (*S*)-valine, respectively. The stereo-control achieved in these reactions is gratifying (Table 7) and indicates that further investigation is warranted. The novel α-alkyl 3-imino lactones **173** and **174** were characterised by 1-D and 2-D NMR techniques. The COSY spectrum of the *sec*-butyl 3-imino lactone **174** (shown in Figure 16) reveals the important correlations between 2'-H and 3'-H nuclei. The doublet at δ 4.20 ppm has been assigned to 2'-H, the coupling to 3'-H, which resonates at δ 2.26 ppm, being clearly evident. The HETCOR spectrum (Figure 17) made it possible to correctly assign the signal at δ 77.2 ppm, which was masked by the solvent signal at δ 77.0 ppm, to C-2, and to differentiate it from the signal at δ 74.8 ppm corresponding to C-2'.

Table 7. Data for the alkylation of enolate **166** using secondary alkyl iodides and allyl iodide (see Schemes 28 and 29).

Entry	Product	R	Yield[a] /%	% d.e.[b]
1	**173**	Pr^i	35	83
2	**174**	*sec*-Bu	31	83
3	**175**	CH_2=$CHCH_2$	27 [c]	88

[a] Yields calculated from crude material except in case of **175**, where it was calculated from ^{1}H NMR spectroscopic data.

[b] Determined by ^{1}H NMR spectroscopy.

[c] Together with the diallylated product **176** (52%; see Scheme 29).

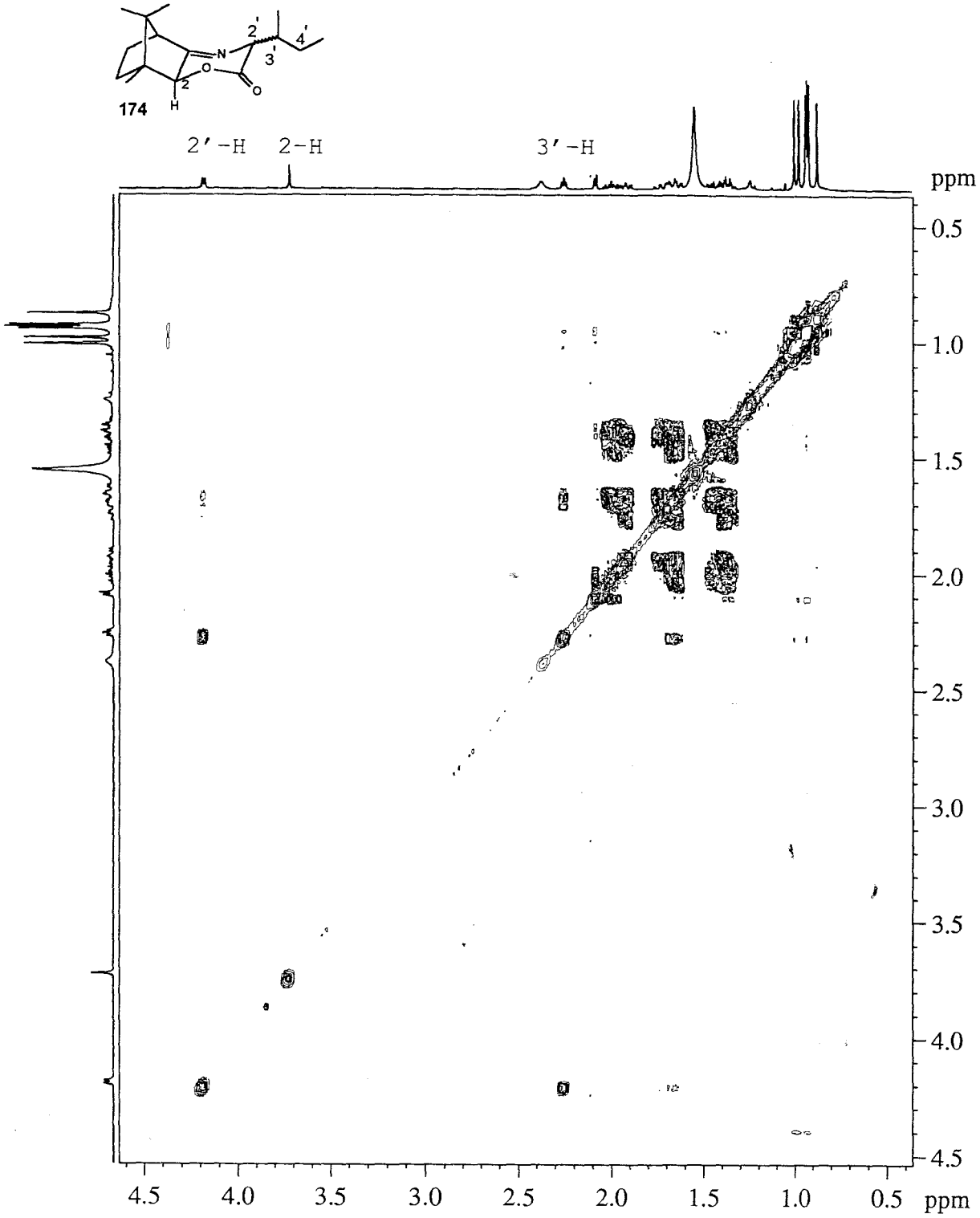


Figure 16. COSY spectrum of the alkylated imino lactone **174** in $CDCl_3$, showing coupling between selected nuclei.

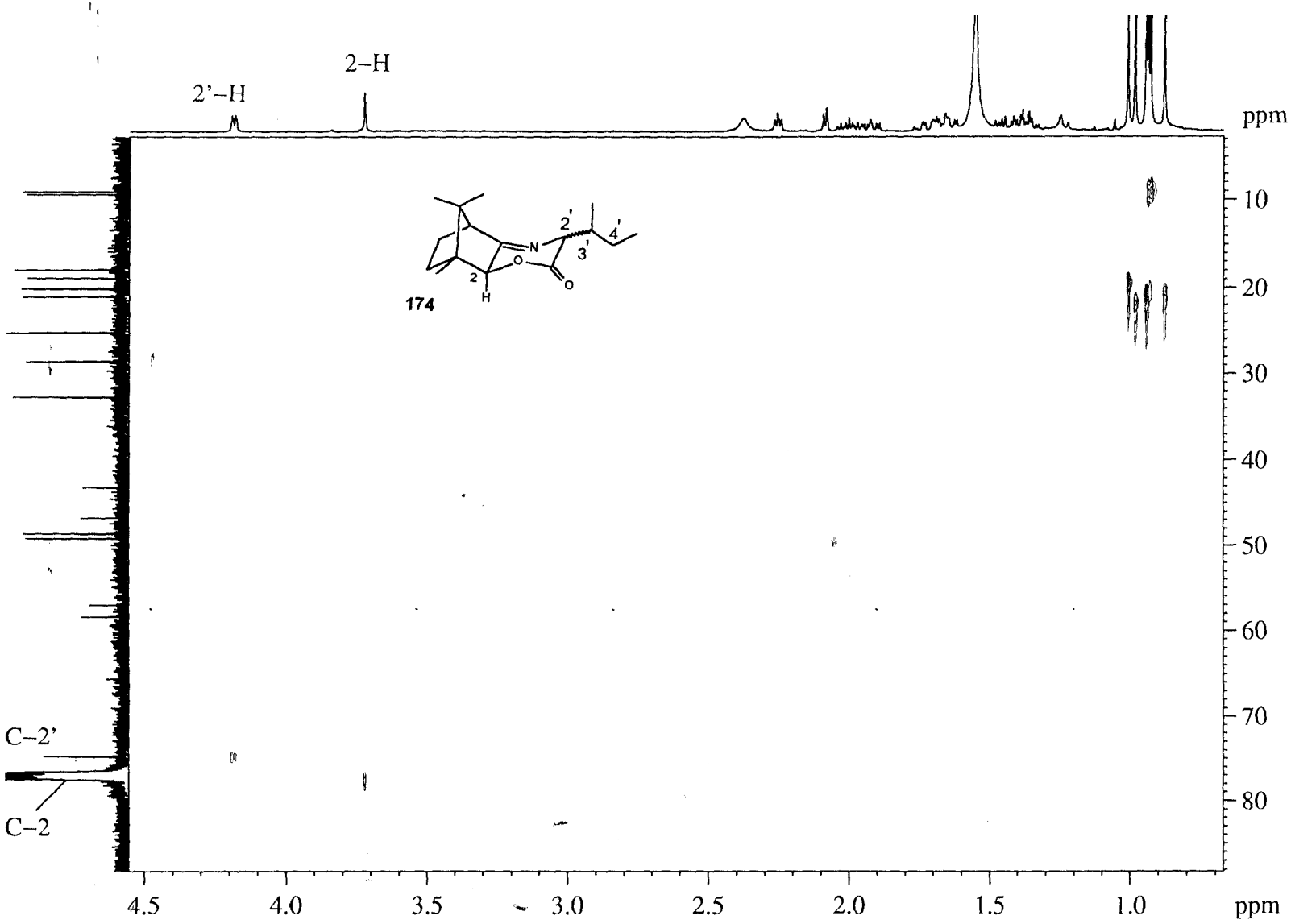
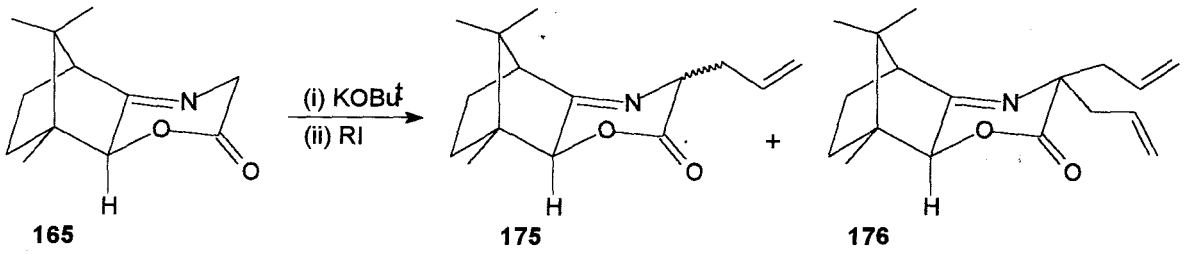


Figure 17. HETCOR spectrum of the alkylated imino lactone **174** in $CDCl_3$.

2.2.2.3 Reaction with allyl iodide

The α-allylation of the 3-imino lactone **165** provided access to the enantiomer of another natural amino acid, 2-amino-4-pentenoic acid. Allyl iodide is a very powerful alkylating agent and this is illustrated by the isolation of the diallylated product **176** together with the expected monoalkylated product **175** (Scheme 29). Both products were isolated by semi-preparative HPLC and fully characterised by 1-D and 2-D NMR, IR and high resolution mass spectroscopy. The COSY and HETCOR spectra for the α,α-diallyl 3-imino lactone **176** are illustrated in Figures 18 and 19, respectively. Of particular interest, is the very weak coupling between the allylic protons (resonating between δ 5.50 and 6.00 ppm) and the 3'-H nuclei (resonating between δ 2.30 and 3.00 ppm). The clear resolution of most of the signals facilitated accurate integration which confirmed the presence of six allylic protons rather than the expected three, as found in the monoalkylated analogue. The coupling between the four methylene protons on C-5 and C-6 is also evident. Clearly, the multiplet at δ 2.00 ppm corresponds to the 5-*exo*-H since it couples with the 4-H nucleus resonating at δ 2.33 ppm. From the HETCOR spectrum (Figure 19) it is possible to assign, with certainty, each of the ^{13}C NMR signals, based on the information obtained from the COSY spectrum. It is interesting to observe that the C-4 nucleus, adjacent to the imine double bond at C-3, appears more deshielded than either of the C-3' nuclei which are adjacent to the allylic double bonds.



165 **175** **176**

Scheme 29.

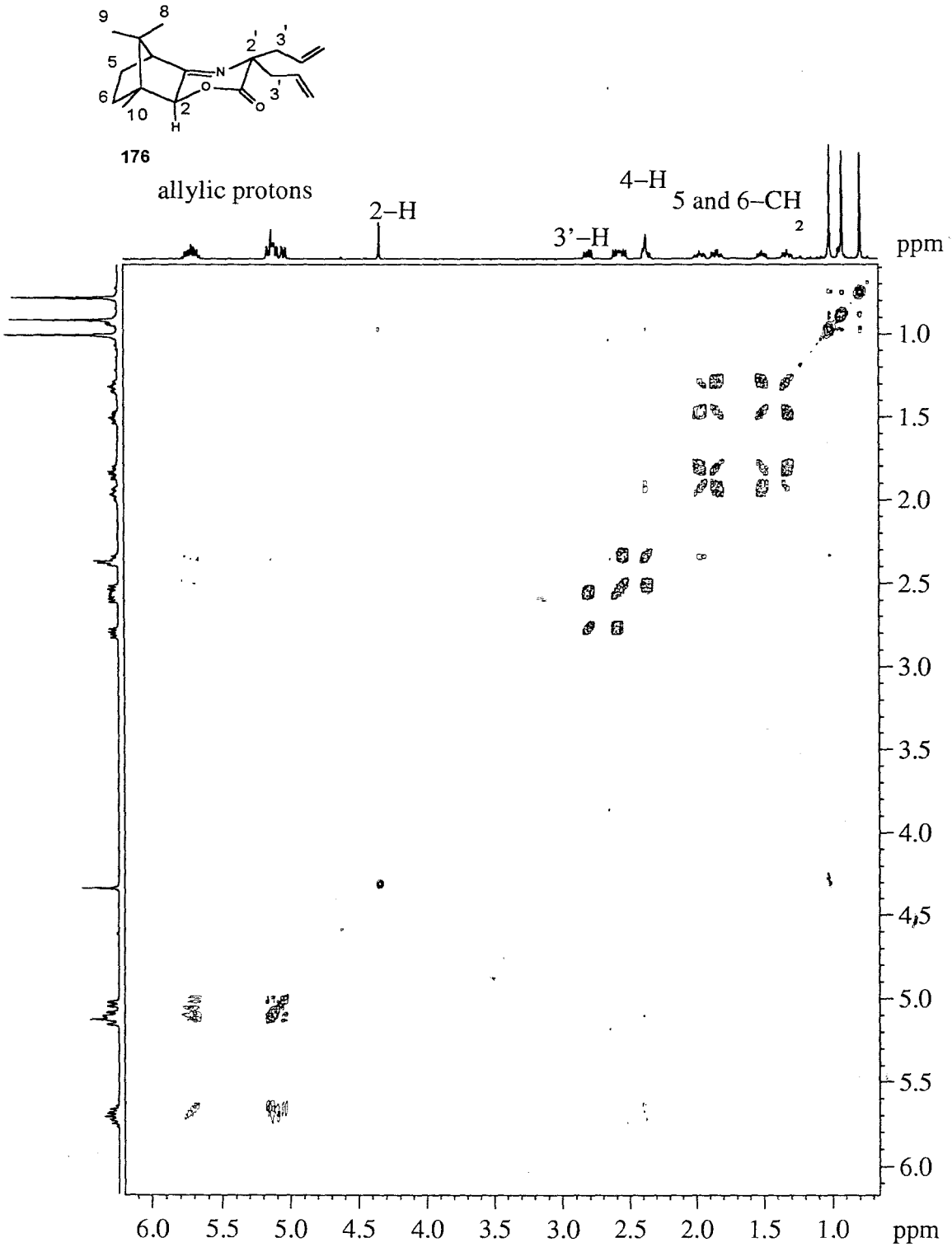


Figure 18. COSY spectrum of the α,α-diallyl 3-imino lactone **176** in $CDCl_3$.

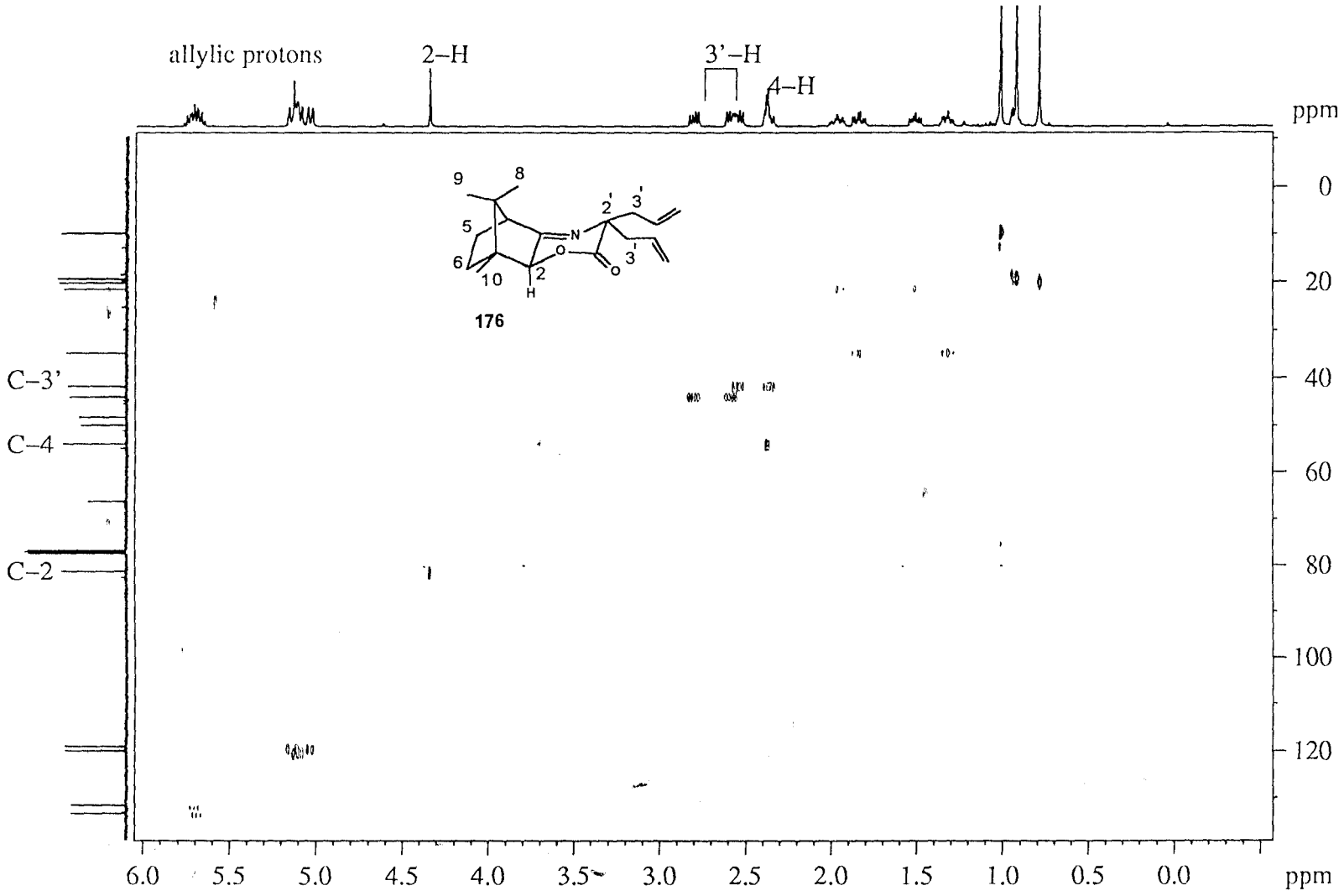


Figure 19. HETCOR spectrum of the α,α-diallyl 3-imino lactone **176** in $CDCl_3$.

The diastereomeric excess (≥ 88% d.e.; Table 7) of the α-allylated 3-imino lactone **175** was calculated from the ratio of the signals at δ 4.28 and 4.60 ppm (Figure 20). However, a similar signal is observed at δ 4.60 ppm in the spectrum for the dialkylated product, suggesting that this peak may originate from a residual impurity rather than from the minor diastereomer. Therefore, it is possible that almost complete stereocontrol was achieved in the formation of the mono-allylated product. This is the first example of the use of a bifunctional alkyl iodide in this series, and its success raises the possibility of extending applications of this reaction to a variety of substituted alkyl iodides.

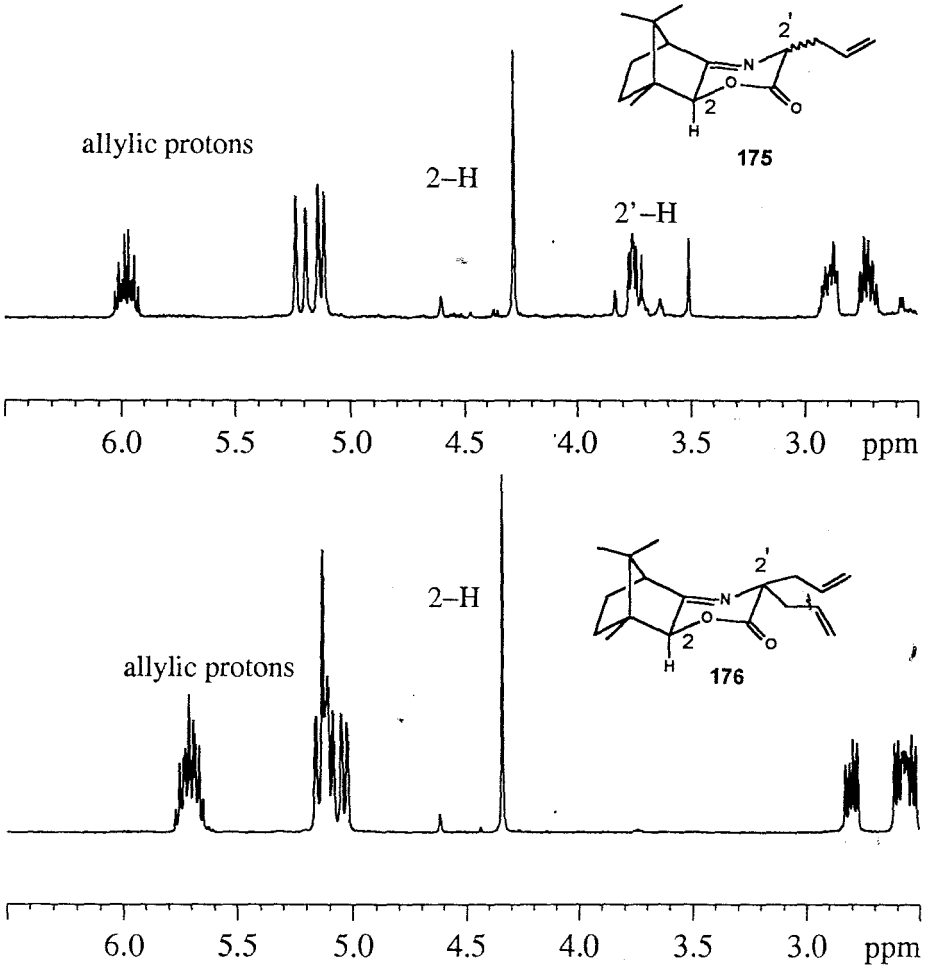
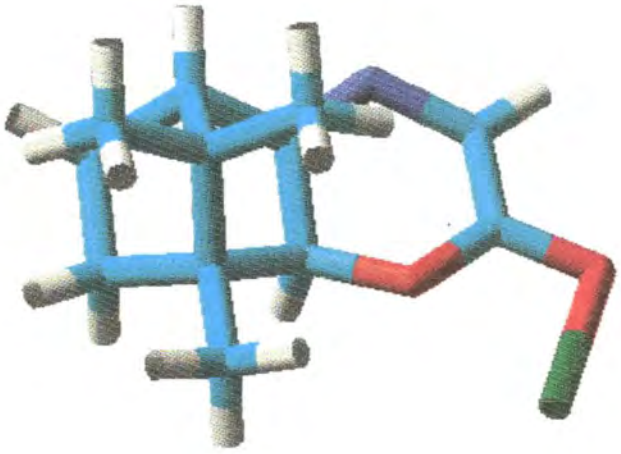


Figure 20. Partial 400 MHz ^{1}H NMR spectra of the α-allyl derivatives **175** and **176** in $CDCl_3$, showing 2-H and allylic protons

2.2.3 Molecular modelling studies

The stereocontrol achieved in the alkylation reactions discussed above may be attributed to the fact that the *exo*-face of the camphor-derived enolate **166** is blocked by the 9-methyl group – a fact which is clearly illustrated in the computer-generated molecular model shown in Figure 21. The *endo*-face, however, appears completely free of obstruction and, moreover, there is no proton capable of participating in an unfavourable 1,3-diaxial interaction with the incoming electrophile. The models in Figure 21 also show that the potassium cation may coordinate with the endocyclic lactone oxygen, thus increasing the stability of the conjugated enolate and preventing rotation about the C(1')–O(K) bond and consequent blocking of the *endo*-face by the bulky cation, K^+. From a consideration of these facts, it is clear why asymmetric reactions involving this system are so successful. In due course, generalising the approach to include the synthesis of polyfunctional amino acids and cyclic systems, may well be possible. Certainly, for the alkylation of α-alkyl α-amino acids, this method constitutes a convenient approach which, depending on the chirality of the starting material [(+)- or (-)-camphor][101] should allow the synthesis of products of specified configuration.

(a)



(b)

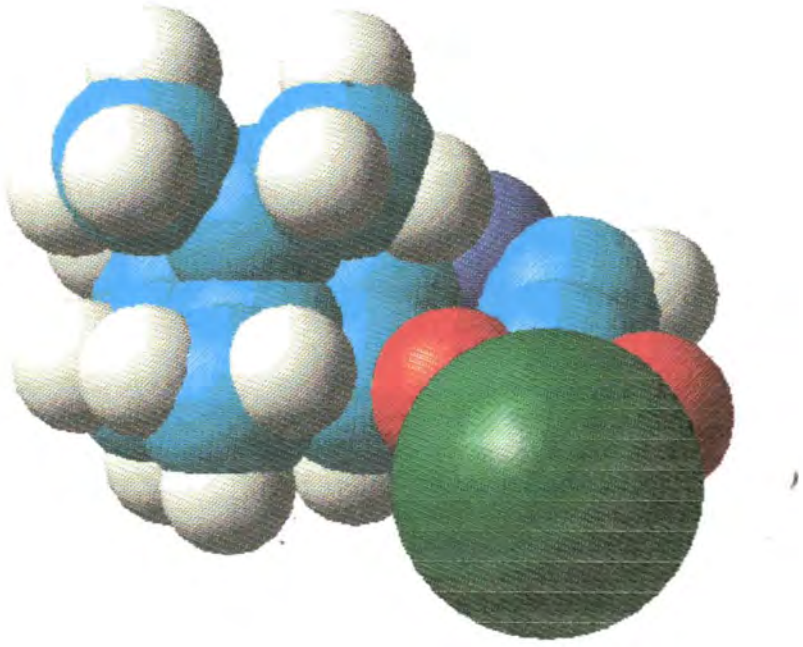


Figure 21. Computer models of the enolate **166**, generated using MSI Cerius^2 software: (a) cylinder; and (b) space-filling representations.

2.3 Concluding Remarks

This research has been concerned with asymmetric α-alkylation reactions. In particular, a previously developed protocol for the α-benzylation of esters of three existing camphor-derived auxiliaries has been extended to include a fourth auxiliary. This work involved the synthesis of the aforementioned chiral auxiliary *via* the elaboration of the synthetic pathway developed for the preceding series of auxiliaries. This included the oxidation of camphor to camphorquinone, followed by protection of the C-2 carbonyl and subsequent reduction of the C-3 carbonyl group. The sodium hydride-generated alkoxide of the resulting camphor-derived alcohol was reacted with the same series of acid chlorides as its predecessors, giving rise to the six ester precursors. These novel esters were benzylated with benzyl bromide under kinetic enolisation conditions using LDA as a base, to afford the α-benzylated esters in moderate yields (39 - 48%). The diastereoselectivities achieved (59 - 83% d.e.) were good to excellent, and constitute a significant improvement on the results obtained with the analogous auxiliaries. A computer modelling study of the enolate intermediate of the *t*-butylacetate ester confirmed that the stereocontrol achieved in this study was due to steric hindrance, provided either by the ketal blocking group or by the overhanging 9-methyl group, depending on the orientation of the planar enolate moiety.

In addition to this work on carboxylic acid derivatives, the α-alkylation of a conformationally rigid imino lactone derived from camphor and glycine was explored. Initially, a series of six primary alkyl iodides, RI [of increasing chain length, from R = Me to R = $CH_3(CH_2)_5$] was reacted with the potassium enolate of the camphor-derived imino lactone. The material yields obtained were good (69 - 84%), while the stereocontrol was varied (54 - 89% d.e.) due to degradation of the imino lactone. The results achieved confirmed the usefulness of this approach to α-alkyl α-amino acids. The series was extended by the use of two secondary alkyl iodides (isopropyl iodide and *sec*-butyl iodide) and allyl iodide. The diastereoselectivities obtained by reaction of the imino lactone enolate with the secondary alkyl iodides were pleasing (83% d.e.), although the material yields were low (35 and 31% respectively) due to decreased reactivity of secondary when compared to primary alkyl iodides. Similarly, in the reaction of the imino lactone enolate with allyl iodide, the diastereocontrol was excellent (≥ 88% d.e.), but the yield obtained for the mono-alkylated product was low (27%). However, in this case, the low yield was due to the

simultaneous production of the dialkylated product (52%), which is formed as a result of the relatively high reactivity of allyl iodide. In all the above alkylations, *endo*-face attack was presumed, in accordance with results obtained in a previous study. This assumption was justified by the results of a computer modelling study conducted on the potassium enolate of the imino lactone precursor.

Future work is expected to include the following:-

(i) the application of a variety of electrophiles in the α-alkylation of the camphor-derived esters;

(ii) the use of bifuntional alkyl iodides in the alkylation of the imino lactone; and

(iii) the application of the camphor-derived 3-imino lactone developed here, in enantiomer beneficiation studies.

(iv) the use of allyl bromide in the allylation reaction in order to increase the yield of the monoalkylated product of this reaction.

3. EXPERIMENTAL

3.1 General

Melting points were determined using a Kofler hot-stage apparatus, and are uncorrected. ^{1}H and ^{13}C NMR spectra were run on a Bruker AMX400 spectrometer; spectra recorded in $CDCl_3$ were calibrated on the solvent signals (7.25 ppm for ^{1}H and 77.00 for ^{13}C). The coupling constants, where specified, are given in hertz (Hz). IR spectra were recorded on a Perkin Elmer Spectrum 2000 FT-IR spectrometer. Low resolution mass spectra were obtained on a Finnegan Mat GCQ mass spectrometer and high-resolution mass spectra on a Kratos MS 80RF mass spectrometer (Cape Technikon Mass Spectrometry Unit).

Semi-preparative HPLC separations were achieved using a Spectra-Physics P100 HPLC fitted with a Whatman Magnum Partisil (10) column and a Waters R-401 differential refractive index detector. Flash chromatography [102] was carried out using Merck silica gel 60 [particle size 0.040 - 0.063 nm (230-400 mesh)] and preparative layer chromatography (PLC) was achieved using Merck silica gel $60PF_{254}$. Routine thin layer chromatography (TLC) was carried out on pre-coated Merck silica gel F_{254} plates, visualisation being achieved by exposure to iodine or inspection under UV light (254 nm).

Solvents were dried using procedures prescribed by Perrin and Armarego.[103] Diethyl ether and THF were dried over benzophenone/Na wire and distilled under nitrogen. Dimethylformamide was refluxed over 4Å molecular seives, distilled under reduced pressure and stored over 4Å molecular seives. All asymmetric reactions, as well as reductions and esterifications, were conducted in flame dried glassware under an inert atmosphere of dried spectroscopic grade nitrogen. All acid chlorides were used as supplied by Aldrich.

Computer modelling was conducted on a Silicon graphics O^2 work-station using the "CERIUS^2" software supplied by Molecular Simulations Inc..Where convenient, the atom numbering used in quoting NMR data complies with systematic nomenclature. However, given the complexity of certain systems, trivial names are used and the numbering follows accordingly. Where necessary, the numbering is indicated by a suitable example.

3.2 Synthetic Procedures

3.2.1 Preparation of camphor-derived chiral compounds 137 and 138

(-)-Camphorquinone **139**

(+)-Camphor (40.94 g, 0.2693 mol) was dissolved in acetic anhydride (40 ml). Selenium dioxide (47.76 g, 0.4304 mol) was added and the resulting suspension was boiled under reflux for 7 hours. After cooling overnight, the black residue was removed by filtration and washed with glacial acetic acid. The filtrate and washings were combined and neutralized with 10% NaOH and the resulting yellow precipitate filtered off and washed with water. The yellow solid was recrystallized from petroleum spirit (80 – 100°C) to afford, as yellow needles, (-)-camphorquinone **139** (26.59 g, 59%), mp 168 - 170°C (from petroleum spirit) (lit.[104] 198 - 201°C); ν_{max} /cm^{-1} ($CHCl_3$) 1765 and 1750 (C=O); δ_H (400 MHz; $CDCl_3$) 0.92, 1.05 and 1.09 (9H, 3xs, 8-, 9- and 10-Me), 1.58 - 2.20 (4H, series of multiplets, 5- and 6-CH_2) and 2.61 (1H, d, *J* 5.3, 4-H)

3,3-(Ethylenedioxy)-2-bornanone **140** *and 2,2;3,3-bis(ethylendioxy)bornane* **141**

Ethylene glycol (20ml, 0.36 mol) and *p*-toluenesulfonic acid (0.5 g, 3 mmol) were added to a solution of (-)-camphorquinone **139** (10.0 g, 60.1 mmol) in benzene (100 ml). The reaction mixture was boiled under reflux in a flask equipped with a Dean and Stark apparatus for 24 hours, during which time H_2O (2.5 ml) was collected. The resulting solution was washed with 1M NaOH (20 ml) and H_2O (20 ml). The aqueous layer was extracted with EtOAc (3 x 20 ml), and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was then removed by evaporation under reduced pressure, and the residual oil refrigerated overnight to facilitate crystallisation.

The crystals were filtered off and recrystallised from hot ethanol to give, as white crystals, 3,3-(ethylenedioxy)-2-bornanone **140** (7.59 g; 60.1%), mp. 77 - 82°C (lit.[105] 88°C); ν_{max} /cm^{-1}

($CHCl_3$) 1752 (C=O); δ_H (400 MHz; $CDCl_3$) 0.89, 0.97 and 1.01 (9H,3xs, 8-, 9- and 10-Me), 1.53 - 2.04 (4H, series of multiplets, 5- and 6-CH_2), 1.67(1H, d, *J* 4.6, 4-H) and 3.95-4.30 (4H, 3xm, OCH_2CH_2O); δ_C (100MHz; $CDCl_3$) 9.1, 19.0 and 21.4 (C-8, C-9 and C-10), 21.5 (C-5), 31.0 (C-6), 43.6 and 58.3 (C-1 and C-7), 51.6 (C-4), 64.5 and 66.1 (OCH_2CH_2O), 107.0 (C-3) and 217.5 (C-2); *m/z* 210 (M^+, 10%) and 162 (100)

The mother liquors were combined, concentrated and chromatographed [flash chromatography on silica; elution with hexane:EtOAc (9:1)] gave 2,2;3,3-bis(ethylenedioxy)-bornane **141** (1.95 g, 12.7%), mp. 58 - 59°C; δ_H (400 MHz; $CDCl_3$) 0.78, 0.85 and 1.16 (9H,3xs, 8-, 9- and 10-Me), 1.29 - 1.97 (4H, series of multiplets, 5- and 6-CH_2), 1.67 (1H, d, *J* 4.6, 4-H), 3.76-3.98 (8H, m, OCH_2CH_2O); δ_C (100MHz; $CDCl_3$) 9.8, 20.7 and 21.0 (C-8, C-9 and C-10), 21.1 (C-5), 29.3 (C-6), 44.5 and 52.7 (C-1 and C-7), 53.3 (C-4), 64.2, 64.5, 65.0 and 65.9 (OCH_2CH_2O) and 113.8 and 114.7 (C-2 and C-3).

2,2-(Ethylenedioxy)-3-bornanone **142**

A solution of 2,2;3,3-bis(ethylendioxy)bornane **140** (3.91 g, 15.4 mmol) and *p*-toluene-sulfonic acid (2.21 g, 11.6 mmol) in aqueous methanol (1:1; 50 ml) was boiled under reflux for 8 hours. The mixture was neutralised with 1M NaOH (20 ml). The methanol was then removed under reduced pressure and the aqueous layer was extracted with EtOAc (3 x 20 ml). The extracts were combined, washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give, as a colourless crystalline solid 2,2-(ethylenedioxy)-3-bornanone **142** (2.08 g, 64%), [a] mp 43°C;ν_{max} 1756cm^{-1} (C=O);δ_H (400 MHz; $CDCl_3$) 0.89, 0.94 and 1.03 (9H, 3xs, 8-, 9- and 10-Me), 1.51 - 2.08 (4H, series of multiplets, 5- and 6-CH_2), 2.15 (1H, d, *J* 5.4, 4-H), 3.95-4.29 (4H, m, OCH_2CH_2O); δ_C (100MHz; $CDCl_3$) 8.71, 18.2 and 21.5 (C-8, C-9 and C-10), 22.8 (C-5), 29.2 (C-6), 43.7 and 51.4 (C-1 and C-7), 59.2 (C-4), 64.9 and 66.4 (OCH_2CH_2O), 107.4 (C-2) and 216.6 (C-3); *m/z* 210 (M^+, 17%) and 162 (100).

[a] This compound has been previously cited [106] but was not fully characterised.

2,2-(Ethylenedioxy)-3-exo-*hydroxybornane* **138**.

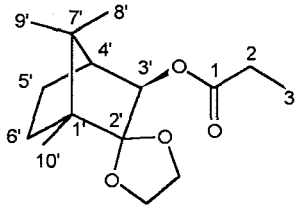
A suspension of $LiAlH_4$ (0.46 g, 12 mmol) in dry ether (100 ml) was boiled under reflux in an atmosphere of dry nitrogen for 1 hour. A solution of 2,2-(ethylenedioxy)-3-bornanone **142** (8.17 g, 38.9 mmol) in ether (10 ml) was added slowly, and the resulting mixture was boiled under reflux for 3 hours and then stirred overnight. The reaction was quenched by the sequential addition of 3M NaOH (5 ml) and H_2O (5 ml). The white precipitate was filtered off, and washed by boiling in EtOAc for 1 hour. The combined filtrates were then extracted with EtOAc (3 x 20ml); the extracts were combined, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude extract was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (9:1)] to give *2,2-(ethylenedioxy)-3*-exo-*hydroxybornane* **138** (7.28 g, 88.1%); ν_{max} /cm^{-1} ($CHCl_3$) 3045 (OH); δ_H (400 MHz; $CDCl_3$) 0.76, 0.78 and 1.04 (9H,3xs, 8-, 9- and 10-Me), 1.04-1.80 (5H, series of multiplets, 4-CH, 5- and 6-CH_2), 1.99 (1H, s, OH), 3.39 (1H, s, 3-H), 3.69-4.01 (4H, m, OCH_2CH_2O) ;δ_C (100MHz; $CDCl_3$) 9.26, 21.1 and 21.6 (C-8, C-9 and C-10), 24.5 (C-5), 29.1 (C-6), 47.7 and 51.8 (C-1 and C-7), 51.6 (C-4), 63.9 and 66.5 (OCH_2CH_2O), 83.0 (C-3) and 116.9 (C-2); *m/z* 212 (M^+, 22%) and 162 (100). (Found M^+: 212.1401. $C_{12}H_{20}O_3$ requires *M*, 212.1412).

3,3-(Ethylenedioxy)-2-exo-*hydroxybornane* **137**.

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **138** was followed, using 3,3-(ethylenedioxy)-2-bornanone **140** (4.49g; 21.1 mmol) and $LiAlH_4$ (0.81 g, 21 mmol).Work-up and flash chromatography [elution with hexane-EtOAc (9:1)] gave 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane (4.51 g, 100%).ν_{max} /cm^{-1} ($CHCl_3$) 3020 (OH); δ_H (400 MHz; $CDCl_3$) 0.76, 0.83 and 1.02 (9H, 3xs, 8-, 9- and 10-Me), 1.40-1.69 (5H, series of multiplets, 4-CH, 5- and 6-CH_2), 2.36 (1H, d, *J* 5.8, OH), 3.22 (1H, s, 2-H), 3.72-3.95 (4H, m, OCH_2CH_2O) ; δ_C (100MHz; $CDCl_3$) 10.8, 20.7 and 21.0 (C-8, C-9 and C-10), 21.2 (C-5), 33.4 (C-6), 47.5 and 49.6 (C-1 and C-7), 52.6 (C-4), 63.5 and 65.6 (OCH_2CH_2O), 85.5 (C-2) and 115.2 (C-3); *m/z* 212 (M^+, 12%) and 162 (100).

3.2.2 Preparation of the ester substrates 150 -155.

*2,2-(Ethylenedioxy)-3-*exo*-bornyl propanoate* **150**



A solution of 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **138** (1.08 g, 5.07 mmol) in dry THF (15 ml) was added drop-wise to a pre-washed suspension of NaH (0.44 g, 11 mmol) in dry THF (50 ml) under dry nitrogen. The mixture was stirred for 1.5 hours at room temperature and then boiled under reflux until the bright yellow colour of the alkoxide was observed (1 hour). The reaction mixture was cooled and propanoyl chloride **144** (0.6 ml, 6.9 mmol) was added drop-wise. The resulting mixture was stirred overnight before boiling under reflux for 1.5 hours. The THF was removed *in vacuo* and the residue was partitioned between cold $NaHCO_3$ and EtOAc (3 x 20 ml). The organic fractions were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed [flash chromatography on silica gel; elution with hexane: EtOAc (19:1)] to give, as an oil, *2,2-(ethylenedioxy)-3-*exo*-bornyl propanoate* **150** (0.86 g, 63%); ν_{max} /cm^{-1} ($CHCl_3$) 1737 (C=O); δ_H (400MHz; $CDCl_3$) 0.77, 0.83 and 1.10 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.12 (3H, t, *J* 7.5, 3-Me), 1.25 – 1.79 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 2.32 (2H, q, *J* 7.5, 2-CH_2), 3.73 – 3.95 (4H, m, OCH_2CH_2O) and 4.42 (1H, s, 3'-*endo*-H); δ_C (100MHz; $CDCl_3$) 9.3 (C-9' and C-3), 20.8 and 21.0 (C-8' and C-10'), 24.4 (C-5'), 28.0 (C-2), 29.0 (C-6'), 47.9 and 52.6 (C-1' and C-7'), 49.6 (C-4'), 63.8 and 66.6 (OCH_2CH_2O), 83.5 (C-3'), 116.2 (C-2') and 173.5 (C=O); *m/z* 268 (M^+, 14%) and 141 (100); (Found M^+: 268.1671. $C_{15}H_{24}O_4$ requires *M*, 268.1674)

2,2-(Ethylenedioxy)-3-exo-*bornyl butanoate* **151**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl propanoate **150** was followed, using 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **138** (0.91 g, 4.3 mmol), NaH (0.22 g, 5.5 mmol) and butanoyl chloride **145** (0.6 g, 6 mmol).Work-up and flash chromatography [on silica gel; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3*-exo-*bornyl butanoate* **151** (0.73 g, 60%); ν_{max} /cm^{-1} ($CHCl_3$) 1733 (C=O); δ_H (400 MHz; $CDCl_3$) 0.78, 0.83 and 1.12 (9H, 3xs, 8'-, 9'- and 10'-Me), 0.94 (3H, t, *J* 7.4, 4-Me), 1.21-1.92 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 1.64 (2H, m, 3-CH_2), 2.28 (2H, t, *J* 7.4, 2-CH_2), 3.72-3.95 (4H, m, OCH_2CH_2O) and 4.42 (1H, s, 3'-H); δ_C (100MHz; $CDCl_3$) 9.3, 20.8 and 21.0 (C-8', C-9' and C-10'), 13.7 (C-4), 18.5 (C-3), 24.4 (C-5'), 28.9 (C-6'), 36.6 (C-2), 47.9 and 52.6 (C-1' and C-7'), 49.6 (C-4'), 63.8 and 66.6 (OCH_2CH_2O), 83.5 (C-3'), 116.2 (C-2') and 172.7 (C=O); *m/z* 282 (23%) and 141 (100); (Found M^+: 282.1840. $C_{16}H_{26}O_4$ requires *M*, 282.1831).

2,2-(Ethylenedioxy)-3-exo-*bornyl 3-methylbutanoate* **152**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl propanoate **150** was followed, using 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **138** (0.92 g, 4.4 mmol), NaH (0.20 g, 5.0 mmol) and 3-methylbutanoyl chloride **146** (0.7 g, 6 mmol).Work-up and flash chromatography [on silica gel; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3*-exo-*bornyl 3-methylbutanoate* **152** (1.07 g, 53%); ν_{max} /cm^{-1} ($CHCl_3$) 1729 (C=O); δ_H (400 MHz; $CDCl_3$) 0.78, 0.83 and 1.10 (9H, 3xs, 8'-, 9'- and 10'-Me), 0.95 (6H, d, *J* 6.4, 2 x 4-Me), 1.22 - 1.92 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 2.10 (1H, m, 3-CH), 2.18 (2H, d, *J* 6.4, 2-CH_2), 3.73-3.95 (4H, m, OCH_2CH_2O) and 4.42 (1H, s, 3'-H); δ_C (100MHz; $CDCl_3$) 9.23, 20.8 and 21.0 (C-8', C-9' and C-10'), 22.4 and 22.5 (C-4), 24.4 (C-5'), 25.6 (C-3), 28.9 (C-6'), 43.8 (C-2), 47.9 and 52.6 (C-1' and C-7'), 49.7 (C-4'), 63.8 and 66.5 (OCH_2CH_2O), 83.4 (C-3'), 116.1 (C-2'), 172.2 (C=O); *m/z* 296 (38%) and 141 (100); (Found M^+: 296.1983. $C_{17}H_{28}O_4$ requires *M*, 296.1987).

*2,2-(Ethylenedioxy)-3-*exo*-bornyl 3,3-dimethylbutanoate* **153**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl propanoate **150** was followed, using 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **138** (1.50 g, 7.1 mmol), NaH (0.42 g, 10 mmol) and 3,3-dimethylbutanoyl chloride **147** (1.2 g, 9 mmol).Work-up and flash chromatography [on silica gel; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3-*exo*-bornyl 3,3-dimethylbutanoate* **153** (1.74 g, 80%); ν_{max} /cm^{-1} ($CHCl_3$) 1718 (C=O); δ_H (400 MHz; $CDCl_3$) 0.77, 0.82 and 1.10 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.03 (9H, s, 3×4-Me), 1.26-1.91, (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 2.20 (2H, s, 2-CH_2), 3.74-3.93 (4H, m, OCH_2CH_2O) and 4.42 (1H, s, 3'-H); δ_C (100MHz; $CDCl_3$) 9.3, 20.8 and 21.0 (C-8', C-9' and C-10'), 24.4 (C-5'), 28.9 (C-6'), 29.6 (C-4), 30.8 (C-3), 47.9 and 52.6 (C-1' and C-7'), 48.3 (C-2), 49.8 (C-4'), 63.8 and 66.5 (OCH_2CH_2O), 83.4 (C-3'), 116.2 (C-2') and 171.4 (C=O); *m/z* 310 (36%) and 127 (100) (Found M^+: 310.2144. $C_{18}H_{30}O_4$ requires *M*, 310.2144).

*2,2-(Ethylenedioxy)-3-*exo*-bornyl phenylethanoate* **154**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl propanoate **150** was followed, using 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **138** (0.94 g, 4.4 mmol), NaH (0.30 g, 7.5 mmol) and phenylacetyl chloride **148** (0.9 g, 6 mmol).Work-up and flash chromatography [on silica gel; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3-*exo*-bornyl phenylethanoate* **154** (0.58 g, 27%); ν_{max}/cm^{-1} ($CHCl_3$) 1730 (C=O); δ_H (400 MHz; $CDCl_3$) 0.76, 0.82 and 1.06 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.20 - 1.89 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 3.54-3.85 (4H, m, OCH_2CH_2O), 3.60 (2H, s, 2-CH_2), 4.42 (1H, s, 3'-H) and 7.22-7.33 (5H, m, Ar-H); δ_C (100MHz; $CDCl_3$) 9.24, 20.8 and 21.0 (C-8', C-9' and C-10'), 24.4 (C-5'), 28.9 (C-6'), 41.8 (C-2), 47.9 and 52.5 (C-1' and C-7'), 49.5 (C-4'), 63.7 and 66.4 (OCH_2CH_2O), 84.0 (C-3'), 116.0 (C-2'), 126.9, 128.4 and 129.3 (Ar-C) and 170.6 (C=O); *m/z* 330 (55%) and 91 (100); (Found M^+: 330.1823. $C_{20}H_{26}O_4$ requires *M*, 330.1831).

*2,2-(Ethylenedioxy)-3-*exo*-bornyl phenoxyethanoate* **155**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl propanoate **150** was followed, using 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **138** (0.82 g, 3.9 mmol), NaH (0.30 g, 7.5 mmol) and phenoxyacetyl chloride **149** (0.9 g, 5 mmol).Work-up and flash chromatography [on silica gel; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3-*exo*-bornyl phenoxyethanoate* **155** (0.51 g, 39%); ν_{max}/cm^{-1} ($CHCl_3$) 1733 (C=O); δ_H (400 MHz; $CDCl_3$) 0.78, 0.84 and 1.07 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.26-1.92 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 3.67-3.92 (4H, m, OCH_2CH_2O), 4.50 (1H, s, 3'-H), 4.62 (2H, s, 2-CH_2) and 6.91-7.28 (5H, m, Ar-H); δ_C (100MHz; $CDCl_3$) 9.2, 20.7 and 21.0 (C-8', C-9' and C-10'), 24.3 (C-5'), 28.8 (C-6'), 47.9 and 52.8 (C-1' and C-7'), 49.3 (C-4'), 63.8 and 66.5 (OCH_2CH_2O), 65.2 (C-2), 84.5 (C-3'), 115.9 (C-2'), 168.1 (C=O), 157.9, 114.7, 121.6 and 129.5 (Ar-C); *m/z* 346 (46%) and 141 (100); (Found M^+: 346.1791. $C_{17}H_{28}O_5$ requires *M*, 346.1780).

3.2.3 Asymmetric alkylation of esters 150 - 155

*2,2-(Ethylenedioxy)-3-*exo*-bornyl 2-methyl-3-phenylpropanoate* **157**

A solution of 2,2-(ethylenedioxy)-3-*exo*-bornyl propanoate **150** (0.44 g, 1.62 mmol) in THF (10 ml) was added dropwise to a stirred solution of LDA (2.8 mmol; generated *in situ* from diisopropylamine and *n*-BuLi) in THF (40ml) at -78°C under dry N_2. The mixture was then stirred for one hour. Benzyl bromide (0.4 g, 3 mmol) was added to the bright yellow solution and stirring was continued for two hours at -78°C before the mixture was allowed to warm to room temperature overnight. The reaction was quenched with a cold, saturated, aqueous solution of $NaHCO_3$ and extracted with EtOAc (4×10 ml). The combined organic axtracts were dried over $MgSO_4$ (anhyd.) and concentrated *in vacuo*. Chromatography [HPLC; elution with hexane-EtOAc (19:1)] gave, as an oil, *2,2-(ethylenedioxy)-3-*exo*-bornyl 2-methyl-3-phenylpropanoate* **157** (0.23 g, 39%; 59.5% d.e.[b]); ν_{max} /cm^{-1} ($CHCl_3$) 1643 (C=O); δ_H (400MHz; $CDCl_3$) 0.76, 0.82 and 1.10 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.12 (3H, t, *J* 7.5, 3-Me), 1.25 -1.99 (7H, series of multiplets, 4'-CH, 5'-, 6'- and Ph-CH_2), 2.31 (2H, q, *J* 7.5, 2-CH), 3.72 – 3.98 (4H, m, OCH_2CH_2O), 4.42/4.40 [c] (1H, s, 3-H) and 7.20-7.39 (5H, Ar-H); δ_C (100MHz; $CDCl_3$) 9.2 (C-9' and C-3), 20.8 and 20.9 (C-8' and C-10'), 25.0 (C-5'), 27.9 (C-2), 28.9 (PhCH_2), 33.9 (C-6'), 47.8 and 52.5 (C-1' and C-7'), 49.5 (C-4'), 63.7 and 66.6 (OCH_2CH_2O), 83.5 (C-3'), 116.1 (C-2'), 128.2, 128.4, 128.5, 128.7, 129.0 and 137.8 (Ar-C) and 173.6 (C=O); *m/z* 358 (M^+, 4%) and 155 (100) (Found M^+: 358.2136. $C_{22}H_{30}O_4$ requires *M*, 358.2144).

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[b] The diasteromeric excess (%d.e.) observed for each of the benzylated esters was determined from the integral ratios of the 3'-H signals for the diasteromeric components.

[c] Where two chemical shift values are cited in this format, here and elsewhere, they refer to corresponding signals for the diastereomeric components.

2,2-(Ethylenedioxy)-3-exo-*bornyl 2-benzylbutanoate* **158**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl 2-methyl-3-phenylpropanoate **157** was followed, using 2,2-(ethylenedioxy)-3-*exo*-bornyl butanoate **151** (0.47 g, 1.7 mmol), LDA (2.6 mmol) and benzyl bromide (0.4 g, 3 mmol).Work-up and chromatography [HPLC; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylene-dioxy)-3*-exo-*bornyl 2-benzylbutanoate* **158** (0.29 g, 46%; 83.0% d.e.); ν_{max} /cm^{-1} ($CHCl_3$) 1641 (C=O); δ_H (400 MHz; $CDCl_3$) 0.75/0.76, 0.82/0.78 and 1.02/1.11 (9H, 3xs, 8'-, 9'- and 10'-Me), 0.93 (3H, t, *J* 7.4, 4-Me), 1.19-1.89 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 1.50-1.61 (2H, m, *J* 7.4, 3-CH_2), 2.56-2.63 (2H, 2t, *J* 7.4, 2-CH), 3.52-3.90 (4H, m, OCH_2CH_2O), 4.36/4.35 (1H, 2s, 3'-H), 2.67-2.76/2.91-2.99 (2H, m, Ph*C*H_2) and 7.14-7.27 (5H, m, Ar-H) ; δ_C (100MHz; $CDCl_3$) 9.2, 20.8 and 20.9 (C-8', C-9' and C-10'), 11.7/11.8 (C-4), 24.4 (C-5'), 25.3/24.9 (C-3), 28.9 (C-6'), 38.1 (Ph*C*H_2), 43.8 (C-2), 47.9 and 52.6 (C-1' and C-7'), 49.6 (C-4'), 63.7/63.5 and 66.4/66.2 (OCH_2CH_2O), 83.4/84.3 (C-3'), 116.1/116.0 (C-2'), 126.1, 128.3, 129.0 and 139.8 (Ar-C) and 174.6/174.4 (C=O); *m/z* 372 (92%) and 155 (100); (Found M^+: 372.2302. $C_{23}H_{32}O_4$ requires *M*, 372.2300).

2,2-(Ethylenedioxy)-3-exo-*bornyl 2-benzyl-3-methylbutanoate* **159**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl 2-methyl-3-phenylpropanoate **157** was followed, using 2,2-(ethylenedioxy)-3-*exo*-bornyl 3-methyl-butanoate **152** (0.61 g, 2.1 mmol), LDA (2.6 mmol) and benzyl bromide (0.3 g, 2 mmol). Work-up and chromatography [HPLC; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3*-exo-*bornyl 2-benzyl-3-methylbutanoate* **159** (0.37 g, 46%; 82.4% d.e.); ν_{max} /cm^{-1} ($CHCl_3$) 1638 (C=O); δ_H (400 MHz; $CDCl_3$) 0.78, 0.83 and 1.10 (9H, 3xs, 8'-, 9'- and 10'-Me), 0.96 (6H, d, *J* 6.4, 2×4-Me), 1.20 - 1.90 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 2.10 (1H, h, *J* 6.4, 3-CH), 2.19 (1H, d, *J* 6.4, 2-CH), 2.82-2.85 (2H, m, Ph*C*H_2), 3.73-3.93 (4H, m, OCH_2CH_2O), 4.49/4.49 (1H, s, 3'-H) and 7.18-7.39 (5H, m, Ar-H); δ_C (100MHz; $CDCl_3$) 9.27, 20.8 and 21.0 (C-8', C-9' and C-10'), 22.4 and 22.5 (C-4), 24.5 (C-5'), 25.6 (C-3), 28.9 (C-6'), 36.0 (PhCH_2),

43.8 (C-2), 47.9 and 52.6 (C-1' and C-7'), 49.7 (C-4'), 63.8 and 66.5 (OCH_2CH_2O), 83.4 (C-3'), 116.1 (C-2'), 128.3, 128.4, 128.8 and 129.0 (Ar-C) and 172.2 (C=O); *m/z* 386 (76%) and 91(100); (Found M^+: 386.2460. $C_{24}H_{34}O_4$ requires *M*, 386.2457).

*2,2-(Ethylenedioxy)-3-*exo*-bornyl 2-benzyl-3,3-dimethylbutanoate* **160**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl 2-methyl-3-phenylpropanoate **157** was followed, using 2,2-(ethylenedioxy)-3-*exo*-bornyl 3,3-dimethylbutanoate **153** (0.60 g, 1.9 mmol), LDA (2.8 mmol) and benzyl bromide (0.4 g, 3 mmol).Work-up and chromatography [HPLC; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3-*exo*-bornyl 2-benzyl-3,3-dimethylbutanoate* **160** (0.36 g, 47%; 59.3% d.e.); ν_{max} /cm^{-1} ($CHCl_3$) 1638 (C=O); δ_H (400 MHz; $CDCl_3$) 0.88, 0.91 and 0.97 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.26 (9H, s, 3×4-Me), 1.32-2.08, (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 2.41-2.48 (1H, m, 2-CH), 2.69-2.78 (2H, m, PhCH_2), 3.70-3.95 (4H, m, OCH_2CH_2O), 4.42/4.49 (1H, s, 3'-H); δ_C (100MHz; $CDCl_3$) 9.24/9.19, 20.1 and 20.9/20.7 (C-8', C-9' and C-10'), 24.4/24.6 (C-5'), 27.9/28.0 (C-4), 28.9/29.0 (C-6'), 33.2/33.5 (C-3), 47.9 and 52.6 (C-1' and C-7'), 49.8/50.1 (C-4'), 58.7/58.8 (C-2), 63.7/63.1 and 66.2/66.6 (OCH_2CH_2O), 83.1/83.6 (C-3'), 115.8/116.2 (C-2'), 126.0, 128.2/128.3 and 129.1/129.2 (Ar-C) and 173.6/173.9 (C=O); *m/z* 400 (100%); (Found M^+: 400.2607. $C_{25}H_{36}O_4$ requires *M*, 400.2613).

*2,2-(Ethylenedioxy)-3-*exo*-bornyl 2,3-diphenylpropanoate* **161**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl 2-methyl-3-phenylpropanoate **157** was followed, using 2,2-(ethylenedioxy)-3-*exo*-bornyl phenylethanoate **154** (0.34 g, 1.2 mmol), LDA (2.6 mmol) and benzyl bromide (0.3 g, 2 mmol). Work-up and chromatography [HPLC; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3-*exo*-bornyl 2,3-diphenylpropanoate* **161** (0.19 g, 44%; 59.5% d.e.); ν_{max} /cm^{-1} ($CHCl_3$) 1638 (C=O); δ_H (400 MHz; $CDCl_3$) 0.73, 0.76 and 0.83 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.14-1.95 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 3.02-4.13 (7H, series of multiplets, OCH_2CH_2O, 2-CH,

PhCH_2), 4.38/4.44 (1H, s, 3'-H) and 7.24-7.41 (10H, m, Ar-H); δ_C (100MHz; $CDCl_3$) 9.24, 20.8 and 20.9 (C-8', C-9' and C-10'), 24.4 (C-5'), 28.9 (C-6'), 39.2 (Ph*C*H_2), 59.1 (C-2), 47.8 and 52.3 (C-1' and C-7'), 49.6 (C-4'), 63.6 and 66.1 (OCH_2CH_2O), 83.7/83.9 (C-3'), 115.9 (C-2'), 126.0-130.0 (Ar-C) and 172.0/173.3 (C=O); *m/z* 420 (33%) and 155 (100); (Found M^+: 420.2290.$C_{27}H_{32}O_4$ requires *M*,420.2300).

2,2-(Ethylenedioxy)-3-exo-bornyl 2-phenoxy-3-phenylpropanoate **162**

The procedure described for the synthesis of 2,2-(ethylenedioxy)-3-*exo*-bornyl 2-methyl-3-phenylpropanoate **157** was followed, using 2,2-(ethylenedioxy)-3-*exo*-bornyl phenoxy-ethanoate **155** (0.48 g, 1.4 mmol), LDA (2.6 mmol) and benzyl bromide (0.3 g, 2 mmol).Work-up and chromatography [HPLC; elution with hexane-EtOAc (19:1)] gave *2,2-(ethylenedioxy)-3-exo-bornyl 2-phenoxy-3-phenylpropanoate* **162** (0.29 g, 48%; 43% d.e.[d])ν_{max}/cm^{-1} ($CHCl_3$) 1641 (C=O); δ_H (400 MHz; $CDCl_3$) 0.77, 0.85 and 1.12 (9H, 3xs, 8'-, 9'- and 10'-Me), 1.20 - 1.90 (5H, series of multiplets, 4'-CH, 5'- and 6'-CH_2), 3.15 - 3.34 (2H, m, PhCH_2), 3.52-3.84 (4H, m, OCH_2CH_2O), 4.36/4.43 (1H, s, 3'-H), 4.78-4.84 (1H, m, 2-CH) and 6.80-7.31 (10H, m, Ar-H); δ_C (100MHz; $CDCl_3$) 9.2, 20.8 and 21.0 (C-8', C-9' and C-10'), 24.4 (C-5'), 28.8 (C-6'), 38.9 (Ph*C*H_2), 47.9 and 52.7 (C-1' and C-7'), 49.5 (C-4'), 63.8 and 66.5 (OCH_2CH_2O), 78.0 (C-2), 84.7 (C-3'), 116.0 (C-2'), 115.4, 121.6, 126.8, 128.4, 129.4, 129.5, 137.0 and 157.9 (Ar-C) and 171.3 (C=O); *m/z* 436 (19%) and 162 (100); (Found M^+: 436.2242. $C_{27}H_{32}O_5$ requires *M*,436.2250).

[d] Determined by ^{13}C NMR spectroscopy.

3.2.4 Synthesis of the 3-imino lactone 165

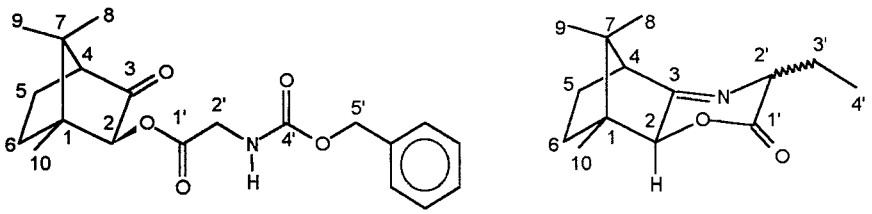

Figure 22. Structures illustrating numbering convention used below.

2-Exo-*hydroxybornanone* **163**

A solution of 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane **137** (8.10 g, 38.2 mmol) in THF (20 ml) was added to 1M HCl (38 ml, 38 mmol), and the stirred mixture boiled under reflux for 2.5 h. After cooling, the solution was neutralised with 3M NaOH (10 ml) and the THF was removed under reduced pressure. The product was extracted into EtOAc (4 × 30 ml), and the organic extracts were combined and dried over $MgSO_4$ (anhyd). The solvent was removed under reduced pressure and the residue chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (8:2)] to give, as white crystals, 2-*exo*-hydroxybornanone **163** (5.35 g, 83%); mp. 43 °C; ν_{max} /cm^{-1} ($CHCl_3$) 1659 (C=O), 3020 (OH); δ_H (400 MHz; $CDCl_3$) 0.93, 1.02 and 1.03 (9H, 3xs, 8-, 9- and 10-Me), 1.34 - 1.92 (4H, series of multiplets, 5- and 6-CH_2), 2.16 (1H, d, *J* 4.9, 4-H), 2.37 (1H, br.s., OH) and 3.34 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 10.0, 18.5 and 20.9 (C-8, C-9 and C-10), 20.2 (C-5), 33.6 (C-6), 46.2 and 49.0 (C-1 and C-7), 58.5 (C-4), 79.2 (C-2) and 171.0 (C-3); *m/z* 168 (M^+, 17%) and 147 (100).

N-*(Carbobenzyloxy)glycine 3-oxo-2*-exo-*bornyl ester* **164**

To a solution of *N*-(CBZ)-glycine (7.70 g, 36.8 mmol) in dry DMF (12 ml) was added carbonyldiimidazole (6.00 g, 37.0 mmol). After stirring for 30 minutes, this solution was added

dropwise to a solution of 2-*exo*-hydroxybornanone **163** in DMF (8 ml). The reaction mixture was stirred overnight at room temperature, and the DMF removed under reduced pressure. The residual oil chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:1)] to give, as a pale yellow oil, *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **164** (8.06 g, 61%); ν_{max} /cm^{-1} ($CHCl_3$) 1641 (C=O); δ_H (400 MHz; $CDCl_3$) 0.91, 0.93 and 0.96 (9H, 3xs, 8-, 9- and 10-Me), 1.50-2.00 (4H, series of multiplets, 5- and 6-CH_2), 2.20 (1H, d, *J* 4.5, 4-H), 2.42 (1H, br.s,NH), 3.91-4.05 (2H, m, PhCH_2), 4.89 (1H, s, 2-H), 5.11 (2H, m, 12-CH_2), 7.25-7.35 (5H, m, Ar-H); δ_C (100MHz; $CDCl_3$) 10.3, 18.4 and 21.0 (C-8, C-9 and C-10), 20.3 (C-5), 33.4 (C-6), 42.7 (C-4'), 46.6 and 49.4 (C-1 and C-7), 58.7 (C-4), 79.2 (C-2), 128.1, 128.2, 128.5 and 136.1 (Ar-C), 156.2 (C-3'), 169.4 (C-3) and 212.2 (C-1'); *m/z* 359 (M^+, 2.9%) and 162 (100).

The 3-imino lactone **165**

A solution of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **164** (4.83 g, 13.5 mmol) in absolute ethanol (40 ml) was placed in a 3-necked round-bottomed flask fitted with gas inlet and outlet tubes. Air was displaced by a slow stream of nitrogen. 10% Pd/C (1.10 g) was added, followed by a slow stream of nitrogen for 5 minutes. The catalyst was kept in suspension by vigorous stirring. A slow stream of hydrogen was then introduced. Escaping gas was passed through a saturated solution of aqueous $Ba(OH)_2$. After the evolution of CO_2 had ceased (as evidenced by cessation of $BaCO_3$ formation), the mixture was heated to *ca.* 50°C until no more CO_2 was detected. The mixture was then cooled and the flow of H_2 was terminated and replaced by nitrogen gas. The suspension was filtered through celite and the solid washed with ethanol. The filtrate and washings were combined and the solvent was evaporated under reduced pressure. Chromatography [flash chromatography on silica gel; elution with hexane-EtOAc (1:1)] gave the 3-imino lactone **165** (1.19g, 43%); ν_{max} /cm^{-1} ($CHCl_3$) 1644 (C=O); δ_H (400 MHz; $CDCl_3$) 0.75, 0.82 and 0.99 (9H, 3xs, 8-, 9- and 10-Me), 1.26-1.96 (4H, series of multiplets, 5- and 6-CH_2), 2.34 (1H, d, *J* 5.4, 4-H), 3.81 (1H, d, *J* 18.5, 2'-CH), 4.24 (1H, s, 2-H), 4.38 (1H, d, *J* 18.5, 12-CH); δ_C (100MHz; $CDCl_3$) 9.6, 19.1 and 19.8 (C-8, C-9 and C-10), 21.4 (C-5), 33.7 (C-6), 48.7

and 49.1 (C-1 and C-7), 52.3 (C-4), 53.0 (C-2'), 81.5 (C-2), 168.6 (C-3) and 181.6 (C-11); *m/z* 207 (M^+, 32%) and 359 (100).

3.2.5 Alkylation of 3-imino lactone

The α-methyl 3-imino lactone **167**

$KOBu^t$ (as supplied by Fluka; 0.26 g, 2.3 mmol), was added to dry THF (20 ml) at -70°C under nitrogen. A solution of the 3-imino lactone **165** (0.34 g, 1.7 mmol) in dry THF (10 ml) was added slowly to the stirred slurry. The colour changed immediately to a bright yellow, and the mixture was stirred for 45 minutes to ensure complete enolisation. Iodomethane (0.25 g, 1.8 mmol) in dry THF (8 ml) was added slowly to the enolate solution; the resulting mixture was stirred at -70°C for 3 h and then allowed to warm to room temperature overnight. The THF was removed *in vacuo* and water (10 ml) was added to the residue. The mixture was extracted with EtOAc (4×20 ml), and the combined organic extracts were dried over $MgSO_4$ (anhyd). The solvent was removed under reduced pressure to afford the crude product (0.31 g, 84%;[e] 86.5 % d.e.[f]) and the residue was chromatographed [HPLC on silica gel; elution with EtOAc-hexane (4:1)] to give the α-methyl 3-imino lactone **167**; ν_{max} /cm^{-1} ($CHCl_3$) 1637 (C=O); δ_H (400 MHz; $CDCl_3$) 0.83, 0.95/0.97 and 1.05/1.07 (9H, 3xs, 8-, 9- and 10-Me), 1.26-1.96 (4H, series of multiplets, 5- and 6-CH_2), 1.41/1.64 (3H, d, *J* 7.6, 2'-CH_3), 2.38/2.51 (1H, d, *J* 4.4, 4-H), 3.81/4.55 (1H, d, *J* 7.5, 2'-CH), 4.30/4.37 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 9.7, 19.3 and 19.9 (C-8, C-9 and C-10), 16.4 (C-3'), 21.3 (C-5), 34.4 (C-6), 48.2 and 50.0 (C-1 and C-7), 53.6 (C-4), 57.5 (C-2'), 80.3 (C-2), 171.8 (C-3) and 179.1 (C-1'); *m/z* 223 (M^+, 12%) and 189 (100).

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[e] The reactions in this series were essentially complete; thus, the crude yield was considered an adequate assessment of the chemical transformation in each reaction.

[f] The diastereomeric excess (% d.e.) was determined from the integral ratios of the 2-H signals for the diastereomeric components of the α-alkylated 3-imino-lactone.

The α-ethyl 3-imino lactone **168**

The procedure described for the synthesis of the α-methyl 3-imino lactone **167** was followed, using the 3-imino lactone **165** (0.39 g, 1.9 mmol), $KOBu^t$ (0.21 g, 1.9 mmol) and ethyl iodide (0.3 g, 2 mmol). Work-up gave the α-ethyl 3-imino lactone **168** (0.32 g, 72%; 68.7 % d.e.) which was then chromatographed [HPLC; elution with EtOAc-hexane (4:1)]; ν_{max} /cm^{-1} ($CHCl_3$) 1641 (C=O); δ_H (400 MHz; $CDCl_3$) 0.75/0.77, 0.89/0.90 and 0.99/1.01 (9H, 3xs, 8-, 9- and 10-Me), 1.04 (3H, t, *J* 7.3, 4'-CH_3) 1.26-1.96 (4H, series of multiplets, 5- and 6-CH_2), 1.87/2.08 (2H, m, 3'-CH_2), 2.37/2.49 (1H, d, *J* 4.5, 4-H), 3.56 (1H, dd, 2'-CH) and 4.23/4.31 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 9.9, 18.8 and 19.3 (C-8, C-9 and C-10), 10.2 (C-4'), 21.6 (C-5), 24.3 (C-3'), 33.9 (C-6), 48.9 and 49.3 (C-1 and C-7), 53.1 (C-4), 61.9 (C-2'), 81.5 (C-2), 170.6 (C-3) and 181.5 (C-1'); *m/z* 235 (M^+, 8%) and 162 (100).

The α-propyl 3-imino lactone **169**

The procedure, as described for the synthesis of the α-methyl 3-imino lactone **167**, was followed, using the 3-imino lactone **165** (0.31 g, 1.5 mmol), $KOBu^t$ (0.20 g, 1.7 mmol) and propyl iodide (0.3 g, 2 mmol). Work-up gave the α-propyl 3-imino lactone **169** (0.26 g, 69%; 60.6 % d.e.) which was then chromatographed [HPLC; elution with EtOAc-hexane (4:1)]; ν_{max} /cm^{-1} ($CHCl_3$) 1642 (C=O); δ_H (400 MHz; $CDCl_3$) 0.80/0.83, 0.92/0.94 and 1.02/1.07 (9H, 3xs, 8-, 9- and 10-Me), 0.89/0.97 (3H, t, *J* 7.6, 5-CH_3) 1.01-2.12 (8H, series of multiplets, 5-, 6-CH_2, 3'- and 4'-CH_2), 2.14/2.42 (1H, d, *J* 4.8, 4-H), 3.56 (1H, dd, 2'-CH) and 4.27 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 9.9/10.2, 18.9/19.3 and 20.0/20.3 (C-8, C-9 and C-10), 13.9 (C-5'), 19.1 (C-4'), 21.1/21.7 (C-5), 33.2 (C-3'), 33.9 (C-6), 48.9/46.5 and 49.2/49.3 (C-1 and C-7), 53.1/58.6 (C-4), 60.7 (C-2'), 81.5/81.6 (C-2), 170.8 (C-3) and 181.5 (C-1'); *m/z* 249 (M^+, 33%) and 176(100).

The α-butyl 3-imino lactone **170**

The procedure described for the synthesis of the α-methyl 3-imino lactone **167** was followed, using the 3-imino lactone **165** (0.32 g, 1.5 mmol), KOBu^t (0.20 g, 1.7 mmol) and butyl iodide (0.3 g, 2 mmol). Work-up gave the α-butyl 3-imino lactone **170** (0.31 g, 75%; 53.7 % d.e.) which was then chromatographed [HPLC; elution with EtOAc-hexane (4:1)]; ν_{max} /cm^{-1} ($CHCl_3$) 1644 (C=O); δ_H (400 MHz; $CDCl_3$) 0.75/0.91, 0.96/1.00 and 1.01/1.06 (9H, 3xs, 8-, 9- and 10-Me), 0.92 (3H, t, 6'-CH_3) 1.32-2.12 (10H, series of multiplets, 5-, 6-, 3'-, 4'- and 5'-CH_2), 2.14/2.42 (1H, d, *J* 4.8, 4-H), 3.64 (1H, dd, 2'-CH) and 4.35 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 9.9/10.2, 18.9/19.3 and 21.1/21.7 (C-8, C-9 and C-10), 13.9 (C-6'), 20.0/20.3 (C-5), 22.6 (C-5'), 28.0 (C-4'), 30.9 (C-3'), 33.9 (C-6), 46.5/48.9 and 49.1/49.3 (C-1 and C-7), 53.0/58.6 (C-4), 61.1 (C-12), 79.5/81.5 (C-2), 171.0 (C-3) and 181.5 (C-1'); *m/z* 263 (M^+, 11%) and 164 (100).

The α-pentyl 3-imino lactone **171**

The procedure described for the synthesis of the α-methyl 3-imino lactone **167** was followed, using the 3-imino lactone **165** (0.31 g, 1.5 mmol), KOBu^t (0.17 g, 1.5 mmol) and pentyl iodide (0.3 g, 1.5 mmol). Work-up gave the α-pentyl 3-imino lactone **171** (0.31 g, 73%; 59.5 % d.e.) which was then chromatographed [HPLC; elution with EtOAc-hexane (4:1)]; ν_{max} /cm^{-1} ($CHCl_3$) 1642 (C=O); δ_H (400 MHz; $CDCl_3$) 0.81/0.84, 0.93/0.95 and 1.06/1.08 (9H, 3xs, 8-, 9- and 10-Me), 0.88 (3H, t, 7'-CH_3), 1.30 - 2.14 (12H, series of multiplets, 5-, 6-, 3'-, 4'-, 5'- and 6'-CH_2), 2.40/2.43 (1H, d, *J* 4.4, 4-H), 3.64 (1H, dd, 2'-CH) and 4.27/4.36 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 10.0, 19.4 and 20.1 (C-8, C-9 and C-10), 14.1 (C-7'), 21.7 (C-5), 22.6 (C-6'), 25.6 (C-4'), 31.8 (C-5'), 34.0 (C-6), 49.0 and 49.3 (C-1 and C-7), 53.1/58.6 (C-4), 61.0 (C-2'), 79.5/81.5 (C-2), 170.8 (C-3) and 181.5 (C-1'); *m/z* 277 (M^+, 25%) and 162 (100).

The α-hexyl 3-imino lactone **172**

The procedure described for the synthesis of the α-methyl 3-imino lactone **167** was followed, using the 3-imino lactone **165** (0.28 g, 1.4 mmol), KOBu^t (0.16 g, 1.4 mmol) and hexyl iodide (0.3 g, 1.4 mmol). Work-up gave the α-hexyl 3-imino lactone **172** (0.33 g, 83%; 80.8 % d.e.) which was then chromatographed [HPLC; elution with EtOAc-hexane (4:1)]; ν_{max} /cm^{-1} ($CHCl_3$) 1642 (C=O); δ_H (400 MHz; $CDCl_3$) 0.82, 0.95 and 1.08 (9H, 3xs, 8-, 9- and 10-Me), 0.87 (3H, t, *J* 7.2, 8-CH_3), 1.23 - 2.16 (14H, series of multiplets, 5-, 6-, 3'-, 4'-, 5'-, 6'- and 7'-CH_2), 2.42/2.43 (1H, d, *J* 4.4, 4-H), 3.65 (1H, dd, 2'-CH) and 4.27/4.36 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 10.0, 19.4 and 20.1 (C-8, C-9 and C-10), 14.1 (C-8'), 21.7 (C-5), 22.6 (C-7'), 25.9, 29.3, 31.2 and 31.8 (C-3', C-4', C-5' and C-6'), 34.0 (C-6), 49.0 and 49.3 (C-1 and C-7), 53.1 (C-4), 61.0 (C-2'), 81.6 (C-2), 170.8 (C-3) and 181.4 (C-11); *m/z* 291 (M^+, 36%) and 248 (100).

The α-isopropyl 3-imino lactone **173**

The procedure described for the synthesis of the α-methyl 3-imino lactone **167** was followed, using the 3-imino lactone **165** (0.27 g, 1.3 mmol), KOBu^t (0.15 g, 1.3 mmol) and isopropyl iodide (0.2 g, 1.3 mmol). Work-up gave the α-isopropy-3-imino lactone **173** (0.11 g, 35%; 83.2% d.e.) which was then chromatographed [HPLC; elution with EtOAc-hexane (4:1)]; ν_{max} /cm^{-1} ($CHCl_3$) 1642 (C=O); δ_H (400 MHz; $CDCl_3$) 0.90, 0.99 and 1.03 (9H, 3xs, 8-, 9- and 10-Me), 1.28 (6H, m, 4'-CH_3), 1.40-2.29 and 2.47-2.64 (4H, series of multiplets, 5- and 6-CH_2), 2.30/2.37 (1H, d, *J* 4.8, 4-H, and 1H, 3'-H), 5.29 (1H, s, 2-H) and 5.34 (1H, s, 2'-H); δ_C (100MHz; $CDCl_3$) 9.3, 19.5 and 20.9 (C-8, C-9 and C-10), 21.6 and 22.9 (C-4'), 24.2 (C-5), 32.3 (C-6), 46.7 (C-3'), 47.4 and 50.0 (C-1 and C-7), 59.5 (C-4), 75.5 (C-2'), 79.2 (C-2), 173.4 (C-3) and 174.9 (C-1'); *m/z* 249 (M^+, 4%) and 109 (100).

The α-sec-*butyl 3-imino lactone* **174**

The procedure described for the synthesis of the α-methyl 3-imino lactone **167** was followed, using the 3-imino lactone **165** (0.26 g, 1.2 mmol), $KOBu^t$ (0.14 g, 1.2 mmol) and *sec*-butyl iodide (0.2 g, 1.2 mmol). Work-up gave the α-*sec*-butyl 3-imino lactone **174** (0.10 g, 31%; 83.2% d.e.) which was then chromatographed [HPLC; elution with EtOAc-hexane (4:1)]; ν_{max} /cm^{-1} ($CHCl_3$) 1638 (C=O); δ_H (400 MHz; $CDCl_3$) 0.88, 0.98 and 1.01 (9H, 3xs, 8-, 9- and 10-Me), 0.93-0.96 (6H, m, 3'-CH_3 and 5'-CH_3), 1.23-2.05 (6H, series of multiplets, 5-, 6- and 4'-CH_2), 2.09 (1H, d, *J* 5.0, 4-H), 2.26 (1H, m, 3'-CH), 3.73 (1H, s, 2-H) and 4.19 (1H, d, *J* 5.0, 2'-CH); δ_C (100MHz; $CDCl_3$) 9.3, 18.9 and 21.0 (C-8, C-9 and C-10), 25.2 (C-5), 28.6 (C-4'), 32.7 (C-6), 43.0 and 46.8 (C-1 and C-7), 48.7 (C-3'), 49.2 (C-4), 74.8 (C-2'), 77.2 (C-2), 170.8 (C-3) and 181.5 (C-1'); m/z 263 (M^+, 13%) and 162 (100).

The α-*allyl 3-imino lactone* **175** *and the* α,α-*diallyl 3-imino lactone* **176**

The procedure described for the synthesis of the α-methyl 3-imino lactone **167** was followed, using the 3-imino lactone **165** (0.28 g, 1.4 mmol), $KOBu^t$ (0.16 g, 1.4 mmol) and allyl iodide (0.2 g, 1.4 mmol). Work-up and chromatography [HPLC; elution with EtOAc-hexane (4:1)].gave: The α-*allyl 3-imino lactone* **175** (0.18 g, 11%; 88.0%); ν_{max} /cm^{-1} ($CHCl_3$) 1746 (C=O); δ_H (400 MHz; $CDCl_3$) 0.80, 0.94 and 1.07 (9H, 3xs, 8-, 9- and 10-Me), 1.33-2.82 (4H, series of multiplets, 5- and 6-CH_2), 2.45 (1H, d, *J* 4.4, 4-H), 2.68-2.93 (2H, m, 3'-CH_2), 3.74 (1H, m, 2'-CH), 4.28 (1H, s, 2-H) and 5.18, 5.97 (3H, 2×m, 4'-CH and 5'-CH_2); δ_C (100MHz; $CDCl_3$) 9.9, 19.3 and 20.0 (C-8, C-9 and C-10), 21.7 (C-5), 33.9 (C-6), 35.4 (C-3'), 49.0 and 49.3 (C-1 and C-7), 53.0 (C-4), 60.9 (C-2'), 81.7 (C-2), 117.7 and 134.6 (C-4' and C-5'), 170.3 (C-3) and 181.8 (C-11); *m/z* 247 (M^+, 11%) and 162 (100); (Found M^+: 247.1571. $C_{15}H_{21}NO_2$ requires *M*, 247.1572).

And the α,α-*diallyl 3-imino lactone* **176** (0.39 g, 21%); ν_{max} /cm^{-1} ($CHCl_3$) 1742 (C=O); δ_H (400 MHz; $CDCl_3$) 0.78, 0.92 and 1.01 (9H, 3xs, 8-, 9- and 10-Me), 1.29-2.03 (4H, series of

multiplets, 5- and 6-CH_2), 2.34-2.83 (5H, series of multiplets, 4-H, and 3'-CH_2), 4.34 (1H, s, 2-H) and 5.02-5.73 (6H, 2×m, 4'-CH and 5'-CH_2); δ_C (100MHz; $CDCl_3$) 9.7, 19.3 and 20.1 (C-8, C-9 and C-10), 21.5 (C-5), 34.6 (C-6), 41.6 and 43.7 (C-3'), 48.1 and 49.7 (C-1 and C-7), 53.9 (C-4), 66.1 (C-2'), 81.3 (C-2), 119.1, 120.0, 131.5 and 133.3 (C-4' and C-5') 171.9 (C-3) and 178.3 (C-11); *m/z* 287 (M^+, 12%) and 245 (100); (Found M^+: 287.1877. $C_{18}H_{25}NO_2$ requires *M*, 287.1885).

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