# APPLICATIONS OF CAMPHOR-DERIVED CHIRAL AUXILIARIES IN THE ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS AND OTHER SYSTEMS

**THESIS**

Submitted in Fulfilment of the Requirements for the Degree of

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by

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*Dedicated to my parents*

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A very special thank you to my parents and family who have always supported me in everything I have done.

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## LIST OF SELECTED ABBREVIATIONS

| | |
|---|---|
| BINAP | 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl |
| Bn | benzyl |
| BOC | *t*-butoxycarbonyl |
| BPE | 1,2-*bis*(phospholano)ethane |
| CDI | carbonyldiimidazole |
| COSY | $^{1}H$ - $^{1}H$ shift-correlated spectroscopy |
| DABCO | 1,4-diazobicyclo[2.2.2]octane |
| DCC | 1,3-dicyclohexylcarbodiimide |
| DCME | *bis*-(α,α-dichloromethyl)ether |
| DIPT | diisopropyl tartrate |
| DMAP | 4-dimethylaminopyridine |
| DMF | dimethylformamide |
| HMBC | heteronuclear multiple bond connectivity |
| HMPA | hexamethylphosphoramide |
| HMQC | $^{1}H$ - $^{13}C$ shift-correlated spectroscopy |
| HPLC | high performance liquid chromatography |
| IR | infrared |
| LAH | lithium aluminium hydride |
| LDA | lithium diisopropylamide |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear Overhauser enhancement spectroscopy |
| PTSA | *p*-toluenesulfonic acid |
| TBDMSOTf | *t*-butyldimethylsilyl trifluoromethanesulfonate |
| TBHP | *t*-butyl hydroperoxide |
| TLC | thin layer chromatography |

# ABSTRACT

A viable synthetic route to camphor-derived imino lactones as precursors for the asymmetric synthesis of α-amino acids has been established. Several synthetic strategies have been investigated and the required regioisomeric imino lactones were finally obtained *via* the step-wise condensation of *N*-(carbobenzyloxy)glycine with the α-ketols, 3-*exo*-hydroxycamphor and 2-*exo*-hydroxy-3-bornanone. Enolates of the camphor imino lactones, generated using potassium *tert*-butoxide, were reacted with a range of alkyl halides. Dialkylation was observed using the 2-imino lactone, while the regioisomeric 3-imino lactone derivative gave monoalkylated products with diastereoselectivities, shown by $^1$H NMR spectroscopy, to range from 43% d.e. for the methylated product to > 99% d.e. for larger alkyl groups. The expected preference for *endo*-alkylation is supported by NMR (chemical shift, coupling constant and NOE) data and was confirmed by acidic hydrolysis of the pentylated 3-imino lactone to afford the known acid. Computer modelling, with the software package HYPERCHEM®, was used to explore the conformational properties of the alkylated products and their enolate precursors. Exploratory work on the enantiomeric beneficiation of racemic amino acids, using alkylated imino lactone derivatives, revealed preferential *exo*-protonation of the enolate intermediates.

Asymmetric Baylis-Hillman reactions between a novel camphor-derived acrylic ester and a range of aldehydes afforded the corresponding 2-(hydroxyalkyl)acrylates in up to 59% d.e., the observed stereoselectivities being sensitive to both steric and electronic factors.

Attempts to prepare imino lactone derivatives from ketopinic acid, although unsuccessful, led to the isolation of two novel *N*-(carbobenzyloxy)glycinates, whose structures were established by 1- and 2-D NMR spectroscopy. Attempts to prepare "BINAP" analogues from dibornyl ethers also proved unsuccessful, but the investigation led to the discovery of a third, novel dibornyl ether.

# CHAPTER ONE: INTRODUCTION

## 1.1 THE IMPORTANCE OF ASYMMETRIC SYNTHESIS

The challenges of chemo- and regioselective bond formation are well understood and have, to some extent, been conquered. However, stereoselective reactions still present considerable difficulties and constitute a formidable challenge when required for the plant scale manufacture of enantiopure food additives, fragrances, agrochemicals and pharmaceuticals. Over 50% of commercially available drugs are chiral and may thus exist as enantiomeric pairs.[1] One enantiomer may be pharmacologically active while the other may be inactive or even toxic, a situation exemplified by the thalidomide tragedy.[2] Of the ten most important pharmaceutical compounds listed according to estimated worldwide sales in 1990, five were chiral.[3] Asymmetric synthesis is, perhaps, the single area in organic synthesis that has undergone the greatest development during the last ten years, and there is a sense in which asymmetric synthesis constitutes one of the major frontiers in modern organic chemistry.[4]

## 1.2 DEVELOPMENT PHASES IN ASYMMETRIC SYNTHESIS

Methods in asymmetric synthesis may be classified in terms of 'generations', which indicate the increasing sophistication of approach. These are:-

(i) 'first generation' or substrate-controlled methods;

(ii) 'second generation' or auxiliary-controlled methods;

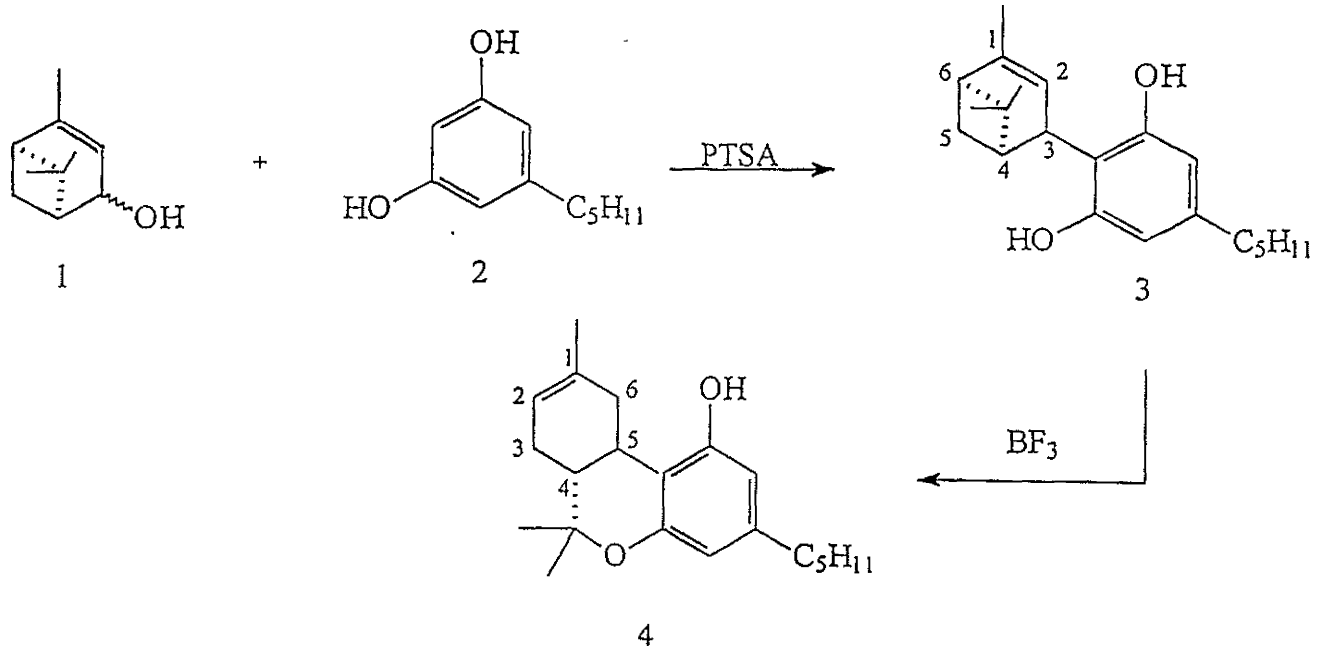
(iii) 'third generation' or reagent-controlled methods; and

(iv) 'fourth generation' or catalyst-controlled methods.

### 1.2.1 First generation methods: substrate-controlled asymmetric synthesis

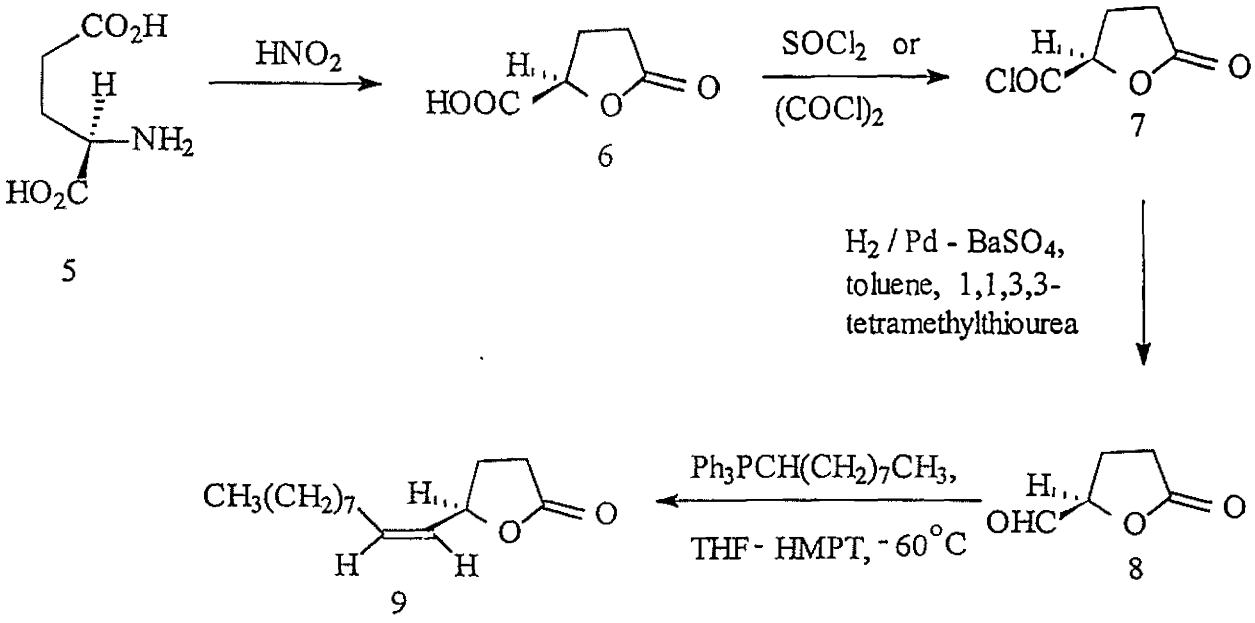
This approach involves diastereoselective reactions in which the formation of a new chiral centre is under the control of an existing centre in the substrate molecule.[5] Many natural products, such as amino acids, carbohydrates and alkaloids, are available in enantiomerically pure form and can be transformed into other chiral compounds. Such natural products constitute the "chiral pool".[6]

Many of the products targeted using this synthetic approach have themselves been naturally occurring compounds with desirable chemotherapeutic or pharmacological activity. For example, the condensation of olivetol (**2**) with an isomeric mixture of verbenol (**1**) gave the intermediate (**3**) in 45% yield (**Scheme 1**). Rearrangement of this intermediate with boron trifluoride afforded the cannabinol (**4**) with an optical purity of *ca.* 97%.[7] This product, one of the bioactive constituents of marijuana, is of particular interest since it is believed to inhibit nausea resulting from chemotherapy and is also effective in inhibiting glaucoma.[8] Since the transformation (**3** → **4**) can hardly involve epimerization at C-3(5) and C-4 of the cyclohexane system, the intermediate was concluded to possess a trans arrangement of the phenyl substituent and the bimethylene bridge. The exclusive formation of the trans intermediate (**3**) and, hence, the trans product (**4**), is believed to be due to steric factors.




SCHEME 1

Another example of this approach involves the preparation of the Japanese beetle pheromone (9), which was obtained from (*R*)-glutamic acid (5) in four steps as illustrated in **Scheme 2**. In this particular synthesis, the stereospecificity is pre-determined by the stereospecific deamination of *(R)*-glutamic acid (5) to give the lactone acid (6) . The transformation of compound (6) to the acid chloride (7) proceeded smoothly, and was followed by Rosenmund reduction to the aldehyde (8). The pheromone (9) was finally obtained *via* a Wittig reaction involving inverse addition.[9]




SCHEME 2

While numerous asymmetric syntheses have been successfully achieved using substrate-controlled methods, there are several disadvantages to this approach, *viz.*,

(i) the chiral substrate is consumed in the process;

(ii) the range of naturally occurring chiral subsrates is limited and, consequently, extensive synthetic modification is often necessary to obtain the required product;

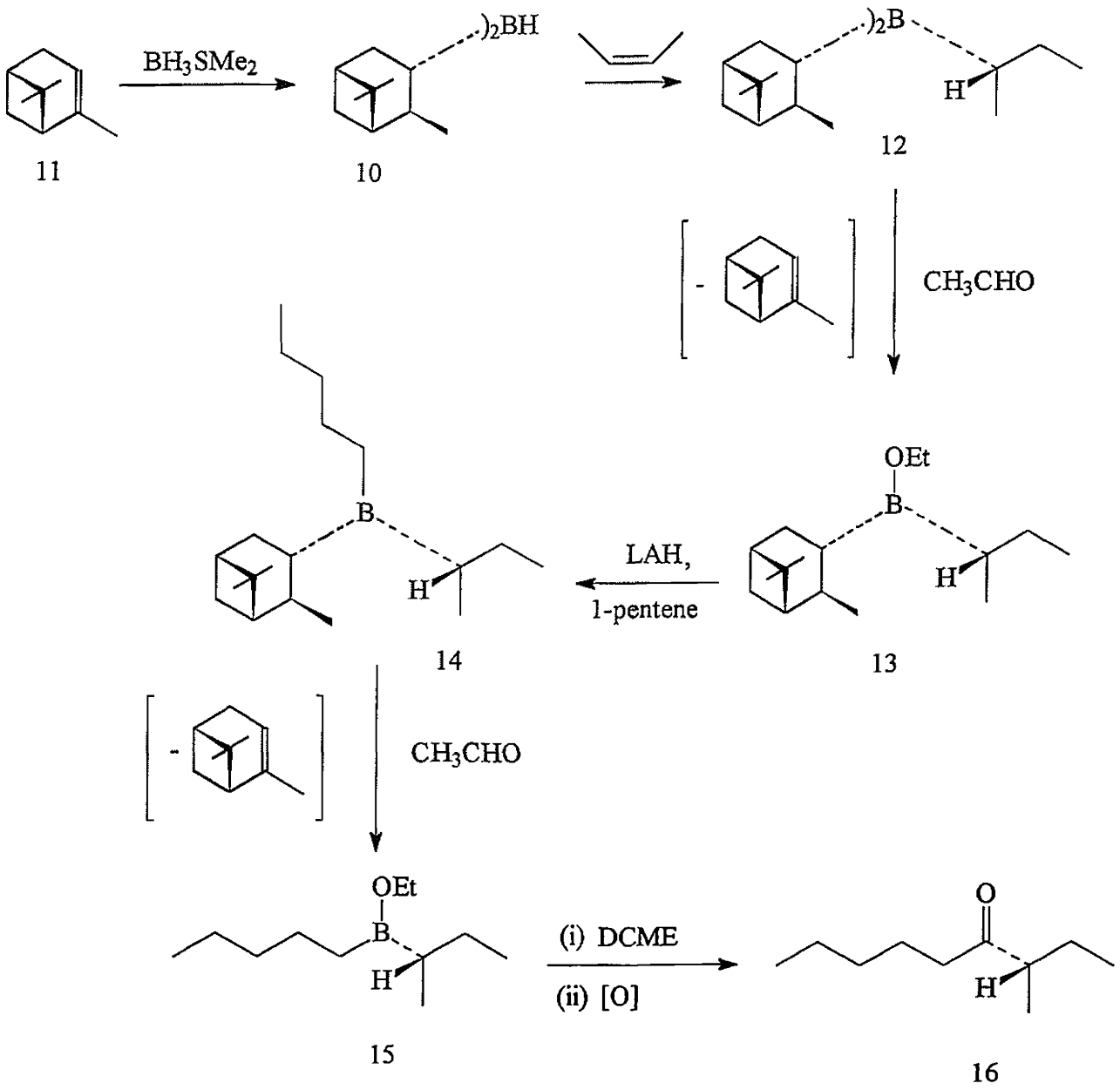
(iii) commercially available, optically pure, compounds can be very expensive;

(iv) natural products are seldom available in both enantiomeric forms, thus limiting access to a particular enantiomeric product; and

(v) the possibility exists of racemisation during the synthetic pathway.

### 1.2.2 Second generation methods: auxiliary-controlled asymmetric synthesis

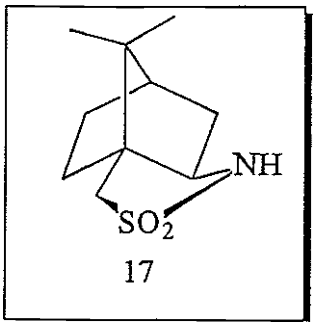
In this approach, a chiral auxiliary is attached to the substrate before the chiral induction is performed. Chirality in the auxiliary then controls the asymmetric induction, and the auxiliary is removed for re-use once the new chiral centre has been generated.[5] Chiral auxiliaries are typically naturally occurring, enantiomerically pure compounds or their derivatives. For example, the monoterpene, α-pinene (**11**) has been used as a chiral auxiliary in the synthesis of (*S*)-(+)-3-methyl-4-nonanone (**16**), an ant alarm pheromone (**Scheme 3**).[10] In this case, *cis*-2-butene was hydroborated with (+)-diisopinocamphenylborane ($Ipc_2BH$) (**10**) to yield the organoborane (**12**) containing the chiral butyl group in 98% e.e. Selective elimination of α-pinene by treatment of the trialkylborane (**12**) with acetaldehyde under mild conditions afforded the boric ester (**13**), reduction of which, with lithium aluminium hydride (LAH) in the presence of 1-pentene, yielded the trialkylborane (**14**). Similar treatment of compound (**14**) with acetaldehyde selectively eliminated the remaining α-pinanyl group to provide the ethylborinate (**15**). Treatment of the ester (**15**) with *bis*-(α,α-dichloromethyl)ether (DCME), followed by oxidation afforded (*S*)-(+)-3-methyl-4-nonanone (**16**) in 95% e.e. The high stereoselectivity realized in the asymmetric hydroboration steps is clearly maintained in the formation of the carbon-carbon bond during the final oxidation.




SCHEME 3

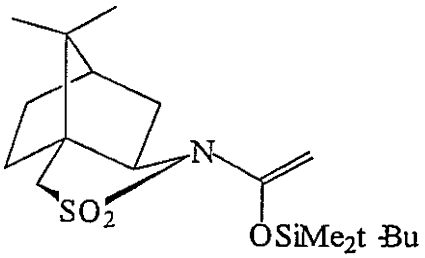
One of the most efficient chiral auxiliaries to have been developed is the sultam (**17**), which was introduced by Oppolzer.[11] The efficiency of this auxiliary is demonstrated in the titanium tetrachloride-promoted addition of the *O*-silyl-*N,O*-ketene acetal (**18**) to aldehydes to afford enantiomerically pure α-unsubstituted β-hydroxy carboxylic acids (**20**) in good chemical and

optical yield[12] (**Scheme 4**). The sultam-derived *O*-silyl-*N,O*-ketene acetal is readily prepared by acetylating bornane-10,2-sultam (**17**) with acetyl chloride/NaH and then treating the resulting amide with *t*-butyldimethylsilyltriflate and triethylamine in dichloromethane. Aldolisation of the *O*-silyl-*N,O*-ketene acetal (**18**) with various aldehydes, followed by hydrolysis, gave the β-hydroxy carboxylic acids (**20**) in 82 - 93% e.e. (**Scheme 4**).




17

(i) NaH, $CH_3COCl$
(ii) TBDMSOTf, $NEt_3$, $CH_2Cl_2$

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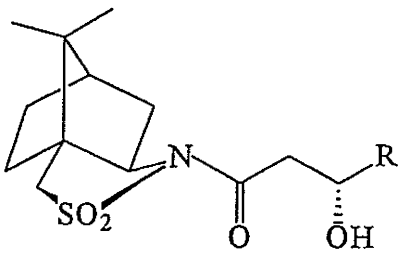
RCHO , $CH_2Cl_2$
$TiCl_4$ , - 78°C

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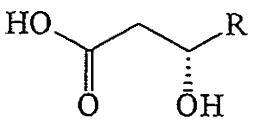
$LiOH$ , $H_2O_2$




20

| R | % e.e. |
|---|---|
| Ph | 82 |
| Et | 82 |
| i-Pr | 93 |
| $C_6H_{11}$ | 90 |

SCHEME 4

The observed stereoselectivity can be explained by comparing the two "open" transition states A* and B*, in which steric interactions involving the R-group are considered critical (**Figure 1**). Apparently the gauche interaction R/OSiMe$_2$Bu$^t$ in the preferred transition state A* is less serious than the interaction between the R-substituent and the 3-CH$_2$ group in transition state B*.

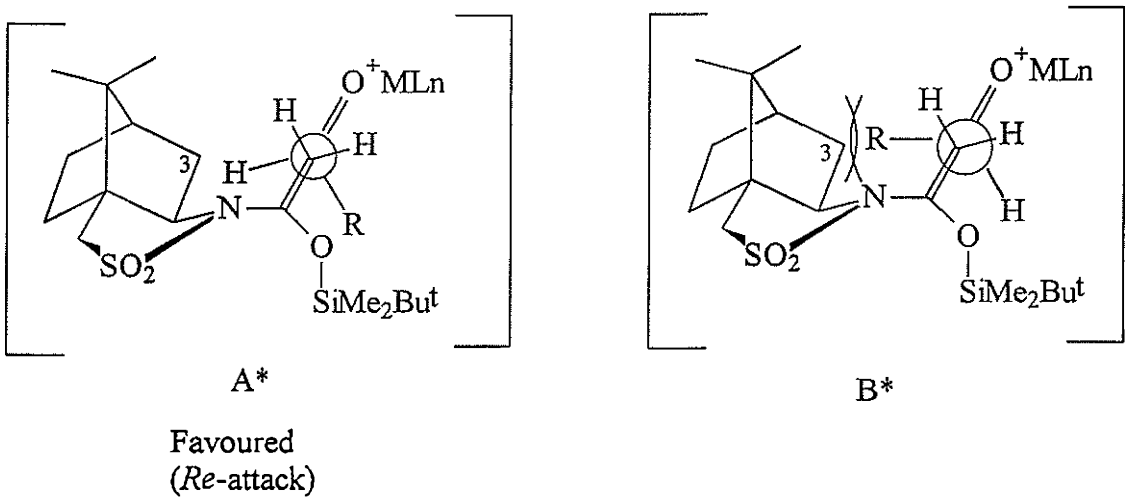
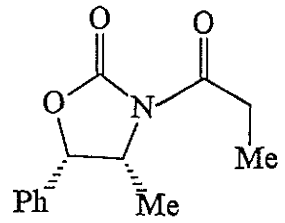



FIGURE 1. Comparison of the two "open" transition states A* and B*.

A range of efficient chiral auxiliaries has been introduced, including Evans' *N*-acyl oxazolidinone (**21**)[13] and Masamune's chiral ethyl ketone (**24**).[14] These auxiliaries, when bound to dialkylboron enolates, have been used in highly enantioselective aldol reactions with numerous aldehydes to afford β-hydroxycarbonyl compounds (**Scheme 5**). Evans prepared the oxazolidone (**21**) in good yield by treating (*1S,2R*)-norephedrine with phosgene or diethyl carbonate, followed by lithiation and subsequent reaction with propionyl chloride. Highly stereoselective enolization of the auxiliary to the enolate (**22**) may be achieved with either a lithium amide base or dibutylboryl trifluoromethanesulphonate. Masamune, on the other hand, prepared the chiral ethyl ketone (**24**) from (*S*)-mandelic acid, which was catalytically hydrogenated, using a Rh/Al$_2$O$_3$ catalyst stem, to yield the saturated ring prior to introduction of the ethyl group and silylation of the hydroxyl

group. The enolate (25), prepared using diallylboron trifluoromethanesulphonate, was then reacted with various aldehydes. In all cases, the *syn* products were isolated with no trace of the corresponding *anti* products, indicating exclusive formation of the (*Z*)-enolate (25).

EVAN'S ROUTE



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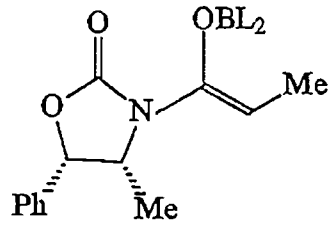

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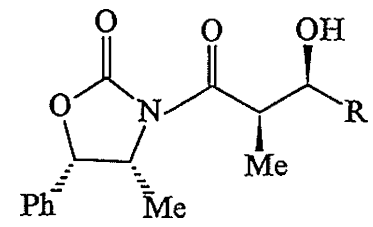

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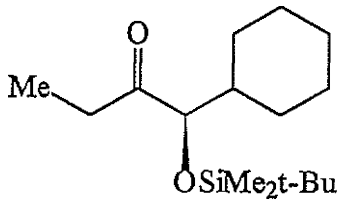
MASAMUNE'S ROUTE



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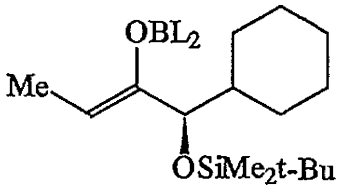

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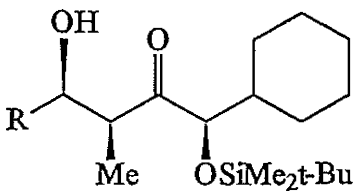

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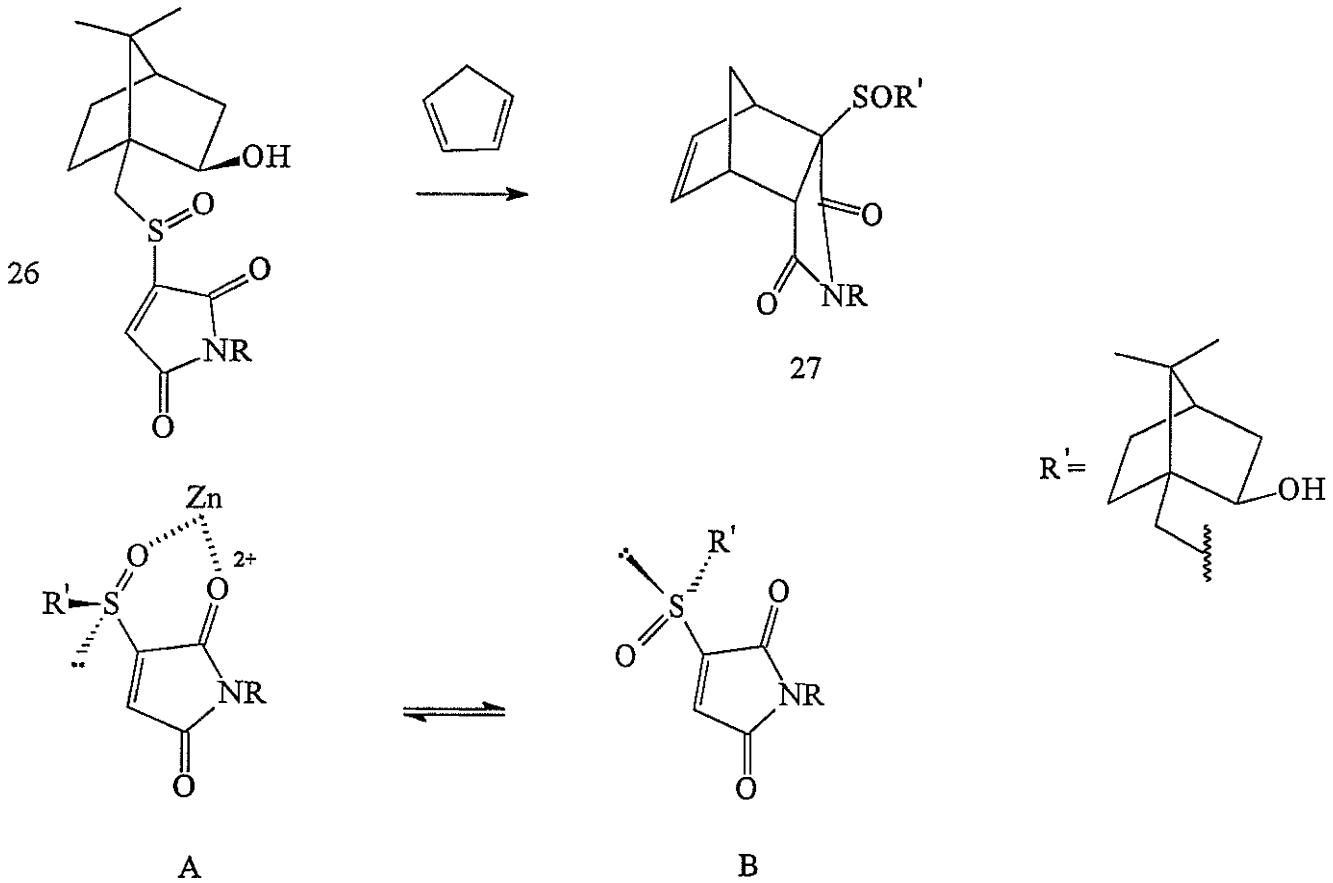
SCHEME 5

Chiral auxiliaries have been used in asymmetric Diels-Alder reactions by attaching the auxiliary to the dienophile or to the diene.[15] The doubly-activated dienophile (**26**), which exhibits good diastereoselectivity[16] when reacted with cyclopentadiene to give the adduct (**27**), is readily prepared by reacting maleimides with 10-mercaptoisoborneol, followed by chlorination, elimination and oxidation. These chiral maleimides have been found to be quite reactive towards cycloaddition. It has been observed that, under chelation-controlled conditions, the sulfoxide exists predominantly in conformation A, in which the zinc cation co-ordinates with one of the imido carbonyl groups and the sulfinyl oxygen, and preferential attack of the diene occurs on the less hindered "lone-pair side" of the dienophile (**Scheme 6**).

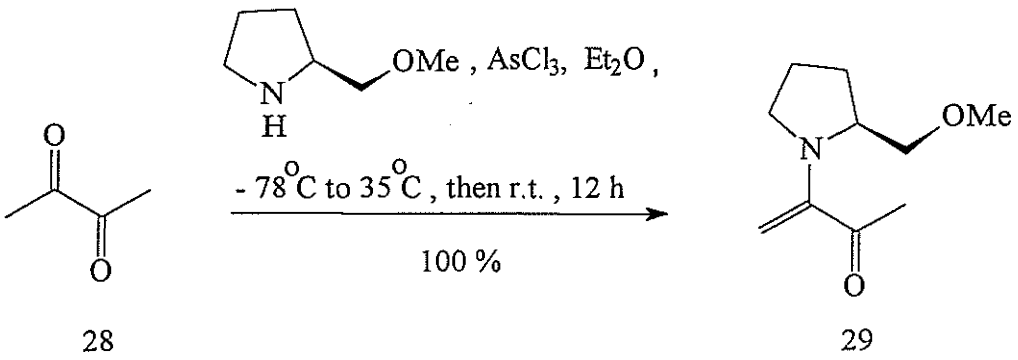



SCHEME 6

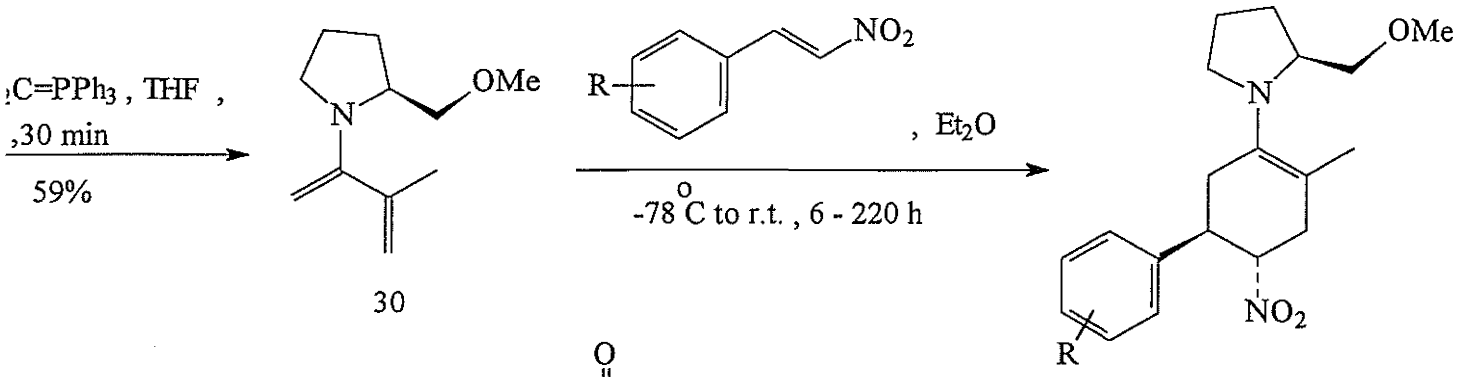
Amino acid-derived dienes, used in Diels-Alder reactions, include the butadiene derivatives (**29**) and (**30**) which undergo diastereo- and enantioselective [4 + 2] cycloadditions with 2-aryl-1-nitroethanes.[17] The chiral diene (**30**) was prepared by reacting 2,3-butanedione (**28**) with (*S*)-2-(methoxymethyl)pyrrolidine using a modified Weingarten procedure. Witting olefination of the resulting enamine (**29**) afforded the substituted 1,3-butadiene (**30**) (**Scheme 7**).

The stereochemical outcome of the [4 + 2] carbocyclisation can be rationalised in terms of transition state A*; the annulation process is considered to involve 1,4-addition of the amino-butadiene to the nitroalkene and, after a rotation of *ca.* 120° around the newly-formed C-C bond, addition of the nitronate anion to the vinylogous carbammonium ion.

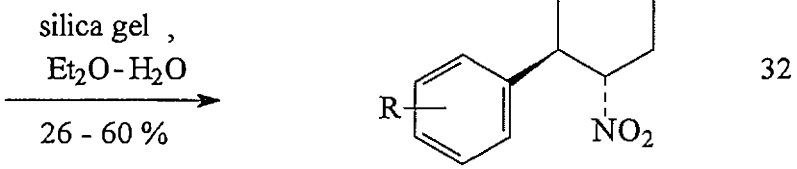
Important guidelines to be considered in the chiral auxiliary approach were proposed by Eliel in 1974.[18] These are that the chiral auxiliary must lead to the desired enantiomer in high optical and chemical yields, the chiral product must be readily separable from the chiral auxiliary, and it must be possible to recover the chiral auxiliary for re-use in good yield in undiminished optical purity.




28 29



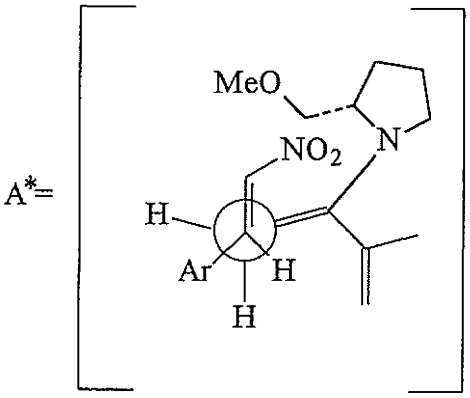

30 31




32

95 - 99 % e.e

CHEME 7



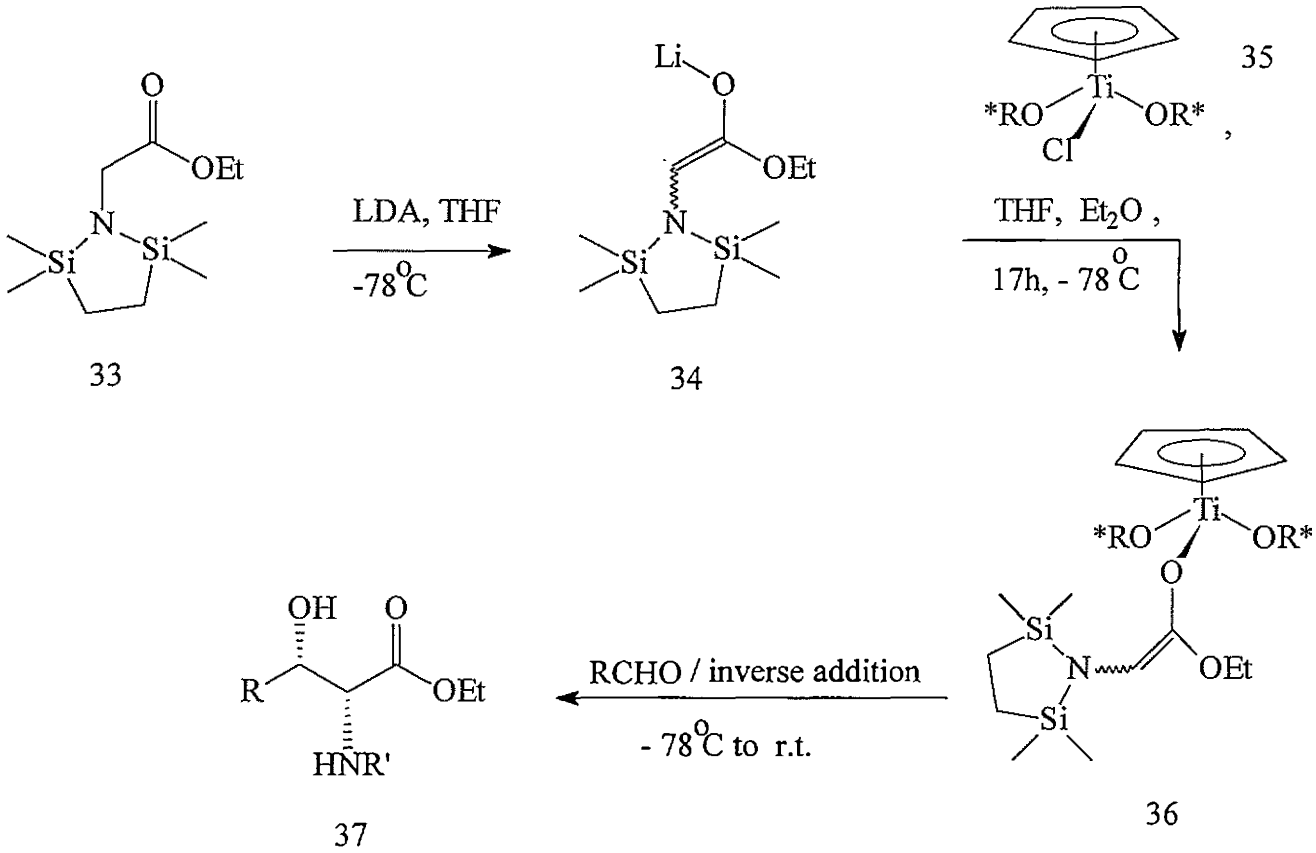

**Proposed transition state complex**

### 1.2.3 Third generation asymmetric synthesis: reagent-controlled methods

In this approach, a chiral reagent is used in stoichiometric quantities to effect asymmetric induction. The chiral centre is not vested in the substrate and, consequently, is not determined directly, in the planning process, by the structure of the target molecule; efficient asymmetric induction is the only concern. The synthesis of *N*- and *O*-protected D-threo-β-hydroxy-α-amino acids (**37**) demonstrates this approach (**Scheme 8**).[19] In this case, the lithium enolate (**34**) of ethyl (2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopent-1-yl)acetate (**33**) was transmetallated in a slow reaction with chloro(cyclopentadienyl)*bis*(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) titanate (**35**). Subsequent aldol reaction of the titanium enolate (**36**) with aldehydes yielded the D-*threo*-β-hydroxy-α-amino acid esters (**37**) with astonishingly high stereoselectivity (87 - > 98% d.e.).

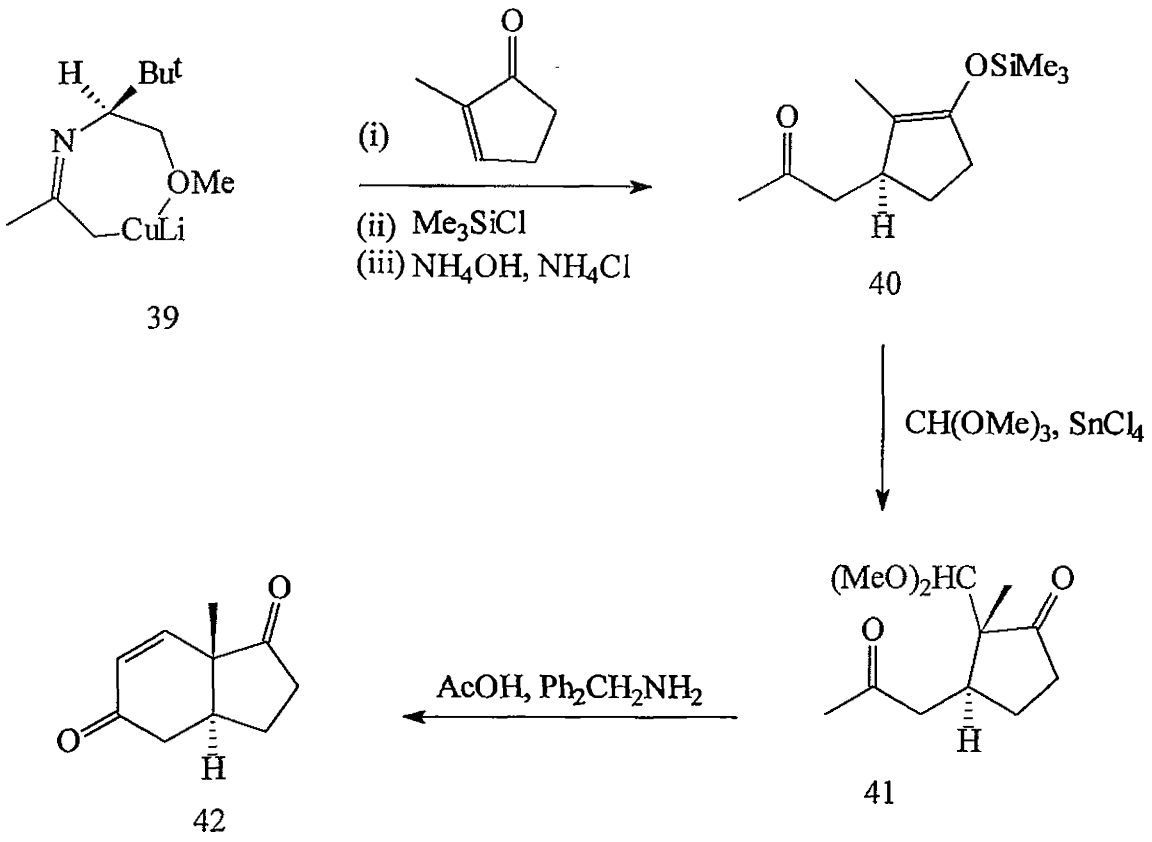
The synthesis of the cyclopentanone derivative (**40**) is another example of the 'third generation' approach to asymmetric synthesis.[20] In this synthesis, the acetone imine of cyclohexylamine in dry THF was treated with BuLi, followed by the addition of CuI and $Me_2S$ in THF at -60 °C. The resulting solution, containing the copper azaenolate (**39**), was kept at -60 °C for 1 h; thereafter, 2-methylcyclopentenone was added slowly, yielding the chiral silyl enol ether (**40**). Tin chloride-catalysed formylation, using methyl orthoformate, afforded 3-acetonyl-2-(dimethoxymethyl)-2-methylcyclopentanone (**41**), which was then subjected to acid catalysed aldol condensation by heating with $PhCH_2NH_2$ in acetic acid to yield the trans indandione derivative (**42**), with only 2% of the cis isomer, in 48% yield (**Scheme 9**).

R* = 1,2;5,6-di-*O*- isopropylidine-α-D-glucofuranos-3-yl




33 34 36 37

SCHEME 8




SCHEME 9

### 1.2.4 Fourth generation methods: catalyst-controlled asymmetric synthesis

Chiral catalysts may be covalently attached to the substrate in an intermediate in the catalytic cycle or may act in an intermolecular fashion, inducing asymmetry in a single step. Asymmetric catalysis can be divided into the following classes:-

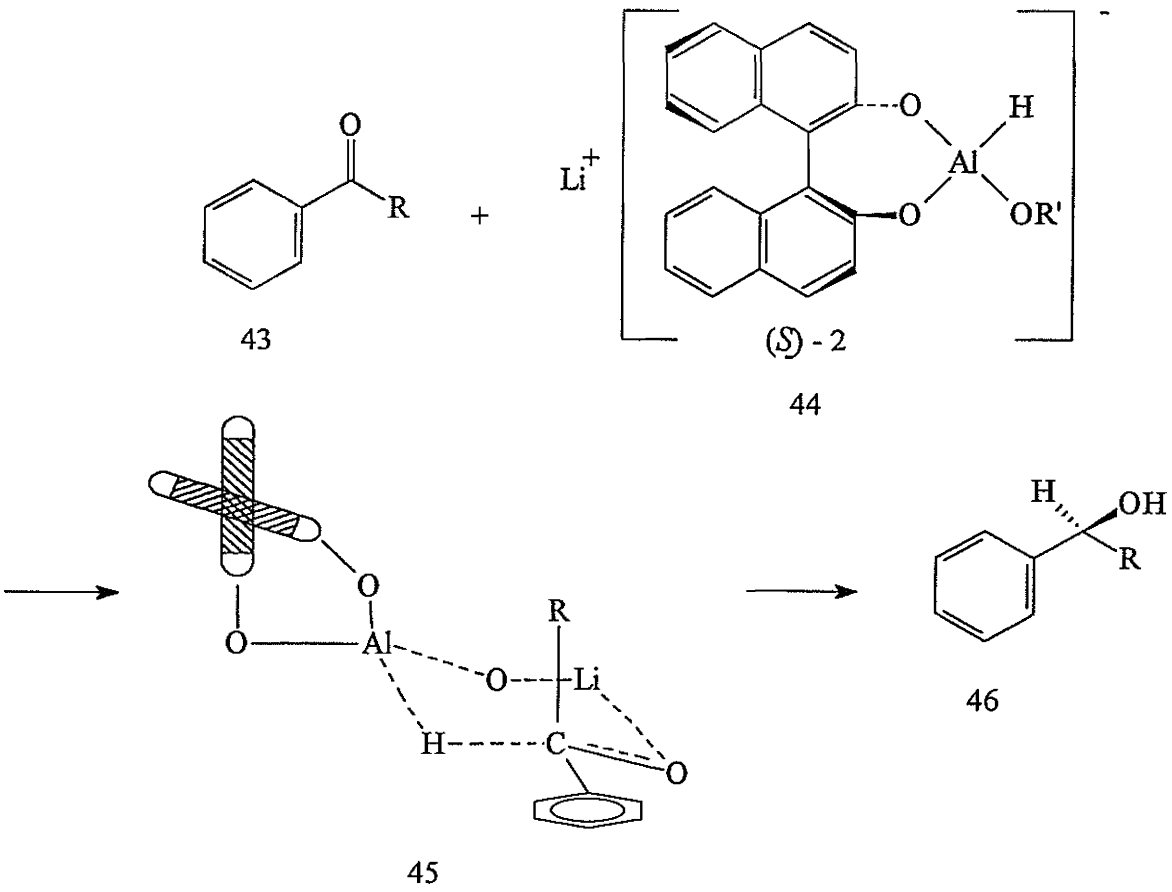
(i) asymmetric catalysis by organometallic species;

(ii) asymmetric catalysis by organic compounds; and

(iii) biochemical methods.

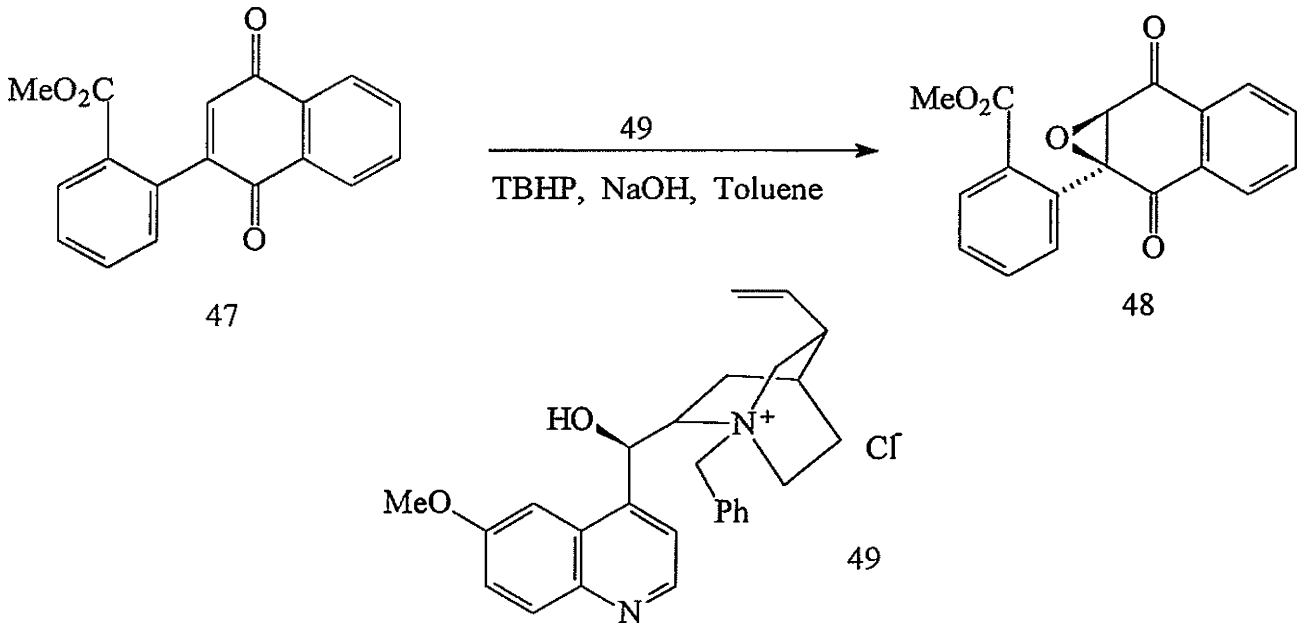
A wide spectrum of chiral organometallic complexes have been used successfully in asymmetric

hydrogenation, cyclopropanation, oxidation and epoxidation reactions.[21] Binaphthol and its derivatives (BINAP systems) are readily prepared and serve as excellent ligands for chiral organometallic complexes. For example, complex aluminium hydride reagents (**44**) may be prepared *in situ* from lithium aluminium hydride, optically pure 2,2′-dihydroxy-1,1′-binapthyl and a hydroxylic compound (R′OH).[22] Such an aluminium hydride reagent was used to reduce butyrophenone (**43**, R = $CH_3CH_2CH_2$) with complete topological control, the favoured conformation of the intermediate (**45**) containing an axial alkyl and an equatorial phenyl group. Work-up and purification afforded the optically pure alcohol (**46**) (**Scheme 10**).




SCHEME 10

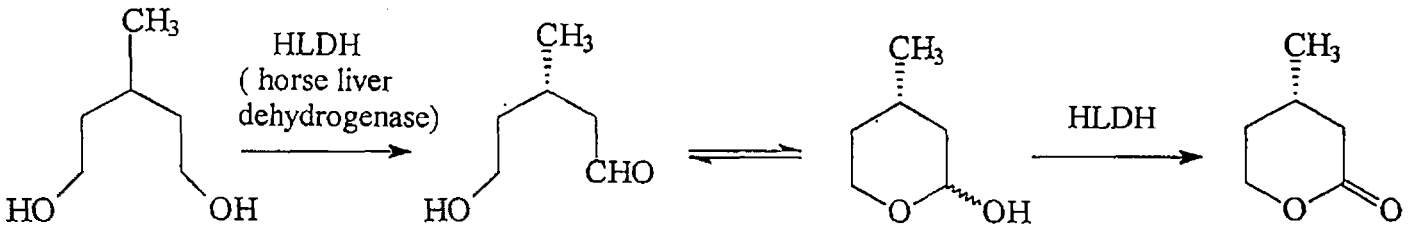
The application of non-metal based asymmetric catalysts in asymmetric synthesis can be demonstrated by the epoxidation of the quinone derivative (**47**) in 78% e.e. using the quinine derivative (**49**) as a catalyst.[23a,23b] The procedure employs anhydrous TBHP as an oxidant under basic conditions, the catalyst (**49**) acting as a chiral organo phase transfer agent (**Scheme 11**).




SCHEME 11

The importance of enzymes in asymmetric synthesis stems from their capacity to exert unique control over several stereochemical aspects in single-step reactions, their high efficiency in asymmetric reactions (which can be up to $10^{12}$ times faster than non-enzymatic reactions), their applicability to a wide spectrum of reaction types, and their selectivity with respect to structure and stereochemistry. For example, horse liver dehydrogenase (HLDH) effects oxidation of 3-methyl-pentane-1,5-diol (**50**) in greater than 90% yield with total pro-*S* hydroxyl specificity to give (3*S*)-3-methylvalerolactone (**53**) exclusively, as illustrated in **Scheme 12**. The observed

stereoselectivity has been explained by diamond lattice analysis[24] with the oxidation involving removal of the pro-*R* hydrogen from the *Re* lattice direction.

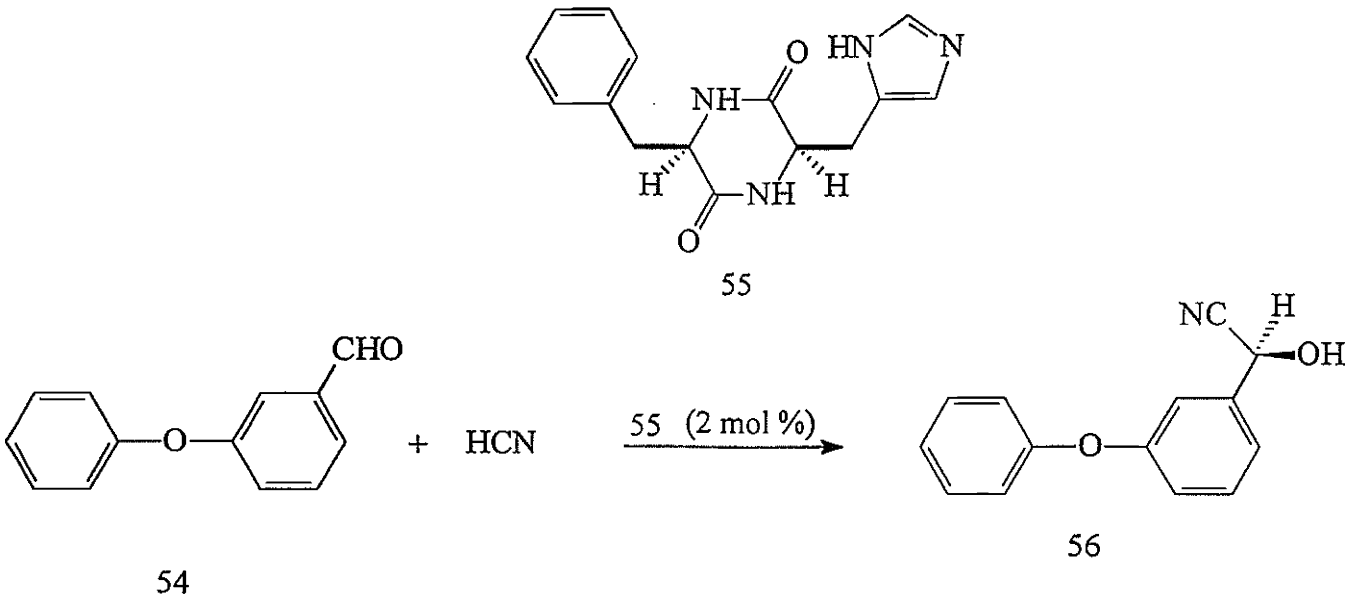



50 51 52 53

SCHEME 12

Finally, emerging methodologies, still in their infancy, are broadly termed 'beyond the fourth generation'. These encompass the following processes.

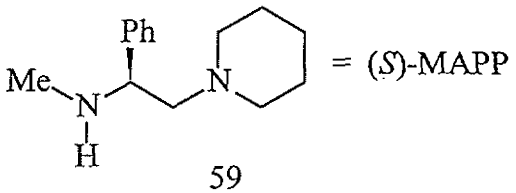
(i) Enantioselective autocatalysis, *i.e.* when reaction products catalyse their own enantioselective formation.[25] Such autocatalysis is demonstrated by the addition of HCN to 3-phenoxybenzaldehyde (**54**) to afford the cyanohydrin (**56**) in a process which is catalysed by the cyclic dipeptide (**55**) (**Scheme 13**). The non-linear effect of catalyst concentration on the observed enantiomeric excess of the cyanohydrin (**56**) is ascribed to the product influencing its own formation, with more efficient catalysis being achieved when small amounts of cyanohydrin (with appopriate absolute configuration) are present initially. The actual catalyst is considered to be a complex composed of both dipeptide and product. Thus, the product accelerates its own asymmetric formation.




SCHEME 13

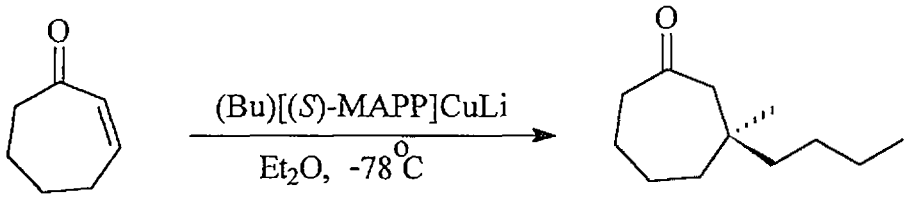
(ii) Unexpected effects observed when several auxiliaries operate together in the same process.[5]

(iii) 'Asymmetric amplification', a term introduced by Oguni *et al.*[26] in 1988 describing the phenomenon of obtaining products in very high enantiomeric excess using a chiral auxiliary of low % e.e. Asymmetric amplification is illustrated by the conjugate addition of a chiral cuprate to the cyclic enone (57) observed by Rossiter *et al.*[27] (**Scheme 14**). The enantiopure amidocuprate, derived from (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine [(*S*)-MAPP] (59) and butyllithium, reacted enantioselectively with 2-cycloheptenone (**57**) to give 3-butylheptanone (**58**) in 96% e.e. Decreasing the optical purity of (*S*)-MAPP to 56% e.e. gave 3-butylheptanone (**58**) in 82% e.e.




= (*S*)-MAPP

59




57 58

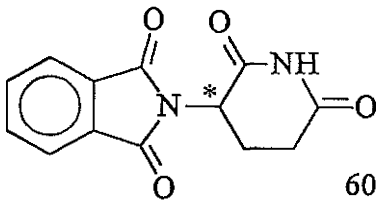
SCHEME 14

## 1.3 ASYMMETRIC SYNTHESIS OF AMINO ACIDS

It is hardly surprising that the investigation of amino acids is of fundamental interest to scientists in so many diverse fields. Their primary importance stems, of course, from the fact that they are the basic constituents of enzymes as well as structural and other proteins. They can support the biosynthesis of myriad natural products including non-protein amino acids, cyanogenic glycosides, pharmacologically active alkaloids, certain phenols, purines and pyrimidines, nucleic acids, condensed tannins, lignins and other metabolites.[28] This wide spectrum of applications of amino acids and their consequent economic significance has led to the development of a variety of procedures for their extraction from natural sources and for their chemical synthesis.

The chirospecific synthesis, separation and analysis of optically active amino acids is of considerable current interest. The number of known, naturally occurring α-amino acids has grown substantially from the 20 odd amino acids commonly found in proteins to over 500.[28] In addition, there has been a tremendous surge of interest in the asymmetric synthesis of relatively inaccessible natural amino acids whose biological potential and general synthetic utility are just beginning to be realized. Much of this interest emanates from the expanding need to synthesize new, enantiomerically pure drugs. The issue of enantiomeric purity was highlighted by the thalidomide tragedy in the late 1950's and early 1960's. Considered safe, racemic thalidomide (**60**) was used as a tranquilizer, but the disastrous teratogenic effects of the (*S*) enantiomer were subsequently established.[29]

There are now several methods for preparing amino acids in high enantiomeric purity. These include asymmetric hydrogenation, alkylation, amination and other transformations, and the examples which follow provide an illustrative rather than exhaustive overview of such methods..



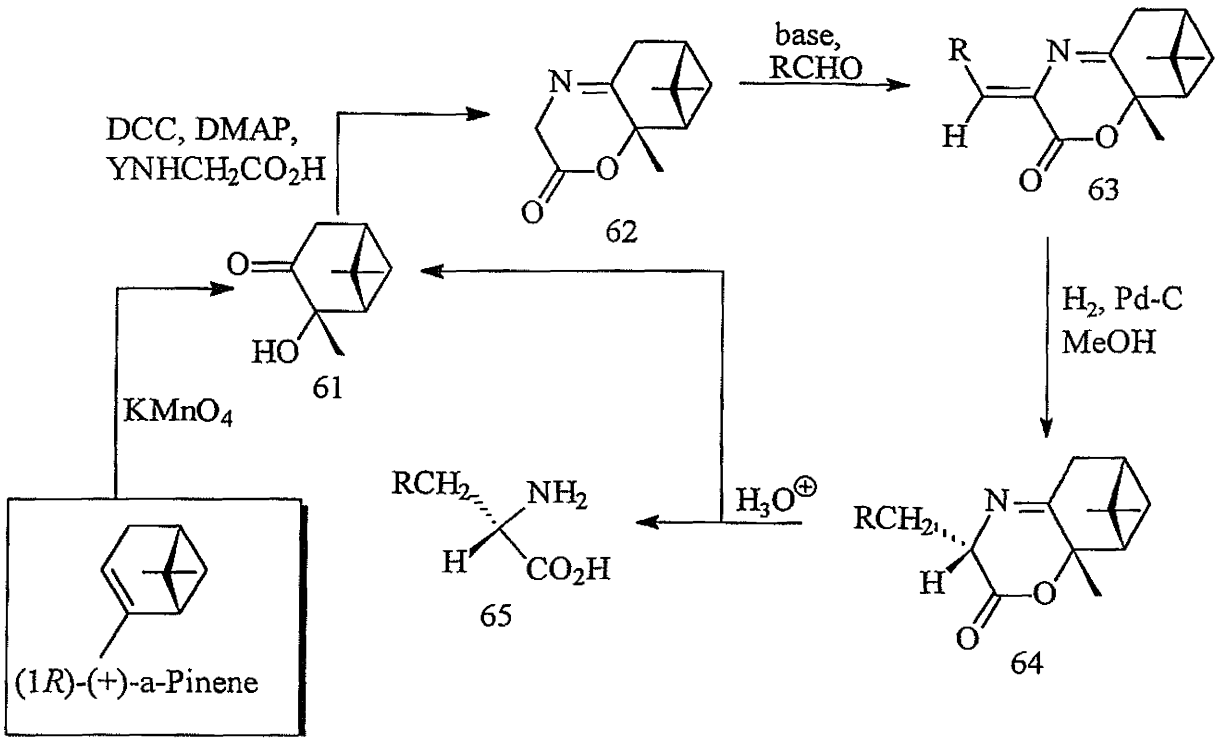
60

Thalidomide

### 1.3.1 Asymmetric Hydrogenation

#### 1.3.1.1 Chiral Auxiliary-Mediated Hydrogenation[30]

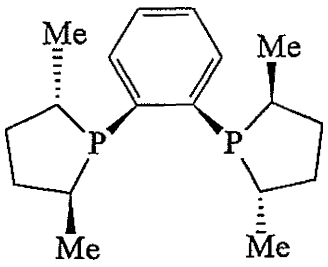
The bicyclic chiral auxiliary, 2-hydroxypinan-3-one (**61**), is obtained as outlined in **Scheme 15.** Permanganate oxidation of α-pinene affords an α-ketol, which may be reacted with *N*-carbobenzyloxyglycine to generate the imino lactone (**62**). The lactone may be condensed with a variety of aldehydes to afford the corresponding, cyclic α,β-didehydroamino acid derivatives (**63**). Hydrogenation of the α,β-didehydroamino acid derivatives (**62**) at 1 atmosphere, using a palladium on charcoal catalyst at room temperature, gave the corresponding (*S*)-amino acid derivatives (**64**), hydrolysis of which afforded the chiral α-amino acids (**65**) together with the chiral auxiliary (**61**). The quantitative topological control, observed in these reactions, suggests that hydrogenation occurs at the same face as the pinane *gem*-dimethyl group.




SCHEME 15

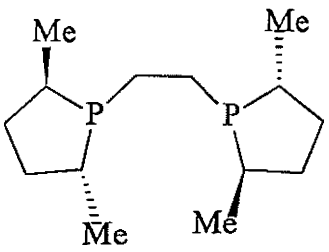
### 1.3.1.2 Chiral Catalyst-Mediated Hydrogenation

Asymmetric catalytic hydrogenation represents one of the most efficient and convenient methods of preparing a wide range of enantiomerically pure compounds.[31] Interest in practical routes to α-amino acids has ultimately led to the development of various, effective diphosphine-rhodium catalysts.



(*S,S*)-Me-DuPHOS

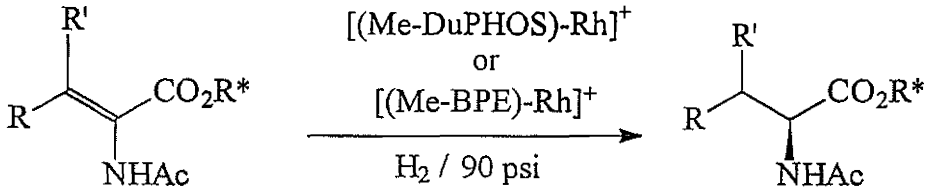
66



(*R,R*)-Me-BPE

67

Rhodium complexes of the chiral ligands, Me-Duphos (**66**) and Me-BPE (**67**) induce high enantioselectivity (up to 96% e.e.) in the hydrogenation of β,β-disubstituted α-enamides at 90 psi in benzene (**Scheme 16**). When dissimilar groups occupy the β-position of α-enamide substrate (**68**) ($R \neq R^1$), a second stereogenic centre is established.[32] These catalysts have provided access to a broad range of diastereomerically pure, β-branched amino acids (**69**) with high levels of enantioselectivity.




68 69

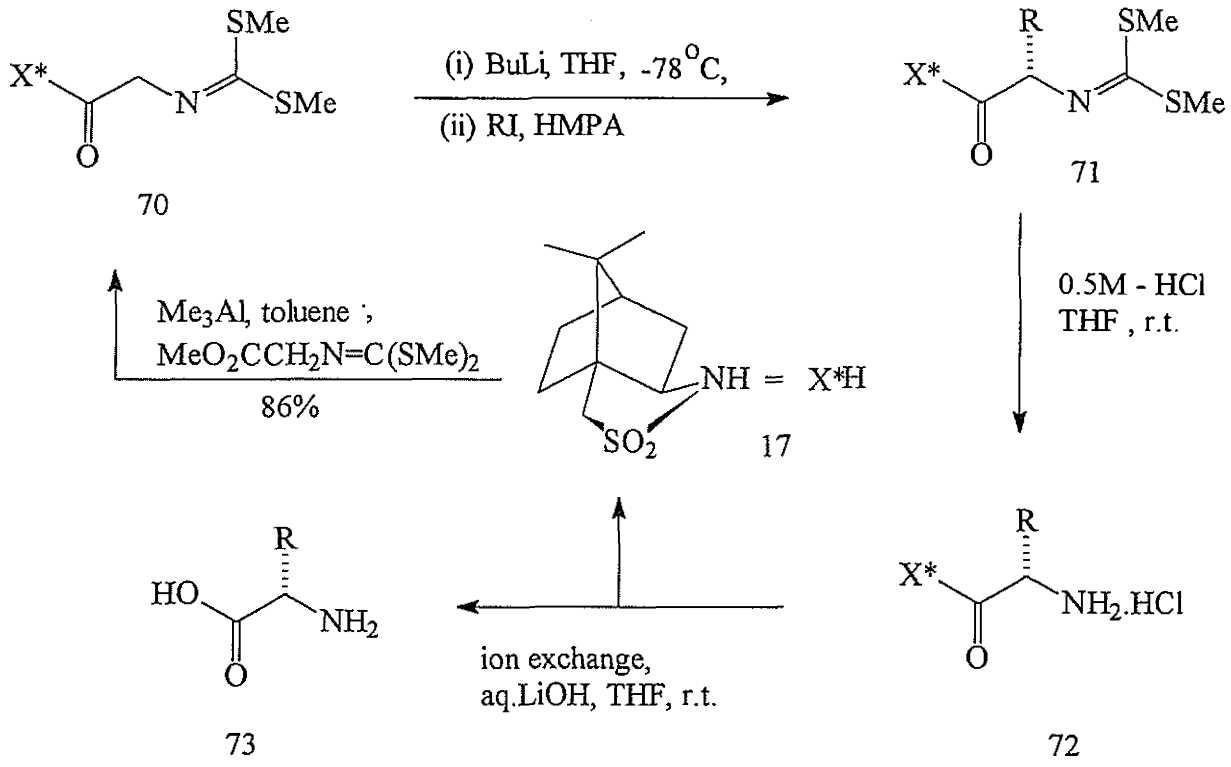
R* = Me

SCHEME 16

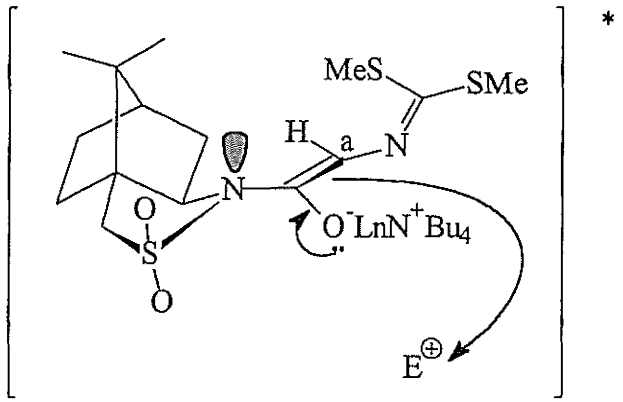
### 1.3.2 Asymmetric Alkylation

#### 1.3.2.1 Nucleophilic Asymmetric Alkylation

Since the mid 1980's significant progress has been made in controlling stereochemical reactions involving chiral enolates for the purpose of constructing single diastereomers. Application of this approach to the alkylation of chiral glycine enolates is illustrated by the alkylation of the *N*-acylated bornane-10,2-sultams (**70**) developed by Oppolzer *et al.*[33] The chiral auxiliary was prepared by $Me_3Al$-mediated acylation of the camphor sultam (**17**) with methyl-*N*-[bis(methylthio)methylidene]glycinate. Deprotonation of the *N*-acylated bornane-10,2-sultam (**70**) with either BuLi or sodium hexamethylsilazide in THF affords the chelated lithium or sodium (*Z*)-enolates. Alkylation of the enolate intermediates with a variety of alkyl iodides leads to the alkylated products (**71**) in 94.7 - 98.4% d.e. (**Scheme 17**). It has been observed that the products exhibit π-face selective alkylation, and it has been postulated that attack occurs from the (α)-*Si* face, *i.e.* opposite to the sterically demanding $SO_2$ group as illustrated in the proposed transition state complex (TSC) (**Figure 2**). These glycine enolates are of sufficient nucleophilicity to readily displace halide even from secondary alkyl iodides. The *N*-deprotection of the alkylated compounds (**71**) is accomplished by mild acid hydrolysis and the bornane-10,2-sultam (**17**) is detached by saponification. This methodology has provided access to a wide variety of α-amino acids (**73**) in high enantiomeric purity.



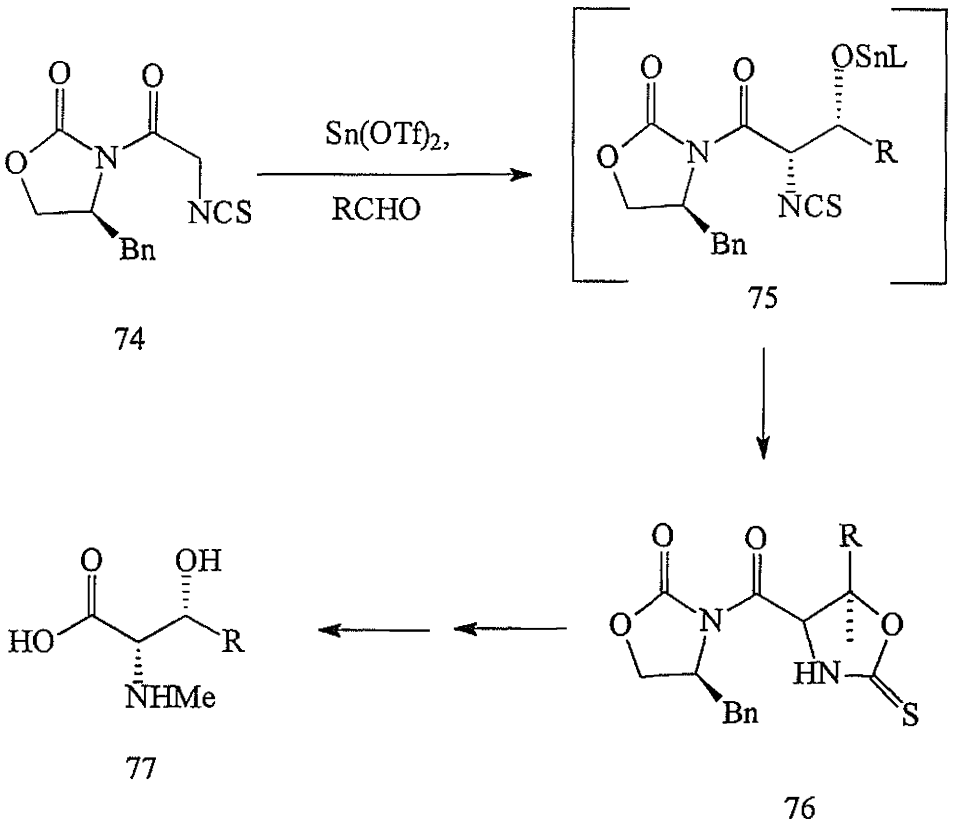

SCHEME 17




C(a)-*Si*-face attack

Figure 2 : Proposed transition state complex

Evans' group have demonstrated the use of the chiral glycine synthon (74);[34] the stannous enolates of which undergo diastereoselective aldol reactions with aldehydes to give the adducts (76) in material yields ranging from 71 to 92%. These adducts have been transformed in three steps to the enantiomerically pure *N*-methyl-β-hydroxy amino acids (77) (**Scheme 18**).



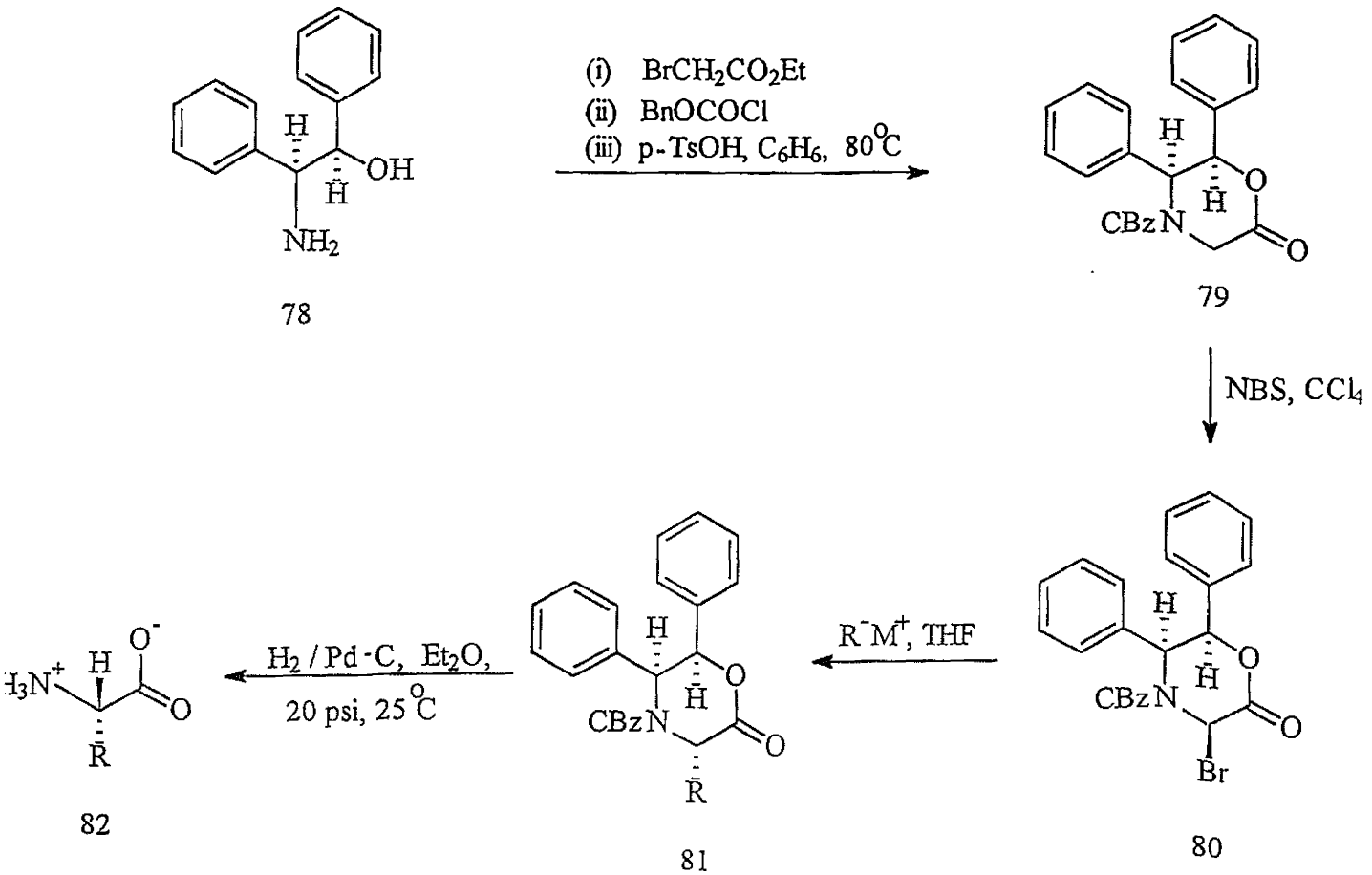

74 75 76 77

SCHEME 18

## 2.2 Electrophilic Asymmetric Alkylation

This concept originated in the research related to the synthesis of bicyclomycin undertaken by Williams *et al.*.[35] Monosubstituted D- and L- α-amino acids were prepared *via* C-C bond-forming reactions on electrophilic glycinates in an approach which complements the existing enolate-based methodologies mentioned above.

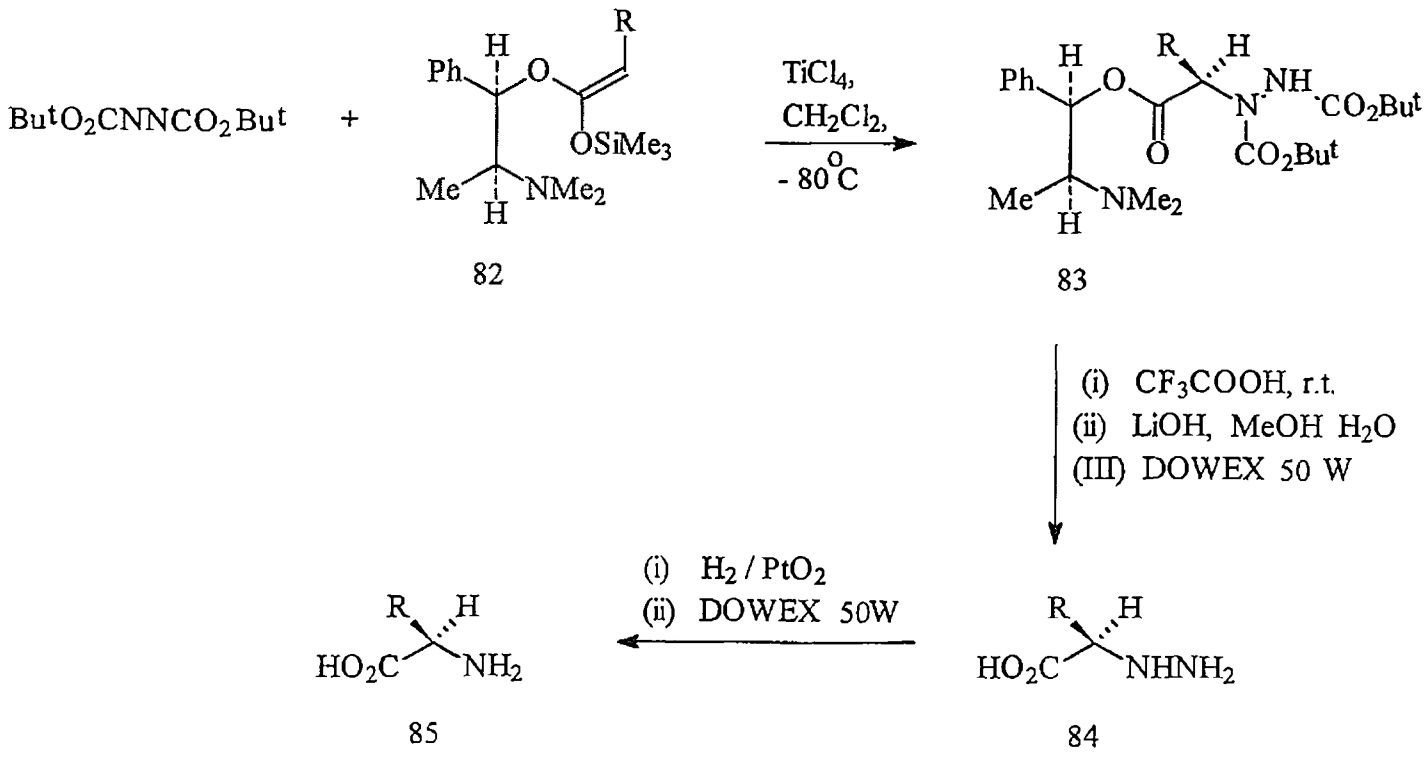
In this synthesis, optically pure *erythro*-α,β-diphenyl-β-hydroxyethylamine (78) was sequentially *N*-alkylated with ethyl bromoacetate, *N*-acylated with benzyloxycarbonyl chloride and cyclised to afford the optically pure lactone (79). The bromoglycinate (80), prepared by bromination of lactone (79) with NBS, was found to be very reactive towards a variety of nucleophiles, affording the derivatives (81). The optically pure amino acids were obtained by catalytic hydrogenation of these derivatives (81). The X-ray crystallographic data indicate that nucleophilic attack occurs from the less hindered face of the brominated species (80), presumably *viz* an $S_N1$ process, to afford, after hydrogenation the D-series amino acids in enantiomeric excess ranging from 96% to 99.5% **(Scheme 19)**.




SCHEME 19

### 1.3.3 Asymmetric Amination

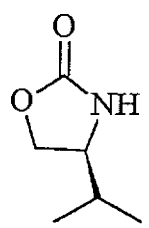
This approach affords α-hydrazino acids and, following reduction, natural and unnatural amino acids in both *R* and *S* configurations. The silyl ketene acetal (**82**) on treatment with a di-*tert*-butyl azadicarboxylate (DTBAD)-$TiCl_4$ complex yields the aminated adduct (**83**) with remarkable stereoselectivity (> 98% d.e.). Sequential treatment with $CF_3COOH$ and with LiOH in MeOH-$H_2O$ at room temperature affords hydrazino acids (**84**) which, on reduction with $H_2/PtO_2$, yield the corresponding α-amino acids (**85**) in high yield (**Scheme 20**).[36]




82 83 84 85

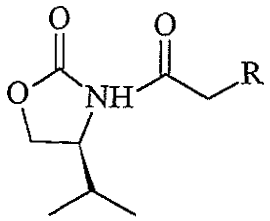
SCHEME 20

Vederas *et al.*[37] also used the amination of chiral enolates as a route for the asymmetric synthesis of amino acids. In their synthesis, the oxazilidinone (**86**) was acylated to give the chiral carboximides (**87**), which afforded the corresponding (*Z*)-enolates on reaction with LDA. Treatment of the enolates with dialkylazodiformate gave the intermediates (**88**), which were hydrolysed to the derivatives (**89**) with no loss of stereochemistry; hydrogenation with palladium on charcoal and then with Raney-Ni finally afforded the optically pure amino acids (**91**) (**Scheme 21**). The observed diastereoselectivities indicated that the substituents R and R′ (in the acid chloride and dialkyl azodiformate respectively) influence the selectivity with increasing bulk improving the diastereoselectivity.



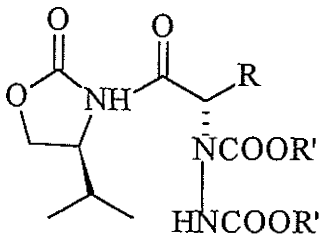
86

(i) BuLi
(ii) $RCH_2COCl$



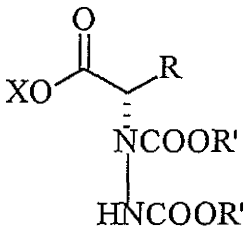
87

(i) LDA
(ii) $R'O_2CNNCO_2R'$



88

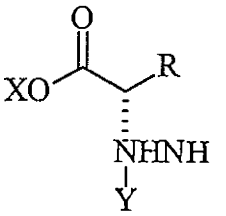
$PhCH_2OLi$
or
(i) LiSH
(II) AcOOH



$X = CH_2Ph$, H

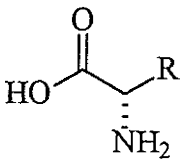
89

$H_2$ / Pd -C



90

$H_2$ / Raney Ni



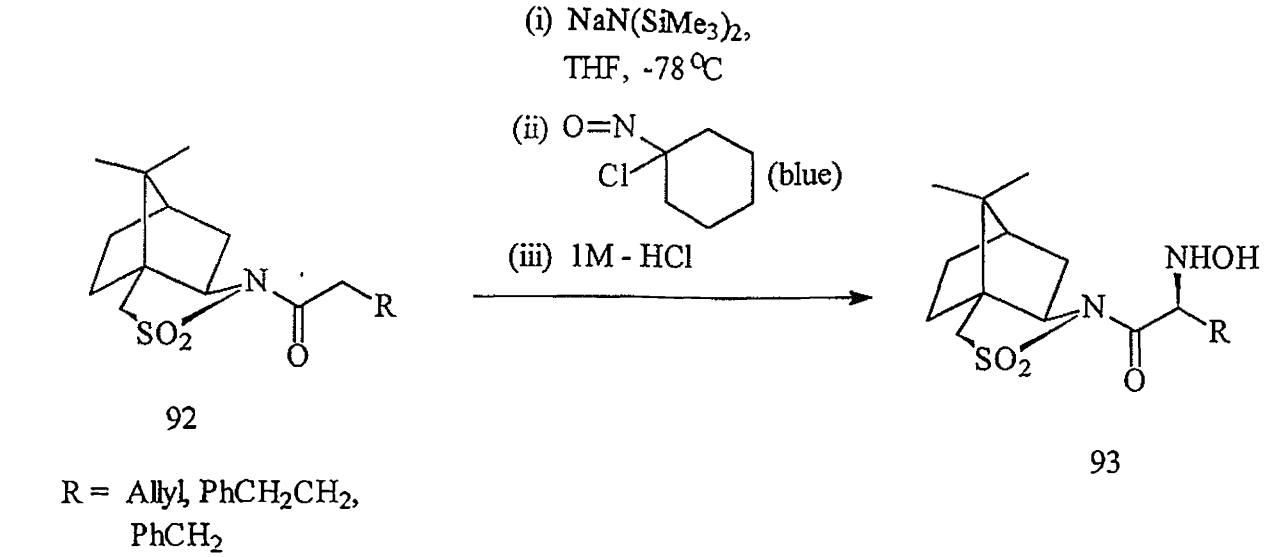
91

90(a):X=Y=H
90(b):X=Me

SCHEME 21

### 1.3.3.1 Nucleophilic Asymmetric Amination

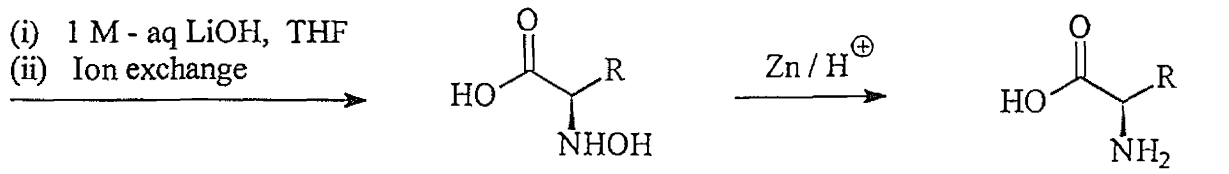
Oppolzer[38] has exploited the reaction of 1-chloro-1-nitrosocyclohexane with the chelated (*Z*)-sodium enolates of *N*-acylated bornane-10,2-sultams (**92**). In this approach, the enolate is attacked preferentially at the α-*Re*-face by $[NHOH]^+$ to generate a hydroxylamine intermediate, which undergoes reductive α–alkylation to afford the α-alkylhydroxyamines (**93**). Mild saponification of the α-alkylhydroxyamines affords crystalline *N*-hydroxy amino acids, the reductive cleavage of which (by zinc in acid) gives access to the chiral α-amino acids (**95**) (**Scheme 22**).




92

R = Allyl, $PhCH_2CH_2$, $PhCH_2$

93




94

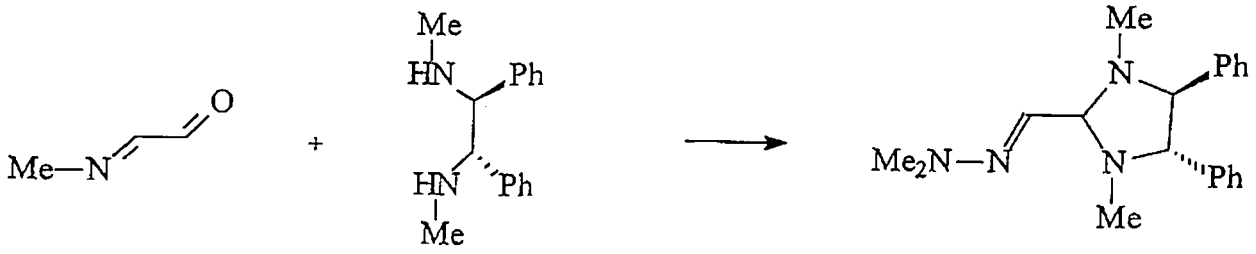
(75-100%), > 99% e.e.

95

SCHEME 22

### 1.3.4 Chiral Aminals[39]

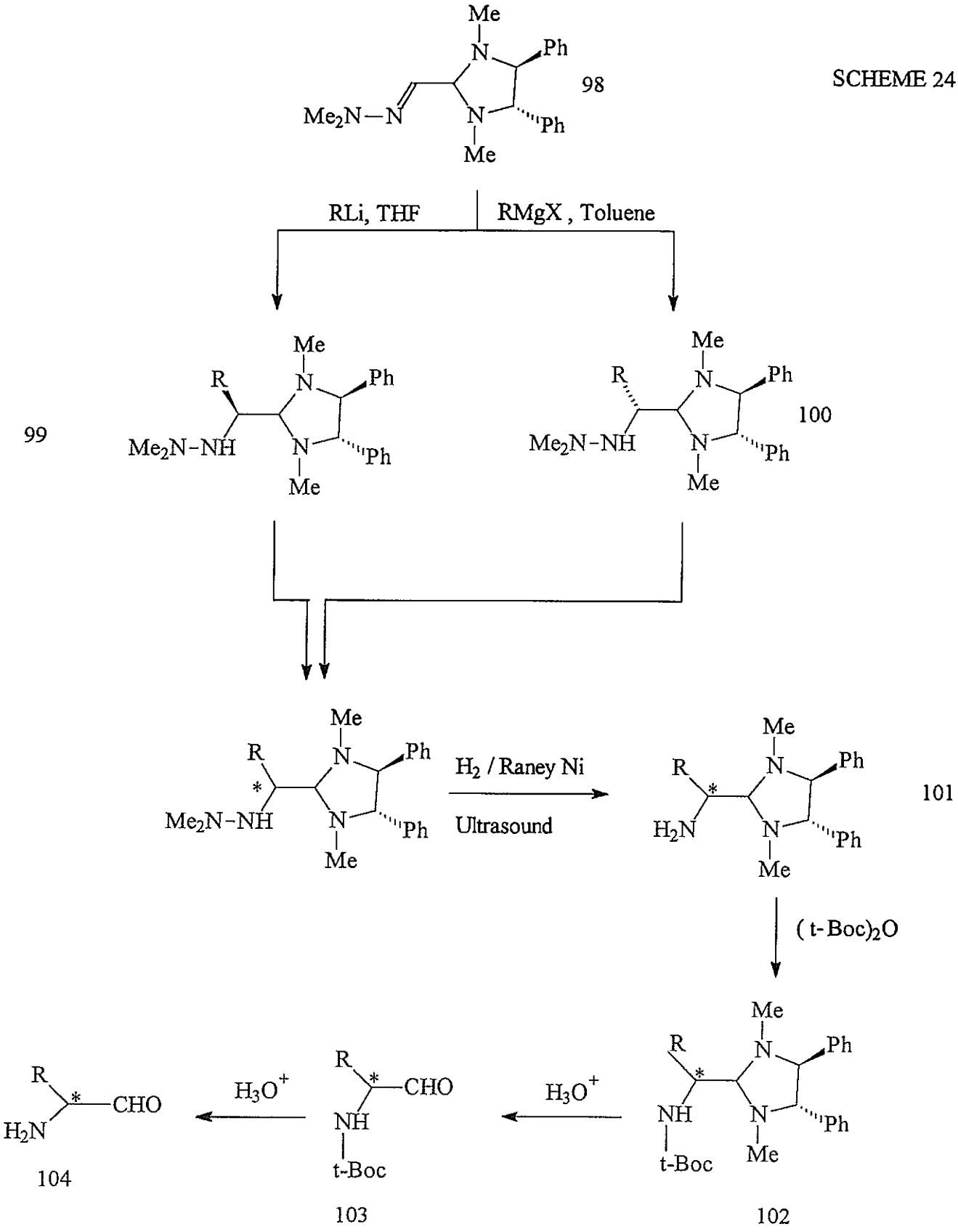
Aminals, the nitrogen equivalents of acetals, have been used for the synthesis of α-amino aldehydes (104) and are ideal precursors for α-amino acids. Alexakis *et al.*[40] treated the glyoxal (96) with the diamine (97) to obtain the crystalline aminal (98) (**Scheme 23**). The aminal (98) gave single diastereomers (99) on reaction with organolithium reagents in THF, the observed stereoselectivity being attributed to steric control. In contrast, reactions with Grignard reagents afforded the adducts (100) with the opposite stereochemistry (88 - 99% d.e.) through chelation-controlled reactions. Raney nickel reduction of the diastereomers, (99) and (100), under ultrasonic conditions, afforded the corresponding primary amines (101). Acidic hydrolysis of the *t*-Boc-protected derivatives (102) gave the enantiomerically pure α-amino aldehydes (104), oxidation of which would afford the corresponding α-amino acids (104) (**Scheme 24**).




96 97 98

SCHEME 23

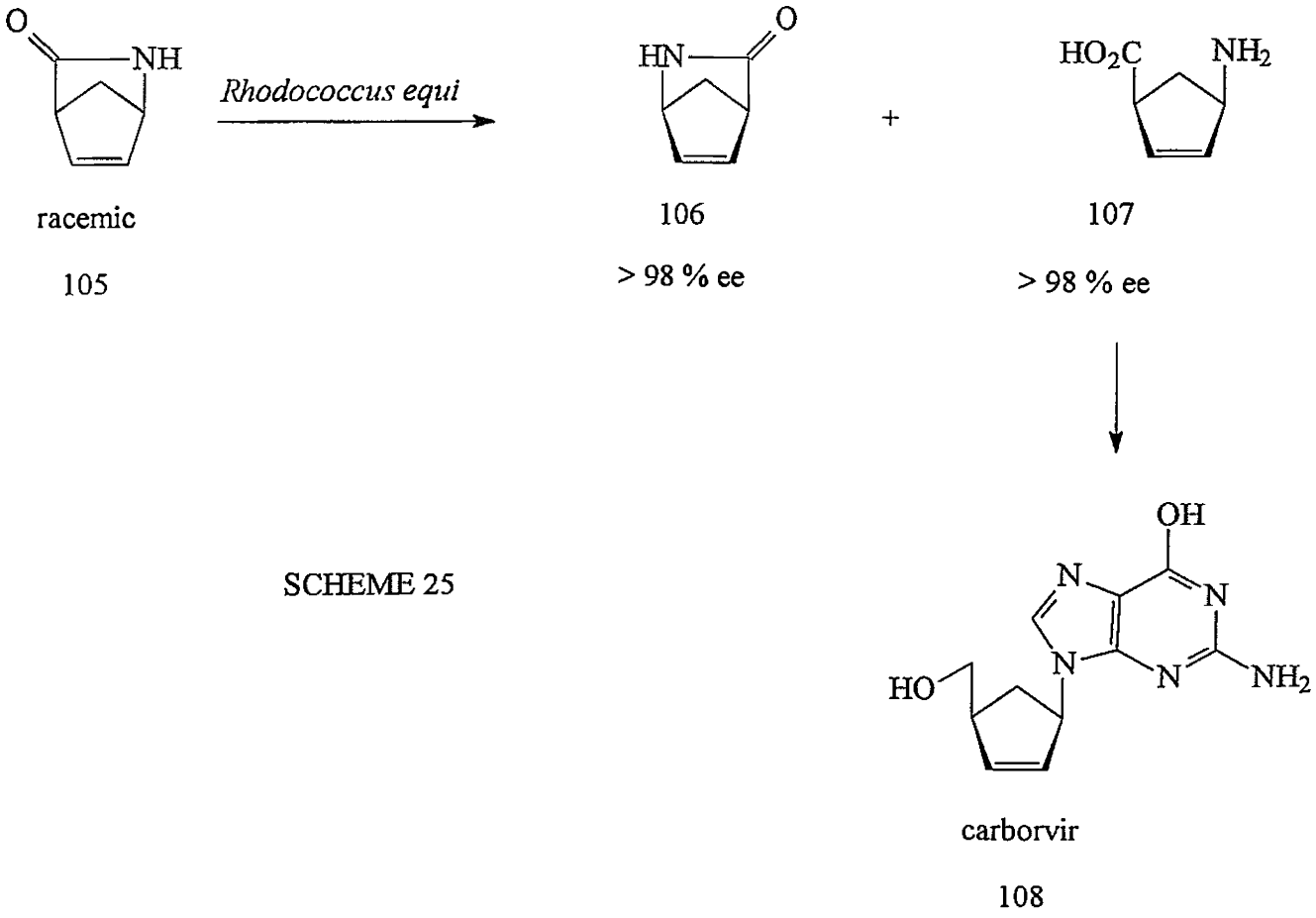
SCHEME 24


98
RLi, THF
RMgX , Toluene
99
100
H2 / Raney Ni
Ultrasound
101
(t-Boc)2O
H3O+
H3O+
102
103
104
t-Boc

### 1.3.5 Miscellaneous Strategies

#### 1.3.5.1 Whole Cell Hydrolysis[41]

Enzyme-catalysed reactions are being increasingly exploited for asymmetric synthesis because they possess a number of attractive features. They occur under mild conditions with good chemo-, regio- and stereoselectivity and, typically, afford a single stereoisomeric product. For example, the hydrolysis of the racemic bicyclic lactam (**105**), using a whole-cell system (*Rhodococcus equi*) containing a γ-lactamase, afforded the optically pure γ-amino acid (**107**), a valuable synthon for the synthesis of the nucleoside, carborvir (**108**) (**Scheme 25**). The enantiomeric lactam (**106**) was recovered in greater than 98% e.e.




racemic 105

106 > 98 % ee

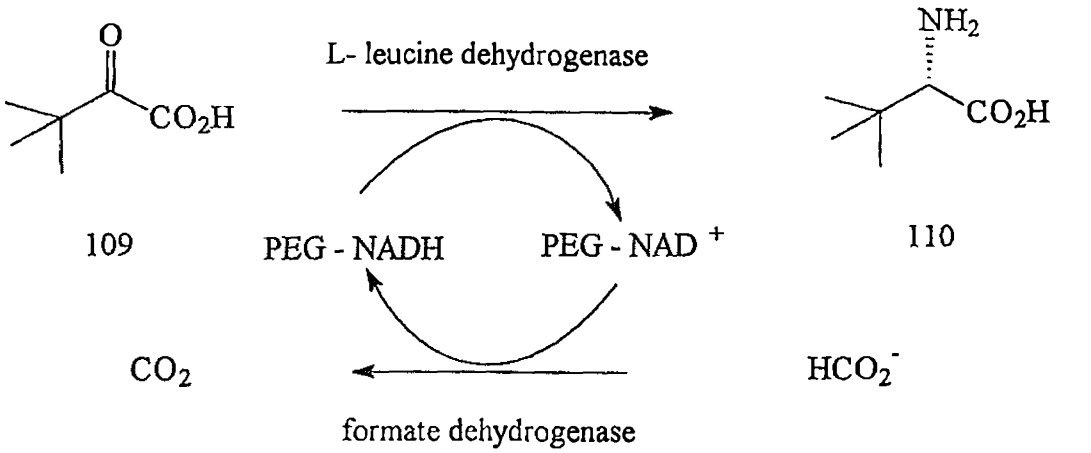
107 > 98 % ee

carborvir 108

SCHEME 25

### 1.3.5.2 Enzymatic Reduction

The asymmetric reduction of prochiral functional groups is an extremely useful transformation, and has been investigated extensively using biocatalytic methods. For example, asymmetric reductive amination of the α-keto acid (**109**) to afford optically pure L-leucine has been achieved using L-leucine dehydrogenase (**110**) in a method which incorporates large-scale recycling of the NADH co-factor (**Scheme 26**).[42]

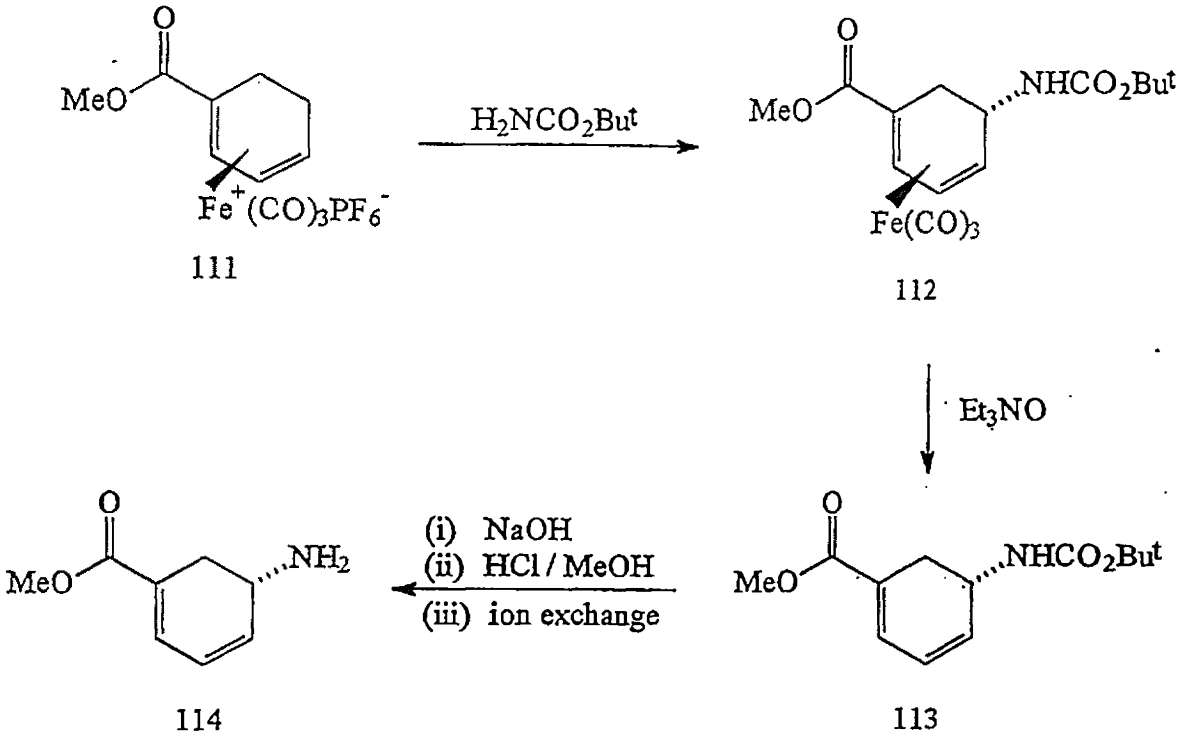



SCHEME 26

### 1.3.5.3 Π-Complexes in the Asymmetric Synthesis of Amino Acids.[43]

Generally known as "Birch's" approach, this strategy is demonstrated by the enantioselective synthesis of (-)-gabaculin (**114**).[43] This synthesis makes use of natural regio-control in a nucleophilic addition step which occurs with complete diastereoselectivity, resulting from *endo*-addition to the metal π-complex (**111**). Removal of the metal from the intermediate (**112**) using

triethylamine *N*-oxide produced the free ligand (113), deprotection of which afforded pure (-)-gabaculine (114) (Scheme 27).

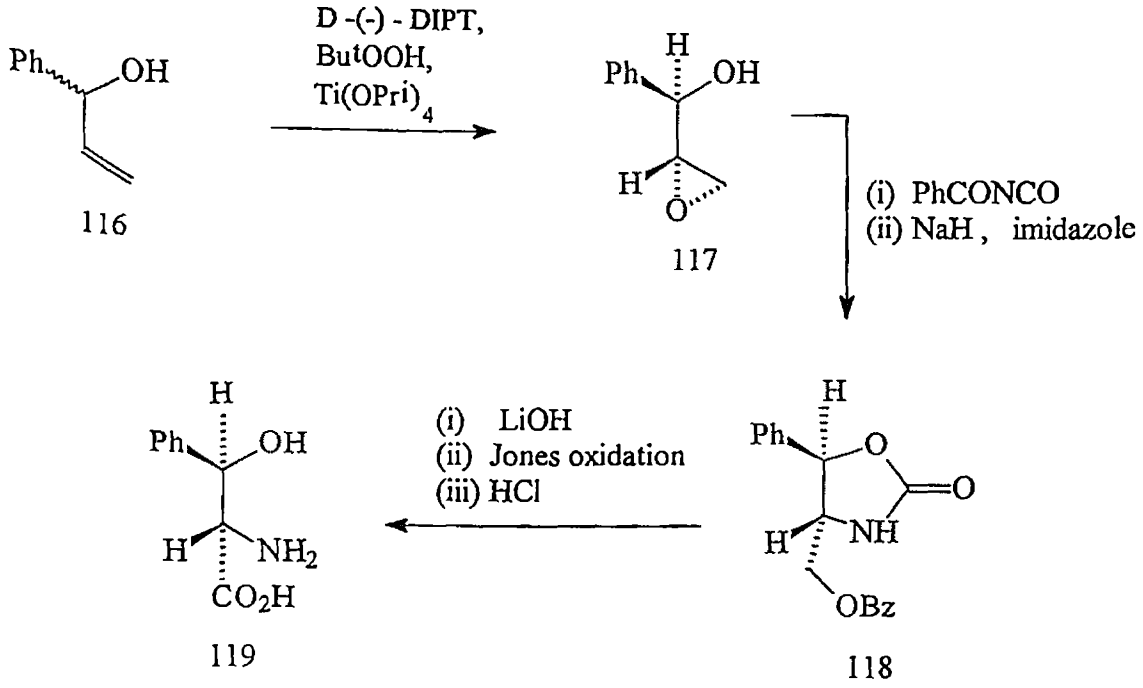



SCHEME 27

### 1.3.5.4 Asymmetric epoxidation

The epoxidation process developed by Sharpless *et al.*[44] is one of the major, recent developments in asymmetric synthesis. The impact of this reaction can be seen in the growing popularity of epoxides as intermediates in the synthesis of target molecules. For example, the initial step in the synthesis of β-hydroxy-α-amino acids (119) involves Sharpless epoxidation of an allylic alcohol (116), followed by stereocontrolled introduction of nitrogen *via* an amino lactone (118).

Hydrolysis of the intermediate (**118**) and Jones oxidation of the resulting primary alcohol moiety affords the β-hydroxy-α-amino acid (**119**) (**Scheme 28**).




D -(-) - DIPT = D-(-)-diisopropyl tartrate

SCHEME 28

## 1.4 PREVIOUS WORK BY THE RHODES RESEARCH GROUP

For some years, research in our laboratories has been concerned with the development and application of new chiral auxiliaries in asymmetric synthesis.

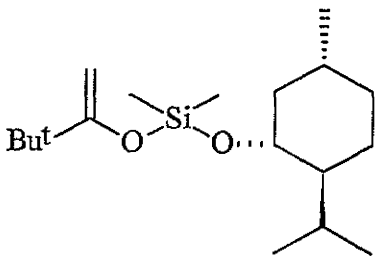
### 1.4.1 Electrophilic reactions of chiral silyl enol ethers

The successful preparation of chiral silyl enol ethers, structures (120) and (121) (**Figure 3**) was achieved by Learmonth,[45] who used a convergent approach involving reaction between chiral alkoxychlorosilanes and lithium enolates of selected ketones. Stereocontrol was explored in various reactions, using borneol and menthol-derived silyl enol ethers (**Scheme 29**). These reactions involved:-

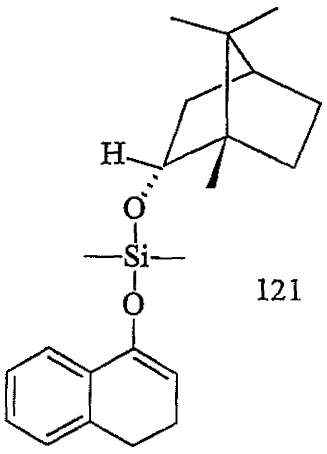
(i) MCPBA oxidation with 0 - 14% d.e.;[46]

(ii) alkylation using *t*-butyl chloride;[47] and

(iii) the Mukaiyama reaction with benzaldehyde with 6 - 14% d.e.[48]



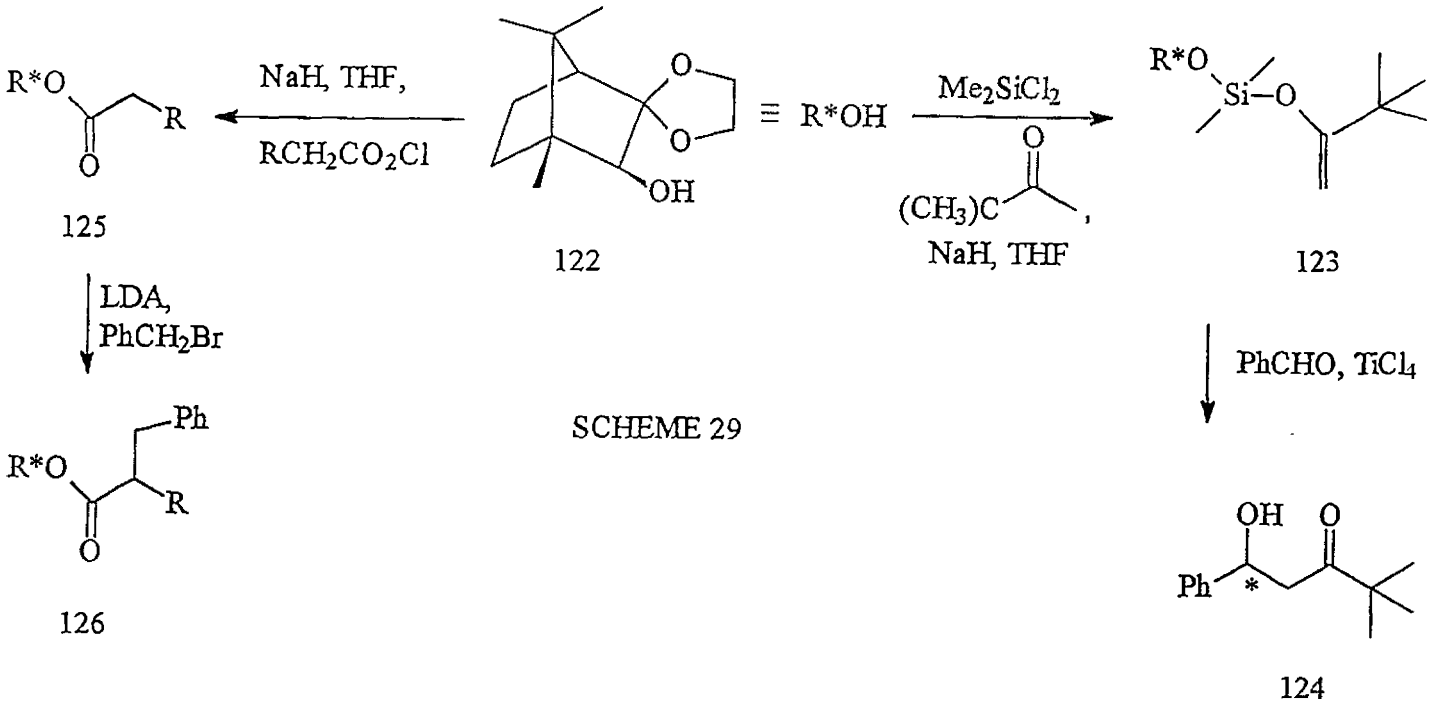

120




121

FIGURE 3

Attention was then focused on the borneol ketal(122) as a chiral auxiliary which was expected to enhance the rigidity in the transition state. The reaction of the silyl enol ether (123) with benzaldehyde in the presence of $TiCl_4$ afforded the β-hydroxy ketone (124) in good chemical yield and with moderate stereoselectivity (26% e.e.) (Scheme 29).

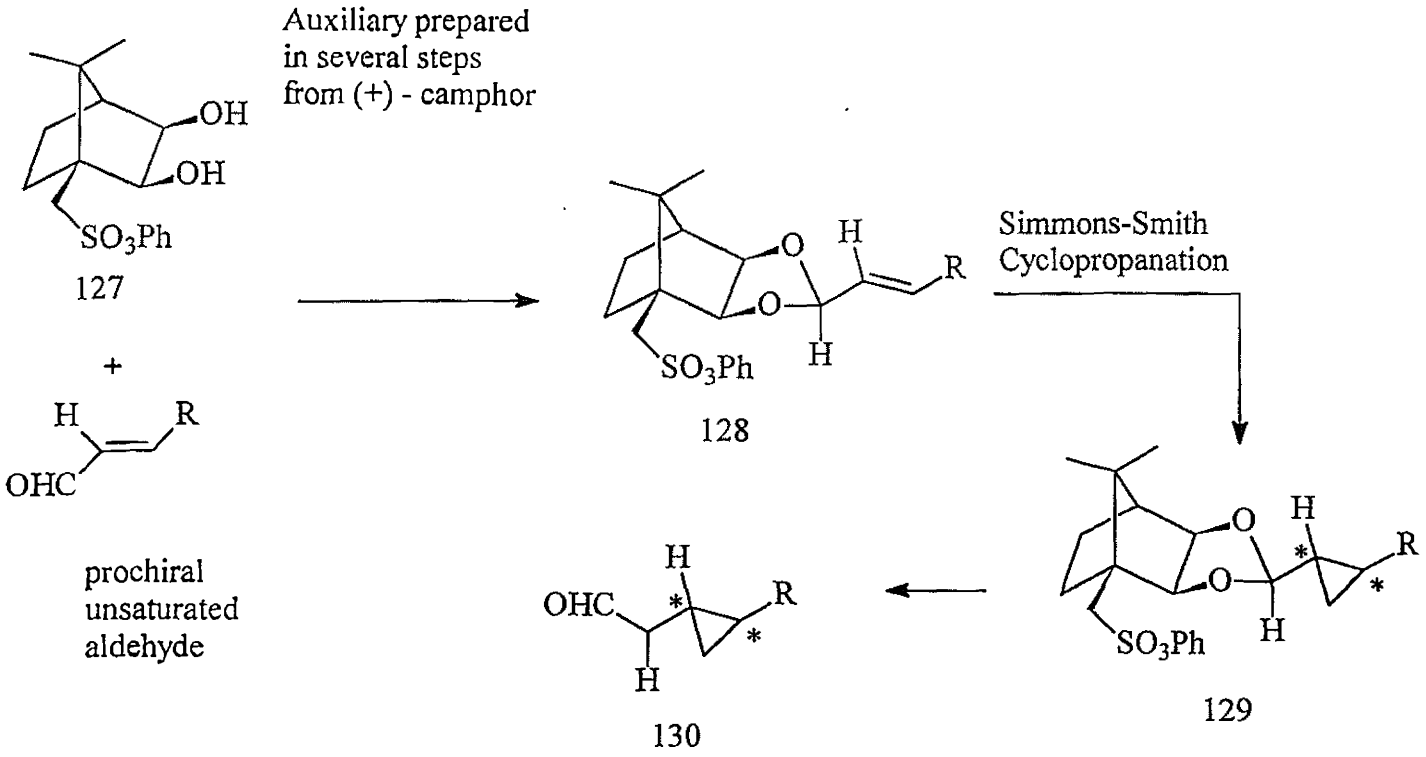



SCHEME 29

The hydroxy acetal (122) was further explored by Ravindran in stereoselective α-alkylation of enolate systems derived from the esters (125).[49] The synthesis and α-benzylation of a series of six alkanoic esters was investigated (Scheme 29), and the measured diastereomeric excesses range from 16 to 47% reflecting a marked improvement in the stereocontrol compared to that obtained during hydroxyalkylation of silyl enol ethers attached to the same auxiliary.

Further investigations on applications of novel camphor-derived chiral auxiliaries are in progress in our laboratories and are providing encouraging results. For example, Simmon-Smith[50]

cyclopropanation of unsaturated acetals of the bornanediol (**127**) proceeds with excellent diastereoselectivity (> 99% d.e.) (**Scheme 30**).




SCHEME 30

## 1.5 AIMS OF THE PRESENT STUDY

Previous studies had clearly indicated the potential of camphor-derived systems for achieving asymmetric induction, and it was decided to explore the application of such systems as auxiliaries and reagents in the synthesis of chiral α-amino acids and other products. Specific objectives have included the following.

(i). The development and evaluation of camphor-derived imines and esters as precursors for the synthesis of chiral α-amino acids.

(ii) An investigation of diastereoselectivity in asymmetric Baylis-Hillman reactions of acrylate esters of camphor-derived alcohols.

(iii) The development of ketopinic acid derivatives as auxiliaries in the asymmetric synthesis of α-amino acids.

(iv) The reduction of novel dibornyl ethers and an investigation of the use of the resulting diols as BINAP analogues in the development of chiral reagents.

# CHAPTER TWO: DISCUSSION

This research was focused on the development of novel camphor-derived auxiliaries, with the initial objective having been to prepare optically pure α-amino acids.

## 2.1 APPLICATION OF CAMPHOR-DERIVED GLYCINATES IN THE ASYMMETRIC SYNTHESIS OF AMINO ACIDS

As mentioned previously (**Section 1.3**), chiral glycinate derivatives have provided useful substrates for the synthesis of chiral α-amino acids. Given the conformational rigidity of the camphor skeleton and the diastereofacial control observed in the reactions of many of its derivatives, it was decided to concentrate our investigation on the development of novel, camphor-based glycinate derivatives. In the discussion which follows, attention will be given to the use of camphor-derived imino lactones (**Section 2.1.1**).

### 2.1.1 Synthesis of camphor-derived imino lactones

#### 2.1.1.1 Synthetic rationale

The two cyclic camphor derivatives (**131**) and (**132**) (**Scheme 31**) were considered to be important potential substrates for the asymmetric synthesis of α-amino acids since:-

i) the respective enolates (**133**) and (**134**) of these derivatives were expected to be rigid due to the cyclic arrangement;

ii) it was envisaged that, during alkylation, the electrophile would approach each enolate from the *endo* face to yield the alkylated cyclic derivatives (**135**) and (**136**)

(see **Figure 4**);

iii) mild acidic hydrolysis should afford the chiral, alkylated α-amino acids and the auxiliary for re-use; and

iv) the configuration of the resulting α-amino acids would be determined by the regiochemistry of the imino lactone substrates (**131**) and (**132**).

The regioisomeric α-ketols (**137**) and (**138**) (**Scheme 32**), accessible by the previously established procedures[51] outlined in **Scheme 34**, were expected to provide access to the regioisomeric, chiral glycine derivatives (**131**) and (**132**). The two, regioisomeric α-ketols (**137**) and (**138**) have the advantage of being bifunctional, each possessing a hydroxyl group, which may be esterified, and a carbonyl group, which may be converted to an imine. Consequently, the required imino lactones (**131**) and (**132**) could be constructed from 3-*exo*-hydroxycamphor (**137**) and 2-*exo*-hydroxy-3-bornanone (**138**) respectively.

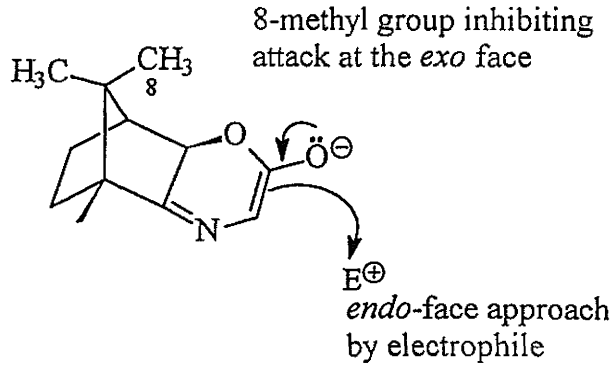
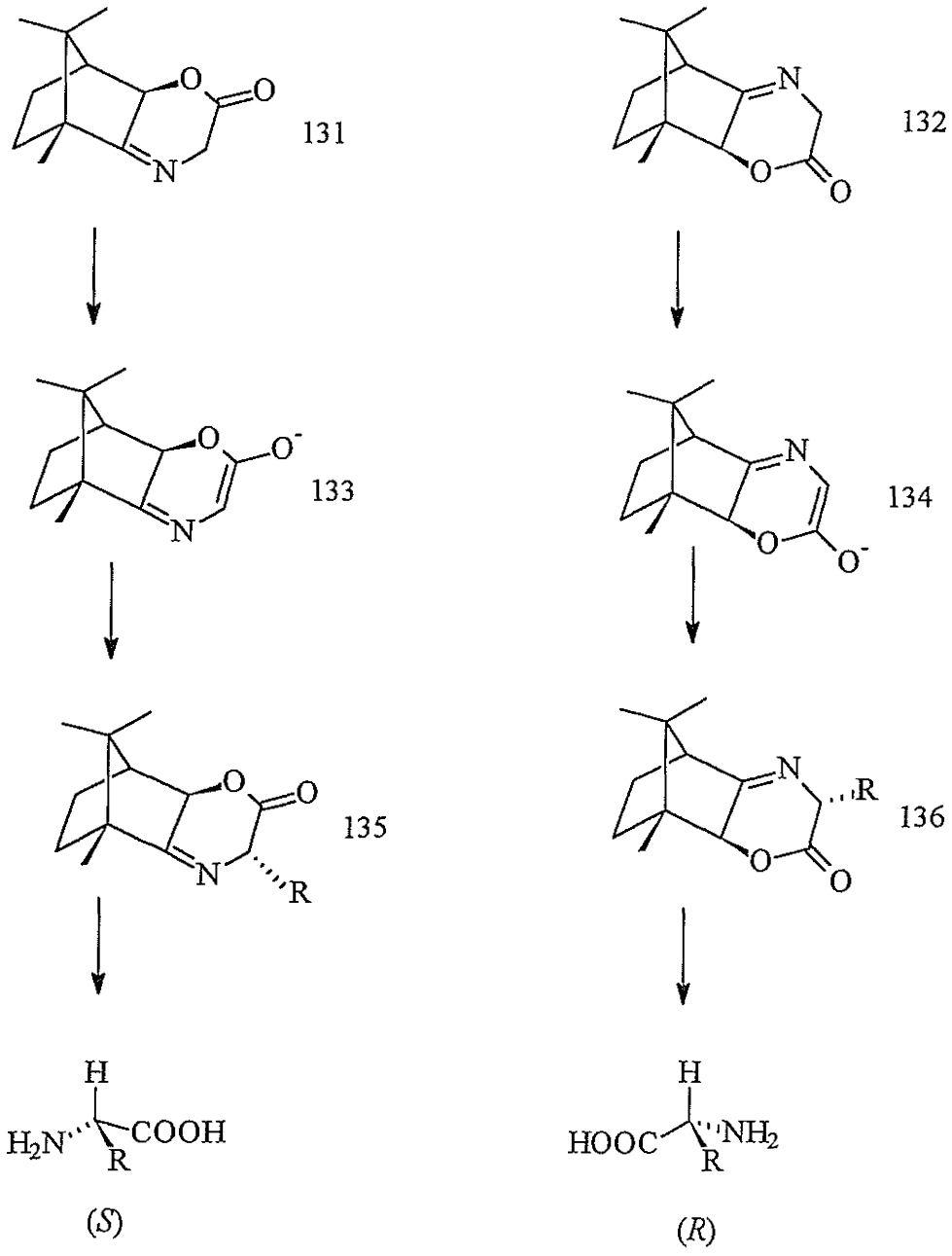
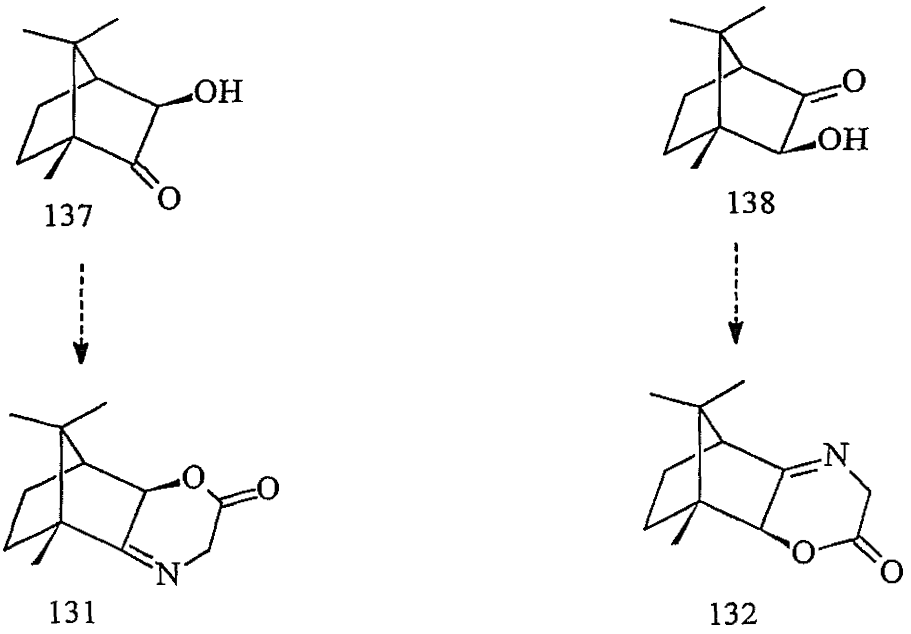



**FIGURE 4.** Expected approach by an electrophile ($E^{\oplus}$) at the *endo* face of the enolate (**133**).

Proposed routes to enantiomeric α-amino acids using camphor-derived imino lactone precursors




SCHEME 31




SCHEME 32

### 2.1.1.2 Preparation of the imino lactone (131) from 3-hydroxycamphor (137)

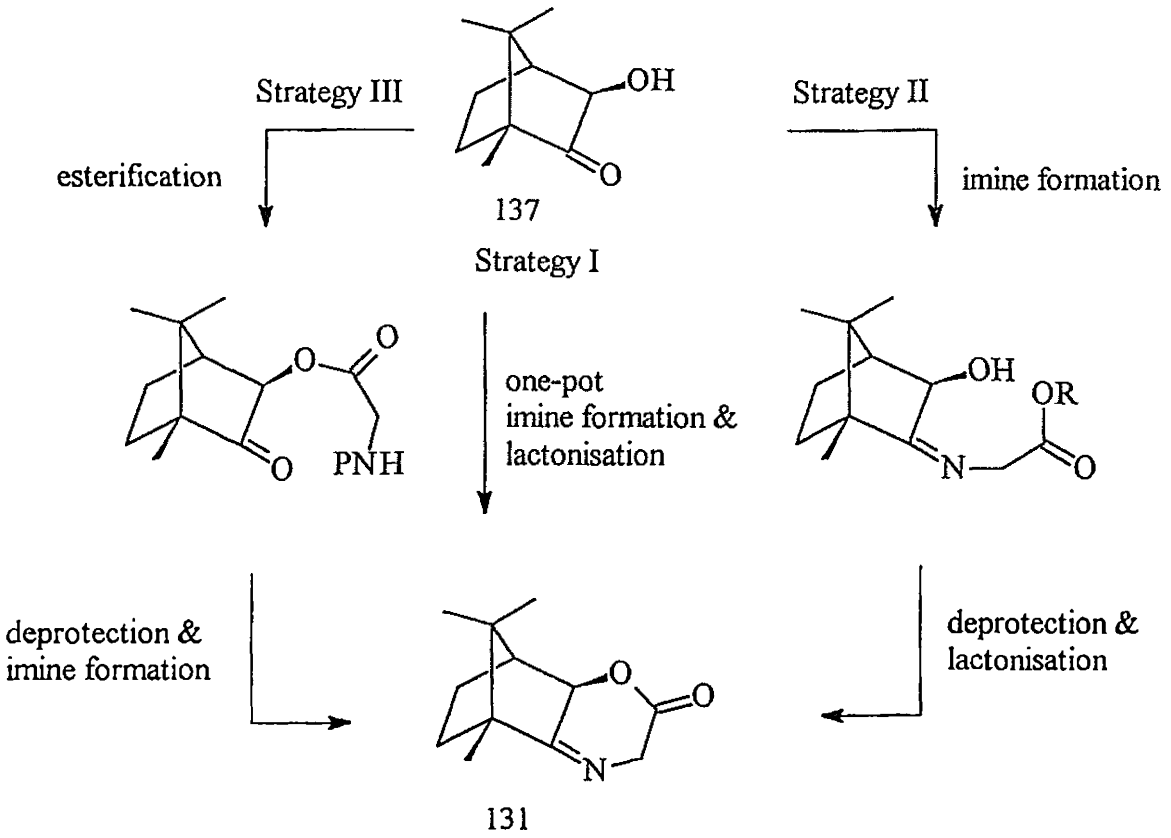
The three different strategies identified to provide access to the required imino lactone (**131**) are outlined in **Scheme 33** .

Strategy I: Direct condensation of 3-*exo*-hydroxycamphor with glycine.

Strategy II: Formation of an imine intermediate using an acyl-protected glycine, followed by deprotection and lactonisation.

Strategy III: Formation of an ester intermediate using an *N*-protected glycine, followed by deprotection and cyclisation by forming an imine.

Possible strategies for the synthesis of the imino lactone ( **131**)



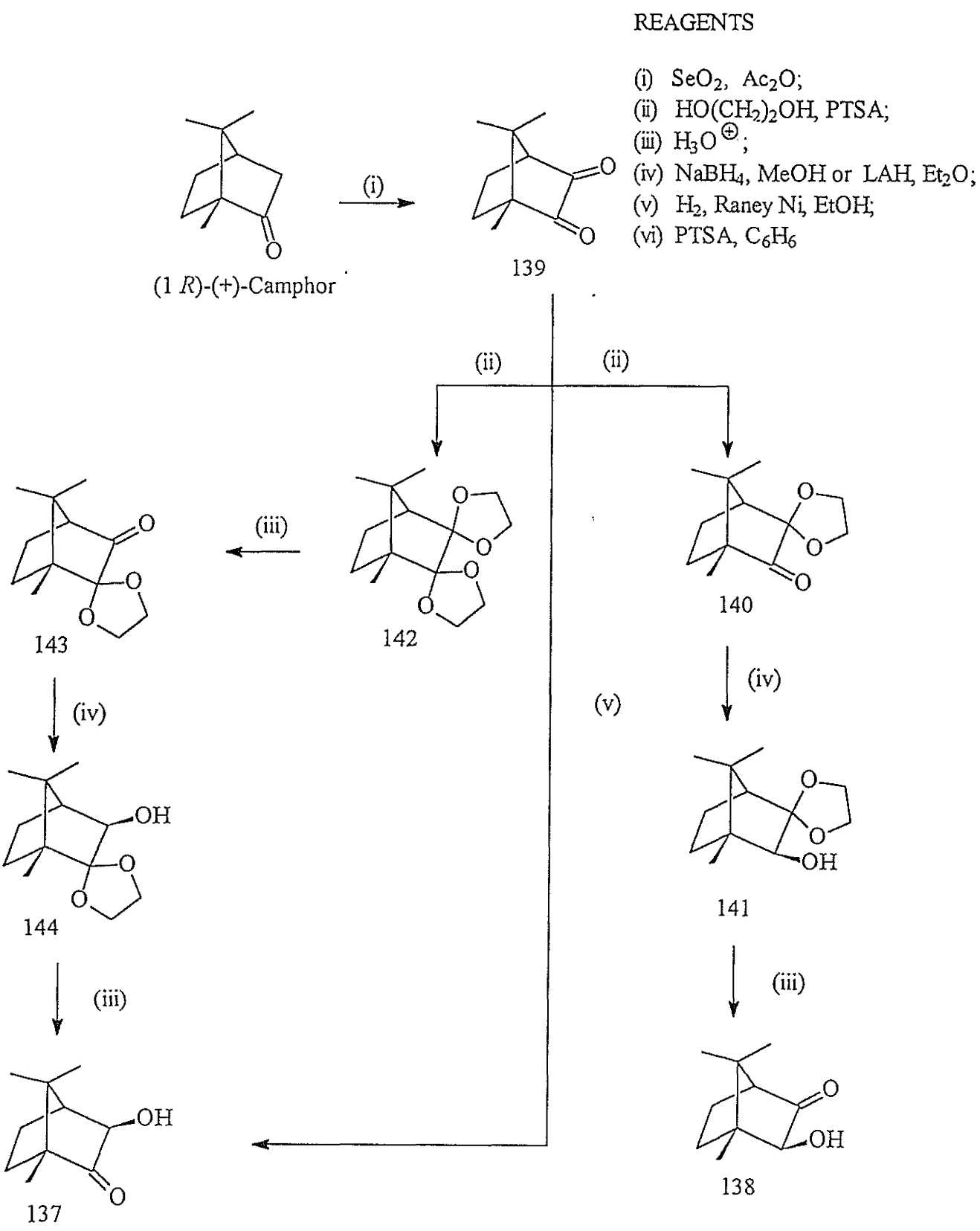

SCHEME 33

Synthesis of the required α-ketols (**137**) and (**138**) was achieved *via* the routes outlined in **Scheme 34**.[51] Camphorquinone (**139**) was obtained by selenium dioxide oxidation of (1*R*)-(+)-camphor. Acetalisation of camphorquinone with ethylene glycol afforded the monoketal (**140**) as the major product together with the diketal (**142**). Stereoselective reduction of the monoketal to alcohol (**141**) requires *endo* attack, and this was achieved with a variety of metal hydride reducing agents. Acid catalysed hydrolysis of the hydroxy ketal (**141**) afforded the α-ketol (**138**).

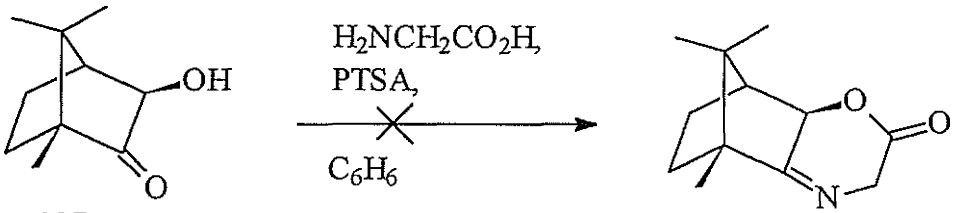
The regioisomeric α-ketol (**137**) was obtained by two routes. In the first, regioselective acid-catalysed hydrolysis of the diketal (**142**) afforded the monoketal (**143**). Stereoselective metal-hydride reduction gave the hydroxyketal (**144**), acidic hydrolysis of which afforded the α-ketol (**137**). In the second route, the α-ketol (**137**) was obtained directly by the regio- and stereoselective reduction of camphorquinone (**139**)using Raney-nickel.

With both α-ketals (**137**) and (**138**) in hand, the cyclisation strategies outlined in **Scheme 33** could be explained. Strategy I, involving a on-pot process, in which the carbonyl group and the hydroxy group of the α-ketol react, simultaneously or consecutively, with the glycine amino and carboxylic groups respectively, was attempted by heating the α-ketol (**137**) and glycine in dry benzene, using a catalytic amount of *p*-toluene-sulfonic acid (PTSA) and a Dean-Stark trap. However, the expected imino lactone (**131**) was not formed. Instead, work-up and chromatography afforded three compounds which were identified as dibornyl ethers and designated dimers **(I)**, **(II)**, and **(III)** (**Scheme 35**). The regioisomeric 2-*exo*-hydroxy analogue (**138**) was treated similarly but yielded the dibornyl ether, dimer **II**, as the only product. The structure determination and formation of these dibornyl ethers are discussed fully in **Section 2.4**.

Preparation of the imino lactone (**131**) was also attempted by heating the neat reagents, 3-*exo*-hydroxybornanone (**137**) and glycine, but this approach was also unsuccessful due to sublimation of the 3-*exo*-hydroxybornanone (**137**).


REAGENTS
(i) $SeO_2$, $Ac_2O$;
(ii) $HO(CH_2)_2OH$, PTSA;
(iii) $H_3O^{\oplus}$;
(iv) $NaBH_4$, MeOH or LAH, $Et_2O$;
(v) $H_2$, Raney Ni, EtOH;
(vi) PTSA, $C_6H_6$
(1 *R*)-(+)-Camphor
139
140
141
142
143
144
137
138

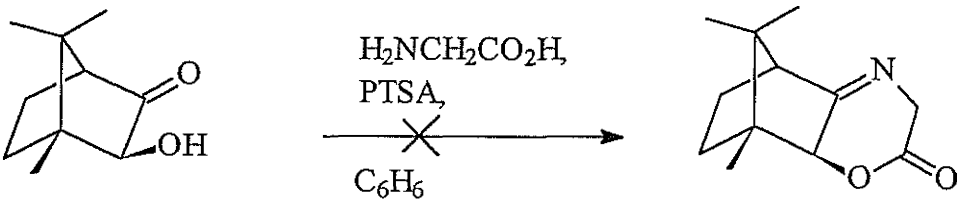
SCHEME 34




137 131

dibornyl ethers* I,II and III

dibornyl ether* II

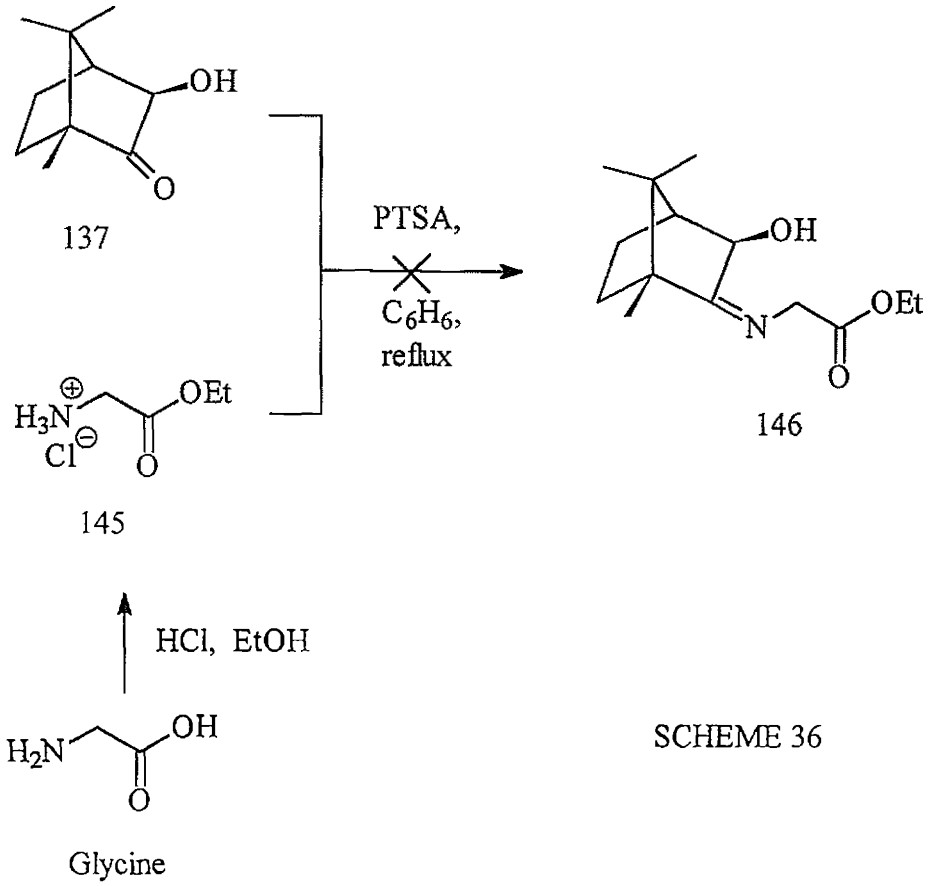



138 132

* See section 2.4

SCHEME 35

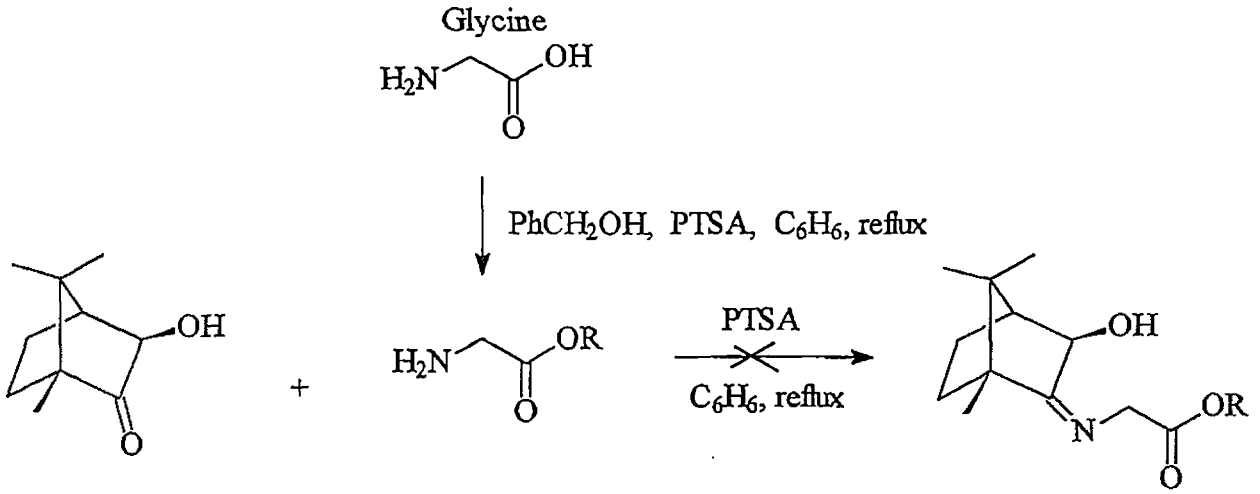
It is possible that, under these conditions, the glycine was being consumed by dimerization[53] and, consequently, use of an ester-protected glycine derivative was considered (Strategy II). The hydrochloride salt of ethyl glycinate (**145**) was furnished by bubbling dry HCl gas through a suspension of glycine in ethanol.[54] A solution of the α-ketol (**137**) in benzene, the ethyl glycinate hydrochloride salt (**145**) and a catalytic amount of PTSA were heated under reflux using a Dean-Stark trap (**Scheme 36**), but none of the desired imine (**146**) was obtained. The failure of the reaction was attributed to the poor solubility of the hydrochloride salt in benzene and the unavailability† of a "free" amino group in ethyl glycinate due to its existence as a hydrochloride salt.




SCHEME 36

†In imine formation, acid-catalysed nucleophilic addition to the carbonyl group requires the presence of, at least, a low equilibrium concentration of the nucleophilic amino moeity.

Use of the "neutral" benzyl ester (147) of glycine was then considered.[55] A mixture of glycine, benzyl alcohol and PTSA in benzene was boiled under reflux, using a Dean-Stark apparatus, to yield the crystalline PTSA benzyl glycinate salt (148), which was treated with a 10% excess of triethylamine to give the nucleophilic amino ester (147). The $^1$H NMR spectra of the PTSA salt (148) and the amino ester (147) are illustrated in Figure 5.




147 : $PhCH_2$
149 : $Bu^t$

150 : $PhCH_2$
151 : $Bu^t$

SCHEME 37

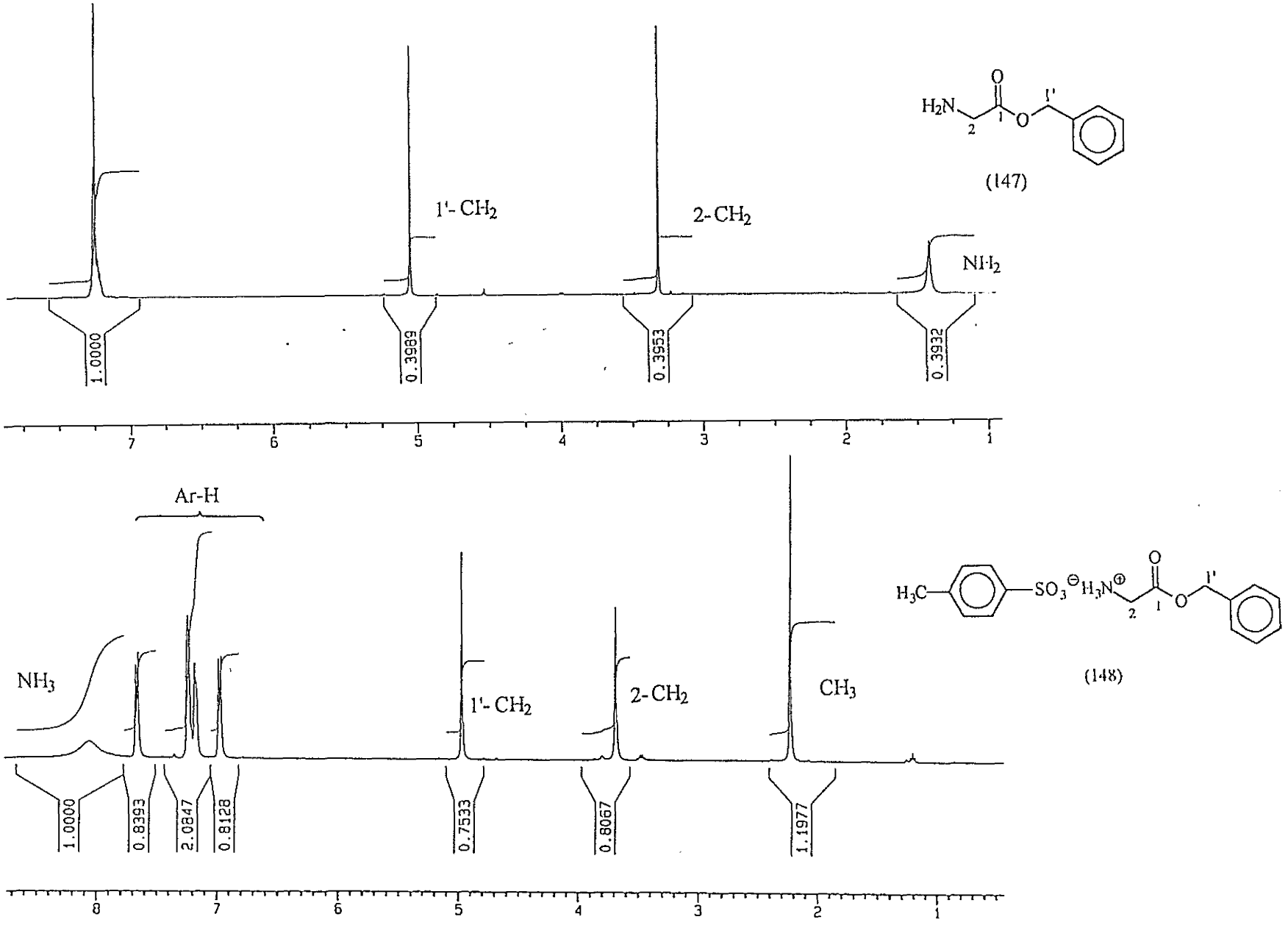
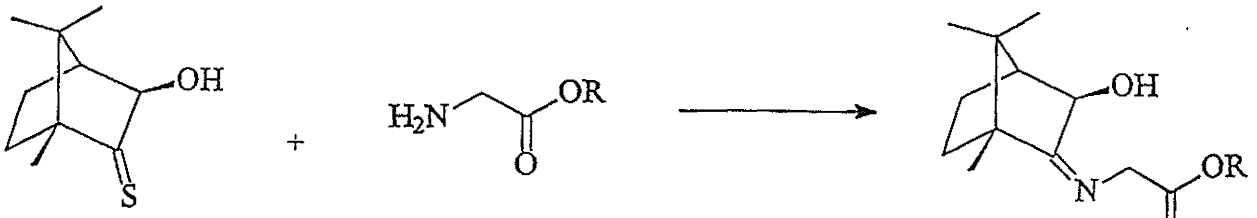



FIGURE 5. The 400 MHz $^1H$ spectra of benzyl glycinate (**147**) in $CDCl_3$ and its PTSA salt in DMSO - $d_6$

Following an approach used by Tabchem *et al.*[56] to prepare the imino derivative of 2-hydroxy-3-pinanone and methyl glycinate, a solution of the α-ketol (**137**) and benzyl glycinate (**147**) in benzene was boiled under reflux with a catalytic amount of $BF_3.Et_2O$. However, work-up, followed by flash chromatography, yielded the the unreacted α-ketol and benzyl glycinate (**Scheme 37**). In a slight variation, the reaction was repeated using *t*-butyl glycinate (**149**), but this reaction also proved unsuccessful.

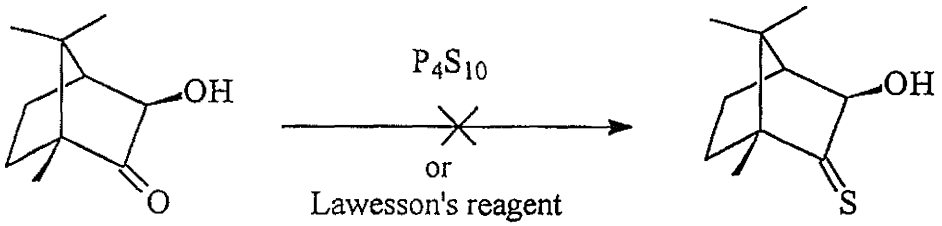
A camphor imine has been successfully prepared by McIntosch and Mishra[57] *via* thiocamphor. Shahak and Sasson[58] attributed the difficulty in forming an imine from camphor itself to the hindered position of the 2-carbonyl group. Based on this approach, it was considered that the thiocarbonyl analogue (**152**) of the α-ketol (**137**) might well provide an effective route (as in Scheme 38) to the required derivative (**153**).




152 153

SCHEME 38

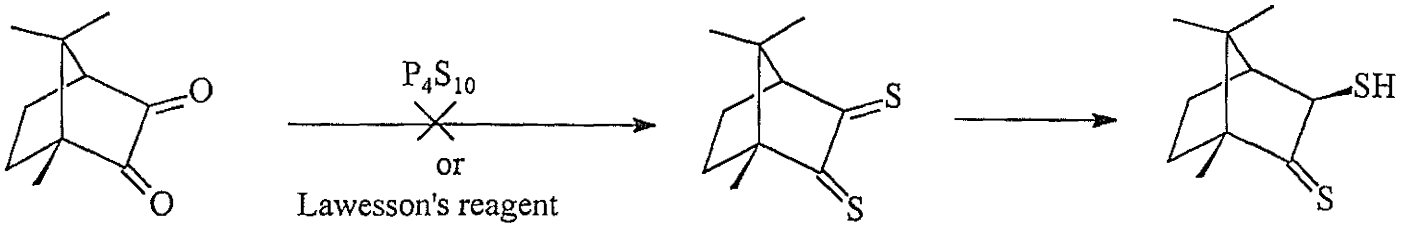
Several approaches to the thiocarbonyl analogue (152) were explored. In the first, thionation was attempted by treating a solution of the α-ketol (137) in diglyme with tetraphosphorus decasulphide ($P_4S_{10}$) (**Scheme 39**). However, work-up and chromatography yielded the unreacted α-ketol (137). Thionation was then attempted using Lawesson's reagent as a thionating agent,[59] but this approach also failed to yield the desired hydroxythione product. At this stage, it was considered possible that thionation was being inhibited by keto-enol tautomerism in the α-ketol (137).




137 152

SCHEME 39

An alternative approach, aimed at obviating the possibility of tautomerism, was then attempted, *viz.*, thionation of camphorquinone (139), followed by regioselective reduction of the resulting dithione (154) at the less hindered 3-position to afford the 3-*exo*-mercapto-2-thione (155) as an even more reactive substrate than the oxygenated analogue (137) (**Scheme 40**).



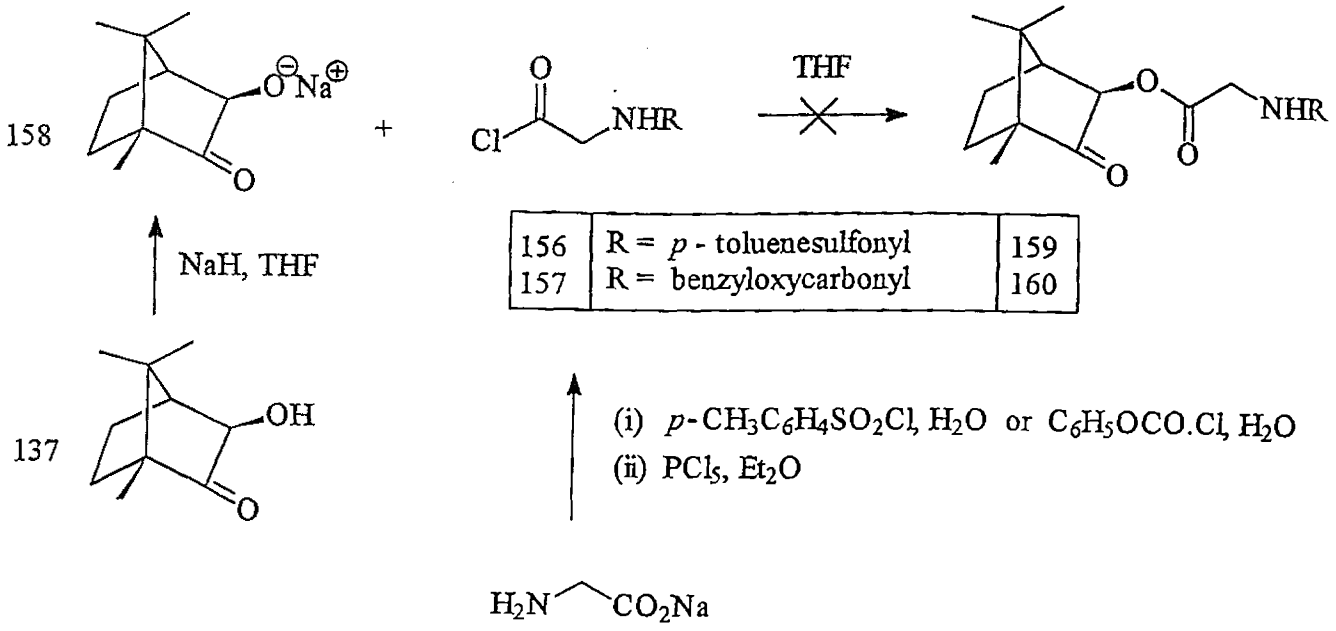

139 154 155

SCHEME 40

As previously mentioned (see Section 2.1.1), camphorquinone (139) was prepared in good yield from the oxidation of (1*R*)-(+)-camphor with selenium dioxide.[51] Thionation of the camphorquinone was then attempted using tetraphosphorous decasulphide ($P_4S_{10}$) and Lawesson's reagent following the procedures used for the α-ketol (137), but unreacted camphorquinone was recovered in both cases. In view of the failure of Strategies I and II, attention was given to Strategy III, *viz.*, initial esterification of the α-ketol with an *N*-protected glycine derivative followed by deprotection and cyclisation.

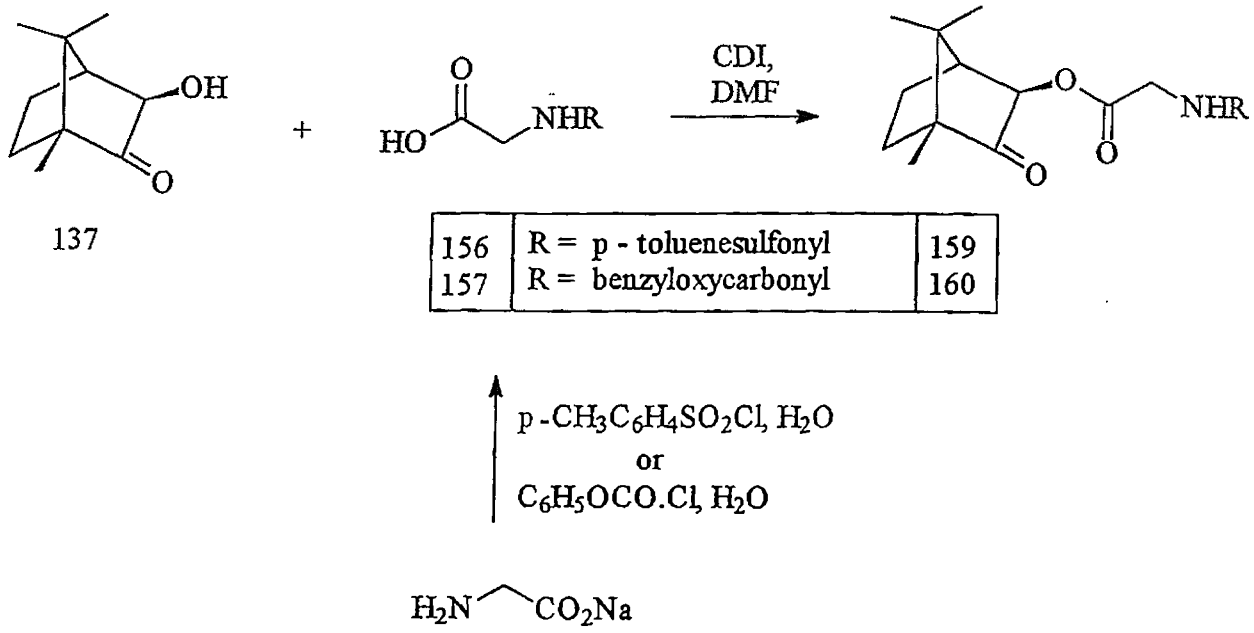
The preparation of esters of hydroxy acetal derivatives of camphor has been achieved previously in our laboratories[51] by reacting the sodium hydride-generated alkoxide with acid chlorides (see **Section 1.4**). Using the same general approach, acylation of the sodium hydride-generated alkoxide of the α-ketol (137) was attempted using the acid chlorides of the *N*-protected glycines (156) and (157) (**Scheme 41**). The crystalline acid chloride (156) was furnished in 86% yield by reacting *p*-toluenesulfonylchoride and sodium glycinate in water,[60] and treating the resulting, dry *N*-(*p*-toluenesulfonyl)glycine with phosphorus pentachloride in dry ether . The *N*-carbobenzyloxy derivative (157) was obtained similarly in 88% yield using benzyl chloroformate with glycine in a basic aqueous solution,[†61] followed by treatment with phosphorus pentachloride in dry ether. The alkoxide (158) was reacted, in turn, with the acyl chlorides (156a) and (157a) of the *N*-protected glycine derivatives, (156) and (157), but, in both cases, the α-ketol (137) was recovered with none of the expected esters (159) and (160).

[†]For the subsequent reactions *N*-(carbobenzyloxy)glycine was purchased from Aldrich.




SCHEME 41

El-Achqar *et al.*[62] have successfully esterified 2-hydroxy-3-pinanone with an *N*-protected glycine derivative using dicyclohexylcarbodiimde (DCC) and dimethylaminopyridine (DMAP) as coupling agents. This approach was then explored using carbonyldiimidazole (CDI) as an alternative coupling agent. The acylimidazole derivatives of *N*-(*p*-toluenesulphonyl)glycine (**156**) and *N*-(carbobenzyloxy)glycine (**157**) were reacted with the α-ketol (**137**) in dimethylformamide to afford the corresponding *exo*-esters (**159**) and (**160**) in good yields (82% and 86% respectively) (Scheme 42). Both esters were fully characterised by spectroscopic methods and the HMQC spectrum for *N*-(carbobenzyloxy)glycinate derivative (**160**) (**Figure 6**) reflects requisite correlation between the carbon and proton signals. An efficient route to the *N*-protected glycinates had thus been finally established and the next challenge in following strategy III was to deprotect the amino group and effect cyclisation to the required imino lactone (**131**) (**Scheme 42**).




SCHEME 42

One of the standard deprotection procedures[63] for the *p*-toluenesulphonyl group employs sodium in liquid ammonia. These fairly harsh reaction conditions seemed inappropriate for the relatively labile glycine ester bond and, consequently, deprotection of the *N*-(carbobenzyloxy)glycine analogue (**160**) was considered instead. Aniline and cysteine *N*-carbobenzyloxy derivatives have previously been deprotected using hydrobromic acid in acetic acid.[64] Thus, the *N*-protected glycinate (**160**) in acetic acid was treated with a 33% solution of hydrogen bromide in acetic acid (**Scheme 43**). However, work-up and chromatography afforded the α-ketol (**137**), indicating cleavage of the ester bond during deprotection .

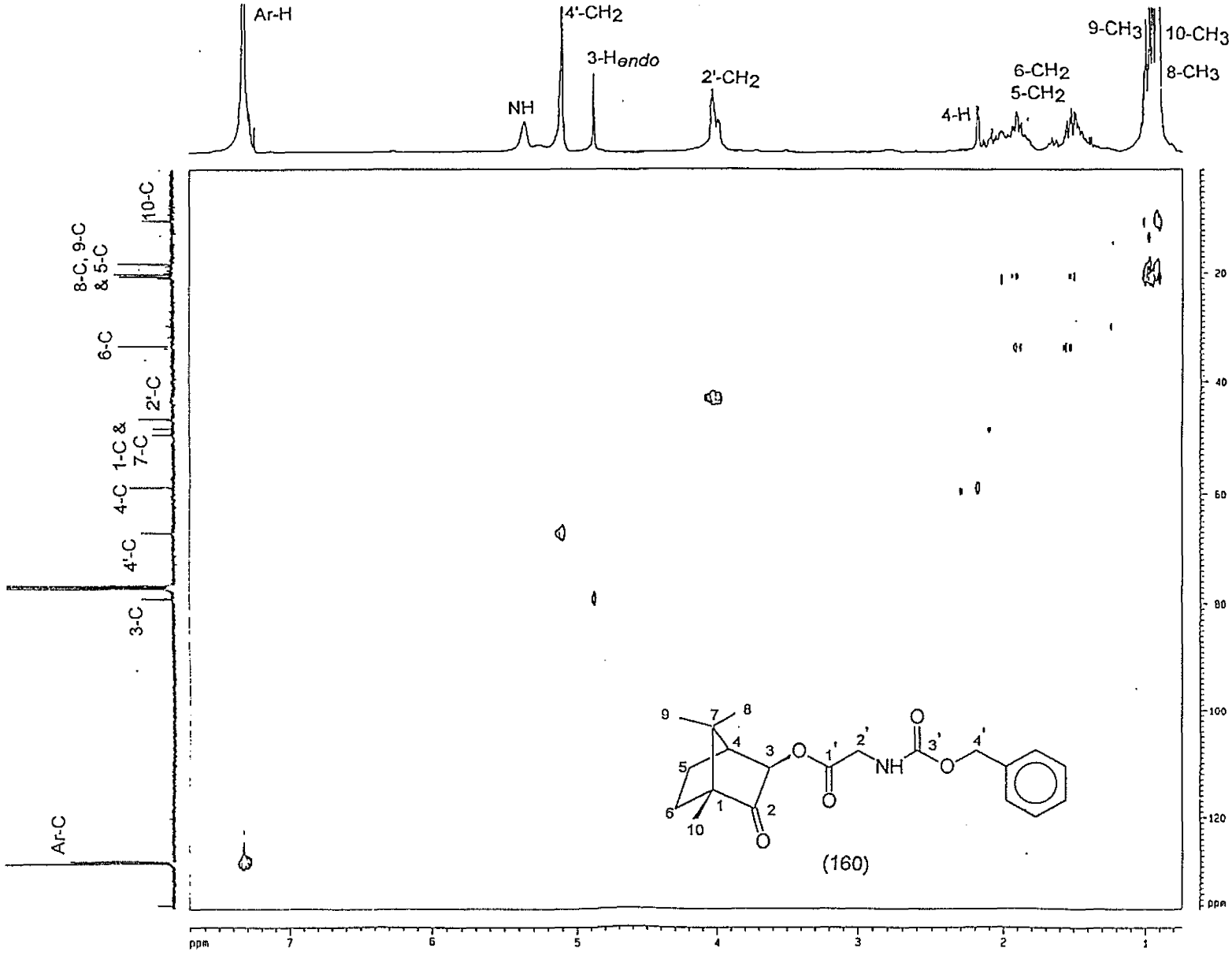
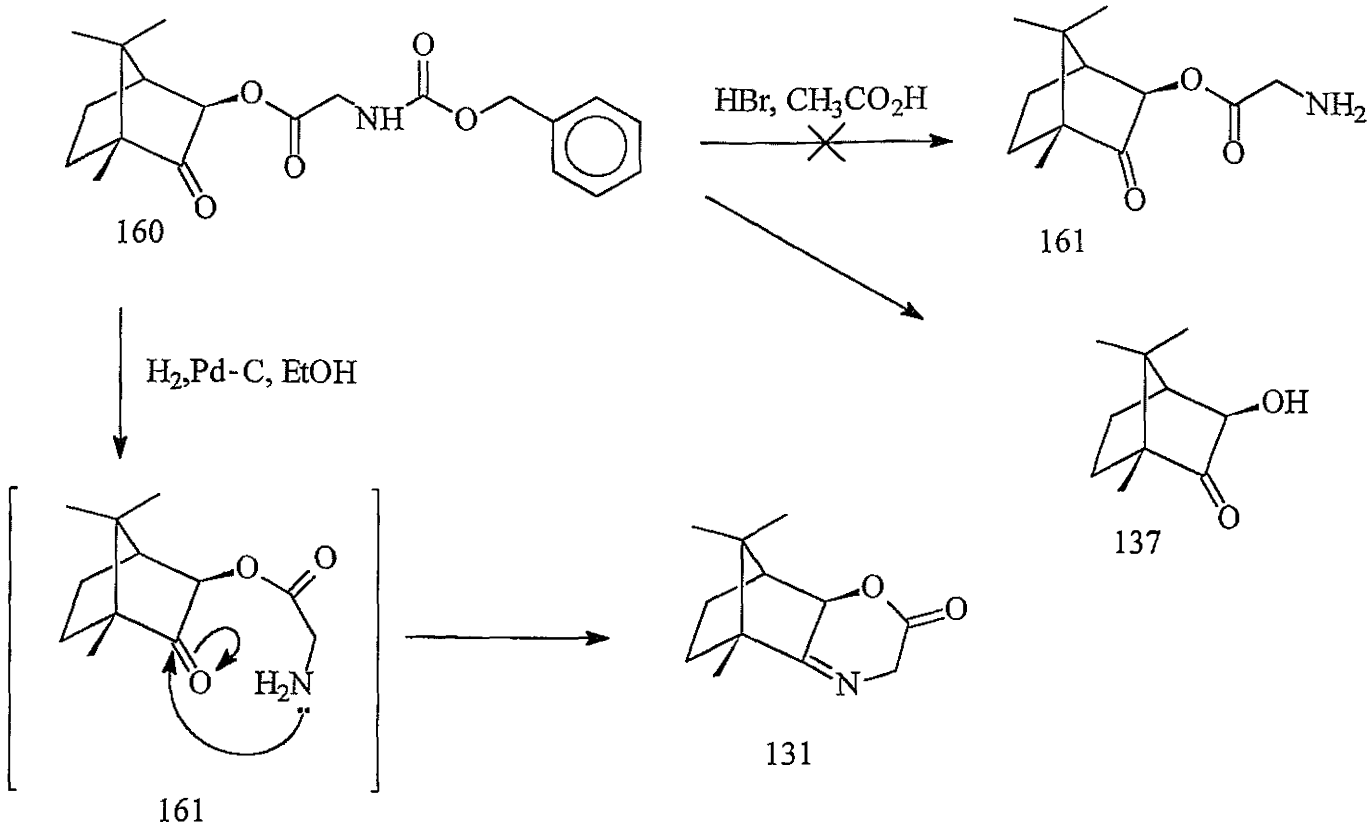



FIGURE 6. The HMQC spectrum of ester (**160**) in $CDCl_3$




SCHEME 43

Hydrogenolysis of carbobenzyloxy groups has previously been effected successfully using a 10% palladium on charcoal catalyst.[62] Thus, a solution of the *N*-carbobenzyloxy derivative (**160**) in ethanol was subjected to hydrogenatation over 10% Pd on carbon, following a procedure reported by Bodansky *et al.*.[65] Work-up and chromatography finally yielded the target imino lactone (**131**) directly in 90% yield (**Scheme 43**); once deprotection is effected, it is apparent that cyclisation, *via* intramolecular nucleophilic attack on the carbonyl carbon by the free amino group, occurs readily. The imino lactone (**131**) was fully characterized by spectroscopic ($^1H$ and $^{13}C$ NMR, IR and high resolution MS) techniques, and the $^1H$, HMQC and COSY NMR spectra of this crucial compound are illustrated in **Figures 7 - 9**.

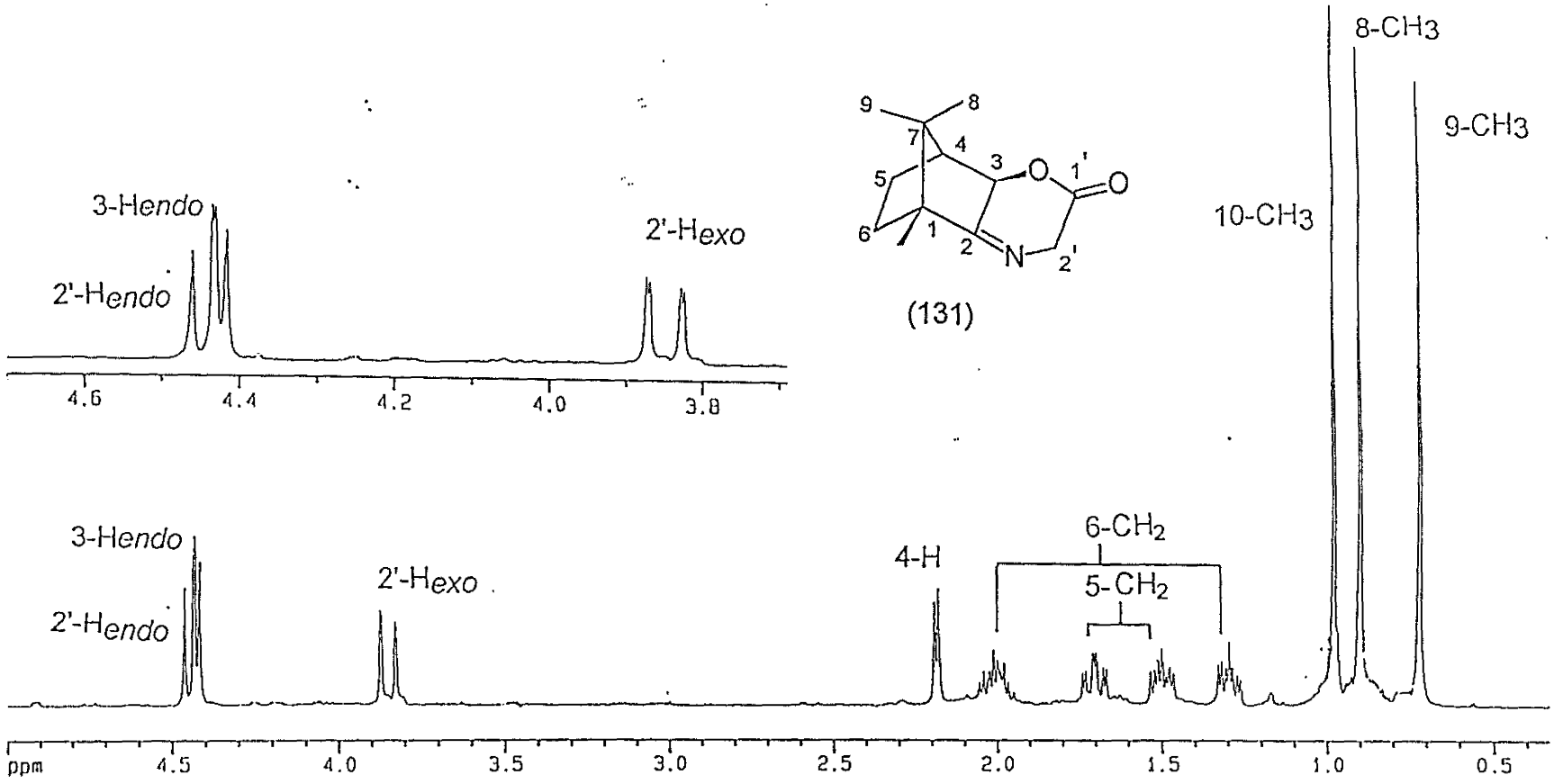



FIGURE 7. The partial 400 MHz $^1$H NMR spectrum of the imino lactone (131 ) in $CDCl_3$.

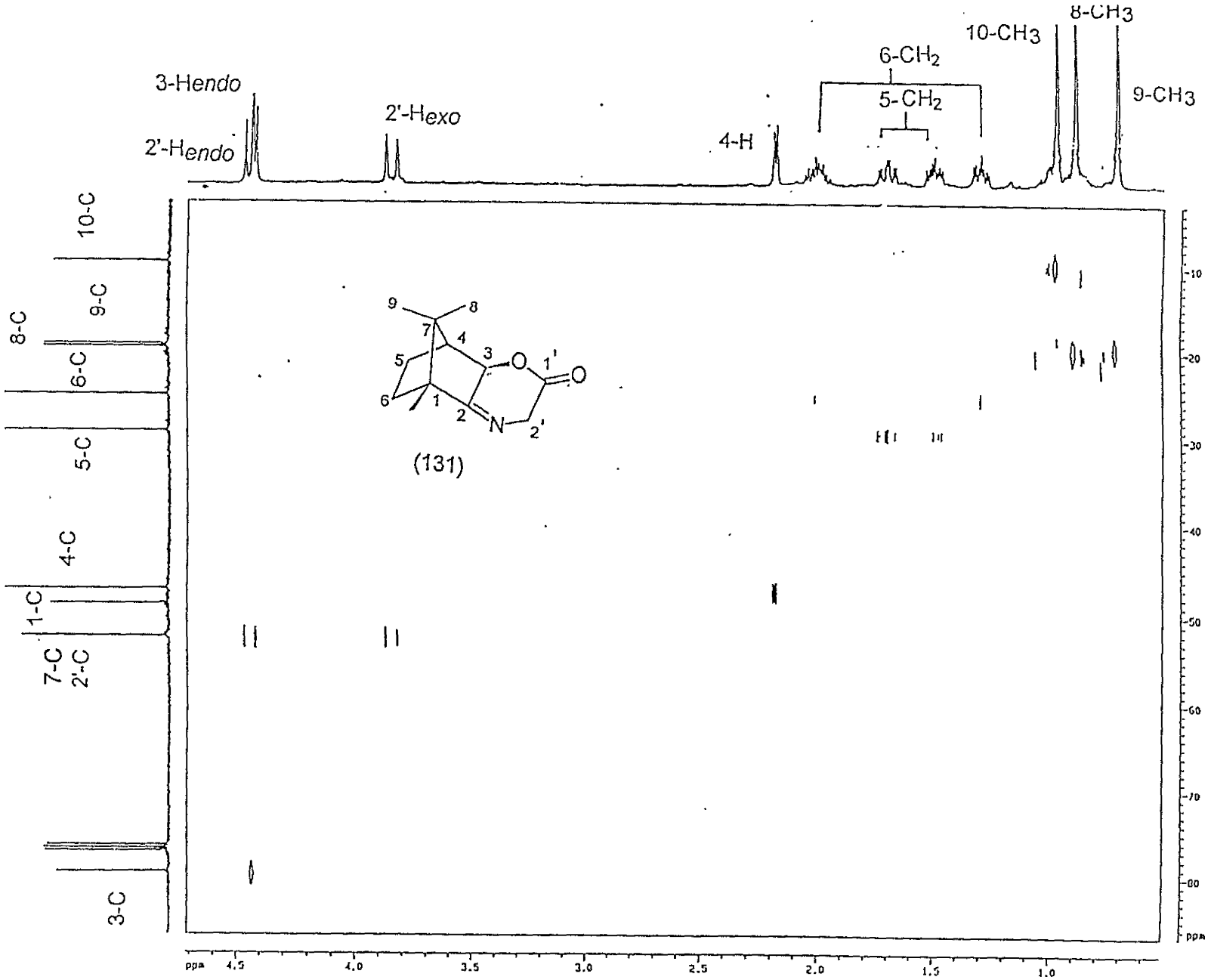



FIGURE 8. The HMQC spectrum of imino lactone (131) in $CDCl_3$

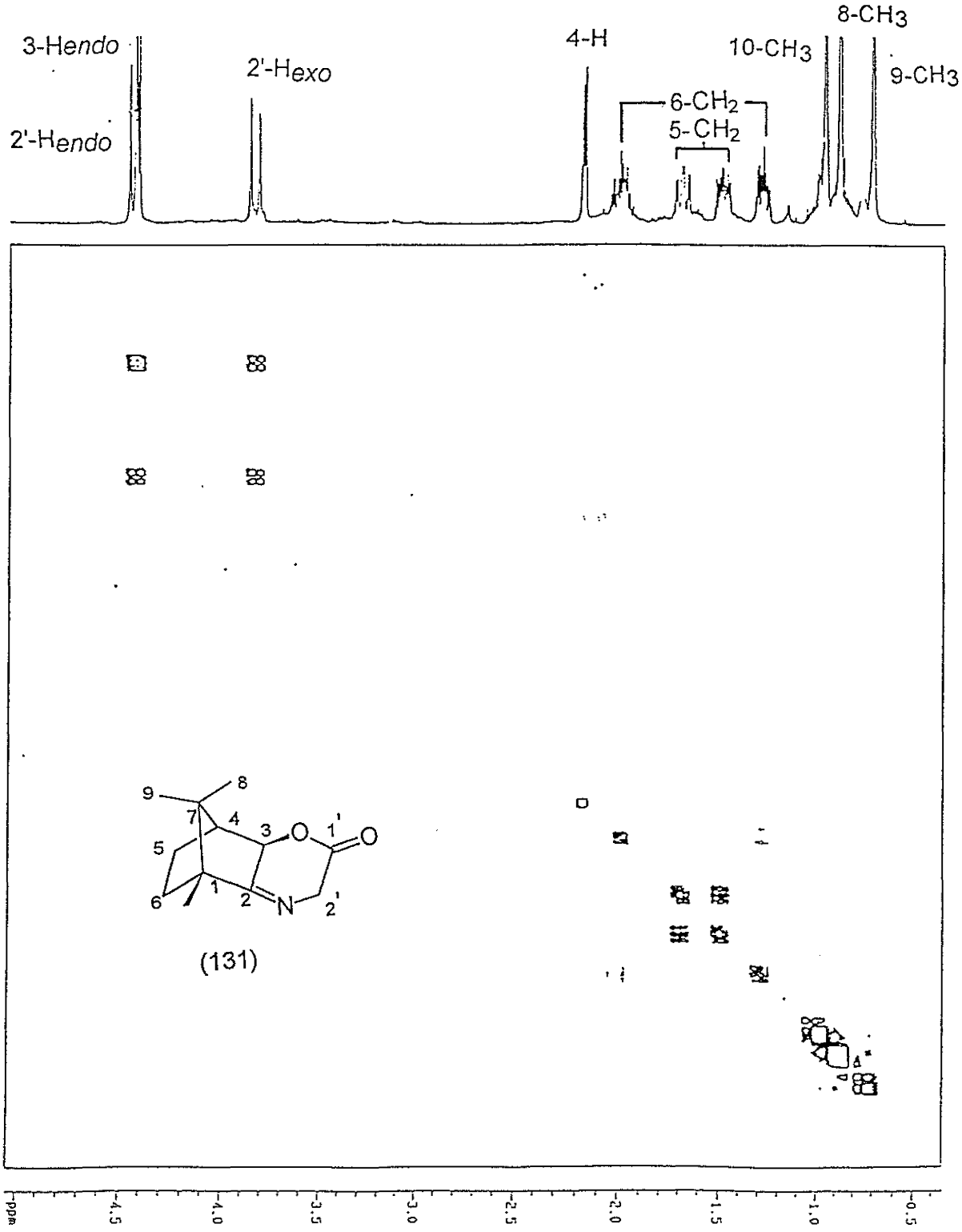


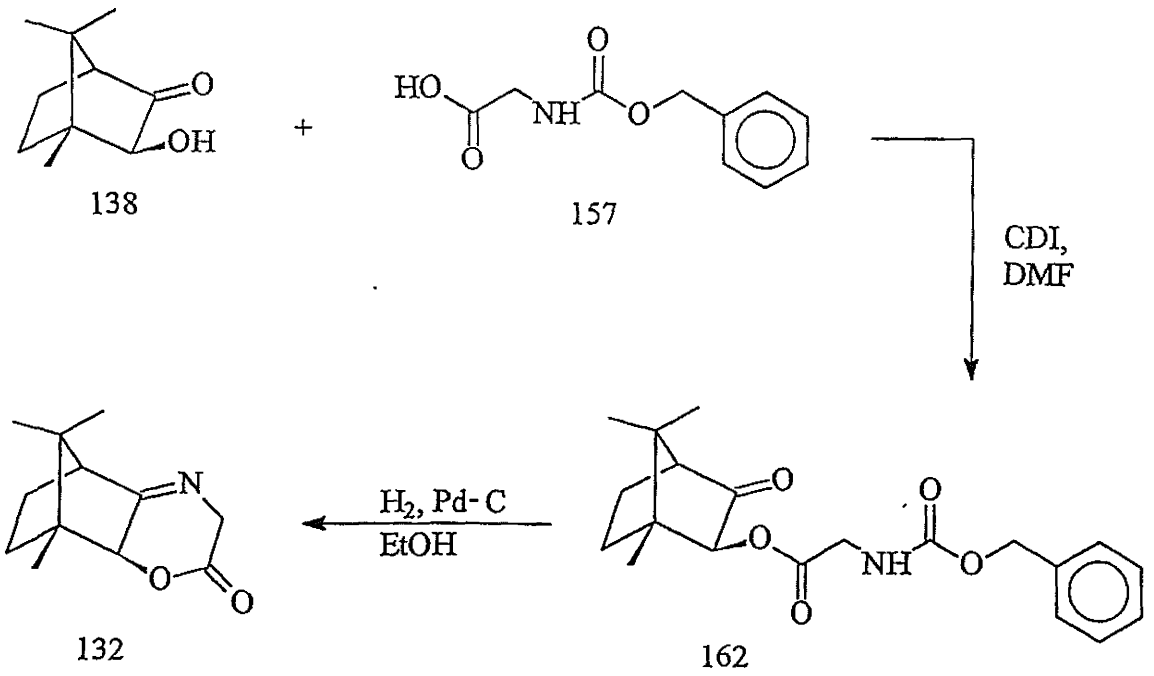

FIGURE 9. The COSY spectrum of imino lactone (**131**) in $CDCl_3$

The HMQC spectrum of the imino lactone (**131**) (**Figure 7**) exhibits correlations between the pair of double doublet at 3.85 ppm (*J* 17.8 Hz) and 4.46 ppm (*J* 17.8 Hz), corresponding to the diastereotopic glycinate 2′-methylene protons, and the 2′-C signal at 52.5 ppm. The *endo* 3-H nucleus resonates as a narrow doublet at 4.43 ppm (*J* 1.6 Hz), indicating a remarkable long-range (5-bond) coupling to one of the glycinate methylene protons. This coupling, apparent in the expanded $^1$H NMR spectrum (**Figure 8**), was initially ascribed to the 2′-$H_{endo}$ proton, but it was later established to be due to interaction with the 2′-$H_{exo}$ proton (see **Section 2.2.1**). The twelve $^{13}$C NMR signals confirm the expected camphor imino lactone structure, with the typical C-1′ (carbonyl), C-2 (imino) and C-3 (ester *O*-alkyl) signals, at 183.6, 168.8 and 79.5 respectively (**Figure 7**). The $^1$H-$^1$H coupling interactions involving the 2′-, 5- and 6-methylene protons are evident in the COSY spectrum (**Figure 9**).

### 2.1.1.3 Preparation of the imino-lactone (132) from 2-*exo*-hydroxy-3-bornanone (138)

Having successfully established a synthetic route to the imino lactone (**131**), the synthesis of the regioisomeric compound (**132**) was undertaken. Following the same procedure[62] used for the synthesis of the *N*-protected glycine ester (**160**), the 2-*exo*-bornyl analogue (**162**) was prepared from 2-*exo*-hydroxy-3-bornanone (**138**), and *N*-(carbobenzyloxy)glycine and carbonyldiimidazole in DMF (**Scheme 44**). The esterification proceeded smoothly yielding the ester (**162**) in 96% yield after work-up and chromatographic purification. Deprotection of the *N*-protected glycine ester (**162**) and cyclisation to the imino lactone was achieved by hydrogenolysis in ethanol using 10% Pd on carbon as catalyst.[65] The required imino lactone (**132**) was isolated in 85% yield after chromatographic purification, and was fully characterised by high resolution mass spectrometry,

IR and NMR ($^1$H, $^{13}$C, DEPT, HETCOR and COSY) spectroscopy (see **Figures 10 - 12**).




SCHEME 44

As was the case with the regioisomeric camphor 2-imino lactone (**131**), the diastereotopic glycinate methylene protons also resonate as a doublet [at 3.77 ppm (*J* 17.9 Hz)] and a doublet of doublets [at 4.30 ppm (*J* 17.8 Hz and *J* 1.6 Hz)] (**Figure 10**), the unusual long-range (5-bond) coupling between the *endo* 2-H and one of the glycinate methylene protons once more being observed. The $^{13}$C NMR spectrum shows twelve carbon peaks with the C-1′ (carbonyl), C-3 (imino) and C-2 (ester *O*-alkyl) signals resonating at 181.4, 168.4 and 81.3 ppm respectively. The skeletal connections were confirmed by the HMQC spectrum (**Figure 11**) which shows correlations between:- the diastereotopic glycinate methylene protons and C-2′; the 2-$H_{endo}$ and C-2 nuclei; and the 4-H and C-4 nuclei. The HMQC spectrum also confirms that the 5- and 6-methylene multiplets are interspersed with each other whereas, in compound (**131**), the 6-methylene multiplets straddle the 5-methylene signals (see **Figure 9**); the coupling relationships in the COSY spectrum (**Figure 12**) confirm these assignments.

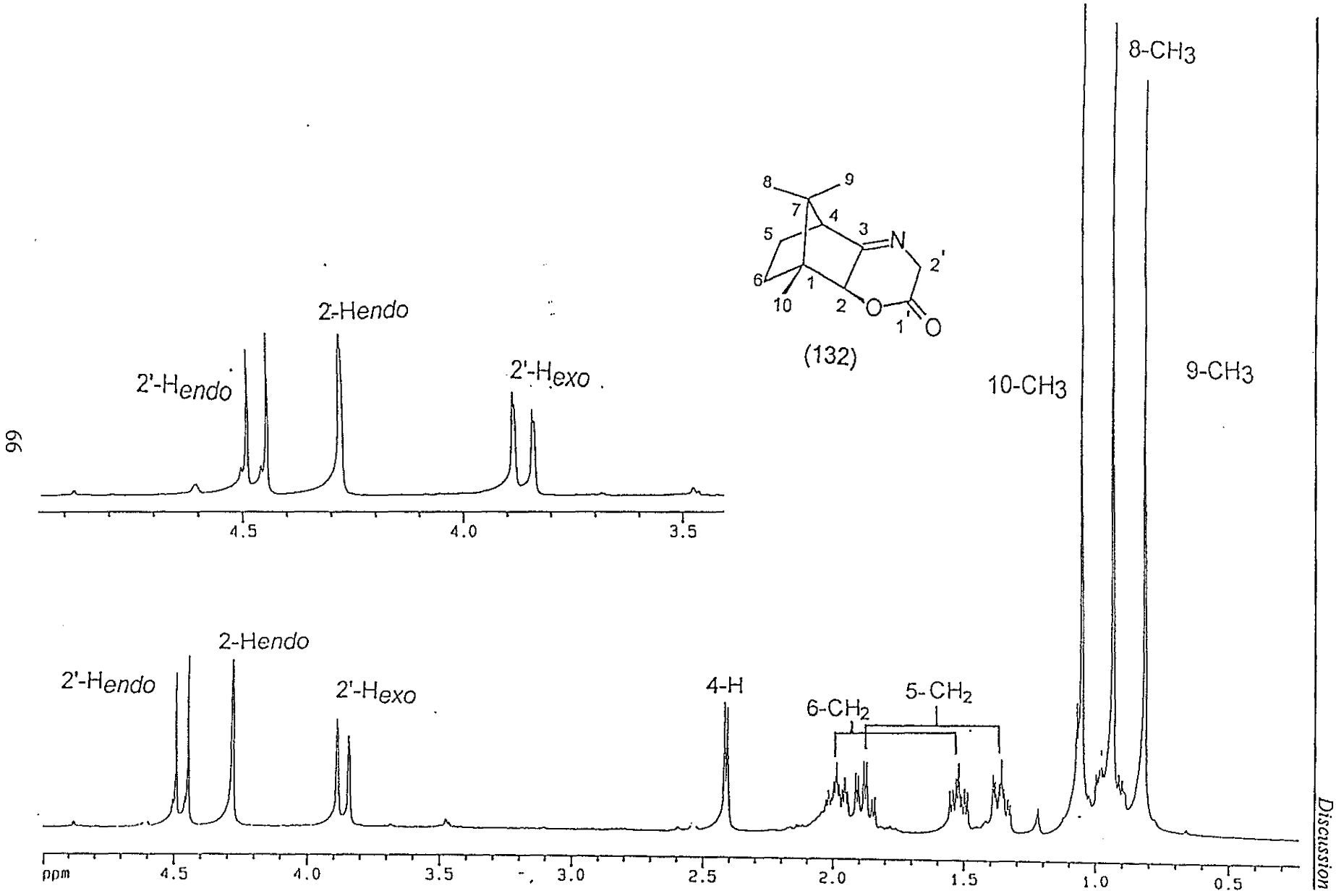



FIGURE 10. The partial 400 MHz $^1H$ NMR spectrum of the imino lactone (132) in $CDCl_3$.

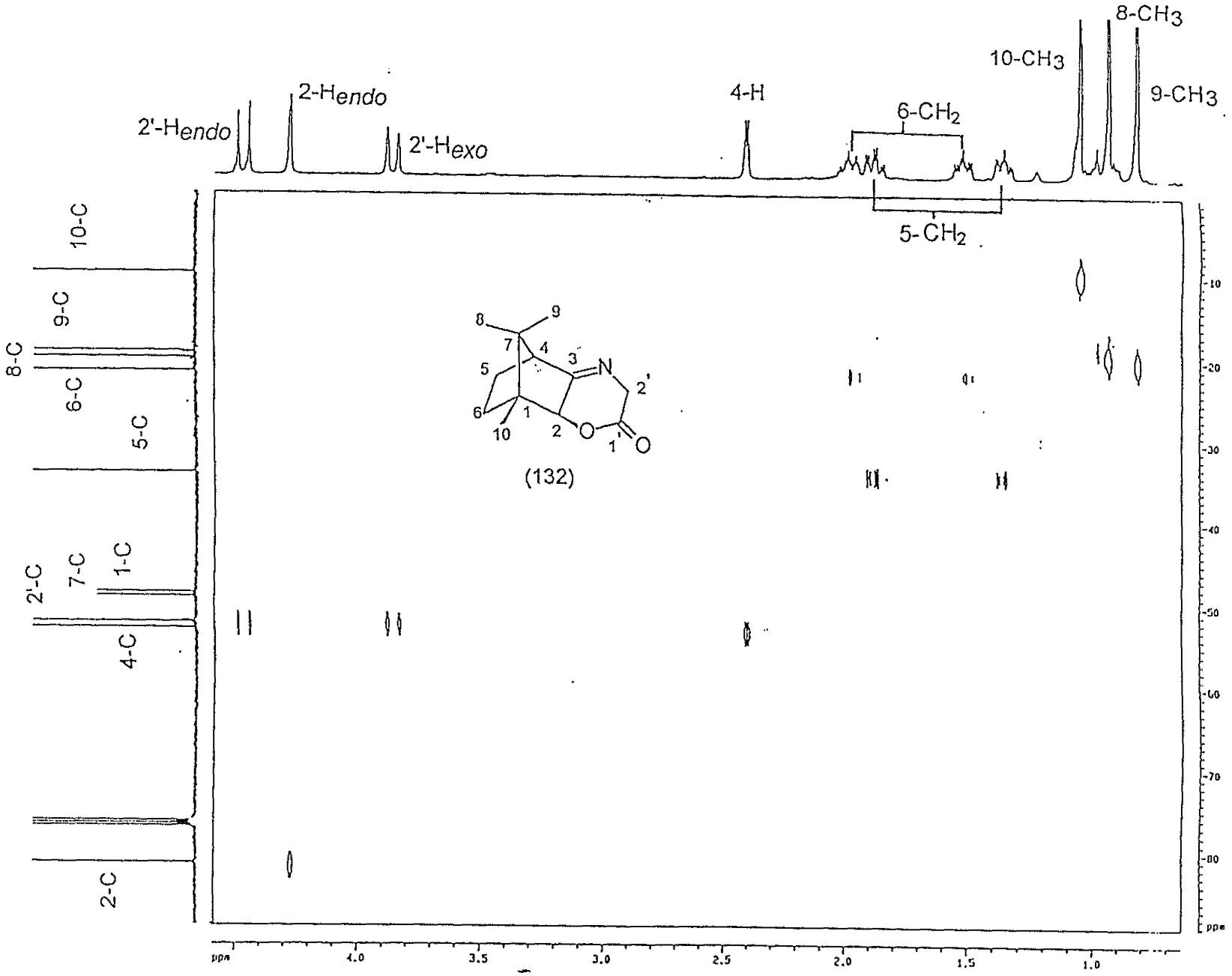



FIGURE 11. The HMQC spectrum of the imino lactone (**132**) in $CDCl_3$

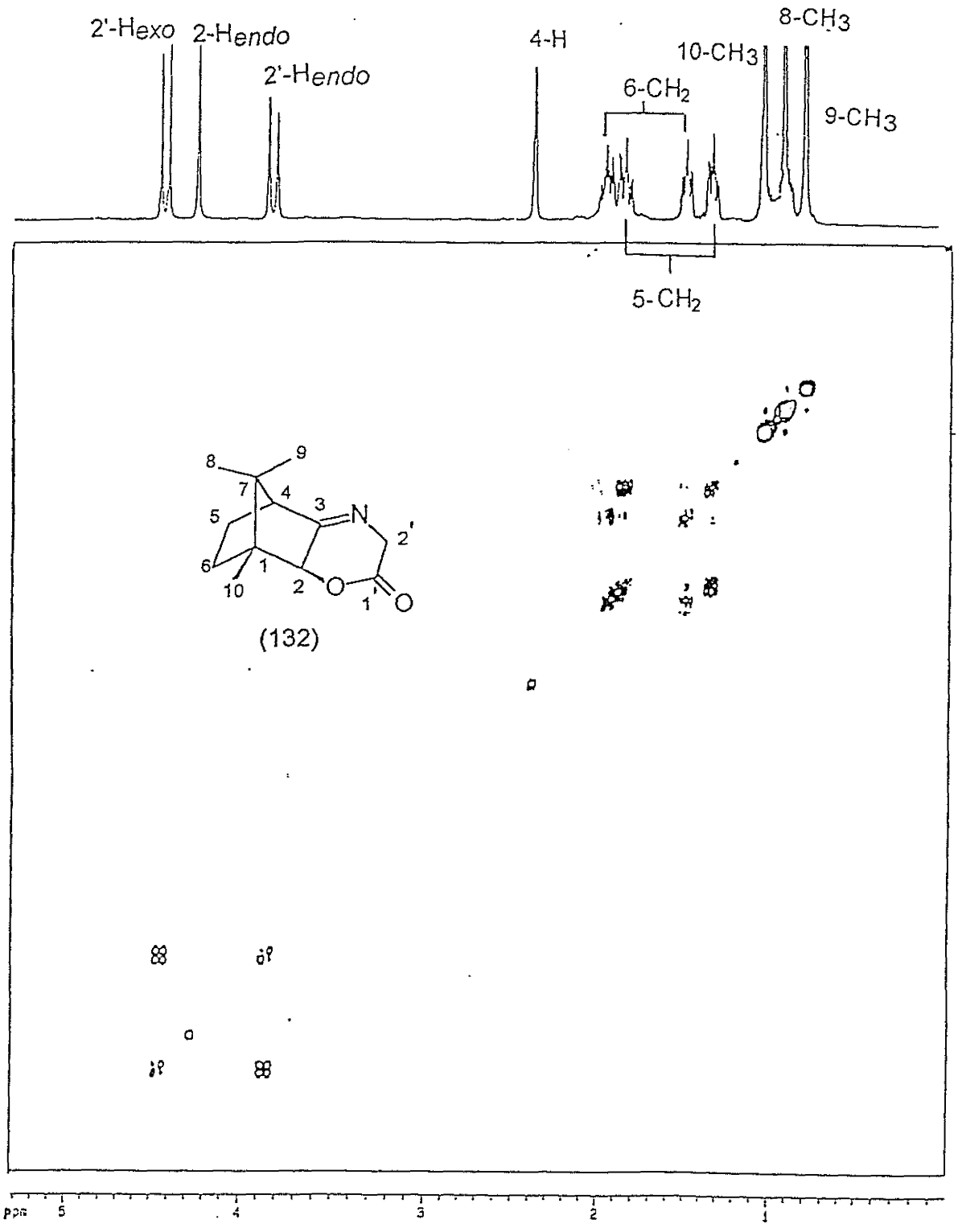
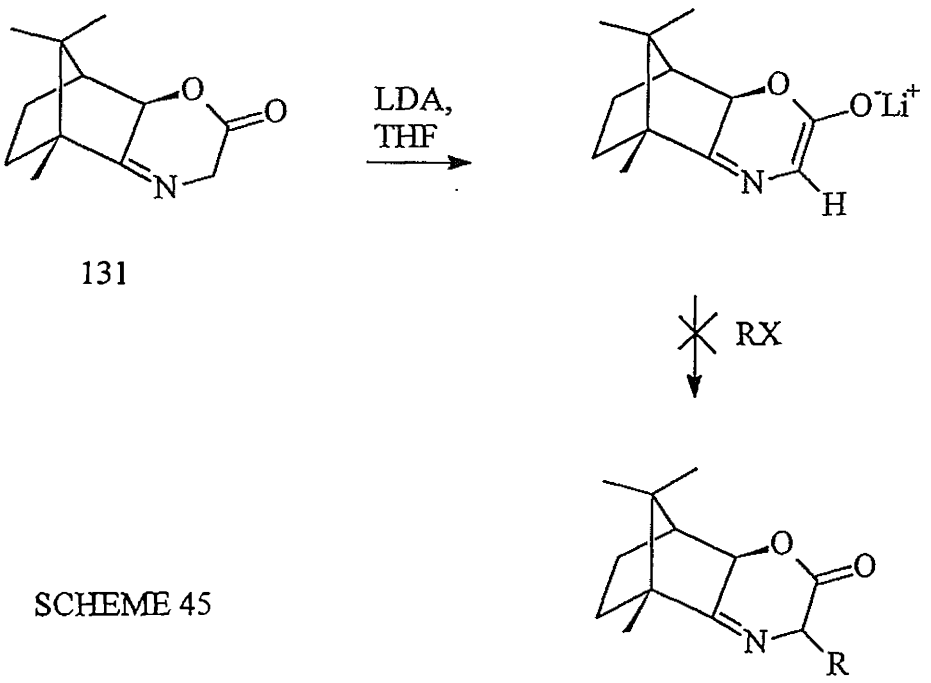



FIGURE 12. The COSY spectrum of the imino lactone (**132**) in $CDCl_3$

### 2.1.2 Alkylation of the camphor imino lactones (131) and (132)

With access to the chiral substrates (131) and (132) well established, their stereo-directing potential was then explored. Nucleophilic attack by glycine-derived enolates on alkyl halides has been previously investigated by Tabchem *et al.*,[56] who studied the use of LDA, LTMP, potassium *t*-butoxide (*t*-BuOK) and lithium *t*-butoxide ( *t*-BuOLi), in an attempt to understand the influence of the various bases on these reactions. It was observed that *t*-BuOLi was the least reactive of the series of bases and, when used, no alkylation was observed; with the other three bases, it was apparent that the chemical yields were not affected by the choice of base, but better diastereoselectivities were obtained with LDA and LTMP than with *t*-BuOK.

In our investigation LDA was initially considered for abstraction of the α-proton in the glycine derivatives (131) and (132). A series of preliminary reactions was conducted using the imino lactone (131) to optimise the conditions for generating the enolate and its subsequent alkylation. The LDA was prepared *in situ* under anhydrous conditions from diisopropylamine and butyllithium at *ca.* -78°C, using THF as a solvent; the imino lactone (131) was then added at low temperature, of the enolate being indicated by the development of a bright yellow colour. Alkylation of the enolate was first attempted using ethyl bromide. This alkyl halide was added to a stirred solution of the lithium enolate of the imino lactone (131) (**Scheme 45**). The reaction mixture was stirred at *ca.* -78°C for two hours and then allowed to warm to room temperature. One half of the resulting mixture was quenched, while the other half was allowed to stir overnight. Work-up and preparative chromatography of both fractions failed to yield any ethylated imino lactone (**163; R = Et**). The above procedure was repeated using various alkyl iodides and bromides, but with no success.



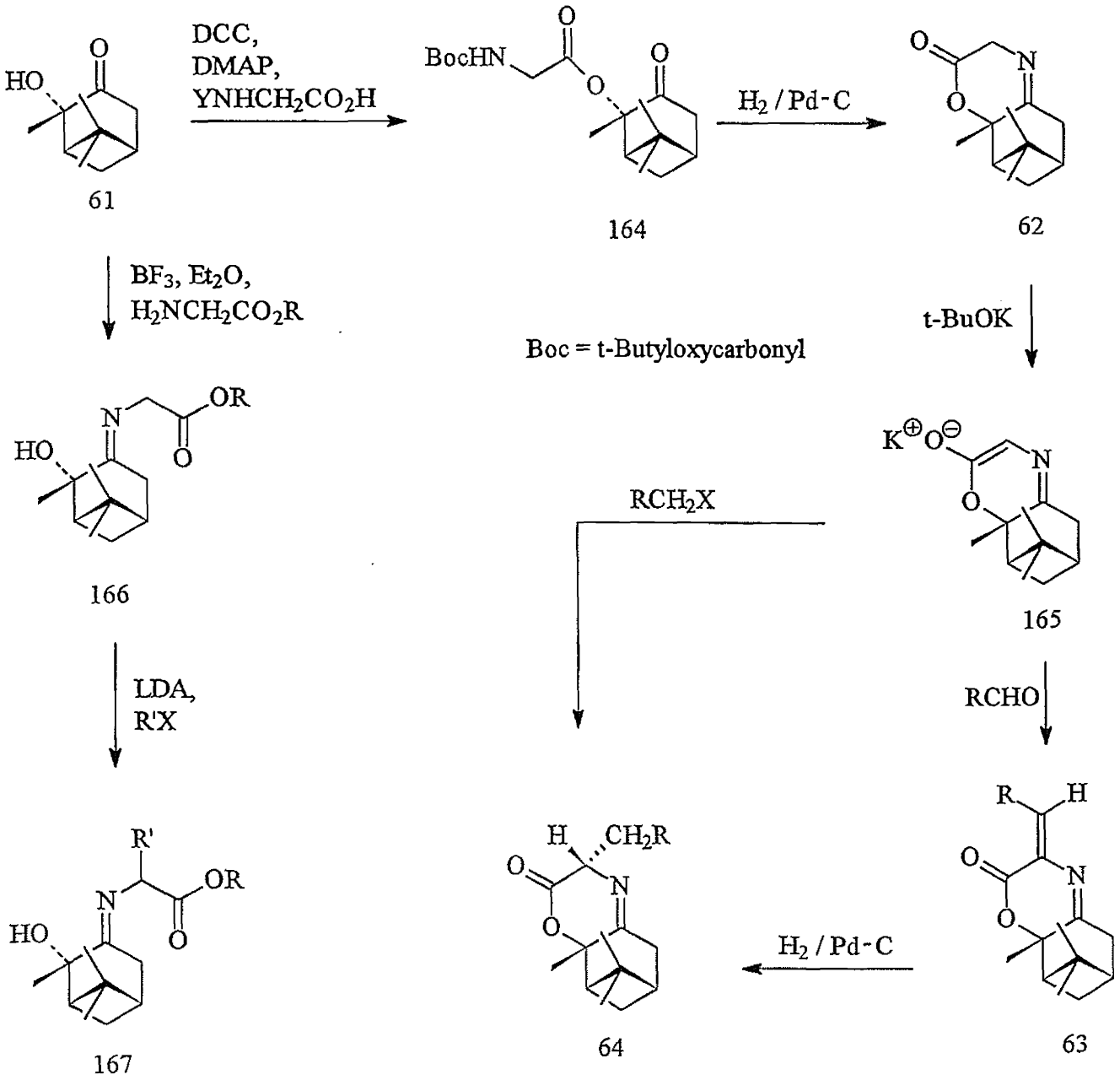

131

163

SCHEME 45

As previously mentioned (**Section 1.3.1.1**), El-Achqar *et al.*,[62] using a similar general approach, have prepared the pinane imino lactone (**62**). Coupling of *N*-BOC-glycine and 2-hydroxy-3-pinanone (61), in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) was followed by deprotection of the intermediate ester (**164**) and cyclisation to lactone (**62**) in 55% yield. Cativiela *et al.*[30] reacted the imino lactone (**62**) with a series of aldehydes in the presence of *t*-BuOK to furnish the corresponding conjugated (*E*)-derivatives (**63**) in 60% to 85% yield; hydrogenation of the intermediates (**63**) with palladium on charcoal in methanol at room temperature provided the corresponding *S*-amino acid derivatives (**64**) in high chemical yield and with virtually quantitative topological control. $^1$H NMR Data showed that the hydrogen entered on the same face as the *gem*-dimethyl group, whereas direct alkylation of the enolate (**165**) was shown to occur at the opposite face, both approaches thus yielding amino acid derivatives of the same configuration. In an acyclic approach,[56] involving the Schiff base (**166**),

the alkylated derivatives (**167**) were hydrolysed to afford amino acids, the chemical and optical yields of which were shown to depend on the *O*-alkyl substituent, R (**Scheme 46**). El Achqar *et al.*[62] commented on the difficulty in effecting alkylation using LDA as a base and stated that alkylation was only achieved when *t*-BuOK was used instead.




SCHEME 46

Encouraged by the success of Cativiela's work on pinane systems,[30] we decided to attempt alkylation of the camphor-derived imino lactone (**131**) using *t*-BuOK as base. When the potassium enolate (**168**) was treated with the alkylating agents methyl iodide, ethyl iodide and benzyl bromide, work-up and preparative thin layer chromatography furnished, in each case, the dialkylated imino lactones, in (47 - 50%) yield, and the starting 3-*exo*-hydroxycamphor (**137**) (**Scheme 47**). The observed dialkylation clearly confirmed the formation of reactive enolate intermediates, and attention was given to achieving monoalkylation by:-

(i) reducing the reaction time, *i.e.* by quenching the reaction after stirring at -78°C for one hour;

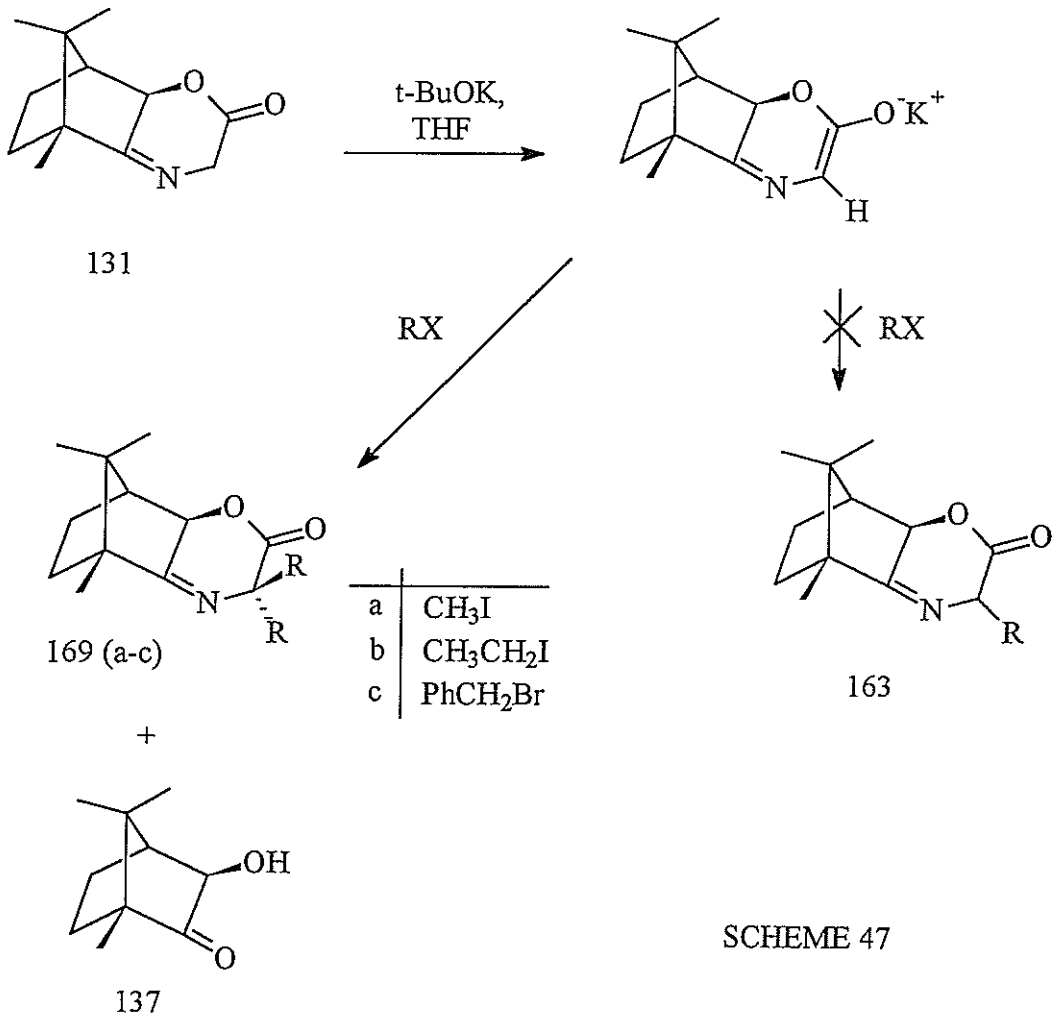
(ii) diluting the reaction mixture two-fold; and

(iii) using half the molar quantity of the alkyl halide.

These methods failed to limit alkylation and, in each case, the dialkylated product was isolated. The dialkylated products (**169 a - c**) were unanbiguously characterised using high resolution MS and 1- and 2-D NMR techniques. The $^1$H NMR spectra of the dimethyl (**169 a**) and dibenzyl derivative (**169 c**) are illustrated in **Figure 13**. Interestingly, El-Achqar *et al.*[62] also isolated the dimethyl and dibenzyl products in approximately 14% yield in their alkylation of the pinane-derived imino lactone (**62**) (**Scheme 47**).

The unusually high field chemical shifts of the 2-$H_{endo}$ (2.9 ppm) and 8-Me (-0.3 ppm) nuclei in the dibenzyl derivative (**169c**) [compared to the dimethyl analogue (**169a**)] can be attributed to the anisotropic shielding effect of the two phenyl groups in the former compound. Molecular modelling of the dibenzyl derivative (**169c**) (**Figure 14**) afforded an energy-minimized conformation in which the 3-$H_{endo}$ and 8-Me nuclei lie in the anistropic shielding zones of the

phenyl rings.




SCHEME 47

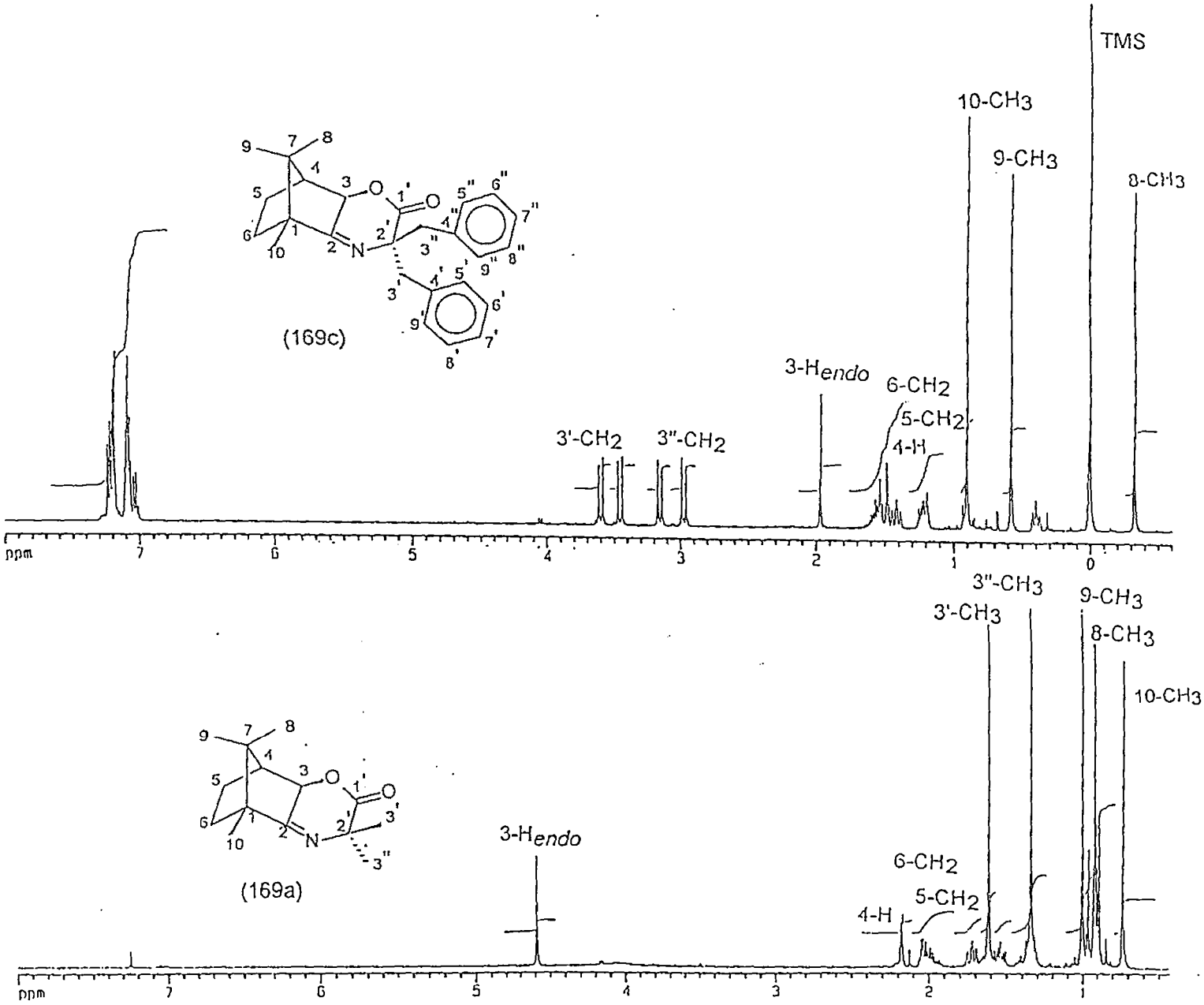



FIGURE 13. The 400 MHz $^1$H NMR spectra of the dimethyl (**169a**) and dibenzyl (**169c**) imino lactone derivatives in $CDCl_3$

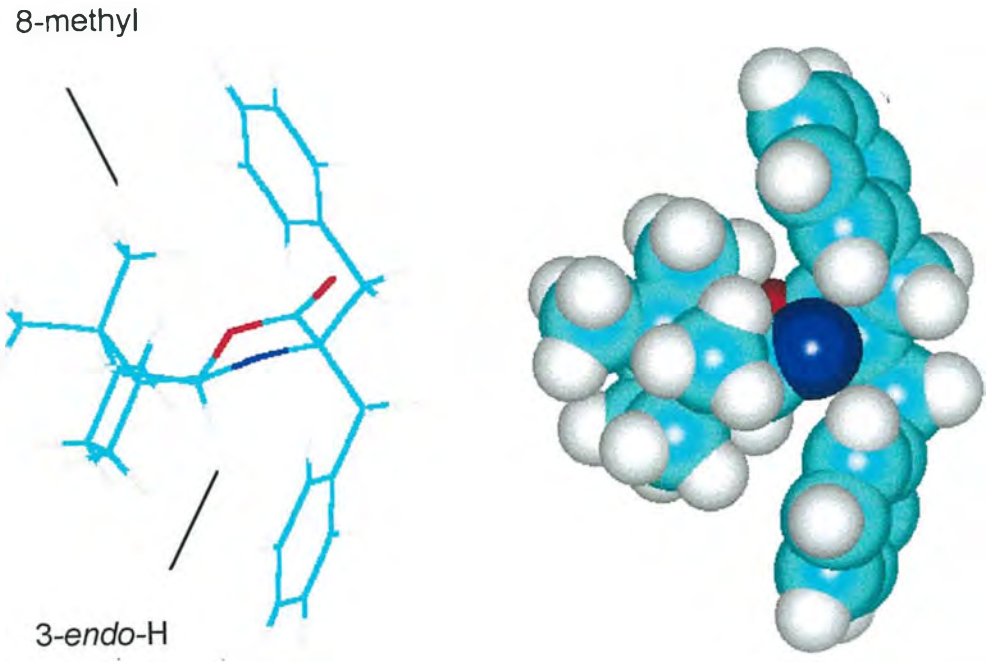



FIGURE 14. Computer-generated molecular model of the dibenzyl imino lactone (169c), showing the 3-$H_{endo}$ and 8-Me nuclei in the shielding zone of the phenyl rings.

Given the complications encountered with the imino lactone (131), attention was turned to exploring the stereo-directing potential of the regioisomeric 3-imino-2-*exo*-lactone (132). Following the established procedure, the lactone enolate (170) was generated under anhydrous conditions at -78°C using *t*-BuOK as base (Scheme 48). Ethyl bromide was then added to a solution containing the enolate and the reaction mixture was stirred at -78°C for two hours before being allowed to warm to room temperature gradually. After stirring overnight, the reaction mixture was worked up, but preparative layer chromatography failed to yield any of the desired α-ethylated product (173). The procedure was then repeated using propyl bromide, butyl

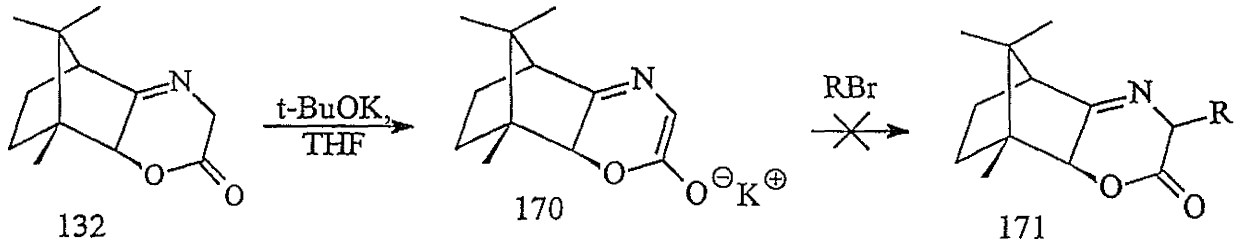
bromide, and *tert*-butyl bromide, but with no success.

It was then decided to attempt alkylation using the more reactive alkyl iodides as alkylating agents. Methyl iodide was added to the potassium enolate (170); work-up and preparative layer chromatography furnished the desired monomethylated imino lactone (172) in 82% yield and a diastereomeric excess of 43% (**Table 1**), with none of the dimethylated product! The diastereoselectivity was determined from the $^1$H NMR integral ratios of the well-resolved 2-$H_{endo}$ singlets and 2′-H quartets corresponding to the two diasteromers in the crude reaction mixture (see **Figure 15**). The amide reaction mixture was examined to ensure that the diastereomeric ratio reflected the diastereoselectivity of the reaction and not selective enrichment of one diastereomer over the other during purification.† The purified mixture of diastereomeric products was subjected to high resolution ms and NMR analysis (IR, $^1$H, $^{13}$C, DEPT, COSY and HMQC), amply confirming formation of the desired products (see **Figure 16 - 17**) (**Scheme 48**).

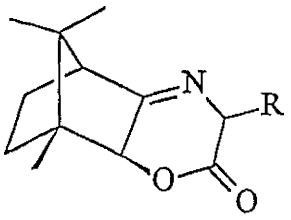
From careful examination of the NMR spectroscopic data, it appears that nucleophilic attack is favoured, as expected, at the less hindered *endo* face of the potassium enolate (170), the *exo* face being hindered by the 8-methyl group. This deduction is based on the nuclear Overhauser effect (NOE) observed between the 2-$H_{endo}$ and the 3′-methyl nuclei of the major component in the NOESY spectrum. A comparison of $^1$H NMR chemical shifts for the imino lactone precursor (132) (see **Figure 10**) and the diastereomeric methylated products (172) (see **Figure 15**) reveals some interesting patterns. Firstly, the 2′-*exo* proton of the major diastereomer (the *endo*-

†In fact, chromatogaphic purification appeared not to have altered the integral ratios.

methylated compound) resonates as a quartet ($J$ = 7.0 Hz) at *ca.*3.8 ppm - a chemical shift value similar to that observed for the 2′-*exo* proton in the imino lactone (**132**). Furthermore, the corresponding 2′-*endo* proton of the minor diastereomer resonates as a quartet ($J$ = 7.6 Hz) at 4.49 ppm – the same chemical shift as the 2′-*endo* proton in the imino lactone (**132**). These observations suggests that there is little change in the conformation of the heterocyclic moeity upon methylation and that the chemical shift of the 2′-methine proton may be used to infer configuration at the 2′-position. Secondly, the 2-*endo* and 2′-*exo* protons exhibit small but observable long-range couplings ( $^5J$ = 1.7 Hz), which may also be of value in determining configuration at C-2. This deduction was further confirmed by the NOE interaction observed between the 2′-*exo* proton (3.8 ppm) and the 8-methyl group (0.9 ppm) in the imino lactone precursor (**132**).




RI
(or, $PhCH_2Br$ for $PhCH_2$)



| | R |
|---|---|
| 172 | $CH_3$ |
| 173 | $CH_3CH_2$ |
| 174 | $CH_3(CH_2)_2$ |
| 175 | $CH_3(CH_2)_3$ |
| 176 | $CH_3(CH_2)_4$ |
| 177 | $CH_3(CH_2)_5$ |
| 178 | $(CH_3)_2CH(CH_2)_4$ |
| 179 | $PhCH_2$ |

| | R |
|---|---|
| a | $CH_3CH_2$ |
| b | $CH_3(CH_2)_2$ |
| c | $CH_3(CH_2)_3$ |
| d | $(CH_3)_3C$ |

SCHEME 48

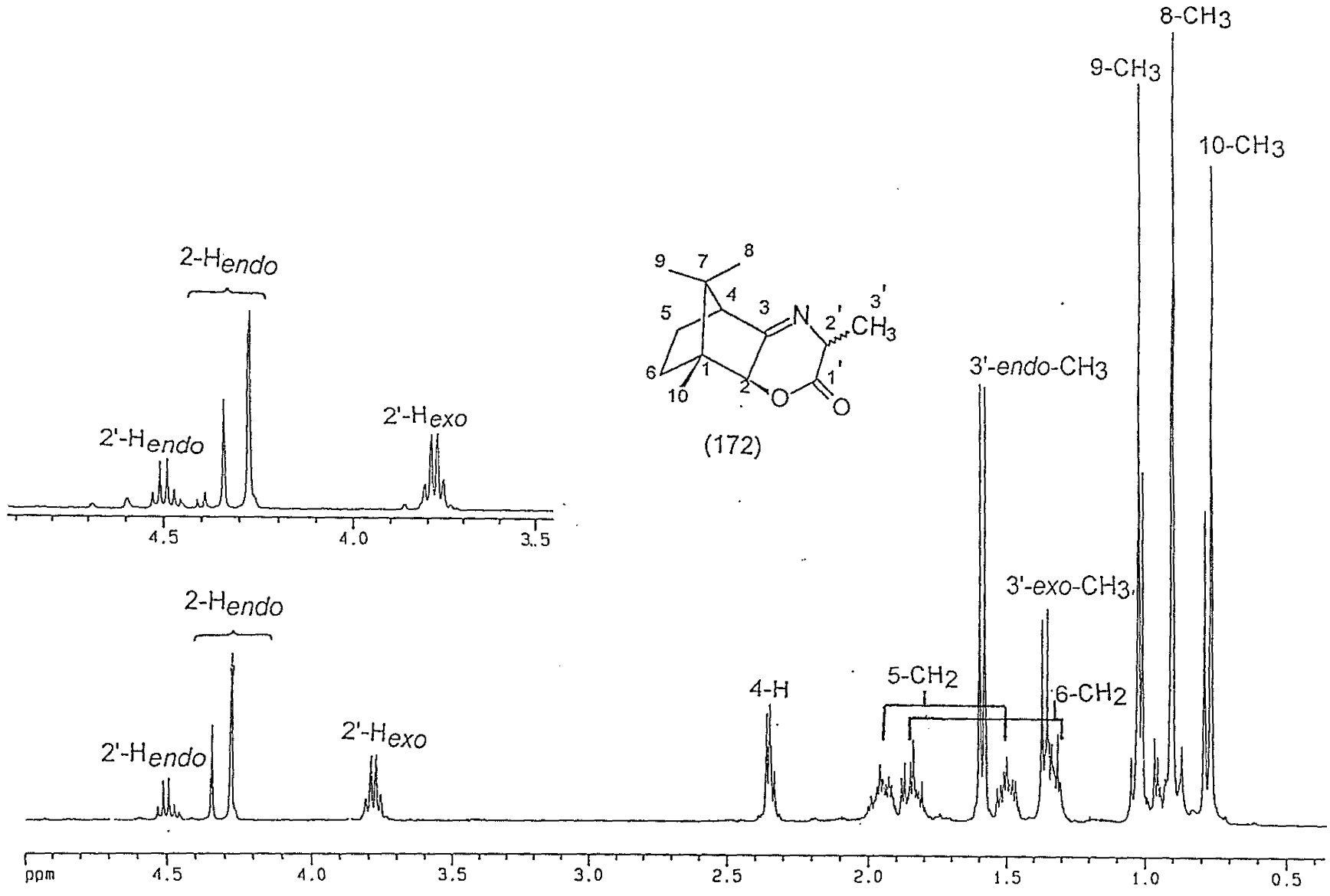



FIGURE 15. The 400 MHZ $^1$H NMR spectrum of a mixture of the diastereomeric products (172) in $CDCl_3$

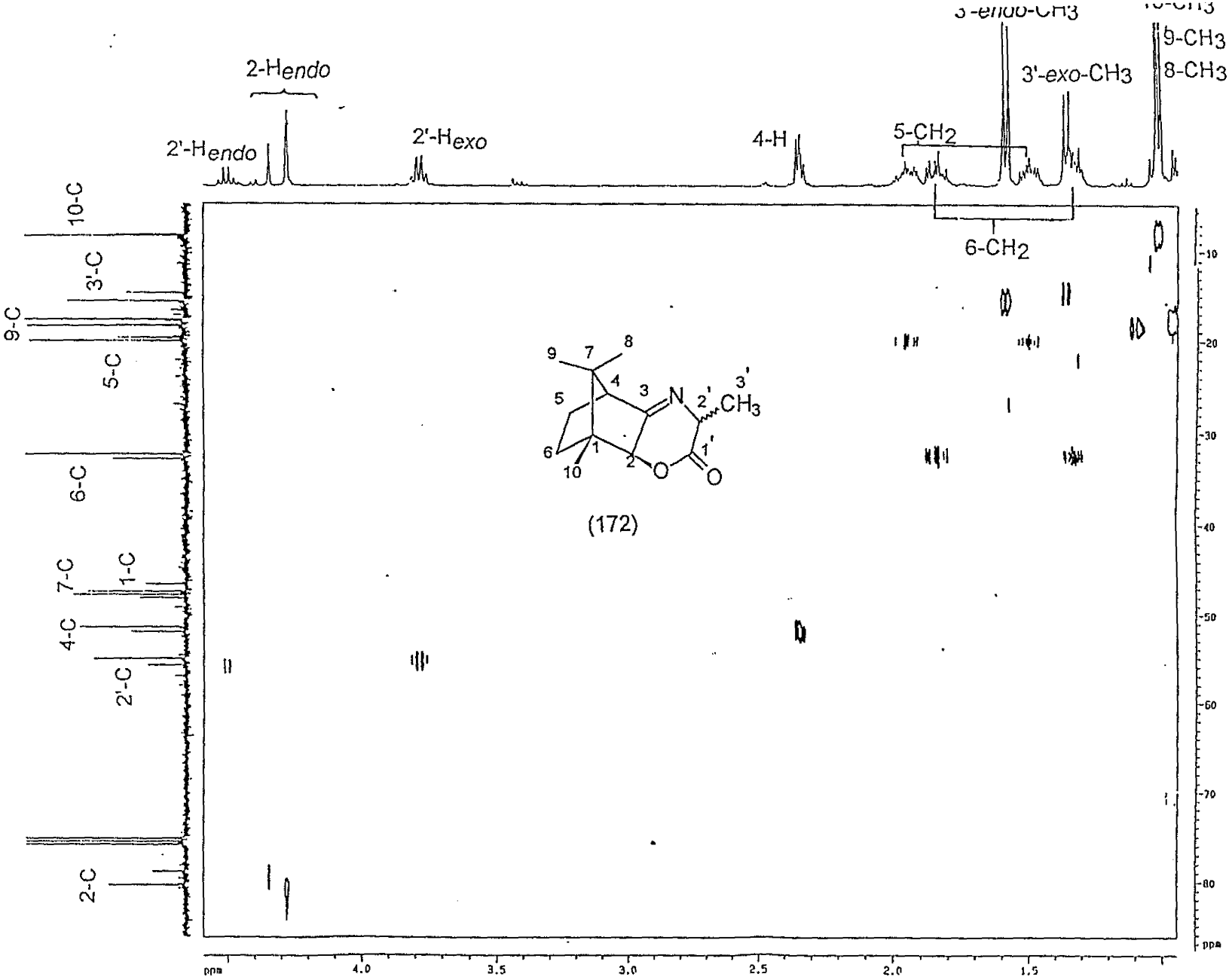



FIGURE 16. The HMQC spectrum of the diastereomeric products (**172**) in $CDCl_3$

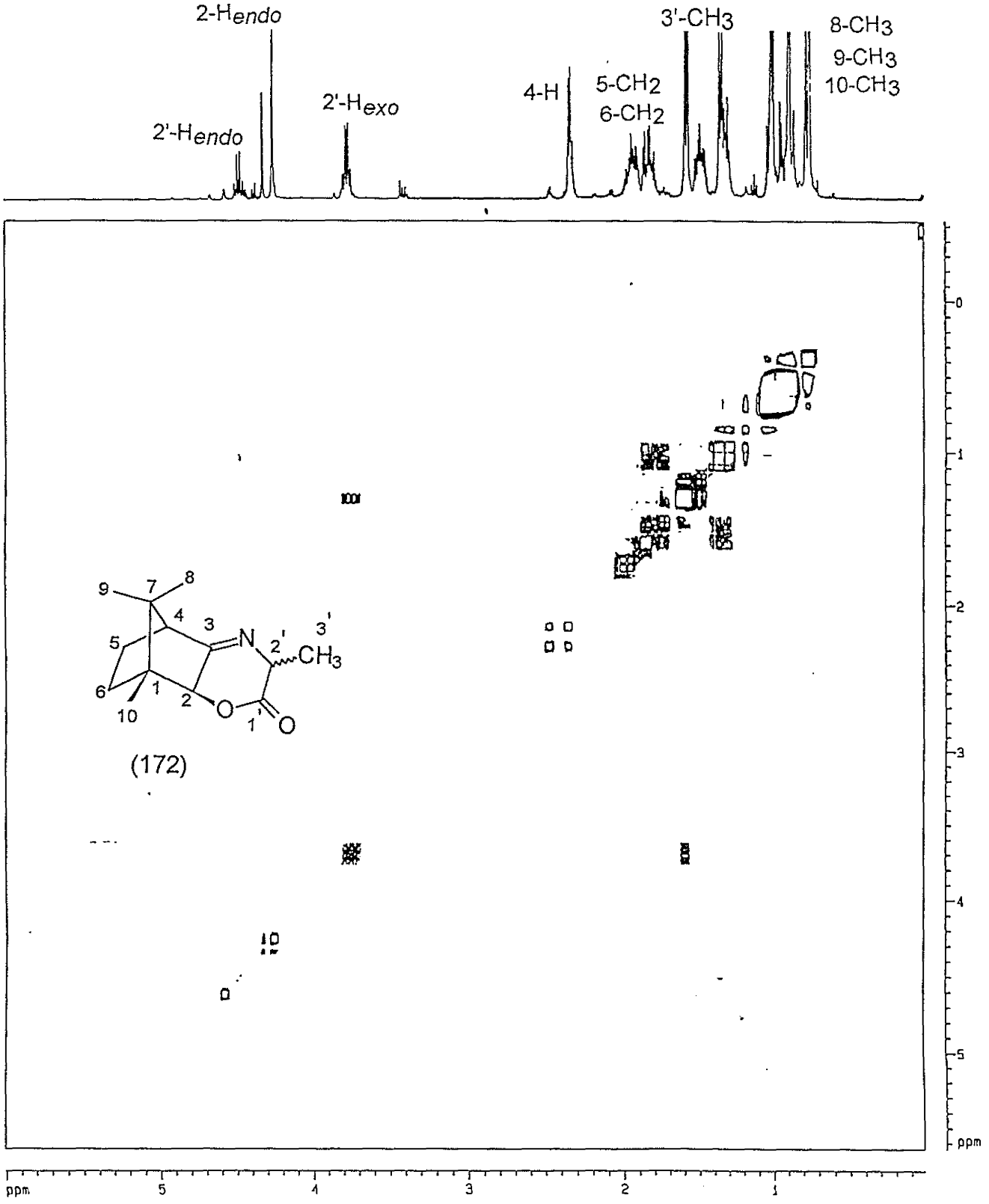



FIGURE 17. The COSY NMR spectrum of a mixture of the diastereomeric products (**172**) in $CDCl_3$

The HMQC spectrum of the methylated imino lactone (172) (**Figure 16**) confirmed the skeletal connections, and the COSY spectrum (**Figure 17**) confirmed the coupling between the 3′-Me and 2′-H nuclei.

These results encouraged us to explore the stereo-directing potential of the imino lactone (**132**) using alkyl iodides of increasing size (**Scheme 48**). The diastereomeric excesses obtained in these reactions (see **Table 1**) were determined from the $^1$H NMR integratal ratios of the 2′-H signals in the crude reaction mixtures. In the systems examined, the 2′-H nucleus resonates as a double doublet which, in some cases, overlap to give the appearance of a triplet - a situation which is illustrated in the $^1$H NMR spectrum of compound (**173**) (**Figure 18b**); the double doublet is clearly exhibited by the butyl derivative (**175**) in **Figure 18a**. In the latter spectrum, the complete dominance of the 2′-*endo* alkylated product (**175**) is clearly evidenced by the absence of a 2′-$H_{endo}$ signal.

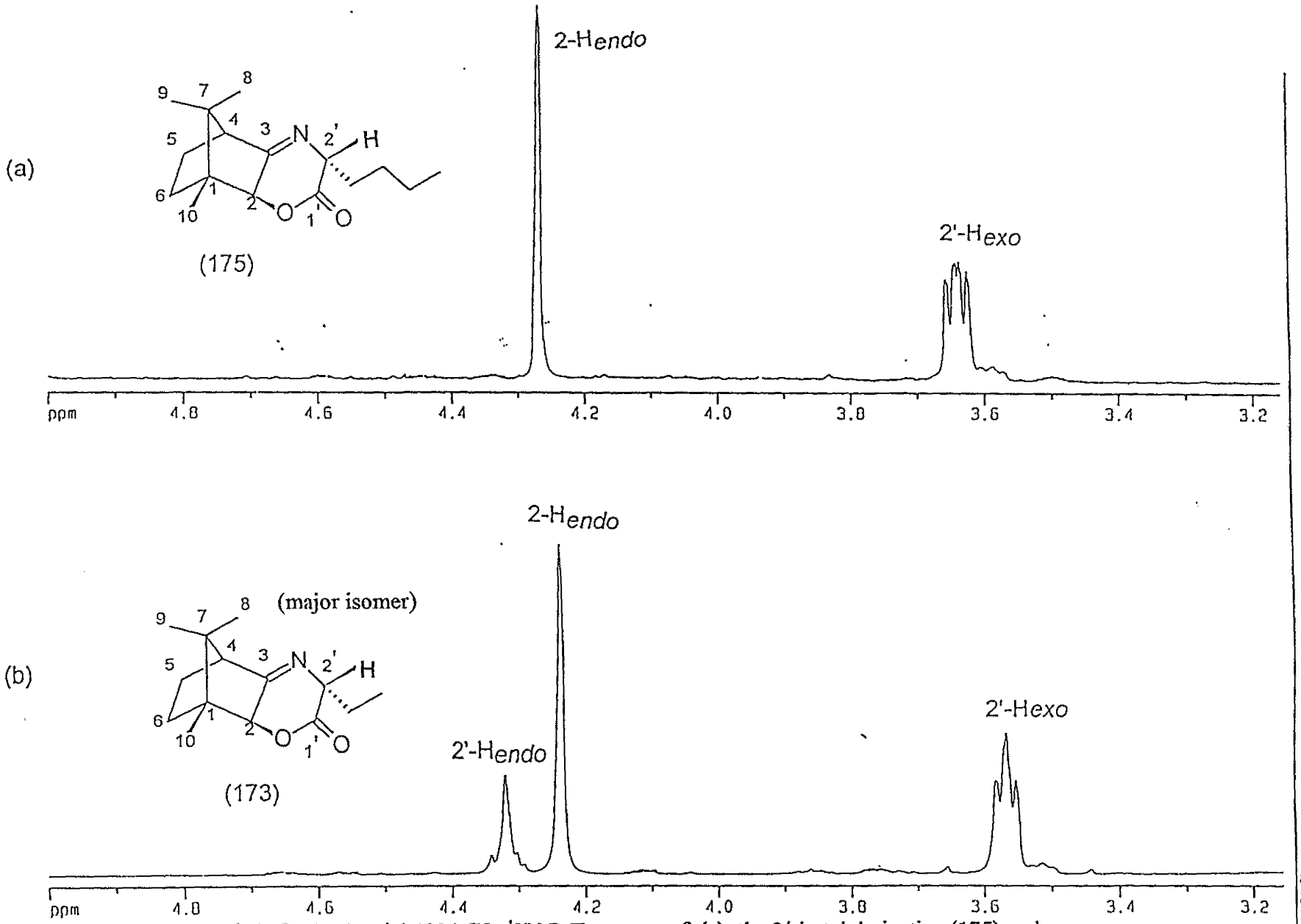
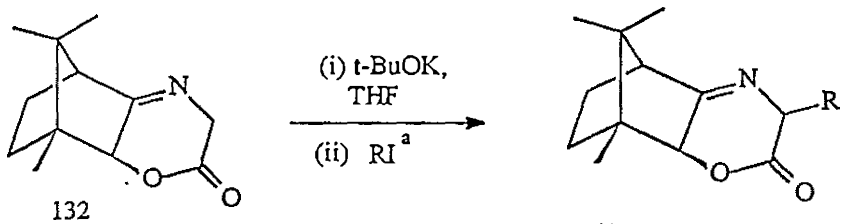



FIGURE 18. Partial 400 MHz $^1$H NMR spectra of (a) the 2′-butyl derivative (175) and (b) the 2′-ethyl derivative (173).

**Table 1 : Data for the the diastereoselective monoalkylation of the imino lactone (132).**




132 172 - 179

| product | R | Isolated % yield | % d.e. [b] |
|---|---|---|---|
| 172 | $CH_3$ | 82 | 43 |
| 173 | $CH_3CH_2$ | 79 | 60 |
| 174 | $CH_3(CH_2)_2$ | 77 | 70 |
| 175 | $CH_3(CH_2)_3$ | 76 | >99 |
| 176 | $CH_3(CH_2)_4$ | 73 | >99 |
| 177 | $CH_3(CH_2)_5$ | 70 | >99 |
| 178 | $(CH_3)_2CH(CH_2)_4$ | 69 | >99 |
| 179 | $PhCH_2$ | 63 | 50 |

[a] Benzyl Bromide was used to obtain the benzylated analogue
[b] Determined by $^1H$ NMR spectroscopy

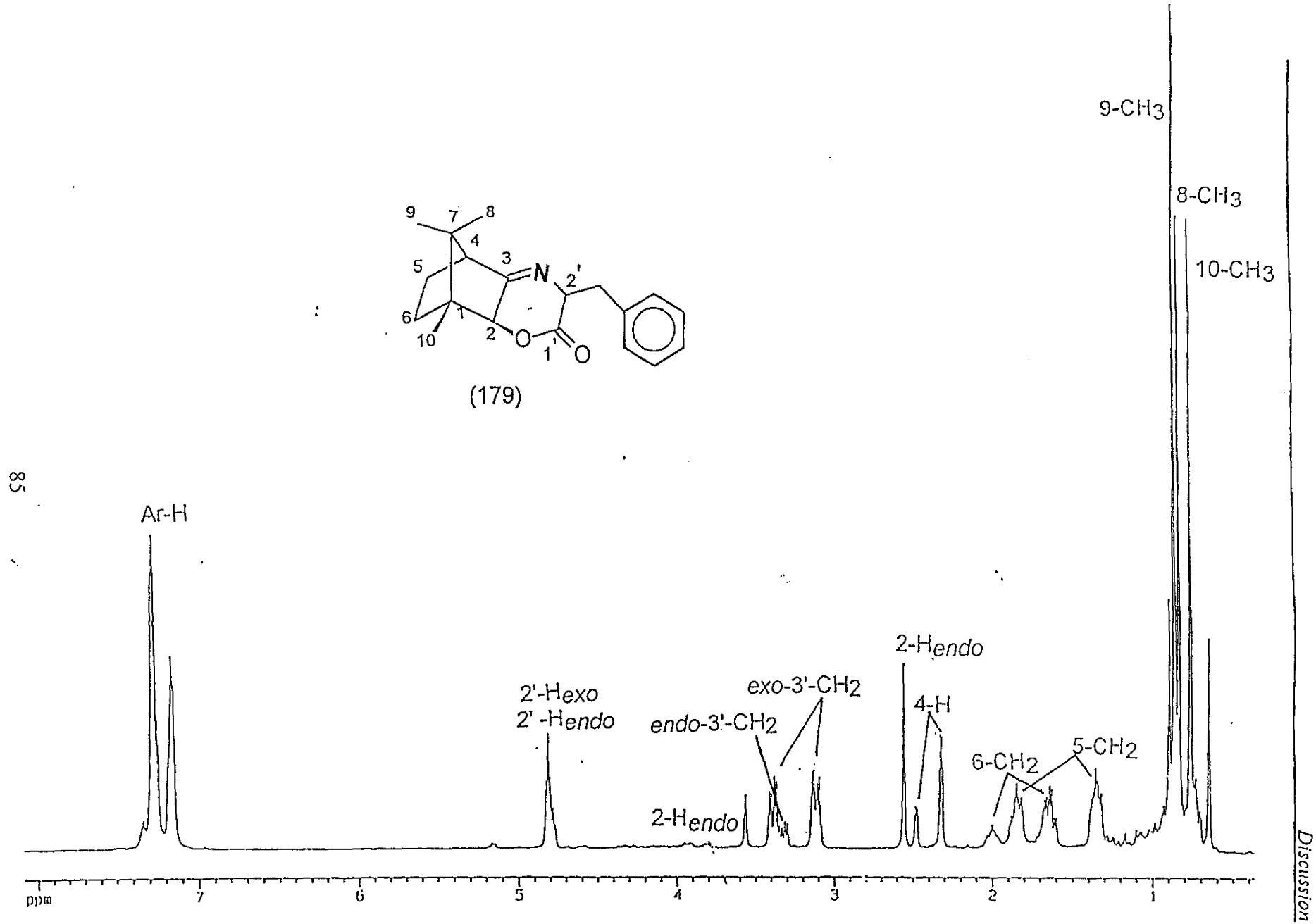
From the data in Table 1, it is apparent that efficient diastereocontrol may be achieved by increasing the steric bulk of the alkyl halide. Thus, as the R group is changed from methyl to butyl the diastereoselectivity increases from moderate (43% d.e.) to excellent (> 99% d.e.). In fact, in four of the systems examined (R = butyl, pentyl, hexyl and heptyl), total diastereocontrol (> 99%) was achieved. Somewhat surprisingly, use of benzyl bromide gave lower chemical (63%) and optical yields (50% d.e.); this observation can be attributed to two factors, *viz.*,

(i) compared to iodide, bromide is a poorer leaving group, resulting in the lower reactivity and consequently in reduced yields; and

(ii) Although *endo*-face attack is still dominant (50% d.e.), the planar structure of benzyllic carbocation (assuming an $S_N1$ process) may permit a somewhat less hindered approach to the *exo* face of the enolate.

It is interesting to note the previously mentioned shielding effect of the benzyl group (**Figure 19**) on the 2-$H_{endo}$ nucleus (resonating at 2.59 ppm) of the major diastereomer (179) from *endo* benzylation. In this case, the 2′-*exo* and 2′-*endo* proton signals overlap at 4.8 ppm and, consequently, the diastereomeric ratio was determined by comparing the integrals of the respective 2-$H_{endo}$ signals.

Palomo *et al.*[66] have reported the preparation of camphor oxazolidinones and their use in the synthesis of *N*-acyl amides with high levels of asymmetric induction. To our knowledge, however, the use of the camphor-derived imino lactones (**131**) and (**132**) in asymmetric synthesis is unprecedented and, clearly, has considerable potential. The remaining challenge was to effect hydrolysis of the alkylated imino lactones, without compromising the configurational integrity of the new chiral centre, to release the chiral amino acid and the chiral auxiliary. This aspect and the confirmation of the configurational bias in the alkylation reactions will be discussed in **Section 2.1.4.**




(179)

FIGURE 19. The 400 MHz $^1$H spectrum of the benzyl imino lactone (179) in $CDCl_3$.

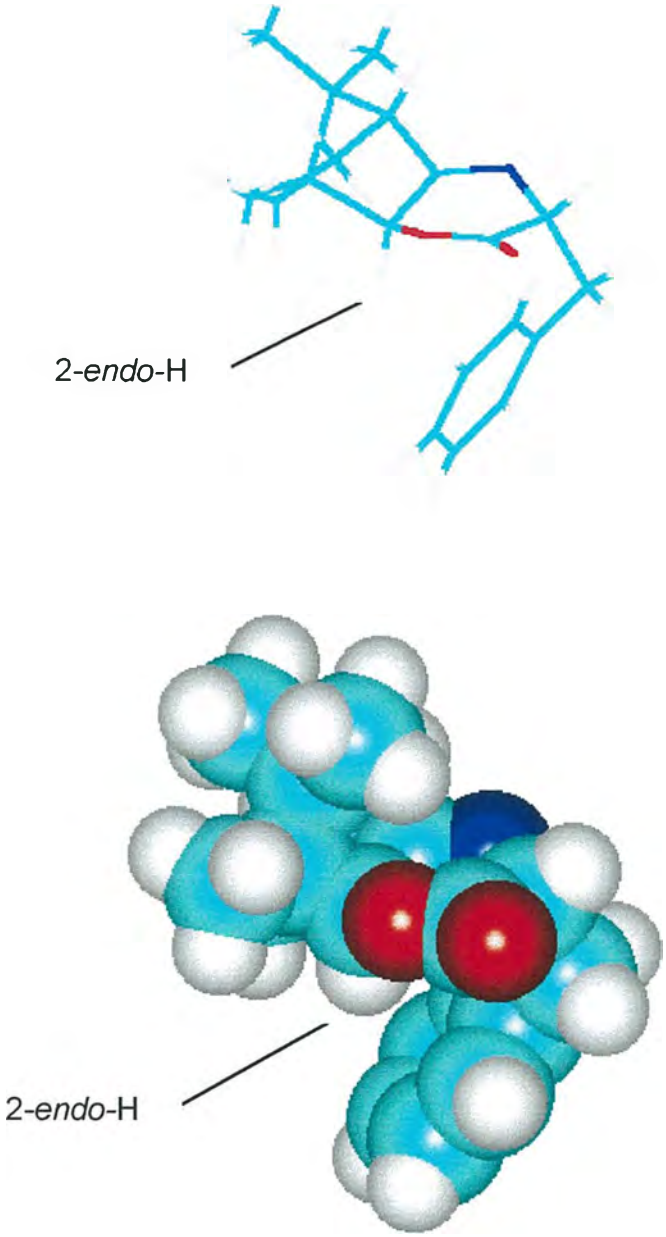
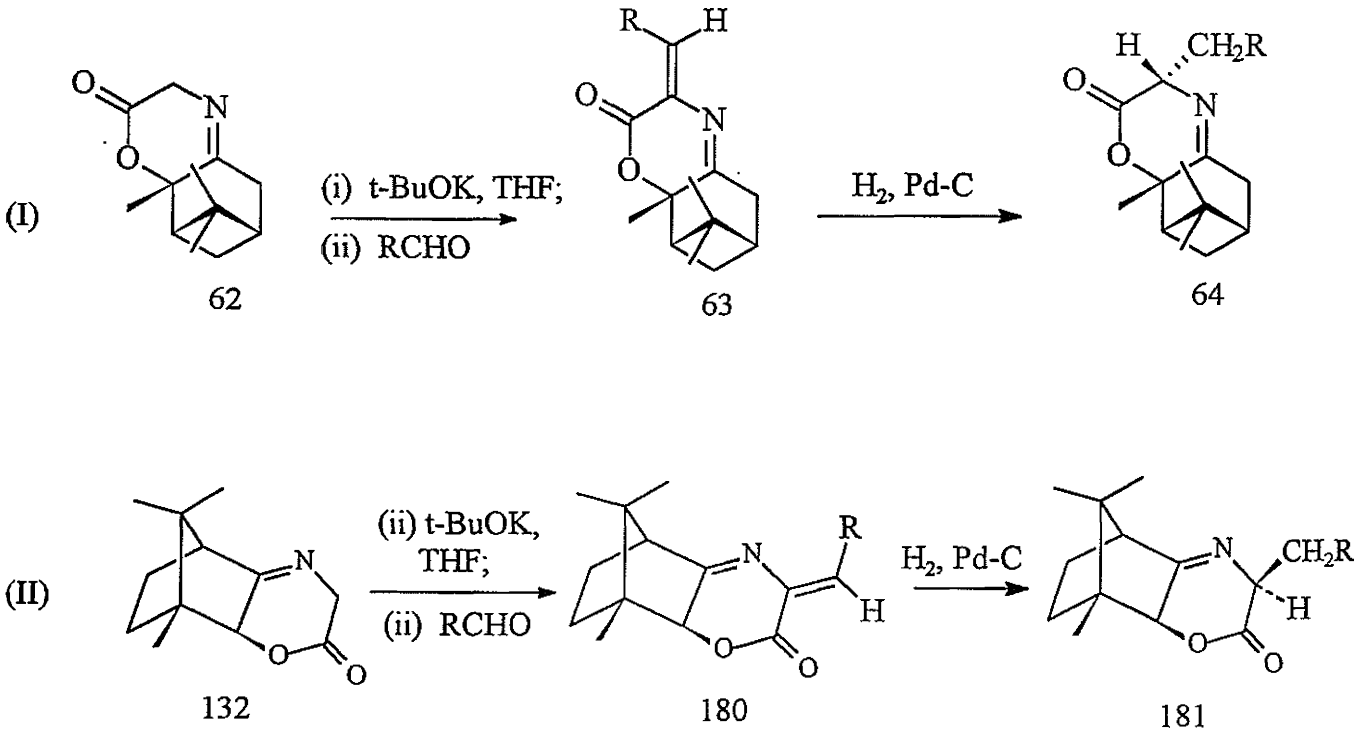



FIGURE 19. Computer-generated molecular model of the *endo*-benzylated imino lactone (179), showing the 2-*endo*-H nucleus in the shielding zone of the phenyl ring.

### 2.1.3 Exploratory studies of further applications of the camphor-derived imino lactone (132) in the asymmetric synthesis of α-amino acid derivatives

#### 2.1.3.1 Attempted preparation of camphor-derived alkylidine derivatives

As indicated in **Scheme 46**, Cativiela *et al.*[30] have prepared chiral amino acids by asymmetric hydrogenation of pinane-derived alkylidine intermediates. Hydrogenation on the same face as the *gem* dimethyl group provided the *S*-amino acid derivative (**64**) in high yield with quantitative topological control (**Scheme 49; Sequence I**). We envisaged that analogous hydrogenation of camphor-derived systems would give similar stereocontrol (**Scheme 49; Sequence II**).




SCHEME 49: (I) Hydrogenation of the pinane-derived alkylidine intermediate (**63**) reported by Catviela *et al.*[30]

(II) Proposed analogous route using the camphor-derived imino lactone (**132**)

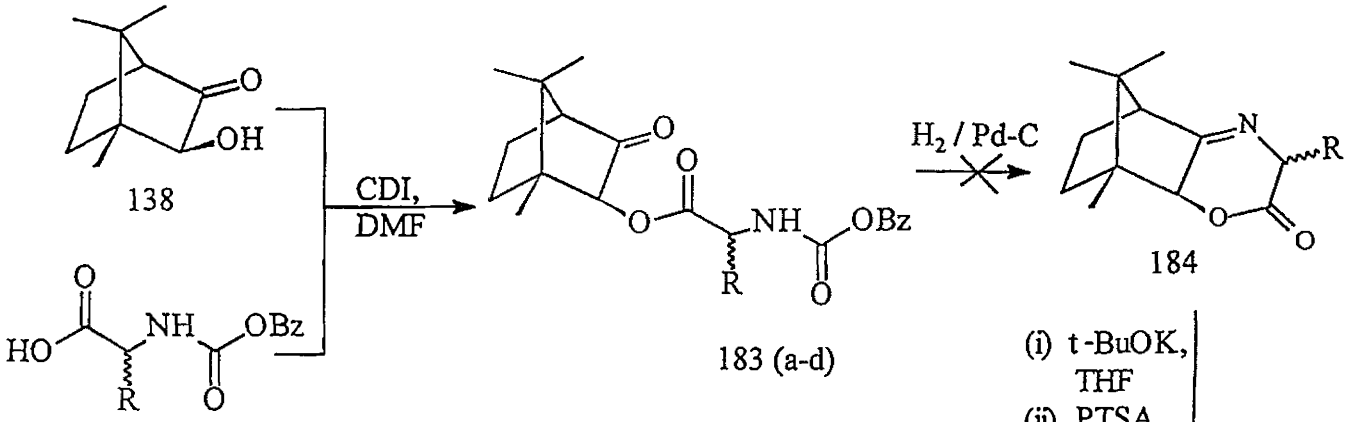
In attempting to synthesise the camphor-derived system (**180**), a procedure similar to the one used by Cativiela *et al.*[30] was followed. A solution of the imino lactone (**132**) in dry THF was added, at -78 °C, to a stirred suspension of *t*-BuOK in dry THF, under $N_2$; acetaldehyde was then added. Work-up and preparative layer chromatography of the residue, however, failed to furnish the desired condensation product (**180**). The method was applied to various aliphatic, aromatic and pyridyl aldehydes, but none of the required alkylidine derivatives was obtained.

### 2.1.3.2 Enantiomeric beneficiation of amino acids

Encouraged by our success in the asymmetric alkylation of the imino lactone (**132**) (**Section 2.1.2**), we decided to explore the possibility of extending this approach to the "enantiomeric beneficiation" of *racemic* α-amino acids. The basic strategy was to prepare the diastereomeric imino lactones (**184**) by condensing the α-ketol (**138**) with a *racemic* α-amino acid. Deprotonation was then expected to afford a ***common*** enolate intermediate, protonation of which (by a bulky proton donor) would occur preferentially from the *endo* face (**Scheme 50**). Hydrolysis of the alkylated derivative (**185**) would then afford the α-amino acid enriched in one enantiomer, while access to the other enantiomer could be achieved by using the enantiomer of the imino lactone (**132**) [derived for L-(-)-camphor]. The proposed route involved preparation of an ester from a racemic, *N*-protected α-amino acid (**182**) and 2-*exo*-hydroxycamphor (**138**). This ester (**183**) would then be *N*-deprotected and cyclised to yield the α-alkylated imino lactone (**184**); a deprotonation-protonation sequence, followed by hydrolysis, would finally afford enantiomerically enriched amino acid. It is significant to note that in this approach, the proton was expected to enter the *endo*-face (opposite the *gem* dimethyl group) to give *exo*-alkylated products, whereas the alkylation approach (**Section 2.1.2**) affords *endo*-alkylated products.

A range of racemic, *N*-protected α-amino acids (**182 a - d**) was quantitatively coupled with 2-*exo*-hydroxybornanone (**138**) in DMF, using carbonyldiamidazole (CDI) as a coupling agent and following a procedure reported by Bodansky and Bodansky;[67] to give the esters (**183 a - d**) (Scheme 50). Attempted *N*-deprotection of the esters (**183 a - d**) *via* hydrogenolysis in absolute ethanol, using 10% Pd on carbon as catalyst, failed to afford the expected deprotected esters or the cyclised products (**184**); 2-*exo*-hydroxybornanone (**138**) was isolated instead, indicating cleavage of the ester bond during hydrogenation.

Deprotection using different solvents was then attempted, *viz.*, methanol, DMF, diisopropylethylamine and cyclohexadiene, all of which have been used in the *N*-deprotection of glycine derivatives;[65] but with no success.



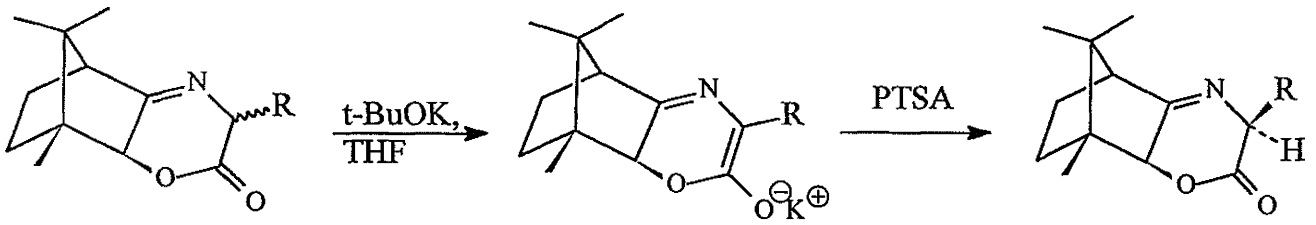

| | R |
|---|---|
| a | $CH_3$ |
| b | $CH_2OH$ |
| c | $CH(CH_3)_2$ |
| d | $(CH_2)_4NH_2$ |

SCHEME 50

Due to the difficulties encountered in deprotecting the esters **(183 a-d)**, attention was diverted to the beneficiation of the alkylated derivatives of the imino lactone (**132**), which had been obtained with low diastereoselectivity (see **Section 2.1.2**), *viz.*, the methyl derivative (**172**) (43% d.e.) and the benzyl derivative (**179**) (50% d.e.). As previously mentioned, formation of an enolate followed by stereoselective *endo* protonation was expected to favour the *exo*-alkyl product at the expense of the initially dominant *endo*-alkyl isomer. The enolate was generated by adding *t*-BuOK to a solution of the diastereomeric methyl derivatives (**172**) in THF at -78°C, while protonation was effected by adding dry *p*-toluenesulfonic acid (**Scheme 51**; R=Me). Work-up and chromatographic purification furnished a clear oil, analysis of which indicated:-

i) a substantial change in the diastereomeric ratio (from 43% to 84% d.e.); and

ii) that the major product was, quite unexpectedly, the initially dominant *endo*-methyl diastereomer.




R = $CH_3$ (172)
$PhCH_2$ (179)

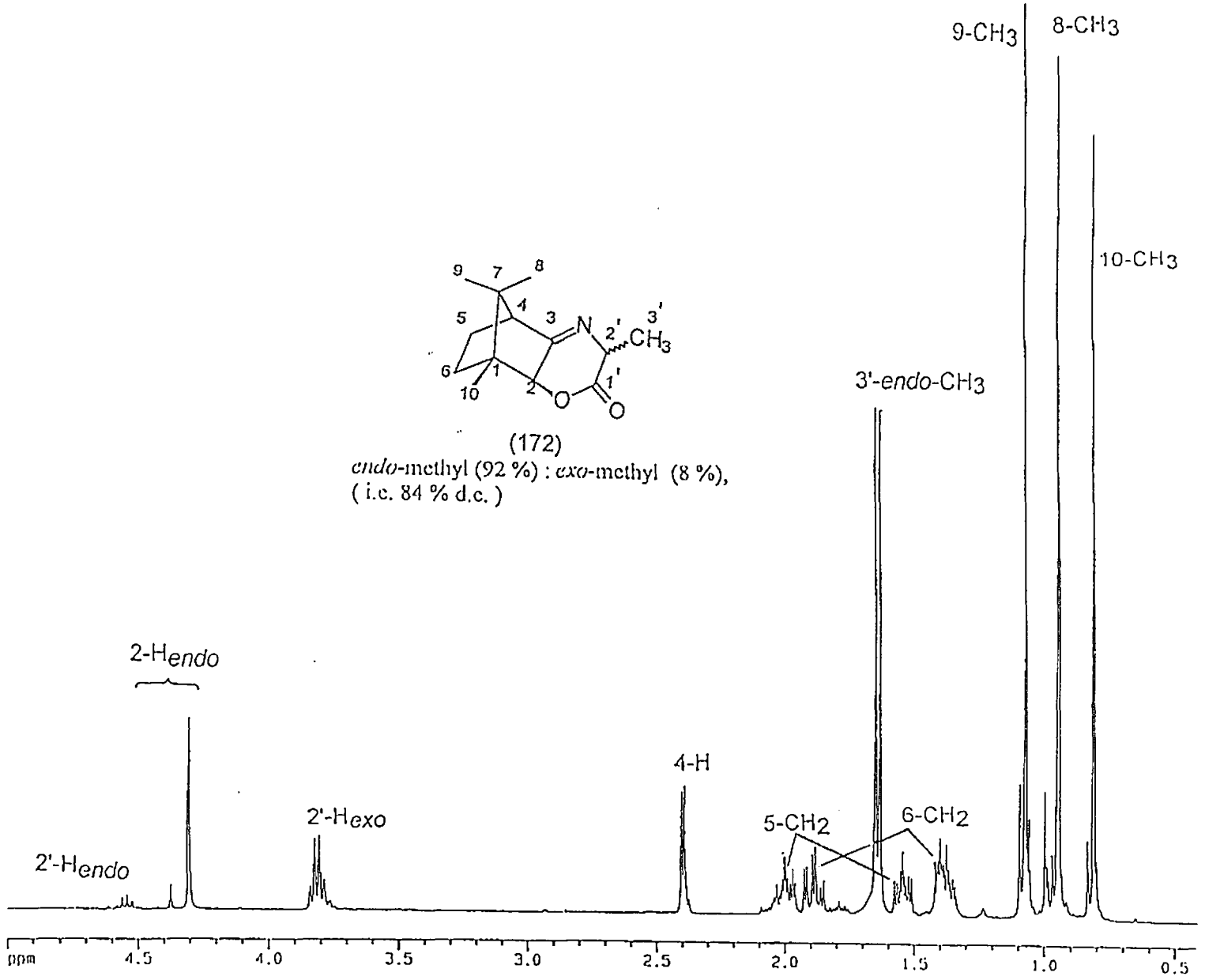
182

183

SCHEME 51

The 3′-methyl protons of the major diastereomer resonate as a doublet at 1.6 ppm ($J$ = 7.0 Hz), the 2′-methine proton as a quartet at 3.8 ppm ($J$ = 7.0 Hz) and the 2-*endo* proton as a singlet at 4.30 ppm; these signals clearly correspond to the 2′-*endo*-methyl diastereomer (*cf.* **Figure 15**). Comparison of the 2-$H_{endo}$ signals at *ca.* 4.3 ppm in **Figures 15** and **21**, clearly reveals the significant diastereomer enrichment obtained. Thus, contrary to the expectation that *endo*-proton delivery would be favoured and lead to beneficiation of the *exo*-methyl diastereomer, protonation appears to occur at the *exo*-face! This apparent reversal of the expected *exo*-alkyl beneficiation is attributed to the operation of "product development control"[68] (*i.e.* determined by the relative stabilities of the diastereomeric products), instead of the anticipated "steric approach control", involving preferential protonation at the less hindered *endo* face. Although preliminary computer modelling (see **Figure 20**) confirms the 2′-*endo* methyl product to be (marginally) more stable than the 2′-*endo* isomer, the need for a more rigorous analysis, in which consideration is given to transition state and solvation effects, is indicated and will be the subject of a future study..

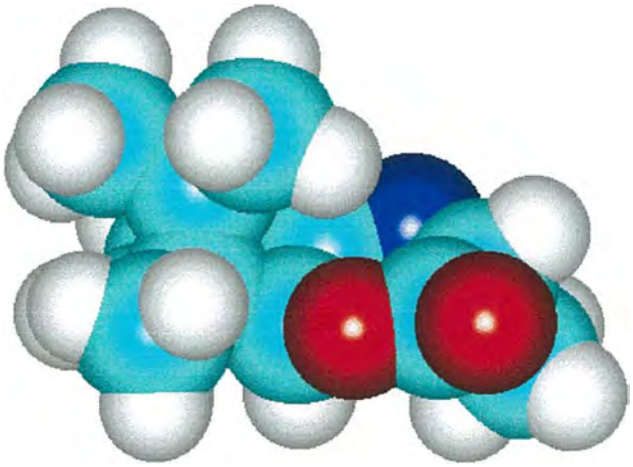
In an attempt to establish the generality of the deprotonation-protonation approach to enantiomer beneficiation, the procedure was repeated using the benzylated analogue (**179**). However, analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated no change in the diastereomeric excess, the bulky and flexible 2′-benzyl group presumably offering more hindrance to *exo*-face protonation of the enolate intermediate than the 3′-methyl group.



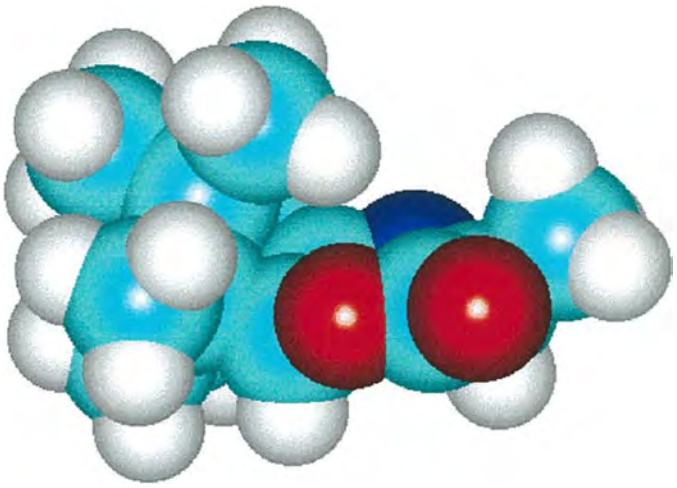

(172)

*endo*-methyl (92 %) : *exo*-methyl (8 %),
( i.e. 84 % d.e. )

FIGURE 21. The 400 MHz $^1$H NMR spectrum, in $CDCl_3$, of the *endo*-methyl imino lactone (**172**), following diasteromer enrichment.



2'-*endo*-methyl derivative
( 45.23 kJ.mol$^{-1}$)



2'-*exo*-methyl derivative
( 45.88 kJ.mol$^{-1}$)

FIGURE 20. Computer-generated molecular models and relative energies of the 2'- *endo*- and 2'-*exo*-methyl imino lactones (172).

### 2.1.4 Determination of the configurational bias at the new chiral centre of the alkylated imino lactones

As mentioned earlier (Section 2.1.1), electrophilic alkylation of the camphor-imino lactones was expected to occur at the less hindered *endo*-face. The energy minimised computer model of the potassium enolate (170) of the imino lactone (Figure 22) clearly illustrates the steric congestion provided by the 8-methyl group on the *exo*-face, and the free access offered to the incoming electrophile at the *endo*-face. In order to confirm the prediction of *endo*-face attack and thus establish the configuration at the new chiral centre, two approaches were explored, *viz.*,

i) examination of NOE interactions in the alkylated imino lactones; and

ii) isolation of product with known optical rotation.

For the second approach, the pentylated lactone (176) was chosen because it was expected to furnish, on hydrolysis, the known, unnatural amino acid, 2-aminoheptanoic acid.[69] The alkylated lactone (176) was hydrolysed by stirring in aq. HCl-THF at 70°C for three hours. Work-up with excess propylene oxide[30] and purification on a SEP-PAK reverse phase column furnished 2-aminoheptanoic acid (187) quantitatively.

The optical rotation ($[\alpha]_D^{20}$ + 4.3°; c,8) of the isolated amino acid (187) in 20% HCl was found to be consistent with the known (*R*)(+)-enantiomer ($[\alpha]_D^{20}$ + 4.2°; c,8 in 20% HCl).[69] (*R*)-(+)-2-aminoheptanoic acid clearly requires the *endo*-alkylation predicted on the basis of the computer modelling data.

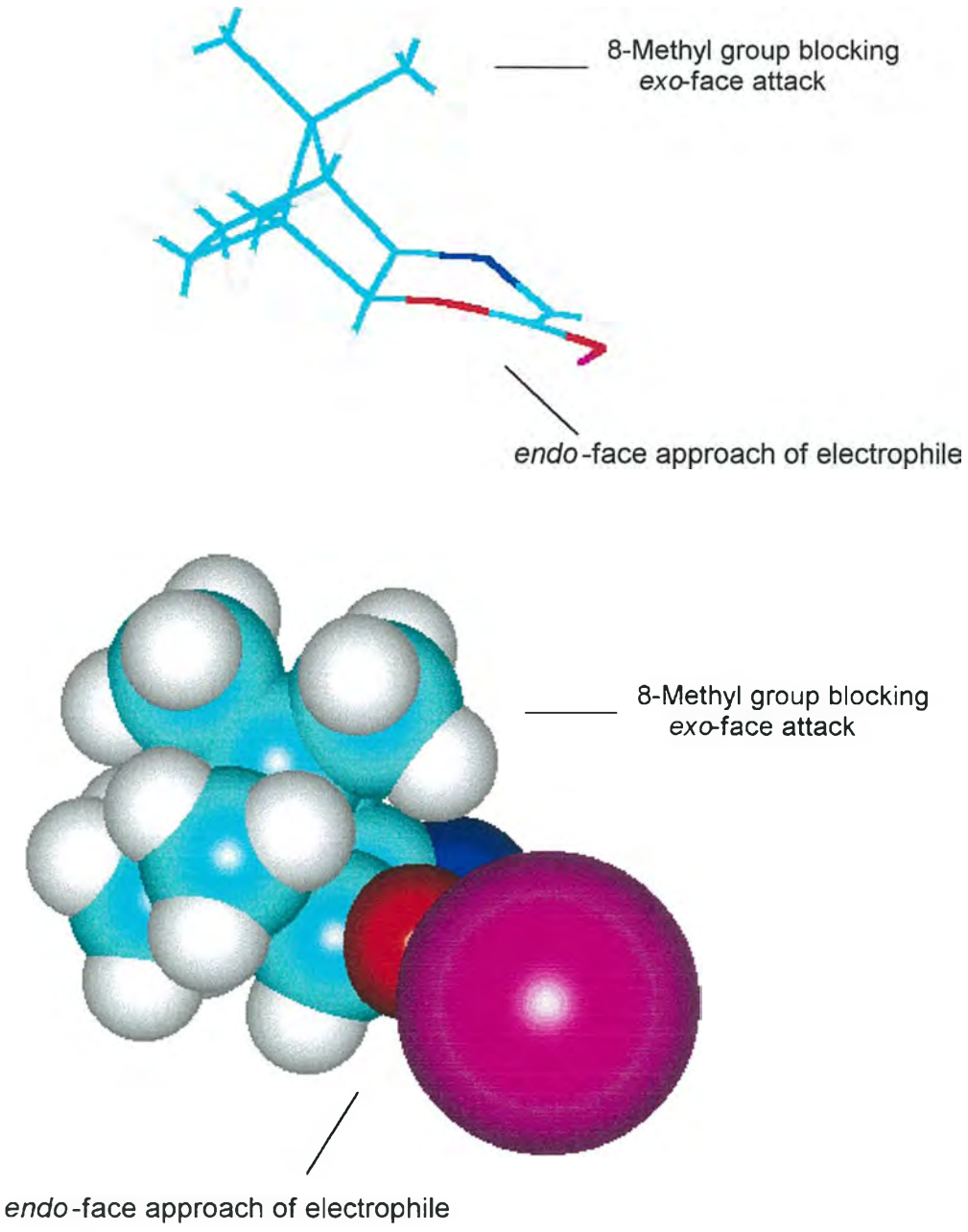



FIGURE 22. Computer-generated molecular model of the potassium enolate (170) of the imino lactone (132).

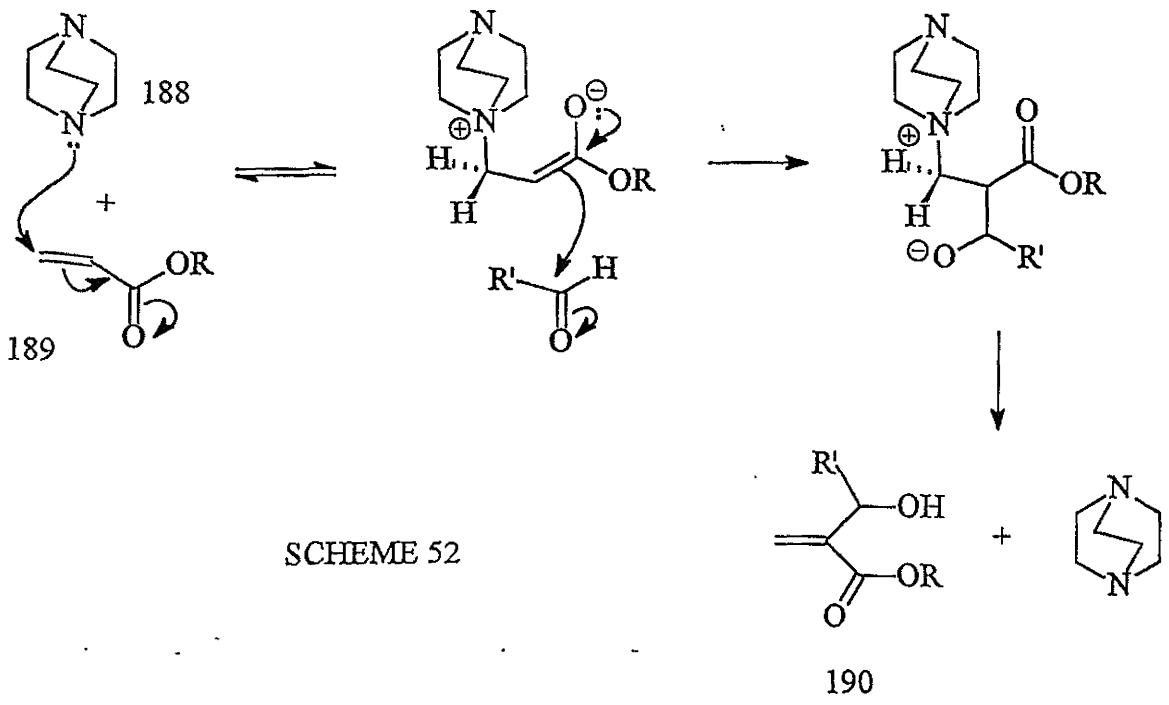
## 2.2 ASYMMETRIC BAYLIS-HILLMAN REACTIONS

The Baylis-Hillman reaction is an important carbon-carbon coupling reaction which links activated alkenes with aldehydes using tertiary amines as catalysts. The reaction was first described by Baylis and Hillman in the patent literature in 1972.[71] The C-C bond is constructed at the α-position of the activated alkenes and the multifunctional products[72] have been widely used in the synthesis of necic acids and other natural products.[73,74]

The α,β-unsaturated systems employed in these reactions can be viewed as vinyl anion equivalents, with the most common substrates being the acrylate esters (**189**) (**Scheme 52**). However, several other systems have also been coupled with aldehydes to give the expected Baylis-Hillman products; examples of these are acrylonitrile,[75] methyl vinyl ketone,[76] diethyl vinyl phosphonate,[77] phenyl vinyl sulphone[78] and acrolein.[79] The most common catalyst used in the Baylis-Hillman reaction is 1,4-diazabicylo[2.2.2]octane (DABCO), but other compounds have been used successfully in this capacity, *viz.*, quinuclidine,[80] 3-hydroxyquinuclidine,[81] triethylamine,[82] tricyclohexylphosphine,[83] tributylphosphine with triethylaluminium and rhodium hydride.[84] Aldehydes have been replaced, albeit less commonly, by substrates such as tosylimines,[85] benzylidenecarbamate[86] and α-keto esters.[87] The Baylis-Hillman reaction is thus extremely versatile and can be represented by a general scheme (**Scheme 52**). Baylis-Hillman reactions are typically conducted at room temperature and are usually slow, requiring several days, or, in some cases, several weeks to go to completion. The reaction may be accelerated, however, by using using electrophilic aldehydes such as the pyridine carboxaldehydes, by using 3-hydroxyquinuclidine as a catalyst instead of DABCO,[81] or by conducting the reaction under

pressure.[79]

In the mechanistic sequence illustrated in **Scheme 52**, the reaction is initiated by conjugate addition of DABCO (**188**) to the acrylate ester (**189**) producing a dipolar ester enolate intermediate (the "Baylis-Hillman zwitterion") that serves as the nucleophile in an aldol-type addition to the aldehyde. Subsequent elimination of the tertiary amine catalyst leads to an α-(hydroxyalkyl)acrylic ester (**190**)[88] - a typical "Baylis-Hillman" product.



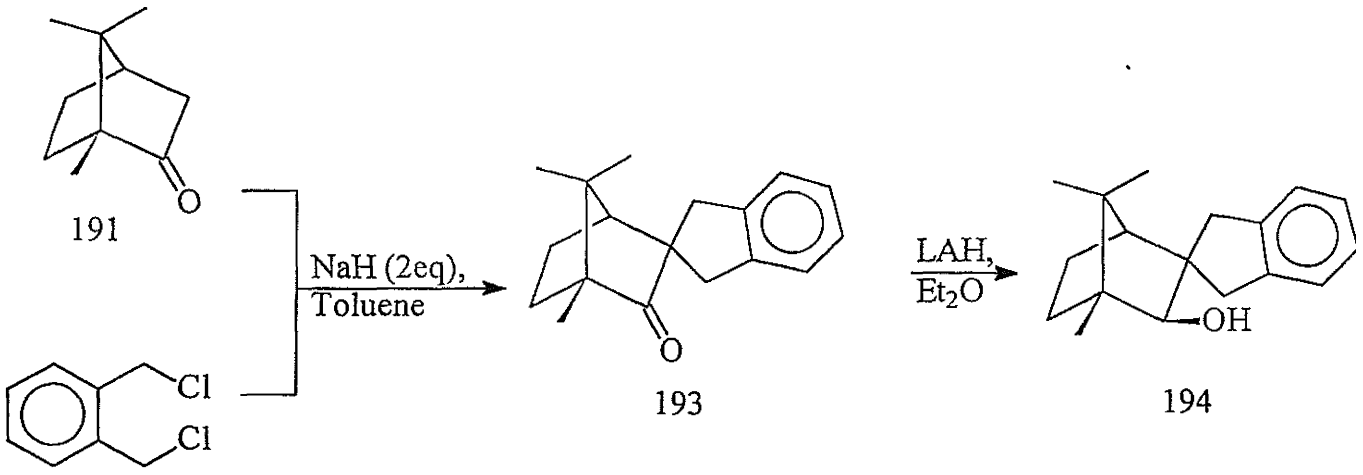

SCHEME 52

### 2.2.1 Preparation of chiral acrylates

Stereoselectivity in the Baylis-Hillman reaction may be directed by chirality in the aldehyde, the acrylate component, the catalyst or the solvent. All of these approaches have been addressed in the past, with varying degrees of success. Results reported from such studies have indicated that only chiral acrylates appear to possess the necessary proximate discriminatory ability to effect stereoselectivity in the C-C bond-forming step.[89-92] Our interest, in the present study, has been to develop camphor-derived chiral acrylates - a theme previously investigated by several authors, including Roos *et al.* who used Oppolzer's sultam (17) to prepare several chiral *N*-substituted acrylamides in yields ranging from 85% to 94%.[92] Coupling of these acrylamides with a range of aldehydes was reported to proceed slowly, with rate enhancement being achieved by the use of a molar equivalent of DABCO and the application of sonication. However, the observed stereoselectivities were disappointing, ranging from 6% to 30% d.e..

As indicated earlier (see **Section 1.4**), there has also been on-going research in our own laboratories on the development of various camphor-derived chiral auxiliaries with particular emphasis on increasing the steric bulk of the blocking group.[49] Particular use has been made of the xylyl derivative (**193**),[93] which we prepared in 83% yield by coupling α,α-dichloroxylene with camphor (**191**) using 2 equivalents of sodium hydride (**Scheme 53**); Günter Helmchen *et al.*[93] have previously synthesized the xylyl derivative (**193**) in 39% yield using sodium amide as base. The xylyl derivative (**193**) was then reduced using LAH in diethyl ether, following Helmchen's method, to obtain the corresponding 2-*exo*-hydroxy derivative (**194**) in 92% yield, after work-up and chromatographic purification. The identity of the chiral auxiliary was confirmed using NMR spectroscopy ($^1$H, $^{13}$C, DEPT and HMQC). The $^1$H NMR spectrum, illustrated in **Figure 23**,

reveals the presence of aromatic protons and the diastereotopic protons of 1′- and 3′-methylene groups, which resonate as double doublets at *ca.* 2.8 and 3.3 ppm.




SCHEME 53

The camphor-derived chiral alcohol (**194**) has been used in our laboratores for the preparation of a range of chiral esters which have been benzylated with moderate stereoselectivity.[49] We were thus encouraged to explore the use of this chiral alcohol in the preparation of a chiral acrylic ester and its application in asymmetric Baylis-Hillman reactions. Computer modelling (see **Figure 24**) suggests the likelihood of preferential electrophilic attack at the *Si*-face (*i.e.* from the "front") of the intermediate (*E*)-enolate derivative (**195**) of the acrylic ester (**196**).

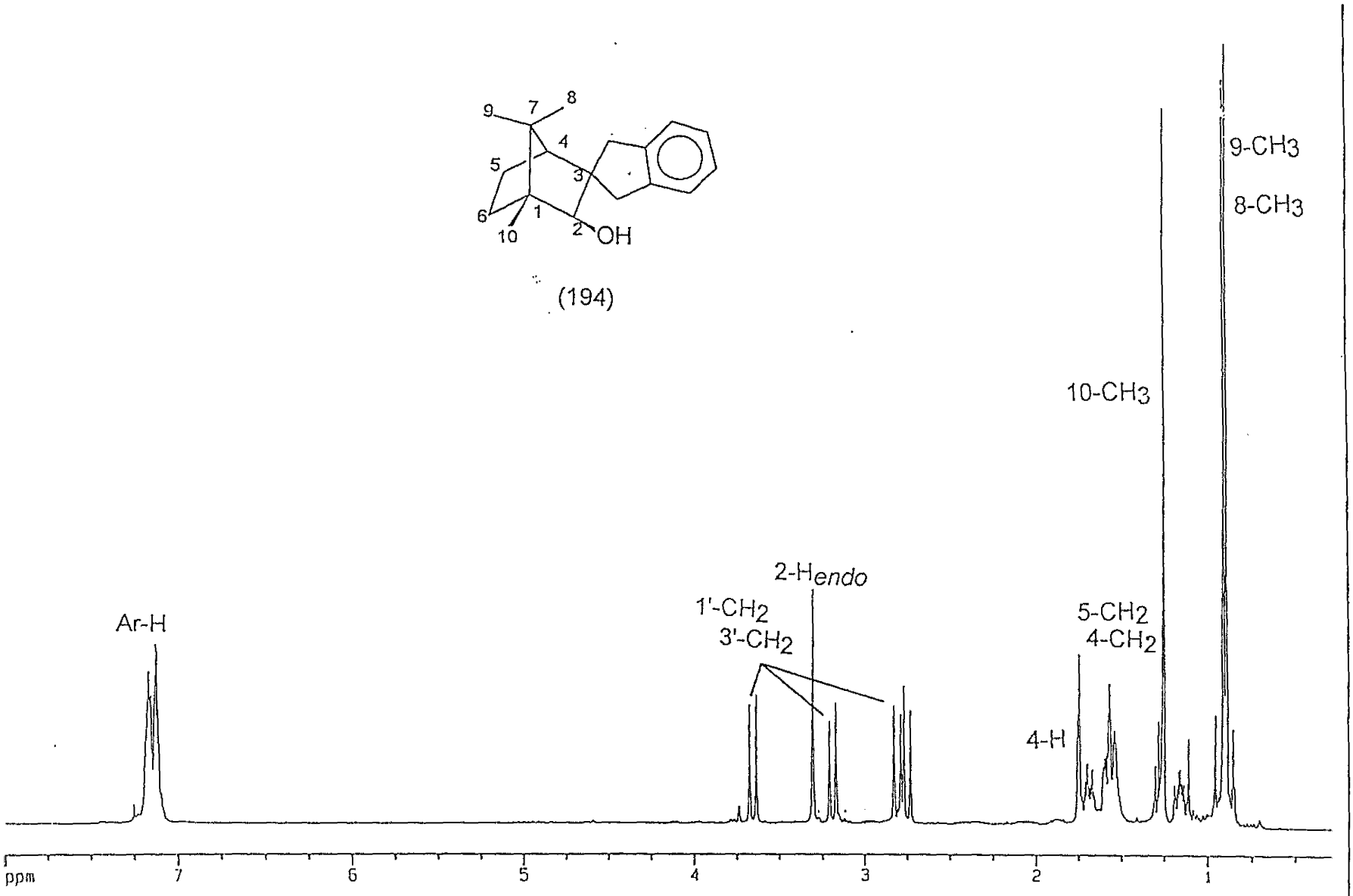
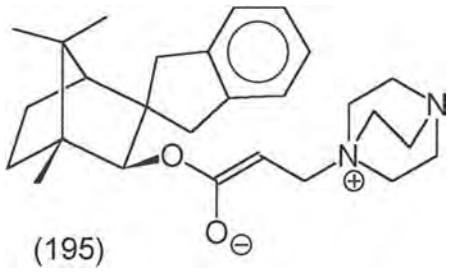
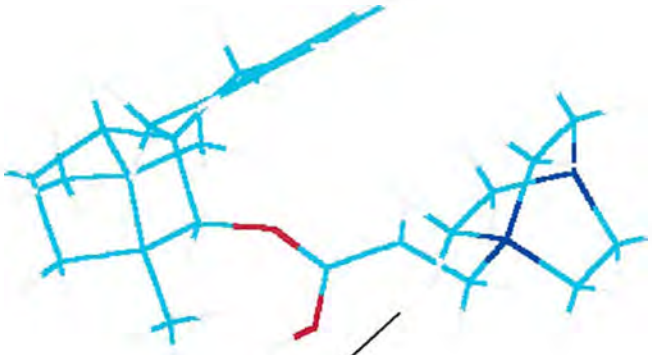



FIGURE 23. The 400 MHz $^1$H NMR spectrum of the camphor-derived chiral alcohol (194) in $CDCl_3$




(195)



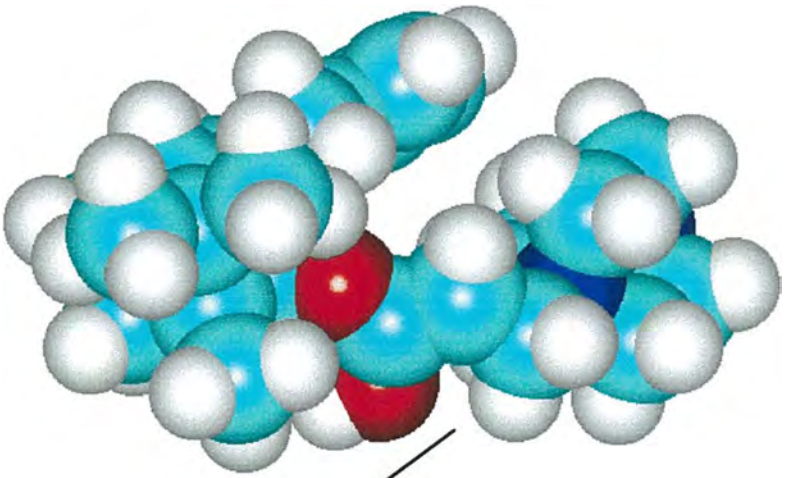
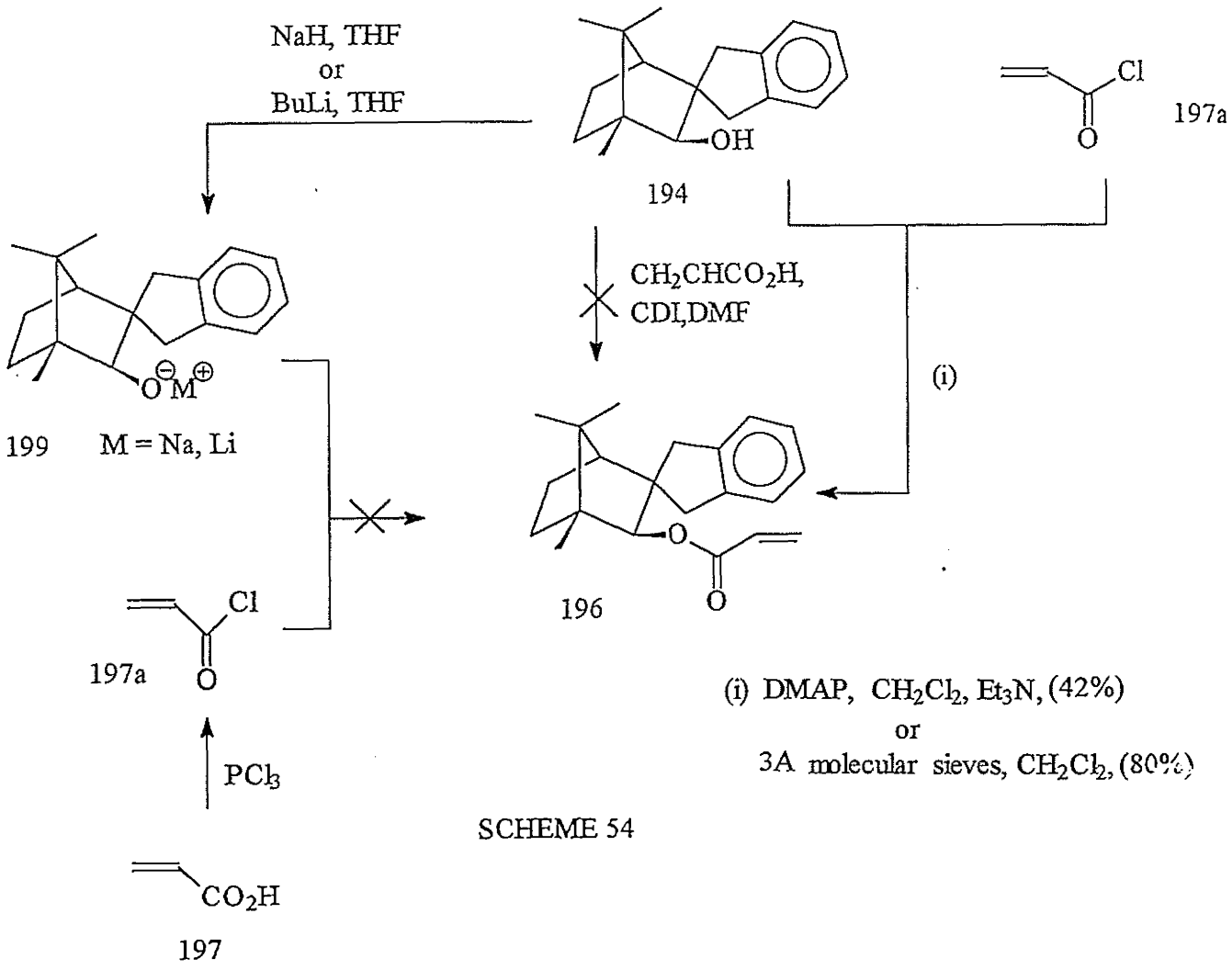




FIGURE 24. Computer-generated molecular model of compound ( **195**) showing an *E*-arrangement of the enolate moiety, and preferential electrophilic attack at the *Si* -face.

Several methods of preparing the acrylic ester (**196**) of the chiral auxiliary (**194**) (**Scheme 54**) were attempted. Firstly, the sodium alkoxide of alcohol (**194**) (generated using sodium hydride) was boiled under reflux with acryloyl chloride in anhydrous THF,[94] the acryloyl chloride having been prepared from acrylic acid using phosphorous trichloride as a chlorinating agent.[95] Work-up and flash column chromatography, however, yielded the unreacted alcohol (**194**). In the second method, the lithium alkoxide was prepared by adding butyllithium to a solution of the alcohol (**194**) at low temperature, before adding acryloyl chloride. Work-up and chromatographic purification once more failed to afford the desired acrylate derivative.

Camphor-derived glycinates have been prepared by reacting 3-hydroxycamphor with *N*-protected glycine derivatives using carbonyldiimidazole as a coupling agent (see **Section 2.1.1**),[62] and this was the third approach to be explored. The acryloylimidazole intermediate was prepared by treating acrylic acid with carbonyldiimidazole in DMF; the chiral alcohol (**194**) was then added and the mixture stirred overnight. Work-up and chromatogaphic purification once more failed to yield the required acrylate derivative (**Scheme 54**).

In the fourth method to be explored, triethylamine was added to a stirred solution of the alcohol (**194**) in anhydrous dichloromethane, followed by 4-dimethylaminopyridine (DMAP), a versatile, hypernucleophilic, acylating catalyst,[62] and acryloyl chloride. Work-up and chromatographic purification of the reaction mixture finally afforded the desired acrylic ester (**196**) in 42% yield. Unreacted alcohol and viscous, brown, polymeric material were also isolated.


NaH, THF
or
BuLi, THF
OH
194
Cl
O
197a
CH2CHCO2H,
CDI,DMF
(i)
O⊖M⊕
199 M = Na, Li
O
O
196
Cl
O
197a
PCl3
CO2H
197
(i) DMAP, CH2Cl2, Et3N, (42%)
or
3A molecular sieves, CH2Cl2, (80%)

SCHEME 54

Freshly distilled acryloyl chloride and dry dichloromethane were then used in an attempt to improve the yield of the ester (**196**). It has been established, however, that polymerization of reactive α,β-unsaturated systems is catalysed by the traces of free acid inevitably present during such reactions, and this is often the primary cause of low yields. It was further established that molecular sieves scavenge small molecules, such as hydrogen chloride. This property has been exploited in the synthesis of an ester from methacryloyl chloride,[96] the molecular sieves favouring the production of the ester product whilst simultaneously preventing polymerization. This method was adopted as the fifth, and best, approach, affording the chiral acrylic ester (**196a**), in significantly improved yield of 82%. The identity of the acrylic ester (**196**) was confirmed by NMR spectroscopy. The $^1$H NMR spectrum (**Figure 25**) reveals a typical pattern for the three acrylate protons, which resonate in the region, 5.7 - 6.3 ppm. In this case, the 3″-methylene protons each resonate as a doublet, due to coupling to the 2″-methine proton which resonates as a double doublet. The downfield doublet (at 6.3 pppm), having the larger coupling constant ($J$ = 17.6 Hz) may be assigned to the *trans*-3″-proton ($J$ = 10.2 Hz). At 400 MHz, such nuclei sometime s constitute an AMX system and give rise to three double doublets. Correlation of the doublets with the 3″-C signal is provided by the HMQC spectrum (**Figure 26**). The absence of coupling between the 3″-methylene protons is also apparent in the COSY spectrum (**Figure 27**).

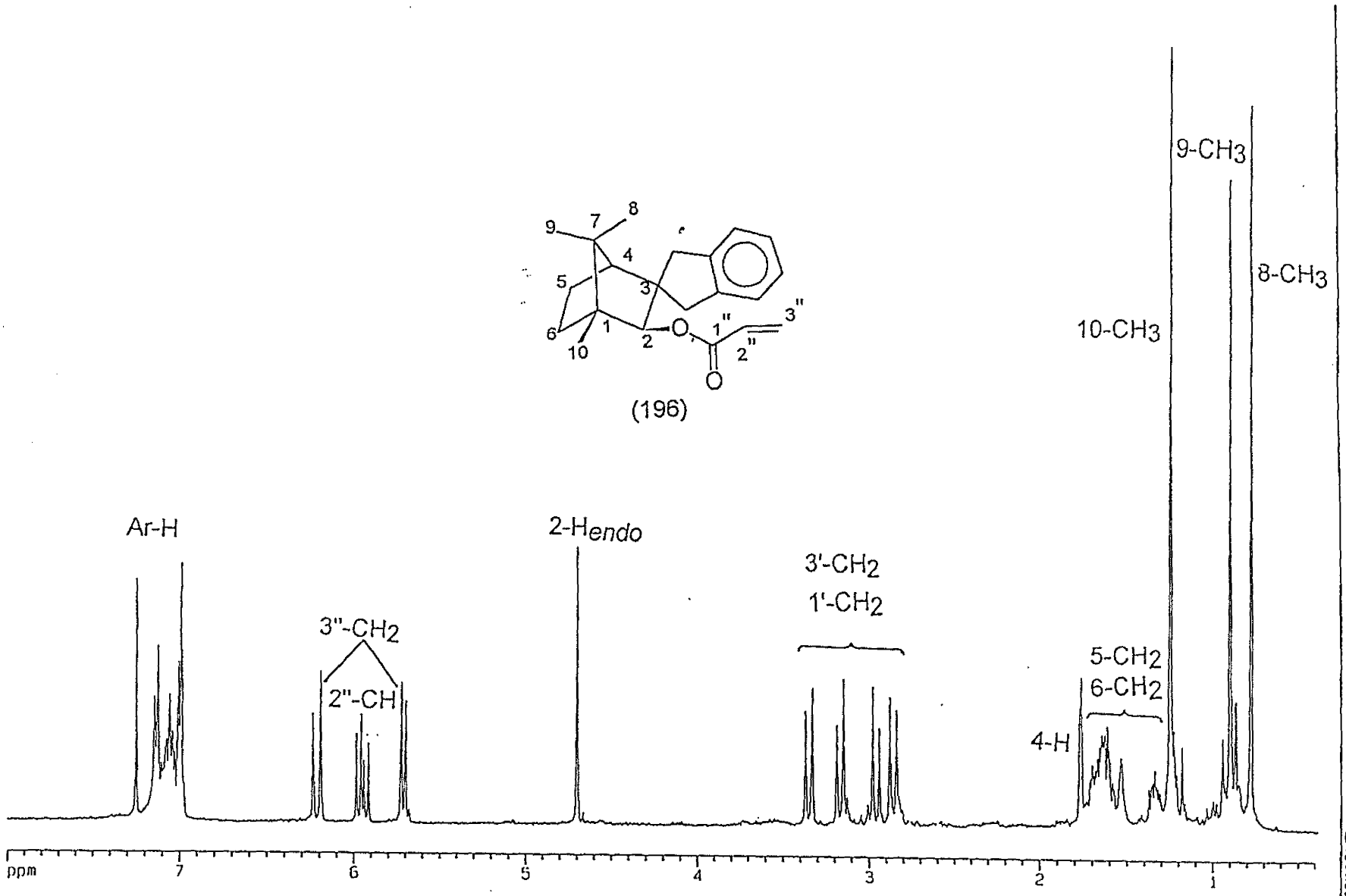



FIGURE 25. The 400 MHz $^1$H NMR spectrum of the acrylic ester (**196**) in $CDCl_3$

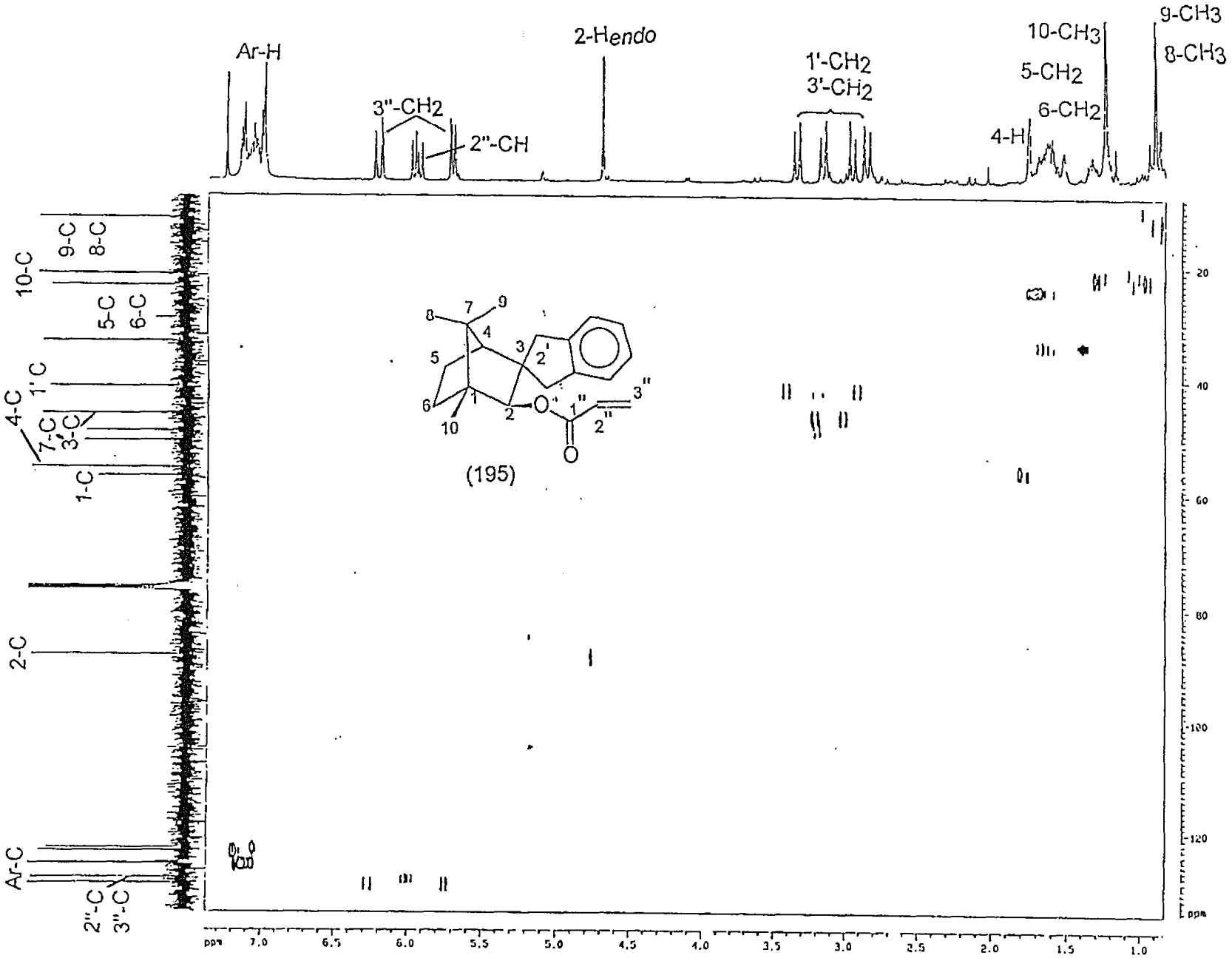



FIGURE 26. The HMQC spectrum of the acrylic ester (196) in $CDCl_3$

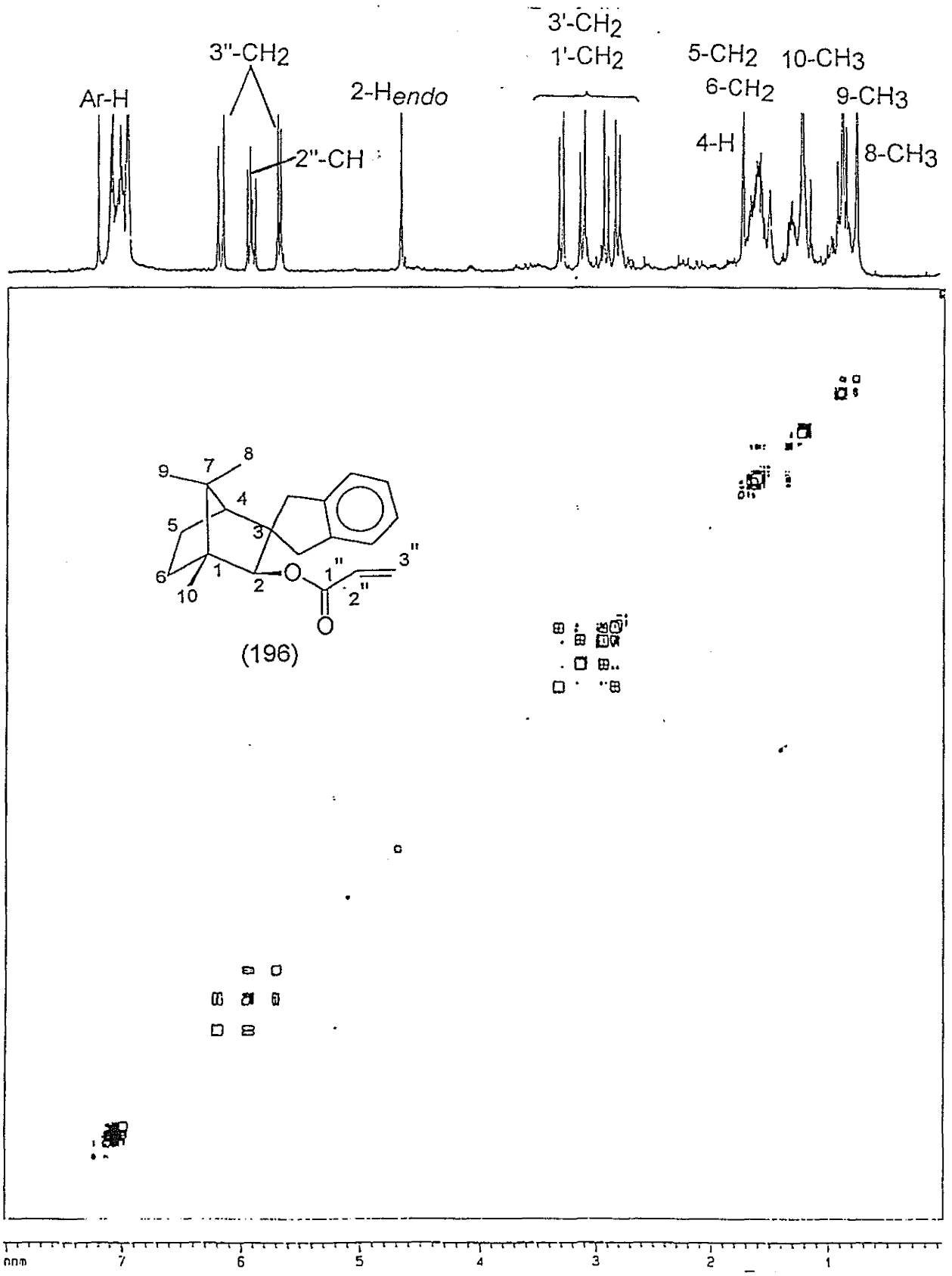
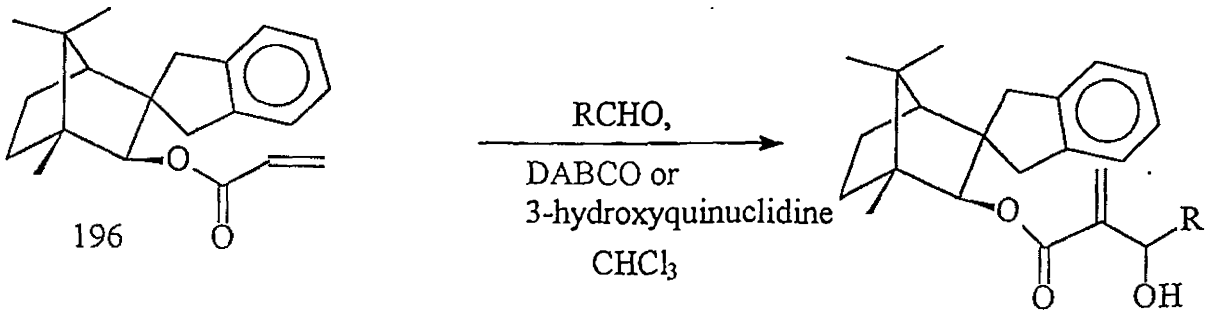



FIGURE 27. The COSY spectrum of the acrylic ester (196) in $CDCl_3$

## 2.3.2 Preparation of the Baylis-Hillman products

The chiral acrylic ester (**196**) was reacted with each of a series of aliphatic, aromatic and pyridyl aldehydes (**Scheme 55**). All the reactions were performed in chloroform and DABCO was initially employed as the catalyst; however, 3-hydroxyquinuclidine[88] furnished better yields. A typical reaction took approximately one week to go to completion, the progress of the reaction being monitored by observing the disappearance of the aldehydic proton signal and the change in the vinyl signals in $^1$H NMR spectra of the reaction mixture. Work-up and chromatography afforded the corresponding Baylis-Hillman products (**197 - 205**) in good yield (**Table 2**).




196

SCHEME 55

| | R |
|---|---|
| 197 | $CH_3$ |
| 198 | $CH_3CH_2$ |
| 199 | $CH_3(CH_2)_2$ |
| 200 | Ph |
| 201 | p-$NO_2$-$C_6H_4$ |
| 202 | p-Cl-$C_6H_4$ |
| 203 | 2-pyridyl |
| 204 | 3-pyridyl |
| 205 | 4-pyridyl |

The products can be readily distinguished from the acrylate precursor (**196**) by means of their $^1H$ NMR spectra, illustrated for compound (**204**) in **Figure 28**. The doubling of peaks is due to the diastereomeric components, and the diastereomeric ratios were readily determined, in each case, from the relative integrals of the 2-$H_{endo}$ signals at *ca.* 4.70 ppm. The chiral discrimination observed in these reactions varied from 5% to 59% d.e. (**Table 2**). The preferred attack by the aldehyde is presumed to be at the less hindered *Si*- face of the chiral dipolar enolate intermediate (**195**), which is proposed to adopt an (*E*)-configuration about the double bond as illustrated in **Figure 29a**. Computer modelling (**Figure 29b**) clearly reveals the exposed face of the enolate intermediate (**195**). However, the stereoselectivity of the Baylis-Hillman product is finally determined by the facial selectivity of nucleophilic attack on the aldehyde. Consequently, it is not surprising that the observed diastereoselectivity (**Table 2**) is very dependent on the nature of the aldehyde. In the series of aliphatic aldehydes examined, increasing the steric bulk (Me → Et →Pr) results in a steady increase in diastereoselectivity; however, the data obtained for the aryl and pyridyl aldehydes suggest that polar effects are also important. The computer-modelled structures (**Figure 29b**) illustrate what is predicted to be the favoured orientation of the reacting species prior to nucleophilic attack at the *Si*-face of the aldehyde.

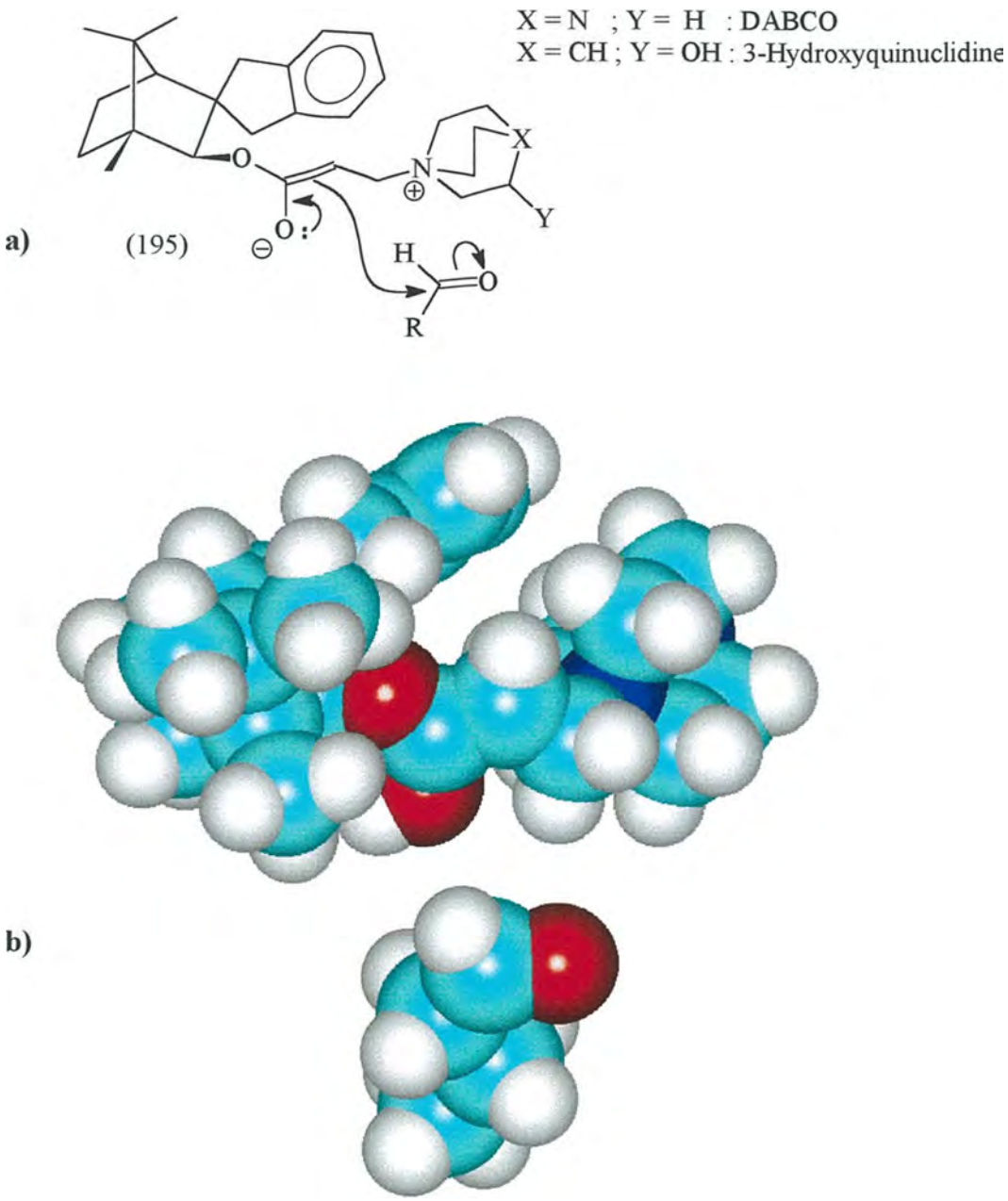



FIGURE 29 : (a) Suggested approach of the aldehyde to the dipolar intermediate.
(b) Computer-generated model of the dipolar intermediate, indicating the more exposed face.

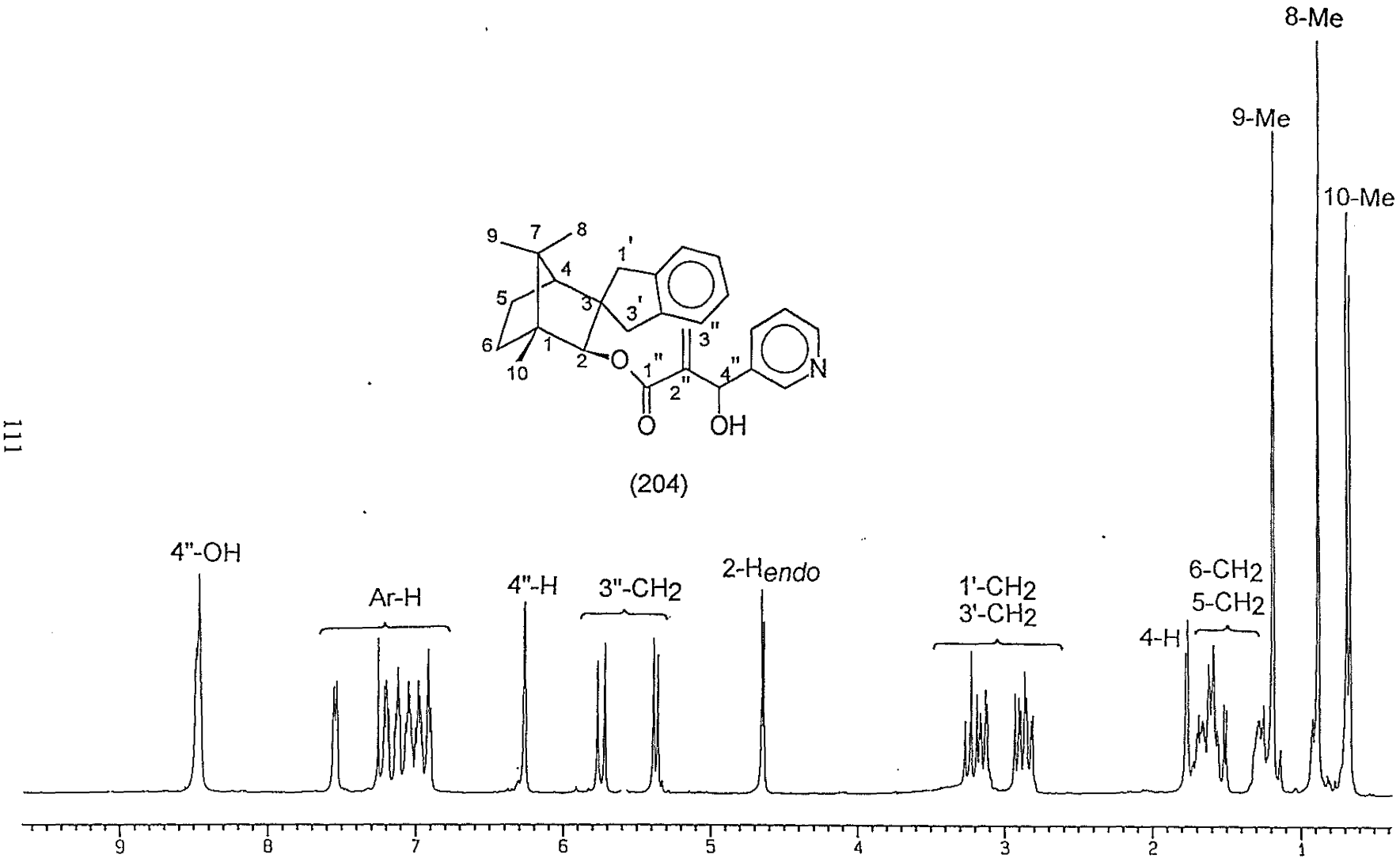
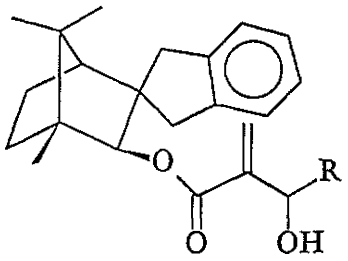



FIGURE 28. The 400 MHz $^1$H NMR spectrum of the mixture of diastereomeric Baylis-Hillman products (**204**) in $CDCl_3$

**Table 2 : Product data for Asymmetric Baylis Hillman reactions of the chiral acrylate ester (196) with aldehydes, RCHO.**

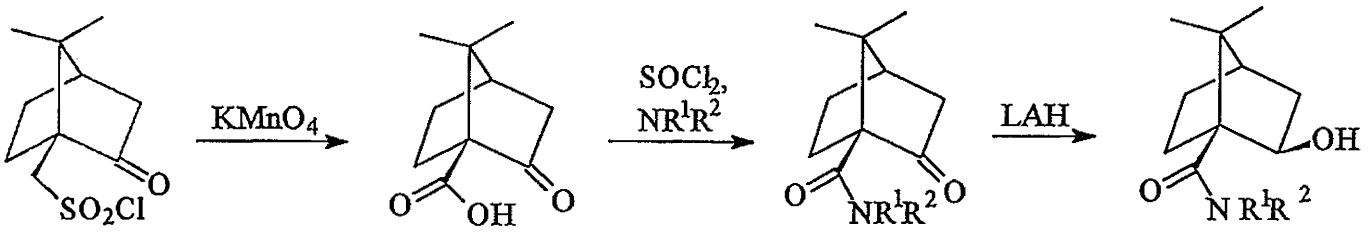



| Compound | R | Yield[a] / % | % d.e.[b] | reaction time/ weeks | Catalyst[c] |
|---|---|---|---|---|---|
| 197 | $CH_3$ | 84 | 20 | 2 | HQ |
| 198 | $CH_3CH_2$ | 77 | 56 | 2 | HQ |
| 199 | $CH_3(CH_2)_2$ | 71 | 59 | 2 | HQ |
| 200 | Ph | 89 | 9 | 1.5 | HQ |
| 201 | p -$NO_2$-$C_6H_4$ | 70 | 26 | 1 | DB |
| 202 | p -Cl-$C_6H_4$ | 86 | 45 | 1.5 | HQ |
| 203 | 2-pyridyl | 94 | 16 | 1 | HQ |
| 204 | 3-pyridyl | 90 | 5 | 1 | HQ |
| 205 | 4-pyridyl | 91 | 10 | 1 | HQ |

[a] Isolated diastereomeric mixtures.
[b] Determined by $^1H$ NMR spectroscopy.
[c] HQ = 3 - hydroxyquinuclidine; DB = DABCO.

## 2.3 APPLICATION OF KETOPINIC ACID DERIVATIVES IN THE ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS

The camphor sultam system used by Oppolzer (see **Section 1.2.2**) has found wide application as a chiral auxiliary. Oppolzer has also explored the use of ketopinic acid-derived auxiliaries in the enantioselective synthesis of secondary allylic alcohols in reactions involving the catalytic asymmetric addition of dialkyl- and divinylzinc to aldehydes.[97] Ketopinic acid (**207**) is produced by potassium permanganate oxidation of camphor-10-sulfonyl chloride (**206**) (**Scheme 56**); subsequent condensation of ketopinic acid with amines affords the chiral bidentate ligands, (**210**) and (**211**), which catalyse the highly *Si*-face selective addition of diethyl-, dipropyl- and divinylzinc to aromatic and aliphatic aldehydes.[97]



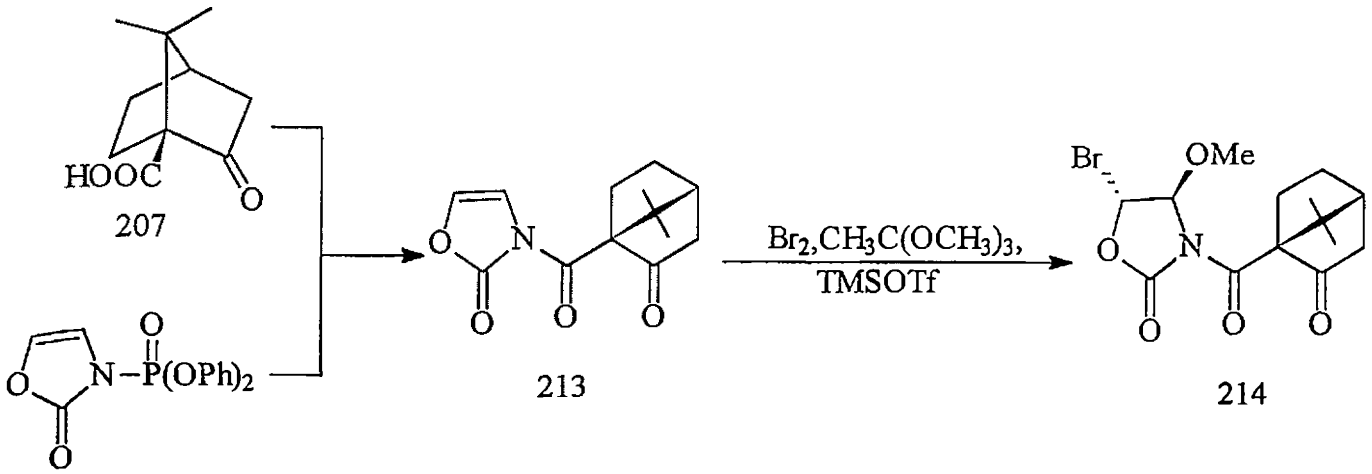

206 207

| | | |
|---|---|---|
| 208 | $R^1$= Me, $R^2$= $(CH_2)_2NMe_2$ | 210 |
| 209 | $R^1$= $R^2$= $Pr^i$ | 211 |

SCHEME 56

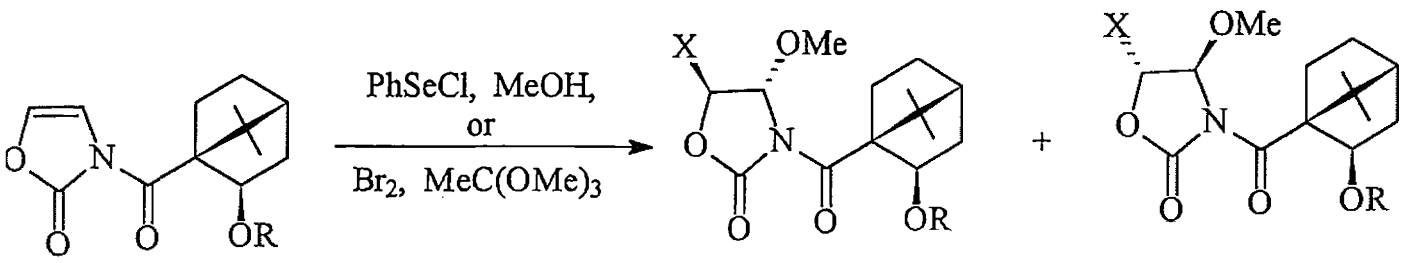
Ketopinic acid has been also derivatized to 3-ketopinyl-2-oxazolone (**213**) by treatment with diphenyl(2-oxo-3-oxazolinyl)phosphonate (DPPOX) (**212**) (**Scheme 57**).[98] Methoxybromination of the oxazolone(**213**) results in the highly diastereoselective formation of the (*S*)-5-bromo-4-

methoxy-2-oxazolidone derivative (**214**) which serves as a versatile chiral synthon in the preparation of biologically significant *vic*-amino compounds.[98]




SCHEME 57

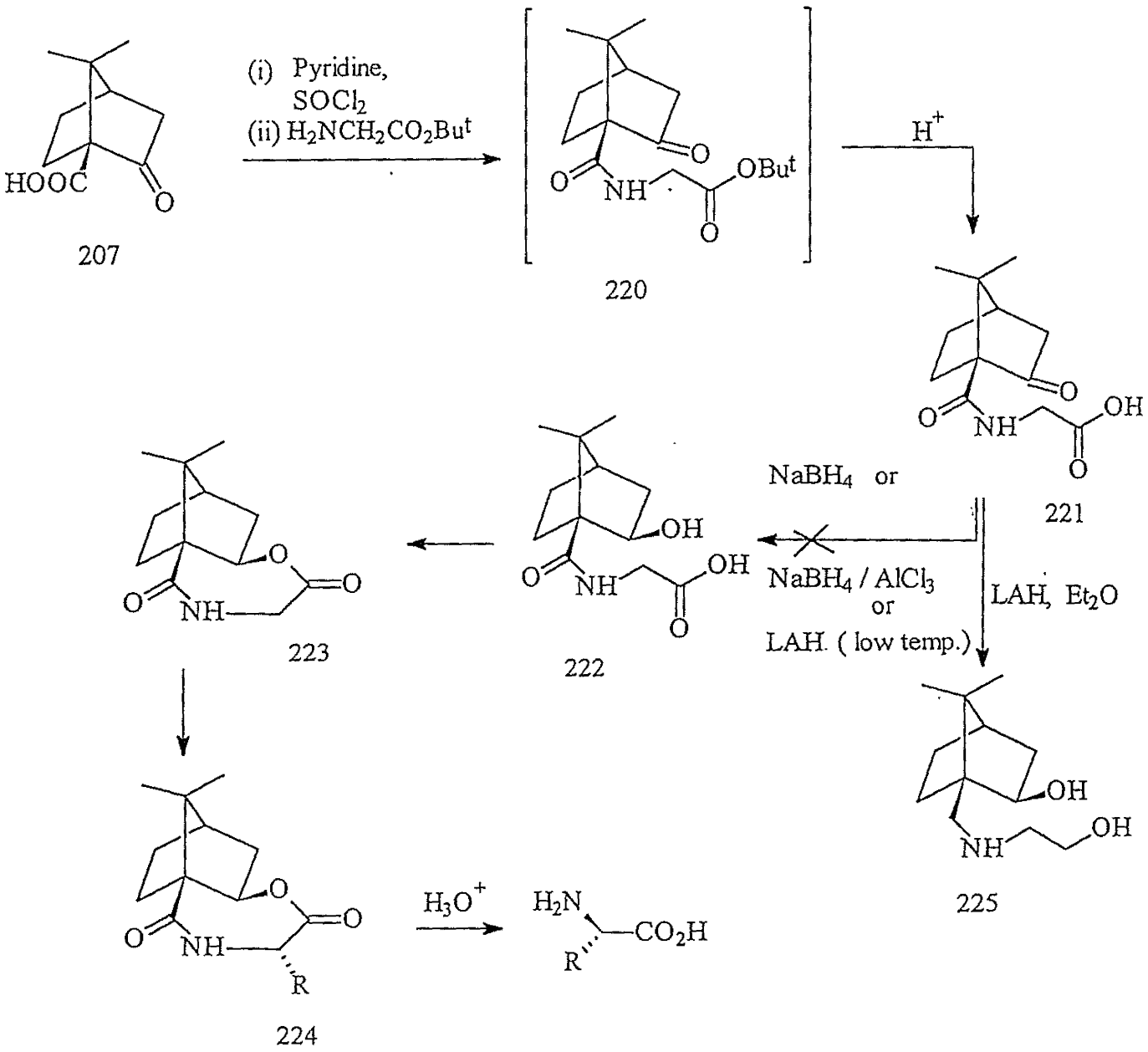
The ketopinic acid derivative (**215**) has also been used as a chiral director in the enantioselective functionalization of oxazolone building blocks in the synthesis of β-amino alcohols.[99] Methoxyselenylation and methoxybromination of the 3-acyl-2-oxazolone (**215**) proceed smoothly to afford chiral synthons for β-amino alcohols with opposite π-facial selectivity (**Scheme 58**).




| | | |
|---|---|---|
| 216<br>217 | X = PhSe<br>X = Br | 218<br>219 |

SCHEME 58

In the light of these successful applications of ketopinic acid-derived chiral auxiliaries, it was anticipated that the lactone-lactam derivative (**223**) (**Scheme 59**) would undergo preferential *endo*-alkylation, thus affording optically active α-amino acids on hydrolysis. Unlike the camphor imino lactone synthesis (see **Section 2.1**), which employs an alcohol and a ketone group to form the imino lactone systems (**131** and **132**), the ketopinic acid approach envisaged use of a hydroxy and a carboxylic acid group, to obtain the lactone-lactam derivative (**223**). Ketopinic acid (**207**) was obtained, following the literature procedure,[97] by oxidising camphor-10-sulfonyl chloride (**206**) with potassium permanganate (see **Scheme 56**). Condensation of ketopinic acid (**207**) with *tert*-butyl glycinate was achieved by firstly converting the acid (**207**) to the acid chloride, using thionyl chloride in pyridine, and then adding *tert*-butyl glycinate at 0°C [97] (**Scheme 59**). Work-up and purification by recrystallization furnished the amide (**221**) containing the free carboxylic acid, loss of the *tert*-butyl group being attributed to acid-catalysed alkyl-*O* cleavage of the ester *via* formation of the stable *tert*-butyl carbocation. The 400 MHz $^1$H NMR spectra of the amido acid (**221**) and the ketopinic acid precursor (**207**) are illustrated in **Figure 30**, the spectrum of the former compound clearly revealing a pair of doublets for the diastereotopic 2′-methylene nuclei at *ca.* 4.1 ppm, a very broad amide NH signal at *ca.* 5.6 ppm and the carboxylic proton signal at 8.2 ppm. With the deprotected amide (**221**) available from a one-pot procedure, the next challenge was to reduce the C-2 carbonyl group to furnish the hydroxyl group required for final cyclisation to the desired lactone-lactam (**223**). Several attempts using various reducing agents, such as $NaBH_4$, low temperature LAH reduction and $NaBH_4/AlCl_3$ (**108**) failed to yield the desired product (**223**), while stronger reducing agents, such as LAH reduced all three carbonyl groups affording the derivative (**225**) quantitatively.[97]




207 220 221 222 223 224 225

SCHEME 59

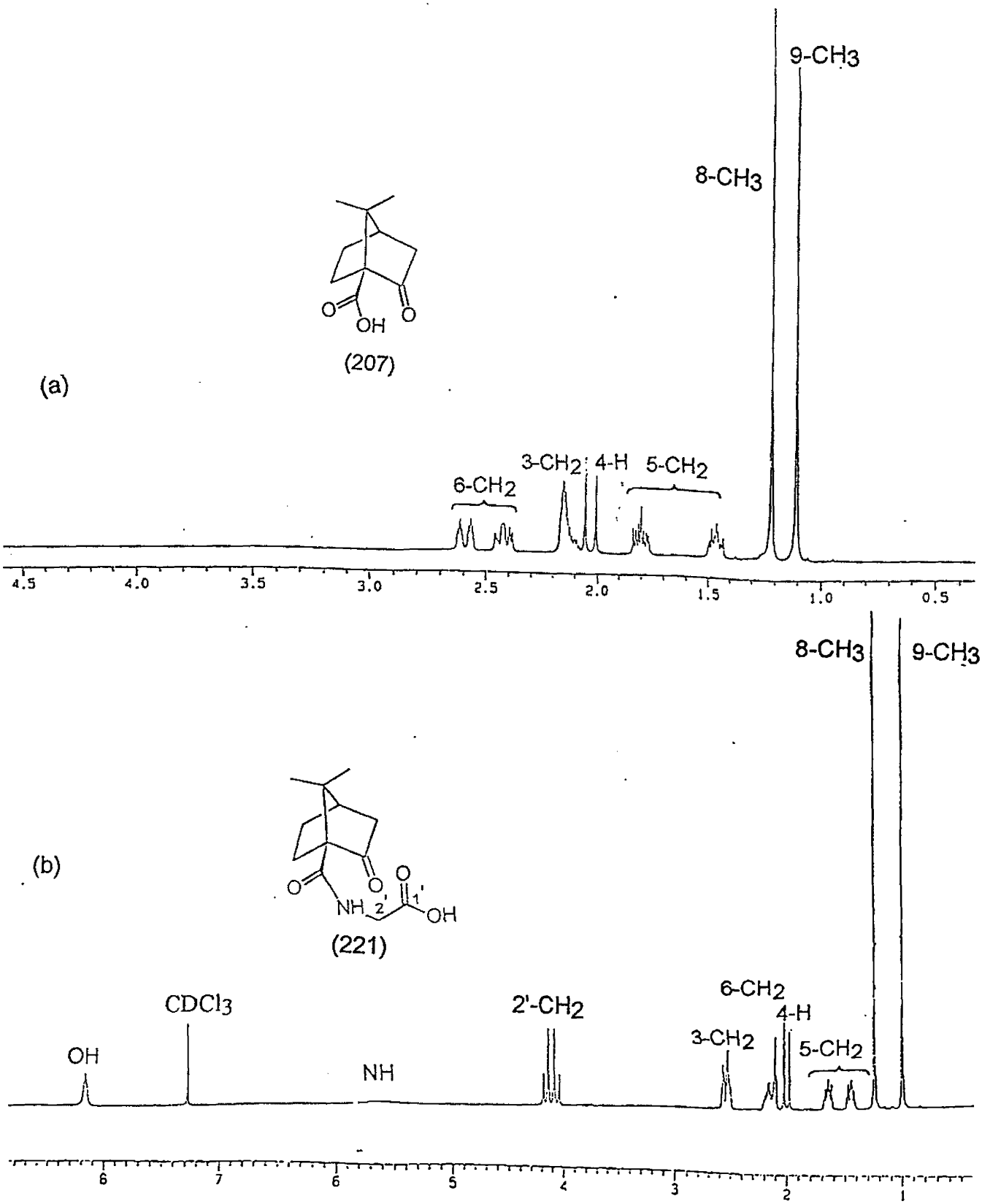
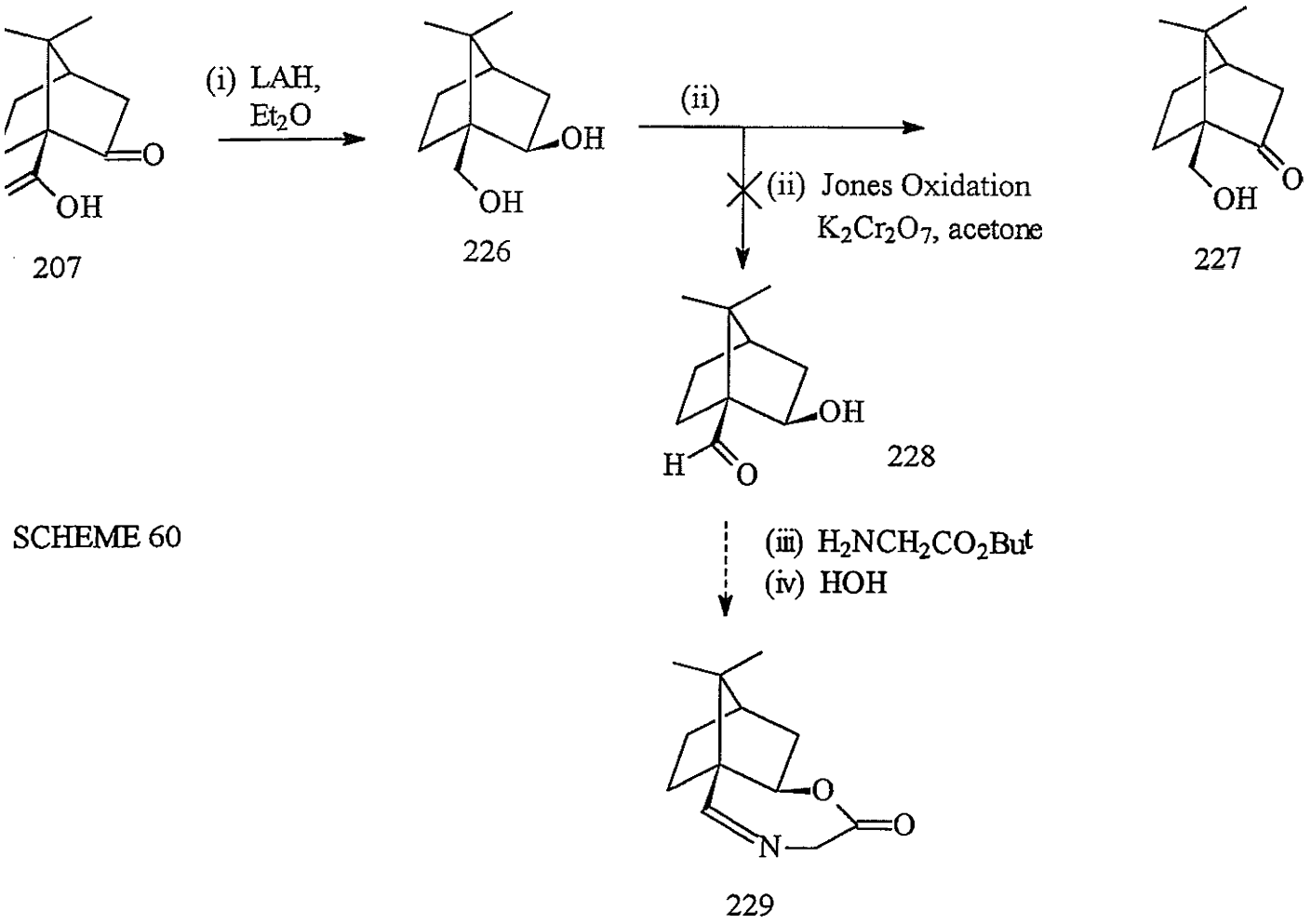



FIGURE 30 (a) Partial 400 MHz $^1$H NMR spectrum of ketopinic acid (**207**) in $CDCl_3$
(b) 400 MHz $^1$H NMR spectrum of the glycine derivative (**221**) in $CDCl_3$

An alternative cyclisation, involving formation of the hydroxy aldehyde (**228**) as a chiral auxiliary, was then explored. Reduction of ketopinic acid (**207**) furnished the bornane-2,10-diol (**226**), and it was expected that selective oxidation[101,102] of the primary 10-hydroxy group to an aldehyde would afford 2-hydroxybornane-10-carboxaldehyde (**228**). The aldehyde functionality could then condense with the amino group of *tert*-butyl glycinate to afford an imine, whilst hydrolysis of the ester moeity and cyclisation would afford the imino lactone (**229**). However, Jones oxidation of the bornane-2,10-diol (**226**) with potassium dichromate in acetone failed to yield the desired 2-*exo*-hydroxybornane-10-carboxaldehyde (**228**) (**Scheme 60**). Instead, the reaction afforded a mixture of the unreacted bornane-2,10-diol (**226**) and 10-hydroxycamphor (**227**), reflecting preferential oxidation of the secondary 2-*exo*-hydroxy group. Interestingly, such oxidation has been employed in the preparation of camphor from borneol.[103]

At this stage, attention was diverted to the use of acyclic derivatives of bornane-2,10-diol (**226**). It was envisaged that *N*-(carbobenzyloxy)glycine could be attached to one hydroxy group and a benzyl blocking group to the other, affording a pair of regioisomeric chiral auxiliaries, (**232**) and (**233**) (**Scheme 61**). The chiral auxiliary was expected to induce *Re*-alkylation of the enolate of compound (**232**) due to the steric effect of the benzyl group, while the regioisomeric system (**233**) was expected to exhibit *Si*-selectivity. The benzyl group was introduced by treating the diol (**226**) with one equivalent of KOBu$^t$ at -78°C, followed by one equivalent of benzyl bromide. Work-up afforded an oily mixture which proved difficult to separate using preparative layer chromatography. Separation was finally achieved using normal phase,semi-preparative HPLC, which gave three components, *viz.*, 10-benzyloxy-2-*exo*-hydroxybornane (**230**) (54%), 2-*exo*-benzyloxy-10-hydroxybornane (**231**)(41%), and the unreacted 2,10-diol (**226**)(5%). The isomeric

hydroxy ethers (**230**) and (**231**), whose $^1$H NMR spectra are illustrated in **Figure 31**, were differentiated by their HMBC spectra, the benzyl carbon (C-1′) in ether (**230**) showing correlation to the 10-methylene protons and the benzyl carbon (C-1′) of the regioisomer (**231**) showing correlation to the 2-*endo* proton.




207 226 227 228 229

SCHEME 60

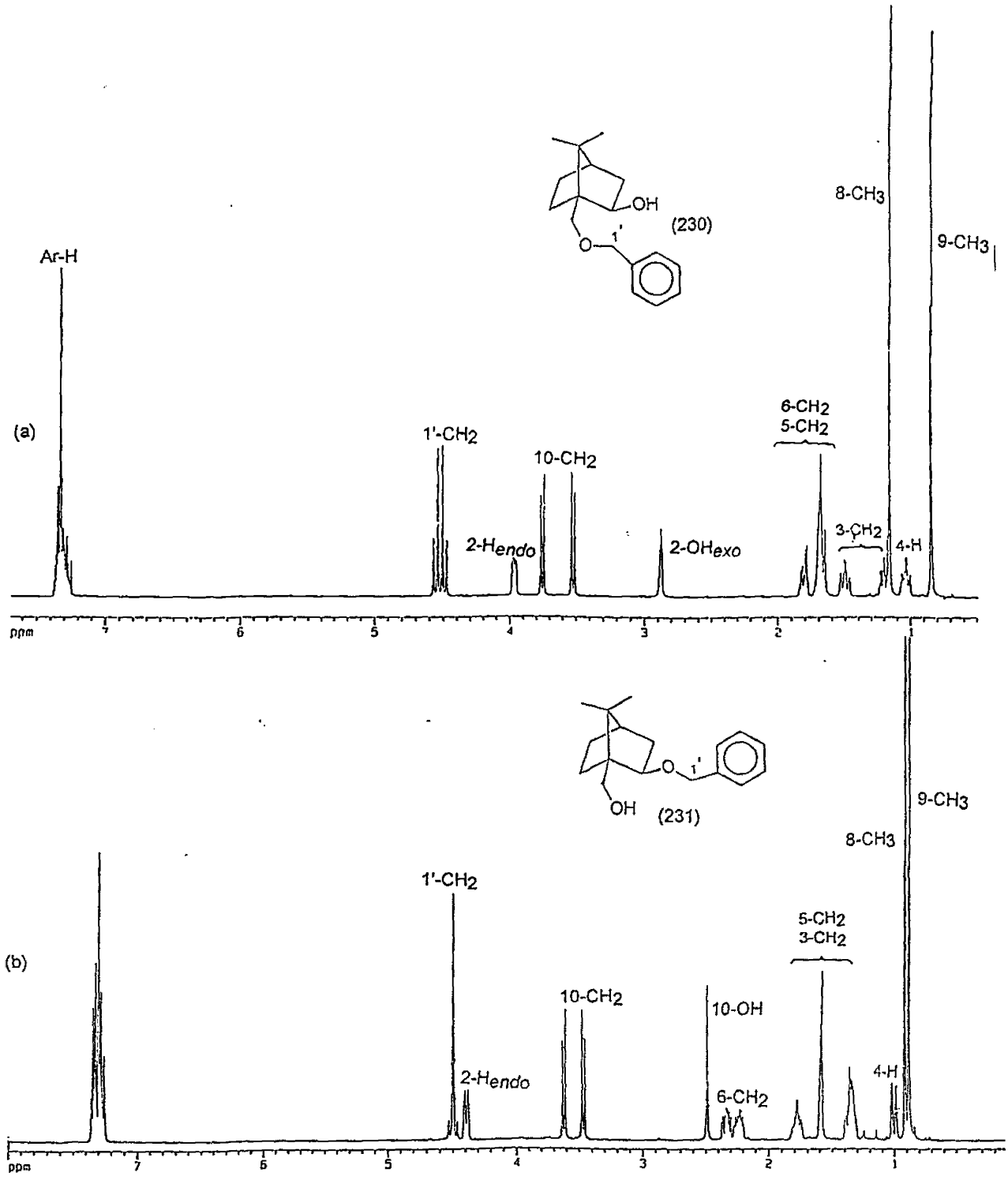
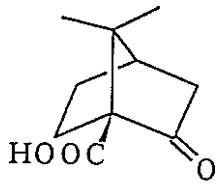
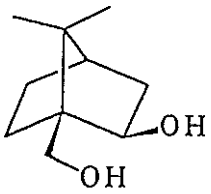



FIGURE 31 (a) The 400 MHz $^1$H NMR spectrum of 10-benzyloxy-2-*exo*-hydroxybornane (**230**) in $CDCl_3$
(b) The 400 MHz $^1$H NMR spectrum of 2-*exo*-benzyloxy-10-hydroxybornane (**231**) in $CDCl_3$



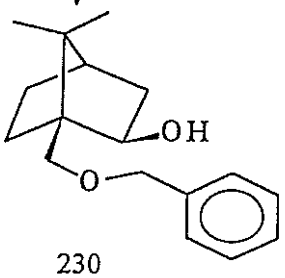

207

(i) LAH
(ii) $Et_2O$

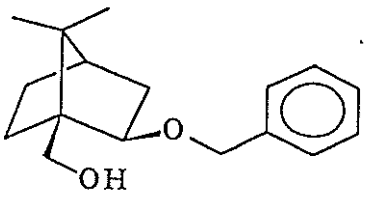



226

(iii) $Bu^tOK$
(iv) $C_6H_5CH_2Br$



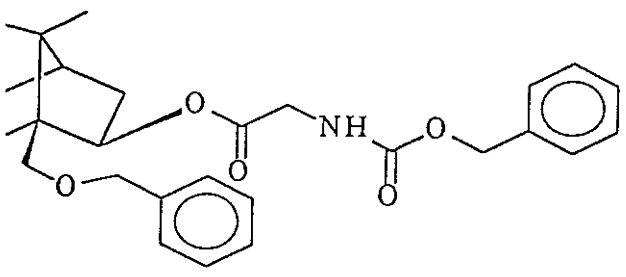

230



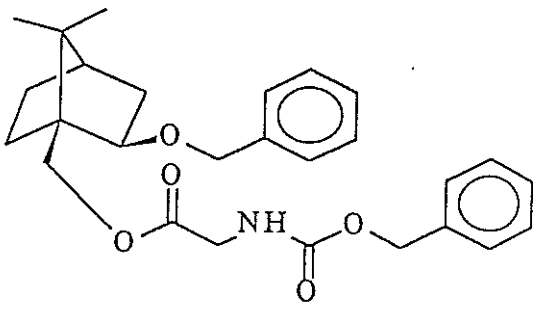

231

(v) CDI
(vi) CBz-glycine

(v) CDI
(vi) CBz-glycine




232




233

SCHEME 61

The oily mixture containing both regioisomers, (**230**) and (**231**), was then reacted with *N*-(carbobenzyloxy)glycine using carbonyldiimidazole as a coupling agent. Work-up and preparative layer chromatography afforded some of the unreacted 10-benzyl-2-*exo*-hydroxybornane (**230**) and an inseparable oily mixture. Normal phase, semi-preparative HPLC once more permitted isolation of the components, *viz.*, the 2-bornyl glycinate (**232**) (43%) and the isomeric 10-bornyl glycinate (**233**) (36%). The products were unambiguously characterised using their 1- and 2-D NMR spectra, the HETCOR spectra of the isomers (**232**) and (**233**) being illustrated in **Figures 32a** and **b.**

A somewhat related acyclic glycinate derivative (**234**) (**Scheme 62**) was also prepared following the route outlined in **Section 2.2.1.** However, this compound could only be obtained in 11% yield despite various attempts to optimise the reaction conditions and, consequently, was not investigated further.

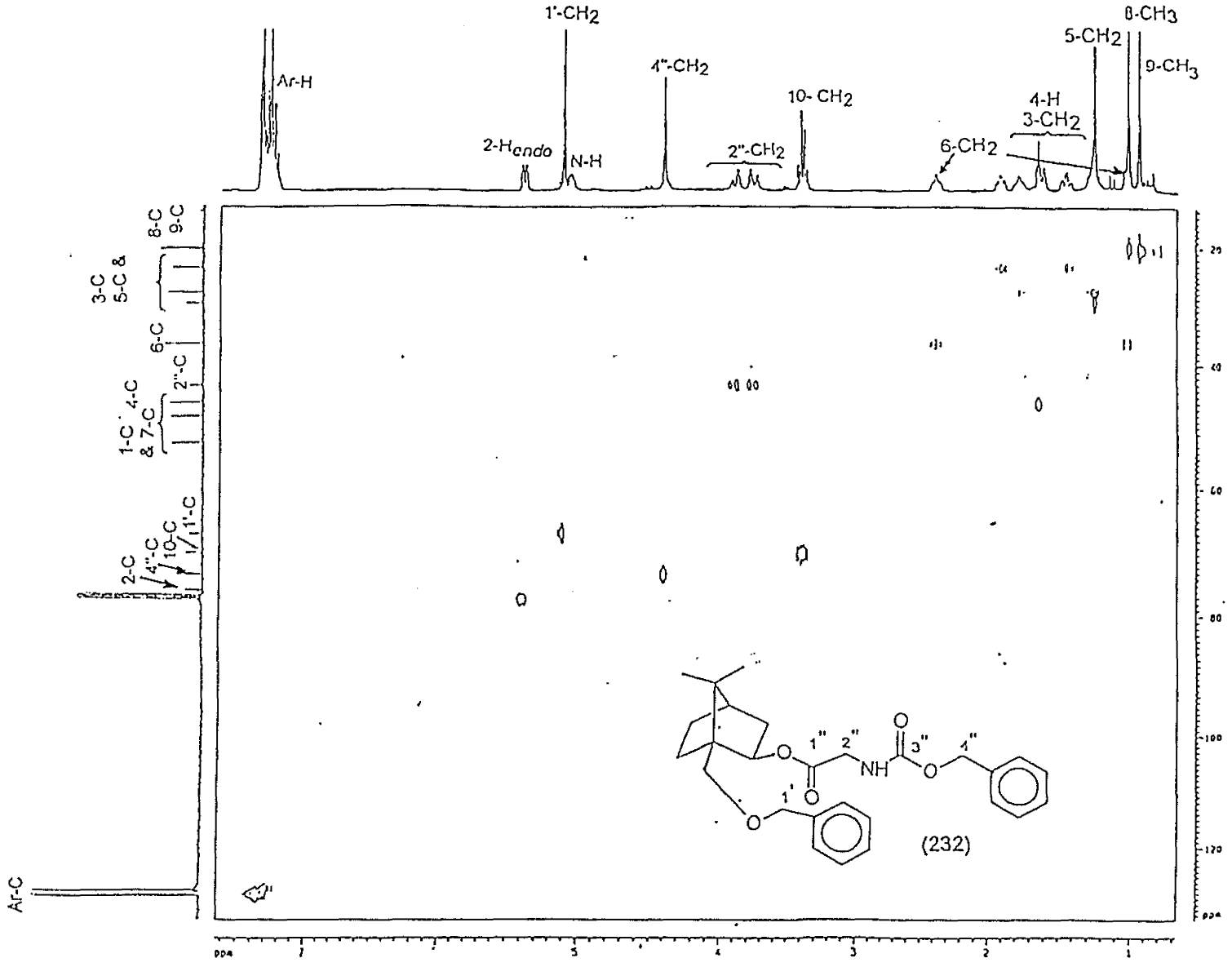



FIGURE 32a. The HMQC NMR spectrum of the 2-bornyl glycinate (232) in $CDCl_3$

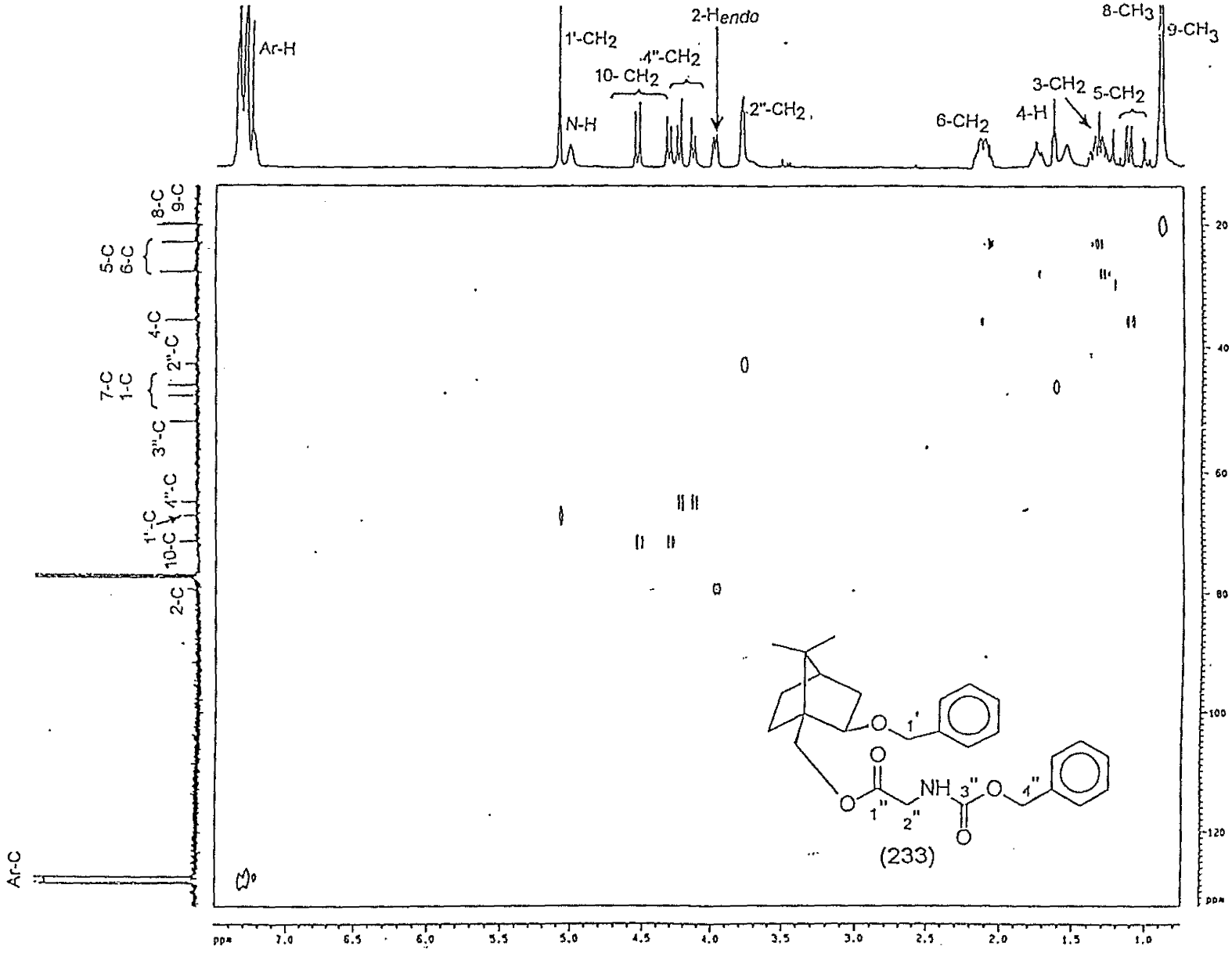
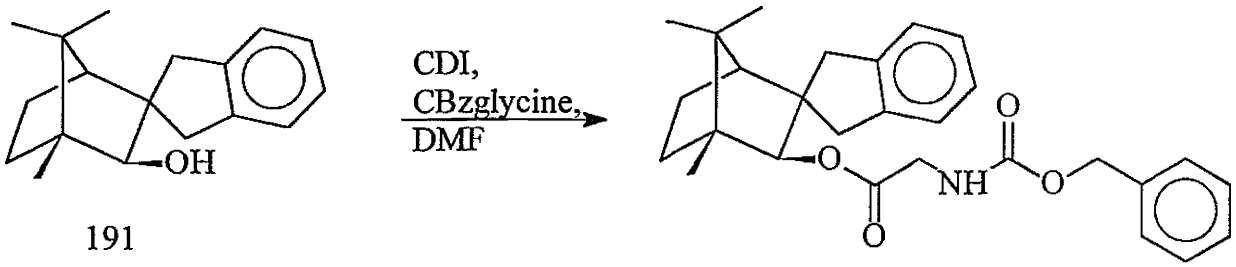



FIGURE 32b. The HMQC NMR spectrum of the 10-bornyl glycinate (233) in $CDCl_3$

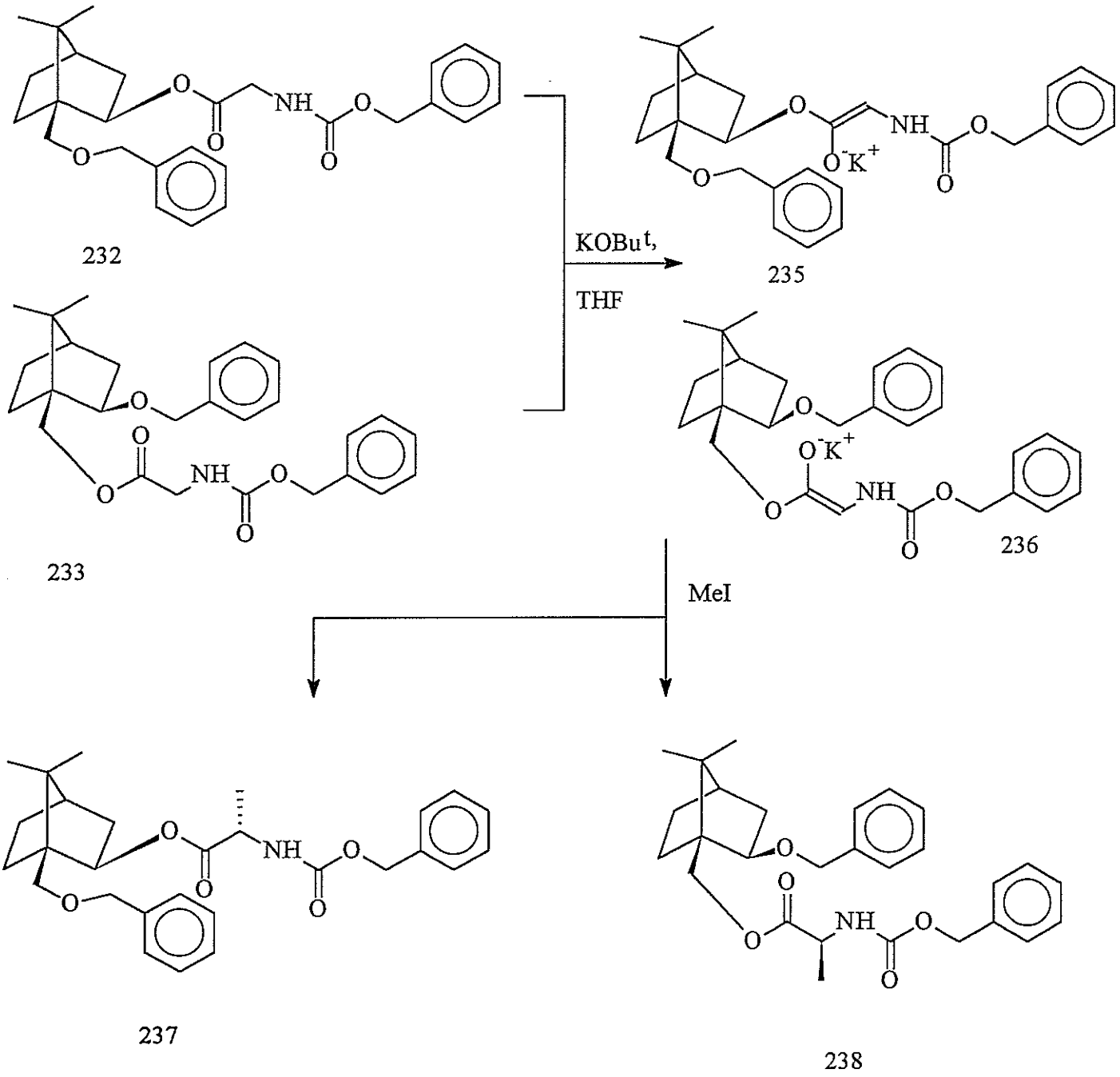



191

234

SCHEME 62

Alkylation of the glycinate derivatives (**232**) and (**233**) (**Scheme 63**) was then investigated. The enolates (**235**) and (**236**) were prepared in THF using KOBu$^t$ and following the procedure described in **Section 2.1.2.** Methyl iodide was added as the alkylating agent, and a $^1$H NMR spectrum of the crude reaction mixture revealed new methyl peaks at *ca.* 1.20 ppm, clearly suggesting that the alkylation was successful. Repeated attempts to separate the products using normal phase preparative HPLC were unsuccessful and , due to time constraints, this approach was not pursued further.

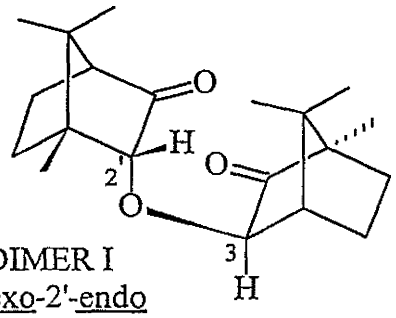



SCHEME 63

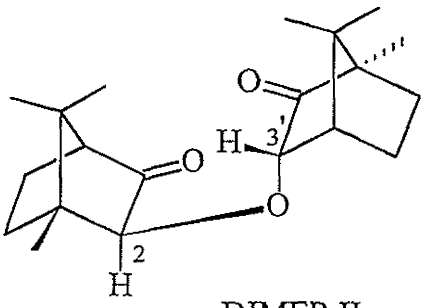
## 2.4 PREPARATION AND IDENTIFICATION OF DIBORNYL ETHERS AND THE APPLICATION OF THEIR DERIVATIVES AS CHIRAL REAGENTS.

### 2.4.1 Preparation and identification of dibornyl ethers

In a previous study,Kaye and Ravindran[49] explored methods of increasing the steric bulk of the blocking group in camphor-derived chiral auxiliaries (see **Section 2.2**).[49,104,105] Several approaches to the chiral auxiliary (**131**) *via* the ketols (**137**) and (**138**) were examined, but without success (**Scheme 35**). The 3-*exo*-hydroxycamphor obtained from camphorquinone (**139**) was heated with glycine in the presence of *p*-toluenesulphonic acid to afford a crystalline material, later identified as a dimeric product, "dimer I" (**239**), NMR spectroscopy of which revealed 6 methyl groups and 20 different carbon atoms. In another approach, the regioisomeric 2-*exo*-hydroxy-3-bornanone was reacted in a similar manner to afford an isomeric product, "dimer II" (**240**). The duplication of camphor peaks in the $^{1}H$ and $^{13}C$ NMR spectra clearly suggested lack of $C_2$-symmetry.



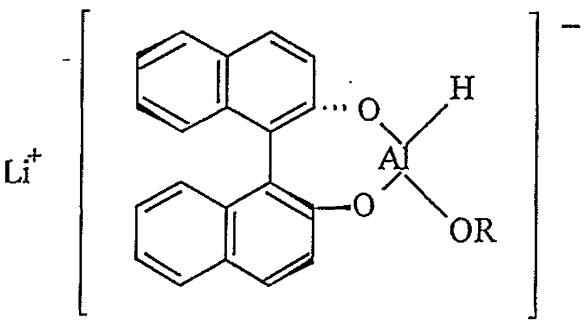

DIMER I
3-exo-2'-endo
239



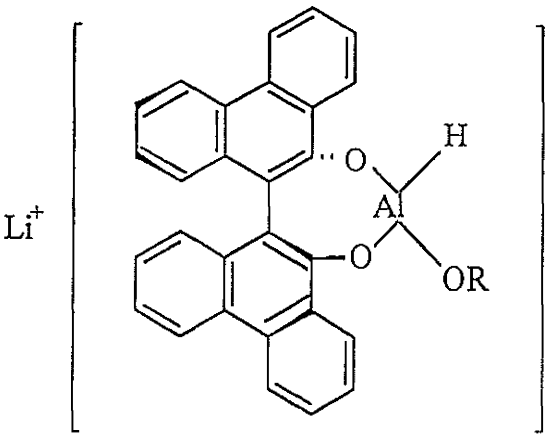

DIMER II
2-exo-3'-endo
240

The oxygen-linked bornyl ethers are, to our knowledge, unprecedented; however Banks *et al.*[106] have identified the 2-*endo*-hydroxycamphor dimer, which was first reported by Mannasse,[107] as a bridged *bis*-(methyl ketal). Two pinacols, obtained by alkali metal-ammonia reduction of (+)-camphor were identified by Rautenstrauch *et al.*[108] as the *endo-exo* and *exo-exo* isomers. However, in a subsequent study Pradhman *et al.*[109] identified these as the *endo-exo* and *endo-endo* products. The monoterpenoid units in these pinacols are thought to be linked by [C(2)–C(2′)] bonds. *Bis*camphor derivatives with C-C linkage from *bis*-(thiocamphor) have also been reported by Bonnat *et al.*.[110]

The axially chiral 2,2′-binaphthols[22] and 10,10′-dihydroxybiphenanthryls[111] exhibit $C_2$-symmetry and have been used to prepare various chiral reagents, examples of which are "BINAP" derivative (44) and compound (241).These derivatives have been shown to effect efficient asymmetric reduction of carbonyl compounds.




44




241

It was anticipated that reduction of the carbonyl groups in the dimers I (**239**) and II (**240**) would afford chiral diols which, while not exhibiting $C_2$-symmetry, might, nevertheless, be used to generate chiral reagents analogous to the BINAP derivatives. Consequently, it was decided to extend Ravindran's work and explore the use of such diols in the preparation of chiral reagents. The regioisomeric α-ketols, (**137**) and (**138**), were prepared as outlined in **Scheme 34** (p. 49). Dimerisation was effected by heating the α-ketols in benzene in the presence of PTSA, and dimers (**239**) and (**240**) were isolated. The $^1$H NMR spectra of these isomeric products are illustrated in **Figure 33**.

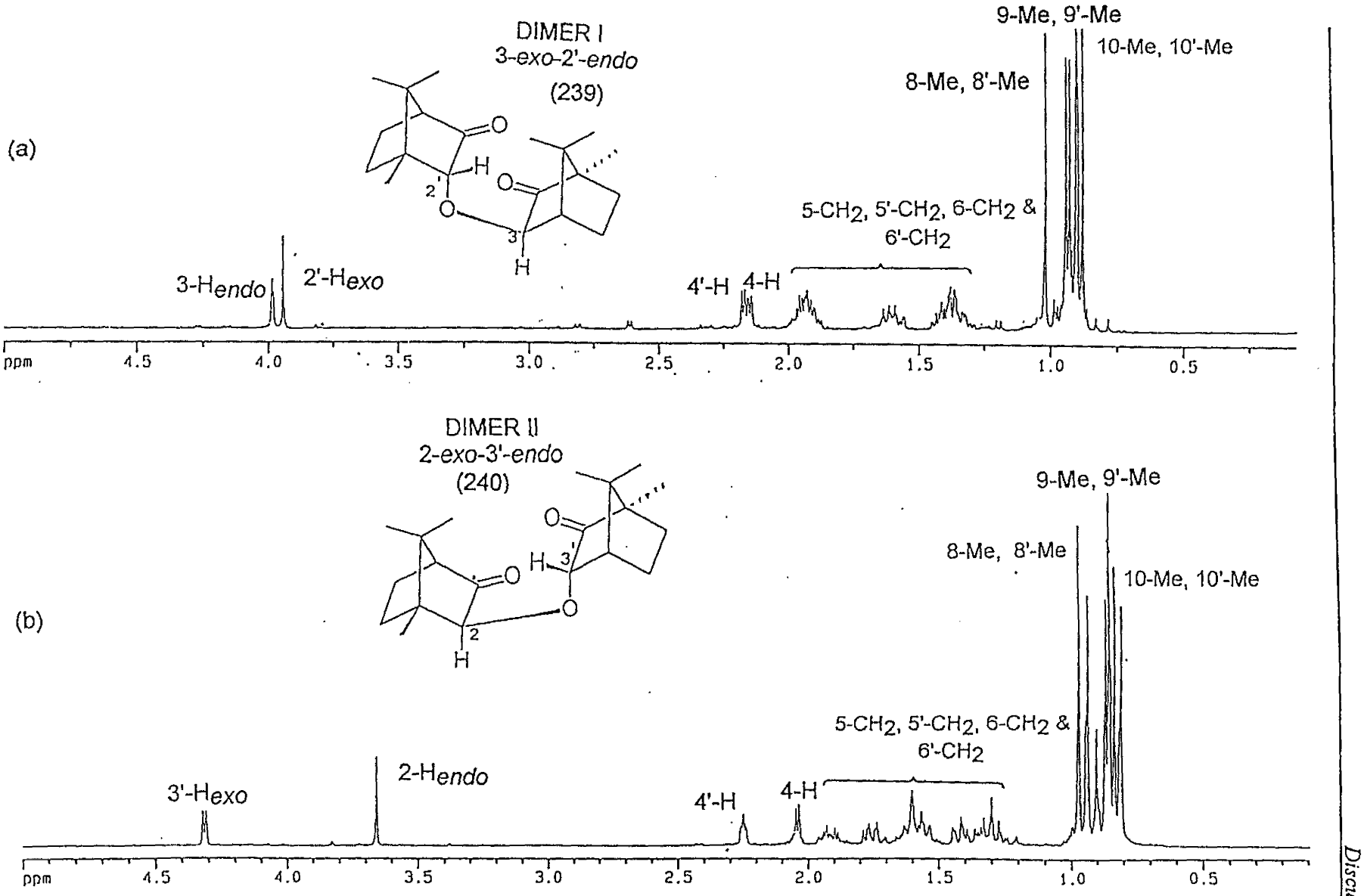
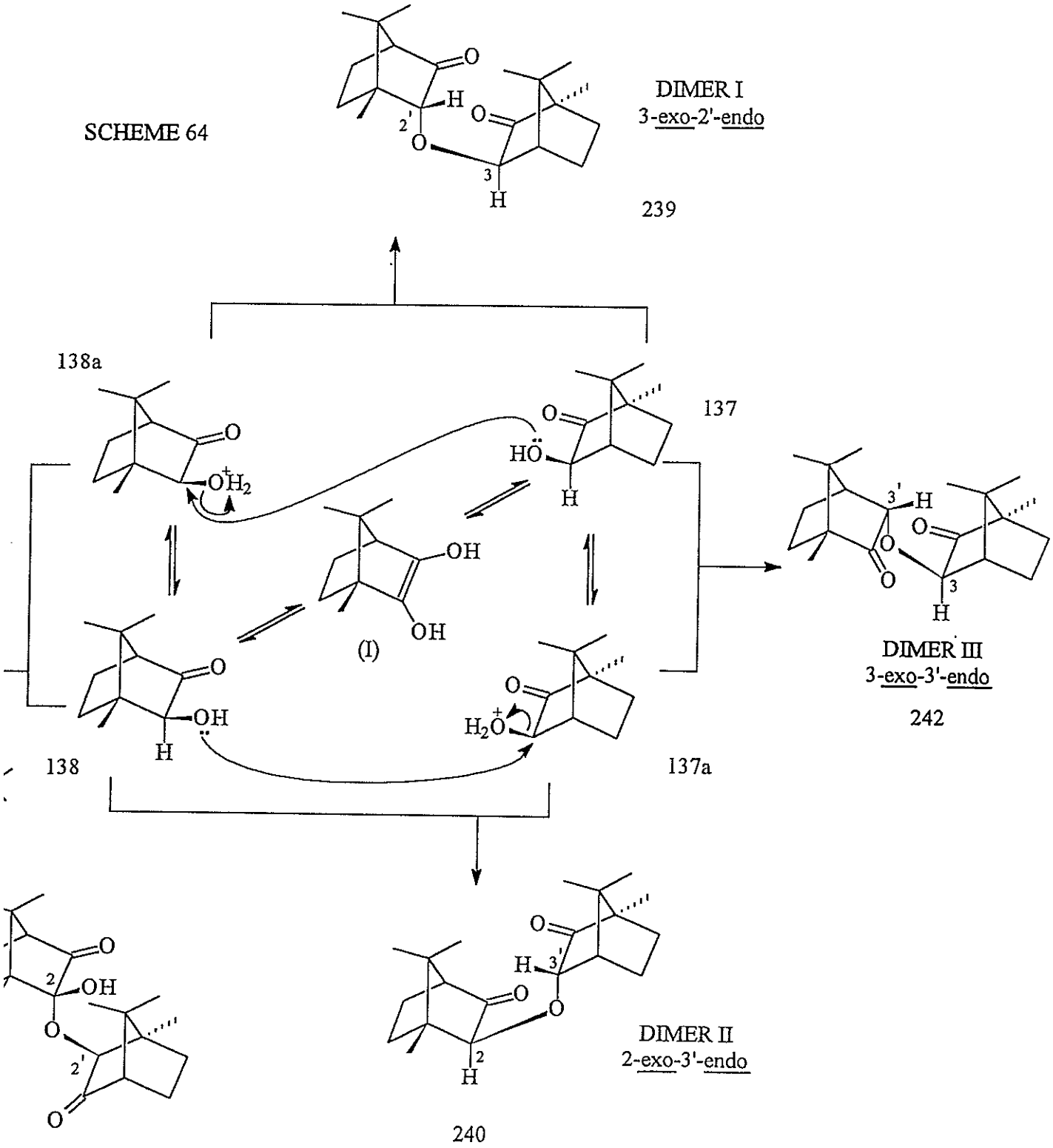
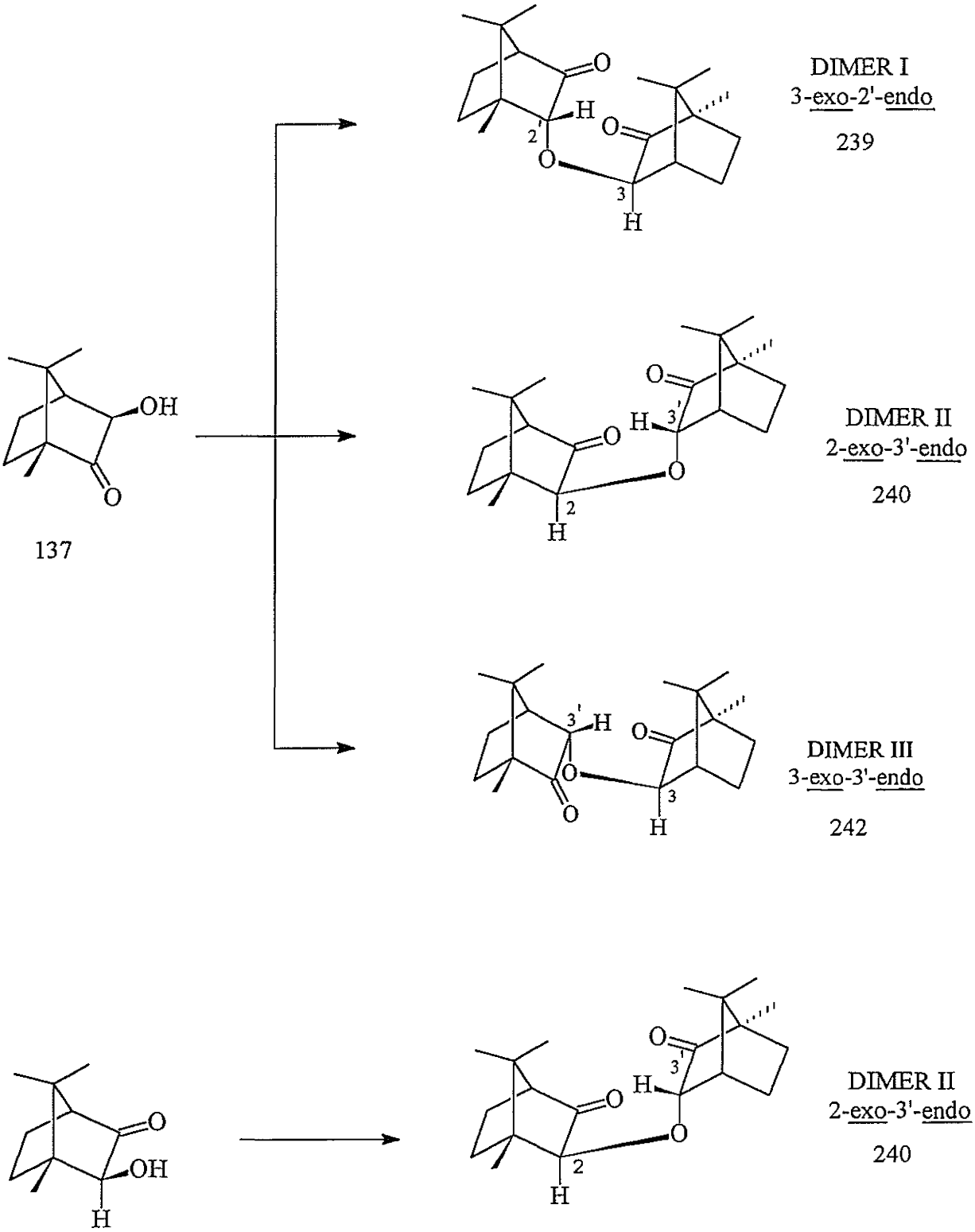



FIGURE 33. (a) The 400 MHz $^1$H NMR spectrum of dimer I (**239**) in $CDCl_3$.
(b) The 400 MHz $^1$H NMR spectrum of dimer II (**240**) in $CDCl_3$.

Ravindran[112] established that the formation of the 3-*exo*-2′-*endo* link in (**239**) ("dimer I") clearly requires isomerisation of the 3-*exo*-hydroxycamphor precursor (**137**), while formation of (**240**) ("dimer II") requires similar isomerisation of the 2-*exo*-hydroxy-3-bornanone precursor (**138**). A mechanism, which accounts for the observed isomerisation, is outlined in **Scheme 64** and involves an equilibrium between the regio-isomeric precursors (**137**) and (**138**). The fact that either one of the precursors might thus be expected to afford both "dimer I" and "dimer II" prompted careful examination of the reaction mixtures. This led to the discovery that, whereas the 2-*exo*-hydroxy-3-bornane (**138**) affords a single product, *viz.*,"dimer II " (**240**), the 3-*exo*-hydroxycamphor (**137**) not only affords both "dimer I" (**239**: 47%) and "dimer II" (**240**: 27%), but also a third product, "dimer III" (19%), which has been identified as the novel 3-*exo*-3′-*endo* isomer (**242**), using high resolution MS and NMR spectroscopic data. As in the case of "dimer I" and "dimer II", the $^{1}$H NMR data revealed six well-resolved methyl singlets (**Figure34**), the corresponding six methyl carbons being confirmed by DEPT and $^{13}$C NMR data. The lack of $C_2$-symmetry was supported by the presence of two different carbonyl carbons, and the skeletal connections were confirmed using HETCOR(HMQC)(**Figure 35**), COSY(**Figure 36**) and HMBC (**Figure 37**) data.

SCHEME 64


DIMER I
3-exo-2'-endo
239
138a
137
138
(I)
137a
DIMER III
3-exo-3'-endo
242
DIMER II
2-exo-3'-endo
240
DIMER IV
2-endo-2'-exo
243


OH
O
137
DIMER I
3-exo-2'-endo
239
DIMER II
2-exo-3'-endo
240
DIMER III
3-exo-3'-endo
242
OH
H
138
DIMER II
2-exo-3'-endo
240

SCHEME 65

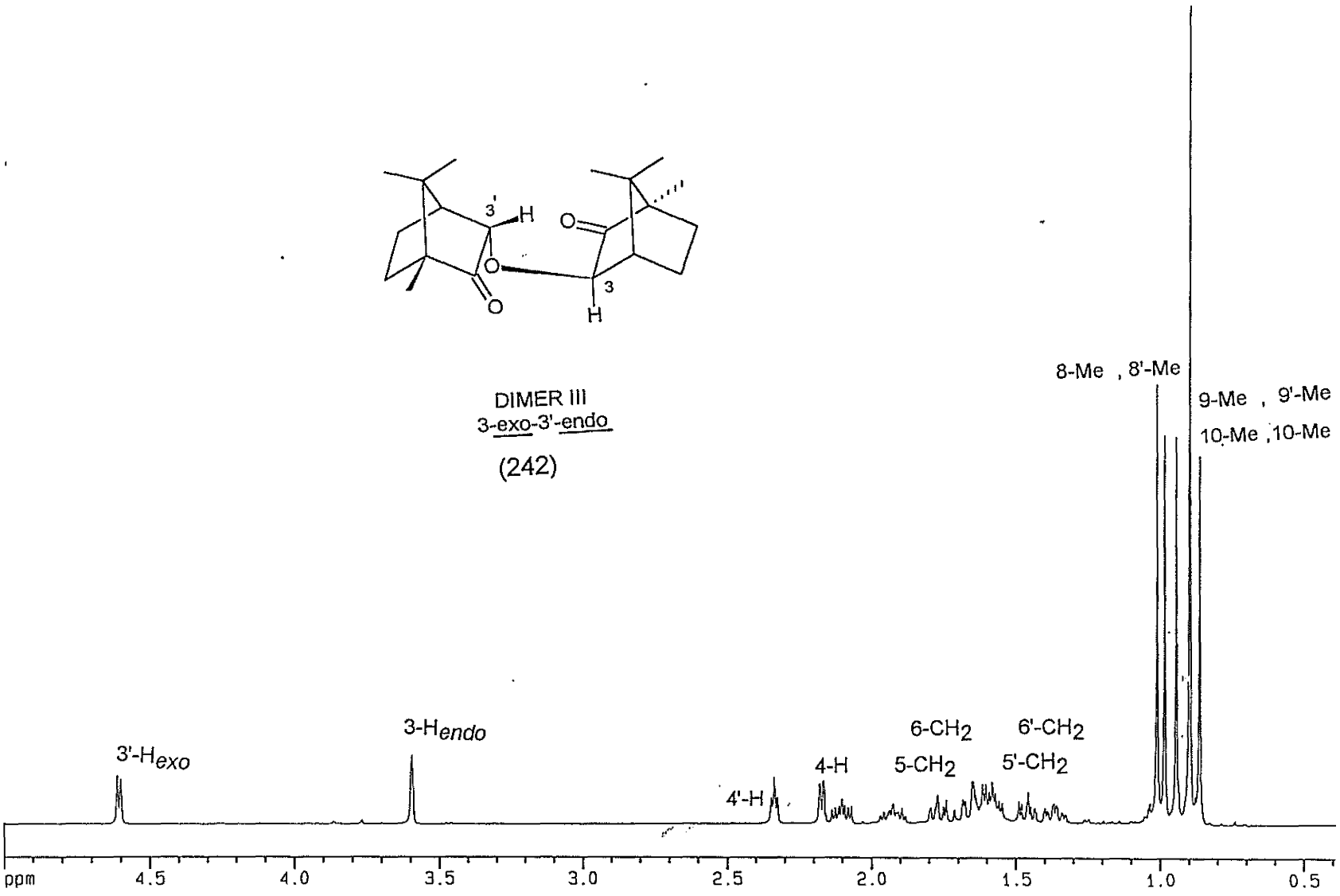



FIGURE 34. The 400 MHz $^1$H NMR spectrum of dimer III (**242**) in $CDCl_3$.

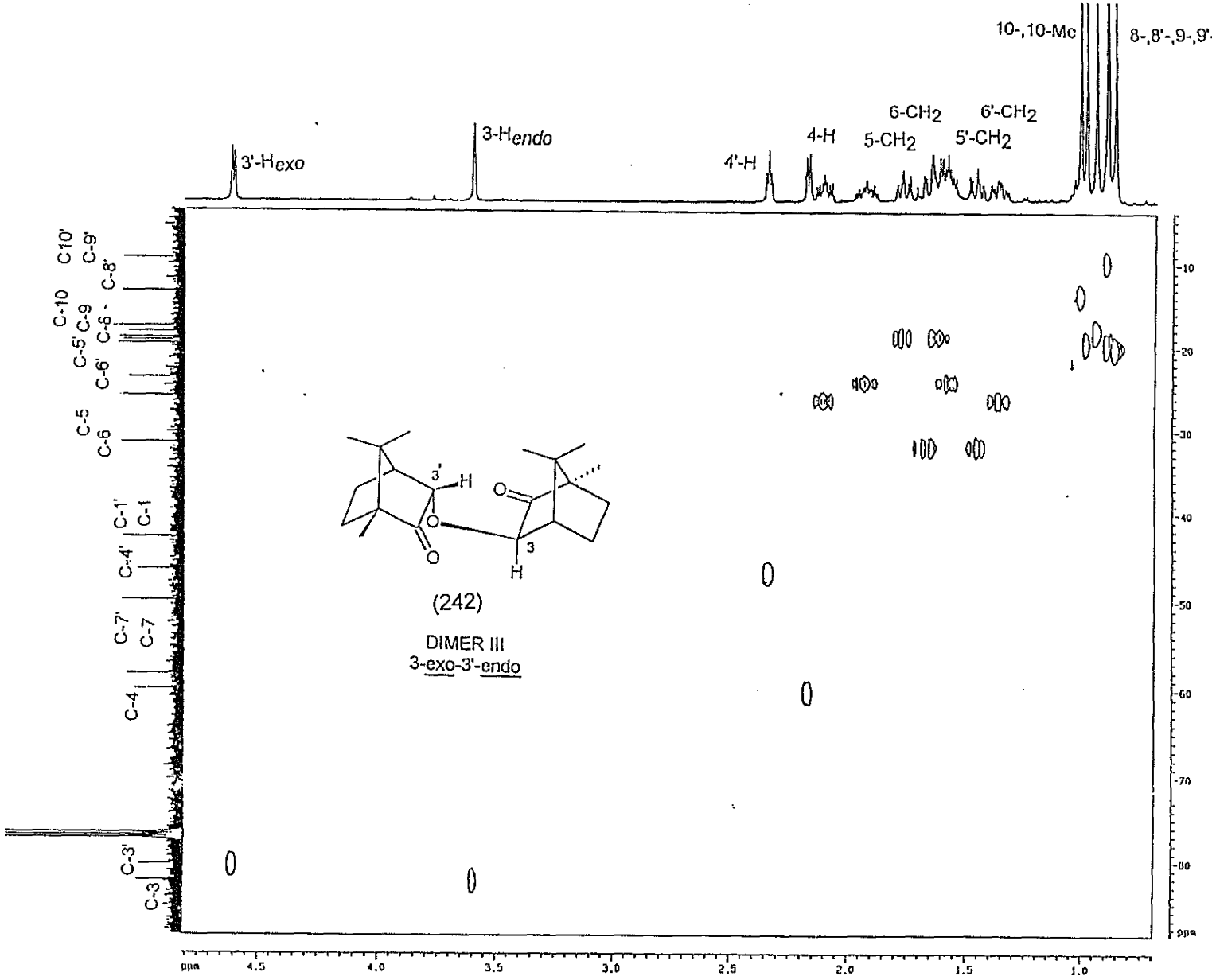



FIGURE 35. The HMQC NMR spectrum of dimer III (**242**) in $CDCl_3$

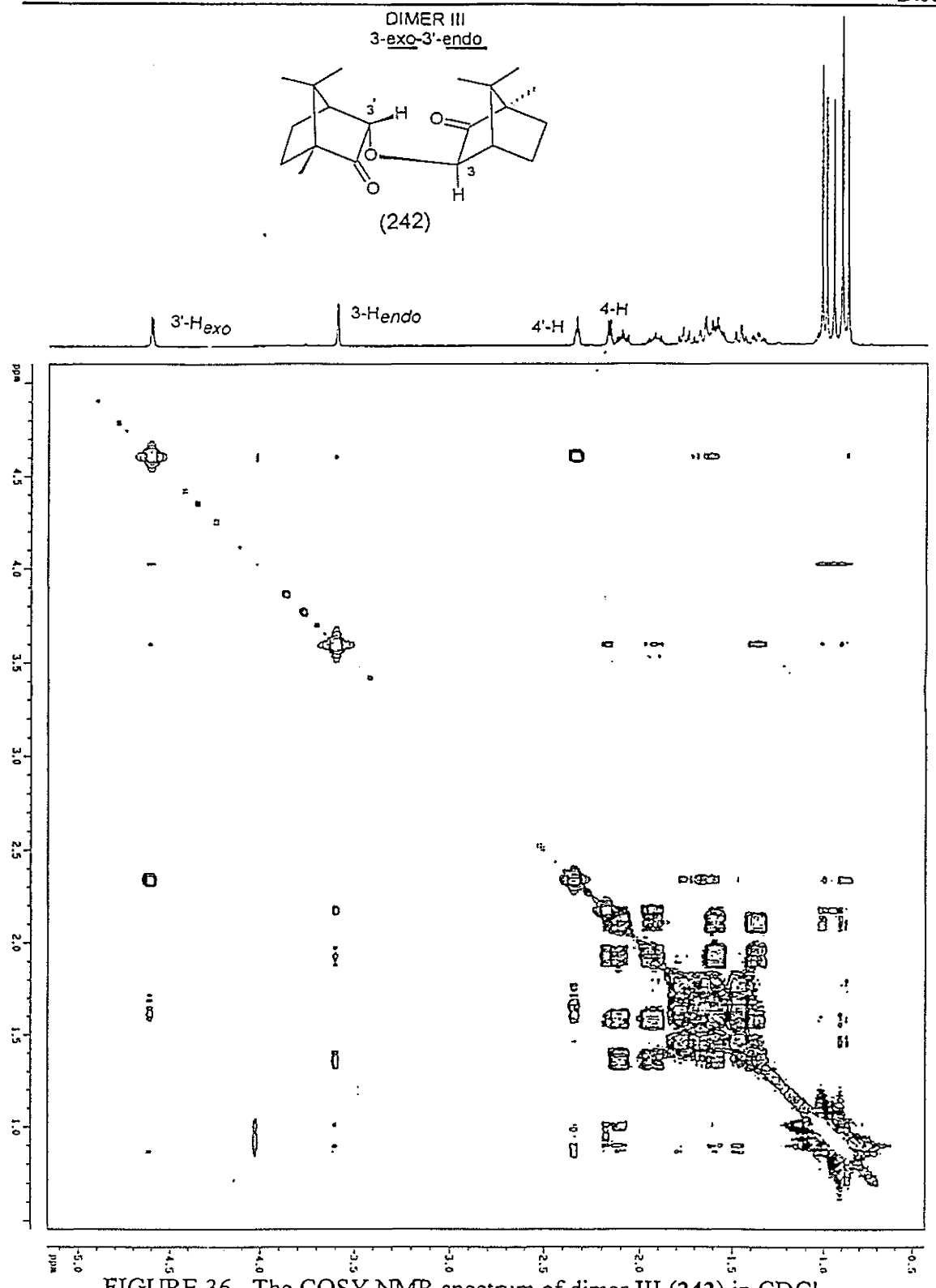



FIGURE 36. The COSY NMR spectrum of dimer III (**242**) in $CDCl_3$

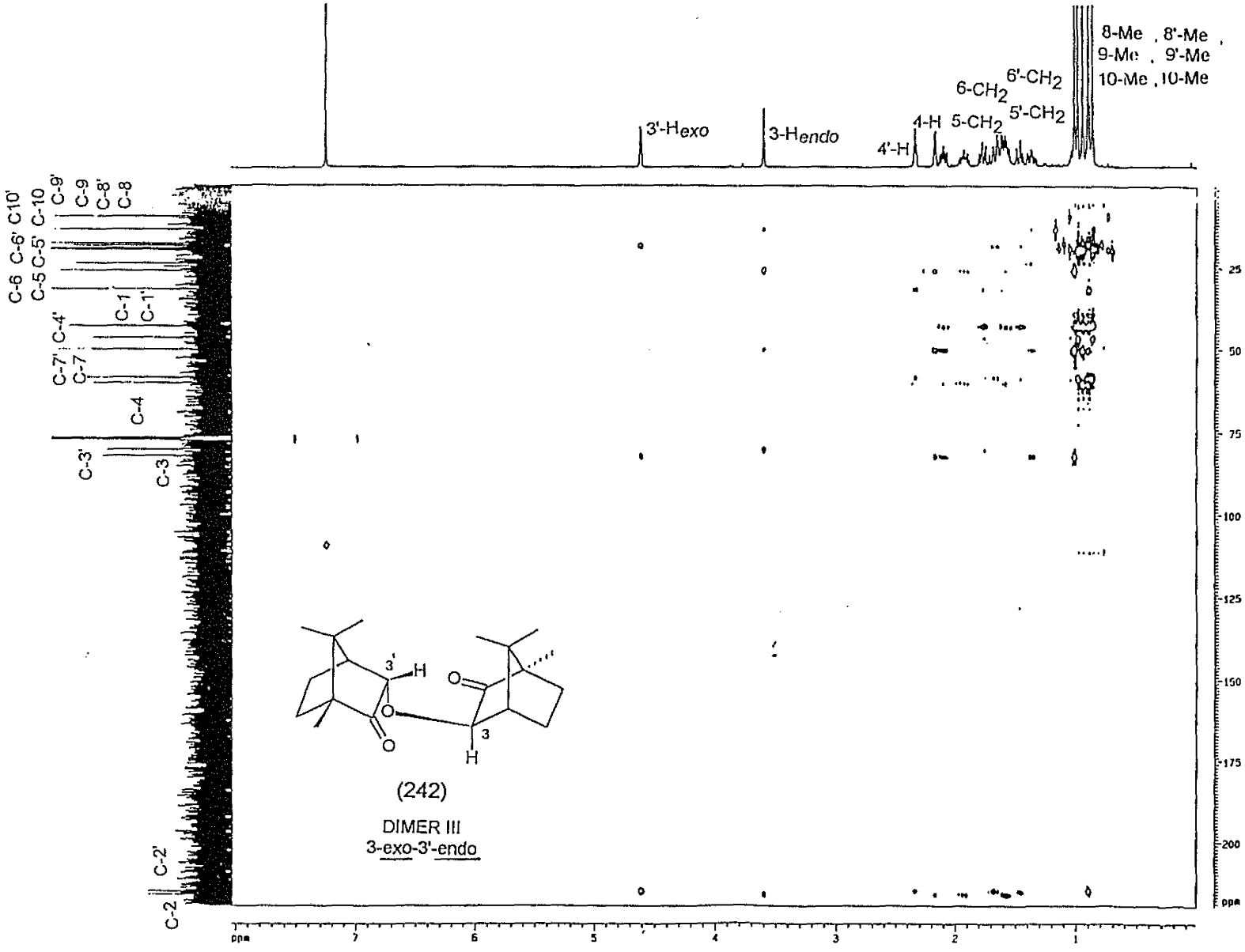



FIGURE 37. The HMBC NMR spectrum of dimer III (**242**) in $CDCl_3$

As indicated above, the α-ketol (**138**) appears to form "dimer II" exclusively. This selectivity may be explained by considering the relative instantaneous populations of the equilibrating systems and the greater accessibility of the sterically less hindered 3-*exo*-alcohol systems (**137**) and (**137a**). Thus, the protonated ketol (**137a**), once formed *via* the enediol (**I**), is more likely to act as an electrophile than the sterically hindered 2-*exo*-analogue (**138a**) and is consequently attacked by the presumably concentrated precursor (**138**) (**Scheme 64**). On the other hand, the less hindered 3-*exo*-hydroxycamphor (**137**) more readily attacks the oxonium ion (**138a**) to give "dimer I" and, in its protonated form (**137a**), reacts with the α-ketol (**138**) to afford "dimer II". "Dimer III" arises from condensation of the α-ketol (**137**) with its protonated derivative (**137a**). The observed regio- and stereoselectivity of dimer formation is outlined in **Scheme 65**, while the comparative NMR data for the three, isolated dimers is summarised in **Table 3**.

A fourth possibility, the 2-*endo*-2'-*exo*-linked "dimer IV" (**243**) was not observed, the unfavourable steric demand at C-2 in both monomeric units presumably inhibiting formation of an ether link.

**Table 3: 400 MHz $^{1}H$ and 100 MHz $^{13}C$ NMR data (ppm) for the dibornyl ethers (239), (240) and (242) in $CDCl_3$**

| Nucleus[a] | 239 ("Dimer I") | 240 ("Dimer II") | 242 ("Dimer III") |
|---|---|---|---|
| 8-, 8′-, 9′-, 9′-Me, 10- and 10′-Me | 0.82, 0.84, 0.85, 0.88 and 0.96 (18H, 5 x s) | 0.82, 0.86, 0.95, 0.96, 0.97 and 0.99 (18H, 6 x s) | 0.83, 0.90, 0.95, 0.99 and 1.01 (18H, 5xs) |
| 5-, 5′, 6- and 6′-$CH_2$ | 1.22 - 2.01 (8H, m[b]) | 1.36 - 1.89 (8H, multiplets m[b]) | 1.32 - 2.16 (8H, m[b]) |
| 4-H and 4′-H | 2.08 and 2.11 (2 x d) | 2.05 (1H, d) and 2.31 (1H, t) | 2.18 (1H, d) and 2.33 (H, t) |
| 2′-H and 3-H | 3.88, 3.92 (2H, 2 x s) | 3.60 (1H, s, 2-H) and 4.25 (1H, d, 3′-H) | 3.60 (1H, s, 3-H) and 4.61 (1H, d, 3′-H) |
| C-10 and C-10′ | 8.9 and 12.9 | 9.3 and 10.5 | 9.4 and 13.4 |
| C-9 and C-9′ | 17.0 and 19.3 | 18.5 and 18.7 | 17.8 and 19.1 |
| C-8 and C-8′ | 19.7 and 21.1 | 18.6 and 19.9 | 19.4 and 19.8 |
| C-7 and C-7′ | 42.6 and 46.2 | 42.6 and 46.1 | 42.9 and 46.5 |
| C-6 and C-6′ | 23.9 and 24.8 | 20.7 and 21.3 | 18.4 and 23.7 |
| C-5 and C-5′ | 25.8 and 28.9 | 31.8 and 33.7 | 25.9 and 31.7 |
| C-4 and C-4′ | 49.1 and 59.9 | 48.8 and 59.2 | 46.5 and 50.1 |
| C-3 and C-2′ | 84.3 and 85.3 | 217.8 and 217.9 | 80.4[c] and 82.3[c] |
| C-2 and C-3′ | 216.9 and 218.1 | 85.6 and 81.7 | 215.9[d] and 217.3[d] |
| C-1 and C-1′ | 50.2 and 57.2 | 50.0 and 58.4 | 58.4 and 60.1 |

[a]The order of citation does not imply signal assignment. [b]Complex of multiplets. [c]C-3 and C-3′. [d]C-2 and C-2′.

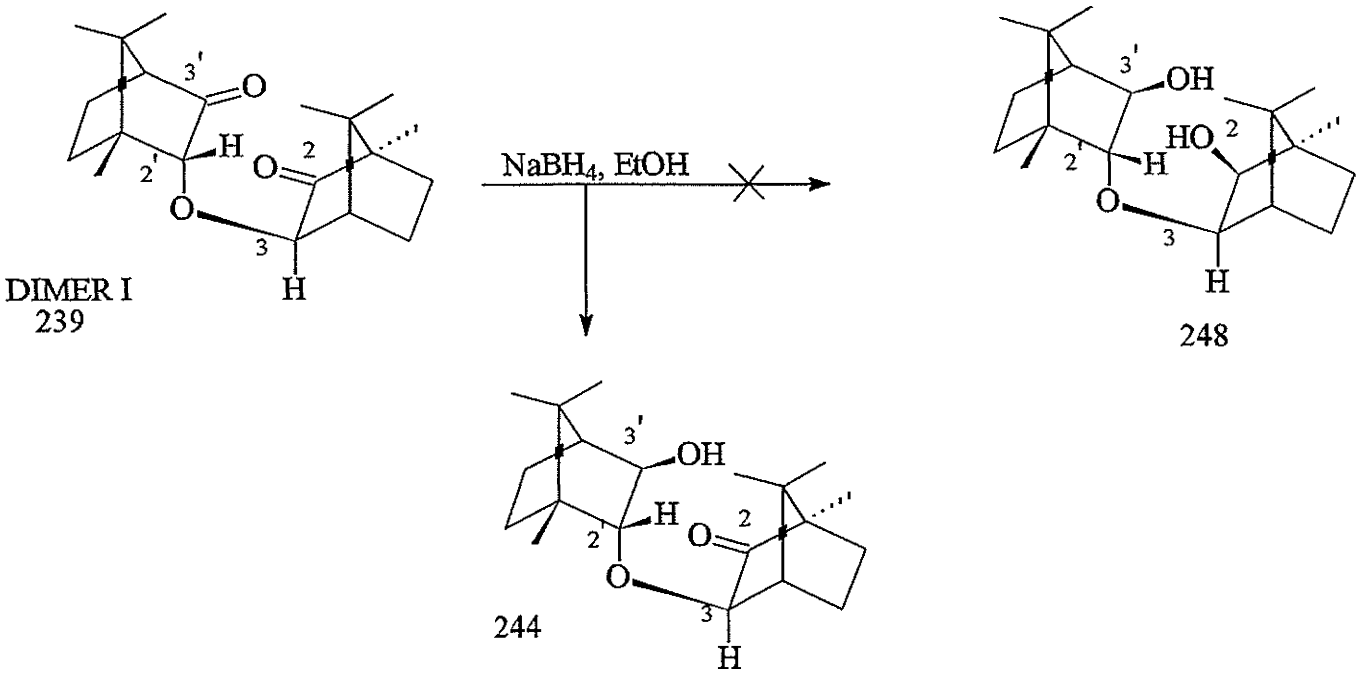
### 2.4.2 Preparation of Dibornyl Reagents

As previously mentioned, (**Section 2.4.1**) it was envisaged that, following reduction of the diketones (**239**) and (**240**), the resulting diols could be derivatised to "BINAP"-type reagents. The $NaBH_4$ reduction of "dimer I" (**239**) afforded a partially reduced monohydroxy derivative (**244**), instead of the expected diol (**248**) (**Scheme 66**). Recrystallisation of the monohydroxy component from petroleum ether (80 - 100°C) afforded needle-like crystals, which were identified as the 3′-*exo*-hydroxy derivative (**244**) . Single crystal X-ray analysis (**Figure 38**) confirmed the structure of the monohydroxy compound (**244**) and, perhaps more importantly, the regio- and stereochemistry of the 3-*exo*-2′-*endo* ether link in the precursor, "dimer I", which had previously been deduced from the NMR data.† Selective reduction of the 3′- rather than the 2-carbonyl group, under these conditions, undoubtedly reflects the steric hindrance at C(2) in camphor systems.

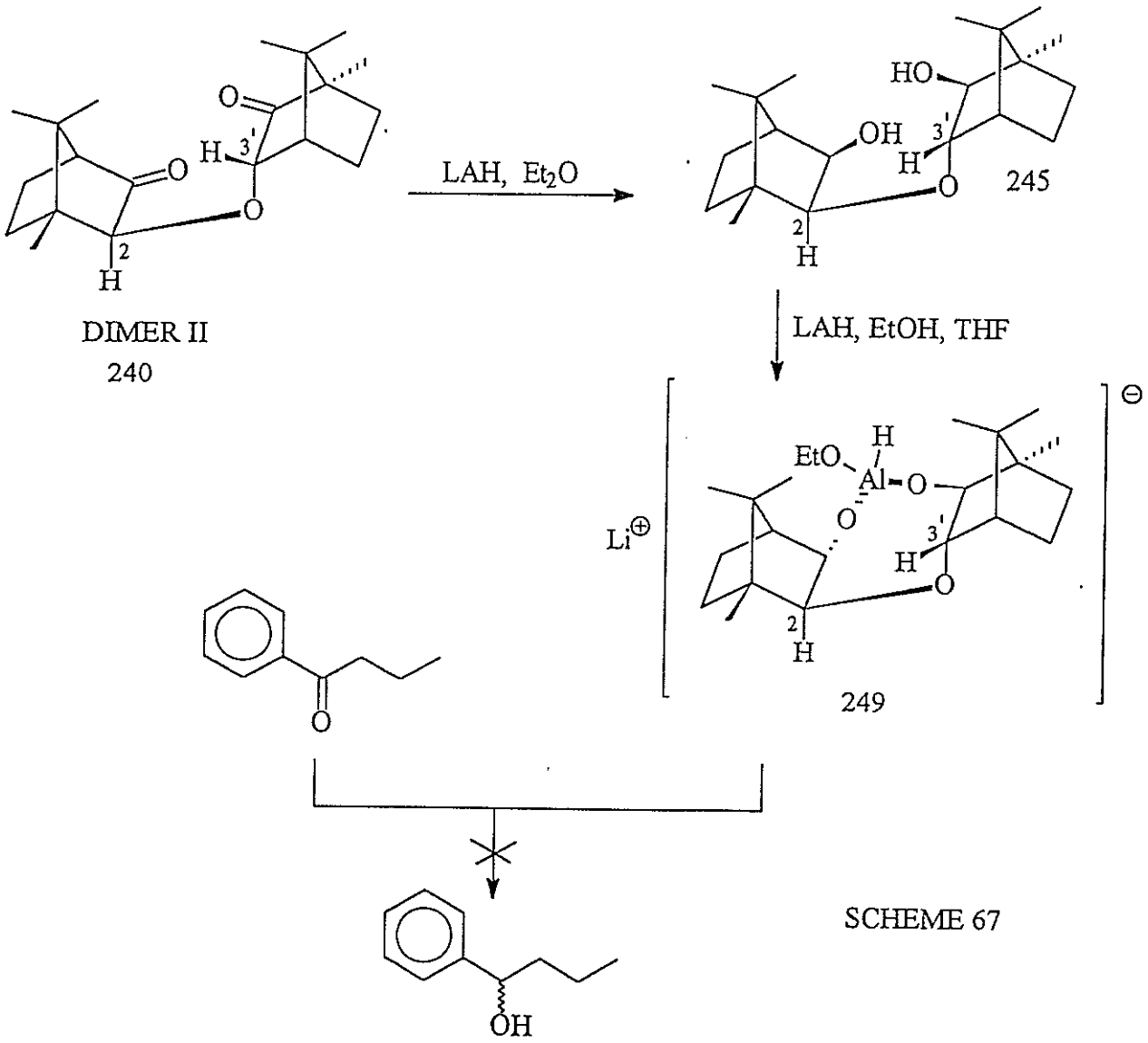
The exclusive formation of "dimer II" (**240**) by 2-*exo*-hydroxy-3-bornanone (**138**) made this dimer a more attractive choice for derivatisation. The dihydroxy derivative (**245**) was furnished by LAH reduction of "dimer II" (**240**) in diethyl ether (**Scheme 67**). The "BINAP" aluminium hydride reagent (**44**), prepared *in situ* at low temperature, has been reported to exhibit complete topological control in the reduction of carbonyl compounds. Following the reported procedure, the diol (**245**) was treated with $LiAlH_4$ and ethanol in THF in an attempt to produce the chiral aluminium hydride (**249**); butyrophenone (**246**) was then added, but work-up and chromatography simply furnished the diol (**247**) and butyrophenone (**Scheme 67**). It is possible

†One and two dimensional NMR spectroscopic techniques have been used to establish the regio- and stereochemistry of the isomeric dibornyl ethers.

that the *in situ* preparation of the reagent was unsuccessful but, due to time constraints, this could not be investigated further.




SCHEME 66




DIMER II
240

SCHEME 67

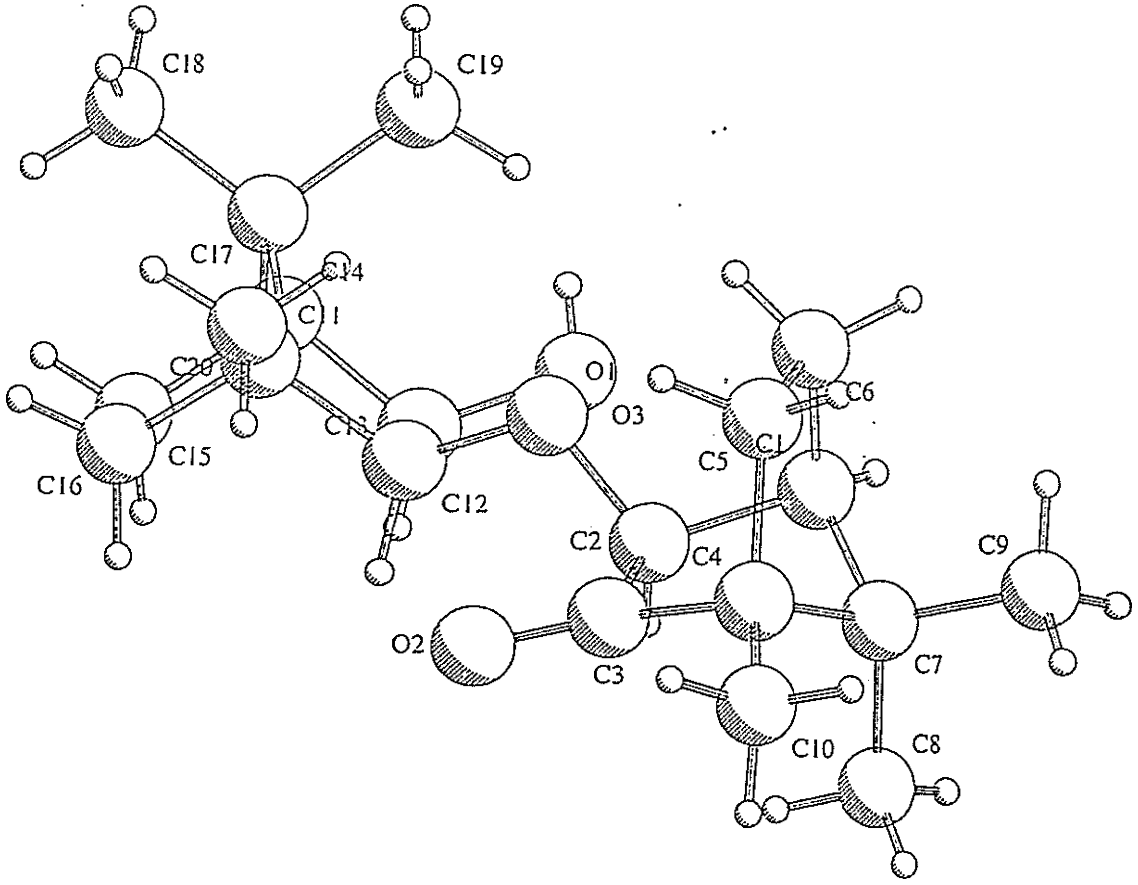



FIGURE 38. Crystal structure of the 3'-*exo*-hydroxy derivative of "dimer I' (**239**), showing the crystallographic numbering.

## 2.5 CONCLUSION

This research has been concerned largely with the development of new asymmetric syntheses of α-amino acids and, to this end, various approaches have been investigated.

Conformationally rigid imino lactones, prepared from glycine and regioisomeric camphor-derived α-ketols, were identified as potentially useful intermediates. Several strategies for the synthesis of these intermediates were explored, a step-wise cyclisation finally affording the regioisomeric imino lactones. With access to the derived intermediates established, their stereo-directing potential in α-alkylation of the glycine moiety was explored. The potassium enolates of the imino lactones, generated using potassium *tert*-butoxide, were typically alkylated using alkyl bromides. Although the 2-imino lactone proved disappointing by persistently affording the α,α-dialkylated derivatives, the regioisomeric 3-imino lactone gave the α-alkylated products in diastereoselectivities ranging from moderate (43% d.e.) for methyl, to complete topological control (> 99% d.e.) for some of the larger groups. Acid-catalysed hydrolysis of the pentylated 3-imino lactone furnished (*R*)-(+)-2-aiminoheptanoic acid, polarimetric analysis of which permitted the configuration at the new stereogenic centre to be established. This configurational assignment was consistent with the transition state proposal involving *endo* alkylation of the potassium enolate; computer modelling of the enolate shows *exo* attack to be sterically hindered by the 8-methyl group of the camphor skeleton. Careful NMR analysis of the monoalkylated imino lactones (using chemical shift, coupling constant and NOE data) revealed long-range (5-bond) coupling between the *exo*-α and *endo*-4-protons, thus providing a convenient spectroscopic probe for determining the configuration of the new stereogenic centre.

Given the obvious success of this approach to the synthesis of optically pure α-amino acids, attention was given to developing a method for the enantiomer beneficiation of racemic amino acids, but the preference of α-substituents appears to inhibit the crucial cyclisation step. Chiral discrimination observed in Baylis-Hillman reactions of a novel bornyl acrylate ester with a range of aldehydes varied from 5% d.e. to 59% d.e., the results indicating that stereoselectivity is influenced by both steric and polar factors.

Two further studies were initiated. The first, involving attempts to explore the use of ketopinic acid derivatives in the asymmetric synthesis of α-amino acids, proved disappointing, although two, isomeric, acyclic *N*-carbobenzyloxy glycine derivatives with some potential, were prepared. In the second, an extension of previous work on the acid-catalysed dimerisation of camphor-derived α-ketols, a novel dicarbonyl dibornyl ether was isolated and characterised. Reduction of the dicarbonyl dimers to the corresponding diols for use as "BINAP" analogues was also investigated. Complete reduction of one of the dimers was achieved with $LiAlH_4$, while treatment of an isomeric system with $NaBH_4$ gave a partially reduced, monohydroxy derivative. Single crystal X-ray analysis of the latter product provided independent confirmation of the regio- and stereochemistry of the ether link in this compound and its precursor.

Future work is expected to address:–

(i) monoalkylation of the 2-imino lactone, the preparation of alkylidine derivatives of the regioisomeric camphor-derived imino lactones as precursors for the preparation of chiral α-amino acids;

(ii) the synthesis of racemic camphor-derived imino lactones in α-amino acid, essential to the enantiomer beneficiation methodology; and

(iii) the application of camphor-derived diols as "BINAP" analogues in the preparation of chiral reagents.

# CHAPTER THREE: EXPERIMENTAL

## 3.1 GENERAL

Melting points were determined using a Kofler hot-stage apparatus, and are uncorrected. The $^1$H NMR spectra were typically run on a Bruker AMX400 spectrometer, using $CDCl_3$ and DMSO-$d_6$ as solvents. Spectra recorded in $CDCl_3$ were calibrated on the chloroform signals (7.25 ppm for $^1$H and 77.00 for $^{13}$C), while spectra run in DMSO-$d_6$ were calibrated using the DMSO signals (2.5 ppm for $^1$H and 39.7 ppm for $^{13}$C). IR spectra were recorded on a Perkin Elmer 180 spectrometer using KBr discs, liquid films or nujol mulls. Low-resolution mass spectra were obtained using a Hewlett-Packard 5988A mass spectrometer, and high-resolution mass spectra using a Kratos MS 80RF mass spectrometer (Cape Technikon Mass Spectrometry Unit). Optical rotations were measured on a Perkin Elmer 141 polarimeter.

Semi-preparative HPLC separations were achieved using a Spectra-Physics P100 HPLC with a Spectra-Physics UV100 detector set to 280 nm. The column used was a Whatman Magnum Partisil (10). Flash chromatography[113] was carried out on Merck silica gel 60 [particle size 0.040 - 0.063 nm (230 - 400 mesh)]. Preparative layer chromatography (PLC) was achieved using Merck silica gel $60PF_{254}$. Routine thin layer chromatography (TLC) was performed on pre-coated Merck silica gel $F_{254}$ plates, with inspection under UV light or exposure to iodine vapour for visualisation of compounds.

Solvents were dried using procedures described by Perrin and Armarego[114].

(1) Diethyl ether and tetrahydrofuran were dried over Na wire, and distilled from Na wire

under $N_2$ with benzophenone as an indicator.

(2) Benzene and toluene were distilled over CaH under $N_2$.

(3) Dimethylformamide and triethylamine were refluxed over 4Å molecular sieves, distilled under reduced pressure, and stored over 4Å molecular sieves.

(4) Ethanol was refluxed over $Mg(OEt)_2$.

(5) Pyridine was dried over KOH overnight and distilled from fresh KOH.

Except for the asymmetric Baylis-Hillman reactions, all asymmetric induction reactions were conducted in flame-dried glassware and under an inert atmosphere using dried, spectroscopic grade nitrogen. The computer modelling was conducted on a Pentium microcomputer using the "HYPERCHEM®" software package supplied by Autodesk Inc.

Where convenient, the atom numbering used in quoting the NMR data follows the systematic nomenclature. Given the complexity of the systematic nomenclature for the camphor imino lactone derivatives, trivial names are used and, where necessary, the numbering is indicated by a suitable example.

## 3.2 SYNTHETIC PROCEDURES

### 3.2.1 Preparation of the 2-imino lactone (131) and the 3-imino lactone (132)

*Camphorquinone* (**139**).–

Selenium dioxide (50 g, 0.45 mol) was added to a stirred solution of (1*R*)-(+)-camphor (40 g, 0.26 mol) in acetic anhydride (40 ml) and the resulting suspension was boiled under reflux for 5 h and then left stirring overnight at room temperature. The resultant black selenium powder was removed by filtration and the filtrate was neutralised by adding 10% aqueous sodium hydroxide solution. The yellow precipitate was filtered off, washed with of water (100 ml) and suction dried. The semi-dry material was dissolved in petroleum ether (80 - 100°C boiling range) and the residual aqueous layer was separated off. The organic layer was concentrated *in vacuo* until crystallisation began, and the solution was then stored overnight at 10°C to facilitate complete crystallisation. Filtration gave bright yellow needles of camphorquinone (**139**) (34 g; 74%); m.p. 195 - 196°C (lit.[115] 183 - 186°C); $\nu_{max}$ (KBr/cm$^{-1}$) 1770 and 1750 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.90, 1.03 and 1.07 (9H, 3 x s, 8-, 9-, and 10-Me), 1.56 - 2.19 (4H, m, 5- and 6-$CH_2$) and 2.59 (1H, d, 4-H).

*3*-Exo-*hydroxy-2-bornanone* (**137**).–

A mixture of camphorquinone (**139**) (6.14 g, 36.9 mmol) in absolute ethanol (200 ml) and activated Raney Nickel (3.50 g) was stirred at room temperature under a hydrogen atmosphere(at atmospheric pressure)overnight. Approximately 0.8 Lof hydrogen was taken up by the reaction.The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo*.Flash chromatography of the residue[elution with hexane:$Et_2O$ (9:1)]

afforded 3-*exo*-hydroxy-2-bornanone (**137**) (4.20 g; 70%); m.p. 206 - 209°C (lit.,[104] 209 - 211°C; $\nu_{max}$ (KBr/cm$^{-1}$) 3560 (OH) and 1740 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.90, 1.06, 1.09 (9H, 3 x s, 8-, 9- and 10-Me); 1.30 - 2.10 (4H, 5- and 6-$CH_2$), 2.16 (1H d, 4-H), 2.80 (1H, br s, OH, $D_2O$ exchangeable) and 3.50 (1H, s, 3-H); $\delta_C$ (100 MHz; $CDCl_3$) 10.3, 18.9 and 20.1 (C-8, C-9 and C-10), 21.3 and 33.9 (C-5 and C-6), 47.0 (C-1), 49.0 (C-7), 59.2 (C-4), 80.3 (C-3) and 211.3 (C=O).

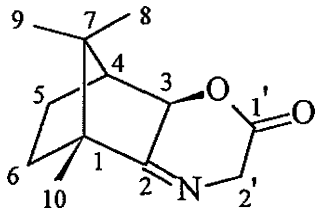
N-*(carbobenzyloxy)glycine 2-Oxo-3*-exo-*bornyl ester* (**160**).–

Carbonyldiimidazole(2.43 g,15 mmol) was added to a solution of *N*-(carbobenzyloxy)-glycine (3.14 g, 15 mmol) in dry DMF (15 ml). After 30 min., 3-*exo*-hydroxy-2-bornanone (**137**) (2.52 g, 15 mmol) was added and the reaction mixture was stirred at room temperature overnight. the solvent was removed *in vacuo*, and the residue was purified by flash chromatography [elution with hexane-EtOAc (1:1)] to afford, as a clear oil, N-*(carbobenzyloxy)glycine 2-Oxo-3*-exo-*bornyl ester*(**160**) (5.18 g; 96%), (Found $M^+$, 359.1743. $C_{20}H_{25}O_5N$ requires *M*, 359.1733); $\nu_{max}$ (liquid film/cm$^{-1}$) 1750 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.91, 0.92 and 0.97 (9H, 3 x s, 8-, 9- and 10-Me), 1.25 - 2.00 (5H, m, 4-H, 5- and 6-$CH_2$), 2.78 (1H, s, NH), 3.93 - 3.96 (2H, m, C*H*$_2$NH), 4.65 (1H, s, 3-H), 4.80 - 5.32 (2H, m, $CH_2Ph$) and 7.54 - 7.34 (5H, m, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 9.0 (C-10), 20.9 (C-9), 21.0 (C-8), 25.2 (C-5), 28.4 (C-6), 42.8 ($CH_2NH$), 48.3 (C-1), 57.0 (C-7), 59.8 (C-4), 67.1 ($CH_2Ph$), 77.5 (C-3), 128.1, 128.2, 128.5 and 136.2 (ArC), 169.4 and 156.2 ($O_2CCH_2$ and $NHCO_2$) and 212.2 (C-2); *m/z* 359 ($M^+$,2.5%).

N-(*Benzyloxycarbonyl)glycine* (**157**).–

To a stirred solution of glycine (7.5 g, 0.1 mol) in $H_2O$ (30 ml), 0.5 *M* NaOH (20 ml) was added and the mixture was then cooled in an ice-water bath. Benzyl chlorocarbonate (18.7 g) and 2 *M* NaOH (55 ml) were added in portions over 30 min. The pH was adjusted to *ca.* pH 10, and the mixture was extracted with $Et_2O$ ( 4 x 50 ml ). The aqueous solution was acidified with 5 *M* HCl (20 ml) and the mixture extracted with $Et_2O$ (3 x 40 ml). The combined organic extracts were dried (anhyd. $MgSO_4$) and the solvent was evaporated *in vacuo*, to afford *N*-(carbobenzyloxy)glycine (**157**) (19.2 g; 92%); m.p. 120 - 121 °C (lit.,[61] 120 - 122°C); $\nu_{max}$ (KBr/$cm^{-1}$) 1780 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 4.00 and 4.35 (4H, 2 x s, 1'- and 2-$CH_2$), 5.91 - 5.21 (5H, m, Ar-H) and 5.25 (1H, NH).

*The 2-imino lacto*ne (**131**).†–




(131)

A solution of the *N*-(carbobenzyloxy)glycine ester (**160**) (5.76 g, 16 mmol) in absolute ethanol (40 ml) was placed in a round-bottomed flask fitted with gas inlet and outlet tubes.The air was displaced by a slow stream of $N_2$ and a10% palladium on charcoal catalyst (0.74 g ; 0.074 g palladium metal ) was added , followed by a slow stream of $N_2$ for 5 min.

†The systematic name for the 2-imino lactone (**131**), excluding stereochemical designations is:– 7,11,11-trimethyl-2-oxa-5-azatricyclo[4.4.$1^{7,10}$]undec-5-en-2-one.

A slow stream of $H_2$ was then introduced and the catalyst was kept in suspension by vigorous stirring. The escaping gas was led through a filtered,saturated solution of $Ba(OH)_2$ in water. After the evolution of $CO_2$ ceased (as evidenced by ceasure of $Ba(CO_3)_2$ being formed), the reaction mixture was warmed on a water bath to 50°C until no more $CO_2$ was detected in the escaping gas. The reaction mixture was cooled to room temperature and the flow of $H_2$ was terminated. The reaction mixture was flushed with $N_2$ to remove the remaining $H_2$, and the catalyst was filtered off under a blanket of $N_2$. The solvent was evaporated *in vacuo*, and the residue flash chromatographed [elution with hexane-EtOAc (1:1)] to afford, as a yellow oil, the *2-imino lactone* (131) (2.98 g; 90%), (Found: $M^+$, 207.1258. $C_{12}H_{17}NO_2$ requires *M*, 207.1259); $\nu_{max}$ (liquid film/$cm^{-1}$) 1745 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.72, 0.89 and 0.97 (9H, 3 x s, 8-, 9- and 10-Me), 1.30 - 2.01 (4H, m, 5-$CH_2$ and 6-$CH_2$ ), 2.18 (1H, d, *J* 4.4 Hz, 4-H), 3.85 (1H, dd, *J* 1.7 and 17.8 Hz, 2'-$H_{exo}$), 4.42 (1H, d, 17.8Hz, 3-H) 4.43 (1H, d, *J* 1.6 Hz, 2'-$H_{endo}$); $\delta_C$ (100 MHz; $CDCl_3$) 9.7, 19.5 and 19.8 ( C-10, C-9 and C-8), 25.2 and 29.3 (C-5 and C-6), 47.3 (C-4), 49.6 and 52.4 (C-1 and C-7), 52.5 (C-2'), 79.5 (C-3), 168.8 (C-2) and 183.6 (C-1'); *m/z* 207 ($M^+$, 0.3%).

*3,3-(Ethylenedioxy)-2-bornanone* (140).–

A solution of camphorquinone (139) (20.0 g, 0.12 mol), ethylene glycol (15.0 g, 0.24 mol) and *p*-toluenesulfonic acid (1.20 g) in anhydrous benzene (96 ml) was boiled under reflux in a reaction vessel equipped with a Dean Stark trap. After approximately 2.5 ml of water was collected, the reaction mixture was washed with 1*M* NaOH (80 ml) and $H_2O$ (80 ml). The organic layer was separated, dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The residual oil was stored ( for 2 d.) at10°C to facilitate crystallisation. The solid was filtered

off and recrystallised from hot EtOH to afford transparent needles of 3,3-(ethylenedioxy)-2-bornanone (**140**) (11.68 g; 46%); m.p. 86 - 88°C (lit.[116] 88°C); $\delta_H$ (400 MHz; $CDCl_3$) 0.86, 0.94 and 0.98 (9H, 3 x s, 8-, 9- and 10-Me),1.51 - 1.97 (5H, m, 4-H, 5- and 6-$CH_2$) and 3.39 - 4.26 (4H, m,$OCH_2CH_2O$).Concentration and flash chromatography [elution with hexane-EtOAc (8:2)] of the mother liquor gave 2,2;3,3-bis(ethylenedioxy)bornane (**142**) (5.9 g, 20%), m.p. 120°C ; $\nu_{max}$ (KBr/$cm^{-1}$) 1740 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.17, 0.86 and 0.79 (9H, 3 x s, 8-, 9- and 10-Me), 1.30 - 1.98 (5H, m, 4-H, 5- and 6-$CH_2$) and 3.27 - 3.94 (4H, complex of multiplets, $OCH_2CH_2O$); $\delta_C$ (100 MHz; $CDCl_3$) 9.9 (C-10), 20.7 (C-9), 20.9 (C-5), 21.1 (C-8), 29.3 (C-6), 44.5 (C-7), 53.8 (C-1), 53.4 (C-4) and 64.3, 64.5, 64.9 and 65.9 ($OCH_2CH_2O$), 114.3 (C-3) and 124.9 (C-2) ; *m/z* 254 ($M^+$, 0.08%).

*3,3-Ethylenedioxy-2*-exo-*hydroxybornane* (**141**).[104]–

A solution of 3-3-(ethylenedioxy)-2-bornanone (**140**) (2.0 g, 10 mmol) in anhydrous $Et_2O$ (50 ml) was added with stirring to a slurry of lithium aluminium hydride ($LiAlH_4$) (0.45 g) in anhydrous ether (50 ml) at 0°C, and the mixture was boiled under reflux for 2 h. Excess $LiAlH_4$ was decomposed by the addition of moist ether, and the resulting precipitate removed by filtration. The organic layer was dried (anhyd. $MgSO_4$), concentrated under reduced pressure and chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc,(9:1)] to afford 3,3-ethylenedioxy-2-*exo*-hydroxybornane(**141**)(1.48 g;70%); $\nu_{max}$ (liquid film/$cm^{-1}$) 3530 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.82, 0.89 and 1.08 (9H,3 x s,8-, 9- and 10-Me),1.12 -1.74(5H,m, 4-H, 5- and 6-$CH_2$), 2.34(1H,d, OH), 3.27(1H,d, 2-H); $\delta_C$ (100 MHz;$CDCl_3$)11.3(C-10),20.3(C-9),21.1(C-8),27.1(C-5),32.3(C-7),33.7(C-6),45.5 (C-1),52.9(C-4),64.5 and 66.3($OCH_2CH_2O$), 86.5(C-2) and 128.5 (C-3); *m/z* 212 ($M^+$, 7.4%).

*2-Exo-hydroxy-3-bornanone* (**138**).–

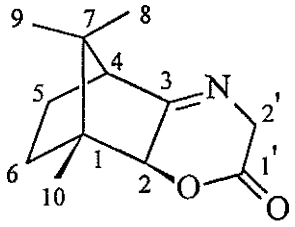
To a solution of 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane (**141**) (3.0 g, 15 mmol) in THF (60 ml) was added dilute HCl (1*M* ; 15 ml) and the resulting mixture was boiled gently under reflux for 2 h. The resulting solution was concentrated *in vacuo* and the residue was washed with water and extracted into EtOAc (4 x 30 ml). The dried organic layers were concentrated and flash chromatographed [elution with hexane-$Et_2O$ (9:1)] to afford, as white crystals, 2-*exo*-hydroxy-3-bornanone (**138**) (2.3 g; 90%); m.p. 225°C (lit.,[104] 228 - 230°C); $\nu_{max}$ (KBr/$cm^{-1}$) 3550 (OH) and 1750 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.92, 1.01 and 1.03 (9H, 3 x s, 8-, 9- and 10-Me), 1.24 - 1.93 (4H, 5- and 6-$CH_2$), 2.13 (1H, d, 4-H), 2.56 (1H, br s, OH) and 3.52 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 10.2 (C-10), 18.9 (C-9), 20.3 (C-5), 21.1 (C-8), 33.9 (C-6), 46.6 (C-1), 49.2 (C-7), 58.7 (C-4), 79.5 (C-2) and 218.5 (C-3).

N-*(Carbobenzyloxy)glycine 3*-oxo-*2-exo-bornyl ester* (**162**).–

To a solution of *N*-(carbobenzyloxy)glycine (2.00g, 9.5 mmol) in anhdrous DMF (10 ml), was added carbonyldiimidazole (1.55 g, 9.5 mmol), and the mixture stirred for 30 min. The resulting solution was added dropwise to a solution of 2-*exo*-hydroxy-3-bornanone (**138**) (1.61 g, 9.5 mmol) in DMF (10 ml). The solution was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and flash chromatography of the residue [elution with hexane-EtOAc (1:1)] afforded, as a clear oil, the N-*(carbobenzyloxy)glycine ester* (**162** )(3.18 g; 96%),(Found: $M^+$ 359.1743; $C_{20}H_{25}O_5N$ requires *M*: 359.1733); $\nu_{max}$ (liquid film/$cm^{-1}$) 1750 ( C=O) ; $\delta_H$ (400 MHz; $CDCl_3$) 0.89, 0.91 and 0.97 (9H, 3 x s, 8-, 9- and 10-Me) , 1.25 - 2.20 (5H, m, 4-H, 5- and 6-$CH_2$), 2.78 (1H, NH),

3.95 - 3.98 (2H,m, C$H_2$NH), 4.64 (1H, s, 2-H), 4.82 - 5.32 (2H, m, $CH_2$Ph) and 7.25 - 7.32 (5H,m, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 8. (C-10), 20.1 (C-9), 21.0 (C-8), 25.2 (C-5), 28.6 (C-6), 42.8($CH_2NH_2$), 48.3(C-1), 57.2(C-7), 67.0($CH_2$Ph), 77.5(C-2),128.1,128.2,128.5 and 136.2 (ArC), 169.3 (OC$CH_2$NH), 210.0, 211.4 and 219.8 (3 x C=O) ; *m/z* 359 ($M^+$, 2.5%).

*The 3-imino lacto*ne (**132**).†–




(132)

A suspension of ester (**162**) (3.59 g, 10 mmol) and 10% palladium on charcoal (0.42 g) in absolute ethanol (25 ml) was stirred under hydrogen for 30min. according to the procedure described for the 2-imino lactone (**131**). Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] yielded, as a clear oil, the *3-imino lactone* (**132**) (1.76 g, 85%); (Found:$M^+$, 207.1258;$C_{12}H_{17}NO_2$ requires: *M*, 207.1259);$\nu_{max}$ (liquid film/$cm^{-1}$)1720(C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.69, 0.82 and 1.89 (9H, 3 x s, 8-, 9- and 10-Me), 1.29 - 1.75 (4H, m, 5- and 6-$CH_2$), 2.29 (1H, d, *J* 4.3 Hz, 4-H), 3.77 (1H, d, *J* 17.9 Hz, 2-$H_{endo}$), 4.20 (1H, d, *J* 1.6 Hz, 2-H), 4.31 (1H, dd, *J* 1.6 and 17.8 Hz, 2-$H_{exo}$); $\delta_C$ (100 MHz; $CDCl_3$) 9.5, 18.9 and 19.6 (C-8, C-9 and C-10), 21.3 and 33.6 (C-5 and C-6), 48.9 and 48.5 (C-1 and C-7), 52.2 (C-2′), 52.9 (C-4), 81.3 (C-2),168.4 (C-3) and 181.4 (C-1′); *m/z* 207 ($M^+$,0.4%).

†The systematic name for the 3-imino lactone (**132**), excluding stereochemical designations, is:– 10,11,11-trimethyl-2-oxa-5-azatricyclo[4.4.$1^{7,10}$]undec-5-en-2-one.

*PROCEDURES used in ATTEMPTED PREPARATIONS of the IMINO LACTONES*

*Attempted preparation of the 2-imino lactone* (**131**).–

The α-ketol (**137**) (1.5 g, 8.9 mmol) and glycine (0.67 g, 8.9 mmol) were heated neat. Flash chromatography [elution with hexane-EtOAc (9:1)] of the mixture afforded the unreacted alcohol (**137**) (1.23 g).

*Ethyl glycinate hydrochloride* (**145**).–

Dry HCl was bubbled through a stirred suspension of glycine (15 g, 0.2 mol) in absolute ethanol (100 ml) until the solution became clear. The reaction mixture was then boiled under reflux for15 min.The solution was cooled in an ice bath and the white crystals which formed were filtered and washed with cold ethanol.Recrystallisation of the crude product from ethanol gave ethyl glycinate hydrochloride(**145**)(60 g;60 %); m.p.142°C(lit.,[54]142°C); $\delta_H$ (400 MHz; $CDCl_3$) 1.40 (3H, t, $CH_3$), 4.03 (2H, $NH_3$) and 4.41 (2H, q, $CH_2NH_2$).

*Attempted preparation of 2-(carbethoxymethylimino)-3-*exo*-hydroxybornanone* (**146**).–

A mixture of the α-ketol(**137**)(1.0 g,6 mmol) and ethyl glycinate hydrochloride(**145**)(0.83g, 6 mmol) in dry benzene (30 ml) was boiled under reflux overnight with a catalytic quantity of *p*-toluenesulfonic acid (0.1 g). Work-up and flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded the unreacted α-ketol (**137**) quantitatively.

*Attempted preparation of 2-[(benzyloxycarbonyl)methylimino]-3-*exo*-hydroxybornane* (**150**).–Method 1.

The α-ketol (**137**) (1.0 g, 6 mmol), benzyl glycinate (**147**) (0.98 g, 6 mmol) and *p*-toluene-

sulfonic acid (0.1 g) were reacted in benzene (30 ml), following the procedure outlined in the attempted preparation of 2-(carbethoxymethylimino)-3-*exo*-hydroxybornane (**146**). Work-up and flash chromatography [elution with hexane-EtOAc (4:1)] afforded the α-ketol (**137**) (0.8 g).

Method 2.

To a solution of the α-ketol (**137**) (1.00 g, 6 mmol) and benzyl glycine (0.96 g, 6 mmol) in dry benzene (30 ml), $BF_3.Et_2O$ (0.85 g, 6 mmol) was added. The reaction mixture was boiled under reflux. Work-up and flash chromatography [elution with hexane-EtOAc (9:1)] afforded the unreacted α-ketol (**137**) quantitatively.

*Attempted preparation of glycine 2-oxo-3-*exo*-bornyl ester* (**161**).–

The *N*-(carbobenzyloxy)glycine ester (**160**) (5.76 g, 16 mmol) was added to a 33% solution of HBr in acetic acid (10 ml) and the resulting mixture was stirred at room temperature for 20 min. After neutralising with a 1*M* NaOH solution, the aqueous layer was washed with EtOAc (4 x 20 ml). The organic layer and the EtOAc washings were combined and the solvent was evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded the α-ketol (**137**) (2.3 g).

*Attempted preparation of 3-*exo*-hydroxybornane-2-thione* (**152**).–

Method 1.

A mixture of the α-ketol (**137**) (1.00 g, 6 mmol) and Lawesson's reagent (0.32 g) in anhydrous xylene(10 ml) was boiled under reflux, under $N_2$, for *ca.*24 h.Work-up and flash

chromatography [elution with hexane-EtOAc (4:1)] afforded the unreacted α-ketol (**137**) (0.86 g).

Method 2.

To a solution of the α-ketol (**137**) (0.98 g, 6 mmol) and $P_4S_{10}$ (4 g, 9 mmol) was added diglyme (20 ml) and the mixture was stirred at 120°C for 5 h. Work-up and flash chromatography [elution with hexane-EtOAc (4:1)] furnished the unreacted α-ketol (**137**) quantitatively.

*Attempted preparation of bornane-2,3-dithione* (**154**).–

Method 1.

Following the procedure used for the attempted preparation of 3-*exo*-hydroxybornane-2-thione (**152**) (Method 1), camphorquinone (**139**) (0.99 g, 6 mmol) was refluxed with Lawesson's reagent (0.64 g). Work-up and flash chromatography afforded the unreacted camphorquinone (**139**) quantitatively.

Method 2.

Following the procedure used for the attempted preparation of 3-*exo*-hydroxybornane-2-thione (**152**) (Method 2), a mixture of camphorquinone (**139**) (1.00 g, 6 mmol) and $P_4S_{10}$ (8.12 g, 18 mmol) in diglyme (30 ml), was stirred for 5 h at 120°C. Work-up and flash chromatography [elution with hexane-EtOAc (4:1)] furnished the unreacted camphorquinone (**139**) quantitatively.

N-*(p-Toluenesulfonyl)glycine* (**156**).–

Glycine (6.4 g, 50 mmol) was dispersed in water and dissolved by the addition of 1*M* NaOH (50 ml). *p*-Toluenesulfonyl chloride (13 g, 70 mmol) was added, followed by 1*M* NaOH to maintain a pH of *ca.* 9. When the exothermic reaction was complete, the mixture was cooled to room temperature. The unreacted *p*-toluenesulfonyl chloride was filtered off and the reaction mixture stirred at 5°C overnight. The precipitated solid was filtered off, washed with water and dried *in vacuo* to afford *N*-(*p*-toluenesulfonyl)glycine (**156**) (10.1 g; 82%); m.p. 182°C; (lit.,[60] 182°C); $\delta_H$ (400 MHz; $CDCl_3$) 2.35 (3H, Me), 3.55 (2H, 2-$CH_2$), 7.34 - 7.95 (4H, Ar-H) and 8.12 (3H, br s, NH).

N-(p-*Toluenesulfonyl)glycine 2-oxo-3-exo-bornyl ester* (**159**).–

To a solution of *N*-(*p*-toluenesulfonyl)glycine (**156**) (0.90 g, 4.2 mmol) in anhydrous DMF (10 ml) was added CDI (0.68 g, 4.2 mmol), and the resulting mixture was stirred at room temperature for 30 min. 3-*Exo*-hydroxycamphor (**137**) (1.00g, 4.2 mmol) was added to the solution, which was stirred overnight at room temperature. The DMF was evaporated *in vacuo* and flash chromatography of the residue [silica gel;elution with hexane:EtOAc (1:1)] afforded, as an oil, the N-*(p-toluenesulfonyl)glycine ester* (**159**) (1.53 g, 92%), (Found, $M^+$ 397.1521. $C_{19}H_{27}O_6NS$ requires *M*, 397.1559); $\nu_{max}$ (liquid film/$cm^{-1}$) 1730 (C=O); $\delta_H$ (400 MHz;$CDCl_3$) 0.80, 0.83 and 0.86 (9H, 3 x s, 8-, 9- and 10-Me),1.09 - 2.21 (5H, m, 4-H, 5- and 6-$CH_2$), 2.33 (3H, s, Ar-$CH_3$), 3.76 (2H, s, C*H*$_2$NH), 4.62 (1H, s, 3-H), 5.41 (1H, br s, NH), 7.21 and 7.66 (4H, 2 x d, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 12.7 (C-10), 19.3 (C-9), 20.4 (C-8), 16.3 and 24.7 (C-5 and C-6), 43.9 ($CH_2NH$), 27.8 (C-4), 28.0 (C-7), 56.7 (C-1), 76.3 (Ar-$CH_3$), 77.4 (C-3), 114.3, 126.9 and 153.9 (Ar-C), 168.2 (C=O) and

212.9 (C=O); *m/z* 397 ($M^+$, 12%).

### 3.2.2 Alkylation reactions of the 2-imino lactone (131) and the 3-imino lactone (132).

*The α,α-dimethyl 2-imino lactone* (**169a**).–

A solution of the 2-imino lactone (**131**) (0.45 g, 2.2 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.24 g, 2.2 mmol) under $N_2$ at *ca.* -78°C. After stirring for 45 min., methyl iodide (0.30 g, 2.2 mmol) in dry THF (30 ml) was added and the resulting mixture was stirred at *ca.* -78°C for 2 h. The mixture was allowed to warm to room temperature and stirring continued overnight. The solvent was evaporated *in vacuo* and preparative layer chromatography [elution with hexane-EtOAc (1:1)] afforded 3-*exo*-hydroxy-2-bornanone (**137**) (0.17 g) and the α,α-*dimethyl 2-imino lactone* (**169a**) (0.23 g, 50%), (Found: $M^+$, 235.1572. $C_{14}H_{21}NO_2$ requires *M*, 235.1572); $\nu_{max}$ (liquid film/$cm^{-1}$) 1735 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.74, 0.96, 1.00 (9H, 3 x s, 8-, 9- and 10-Me), 1.35 and 1.62 (6H, 2 x s, 2 x 3′-Me), 1.57 - 2.05 (4H, series of multiplets, 5- and 6-$CH_2$), 2.18 (1H, d, 4-H), 4.59 (1H, s, 3-H); $\delta_C$ (100 MHz; $CDCl_3$) 0.9, 10.0, 20.1, 20.9, 29.1 (C-8, C-9, C-10, and 2 x C-3′), 23.6 and 25.2 (C-5 and C-6), 48.0 (C-4), 48.3, 52.5 and 59.9 (C-1, C-2′ and C-7), 79.2 (C-3), 174.3 (C-2) and 179.5 (C-1′).

*The α,α-diethyl 2-imino lactone* (**169b**).–

The imino lactone (**131**)(0.51 g,3 mmol), *t*-BuOK (0.5 g,3 mmol) and ethyl iodide (0.467g, 3 mmol) in dry THF(40 ml) were reacted following the procedure used to prepare the α,α-dimethyl 2-imino lactone (**169a**). Work-up and preparative layer chromatography [elution

with hexane-EtOAc(3:2)]afforded 3-*exo*-hydroxybornanone (**137**)(0.23 g,47%)and the *α,α-diethyl 2-imino lactone* (**169b**) (0.38g, 49%); (Found: $M^+$, 263.1877. $C_{16}H_{25}NO_2$ requires *M*, 263.1885); $\nu_{max}$ (liquid film/$cm^{-1}$) 1720 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.73, 0.91 and 1.00 (9H, 3 x s, 8-, 9- and 10-Me), 0.77 - 0.86 (6H, 2 x t, 2 x $CH_3CH_2$), 1.62 - 2.27 (9H, series of multiplets, 4-H, 5- and 6-$CH_2$ and 2 x $CH_3CH_2$) and 4.51 (1H, s, 3-H); $\delta_C$ (100 MHz;$CDCl_3$) 8.7, 8.8 and 10.1(C-8, C-9 and C-10), 9.5 and 20.1 (2 x $CH_3CH_2$), 25.9, 29.2, 29.8 and 31.3 (C-7, C-5, C-6 and C-1), 53. (C-4), 83.1 (C-3),172.5 (C-2) and 178.9 (C-1′).

*Theα,α-dibenzyl 2-imino lactone* (**169c**).–

The 2-imino lactone (**131**) (0.48 g, 1.9 mmol), *t*-BuOK (0.21 g, 1.93 mmol) and benzyl iodide (0.33 g, 1.9 mmol) in dry THF (30 ml) were reacted following the procedure described for the preparation of the α,α-dimethyl imino lactone (**169a**). Work-up and preparative layer chromatography [elution with hexane-EtOAc (1:1)] afforded the ketol (**137**) (0.14 g, 50%) and the *α,α-dibenzyl 2-imino lactone* (**169c**), (Found: $M^+$, 387.2194. $C_{26}H_{29}NO_2$ requires *M*, 387.2198); $\nu_{max}$ (liquid film/$cm^{-1}$) 1740 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) -0.30, 0.58 and 0.90 (9H, 3 x s, 8-, 9- and 10-Me), 1.18 - 1.60 (5H, series of multiplets, 4-H, 5- and 6-$CH_2$), 1.96 (1H, s, 3-H), 3.06 and 3.61 (4H, 2 x d, $J$ = 13.0 Hz, 2 x $CH_2Ph$), 7.00 - 7.28 (10 H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 10.2, 17.9, 19.9 (C-8, C-9 and C-10), 25.9 and 29.3 (C-5 and C-6), 45.9 and 47.9 ($CH_2Ph$), 46.9 (C-4), 48.1, 52.9 and 69.9 (C-1, C-2′ and C-7), 79.1(C-3), 126.6 -136 (Ar-C), 173.0 (C-2) and 179.1 (C-1′).

*Theα-methyl 3-imino lactone* (**172**).–

A solution of the 3-imino lactone(**132**)(0.45 g, 2.2 mmol) in dry THF (30 ml) was added to

stirred suspension of *t*-BuOK (0.24 g, 2.2 mmol) in dry THF (30 ml) under $N_2$ at -78°C. After stirring for 45 min, methyl iodide (0.30 g, 2.2 mmol) in dry THF (30 ml) was added and the resulting mixture was stirred at -80°C for 2 h. The stirred mixture was allowed to warm to room temperature and then stirred overnight. The solvent was evaporated and the residue chromatographed [preparative TLC on silica gel; elution with hexane-EtOAc (1:1)] to yield, as an oil, the *α-methyl 3-imino lactone* (**172**) (0.38 g; 82%); $\nu_{max}$ (liquid film/ $cm^{-1}$) 1740 (C=O) ; $\delta_H$ (400 MHz; $CDCl_3$) 0.77/0.79,† 0.87 and 1.10/1.03 (9H, 5 x s, 8-, 9- and 10-Me), 1.31 - 1.96 (7H, complex of multiplets, 2'-Me, 5- and 6-$CH_2$), 2.35/2.36 (1H, 2 x d, 4-H), 3.79 / 4.51 (1H, 2 x q, 2'-H) and 4.28/4.35 (1H, 2 x s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.6/9.8, 15.0/16.0, 19.2/19.3 and 19.8/19.2 (C-8, C-9 and C-10 and 2'Me), 33.8 and 34.3 (C-5 and C-6), 48.9 and 49.2 (C-1 and C-7), 52.9 (C-4), 56.6 (C-2'), 81.8 (C-2), 171.3 (C-3) and 181.5 (C-1'); *m/z* 221 ($M^+$ , 0.6 %) ; d.e. 43%††.

*The α-ethyl 3-imino lactone* (**173**).–

A solution of the imino lactone (**132**)(0.50 g, 2.4 mmol) in dry THF(30 ml) was added to a stirred suspension of *t*-BuOK(0.27 g, 2.4 mmol) in dry THF(30 ml) under dry $N_2$ at - 78° C, followed by ethyl iodide(0.37 g,2.4 mmol) in dry THF(30 ml). The procedure followed was as described for the preparation of the α-methyl 3-imino lactone (**172**). Purification of the

†The chemical shift values cited in this format, here and elsewhere, refer to corresponding signals for the diastereomeric components.

††The diastereomeric excess (%d.e.) observed for each of the α-alkylated 3-imino lactones was determined from the integral ratios of the 2-H signals for the diastereomeric components.

residue [preparative TLC on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a clear oil, the *α-ethyl 3-imino lactone* (**173**) (0.43 g; 79%), (Found: $M^+$, 235.1579. $C_{14}H_{21}NO_2$ requires *M*, 235.1572); $\nu_{max}$ (liquid film/$cm^{-1}$) 1750 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.76/0.87, 0.90/1.00 and 1.02/1.04 (9H, 6 x s, 8-, 9- and 10-Me), 1.30 - 2.11 (7H, complex of multiplets, 5- and 6-$CH_2$ and $CH_2CH_3$), 2.37/2.39 (2H, 2 x d, $CH_2CH_3$), 3.57/4 32 (1H, 2 x dd, 2′-H), 4.23 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.9, 10.2, 19.3 and 19.9 (C-8, C-9, C-10 and $CH_2CH_3$), 21.6, 24.3 and 33.8 (C-5, C-6 and $CH_2CH_3$), 38.3 and 48.8 (C-1 and C-7), 38.6 (C-4), 61.9 (C-2′), 81.5 (C-2), 170.5 (C-3) and 181.4 (C-1′); *m/z* 235 ($M^+$, 11 %) d.e. 60%.

*The α-propyl 3-imino lactone* (**174**).–

A solution of the 3-imino lactone (**132**) (0.50 g, 2.4 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.27 g, 2.4 mmol) in dry THF (30 ml) under $N_2$ at -78°C, followed by propyl iodide (0.41 g, 2.4 mmol) in dry THF (30 ml). The procedure followed was as described for the preparation of the α-methyl 3-imino lactone (**172**). Purification of the residue [preparative TLC on silica gel; elution with hexane-EtOAc (1:1)] afforded, as a light yellow oil, the *α-propyl 3-imino lactone* (**174**) (0.44 g; 77%), (Found: $M^+$, 249.1732. $C_{15}H_{23}NO_2$ requires *M*, 249.1729); $\nu_{max}$ (liquid film/$cm^{-1}$) 1730; $\delta_H$ (400 MHz; $CDCl_3$) 0.80, 0.94 and 1.06 (9H, 3 x s, 8-, 9- and 10-Me), 0.98 (3H, m, $CH_2CH_3$), 1.33 - 2.15 (8H, complex of multiplets, $CH_2CH_2CH_3$, 5- and 6-$CH_2$), 2.42 (1H, d, *J* 4.4 Hz, 4-H), 3.65/4.45(1H, dd and t, 2′-H), 4.27/4.35 (1H, 2 x s, 2-H ); $\delta_C$ (100 MHz;$CDCl_3$) 9.9/10.2, 13.9, 18.9/19.1 and 19.3 (C-8, C-9, C-10 and $CH_2CH_3$), 21.1, 21.7, 33.2 and 33. 9 ($CH_2CH_2CH_3$, C-5 and C-6) , 48.9 and 49.3 (C-1 and C-7), 53.1 (C-4) , 60.7 (C-2′), 81.6 (C-2),

170.80 (C-3) and 181.48 (C-1′); d.e. 70%.

*The α-butyl 3-imino lactone* (**175**).–

A solution of the 3-imino lactone (**132**) (0.50 g, 2.4 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.27 g, 2.5 mmol) in dry THF (30 ml) under $N_2$ at -78°C, followed by butyl iodide (0.44 g, 2.4 mmol) in THF (30 ml). The procedure described for the preparation of the α-methyl 3-imino lactone (**172**) was followed. Purification of the residue [preparative TLC on silica gel; elution with hexane-EtOAc (4:1)] afforded, as an oil, the *α-butyl 3-imino lactone* (**175**) (0.46 g, 76%), (Found: $M^+$, 263.1879. $C_{16}H_{25}NO_2$ requires *M*, 263.1883); $\nu_{max}$ (liquid film/$cm^{-1}$) 1710 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.89, 0.94 and 1.07 (9H, 3 x s, 8-, 9- and 10-Me), 0.92 (3H, t, $CH_2CH_3$), 1.37 - 2.42 [10H, complex of multiplets, $(CH_2)_3$, 5- and 6-$CH_2$ ], 2.43 (1H, d, 4-H), 3.64 (1H, dd, $J$ = 4.76 and 4.84, 2′-H) and 4.26 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 13.2, 18.9 and 19.1 (C-10, C-8 and C-9), 13.9 ($CH_2CH_3$), 16.5 and 26.2 (C-5 and C-6), 22.8, 27.3 and 30.8 (C-5′, C-4′ and C-3′), 38.3 (C-7), 38.9 (C-4), 46.6 (C-1), 64.3 (C-2′), 79.7 (C-2), 164.6 (C-3) and 172.0 (C-1′); d.e. > 99%.

*The α-pentyl 3-imino lactone* (**176**).–

Following the procedure used to prepare the α-methyl 3-imino lactone (**172**), a solution of the 3-imino lactone (**132**) (0.49 g, 2.4 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.27 g, 2.4 mmol) in dry THF (30 ml) under $N_2$ at -78°C, followed by pentyl iodide(0.48 g, 2.4 mmol) in THF(30ml). Work-up and purification by preparative layer chromatography [elution with hexane-EtOAc (3:1)] afforded, as a yellow oil, the *α-*

*pentyl 3-imino lactone* (**176**) (0.49 g, 73%); (Found: $M^+$, 277.2042. $C_{17}H_{27}NO_2$ requires *M*, 277.2042); $\nu_{max}$ (liquid film/$cm^{-1}$) 1680 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.79, 0.93 and 1.06 (9H, 3 x s, 8-, 9- and 10-Me), 0.87 (3H, t, $CH_2CH_3$), 1.32 - 1.36 [8H, m, $(CH_2)_4$], 1.40 - 2.25 (4H, 2 x m, 5- and 6-$CH_2$), 2.41 (1H, d, 4-H), 3.62 (1H, dd, *J* 4.9 and 5.00 Hz, 2′-H) and 4.25 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 13.9, 18.6 and 19.3 (C-10, C-8 and C-9), 14.1 (C-7′), 16.5 and 26.8 (C-5 and C-6), 23.1, 32.2, 24.8 and 31.1 [$(CH_2)_4$], 38.3 (C-7), 38.9 (C-4), 46.6 (C-1), 64.3 (C-2′), 79.7 (C-2), 164.6 (C-3) and 172.0 (C-1′); d.e. > 99%.

*The α-hexyl 3-imino lactone* (**177**).–

Following the procedure used to prepare the α-methyl 3-imino lactone (**172**), a solution of the 3-imino lactone (**132**) (0.50 g, 2.4 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.27 g, 2.4 mmol) in dry THF (30 ml) under $N_2$ at -78°C, followed by 1-iodohexane (0.51 g, 2.4 mmol) in THF (30 ml). Work-up and preparative layer chromatography [elution with hexane-EtOAc (2:1)] afforded, as a yellow oil, the *α-hexyl 3-imino lactone* (**177**) (0.48 g, 70%); (Found: $M^+$, 291.2211. $C_{18}H_{29}NO_2$ requires *M*, 291.2198); $\delta_H$ (400 MHz; $CDCl_3$) 0.79, 0.93 and 1.01 (9H, 3 x s, 8-, 9- and 10-Me), 0.97 (3H, t, $CH_2CH_3$), 1.20 - 2.05 [14H, series of multiplets,5- and 6-$CH_2$ and $(CH_2)_5$], 2.13 (1H, d, 4-H), 3.60 (1H, dd, *J* 5.7 and 4.9 Hz, 2′-H), 4.25 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 12.9, 18.6 and 19.2 (C-10, C-8 and C-9), 14.2 ($CH_2CH_3$), 15.9 and 25.2 (C-5 and C-6), 23.1, 32.5, 29.7, 25.1 and 31.1 [$(CH_2)_5$], 38.3 (C-7), 38.9 (C-4), 46.6 (C-1), 64.3 (C-2′), 79.8 (C-2), 163.4 (C-3), 168.9 (C-1′); d.e. >99%.

*The α-(5-methylhexyl) 3-imino lactone* (**178**).–

Following the procedure used to prepare the α-methyl 3-imino lactone (**172**), a solution of the 3-imino lactone (**132**) (0.51 g, 2.4 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.26 g, 2.4 mmol) in dry THF (30 ml) under $N_2$ at -78°C, followed by 1-iodo-5-methylhexane (0.54 g, 2.4 mmol) in THF (30 ml). Work-up and preparative layer chromatography [elution with hexane-EtOAc (4:1)] furnished, as an oil, the *α-(5-methylhexyl) 3-imino lactone* (**178**) (0.51 g, 69%); (Found: $M^+$, 305.2351. $C_{19}H_{31}NO_2$ requires *M*, 305.2355); $\nu_{max}$ (liquid film/$cm^{-1}$) 1710 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.81, 1.00 and 1.10 (9H, 3 x s, 8-, 9- and 10-Me), 0.91 (6H, d, $CH(CH_3)_2$), 1.16 - 2.05 [13H, series of multiplets, $(CH_2)_4CH(CH_3)_2$, 5- and 6-$CH_2$], 2.15 (1H, d, 4-H), 3.61 (1H, dd, *J* = 4.9 and 5.7, 2′-H), 4.26 (1H, s, 2-H); $\delta_C$ (100 MHz; $CDCl_3$) 12.8, 18.6 and 19.0 (C-10, C-8 and C-9), 15.9 and 26.1 (C-5 and C-6), 22.3 22.5, 28.5, 39.1, 26.9, 25.3 and 30.9 $[(CH_2)_4CH(CH_3)_2]$, 38.4 (C-7), 37.3 (C-4), 45.9 (C-1), 63.9 (C-2′), 80.1 (C-1), 163.8 (C-3) and 169.9 (C-1′); d.e. >99%.

*The α-benzyl 3-imino lactone* (**179**).–

A solution of the 3-imino lactone (**132**) (0.50 g, 2.4 mmol ) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.27 g, 2.4 mmol) in THF (30 ml) under $N_2$ at -78°C, followed by a solution of benzyl bromide (0.41 g, 2.4 mmol) in THF (30 ml). The procedure followed was as described for the preparation of the α-methyl 3-imino lactone (**172**). After work-up, the residue was chromatographed [ preparative TLC on silica gel; elution with hexane-EtOAc (1:1)] to afford the α-benzyl 3-imino lactone (**179**) (0.45 g; 63%);(Found $M^+$, 297.1737. $C_{19}H_{23}NO_2$ requires *M*, 297.1728); $\nu_{max}$ (liquid film/$cm^{-1}$) 1740

(C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.65/0.72, 0.83/0.86 and 0.89 (9H, 6 x s, 8-, 9- and 10-Me), 1.35/1.65 and 1.85/2.00 (4H, 4 x m, 5- and 6-$CH_2$), 2.32 / 2.48 (1H, 2 x d, 4-H), 2.56 and 3.56 (1H, 2 x s, 2-H), 3.14 and 3.39 (2H, 2 x dd, $CH_2Ph$), 4.75/4.85 (1H, 2 x t, 2′-H), 7.15/7.28 (5H, 2 x m, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 9.4/12.5, 18.4/19.1 and 19.3/19.8 (C-8, C-9 and C-10), 21.2/25.1 and 29.5/34.4 (C-5 and C-6), 37.7/38.0 (C-3′), 45.2/47.9 and 49.0/50.6 (C-1 and C-7), 53.8/54.4 (C-4),62.7/63.6 (C-2′), 80.9/82.0 (C-2), 127.2 - 136.4 (Ar-C), 171.3/172.1 (C-3) and 180.24/181.22 (C-1′); *m/z* 297 ($M^+$, 3.3%) ; d.e. 50%.

*2-Aminoheptanoic acid* (**187**).–

The α-pentyl 3-imino lactone (**176**) (0.56 g, 2 mmol) was dissolved in THF (10 ml) and 6M HCl (10 ml) was added. The reaction mixture was stirred at *ca.* 70°C for 3 h, and then extracted with $Et_2O$ (3 x 20 ml). The aqueous layer was concentrated *in vacuo* to afford a crystalline residue, to which anhydrous EtOH and propylene oxide (40 ml) were added. The reaction mixture was boiled under reflux for 20 min to afford the crude amino acid as a precipitate. Chromatographic purification of the product through a $C_{18}$ reverse phase SEP-PAK cartride [elution with hexane-EtOAc (1:1)] afforded 2-aminoheptanoic acid (**187**) in quantitative yield; m.p. 272°C (lit.,[69] 275°C); $[\alpha]_D^{20}$ + 4.3; *(c*, 8 in 20% HCl; lit.,[69] $[\alpha]_D^{20}$ + 4.2 (*c*, 8 in 20% HCl); $\nu_{max}$ (KBr/$cm^{-1}$) 1720 (C=O) and 3340 (OH); $\delta_H$ (400 MHz; DMSO-$d_6$) 0.86 - 2.41 (11H, 4 x m, $(CH_2)_4CH_3$), 4.24 (1H, t, $J$ = 7.2 Hz, $H_2NCHCO_2H$); $\delta_C$ (100 MHz; DMSO-$d_6$) 13.1, 22.8, 24.1, 32.2 and 33.6 (C-7, C-6, C-5, C-4 and C-3), 62.4 (C-2) and 176.3 (C-1).

*Attempted preparation of the α-methyl 2-imino lactone* (**163a**).–

To a stirred solution of LDA [3.87 mmol; generated *in situ* from butyllithium (1.5 *M* solution in hexane) and diisopropylamine in THF (20 ml)] under $N_2$ at *ca.* -78 °C, was added a solution of the 2-imino lactone (**131**) (0.67 g, 3.2 mmol) in THF (20 ml). The resulting solution was stirred for 1 h at -78 °C, and MeI (0.45 g, 3.2 mmol) was then added. The reaction mixture was maintained at -78 °C for 3 h, before being quenched with aq. $NaHCO_3$ (10 ml) and extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Preparative layer chromatography of the residue [elution with hexane-EtOAc (4:1)] yielded the unreacted imino lactone (**131**) quantitatively.

**Note:** The above procedure was repeated, replacing the alkyl halide, $CH_3I$, with:–

a) $CH_3CH_2I$; b) $CH_3Br$; c) $CH_3CH_2CH_2Br$; d) $(CH_3)_3Br$; or e) $PhCH_2Br$.

In all five cases, however, the unreacted 2-imino lactone (**131**) was recovered.

*Attempted preparation of the α-methyl 3- imino lactone* (**172**).–

Following the procedure used in the attempted preparation of the α-methyl 2-imino lactone (**163a**), the 3-imino lactone (**132**) (0.50 g, 2.4 mmol) was treated with LDA (2.4 mmol in 20 ml THF) and MeI (0.30 g, 2.2 mmol) . Work-up and chromatographic purification afforded the unreacted 3-imino lactone (**132**) (0.41 g).

### 3.2.3 Enantiomer beneficiation studies

*Diastereomeric beneficiation of the α-methyl 3-imino lactone* (**172**).–

A solution of the α-methyl 3-imino lactone (**172**) (0.49 g, 2.2 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.25 g, 2.1 mmol) in dry THF (30 ml) under $N_2$ at -78°C. After stirring for 45 min, a slurry of dry *p*-toluenesulfonic cid (0.40 g, 2.2 mmol) in dry THF (30 ml) was added, and the resulting mixture was stirred at -80°C for 2 h. The mixture was allowed to warm to room temperature and then stirred overnight. The solvent was evaporated *in vacuo* and preparative layer chromatography of the residue [elution with hexane-EtOAc (1:1)] gave, as an oil, the α-methyl 3-imino lactone (**172**) (0.42 g, 88%), in 84% d.e.

*Diastereomeric beneficiation of the α-benzyl 3-imino lactone* (**179**).–

Following the procedure used for the diastereomeric beneficiation of the α-methyl 3-imino lactone (**172**), the α-benzyl 3-imino lactone (**179**) (0.65 g, 2.2 mmol) in dry THF (30 ml) was treated with *t*-BuOK (0.24 g, 2.2 mmol) and a slurry of dry *p*-toluenesulfonic acid (0.41 g, 2.2 mmol). Work-up and preparative layer chromatography [elution with hexane-EtOAc (1:1)] afforded the α-benzyl 3-imino lactone (**179**) (0.59 g, 91%) in 50% d.e.

N-*(Carbobenzyloxy)-DL-alanine 3-oxo-2-*exo-*bornyl ester* (**183a**).–

To a solution of *N-(*carbobenzyloxy)-DL-alanine(**182a**) (1.12 g, 5 mmol) in anhydrous DMF (15 ml) was added CDI (1.12 g, 5 mmol), and the resulting mixture was stirred at room temperature for 30 min. This was followed by the addition of ketol (**138**) (0.84 g, 5 mmol); the solution was then stirred overnight at room temperature. The DMF was evaporated *in*

*vacuo* and flash chromatography of the residue [ elution with hexane:EtOAc (1:1)] afforded, as an oil, the N-*(carbobenzyloxy)-DL-alanine ester* (**183a**) (1.36 g, 73%), (Found: *m/z* 373.1881. $C_{21}H_{27}NO_5$ requires *M*, 373.1889); $\nu_{max}$ (liquid film)/cm$^{-1}$) 1730 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.89, 0.91 and 0.97 (9H, 3 x s, 8-, 9- and 10-Me), 1.45 - 1.61 (3H, d, C*H*$_3$CH), 1.03 - 2.36 (4H, series of multiplets, 5- and 6-$CH_2$), 2.81 (1H, s, NH), 3.80 (1H, q, $CH_3$C*H*), 4.81 (1H, s, 2-H), 5.65 ( 2H, m, $CH_2$Ph) and 7.36 - 7.57 (5H, m, ArH); $\delta_C$ (100 MHz; $CDCl_3$) 12.6, 17.6 and 18.4 (C-8, C-9 and C-10), 15.9 (*C*H$_3$CH), 17.1, 26.8 and 29.8 (C-4, C-5 and C-6), 34.6 and 57.8 (C-1 and C-7), 52.1 ($CH_3$CH), 65.9 (*C*H$_2$Ar), 79.6 (C-3), 127.6, 129.6 and 137.2 (Ar-C), 157.2 (NH*C*O$_2$), 172.3 ($CO_2$), and 214.6 (C-2); *m/z* 373 ($M^+$, 0.4%) and 260 (100%).

N-*(Carbobenzyloxy)-DL-serine 3-oxo-2*-exo-*bornyl ester* (**183b**).–

The method described for the synthesis of the N-*(carbobenzyloxy)-DL-alanine ester* (**183a**) was followed, using a solution of *N*-(carbobenzyloxy)-DL-serine (**182b**) (1.43 g, 6 mmol) in anhydrous DMF (15 ml), CDI (0.97 g, 6 mmol) and ketol (**138**) (1.42 g, 6 mmol). Work-up and flash chromatography of the residue [silica gel; elution with hexane-EtOAc (1:1)] furnished, as an oil, the N-*(carbobenzyloxy)-DL-serine ester* (**183b**) (1.92 g, 82%); (Found: $M^+$ 389.1824. $C_{21}H_{27}NO_6$ requires *M*, 389.1838); $\nu_{max}$ (liquid film/cm$^{-1}$) 1740 (C=O) and 3490 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.86, 0.90 and 0.98 (9H, 3 x s 8-, 9- and 10-Me), 1.89(1H, t, 4-H), 2.34 (1H, br s, OH), 3.27 (1H, d, 3-H), 4.29 (4H, m, NHC*H*CH$_2$), 4.92 (2H, m, $CH_2$Ph) and 7. 31 - 7.61 (5H, m, Ar-H); $\delta_C$ (100 MHz;$CDCl_3$) 9.7, 19.5 and 19.8 (C-8, C-9 and C-10), 25.2 and 29.3(C-5 and C-6), 47.3 (C-4), 49.6 and 52.4 (C-1 and C-7), 57.9 (*C*HNH), 63.1 (*C*H$_2$O), 67.2 (*C*H$_2$Ph), 89.9 (C-2), 127.4,127.6,128.4, and137.2 (Ar-C), 148.9 (HNCO),

169.3 ($CO_2$) and 214.3 (C-3); *m/z* 389 ($M^+$, 0.11%) and 289 (100).

N-*(Carbobenzyloxy)-DL-valine 3-oxo2*-exo-*bornyl ester* (**183c**).–

The method described for the synthesis of the N-*(carbobenzyloxy)-DL-alanine ester*(**183a**)was followed, using a solution of *N*-(carbobenzyloxy)-DL-valine(**182c**)(1.13g, 4.5mmol)in anhydrous DMF(10 ml),CDI(0.73 g,4.5 mmol)and ketol(**138**)(0.76 g,4.5mmol). Work-up and flash chromatography [silica gel;elution with hexane-EtOAc(2:3 )] afforded, as an oil, *the* N-*(carbobenzyloxy) -DL-valine ester* (**183c**)(1.28 g,71%); (Found $M^+$, 401.2267.$C_{23}H_{31}NO_5$ requires *M*, 410.2202); $\nu_{max}$ (liquid film/$cm^{-1}$)1730(C=O); $\delta_H$(400MHz ;$CDCl_3$) 0.72, 0.77 and 1.04 (9H,3 x s,8-,9- and 10-Me),1.16 and 1.23[6H,2 x s,($CH_3$)$_2$CH], 1.26-2.546H,series of multiplets,4-H,5- and 6-$CH_2$ and ($CH_3$)$_2$C*H*],3.25(1H, br s,NH),3.96 [1H,d,($CH_3$)$_2$CHC*H*],4.36(1H,s,2-H),4.99(2H,m,$CH_2$Ph) and 7.26-7.42(5H,m,Ar-H);$\delta_C$(100 MHz;$CDCl_3$) 11.0,18.9 and 20.9 (C-10,C-8 and C-9),16.9 and 17.5[($CH_3$)$_2$CH],18.3,19.2 and 20.7(C-4,C-5 and C-6), 27.3[($CH_3$)$_2$*C*H], 63.7(CHNH),69.6($CH_2$Ph),81.3(C-2),127.6-137.2(Ar-C),157.2(HNCO),172.0($CO_2$) and 214.3(C-3); *m/z* 401($M^+$, 20.3%) and 369(100).

N-*(Carbobenzyloxy)-DL-lysine 3-oxo-2*-exo-*bornyl ester* (**183d**).–

*N*-(carbobenzyloxy)-DL-lysine (1.07 g, 4 mmol), CDI (0.65 g, 4 mmol) and ketol (**138**) (0.68 g, 4 mmol) in DMF (12 ml) were reacted according to the procedure described for the preparation of the N-*(carbobenzyloxy)-DL-alanine ester* (**183a**). Work-up and flash chromatography of the residue afforded, as an oil, the N-*(carbobenzyloxy)-DL-lysine ester* (**183d**) (1.38 g, 83%); $\nu_{max}$ (liquid film/$cm^{-1}$) 3480 ($NH_2$); $\delta_H$ (400 MHz; $CDCl_3$) 0.80,

0.85 and 1.15 (9H, 3 x s, 8-, 9- and 10-Me), 1.16 - 1.32 (5H, m, 4-H, 5- and 6-$CH_2$), 1.52 - 2.20 (8H, m, $H_2N(CH_2)_4CH$), 3.25 (1H, br s, NH), 4.61 [1H, t, $CH(CH_2)_4NH_2$], 5.09 (2H, m, $CH_2Ph$), 7.21 - 7.81 (5H, m, Ar), 8.24 (2H, br s, $NH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 12.7, 17.6 and 18.2 (C-8, C-9 and C-10), 16.1 and 26.3 (C-5 and C-6), 29.8 (C-4), 34.1 (C-7), 58.7 (C-1), 81.3 (C-3), 56.5 (C-2′), 28.5, 28.7 and 42.0 ($CHCH_2CH_2CH_2NH_2$), 69.6 ($CH_2Ph$, C-4′), 128.4, 127.6 and 137.2 (Ar-C), 157.2 ($HNCO_2$), 172.3 ($CO_2$) and 213.9 (C-3); *m/z* 416 ($M^+$, 5%) and 320 (100).

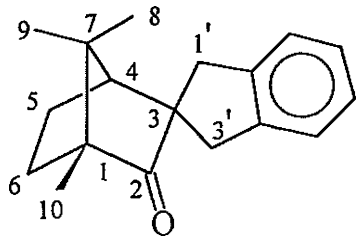
*Attempted deprotection ( decarboxylation ) of the esters* (**183a-d**).–

Typically, a suspension of the ester (**183**) (2.99 g, 8 mmol) and palladium on charcoal (5%, 0.37 g) in absolute ethanol† (20 ml) was stirred under $H_2$ for 30 min., according to the procedure described for the preparation of the 2-imino lactone (**131**). Work-up and chromatographic purification [elution with hexane-EtOAc (9:1)] afforded the α-ketol (**138**) .

†The procedure was also repeated, without success, using the following solvents; cyclohexadiene, diisopropylethylamine, DMF and methanol, all of which have been used previously in decarboxylation with $H_2$/Pd.

### 3.2.4 Asymmetric Baylis-Hillman reactions

*Spiro[bornane-3,2'-indan]-2-one* (**193**).–




(193)

A solution of camphor (1.0 g, 6.6 mol) in dry toluene (10 ml) was added to a pre-washed suspension of NaH (0.63 g) in dry toluene (15 ml), under dry $N_2$, and the resulting mixture was stirred for 1 h at room temperature, boiled under reflux for 1 h, and then allowed to cool. A solution of α,α-dichloro-*o*-xylene (1.14 g, 6.5 mmol) in toluene (10 ml) was added dropwise, and the resulting mixture was stirred overnight at room temperature and then boiled under reflux for 1.5 h. The solvent was evaporated *in vacuo* and the residue treated with cold, satd. $NaHCO_3$ (12 ml) and then extracted with EtOAc (3 x 20 ml). The combined organic extracts were dried (anhyd. $MgSO_4$), concentrated *in vacuo* and flash chromatographed [elution with hexane-EtOAc (7:3)] to give, as an oil, spiro[bornane-3,2'-indan]-2-one (**193**) (1.51 g; 91 %); $\nu_{max}$ (liquid film/$cm^{-1}$) 1740 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.93, 0.99 and 1.03 (9H, 3 x s, 8-, 9- and 10-Me), 1.06 - 1.99 (4H, series of multiplets, 5- and 6-$CH_2$), 2.03 (1H, d, 4-H), 2.96 - 3.31 (4H, 2 x dd, 1'- and 3'-$CH_2$), 7.11 - 7.34 (4H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.9, 20.9 and 22.7 (C-8, C-9 and C-10), 23.4 and 30.2 (C-5 and C-6), 42.4 and 46.7 (C-1'and C-3'), 43.2 (C-3), 53.4 (C-4), 57.8 and 58.9 (C-1 and C-7), 123.7, 126.5, 129.4, 130.7, 141.0 and 141.9 (Ar-C) and 223.8 (C-2; C=O).

*Spiro[bornane-3,2'-indan]-2*-exo-*ol* (**194**). -

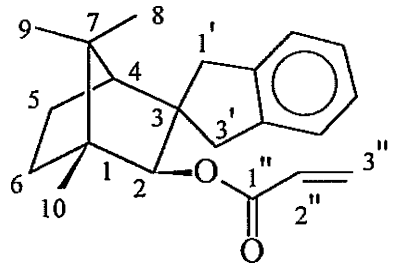
Spiro[bornane-3,2'-indan]-2-one (**193**) (2.75g, 10 mmol) ws added slowly to a slurry of LAH (0.8 g, 22 mmol) in anhydrous $Et_2O$ (25 ml) at 0°C under dry $N_2$. The resulting mixture was boiled under reflux for 2 h. The mixture was cooled in an ice-bath and the reaction was quenched by the sequential addition of water (10 ml) and 3 *M* NaOH (10 ml). The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 x 30 ml). The combined organic solutions were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded, as an oil, spiro[bornane-3,2'-indan]-2-*exo*-ol (**194**) (2.16 g; 85%); $\nu_{max}$ (liquid film/$cm^{-1}$) 3530 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.89, 0.91 and 1.29 (9H, 3 x s, 8-, 9- and 10-Me); 1.54 - 1.73 (4H, series of multiplets, 4- and 5-$CH_2$), 1.75 (1H, d, 4-H), 2.75 and 3.44 (4H, 2 x dd, 1'- and 3'-$CH_2$), 3.20 (1H, s, 2-$H_{endo}$), 6.98 - 7.51 (4H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.9, 21.3 and 21.5 (C-8 C-9- and C-10), 24.7 and 34.4 (C-5 and C-6), 40.9 and 47.4 (C-1' and C-3'), 49.1, 51.1 and 56.1 (C-1,C-3 and C-7), 57.3 (C-4), 89.7 (C-2), 123.6 123.8, 125.9, 126.3, 141.7 and 144.8 (Ar-C).

*Acryloyl chloride* .–

Acrylic acid (36.0 g, 0.4 mol) and $PCl_3$ (23.0 g, 0.17 mol) were placed in a flask fitted with a reflux condenser. The flask was warmed gently until reflux began and the heating was then discontinued. (The reaction is exothermic and may require cooling). The reaction mixture was stirred for 1 h and ,on standing, separated into 2 layers. The upper layer was removed and to this was added CuCl (0.5 g). Distillation afforded pure acryloyl chloride (38.2g; 85%),

b.p. 73 - 75°C (lit.,[95] 74 - 75°C); $\nu_{max}$ (thin film/cm$^{-1}$) 1805 (CO); $\delta_H$ (60 MHz; $CDCl_3$) 6.40 (3H, m, $CH_2$=CH).

*Spiro[bornane-3,2'-indan]-2-*exo*-yl acrylate* (**196**).–




(196)

To a solution of the alcohol (**194**) (2.49 g, 9.6 mmol) in dry $CH_2Cl_2$ (50 ml), were added 4Å molecular sieves (5 g) and acryloyl chloride (0.90 g, 9.8 mmol). The reaction mixture was boiled under reflux overnight. The molecular sieves were filtered off and the filtrate evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded, as an oil, *spiro[bornane-3,2'-indan]-2-*exo*-yl acrylate* (**196**) (2.43 g, 80 %); $\nu_{max}$ (liquid film/cm$^{-1}$) 1740 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.79, 0.92 and 1.26 (9H, 3 x s, 8-, 9- and 10-Me), 1.32 - 1.36 and 1.61 - 1.85 (4H, series of multiplets, 5- and 6-$CH_2$), 1.98 (1H, d, 4-H), 2.83 and 3.38 (4H, 2 x dd, 1'- and 3'-$CH_2$), 4.71 (1H, s, 2-$H_{endo}$), 5.70 and 6.22 (2H, 2 x dd, C=C$H_2$), 5.95 (1H, dd, 2"-H) and 7.00 - 7.15 (4H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.7, 21.8 and 22.1 (C-8, C-9 and C-10), 23.9 and 33.9 (C-5 and C-6), 41.8 and 46.4 (C-1'- and C-3'), 55.8 (C-4), 49.4, 51.1 and 57.2 (C-1, C-3 and C-7), 88.8 (C-2), 123.3, 123.8,

126.0, 126.1, 128.6, 129.7, 141.2 and 143.3 (C=$CH_2$ and Ar-C), and 164.9 (C=O).†

Method 2.

To a solution of alcohol (**194**) (2.54 g, 9.8 mmol) in dry $CH_2Cl_2$ (50 ml), was added DMAP (0.16 g, 9,8 mmol), and the mixture was stirred for 1 h. Acryloyl chloride (0.89 g, 9.8 mmol) was added neat, followed by $Et_3N$, and the resulting mixture was stirred overnight. The solvent was evaporated *in vacuo* and flash chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded spiro[bornane-3,2′-indan]-2-*exo*-yl acrylate (**196**) (1.2 g, 42 %).

*Attempted preparation of spiro[bornane-3,2′-indan]-2-*exo*-yl acrylate* (**196**).–

Method 1.

Carbonyldiimidazole (1.26 g, 7.8 mmol) was added to a solution of acrylic acid (0.56 g, 7.8 mmol) in dry DMF (20 ml). After 30 min, the alcohol (**194**) (2.00 g, 7.8 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded starting material (**194**) (1.8 g).

Method 2.

A solution of the alcohol (**194**) (2 g, 8 mmol) in dry THF (10 ml) was added to a pre-washed suspension of NaH (0.2 g, 8 mmol) in dry THF (10 ml) under dry $N_2$, and the resulting mixture was stirred for 1 h at room temperature, boiled for 1 h under reflux and then allowed to cool to

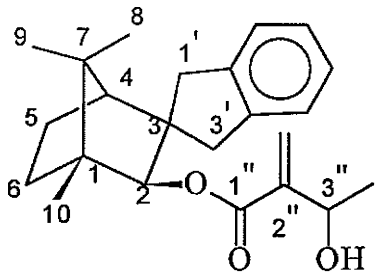
† Presumed polymerisation of the product (and certain derivatives) precluded MS analysis.

room temperature. Acryloyl chloride (0.7 g, 8 mmol) was added dropwise, and the resulting mixture was stirred overnight at room temperature and then boiled under reflux for 1.5 h. The solvent was removed *in vacuo* and the residue treated with cold, satd. aq. $NaHCO_3$ (15 ml) and then extracted with EtOAc (3 x 20 ml). The combined organic extracts were dried (anhyd. $MgSO_4$), concentrated *in vacuo*, and flash chromatographed [elution with hexane-EtOAc (8:2)]. The starting alcohol (**194**) was recovered (1.78 g).

Method 3.

A solution of the alcohol (**194**) (0.82 g, 3.2 mmol) in dry THF (20 ml) was added dropwise to a stirred solution of LDA [ 3.8 mmol ; generated *in situ* from diisopropylamine and butyllithium) in THF (15 ml)] under dry $N_2$ at *ca.* -78°C. After 30 min., neat acryloyl chloride (0.34 g, 3.8 mmol) was added to the cold solution and stirring was continued at *ca.* -78°C for 1 h, before allowing the mixture to warm to room temperature overnight. To the ice-cold solution, satd. aq. $NaHCO_3$ (10 ml) was added and the resulting mixture was extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded the starting material (**194**) (0.72 g).

*Spiro[bornane-3,2'-indan]-2*-exo-*yl 3-hydroxy-2-methylenebutanoate* (**197**).–




(197)

A solution of the chiral acrylate (**196**) (0.31 g, 1.5 mmol), acetaldehyde (0.10 g, 1.5 mmol) and 3-hydroxyquinuclidine (0.20 g, 1.5 mmol) in $CHCl_3$ (1 ml) was allowed to stand at room temperature in a stoppered vessel for 2 weeks. The crude mixture was flash chromatographed [elution with hexane-EtOAc (9:1)] to afford *spiro[bornane-3,2'-indan]-2*-exo-*yl 3-hydroxy-2-methylenebutanoate* (**197**) as an oil (0.40 g; 84%); $\nu_{max}$ (thin film/$cm^{-1}$) 3400 (OH) and 1730 (C=O); $\delta_H$ (400 MHz; $CDCl_3$)0.80, 0.92 and 1.26 (9H, 3 x s, 8-, 9- and 10-Me), 1.16 - 1.20 (3H, t, $CH_3CH_2$), 1.36 - 1.79 (5H, series of multiplets, 4-H, 5- and 6-$CH_2$), 2.89 and 3.33 (4H, m, 2 x dd , 1' and 3'-$CH_2$), 2.85 (1H, OH), 4.39 (1H, m, 3"-H), 4.70 (1H, 2-H), 5.70/5.77 and 6.08/6.14 (2H, 2 x s, C=$CH_2$) and 6.95 - 7.25 (4H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.5/11.8 (C-10), 19.9/20.0 (C-4"), 21.7/21.8 and 22.0/22.1 (C-8 and C-9), 33.7/34.0 and 38.8 (C-5 and C-6), 41.9 and 46.6 (C-1' and C-3'), 42.9, 45.0 and 48.1 (C-1, C-3 and C-7), 57.4 (C-4), 67.2/67.4 (C-3"), 89.3/89.7 (C-2), 122.7 and 123.0 ($C$=$CH_2$) and 126.6 - 126.5 (Ar-C), 165.9 (C-1"); d.e. 20%.

*Spiro[bornane-3,2'-indan]-2*-exo-*yl 3-hydroxy-3-methylenepentanoate* (**198**).–

Employing the same procedure used to prepare compound (**197**), a mixture of the chiral acrylate (**196**) (0.31 g, 1.5 mmol), propionaldehyde (0.12 g, 1.5 mmol), 3-hydroxy-

quinuclidine (0.21 g, 1.5 mmol) and $CHCl_3$ (1 ml) was allowed to stand to room temperature for 2 weeks. Preparative layer chromatography [elution with hexane EtOAc (1:1)] afforded, as an oil, *spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-3-methylenepentanoate* (**198**) (0.34 g; 77%); $\nu_{max}$ (thin film/$cm^{-1}$) 3300 (OH) and 1720 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.79, 0.91 and 1.23 (9H, 3 x s, 8-, 9- and 10-Me), 0.85 (3H, t, 5″-Me), 1.37 - 2.28 (7H, series of multiplets, 4-H, 4″-, 5- and 6-$CH_2$), 2.84 and 3.33 (4H,2 x dd, 1′- and 3′-$CH_2$), 4.12 (1H, OH), 4.63 (1H, 3″-H), 4.69 (1H, 2-H), 5.66/5.77 and 6.08/6.14 (2H, 2 x s, C=C$H_2$) and 6.95 - 7.25 (4H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.8/10.0, 11.4/11.8 and 21.7/21.7 (C-8, C-9 and C-10), 19.8/19.9 (C-5″), 23.9, 28.7/28.8 and 33.7/33.9 (C-4″, C-5 and C-6), 41.9 and 46.58/ 46.64 (C-1′ and C-3′), 48.9/49.3 (C-7), 51.1/51.2 (C-1), 55.9/56.0 (C-4), 57.3/57.4 (C-3), 72.6/73.6 (C-3″), 89.2 (C-2), 123.3, 123.7, 124.2, 125.9, 126.0, 126.1 and 126.2 (Ar-C and C=$CH_2$), 143.9 (*C*=$CH_2$) and 159.6 (C-1″); d.e. 56%.

*Spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylenehexanoate* (**199**).–

The chiral acrylate (**196**) (0.29 g, 1.5 mmol), butyraldehdye (0.14 g, 1.5 mmol) and 3-hydroxyquinuclidine (0.19 g, 1 5 mmol) in $CHCl_3$ (1 ml) were allowed to stand in a closed vessel for two weeks. Preparative layer chromatography [elution with hexane EtOAc (3:2)] gave, as an oil, *spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylenehexanoate* (**199**) (0.41 g, 71%); $\nu_{max}$ (thin film/$cm^{-1}$) 3280 (OH) and 1690 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.79, 0.89 and 1.23 (9H, 3 x s, 8-, 9- and 10-Me), 0.86 (3H, t, 6″-Me), 1.18 - 1.78 (9H, series of multiplets, 4-H, 5-, 6-, 4″-, and 5″-$CH_2$), 2.89 and 3.33 (4H, 2 x dd, 1′- and 3′-$CH_2$), 4.23/4.15 (1H, t, 3″-H), 4.69 (1H, s, 2-$H_{endo}$), 5.66/5.77 and 6.08/6.14 (2H, 2 x s, C=C$H_2$), 6.95 - 7.25 (4H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.5/11.8, 13.8, 19.0/19.4 and 19.9/20.0

(C-6",C-8, C-9 and C-10), 23.9, 26.9, 33.7/33.9 and 38.0/38.2 ( C-4", C-5", C-5 and C-6), 41.9 and 46.6 (C-1' and C-3'), 49.4, 51.1/51.2 and 55.4/56.0 (C-1, C-3 and C-7), 57.3/57.4 (C-4),. 76.7 (C-3"), 89.3 (C-2), 123.0, 123.3, 123.8, 123.9, 124.0, 126.0 and 126.1 (*C*=*C*$H_2$ and Ar-C), 141.1/141/2 (C-1") and 165.3/166.1 C-2"); d.e. 59%.

*Spiro[bornane-3,2'-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-phenylpropanoate* (**200**).– A solution of the chiral acyrylate (**196**) (0.31 g, 1 mmol), benzaldehyde (0.11 g, 1 mmol) and 3-hydroxyquinuclidine (0.12 g, 1 mmol) were reacted following the procedure used to prepare compound (**197**). Preparative layer chromatography [elution with hexane:EtOAc (7:3)] afforded, as an oil, *spiro[bornane-3,2'-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-phenylpropanoate* (**200**) (0.37 g, 89%), (Found: $M^+$, 416.2348. $C_{28}H_{32}O_3$ requires *M*, 416.2351); $\nu_{max}$ (thin film/$cm^{-1}$) 3400 (OH) and 1720 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.56/0.58, 0.79/0.80 and 1.10/1.11 (9H, 3 x s, 8-, 9- and 10-Me), 1.49 - 1.65 (4H, series of multiplets, 5- and 6-$CH_2$), 1.67 (1H, s, 4-H), 2.79 and 3.12 (4H, 2 x m, 1'- and 3'-$CH_2$), 4.57/4.58 (1H, s, 2-H), 5.26/5.29 (1H, s, 3"-H), 5.58/5.60 and 6.14/6.20 (2H, 2 x s, C=C$H_2$), 6.85 - 7.27 (9H, series of multiplets, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.6/11.7, 21.8 and 21.9 (C-8, C-9 and C-10), 23.9 and 26.9 (C-5 and C-6), 33.6/33.9 and 38.5/38.6 (1'- and 3'-$CH_2$), 44.9, 46.4 and 46.8 (C-1, C-3 and C-7), 51.9 (C-4), 73.2 (C-3"), 90.0 (C-2),123.3, 123.4, 123.74/123.83, 125.1, 125.3, 126.1, 126.4, 126.57/126.64, 127.6/127.7, 128.3, 128.4, (Ar-C and C=*C*$H_2$), 141.2/143.2 (*C*=$CH_2$) and 165.1/165.9 (C-1"); d.e. 9%.

*Spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-(*p*-nitrophenyl)propanoate* (**201**).–

A solution of the chiral acrylate(**196**)(0.31 g,1 mmol), *p*-nitrobenzaldehyde(0.13 g,1 mmol) and 3-hydroxyquinuclidine(0.12 g,1 mmol)were reacted following the procedure used to prepare compound (**197**). Preparative layer chromatography [elution with hexane:EtOAc (9:1)] afforded, as an oil, *spiro[bornane-3,2′-indan)-2*-exo-*yl 3-hydroxy-2-methylene-3-(p-nitrophenyl)propanoate*(**201**)(0.32 g, 70%), (Found: $M^+$, 461.2214. $C_{28}H_{31}O_5N$ requires *M*, 461.2202); $\nu_{max}$ (thin film/$cm^{-1}$) 3200 (OH) and 1680 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.99/1.01,1.19 and 1.43(9H, 3 x s, 8-, 9- and 10-Me),1.54 - 1.59 and 1.65 - 1.96(4H, series of multiplets, 5- and 6-$CH_2$), 2.21 (1H, 4-H), 3.20 and 3.66 (4H, 2 x dd,1′- and 3′-$CH_2$), 4.51 (1H, br s, OH), 4.92/4.94 (1H, s, 2-H), 5.67 (3″-H), 5.99/6.07 and 6.57 (2H, 2 x s, C=C$H_2$), 7.24 - 8.68 (8H, series of multiplets, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 0.9, 11.7 and 21.6/21.9 (C-8, C-9 and C-10), 23.9 and 33.8 (C-5 and C-6), 41.9 and 46.6 (C-1′ and C-3′), 49.4, 51.1/51.1 and 57.3/57.5 (C-1, C-3, and C-7), 55.9/56.0 (C-4), 72.7/72.9 (C-3), 89.9 (C-2), 123.1, 123.5/123.6, 124.1, 124.3, 126.1, 126.2, 127.1, 130.4, 141.1, 141.3 and 143.1 (C=$CH_2$ and Ar-C), 148.6 (*C*=$CH_2$) and 165.2 (C-1″); d.e. 26%.[†]

*Spiro[bornane-3,2′-indan]-2*-exo-*yl 3-(*p*-chlorophenyl)-3-hydroxy-2-methylenepropanoate* (**202**).–

A solution of the chiral acrylate(**196**) (0.3 g,1 mmol), *p*-chlorobenzaldehyde (0.14g,1 mmol) and 3-hydroxyquinuclidine (0.12 g,1 mmol) were reacted following the procedure used to

[†]The diastereomeric ratio was determined from the relative integrals of the 2′-$H_{endo}$ signals at *ca.* 4.70 ppm.

prepare compound (**197**). Preparative layer chromatography [elution with hexane:EtOAc (1:1)] afforded, as an oil, *spiro[bornane-3,2′-indan]-2*-exo-*yl 3-(p-chlorophenyl)-3-hydroxy-2-methylenepropanoate* (**202**) (0.38 g; 86%), (Found: $M^+$, 450.1969. $C_{28}H_{31}O_3Cl$ requires *M*, 450.1959); $\nu_{max}$ (thin film/$cm^{-1}$) 3300 (OH) and 1690 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.60/0.63, 0.75 and 1.11/1.12 (9H, 3 x s, 8-, 9- and 10-Me), 1.21 - 1.65 (4H, series of multiplets, 5- and 6-$CH_2$), 1.70 (1H, s, 4-H), 2.65 - 2.85 and 3.10 - 3.25 (4H, series of multiplets, 1′- and 3′-$CH_2$), 4.56/4.57 (1H, s, 2-H), 5.21 (1H, s, 3″-H), 5.57/5.63 and 6.14/6.19 (2H, 2 x s, C=C$H_2$), 6.83 - 7.23 (8H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.6/11.7, 19.9 and 21.8/21.9 (C-8, C-9 and C-10), 23.9 and 33.6/33.9 (C-5 and C-6), 41.9 and 46.7 (C-1′ and C-3′), 38.6, 44.9 and 48.9 (C-1, C-3 and C-7), 57.3/57.4 (C-4), 72.6/72.9 (C-3″), 89.7/89.8 (C-2), 123.1, 123.3, 123.5, 123.8, 125.2, 126.1, 127.8/127.9, 128.0, 128.4/128.5, 133.4 and 139.7 (C=$CH_2$ and Ar-C), 143.0/143.1 (*C*=$CH_2$), 179.6 (C-1′); d.e. 45%.

*Spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate* (**203**).– The chiral acrylate (**196**) (0.31 g, 1 mmol), pyridine-2-carboxaldehyde (0.11 g, 1 mmol) and 3-hydroxyquinuclidine (0.12 g, 1 mmol) were reacted following the procedure used to prepare compound (**197**). Preparative layer chromatography [elution with hexane:EtOAc (3:2)] afforded, as an oil, *spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-(2-pyridyl)-propanoate* (**103**) (0.40 g, 94%), (Found: $M^+$, 417.2317. $C_{27}H_{31}NO_3$ requires *M*, 417.2304); $\nu_{max}$ (thin film/$cm^{-1}$) 3400 and 1720; $\delta_H$ (400 MHz; $CDCl_3$) 0.60/0.71, 0.80/0.81 and 1.19 (9H, 3 x s, 8-, 9- and 10-Me), 1.15 and 1.65 (4H, 2 x m, 5- and 6-$CH_2$), 1.69 (1H, 4-H), 2.65 - 3.91 (4H, 2 x m, 1′- and 3′-$CH_2$), 4.65/4.80 (1H, s, 2-H), 5.29/5.31 (1H, s, 3″-H), 5.78/5.91 and 6.30/6.31 (2H, 2 x s, C=C$H_2$), 6.80 - 7.81 (8H, m, Ar-H), 8.51 (1H, br s, OH); $\delta_C$ (100

MHz; $CDCl_3$) 11.7/11.8, 21.8 and 21.9 (C-8, C-9 and C-10),23.0 and 33.9(C-5 and C-6), 51.2(C-4), 55.8/55.9 and 57.2/57.4(C-1′ and C-3′), 71.6/72.1(C-3″), 89.5(C-2),121.1, 121.2, 122.4, 122.5,123.3,125.7,123.8,136.7/136.9,141.2, 149.9, 143.3, 147.9/148.1, 159.4 (Ar-C and $C=CH_2$) and 165.1 (C=O); d.e. 16%.

*Spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-(3-pyridyl)propanoate* (**204**).– The chiral acrylate (**196**) (0.29 g, 1.1 mmol), pyridine-3-carboxaldehyde (0.11 g, 1 mmol) and 3-hydroxyquinuclidine (0.12 g, 1 mmol) were reacted following the procedure used to prepare compound (**197**). Preparative layer chromatography [elution with hexane:EtOAc (1:1)] afforded, as an oil, *spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylene-2-(3-pyridyl)propanoate* (**204**) (0.41 g, 90%); Found: $M^+$, 417.2310. $C_{27}H_{31}NO_3$ requires *M*, 417.2304); $\nu_{max}$ (thin film/$cm^{-1}$) 3300 (OH) and 1650 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.70/0.75, 0.90 and 1.19/1.21 (9H, 3 x s, 8-, 9- and 10-Me), 1.21 and 1.71 (4H, 2 x m, 5- and 6-$CH_2$), 1.85 (1H, 4-H), 2.81 and 3.20 (4H, 2 x m, 1′- and 3′-$CH_2$), 4.61/4.63 (1H, s, 2-H), 4.71 (1H, br s, OH), 5.31/5.34 (1H, s, 3″-H), 5.81/5.85 and 6.30/6.31 (2H, 2 x s, C=C$H_2$), 6.90 - 7.21(4H, m, Ar-H), 7.51 and 8.51(4H, 2 x m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.7, 21.7 and 21.9 (C-8, C-9 and C-10), 23.9 and 33.9 (C-5 and C-6), 41.9 and 46.6 (C-1′ and C-3′), 49.3, 51.1 and 55.9 (C-1, C-3 and C-7), 57.4/57.6(C-4), 71.1 (C-3″), 89.8 (C-2), 89.8 (C-2″), 123.1, 123.2, 123.8, 125.4, 126.1, 134.1, 141.2, 143.2, 148.3, 148.5, 148.7(Ar-C and C=$CH_2$),152.1(*C*=$CH_2$) and 164.9 (C=O); d.e.5%.

*Spiro[bornane-3,2′-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate* (**205**).– The chiral acrylate (**196**)(0.29 g, 1 mmol), pyridine-4-carboxaldehyde (0.13 g, 1 mmol) and

3-hydroxyquinuclidine (0.12 g, 1 mmol) were reacted following the procedure used to prepare compound (**197**). Preparative layer chromatography [elution with hexane:EtOAc (2:3)] afforded, as an oil, *spiro[bornane-3,2'-indan]-2*-exo-*yl 3-hydroxy-2-methylene-3-(4-pyridyl)propanoate* (**205**) (0.38 g, 91%), (Found: $M^+$, 417.2305. $C_{27}H_{31}NO_3$ requires *M*, 417.2304); $\nu_{max}$ (thin film/$cm^{-1}$) 3410 (OH) and 1650 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.68/0.70, 0.89 and 1.22 (9H, 3 x s, 8-, 9- and 10-Me), 1.28 and 1.66 (4H, 2 x m, 5- and 6-$CH_2$), 1.77 (1H, s, 4-H), 2.86 and 3.23 (4H, 2 x dd, 1'- and 3'-$CH_2$), 4.62/4.64(1H, s, 2-H), 5.29 and 6.26 (2H, 2x s,C=C$H_2$), 5.72/5.78 (1H, s, 3"-H), 6.68 - 8.45 (8H, series of multiplets, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.7, 21.7 and 21.9 (C-8, C-9 and C-10), 23.9 and 33.9 (C-5 and C-6), 41.9 and 46.6 (C-1' and C-3'), 49.3, 51.1/51.2 and 55.8/55.9 (C-1, C-3 and C-7), 57.3/57.5(C-4), 72.2(C-2), 89.9(C-3"), 121.1, 121.2, 123.4, 123.9, 126.0, 126.1, 141.1 and 143.1 (Ar-C), 122.6 (C=$CH_2$), 149.5/150.4 ($C$=$CH_2$) and 164.9 (C=O); d.e. 10%.

N-*(Carbobenzyloxy)glycine spiro[bornane-3,2'-indan]-2*-exo-*yl ester* (**214**).–

To a solution of *N*-(carbobenzyloxy)glycine (**157**) (2.00 g, 9.5 mmol) in anhydrous DMF (10 ml) was added carbonyldiimidazole (1.55 g, 9.5 mmol), and the mixture was stirred for 30 min. The resulting solution was added dropwise to a solution of the alcohol (**191**) (2.43 g, 4.5 mmol) in DMF (10 ml), and the mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and flash chromatography of the residue [elution with hexane-EtOAc (1:1)] afforded, as an oil, N-*(carbobenzyloxy)glycine spiro[bornane-3,2'-indan]-2*-exo-*yl ester* (**214**) (0.46 g, 11%); (Found: $M^+$, 447.2403. $C_{28}H_{33}NO_4$ requires *M*, 447.2409); $\nu_{max}$ (liquid film/$cm^{-1}$) 3300 (NH) and 1750 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.77, 0.89 and 1.18 (9H, 3 x s, 8-, 9- and 10-Me), 1.30 - 1.61 (4H, series of multiplets, 5- and

6-$CH_2$), 1.78 (1H, d, 4-H), 2.86 and 3.12 (4H, 2 x dd, 1′- and 3′-$CH_2$), 3.75 (2H, dd , 2″-$CH_2$), 4.66 (1H, s, 2-H), 4.99 (1H, br s, NH), 5.09 (2H, s, $OCH_2Ph$), 6.84 - 7.34 (9H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 11.6,17.6 and 21.6 (C-8, C-9 and C-10), 21.9 and 27.3 (C-5 and C-6), 33.1 (C-3), 39.4 (C-7), 40.5 and 40.1 (C-1′ and C-3′), 48.0 (C-1), 48.2 ($CH_2N$), 50.1 (C-4), 69.6 ($OCH_2Ph$), 88.3 (C-2), 123.02 - 128.4 (Ar-C), 157.5 (NHCO) and 171.0 ($CO_2$); *m/z* 447 ($M^+$, 11%) and 356 (100).

### 3.2.5 Preparation of ketopinic acid derivatives

*10-Camphorsulfonic acid.–*

Camphor (9 g, 0.6 mol) was added to a stirred mixture of sulphuric acid (5.88 g, 3.66 ml, 60 mmol) and acetic anhydride (12.2 g, 11.70 ml, 120 mmol). Stirring was continued until the camphor had dissolved, the temperature being maintained at 20°C by use of an ice-bath. The reaction mixture was allowed to stand at room temperature for 35 h. The crystalline precipitate was collected by filtration, washed with $Et_2O$ and dried *in vacuo* to afford white crystals of 10-camphorsulfonic acid (5.43 g, 39%), m.p. 201 - 202°C (lit.,[117] 202 - 203°C); $\nu_{max}$ (KBr/$cm^{-1}$) 1720 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.98 and 1.01 (6H, 2 x s, 8- and 9-Me), 1.48 - 2.23 (6H, series of multiplets, 3-, 5- and 6-$CH_2$), 2.59 (1H, d, 4-H), 3.15 and 3.42 (2H, 2 x d, 10-$CH_2$), 9.01 (1H, br s, $SO_3H$, $D_2O$ exchangeable); $\delta_C$ (100 MHz; $CDCl_3$) 18.3 and 18.6 (C-8 and C-9), 22.3, 31.8 and 32.8 (C-3, C-5 and C-6), 27.7 (C-4), 36.1 and 61.2 (C-1 and C-7), 48.5 (C-10) and 213.9 (C-2).

*10-Camphorsulfonyl chloride* (**206**).–

10-Camphorsulfonic acid (4.64g, 20 mmol) was mixed with neat phosphorus pentachloride

(4.16 g, 20 mmol). The reaction mixture was kept in an ice-bath until the mixture had completely lignified. The mixture was allowed to stand for 4 h at room temperature, after which the excess phosphorus pentachloride was reacted with ice (5.0 g). Filtration of the mixture gave, as a white crystalline solid, 10-camphorsulfonyl chloride (**206**) (4.91 g, 98%), m.p. 80°C (lit.,[117] 81 - 83°C); $\nu_{max}$ (KBr/cm$^{-1}$) 1690; $\delta_H$ (400 MHz; $CDCl_3$) 0.96 and 1.03 (6H, 2 x s, 8- and 9-Me), 1.38 - 2.20 (6H, series of multiplets, 3-, 5-, and 6-$CH_2$), 2.41 (1H, d, 4-H), 2.93 and 3.40 (2H, 2 x d, 10-$CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 16.9 and 18.1 (C-8 and C-9), 19.9, 22.0 and 33.1 (C-3, C-5 and C-6), 28.0 (C-4), 37.1 (C-7), 64.5 and 64.6 (C-1 and C-10) and 219 (C=O).

*Ketopinic acid* (**207**).–

Potassium permanganate (3 x 3.5 g) and camphorsulfonyl chloride (**206**) ( 3 x 3.4 g) were added in alternate portions during 30 minutes to a hot solution of anhydrous sodium carbonate (10 g) in water (90 ml), on a hot steam bath. The reaction mixture was heated for an additional hour and the excess permanganate was destroyed by the addition of an acidified solution of sodium sulfite . The mixture was cooled and made strongly acidic by the addition of 20% sulfuric acid. After re-heating the mixture, the precipitated $MnO_2$ was dissoved by stirring in powdered sodium sulfite . The resulting solution was cooled and extracted with $Et_2O$ (3 x 30 ml). The organic layers were combined and the solvent evaporated *in vacuo,* and the residual solid (3.2 g) was recrystallised from hot water to afford ketopinic acid (**207**) (2.2 g, 30%), m.p. 231 - 233°C (lit.,[118] 233 - 234°C); $\delta_H$ (400 MHz; $CDCl_3$) 1.09 and 1.21 (6H, 2 x s, 8- and 9-Me), 1.49- 2.51 (6H, series of multiplets, 3-, 5- and 6-$CH_2$) 2.10 (1H, d, 4-H); $\delta_C$ (100 MHz; $CDCl_3$) 20.0 and 20.6 (C-8 and C-9), 27.0, 27.7, 43.5 and 43.8 (C-3, C-4, C-5,

and C-6), 49.9 (C-7), 66.1 (C-1), 176.1 (C-10) and 220.1 (C-2).

N-*(Carboxymethyl)ketopinamide* (**221**).–

A mixture ketopinic acid (**207**) (5.47 g, 30 mmol), $SOCl_2$ (25 ml) and pyridine (0.2 ml) was stirred at room temperature for 2 h, then co-evaporated with benzene. The residue was dissolved in benzene (25 ml) and *tert*-butyl glycinate was added to the cooled (0°C) solution. After stirring at 0°C for 10 min, the mixture was allowed to warm to room temperature. The precipitated solid was recrystallised from hot water to afford white crystals of N-*(carboxymethyl)ketopinamide* (**221**) (3.80 g, 53%); m.p. 183 - 185°C; (Found: $M^+$, 239.1146. $C_{12}H_{17}NO_4$ requires *M*, 239.1157); $\nu_{max}$ (KBr/$cm^{-1}$) 1730 ($CO_2H$) and 1690 (CONH); $\delta_H$ (400 MHz; $CDCl_3$) 1.00 and 1.21 (6H, 2 x s, 8- and 9-Me), 2.42 and 2.31 (2H, 2 x m, 5-$CH_2$), 2.01 (1H, d, 4-H), 2.21 and 2.59 (4H, 2 x m, 3- and 6-$CH_2$), 4.19 (2H, dd, 2'-$CH_2$), 5.59 (1H, br s, OH) and 8.20 (1H, s, NH); $\delta_C$ (100 MHz; $CDCl_3$) 16.7 and 18.1 (C-8 and C-9), 19.8, 21.4, 27.3 and 32.4 (C-3, C-4, C-5 and C-6), 33.6 and 77.1 (C-1 and C-7), 48.9 (C-2'), 176.0 (C-10), 183.3 ($CO_2H$) and 217.6 (C-2).

*Attempted preparation of* N-*(carboxymethyl)-2*-exo-*hydroxy-7,7-dimethylbicyclo[2.2.1]-10-carboxamide* (**222**).–

Method 1.

Sodium borohydride (0.35 g, 10 mmol) was added to an ice-cold solution of the amide (**221**) (2.4 g, 10 mmol) in methanol (40 ml) and the resulting mixture was stirred for 2 h at 0°C and then for 10 h at room temperature. The reaction was quenched with water (5 ml) and the solvent evaporated *in vacuo*. Recrystallisation of the residue from hot water furnished the

unreacted amide (**221**) (2.1 g).

Method 2.

The amide (**221**) (2.4 g, 10 mmol) was added to a stirred suspension of $LiAlH_4$ (1.8 g, 50 mmol) in THF at -40°C. The mixture was stirred at -40°C for 1.5 h, at -20°C for 1 h, at 0°C for 1 h and, finally, while boiling under reflux for 1 h. The excess $LiAlH_4$ was quenched with 20% aq. NaOH at 0°C. The mixture was extracted with $Et_2O$ and the combined organic extracts were concentrated to afford, as an oil, *2-exo-hydroxy-10-(2-hydroxyethylamino)-bornane* (**225**) (1.78 g, 83%), (Found: $M^+$, 213.1718. $C_{12}H_{23}NO_2$ requires *M*, 213.1728); $\nu_{max}$ (thin film/$cm^{-1}$) 3280 (OH) and 3000 (NH); $\delta_H$ (400 MHz; $CDCl_3$) 1.10 and 1.21 (6H, 2 x s, 8- and 9-Me), 2.42 - 2.59 (6H, series of multiplets, 3-, 5- and 6-$CH_2$), 2.01 (1H, d, 4-H), 2.51 (1H, s, 2-H), 2.91 (2H, d, 10-$CH_2$), 3.59 (4H, m , NHC$H_2$C$H_2$OH), 7.9 (1H, s, NH); $\delta_C$ (100 MHz; $CDCl_3$) 18.1 and 19.4 (C-8 and C-9), 21.7, 22.6 and 29.9 (C-3, C-5 and C-6), 39.1 (C-7), 40.1 (C-4), 45.8 (C-10), 53.0 and 64.9 ($CH_2CH_2OH$), 61.6 (C-1) and 70.4 (C-2).

Method 3.

To a stirred solution of $NaBH_4$ (0.38 g, 10 mmol) and the amide (**221**) (2.4 g, 10 mmol) in THF (40 ml), was added $AlCl_3$ (0.45 g, 3.4 mmol) at a rate permitting the temperature to remain at *ca.* 25°C. The reaction mixture was stirred at room temperature for 1 h and the resulting precipitate filtered off. The crude solid was recrystallised from hot water to afford starting material (**221**) (2.1 g).

*Bornane-2*-exo,*10-diol* (**226**).–

Ketopinic acid (**207**) (1.82 g, 10 mmol) was added to an ice-cold, stirred suspension of LAH (0.46 g, 1.2 mmol) in $Et_2O$ (40 ml). The stirred mixture was boiled under reflux for 2 h and, after cooling to 0°C, the excess $LiAlH_4$ was quenched with $H_2O$ (5 ml) and 3 *M* NaOH (10 ml). The resulting white precipitate was filtered off and the $Et_2O$ was evaporated from the filtrate *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (7:2)] afforded white crystals of *bornane-2*-exo,*10-diol* (**226**) (1.41 g, 83%), m.p. 169°C; $\nu_{max}$ (KBr/cm$^{-1}$) 3200 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.89 and 1.36 (6H, 2 x s, 8- and 10-Me), 1.50 - 1.95 (4H, series of multiplets, 5- and 6-$CH_2$), 2.01 (1H, d, 4-H), 2.46 and 2.52 (2H, 2 x br s, 2 OH), 3.60 (2H, m, 3-$CH_2$), 3.90 (1H, s, 2-H), 4.05 (2H, dd, 10-$CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 18.2 and 19.3 (C-8 and C-9), 19.8 and 20.1 (C-5 and C-6), 29.6 (C-3), 30.2 (C-4), 37.7 (C-7), 56.8 (C-1), 62.6 (C-10) and 69.0 (C-2); *m/z* 170 ($M^+$, 11%) and 154 (100).

*Attempted preparation of 2*-exo-*hydroxybornane-10-carboxaldehyde* (**228**).–

To a solution of bornane-2-*exo*,10-diol (**226**) (1.2 g, 7 mmol) in acetone (10 ml), was added a solution of $Na_2Cr_2O_7$ (7 ml; prepared according to Vogel's procedure[103]) at room temperature. The resulting mixture was stirred overnight. The acetone was evaporated *in vacuo* and preparative layer chromatography of the residue afforded the starting bornane-2-*exo*,10-diol (**226**) (0.89 g).

*Benzylation of bornane-2*-exo,*10-diol* (**226**).–

A solution of bornane-2-*exo*,10-diol (**226**) (0.41 g, 2.4 mmol) in dry THF (30 ml) was added to a stirred suspension of *t*-BuOK (0.25 g, 2.4 mmol) in dry THF (30 ml) under $N_2$ at -78°C.

After stirring for 30 min., benzyl bromide (0.41 g, 2.4 mmol) was added and the resulting mixture was stirred at *ca.* -78°C for 2 h. The stirred mixture was then allowed to warm to room temperature and stirred overnight. The solvent was evaporated and the residual oil was chromatographed using HPLC [elution with hexane-EtOAc (3:2)] to afford three components.

(a) The unreacted bornane-2-*exo*,10-diol (**226**) (0.02 g, 5%).

(b) *2*-Exo-*benzyloxy-10-hydroxybornane* (**231**) (0.27 g, 41%), (Found: $M^+$ 260.1770; $C_{17}H_{24}O_2$ requires: *M*, 260.1776); $\nu_{max}$ (liquid film/$cm^{-1}$) 3340 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.87 and 0.91 (6H, 2 x s, 8- and 9-Me), 1.01 (1H, d, 4-H), 1.36 - 2.23 (6H, series of multiplets, 3-, 5- and 6-$CH_2$), 2.49 (1H, br s, OH, $D_2O$ exchangeable), 3.45 and 3.73 (2H, 2 x d,10-$CH_2$), 4.40 (1H, d, 2-H), 4.49 (2H, s, $CH_2Ph$), 6.98 - 7.53 (5H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 20.7 and 20.8 (C-8 and C-9), 20.6, 22.9 and 28.0 (C-3, C-5 and C-6), 38.0 (C-4), 40.7 and 60.4 (C-1 and C-7), 59.8 (C-10), 61.4 ($CH_2Ph$), 73.9 (C-2), 127.4, 127.6, 128.4 and 138.3 (Ar-C); *m/z* 260 ($M^+$, 14.7%).

(c) *10-Benzyloxy-2*-exo-*hydroxybornane* (**230**) (0.34 g, 54%); $\nu_{max}$ (liquid film/$cm^{-1}$) 3320 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.84 and 1.15 (6H, 2 x s, 8- and 9-Me), 1.02 (1H, d, 4-H), 1.49 - 1.81 (6H, series of multiplets, 3-, 5- and 6-$CH_2$), 2.87 (1H, br s, OH, $D_2O$ exchangeable), 3.50 and 3.75 (2H, 2 x d, 10-$CH_2$), 3.97 (1H, m, 2-H), 4.53 (2H, 2 x d, $CH_2Ph$), 6.50 - 7.52 (5H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 19.6 and 20.1 (C-8 and C-9), 20.6 and 22.9 (C-5 and C-6), 30.2 (C-3), 38.0 (C-7), 40.4 (C-4), 60.4 (C-1), 66.1 (C-10), 69.3 ($CH_2Ph$), 76.3 (C-2), 127.6, 128.4, 127.6 and 128.4 (Ar-C); *m/z* 260 ($M^+$, 16.1%).

*10-Benzyloxy-2*-exo-*bornyl* N-*(carbobenzyloxy)glycinate* (232) *and 2*-exo-*benzyoxy-10-bornyl* N-*(carbobenzyloxyglycinate)* (233).–

Carbonyldiimidazole (1.62 g, 10 mmol) was added to a solution of *N*-(carbobenzyloxy) glycinate(2.09 g, 10 mmol) in dry DMF(15 ml). After 30 min., a mixture of 2-*exo*-benzyloxy-10-hydroxybornane (230) (41%) and 10-benzyloxy-2-*exo*-hydroxybornane (230) (54%) (4.37 g, 10 mmol) was added and the resulting mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and a portion of the residual oil was subjected to semi-preparative HPLC [elution hexane-EtOAc (1:1)] to afford two products.

a) *10-Benzyloxy-2*-exo-*bornyl* N-*(carbobenzyloxy)glycinate* (232) (43%), (Found: $M^+$, 451.2349. $C_{27}H_{33}NO_5$ requires *M*, 451.2358 ); $\nu_{max}$ (liquid film/$cm^{-1}$) 3300 (OH) and 1710 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.93 and 1.01 (6H, 2 x s, 8- and 9-Me), 1.29 - 2.23 (7H, series of multiplets, 4-H, 3-, 5- and 6-$CH_2$), 3.40 (2H, dd, 10-$CH_2$), 3.86 (2H, 2 x d, $CH_2N$), 4.40 (2H, s, $CH_2Ph$), 5.05 (1H, br s, NH), 5.10 (2H, s, $CH_2CO_2$), 5.40 (1H, d, 2-H), 7.22 - 7.35 (10H, m, Ar-H); $\delta_C$ (100 MHz; $CDCl_3$) 18.9 and 19.1 (C-8 and C-9), 20.8 and 22.6 (C-5 and C-6), 26.9 (C-3), 42.5 ($CH_2N$), 46.0 (C-4), 48.0 (C-7), 57.1 (C-1), 66.8 (C-10), 69.6 ($CH_2Ph$), 72.7 (C-2), 76.3 ($CH_2CO_2$), 127.4 - 138.8 (Ar-C), 157.5 (CO.N), 171.0 ($CO_2$); *m/z* 451 ($M^+$, 10%) and 374 (100).

b) 2-*Exo*-benzyloxy-10-bornyl *N*-(carbobenzyloxy)glycinate*)* (233) (46%), (Found: $M^+$, 451.2346. $C_{27}H_{33}NO_5$ requires *M*, 451.2358 ); $\nu_{max}$ (liquid film/$cm^{-1}$) 3300 (OH) and 1720 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.91 and 0.92 (6H, 2 x s, 8- and 9-Me), 1.03 - 1.15 (4H, series of multiplets, 3- and 5-$CH_2$), 1.63 (1H, d, 4-H), 1.64 and 2.15 (2H, 2 x m, 6-$CH_2$), 3.79 (2H, s,$CH_2Ph$), 3.98 (1H, d, 2-H), 4.13 and 4.27 (2H, 2 x d, $CH_2N$), 4.34 and 4.56(4H, 2 x d, 10-$CH_2$), 5.01(1H, br s, NH), 5.09 (2H, s,$CH_2CO_2$), 7.29 - 7.34 (10 H, m, Ar-H); $\delta_C$ (100 MHz;

$CDCl_3$) 18.6 and 19.2 (C-8 and C-9), 20.8 and 22.6 (C-5 and C-6), 27.7 (C-3), 38.2 (C-7), 47.9($CH_2Ph$), 57.1 (C-1); 63.0 (C-10), 69.6 ($CH_2N$), 73.1 ($CH_2CO_2$), 74.0 (C-2), 128.5 - 153.0 (Ar-C), 157.5 (CO.N) and 171.0 ($CO_2$); *m/z* 451 ($M^+$, 13%).

### 3.2.5 Dibornyl ethers

*Preparation of "Dimer I", the 2'-*endo*-3-*exo*-dibornyl ether* (239); *"Dimer II", the 2-*exo*-3'-*endo*-dibornyl ether* (240) *and "Dimer III", the 3-*exo*-3'-*endo*-dibornyl ether* (242).–

A mixture of 3-hydroxycamphor (137) (2.00 g, 11.8 mmol) and *p*-toluenesulfonic acid (0.14 g) in dry benzene (26 ml) was boiled under reflux overnight using a Dean-Stark trap. After cooling, water (20 ml) was added and the resulting mixture was extracted with EtOAc (4 x 20 ml). The combined organic extracts were dried (anhyd. $MgSO_4$) and the solvent was evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded three colourless crystalline products.

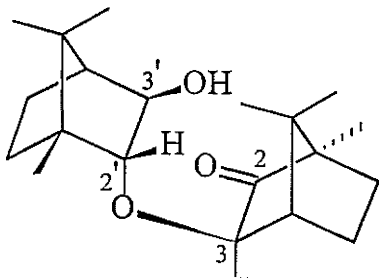
(a) The 2'-*endo*-3-*exo*-dibornyl ether (239) (0.88 g, 47%), m.p. 104°C, (lit.,[52] 104°C), $[\alpha]_D^{27}$ 80.9, (Found $M^+$, 318.2180. Calc. for $C_{20}H_{30}O_3$ *M*, 318.2195); $\delta_H$ (400 MHz; $CDCl_3$) 0.82, 0.84, 0.85, 0.87, 0.88 and 0.96 (18H, 6 x s, 8-, 8'-, 9-, 9'-, 10- and 10'-Me), 1.22 - 2.01 (8H, series of multiplets, 5-, 5'-, 6- and 6'-$CH_2$), 2.08 and 2.11 (2H, 2 x d, 4- and 4'-H), 3.88 and 3.92 (2H, 2 x s, 2'- and 3-H); $\delta_C$ (100 MHz; $CDCl_3$) 8.05 and 12.91 (C-10 and C-10'), 17.6 and 19.2 (C-9 and C-9'), 19.6 and 21.0 (C-8 and C-8'), 23.9 and 24.7 (C-5 and C-5'), 25.7 and 28.8 (C-6 and C-6'), 42.68 and 46.2 (C-7 and C-7'), 49.1 and 59.9 (C-4 and C-4'), 50.2 and 57.2 (C-1 and C-1'), 84.3 and 85.3 (C-2' and C-3) and 216.9 and 218.2 (C-2 and C-3'); *m/z* 318 ($M^+$, 5.9%).

(b) The 2-*exo*-3′-*endo*-dibornyl ether (**240**); (0.5 g, 27%); m.p. 102°C (lit.,[52] 102°C); $[\alpha]_D^{27}$ 90.0; (Found $M^+$, 318.2191. Calc. for $C_{20}H_{30}O_3$ *M*, 318.2195); $\nu_{max}$ (KBr/cm$^{-1}$) 1730 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.82, 0.86, 0.95, 0.96, 0.97 and 0.98 (18H, 6 x s, 8-, 8-′, 9-, 9′, 10-, and 10′-Me), 1.36 - 1.89 (8H, series of multiplets, 5-$CH_2$, 5′-$CH_2$, 6-$CH_2$ and 6′-$CH_2$), 2.05 (1H, d, 4-H), 2.31 (1H, t, 4'-H), 3.60 (1H, s, 2-H) and 4.25 (1H, d, 3′-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.30 and 10.5 (C-10 and C-10′), 18.6 and 19.8 (C-8 and C-8′), 18.5 and 18.7 (C-9 and C-9′), 20.79 and 21.3 (C-6 and C-6′), 31.8 and 33.7 (C-5 and C-5′), 48.8 and 54.2 (C-4 and C-4′), 42.6 and 46.1 (C-7 and C-7′), 50.2 and 57.2 (C-1 and C-1′), 85.6 and 81.7 (C-2' and C-3) and 217.8 and 217.9 (C-2 and C-3′); *m/z* 318 ($M^+$, 33.5%).

(c) The *3*-exo-*3′*-endo-*dibornyl ether* (**242**); (0.36g; 19%), m.p. 82°C; $[\alpha]_D^{27}$ 75.5, (Found: $M^+$, 318.2181. $C_{20}H_{30}O_3$ requires *M*, 318.2195); $\nu_{max}$ (KBr/cm$^{-1}$) 1700 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 0.83, 0.90, 0.95, 0.99 and 1.01 (18H, 5 x s, 8-, 8-′, 9-, 9′-, 10- and 10′-Me), 1.32 - 2.16 (8H, series of multiplets, 5-, 5′-, 6- and 6′-$CH_2$), 2.18 (1H, d, 4-H), 2.33 (1H, t, 4'-H), 3.60 (1H, s, 3-H), 4.61 (1H, d, 3′-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.4, 13.4, 17.8, 19.1, 19.4 and 19.8 (C-8, C-8′, C-9, C-9′, C-10 and C-10′), 42.9 and 46.5 (C-7 and C-7′), 18.4 and 23.7 (C-6 and C-6′), 25.9 and 31.7 (C-5 and C-5′), 46.5 and 50.1 (C-4 and C-4′), 58.4 and 60.1 (C-1 and C-1′) 80.4 and 82.3 (C-2' and C-3), 216.4 and 217.6 (C-2 and C-3′); *m/z* 318 ($M^+$, 18%).

**Note:** The 2-*exo*-3′-*endo*-dibornyl ether (**240**) was also obtained in 90% yield by similar treatment of 2-*exo*-hydroxy-3-bornanone (**138**).

*3*-Exo-*hydroxy-2*-endo-*(2-oxo-3*-endo-*bornyl)bornane* (**244**)

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Sodium borohydride (0.7 g, 20 mmol) was added to an ice-cold solution of the dibornyl ether (**239**) (3.2 g, 10 mmol) in ethanol (40 ml) and the resulting solution stirred for 2 h at 0°C and then for 10 h at room temperature. The reaction was quenched with water (10 ml) and the solvent evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (3:2)] afforded, as colourless crystals, *3*-exo-*hydroxy-2*-endo-*(2-oxo-3*-endo-*bornyl)bornane* (**244**) (1.54 g, 48%); m.p. 196°C; (Found: $M^+$, 320.2317. $C_{20}H_{32}O_3$ requires *M*, 320.2351); $\nu_{max}$ (KBr/cm$^{-1}$) 1680 (C=O) and 3320 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.82, 0.84, 0.85, 0.87, 0.88 and 0.96 (18H, 6 x s, 8-, 8'-, 9-, 9'-, 10- and 10'-Me), 1.22 - 2.08 (8H, series of multiplets, 5-, 5'-, 6- and 6'-$CH_2$), 2.10 and 2.21 (2H, 2 x d, 4- and 4'-H), 2.56 (1H, s, 3-H), 3.89 and 4.10 (2H, 2 x s, 2'- and 3-H); $\delta_C$ (100 MHz; $CDCl_3$) 8.8, 12.9, 17.0, 19.3, 20.1 and 22.1 (C-8, C-8', C-9, C-9', C-10 and C-10'), 23.8 and 24.6 (C-6 and C-6'), 25.8 and 28.9 (C-5 and C-5'), 41.9 and 46.6 (C-7 and C-7'), 48.1 and 51.2 (C-1 and C-1'), 48.9 and 59.2 (C-4 and C-4'), 66.7 (C-3'), 83.9 and 84.8 (C-2' and C-3), 211.3 (C-2); *m/z* 320 ($M^+$, 21%).

*The dihydroxy dibornyl ether* (**245**).–

A solution of the dibornyl ether (**240**) (3.2 g, 10 mmol) in anhydrous $Et_2O$ (50 ml) was added

to a slurry of LAH (0.83 g, 22 mmol) in $Et_2O$ at 0°C under dry $N_2$. The resulting mixture was boiled under reflux for 2 h, and then quenched at 0°C by the successive addition of water (8 ml) and 3*M* NaOH (16 ml). The organic layer was separated and the $Et_2O$ evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-$Et_2O$ (8:2)] afforded, as a white solid, the *dihydroxy dibornyl ether* (**245**) (3.18 g, 100 %); m.p. 212°C; (Found: $M^+$, 322.2512. $C_{20}H_{34}O_3$ requires *M*, 322.2507); $\nu_{max}$ (KBr/$cm^{-1}$) 3300 (OH); $\delta_H$ (400 MHz; $CDCl_3$) 0.81, 0.83, 0.88, 0.91, 0.96 and 1.01 (18H, 6 x s, 8-, 8′-, 9-, 9′-, 10- and 10′-Me), 1.4 - 2.0 (8H, series of multiplets, 5-, 5′-, 6- and 6′-$CH_2$), 2.34 and 2.59 (2H, 2 x d, 4- and 4′-H), 3.50 (1H, d , 2-H) , 3.80 - 3.95 (3H , 2 x m , 2′-H, 3-H and 3′-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.3, 10.5, 18.5, 18.6, 18.9 and 20.1 (C-8, C-8′, C-9, C-9′, C-10 and C-10′), 41.9 and 45.3 (C-7 and C-7′), 20.7 and 21.9 (C-6 and C-6′), 29.9 and 32.8 (C-5 and C-5′), 48.4 and 59.5 (C-4 and C-4′), 68.0 and 78.4 (C-3 and C-2′), 84.9 and 82.3 (C-2 and C-3′), 49.8 and 57.6 (C-1 and C-1′).

*Attempted preparation of the chiral LAH reagent* (**249**).–

To a 1.63 *M* solution of LAH (8.3 mmol) in THF under $N_2$ at 0°C, was added ethanol(2.00 *M* solution in THF; 8.4 mmol); then the *dihydroxy dibornyl ether* (**245**) (0.65 *M* solution in THF; 2.68 g, 8.4 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was then cooled to -100°C and butyrophenone (1.00 *M* solution in THF; 0.40 g, 2.5 mmol) was added. Stirring was continued at this temperature for 3 h and then at -78°C for 16 h. The reaction was quenched with 2 *M* HCl (5 ml) at -78°C. After warming to room temperature, the LiOH was filtered off and the solvent evaporated *in vacuo*. Flash

chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded the dimer diol (**245**) (2.2 g) and the unreacted butyrophenone (**246**).

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## APPENDIX I

### Crystallographic data for 3-*exo*-hydroxy-2-*endo*-(2-oxo-3-*endo*-bornyl)bornane (244)

| | |
|---|---|
| Identification code | PK10/JMM2 |
| Empirical formula | $C_{20}H_{32}O_3$ |
| Formula weight | 320.24 |
| Temperature | 293 (2) K |
| Wavelength | 0.71073 A |
| Space Group | $P2_1$ |
| Unit cell dimension | a = 12.097 (2) A alpha = 90.00 deg.<br>b = 6.908 (3) A beta = 99.09(3) deg.<br>c = 22.873 (6) A gamma = 90.00 deg. |
| Volume | 1887.4(7) $A^3$ |
| Z | 4 (2 asymmetric units but 2 formula units per asymmetric unit) |
| Density (calculated) | 1.128 $mg/m^3$ |
| Absorption coefficient | 0.074 $mm^{-1}$ |
| F (000) | 704 |
| Theta range for data collection | 2.05 to 29.96 deg |
| Index ranges | -17 <= h <= 16, -1 <= k <= 9, -1 <= 1 <= 32 |
| Reflections collected | 6737 |
| Independent reflections | 3483 [>2 sigma(I)]] |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 3474/0/415 |
| Goodness-of-fit on F^2 | 0.930 |
| Final R indices [I > 2 sigma (I)] | R = 0.1013 |

Note : The high R-factor is attributed to disorder in the lattice, particularly in respect of the methyl groups, and the possibility of twinning. The molecular structure, however, is unambiguously defined.

Table 1. Non-hydrogen atomic coordinates (x10000) and equivalent isotropic displacement parameters (x 1000A^2)
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 7313(4) | 1542(10) | 154(2) | 60(2) |
| C(12) | 6518(5) | 844(11) | 489(2) | 40(2) |
| C(2) | 7047(5) | 1201(10) | -467(3) | 39(1) |
| C(17) | 7199(5) | 1857(10) | 1503(3) | 42(2) |
| C(3) | 7483(7) | -771(13) | -653(4) | 56(2) |
| C(1) | 7654(7) | 2580(14) | -827(3) | 55(2) |
| C(11) | 7064(6) | 67(11) | 1093(4) | 51(2) |
| C(4) | 8260(6) | -348(12) | -1096(3) | 49(2) |
| C(10) | 8512(10) | -2041(13) | -1462(5) | 91(3) |
| C(14) | 5940(6) | 2463(14) | 1330(4) | 59(2) |
| O(3) | 5980(6) | 4325(10) | 424(3) | 92(2) |
| C(20) | 8120(8) | -1136(17) | 1080(5) | 89(3) |
| O(2) | 7407(8) | -2266(11) | -387(3) | 105(3) |
| C(7) | 7671(6) | 1479(13) | -1406(3) | 52(2) |
| C(16) | 6117(8) | -1031(16) | 1328(4) | 73(3) |
| C(19) | 8032(7) | 3370(14) | 1340(4) | 71(3) |
| C(5) | 9289(7) | 603(19) | -702(4) | 74(3) |
| C(9) | 8345(9) | 2419(18) | -1831(4) | 84(3) |
| C(6) | 8864(7) | 2628(17) | -543(4) | 74(3) |
| C(15) | 5359(8) | 641(21) | 1493(4) | 86(4) |
| C(13) | 5755(6) | 2492(15) | 659(3) | 59(2) |
| C(18) | 7527(8) | 1434(18) | 2166(3) | 77(3) |
| C(8) | 6503(7) | 982(20) | -1748(3) | 83(3) |
| O(1') | 7289(4) | 6503(11) | 4885(2) | 62(2) |
| C(17') | 6318(5) | 6027(12) | 3544(3) | 42(2) |
| C(2') | 7369(5) | 6801(13) | 5504(3) | 45(2) |
| C(9') | 7511(8) | 6904(23) | 6781(4) | 93(4) |
| C(11') | 6477(6) | 7872(12) | 3922(3) | 44(2) |
| C(13') | 5394(6) | 5548(17) | 4398(4) | 63(3) |
| C(6') | 9246(7) | 5457(16) | 5593(4) | 68(3) |
| C(7') | 8487(6) | 6493(13) | 6449(3) | 49(2) |
| O(3') | 5763(6) | 3781(11) | 4667(3) | 94(2) |
| C(4') | 8904(6) | 8317(14) | 6156(4) | 57(2) |
| C(18') | 6232(8) | 6367(18) | 2874(4) | 81(3) |
| C(14') | 5159(6) | 5568(15) | 3728(4) | 61(2) |
| C(16') | 5390(7) | 9008(16) | 3688(5) | 75(3) |
| O(2') | 7698(9) | 10286(11) | 5414(4) | 133(4) |
| C(20') | 7559(8) | 9023(18) | 3921(5) | 90(3) |
| C(3') | 7872(7) | 8821(17) | 5701(4) | 65(3) |
| C(19') | 7215(7) | 4498(14) | 3701(4) | 60(2) |
| C(1') | 8167(6) | 5425(12) | 5858(3) | 47(2) |
| C(5') | 9744(6) | 7447(17) | 5781(4) | 74(3) |
| C(8') | 9407(8) | 5501(18) | 6885(4) | 80(3) |
| C(12') | 6282(5) | 7237(12) | 4530(3) | 47(2) |
| C(10') | 9356(10) | 9994(17) | 6548(5) | 100(4) |
| C(15') | 4511(7) | 7394(18) | 3353(4) | 77(3) |

Table 1. Non-hydrogen atomic coordinates (x10000) and equivalent isotropic displacement parameters (x 1000A^2)
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 7313(4) | 1542(10) | 154(2) | 60(2) |
| C(12) | 6518(5) | 844(11) | 489(2) | 40(2) |
| C(2) | 7047(5) | 1201(10) | -467(3) | 39(1) |
| C(17) | 7199(5) | 1857(10) | 1503(3) | 42(2) |
| C(3) | 7483(7) | -771(13) | -653(4) | 56(2) |
| C(1) | 7654(7) | 2580(14) | -827(3) | 55(2) |
| C(11) | 7064(6) | 67(11) | 1093(4) | 51(2) |
| C(4) | 8260(6) | -348(12) | -1096(3) | 49(2) |
| C(10) | 8512(10) | -2041(13) | -1462(5) | 91(3) |
| C(14) | 5940(6) | 2463(14) | 1330(4) | 59(2) |
| O(3) | 5980(6) | 4325(10) | 424(3) | 92(2) |
| C(20) | 8120(8) | -1136(17) | 1080(5) | 89(3) |
| O(2) | 7407(8) | -2266(11) | -387(3) | 105(3) |
| C(7) | 7671(6) | 1479(13) | -1406(3) | 52(2) |
| C(16) | 6117(8) | -1031(16) | 1328(4) | 73(3) |
| C(19) | 8032(7) | 3370(14) | 1340(4) | 71(3) |
| C(5) | 9289(7) | 603(19) | -702(4) | 74(3) |
| C(9) | 8345(9) | 2419(18) | -1831(4) | 84(3) |
| C(6) | 8864(7) | 2628(17) | -543(4) | 74(3) |
| C(15) | 5359(8) | 641(21) | 1493(4) | 86(4) |
| C(13) | 5755(6) | 2492(15) | 659(3) | 59(2) |
| C(18) | 7527(8) | 1434(18) | 2166(3) | 77(3) |
| C(8) | 6503(7) | 982(20) | -1748(3) | 83(3) |
| O(1') | 7289(4) | 6503(11) | 4885(2) | 62(2) |
| C(17') | 6318(5) | 6027(12) | 3544(3) | 42(2) |
| C(2') | 7369(5) | 6801(13) | 5504(3) | 45(2) |
| C(9') | 7511(8) | 6904(23) | 6781(4) | 93(4) |
| C(11') | 6477(6) | 7872(12) | 3922(3) | 44(2) |
| C(13') | 5394(6) | 5548(17) | 4398(4) | 63(3) |
| C(6') | 9246(7) | 5457(16) | 5593(4) | 68(3) |
| C(7') | 8487(6) | 6493(13) | 6449(3) | 49(2) |
| O(3') | 5763(6) | 3781(11) | 4667(3) | 94(2) |
| C(4') | 8904(6) | 8317(14) | 6156(4) | 57(2) |
| C(18') | 6232(8) | 6367(18) | 2874(4) | 81(3) |
| C(14') | 5159(6) | 5568(15) | 3728(4) | 61(2) |
| C(16') | 5390(7) | 9008(16) | 3688(5) | 75(3) |
| O(2') | 7698(9) | 10286(11) | 5414(4) | 133(4) |
| C(20') | 7559(8) | 9023(18) | 3921(5) | 90(3) |
| C(3') | 7872(7) | 8821(17) | 5701(4) | 65(3) |
| C(19') | 7215(7) | 4498(14) | 3701(4) | 60(2) |
| C(1') | 8167(6) | 5425(12) | 5858(3) | 47(2) |
| C(5') | 9744(6) | 7447(17) | 5781(4) | 74(3) |
| C(8') | 9407(8) | 5501(18) | 6885(4) | 80(3) |
| C(12') | 6282(5) | 7237(12) | 4530(3) | 47(2) |
| C(10') | 9356(10) | 9994(17) | 6548(5) | 100(4) |
| C(15') | 4511(7) | 7394(18) | 3553(4) | 77(3) |

Table 2. Hydrogen coordinates ( x 10000) and isotropic displacement parameters (A^2 x 1000) for 1.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(12) | 6062(5) | -168(11) | 268(2) | 48 |
| H(2) | 6237(5) | 1294(10) | -595(3) | 46 |
| H(1) | 7308(7) | 3863(14) | -883(3) | 66 |
| H(10A) | 9007(10) | -1643(13) | -1729(5) | 136 |
| H(10B) | 7828(10) | -2523(13) | -1685(5) | 136 |
| H(10C) | 8862(10) | -3043(13) | -1207(5) | 136 |
| H(3) | 5864(6) | 4274(10) | 61(3) | 139 |
| H(20A) | 8409(8) | -1567(17) | 1474(5) | 133 |
| H(20B) | 8672(8) | -360(17) | 932(5) | 133 |
| H(20C) | 7941(8) | -2238(17) | 828(5) | 133 |
| H(16A) | 6406(8) | -1804(16) | 1673(4) | 88 |
| H(16B) | 5712(8) | -1864(16) | 1026(4) | 88 |
| H(19A) | 7852(7) | 3678(14) | 927(4) | 107 |
| H(19B) | 8778(7) | 2857(14) | 1422(4) | 107 |
| H(19C) | 7986(7) | 4521(14) | 1570(4) | 107 |
| H(5A) | 9524(7) | -158(19) | -348(4) | 89 |
| H(5B) | 9914(7) | 723(19) | -919(4) | 89 |
| H(9A) | 8314(9) | 1626(18) | -2178(4) | 126 |
| H(9B) | 9109(9) | 2554(18) | -1643(4) | 126 |
| H(9C) | 8039(9) | 3673(18) | -1942(4) | 126 |
| H(6A) | 8936(7) | 2798(17) | -118(4) | 89 |
| H(6B) | 9267(7) | 3656(17) | -707(4) | 89 |
| H(15A) | 4610(8) | 545(21) | 1269(4) | 104 |
| H(15B) | 5311(8) | 621(21) | 1912(4) | 104 |
| H(13) | 4973(6) | 2150(15) | 514(3) | 70 |
| H(18A) | 7594(8) | 2630(18) | 2382(3) | 115 |
| H(18B) | 8231(8) | 764(18) | 2233(3) | 115 |
| H(18C) | 6962(8) | 644(18) | 2298(3) | 115 |
| H(8A) | 6064(7) | 373(20) | -1485(3) | 125 |
| H(8B) | 6580(7) | 117(20) | -2067(3) | 125 |
| H(8C) | 6138(7) | 2148(20) | -1904(3) | 125 |
| H(2') | 6627(5) | 6671(13) | 5620(3) | 54 |
| H(9'A) | 7784(8) | 7561(23) | 7145(4) | 140 |
| H(9'B) | 7167(8) | 5706(23) | 6865(4) | 140 |
| H(9'C) | 6971(8) | 7705(23) | 6541(4) | 140 |
| H(13') | 4711(6) | 5939(17) | 4547(4) | 76 |
| H(6'A) | 9092(7) | 5341(16) | 5165(4) | 82 |
| H(6'B) | 9745(7) | 4422(16) | 5753(4) | 82 |
| H(3') | 5798(6) | 2965(11) | 4409(3) | 141 |
| H(18A) | 5673(8) | 7332(18) | 2750(4) | 121 |
| H(18B) | 6027(8) | 5179(18) | 2667(4) | 121 |
| H(18C) | 6942(8) | 6800(18) | 2786(4) | 121 |
| H(16A) | 5197(7) | 9893(16) | 3985(5) | 89 |
| H(16B) | 5467(7) | 9731(16) | 3333(5) | 89 |
| H(20A) | 7632(8) | 9356(18) | 3521(5) | 136 |
| H(20B) | 8188(8) | 8251(18) | 4091(5) | 136 |
| H(20C) | 7536(8) | 10184(18) | 4149(5) | 136 |
| H(19A) | 7307(7) | 4232(14) | 4117(4) | 90 |
| H(19B) | 7910(7) | 4959(14) | 3600(4) | 90 |
| H(19C) | 6997(7) | 3334(14) | 3483(4) | 90 |
| H(1') | 7861(6) | 4126(12) | 5896(3) | 57 |
| H(5'A) | 9797(6) | 8249(17) | 5438(4) | 89 |
| H(5'B) | 10482(6) | 7317(17) | 6015(4) | 89 |
| H(8'A) | 10036(8) | 5227(18) | 6690(4) | 120 |
| H(8'B) | 9124(8) | 4314(18) | 7022(4) | 120 |
| H(8'C) | 9638(8) | 6342(18) | 7216(4) | 120 |
| H(12') | 5972(5) | 8306(12) | 4735(3) | 56 |
| H(10A) | 9991(10) | 9569(17) | 6825(5) | 150 |
| H(10B) | 8785(10) | 10456(17) | 6761(5) | 150 |
| H(10C) | 9579(10) | 11019(17) | 6309(5) | 150 |
| H(15A) | 3911(7) | 7562(18) | 3784(4) | 92 |
| H(15B) | 4196(7) | 7377(18) | 3136(4) | 92 |

Table 4. Bond angles [deg]

| | |
|---|---|
| C(12)-O(1)-C(2) | 114.9(5) |
| O(1)-C(12)-C(11) | 112.2(5) |
| O(1)-C(12)-C(13) | 111.7(7) |
| C(11)-C(12)-C(13) | 102.7(5) |
| O(1)-C(2)-C(1) | 112.6(6) |
| O(1)-C(2)-C(3) | 112.7(6) |
| C(1)-C(2)-C(3) | 100.9(6) |
| C(18)-C(17)-C(11) | 115.7(7) |
| C(18)-C(17)-C(19) | 107.0(7) |
| C(11)-C(17)-C(19) | 114.1(6) |
| C(18)-C(17)-C(14) | 112.9(6) |
| C(11)-C(17)-C(14) | 93.2(5) |
| C(19)-C(17)-C(14) | 113.9(7) |
| O(2)-C(3)-C(4) | 127.2(8) |
| O(2)-C(3)-C(2) | 124.0(7) |
| C(4)-C(3)-C(2) | 106.8(7) |
| C(6)-C(1)-C(2) | 107.4(6) |
| C(6)-C(1)-C(7) | 103.9(7) |
| C(2)-C(1)-C(7) | 103.3(7) |
| C(12)-C(11)-C(16) | 104.5(6) |
| C(12)-C(11)-C(17) | 104.9(6) |
| C(16)-C(11)-C(17) | 101.3(6) |
| C(12)-C(11)-C(20) | 114.6(7) |
| C(16)-C(11)-C(20) | 114.1(8) |
| C(17)-C(11)-C(20) | 116.0(7) |
| C(10)-C(4)-C(3) | 115.2(8) |
| C(10)-C(4)-C(7) | 119.8(7) |
| C(3)-C(4)-C(7) | 99.9(6) |
| C(10)-C(4)-C(5) | 115.9(8) |
| C(3)-C(4)-C(5) | 102.5(6) |
| C(7)-C(4)-C(5) | 100.7(7) |
| C(13)-C(14)-C(15) | 105.1(8) |
| C(13)-C(14)-C(17) | 103.9(6) |
| C(15)-C(14)-C(17) | 100.7(7) |
| C(9)-C(7)-C(1) | 115.2(8) |
| C(9)-C(7)-C(4) | 112.6(7) |
| C(1)-C(7)-C(4) | 94.4(5) |
| C(9)-C(7)-C(8) | 108.2(7) |
| C(1)-C(7)-C(8) | 114.4(7) |
| C(4)-C(7)-C(8) | 111.4(8) |
| C(11)-C(16)-C(15) | 102.6(8) |
| C(6)-C(5)-C(4) | 104.6(7) |
| C(1)-C(6)-C(5) | 102.3(8) |
| C(14)-C(15)-C(16) | 104.0(6) |
| O(3)-C(13)-C(14) | 112.9(8) |
| O(3)-C(13)-C(12) | 113.6(6) |
| C(14)-C(13)-C(12) | 104.2(6) |
| C(2')-O(1')-C(12') | 115.4(5) |
| C(19')-C(17')-C(18') | 105.9(6) |
| C(19')-C(17')-C(11') | 115.1(6) |
| C(18')-C(17')-C(11') | 114.7(7) |
| C(19')-C(17')-C(14') | 115.8(7) |
| C(18')-C(17')-C(14') | 112.2(6) |
| C(11')-C(17')-C(14') | 93.1(5) |
| O(1')-C(2')-C(1') | 112.6(6) |
| O(1')-C(2')-C(3') | 112.4(7) |
| C(1')-C(2')-C(3') | 102.9(6) |
| C(12')-C(11')-C(20') | 114.2(6) |
| C(12')-C(11')-C(17') | 104.7(6) |
| C(20')-C(11')-C(17') | 117.5(7) |

Table 3. Bond lengths [A]

| | |
|---|---|
| O(1)-C(12) | 1.406(8) |
| O(1)-C(2) | 1.426(8) |
| C(12)-C(11) | 1.531(10) |
| C(12)-C(13) | 1.554(11) |
| C(2)-C(1) | 1.521(11) |
| C(2)-C(3) | 1.544(11) |
| C(17)-C(18) | 1.534(10) |
| C(17)-C(11) | 1.545(10) |
| C(17)-C(19) | 1.537(10) |
| C(17)-C(14) | 1.569(10) |
| C(3)-O(2) | 1.209(11) |
| C(3)-C(4) | 1.516(11) |
| C(1)-C(6) | 1.505(11) |
| C(1)-C(7) | 1.529(11) |
| C(11)-C(16) | 1.541(11) |
| C(11)-C(20) | 1.528(12) |
| C(4)-C(10) | 1.497(11) |
| C(4)-C(7) | 1.562(11) |
| C(4)-C(5) | 1.562(12) |
| C(14)-C(13) | 1.515(11) |
| C(14)-C(15) | 1.52(2) |
| O(3)-C(13) | 1.419(12) |
| C(7)-C(9) | 1.510(12) |
| C(7)-C(8) | 1.542(11) |
| C(16)-C(15) | 1.56(2) |
| C(5)-C(6) | 1.55(2) |
| O(1')-C(2') | 1.417(8) |
| O(1')-C(12') | 1.445(8) |
| C(17')-C(19') | 1.517(11) |
| C(17')-C(18') | 1.538(10) |
| C(17')-C(11') | 1.535(10) |
| C(17')-C(14') | 1.558(9) |
| C(2')-C(1') | 1.498(11) |
| C(2')-C(3') | 1.560(13) |
| C(9')-C(7') | 1.527(11) |
| C(11')-C(12') | 1.512(10) |
| C(11')-C(20') | 1.533(11) |
| C(11')-C(16') | 1.552(10) |
| C(13')-O(3') | 1.407(13) |
| C(13')-C(14') | 1.515(12) |
| C(13')-C(12') | 1.582(12) |
| C(6')-C(1') | 1.523(11) |
| C(6')-C(5') | 1.53(2) |
| C(7')-C(1') | 1.535(10) |
| C(7')-C(8') | 1.534(12) |
| C(7')-C(4') | 1.549(12) |
| C(4')-C(10') | 1.514(13) |
| C(4')-C(3') | 1.533(12) |
| C(4')-C(5') | 1.550(12) |
| C(14')-C(15') | 1.505(14) |
| C(16')-C(15') | 1.54(2) |
| O(2')-C(3') | 1.206(13) |

| | |
|---|---|
| C(12')-C(11')-C(16') | 102.6(6) |
| C(20')-C(11')-C(16') | 114.5(8) |
| C(17')-C(11')-C(16') | 101.6(6) |
| O(3')-C(13')-C(14') | 116.4(9) |
| O(3')-C(13')-C(12') | 113.5(6) |
| C(14')-C(13')-C(12') | 101.5(7) |
| C(1')-C(6')-C(5') | 103.0(7) |
| C(9')-C(7')-C(1') | 114.9(7) |
| C(9')-C(7')-C(8') | 107.4(7) |
| C(1')-C(7')-C(8') | 114.4(7) |
| C(9')-C(7')-C(4') | 113.2(9) |
| C(1')-C(7')-C(4') | 93.6(6) |
| C(8')-C(7')-C(4') | 113.1(7) |
| C(10')-C(4')-C(3') | 114.1(8) |
| C(10')-C(4')-C(7') | 118.5(8) |
| C(3')-C(4')-C(7') | 101.1(7) |
| C(10')-C(4')-C(5') | 114.7(8) |
| C(3')-C(4')-C(5') | 104.3(7) |
| C(7')-C(4')-C(5') | 102.2(7) |
| C(15')-C(14')-C(13') | 106.5(8) |
| C(15')-C(14')-C(17') | 102.1(8) |
| C(13')-C(14')-C(17') | 104.0(6) |
| C(15')-C(16')-C(11') | 102.9(8) |
| O(2')-C(3')-C(4') | 127.8(10) |
| O(2')-C(3')-C(2') | 124.5(8) |
| C(4')-C(3')-C(2') | 103.4(8) |
| C(2')-C(1')-C(6') | 107.1(6) |
| C(2')-C(1')-C(7') | 102.8(6) |
| C(6')-C(1')-C(7') | 103.4(6) |
| C(6')-C(5')-C(4') | 103.9(6) |
| O(1')-C(12')-C(11') | 112.2(5) |
| O(1')-C(12')-C(13') | 109.6(7) |
| C(11')-C(12')-C(13') | 103.8(5) |
| C(14')-C(15')-C(16') | 103.9(6) |