STUDIES IN ASYMMETRIC SYNTHESIS

THESIS

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by

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DEDICATION

This work is dedicated to my
Beloved Husband Dear Parents and
of course to you Suganthi and

Sugirdha

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Firstly, I would like to thank, Prof. Perry Kaye for the constant support, guidance, and confidence he showed throughout this investigation. It was both a privilege and an invaluable learning experience to work under his supervision. I would also like to thank Dr Richard Liddell, Rosemary George and Carlson Gelebe for help rendered. A special thank you to Stephenie Burton and Justin Hageman for proof reading the manuscript

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ABSTRACT

The stereoselectivity of $TiCl_4$-catalysed Mukaiyama reactions of a camphor acetal-derived chiral silyl enol ether with a range of substituted aromatic aldehydes has been examined. The enantiomeric excess in each of the resulting ß-hydroxy ketones, determined by ^1H NMR spectroscopy using the lanthanide chiral shift reagent $Pr(Etcf_3)$, ranged between 9 and 13%. The stereo-directing potential of the camphor acetal as a chiral auxiliary in the α-benzylation of carboxylate esters has been studied; the acids were chosen to illustrate substituent effects on asymmetric induction. The observed diastereoselectivity increased with increasing steric bulk of the ester group and α-benzylation of the *tert*-butylacetate derivative proceeded with 48% diastereoselectivity. It is proposed that the enolate adopts an *endo-s-trans* conformation in the transition state and preferential attack by the electrophile at the somewhat less hindered *Si*-face is supported by both the optical rotation data and computer modelling studies. Reductive cleavage and hydrolysis of one of the benzylated esters furnished known products from whose optical rotation the configuration of the major diastereomer was established.

In order to imrpove the steric advantage of *Si*-facial attack, methods of increasing the steric bulk of the blocking group were explored. A novel 2,2-propylenedioxy hydroxycamphor acetal and its 3,3-propylenedioxy analogue were prepared. Selected carboxylate esters of these propylenedioxy acetals were subjected to α-benzylation and the 2,2-(propylenedioxy)-3-*exo-tert*-butylacetate derivative showed a diastereoselectivity of 57% during α-benzylation. Hydrolysis of the α-benzylated phenylacetate analogue offered the known 2,3-diphenylpropanoic acid whose optical rotation indicated the preferred configuration at the new chiral centre to be (*R*), a result which is consistent with the proposed approach of the electrophile to the less hindered *Re*-face of the *endo-s-trans* enolate moiety and reflects an inversion of the configurational bias observed with 2-

exo-carboxylate analogues.

Attempts to prepare the monocatechol acetal of the hydroxy camphor derivative although unsuccessful, led to the isolation of two novel dibornyl ethers whose structures were established by 1- and 2-D NMR spectroscopy.

A study of novel applications of camphor-derived auxiliaries in the asymmetric synthesis of α-amino acids has been initiated. The several approaches tried led to the preparation of three novel chiral glycine derivatives in good yield.

1. INTRODUCTION

The art of asymmetric synthesis is in controlling reactions so that one enantiomer or diastereomer is produced predominantly or exclusively. There are many examples of pharmaceuticals, food additives, fragrances, and agrochemicals where the desired biological property is strongly related to a given absolute configuration. Of the 10 most important pharmaceutical compounds listed in order of the revenues from their estimated worldwide sales during 1990, five are chiral.[1] More than 50% of the commercially available drugs have chiral centres and therefore may exist as paired enantiomers.[2] One enantiomer may well be pharmacologically active whereas the other may be inactive or even toxic. For example, pharmacokinetic differences between enantiomers may have contributed to the liver and kidney failure that resulted in some deaths and led to the withdrawal of benoxaprofen (Eli Lilly's Orafex) from the market in 1982.[3] The painful consequences of Thalidomide medication,[4] which have been attributed to the (*S*)-(-)-enantiomer,[5] emphasise the importance of asymmetric synthesis.

1.1 GENERAL ASYMMETRIC SYNTHESIS

Asymmetric synthesis is the single area in Organic Synthesis that has undergone greatest development during the last ten years,[6] and may be described as a process whereby a prochiral unit is converted into a chiral unit in such a way that unequal amounts of stereoisomeric products are formed.[7] The basic strategy underlying all asymmetric synthesis involves using a naturally occurring, enantiomerically pure compound to influence the stereochemical outcome of the reaction sequence. The known methods of asymmetric synthesis may be conveniently classified into four types, according to how the

enantiomerically pure compound is used.

(i). `First generation' or substrate-controlled methods.

(ii `Second generation' or auxiliary-controlled methods.

(iii) `Third generation' or reagent-controlled methods.

(iv) `Fourth generation' or catalyst-controlled methods.

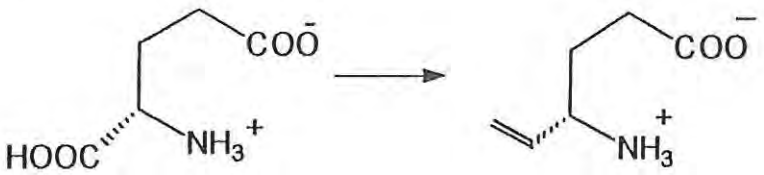
An additional method which involves memory of chirality may well prove to be very useful in the future.[8]

1.1.1 First Generation or Substrate-Controlled Method

The chiral carbon pool consists of enantiomerically pure substances such as amino acids, carbohydrates, terpenes, alkaloids, steroids, *etc.*, that are available in substantial quantities from natural sources. These natural products can be converted synthetically into other chiral compounds with either retention or inversion of configuration about the chiral centre. For example, starting from L-glutamic acid **1**, the asymmetric synthesis of 4-aminohex-5-enoic acid (vinyl GABA) **2**; a potent inhibitor of 4-aminobutyrate-2-oxoglutarate amino-transferase (GABA-T) has been accomplished in six steps, with retention of configuration at the chiral centre (Scheme 1).[9]

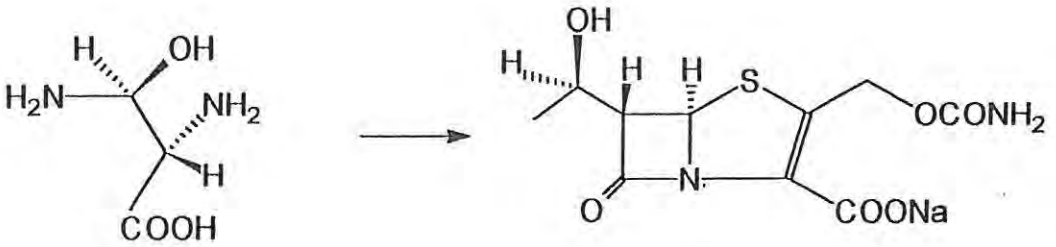
The 15-step conversion of (-)-threonine **3**, a naturally occurring amino acid with two adjacent stereogenic centres, into a **penem** antibiotic **4**, which has three stereogenic centres, also involves first generation processes (Scheme 2).[10]

SCHEME 1



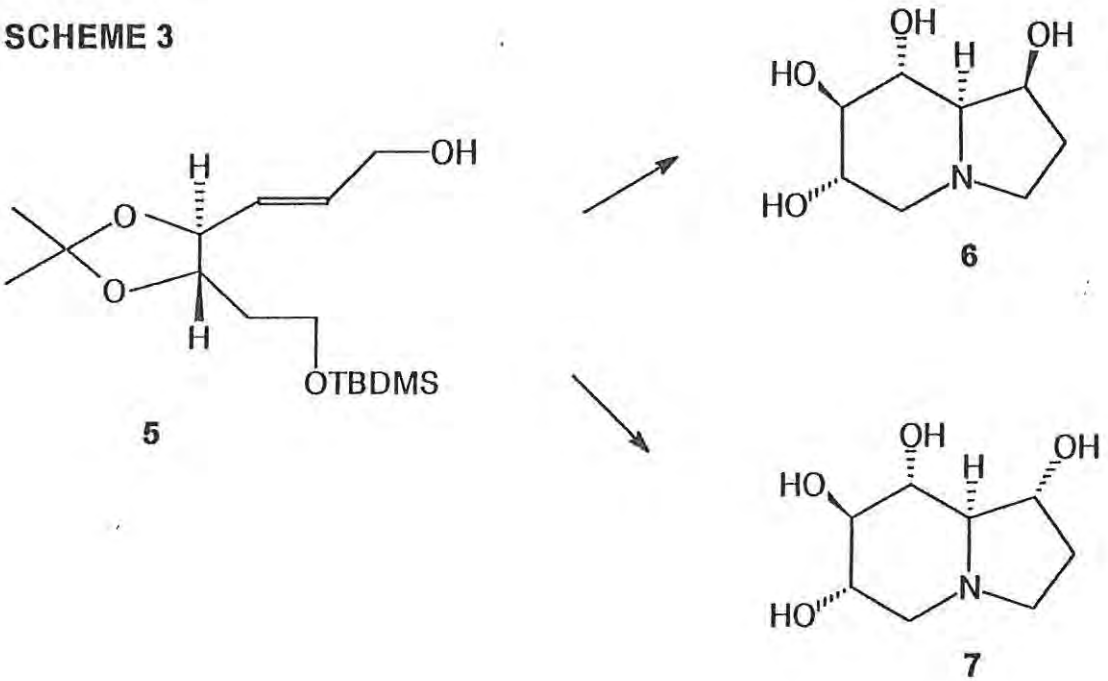
1 **2**

SCHEME 2



3 **4**

SCHEME 3



5 **6** **7**

The stereoselective total syntheses of (+)-castanospermine **6** and (+)-1-epicastanospermine **7**, which are anti-cancer and anti-HIV agents, have been achieved using the chiral allylic alcohol **5** as a common building block.[11] It has been shown that alteration of any of the five chiral centres in compound **7** changes its inhibitory action significantly and so its stereo-controlled synthesis is crucial (Scheme 3).[12]

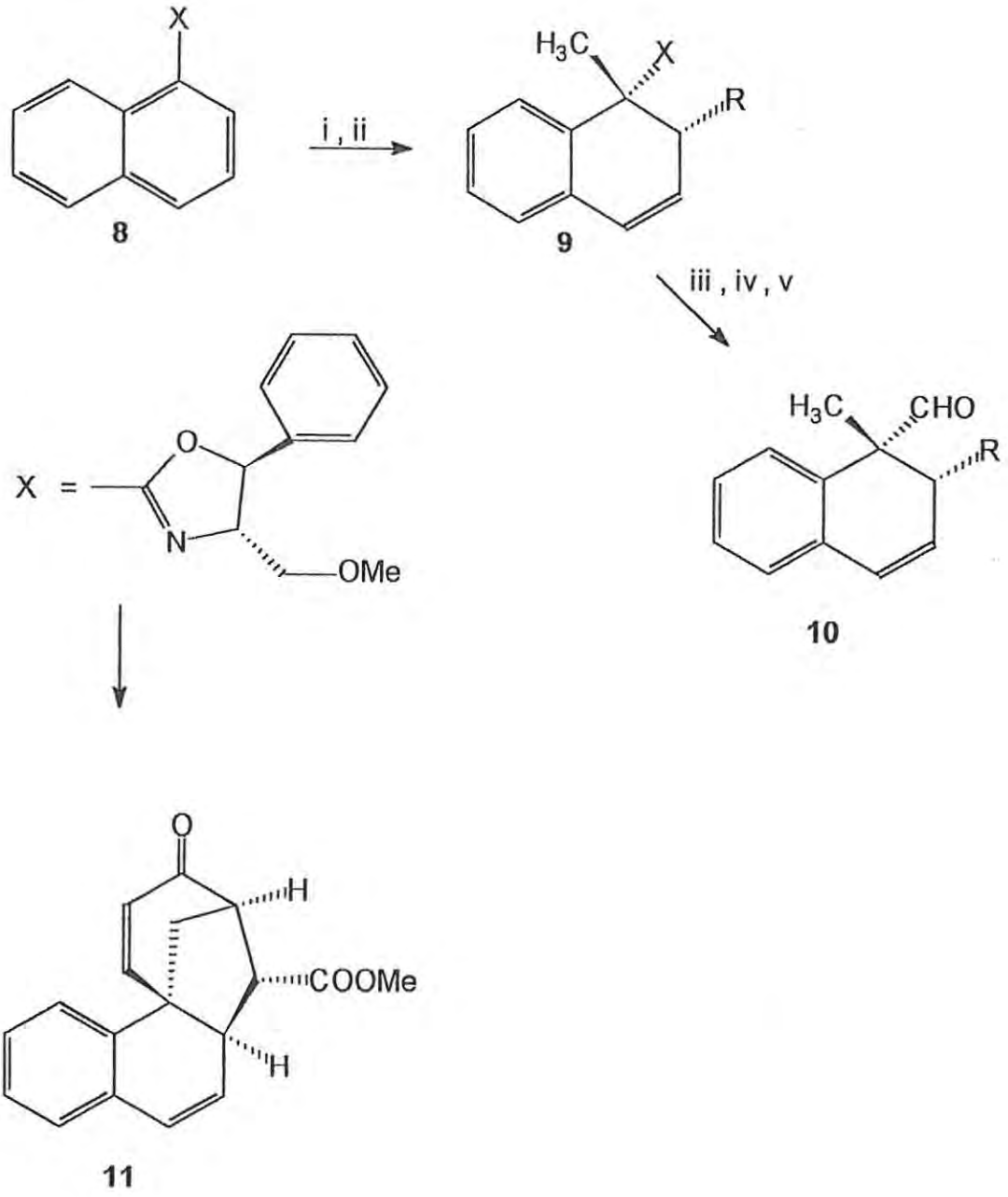
1.1.2 Second Generation or Auxiliary-Controlled Methods

Most of the recently developed methods in asymmetric synthesis fall into this category. In the auxiliary-controlled method, an achiral unit is made chiral by attaching it to a chiral auxiliary, which directs the stereochemical course of the subsequent reaction and is finally removed to give the chiral product. In most cases, the chiral auxiliary can be recycled.

Oxazolidines,[13] chiral oxazolines,[14] camphor sultams[15] and the proline derivatives, RAMP and SAMP,[16] have all been successfully used as chiral auxiliaries. For example, Meyers *et al.*[17] have recently introduced the chiral oxazolines **8**, and have successfully carried out asymmetric reactions on aromatic substrates (Scheme 4) as well as establishing an efficient entry into various tetracyclic terpene systems related to aphidocolin **11**.

The Diels-Alder reaction represents one of the most effective methods of creating four contiguous chiral centres with predictable regio- and stereochemistry. The study of asymmetric Diels-Alder reactions, has focused on the design of chiral dienophiles and dienes and the following examples illustrate recent synthetic accomplishments.

SCHEME 4



REAGENTS

i, RLi ; ii , CH_3I ; iii, MeOTf ; iv , $NaBH_4$; v $(COOH)_2$.

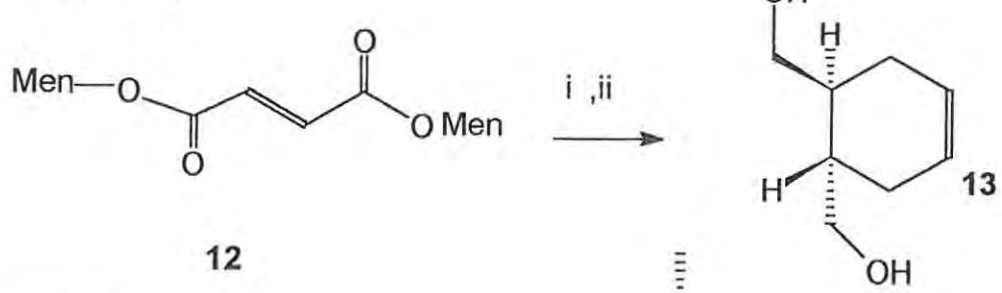
An optically active adduct obtained *via* the Diels-Alder reaction of dimenthyl fumarate and 1,3-butadiene, was used as a key intermediate in the stereospecific synthesis of compound **13**, a monocyclic analogue of compactin, by Heathcock *et al.*[18] (Scheme 5). More recently, the preparation of a new class of camphor lactam imides **14** and **15** as chiral auxiliaries, and their application in the construction of quaternary centres *via* Lewisacid-promoted Diels-Alder cycloaddition reactions, has been accomplished by Boeckman *et al.*[19] (Scheme 6). The major adduct **16** was obtained in a material yield of 98% and in diastereomeric excess of 82%. Removal of the chiral auxiliary by reduction using LAH afforded the alcohol **17**.

The chiral auxiliaries (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine, known more familiarly as SAMP **18** and RAMP **19** respectively, have been developed by Enders and co-workers.[20] Optically active α-substituted aldehydes are available from primary aldehydes *via* alkylation of SAMP hydrazones **21** and reductive amination of these hydrazones provides an enantioselective route to β-chiral primary amines **22** in 99% e.e. (Scheme 7). By simply changing the Cahn-Ingold-Prelog (CIP) priorities of substituents R^1 and R^2, it is possible to prepare both enantiomers of a single aldehyde using only SAMP. This procedure, which is known as "opposite enantioselectivity through synthon control," constitutes a useful trick in asymmetric synthesis.[20]

1.1.3 Third Generation Method - The Use of Chiral Reagents

Use of a chiral reagent, which converts the achiral substrate directly into a chiral product may provide a convenient alternative approach. Asymmetric hydroboration,[21] reduction[22] and epoxidation[23] reactions may fall into this category.

SCHEME 5

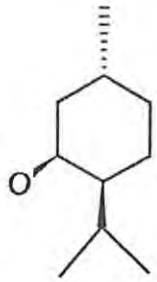


12 **13**

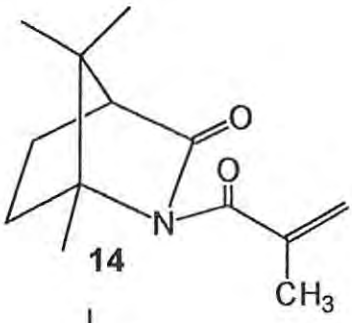
REAGENTS

i,cyclopentadiene; ii, LAH.

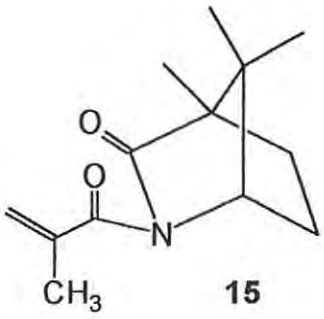
Men =



SCHEME 6

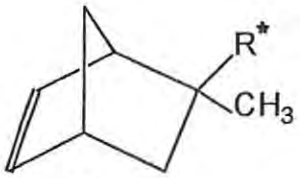


14



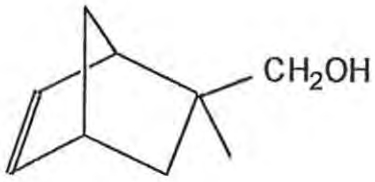
15

i, ii



16

iii



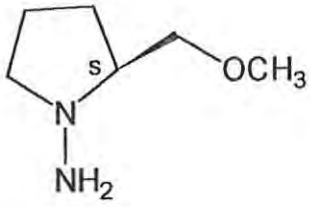
17

REAGENTS

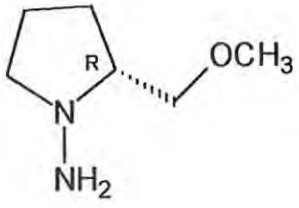
i , cyclopentadiene ii, CH_3AlCl_2 , iii , L A H .

In this and subsequent schemes, the notation R^* indicates the chiral auxiliary

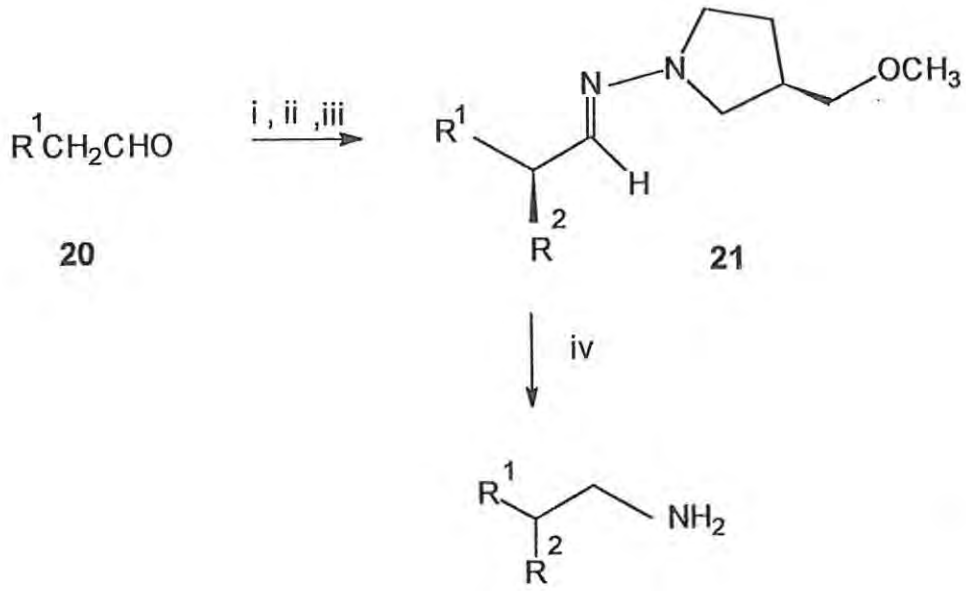
SCHEME 7



18 (SAMP)



19 (RAMP)



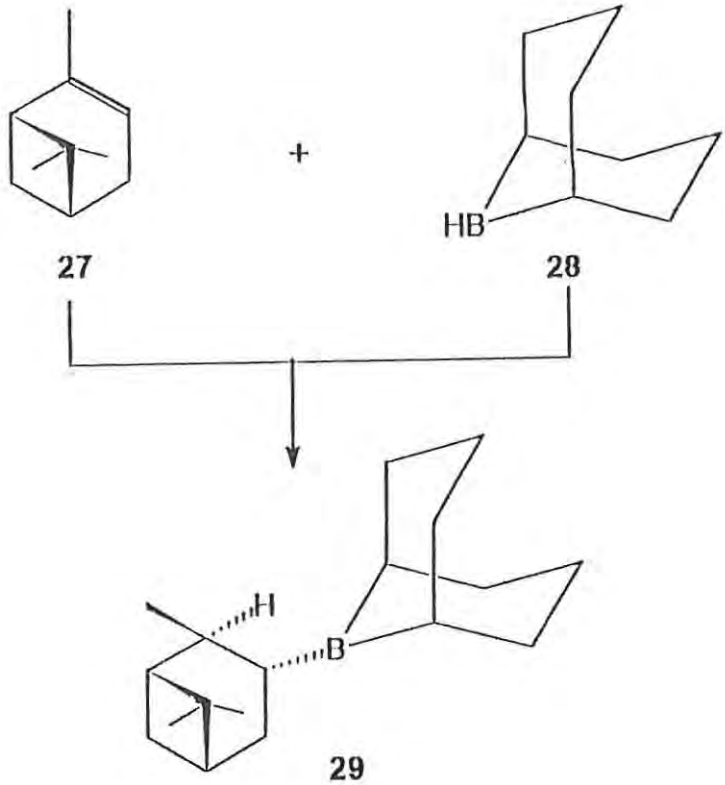
20 **21**

22

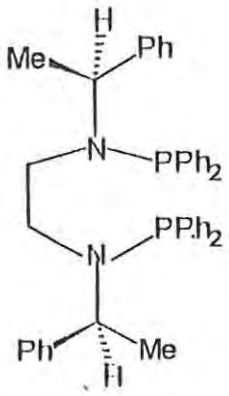
REAGENTS

i SAMP ; ii , LDA ; iii, R_2X ;IV LAH

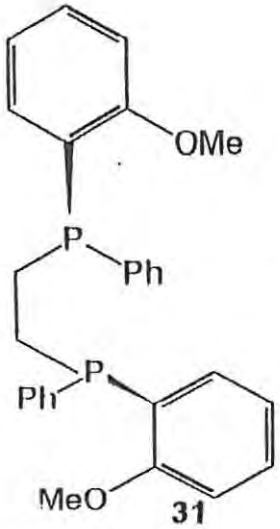
SCHEME 8



27 **28** **29**



30



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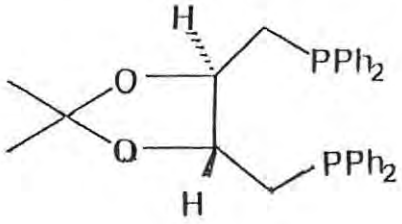


32

Alkyl borane intermediates, obtained by the reaction of diisopinocamphenylbornane (Ipc_2BH) with alkenes, can be easily transformed into a variety of chiral products, such as alcohols, amines, alkyl halides, ketones or α-amino acids.[24,25] The optically active carotenoid building unit **25** has been developed using asymmetric hydroboration as the key reaction. Thus, sanfranyl 2-methoxy-2-propyl ether **24**, on hydroboration with (+)-Ipc_2BH **23** followed by oxidation, afforded the optically pure, key intermediate **25**, which was transformed into the carotenoid (3*R*, 3′*R*)-**3**-zeaxanthin **26**. The formation of chiral boranes by the hydroboration of terpenes yields other useful asymmetric reducing agents. For example, the reaction of (+)-α-pinene **27** with 9-borabicyclo[3.3.1]nonane(9-BBN) **28** is commercially available as `(*R*)-Alpine-Borane® **29** **(Scheme 8)**[26] and has been used to reduce a variety of ketones in high enantiomeric excess.

1.1.4 Fourth Generation or Catalyst-Controlled Methods

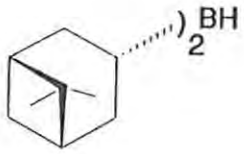
Reactions involving asymmetric catalysts can be arbitrarily divided into three classes, *viz.*,

(i) asymmetric catalysis by organometallic species;

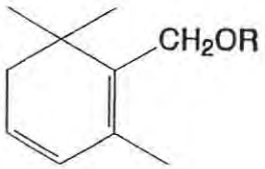
(ii) asymmetric catalysis by organic compounds; and

(iii) biochemical methods.

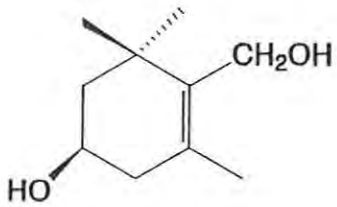
Catalysis by soluble organometallic complexes has opened the way for a generation of catalysts bearing chiral ligands. Chiral, chelating diphosphines, such as Pnnp **30**, dipamp **31** and diop **32** and hundreds of other patented chiral phosphines, have been successfully employed in industry for asymmetric hydrogenation.[27]



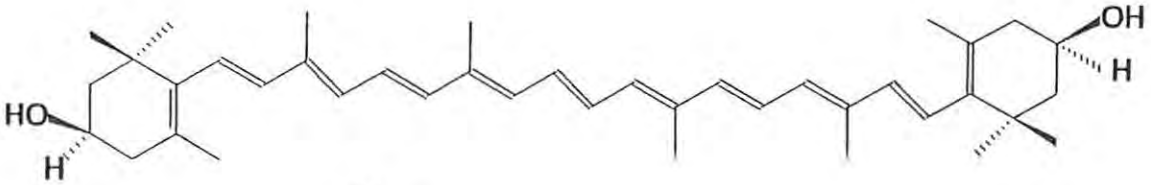
23



24



25



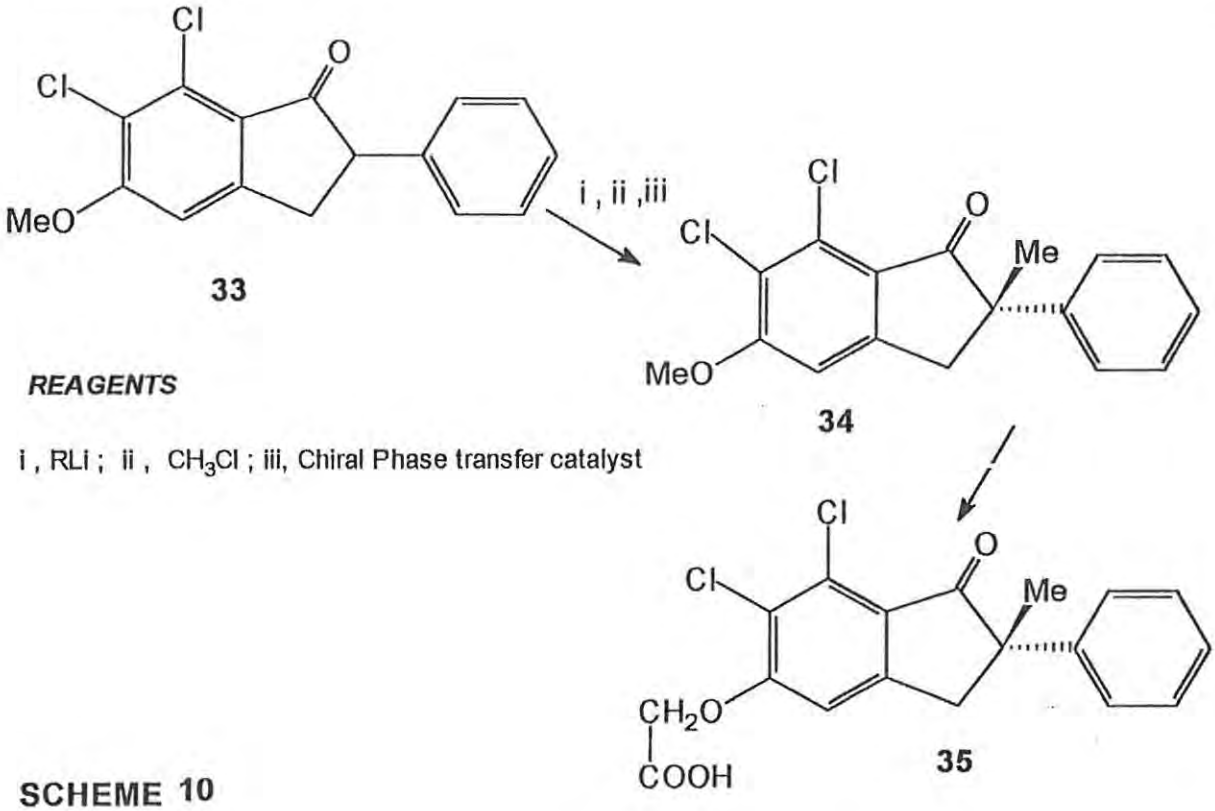
26

The Wilkinson catalyst, a rhodium complex, $RhCl(PPh_3)_3$, is able to catalyse the migration of a double bond to produce chiral products,[28] the major challenge being to find a substrate-catalyst duo such that the reaction is both enantioselective as well as irreversible. Noyori *et al.*[29] have described a unique system in which the isomerisation of prochiral allylamines into chiral enamines is catalysed by the chiral organometallic reagent $[Rh(binap)\ COD]^+\ BF_4^-$ in 99% enantiomeric excess.

The alkylation of the 2-phenyl-1-indanone **33** with methyl chloride to give the (*S*)-2-methyl product **34**, using the chiral phase-transfer catalyst *N*-*p*-trifluoromethyl-benzylcinchonium bromide, was successfully accomplished in 95% material yield and 92% e.e.[30] Compound **34** was subsequently transformed into (*S*)-indacrinone **35**, a drug that eliminates uric acid through the urine (Scheme 10). The (*R*)-enantiomer on the other hand, increases urine production and sodium excretion and is thus useful for treating hypertension. A controlled mixture of both enantiomers close to 90% e.e. in the (*S*)-enantiomer gives a "hybrid drug" of optimum therapeutic value. The molecular structure of the chiral catalyst may be altered to give any desired ratio of the enantiomers.

A novel asymmetric induction[8] which does not fall into any of the above categories is illustrated by the alkylation of the chiral ketone **36** with methyl or ethyl iodide, in the presence of potassium hydride and 18-crown-6, the products **38** being obtained in 66% e.e.. Treatment of the chiral ketone **36** with benzyl bromide or allyl bromide yielded the corresponding alkylated products **38** in 67% e.e.. This novel asymmetric induction can be rationalised in terms of a two step transfer of chirality.

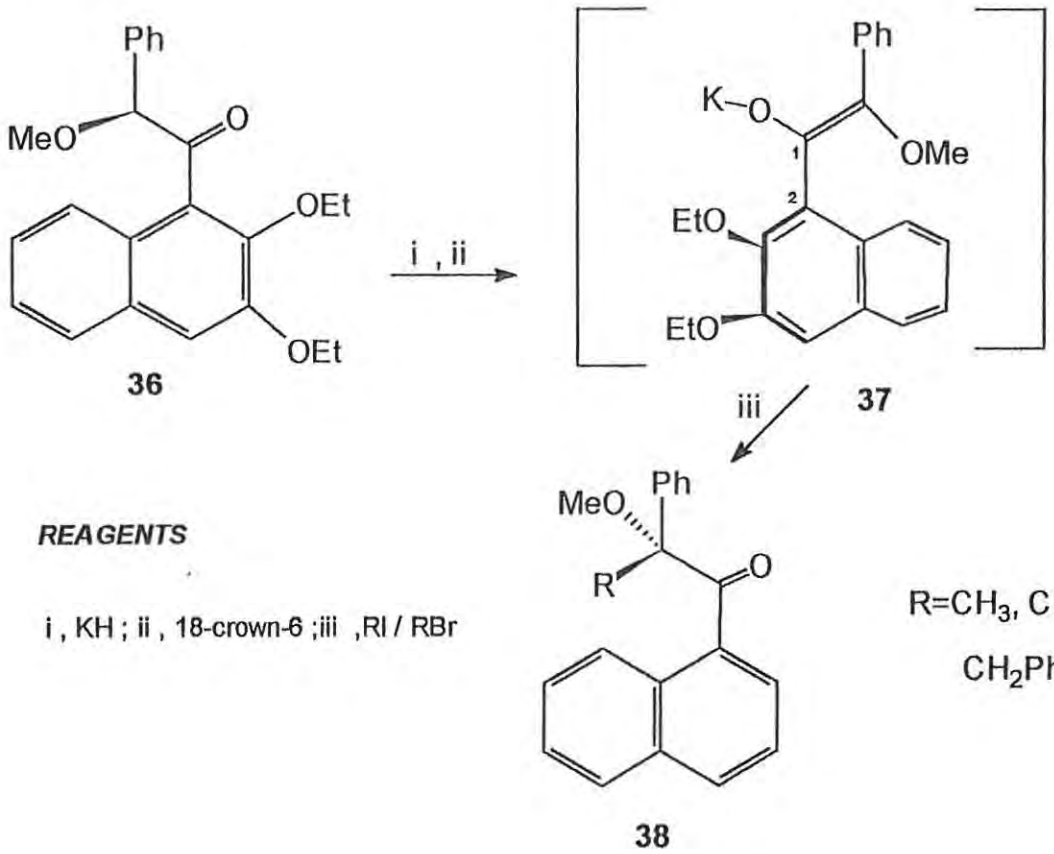
SCHEME 9



REAGENTS

i , RLi ; ii , CH_3Cl ; iii, Chiral Phase transfer catalyst

SCHEME 10



REAGENTS

i , KH ; ii , 18-crown-6 ;iii ,RI / RBr

R=CH_3, CH_2CH_3,
CH_2Ph, $CH_2CH{=}CH$

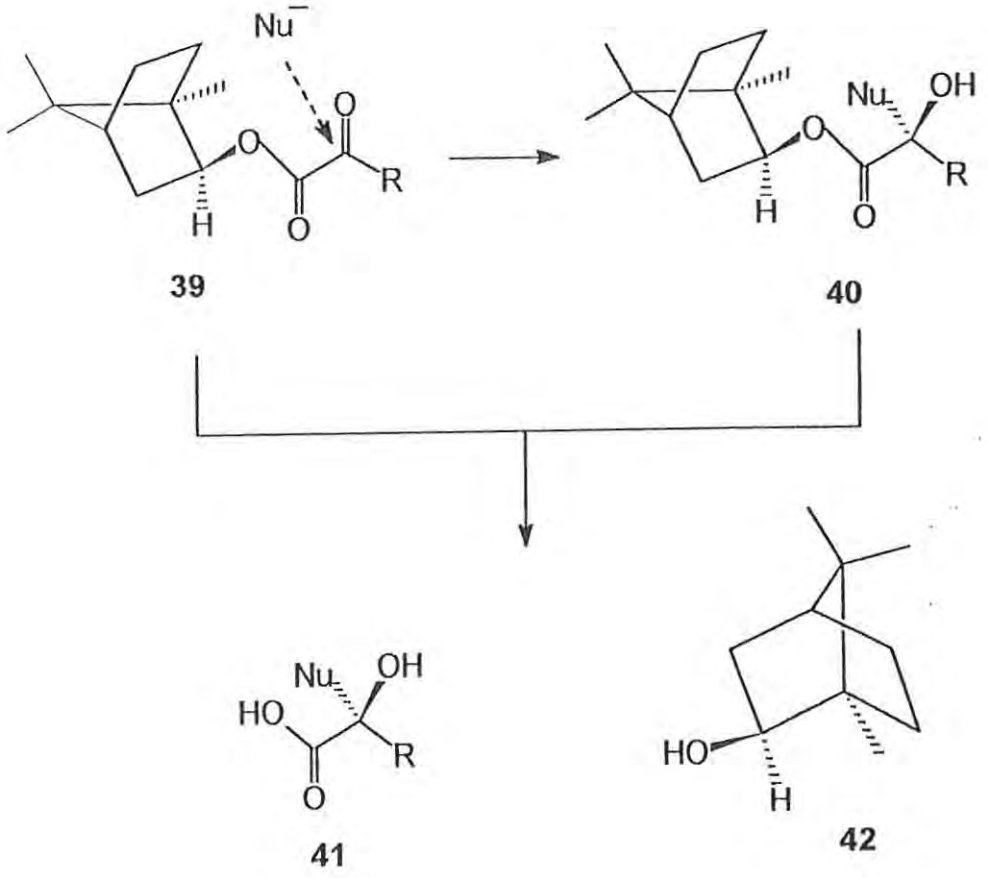
In the first step, the central chirality of the substrate **36** is transferred into axial chirality about the C_1-C_2 bond in the enolate **37**. The second step involves regeneration of central chirality in the product **38** by the reaction of the axially chiral enolate with the electrophile. It has been observed that the bulkiness of the electrophile does not affect enantioselectivity in this reaction. Thus, central chirality at a carbon α to a carbonyl group is preserved as transient axial chirality in the intermediate enolate and is then regenerated as a central chirality in the product reflecting a phenomenon which could be viewed as "*the memory of chirality*".

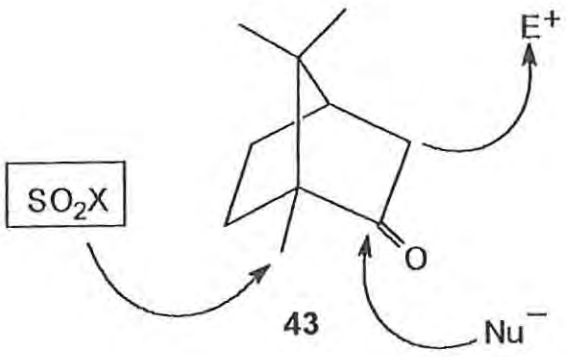
1.2 CAMPHOR DERIVATIVES AS CHIRAL AUXILIARIES IN ASYMMETRIC SYNTHESIS

Early attempts to effect stereoface-selective addition to substrates using camphor-derived chiral auxiliaries date back to 1906 (Scheme 11)[31,32] when Mackenzie reported nucleophilic addition to bornyl esters of α-keto acids (**39-40**). But it was only in 1955 that Prelog rationalised the observed asymmetric induction on the basis of preferred conformations and steric repulsion in the transition states.[33] The Reformatsky reaction of bornyl bromoacetate[34,35] and aldolisation of bornyl esters,[36] reported over the period 1946-1964, proceeded with only moderate asymmetric induction (< 15% and < 36% respectively). Nevertheless, the abundance, crystallinity and the manifold transformations of (+)-camphor **43** [and (-)-camphor] have continued to attracted considerable interest.

Around 1980, the field of asymmetric induction started to expand at an ever increasing rate and simultaneously, the advantage of the differentiating bias of the camphor skeleton became

SCHEME 11





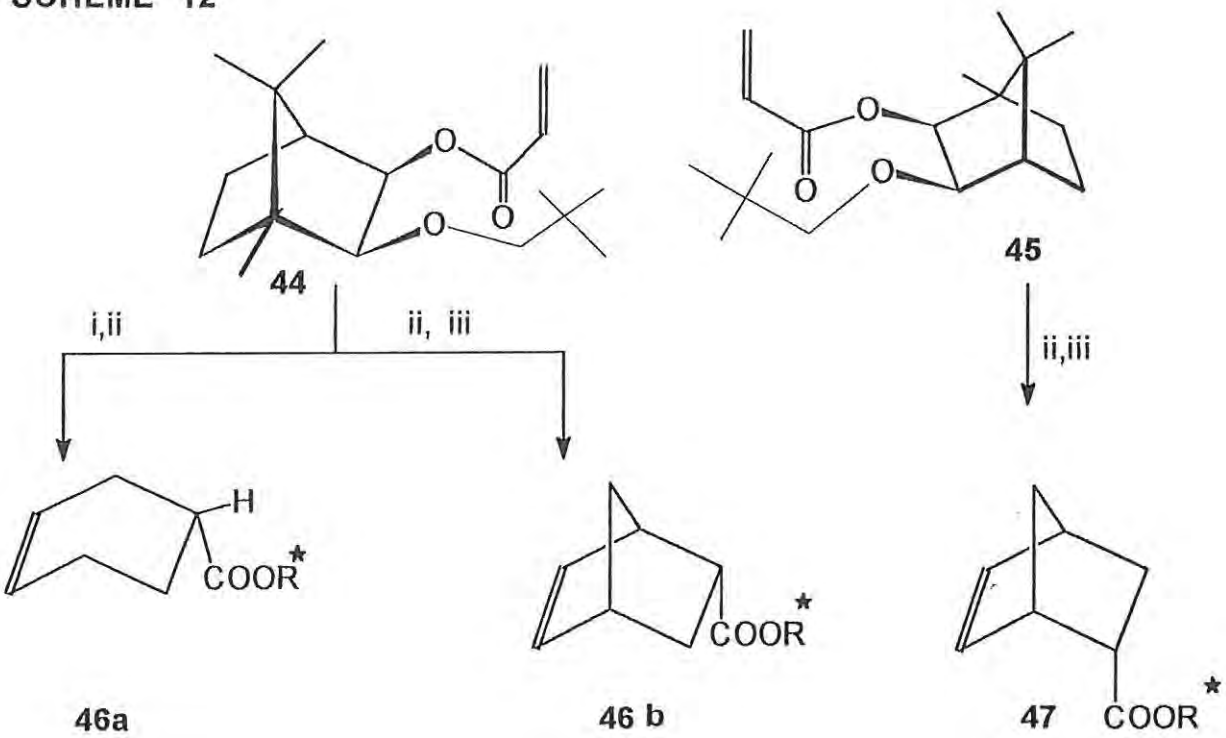
apparent and led to the logical design of conformationally rigid auxiliaries, where one diastereotopic face of a reactive π-bond is sterically shielded. A recent review by Oppolzer[37] addresses the issue of non-destructive chirality transfer from derivatives of camphor which serve as covalently bound auxiliaries. These camphor-derived chiral systems readily undergo a plethora of highly π-face selective Diels-Alder, aldol, Michael addition, alkylation and other reactions.

Application of these reactions in the asymmetric synthesis of natural products demonstrates their preparative potential. On the other hand camphor topicity may be incorporated into the target molecule.[38] This approach may involve direct or indirect introduction of functionality at C(2), C(3), C(5), C(8), C(9) and C(10) as well as cleavage of the C(1)-C(2), C(2)-C(3) and C(1)-C(7) bonds in the camphor system.

1.2.1 Camphor Auxiliaries in Diels-Alder Reactions

The Diels-Alder addition of 1,3-dienes to alkenes is of pre-eminent importance in organic synthesis. Oppolzer[39] reported the first, virtually quantitative asymmetric cycloaddition of dienes to the camphor acrylates **44** and **45** (Scheme 12). Acrylate coordination with a Lewis acid seems to play an essential role in ensuring an *s-trans* acrylate conformation in the transition state as well as increasing the reaction rate and the *endo* selectivity of the Diels-Alder process. Thus, by replacing $TiCl_4$ with a milder Lewis acid catalyst, e.g. $TiCl_2(O_iPr)_2$, and by decreasing the reaction temperature, efficient conversion of the acrylates to the adducts **46** and **47** in 88% to 92% d.e. was achieved.[40,41] By changing the substituent R from phenyl to 1-naphthyl or neopentyl, more efficient induction of up to 99.4% d.e. was achieved.

SCHEME 12



REAGENTS

i, 1,3-butadiene; ii, $TiCl_4$ or $TiCl_2(OiPr)_2$; iii, cyclopentadiene

Figure 1

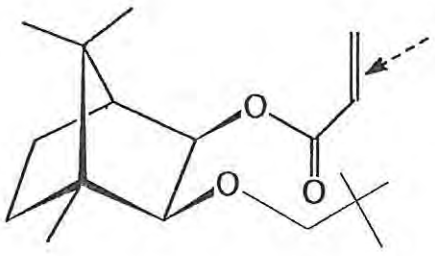
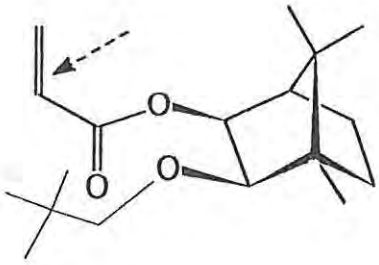


Figure 2

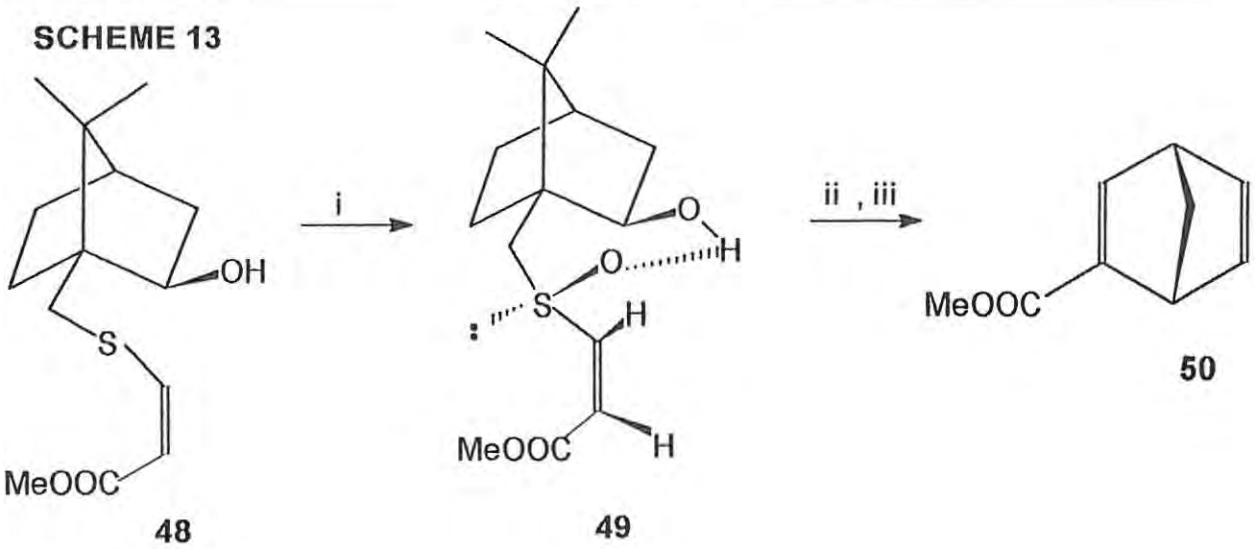


This can be explained[42] by the increased steric blocking of the C_α-*re*-face (and consequent *Si*-attack) in the acrylates **44** (Fig. 1) and the corresponding C_α-*Si*-face shielding (and *Re*-attack) in the enantiomeric systems **45** (Fig. 2). The auxiliary could be regenerated efficiently by reduction using lithium aluminium hydride(LAH).

The availability of both enantiomers of camphor-10-sulphonic acid,an inexpensive chemical, has prompted a most rewarding development of practical chiral auxiliaries. Elliel[43] was the first to develop a camphor-10-sulphonic acid derivative as a covalently bound chiral auxiliary and De Lucchi[44] subsequently used this chiral auxiliary in Diels-Alder reactions (Scheme 13). The reaction of cyclopentadiene with the *bis*-activated dienophile **49** proceeds virtually quantitatively to give the *endo*-adduct *via* addition to the face opposite to the hydrogen-bonded sulphoxide oxygen. The adduct, obtained in 98% d.e. when treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), yielded the enantiomerically pure norbornadiene **50**.

Acrylate derivatives of the commercially available, crystalline sulphonamides **51** and **52** show excellent π-face topology and may also serve as potential dienophile auxiliaries (Scheme 14).[45] The acrylate derivative **53**, for example, undergoes *endo*-selective $TiCl_2(O{i}Pr)_2$ promoted Diels-Alder cyclo-addition with cyclopentadiene to give the adduct **54a**, reductive cleavage of which regenerates the auxiliary **52** and affords the chiral alcohol **54**.

SCHEME 13

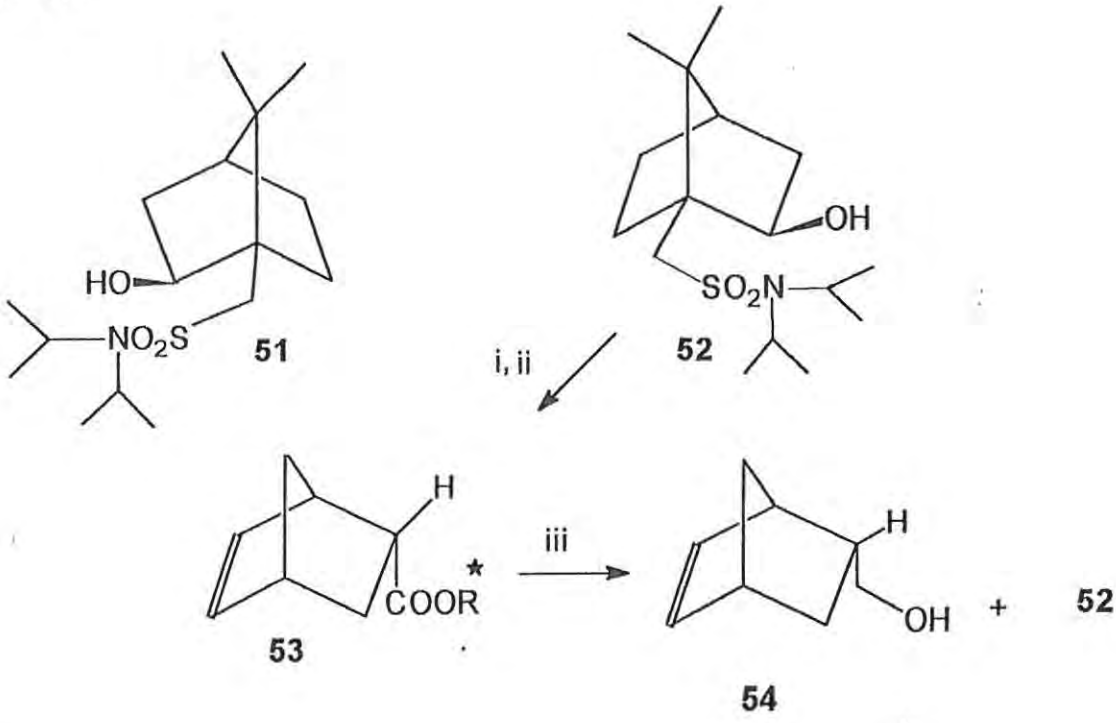


48 **49** **50**

REAGENTS

i, MCPBA; ii, cyclopentadiene; iii DBU.

SCHEME 14



REAGENTS

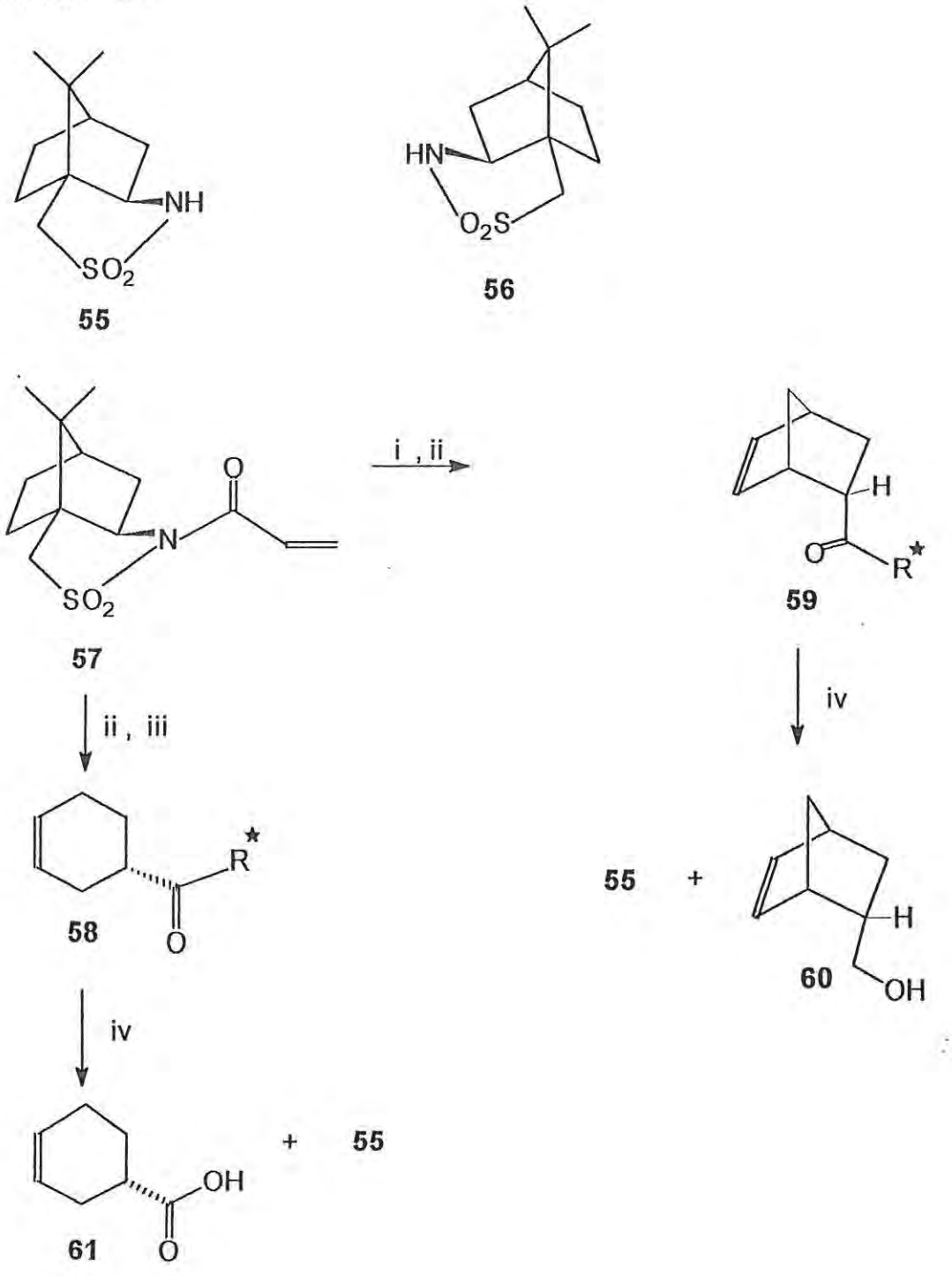
i, cyclopentadiene ; ii , $TiCl_2(OiPr)_2$; iii , LAH

The camphor derived antipodal Sultams **55** and **56** equally accessible in two simple steps from camphor-10-sulphonyl chloride, are today among the most fascinating chiral auxiliaries.[46] In the presence of $EtAlCl_2$ or $TiCl_4$, cyclopentadiene and butadiene add readily to the acryloyl sultam **57** (Scheme 15). The adducts **58** and **59** are formed with excellent *endo* selectivity. LAH reduction of the adduct **59** affords the alcohol **60** while saponification of the adduct **58** forms the acid **61**. Using auxiliary **56** and carrying out the same sequence of reactions, the sense of asymmetric induction was reversed.[47]

.2 Camphor Derivatives in Asymmetric Enolate Reactions

Camphor derivatives have been successfully used in various asymmetric aldol reactions. ›densation of benzylamine with (+)-camphor in the presence of $BF_3.Et_2O$, in toluene, affords the chiral ketimine **62**,[48] aldol condensation of which, with various aldehydes and ketones, provides an efficient synthetic route for the preparation of amines **65** and **66** in 50 to 70% e.e. (Scheme 16).[49] Ketopinic acid **68**, a new chiral synthon which is a 10-substituted (+)-camphor derivative, was successfully used by Yaozhong[50] for the asymmetric synthesis of α-substituted benzylamines with enantioselectivity approaching 100%. Starting from ethyl ketopinate **69**, derived from ketopinic acid,[52] Ahn[51] *et. al.* synthesised the first camphor-derived chiral auxiliary **71** having an oxazinone structure (Scheme 17). The aldol reaction of the *tris*-(isopropoxy)titanium enolate of the *N*-propionyloxazinone **72** with aldehyde afforded the "chelation controlled" *syn* aldols **72** with excellent stereoselection.

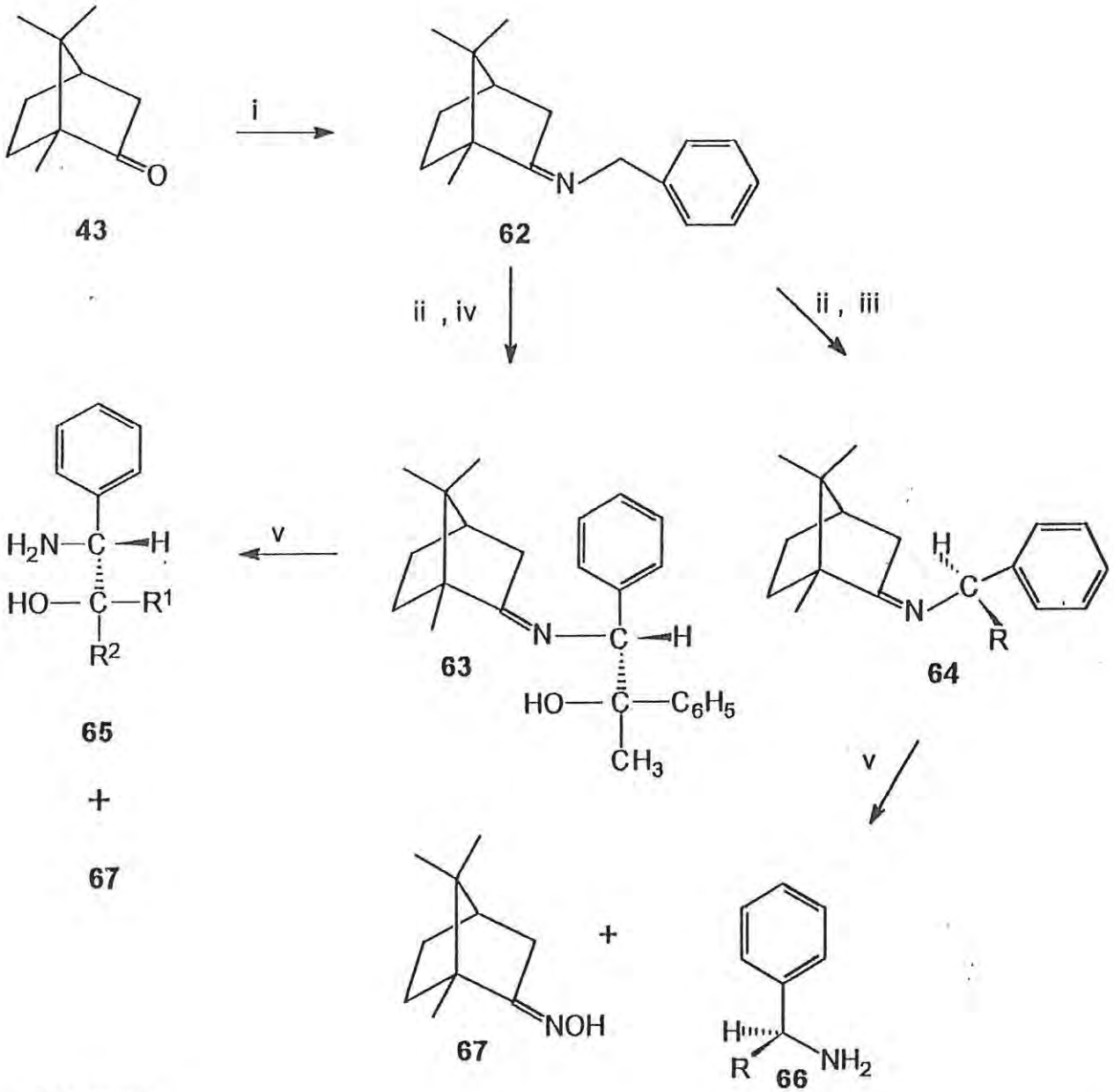
SCHEME 15



REAGENTS

i,cyclopentadiene; ii, $EtAlCl_2$; iii, 1,3-butadiene; iv, LAH.

SCHEME 16

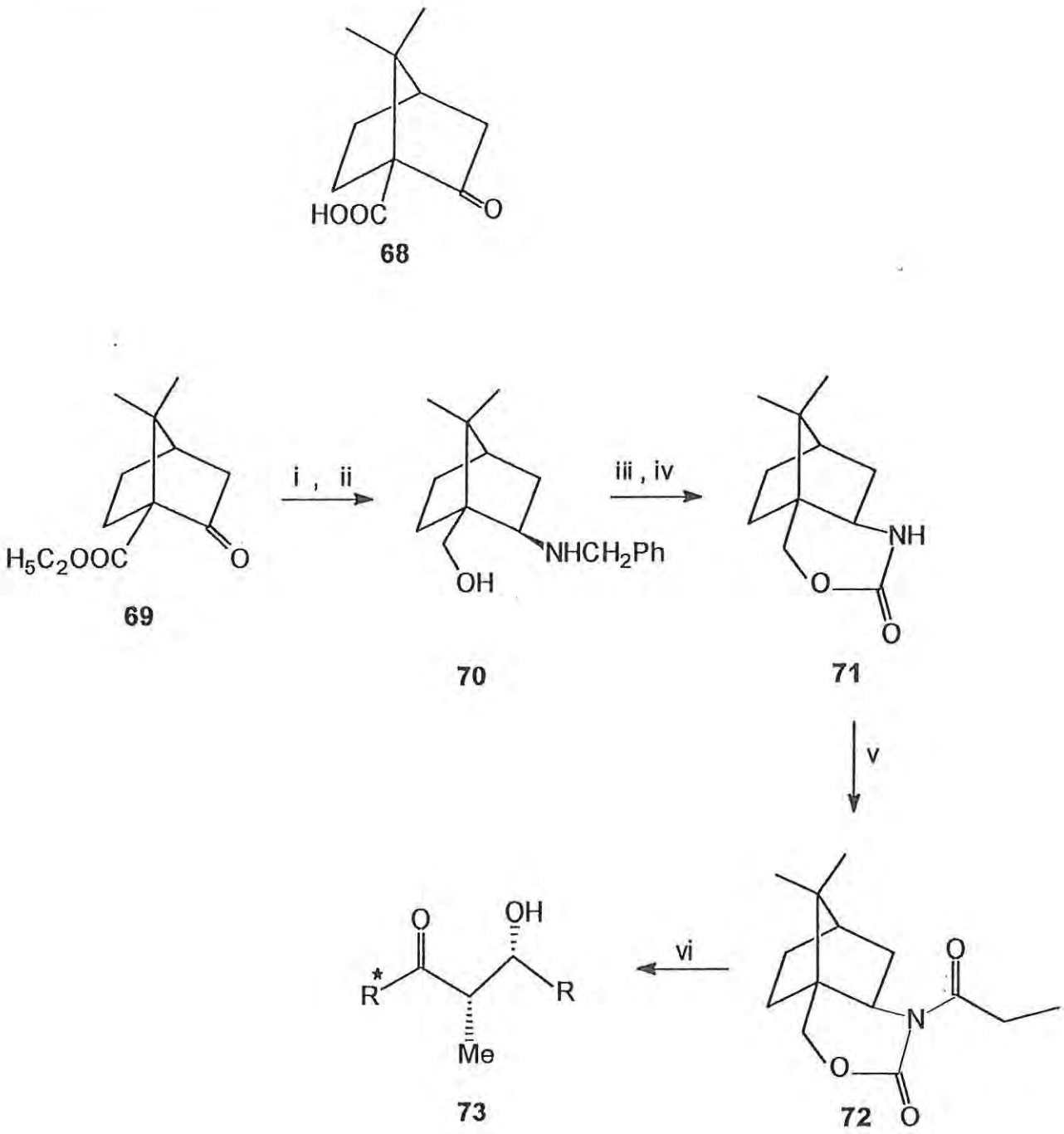


REAGENTS

I, $NH_2CH_2C_6H_5$; ii , BuLi; iii, RX; iv, $C_6H_5COCH_3$;

v, 0.5M $NH_2OH.CH_3COOH$

SCHEME 17



REAGENTS

i, $PhCH_2NH_2$, PTSA ; ii DIBAL–H ; iii, H_2/PdC ; iv,$(CCl_30)_2CO$;

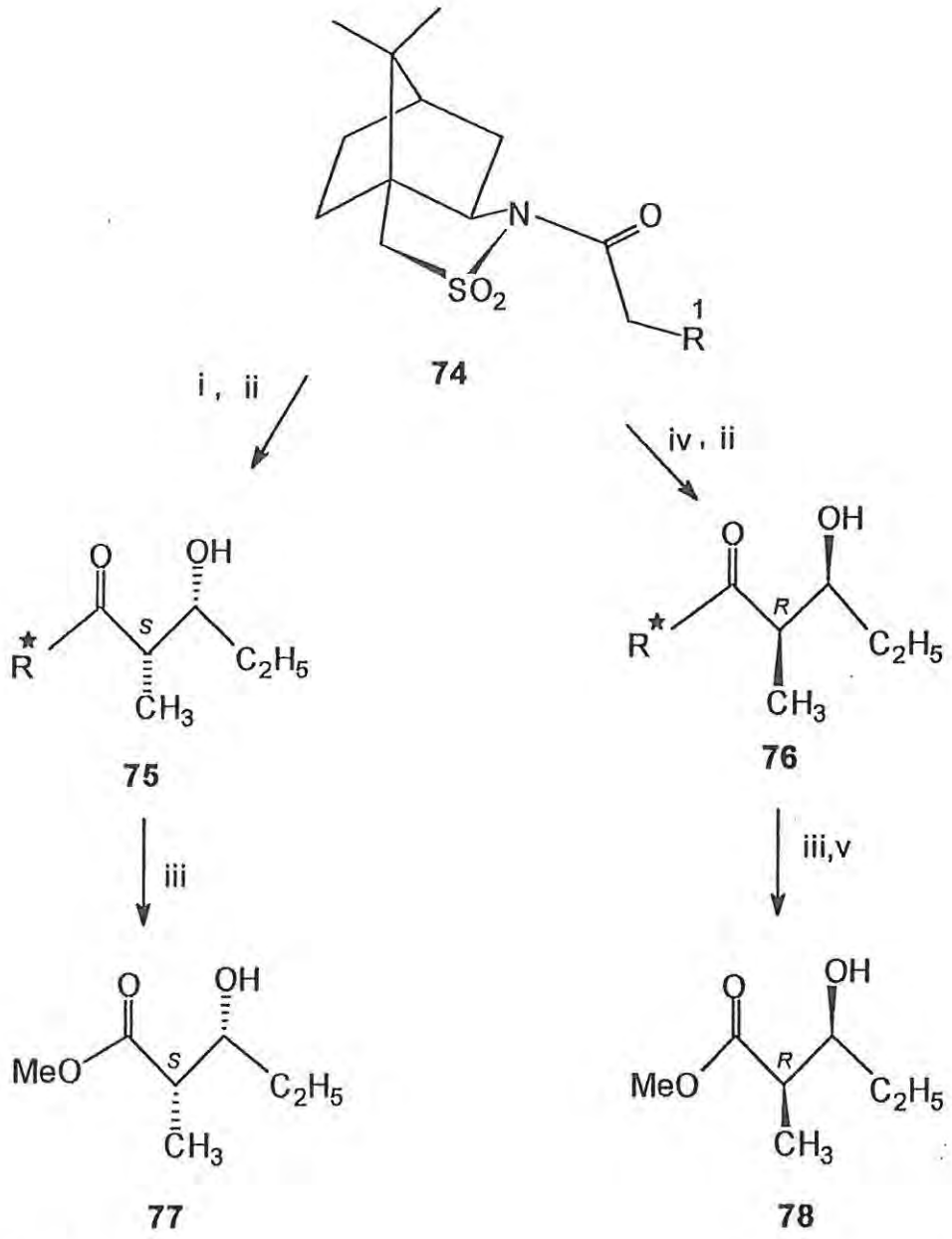
v BuLi, EtCOCl; vi ,LDA , RCHO.

Diastereomerically pure aldols can also be obtained from *N*-acyl camphor sultams **74** *via* aldolisation of their enolates, with aromatic or aliphatic aldehydes, and subsequent crystallisation.[52] The absolute product configuration is controlled by the choice of enolate counter ion. Thus, the boron mediated enolate anion yields the ester **76** with an *R*-configuration at the α-carbon while the Li enolate yields the corresponding ester **75** with an *S*-configuration at the α-carbon. Hydroperoxide assisted esterification provides enantiomerically pure methoxycarbonyl aldols **77** and **78** with complete recovery of the auxiliary (Scheme 18). The ester **78** was silylated and cleaved with diisobutyl aluminium hydride (DIBAL-H) to provide the alcohol **79A** which is a precursor for the cigarette beetle pheromone sericonin **79B**.[52]

Deprotonation of the *N*-acyl sultam **74**[53] (Scheme 19) with BuLi or sodium hexamethyl disilazide (NHDMS) in THF, followed by alkylation with benzylic, allylic or propargylic halides afforded C(α)-alkylated amides **80** in high yield and high diastereoselectivity. Non-destructive hydroperoxide assisted saponification of these products provided the chiral sultam auxiliary **55** and the enantiomerically pure carboxylic acids **81**, whereas reduction by LAH yielded the corresponding alcohols **82**.

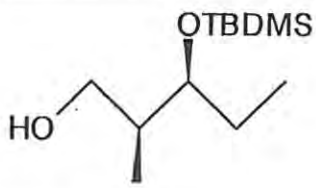
The sulphonamide shielded *exo*- and *endo*- alcohols **83** and **84**, which were introduced by Helmchen,[54] have proved to be valuable chiral auxiliaries in the asymmetric synthesis of various acids and alcohols. The sulphonamide moiety acts both as a steric shield and as a cation coordinating site and, as a result, in the α-alkylation of acylated derivatives of these chiral alcohols both diastereoselectivity and reactivity are enhanced.[55]

SCHEME 18

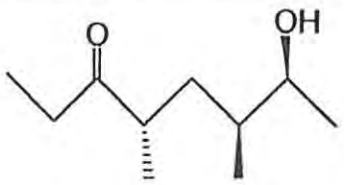


REAGENTS

i, BuLi , THF ; ii , R^2CHO ; iii , H_2O_2 , LiOH; iv , iPr_2NEt , R_2BOTf ; v, CH_2N_2.

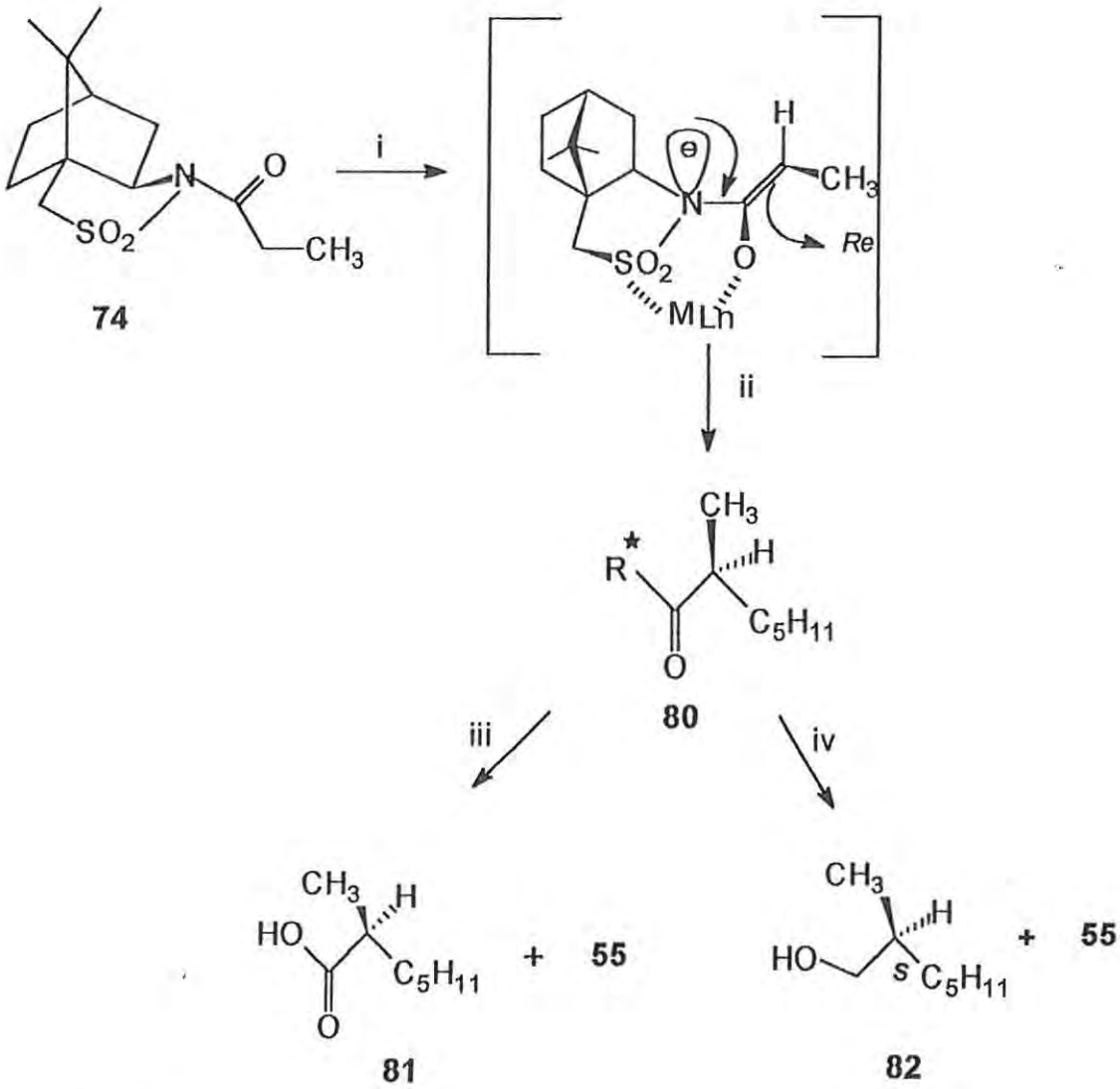


79A



79B

SCHEME 19



REAGENTS

i , BuLi , NHDMS; ii , $C_5H_{11}Cl$; iii, H_2O_2 , LiOH; iv , LAH.

The lithium enolates of the esters **85** and **86**, which are readily obtained from alcohols **84** and **83** respectively, undergo highly stereoselective $S_{cN'}$ type reactions to give the cyclopropyl derivatives **87** and **88**, saponification or reduction of which give the corresponding alcohol **89** or acid **90** with regeneration of the chiral auxiliaries **83** and **84** (Scheme 20).[56]

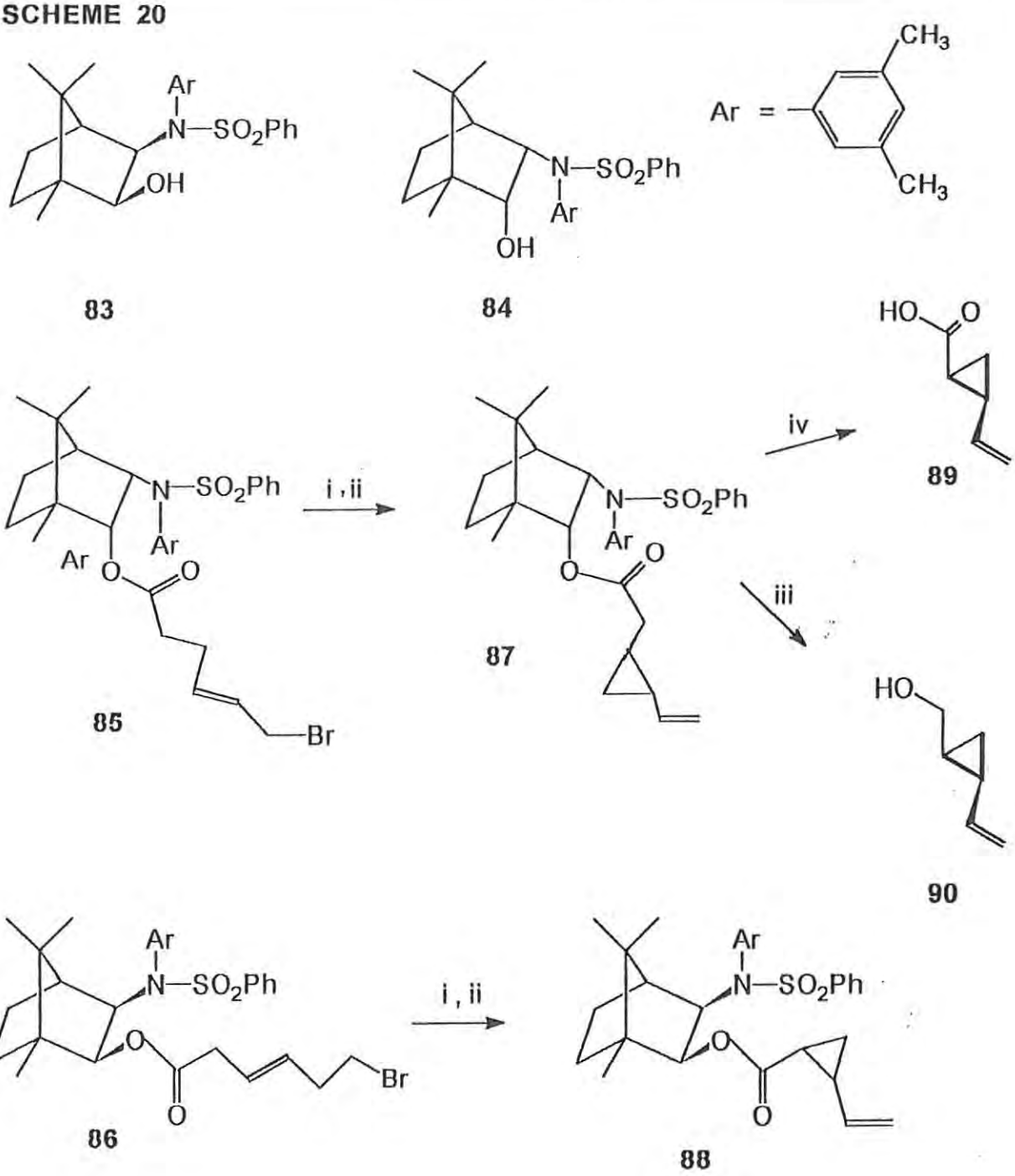
A novel route for the preparation of ß-amino alcohols in both enantiomeric forms, using camphor derivatives as chiral synthons, has been reported by Kunieda.[57] Methoxy-selenation and methoxybromination of the chiral 3-acyl-2-oxazolone **91** (Scheme 21) resulted in the highly stereoselective formation of the chiral synthons **92** and **93** with opposite π-facial selectivity. This is the very first example of introducing selenyl and bromo functions into alkenes with opposite π-facial selectivity.

Tanner's chiral enolate **94**,[58] derived in just two simple steps from (+)-camphor, undergoes asymmetric conjugate addition with the Gilman reagent ($LiBu_2Cu$). Increasing the bulk of the substituent R in the 2-*endo* position of the camphor skeleton, increases diastereoselectivity, the naphthyl substituted derivative reacting with 95% diastereoselectivity. Reduction of the adducts with LAH allowed recovery of the auxiliary alcohol and formation of optically active 3-methyl-1-heptanol.

1.2.4 Camphor Derivatives in the Preparation of Amino Acids

The first practical enantiospecific approach to the preparation of α-amino acids *via* formation of the Cα-N bond was accomplished using the α-halogenated ester derivatives **96**

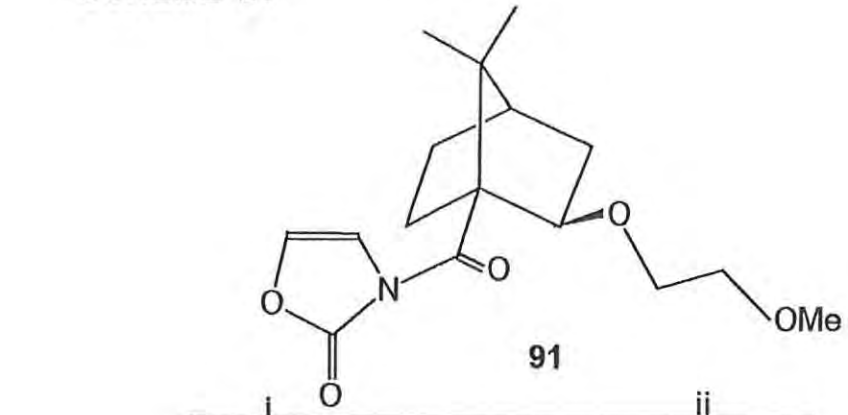
SCHEME 20



REAGENTS

I , THF; II, t-BuOK; iii, LAH ; Iv, KOH.

SCHEME 21

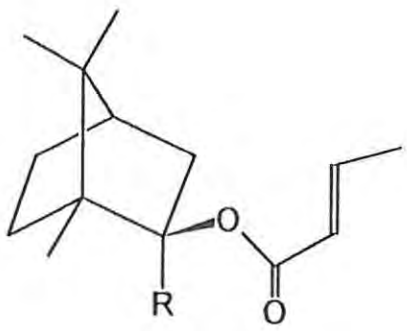


91

92 **93**

REAGENTS

i , PhSeCl , CH_3OH ; ii , Br_2 ; $CH_3C(OCH_3)_3$



94

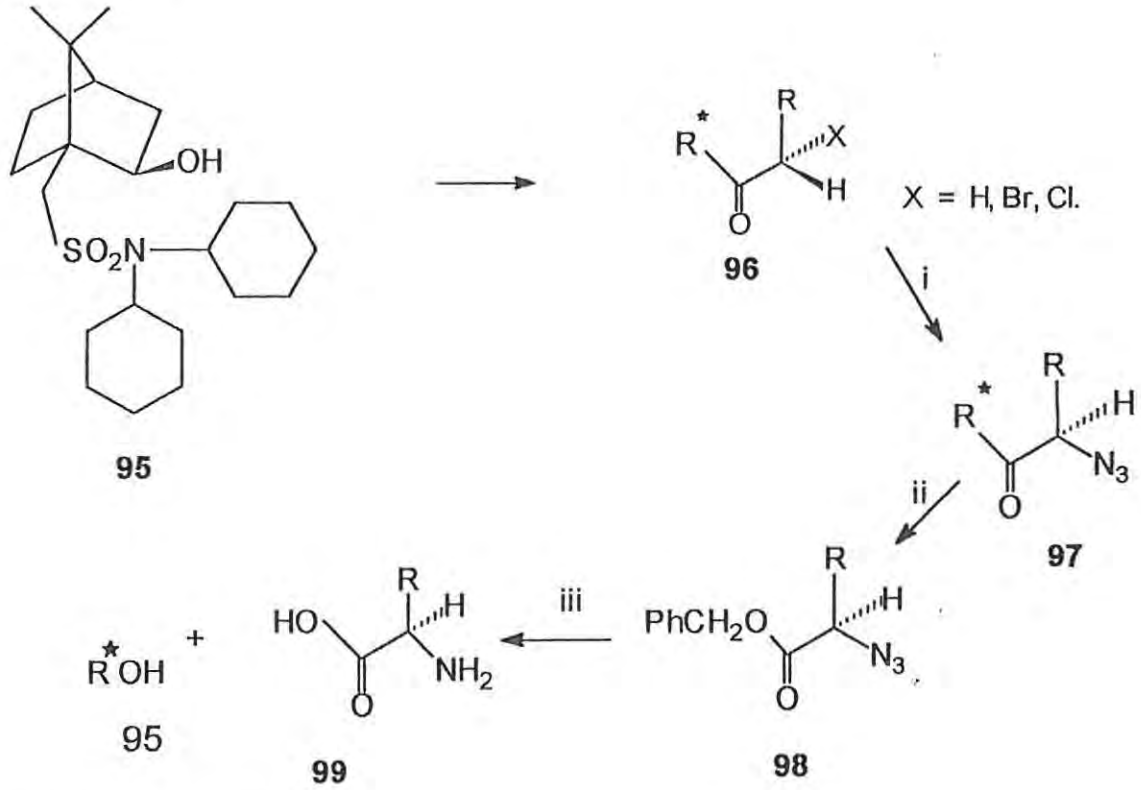
of the camphor-10-sulphonamide **95** (Scheme 22).[59] Nucleophilic displacement of chlorine or bromine by NaN_3 efficiently furnished the azide **97**, $Ti(OCH_2Ph)_4$ mediated trans-esterification of which afforded the benzyl ester **98** and regenerated the chiral auxiliary **95**. The resulting benzyl ester **98** underwent concomitant hydrogenolysis of the benzyloxy and azide groups to afford the (*R*)-α-amino acid **99** in 94-98% e.e. By employing the antipodal auxiliary **100** and following the same sequence of reactions, (*S*)-amino acids **101** were obtained. The uncommon amino acid L-alloisoleucine **102** which is an essential precursor for the psychotropic ergot peptide, eticriptine, is obtained in this way.

Oppolzer [60] has devised yet another attractive route for the synthesis of enantiomerically pure α-amino acids by alkylating the chiral glycine derivative **103**, which is obtained from the camphor sultam auxiliary **55** as shown in Scheme 23. Deprotonation of this derivative **103**, followed by alkylation, yielded the intermediate **104**, selective *N*-deprotection of which afforded the amine hydrochloride **105**. The enantiomerically pure amino acids **106** were obtained in 100% e.e. by the hydrolysis of compounds **105** with aqueous LiOH and the chiral auxiliary was recovered. Scheme 23 illustrates the general route employed and the various amino acids prepared by this method.

By trapping the (*E*)- and (*Z*)-lithium enolates (derived from ester **107**) with di(*tert*-butyl)azodicarboxylate, Oppolzer[61] was also able to achieve the predictable enantioselective preparation of (*S*)-α-amino acids.

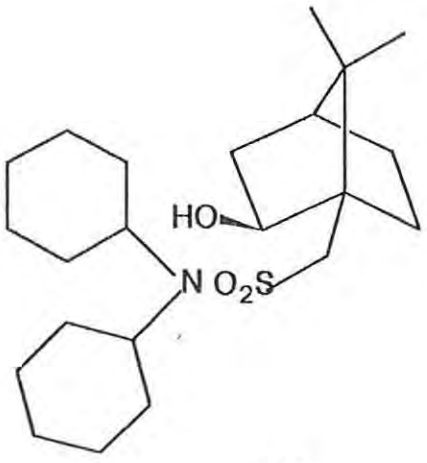
In an alternative route[63] to enantiomerically pure α-amino acids, hetero atoms can be

SCHEME 22

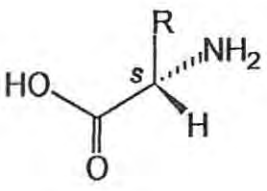


REAGENTS

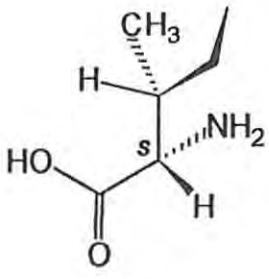
i , NaN_3 ; ii $Ti(OCH_2Ph)_4$; Pd / $BaSO_4$



100

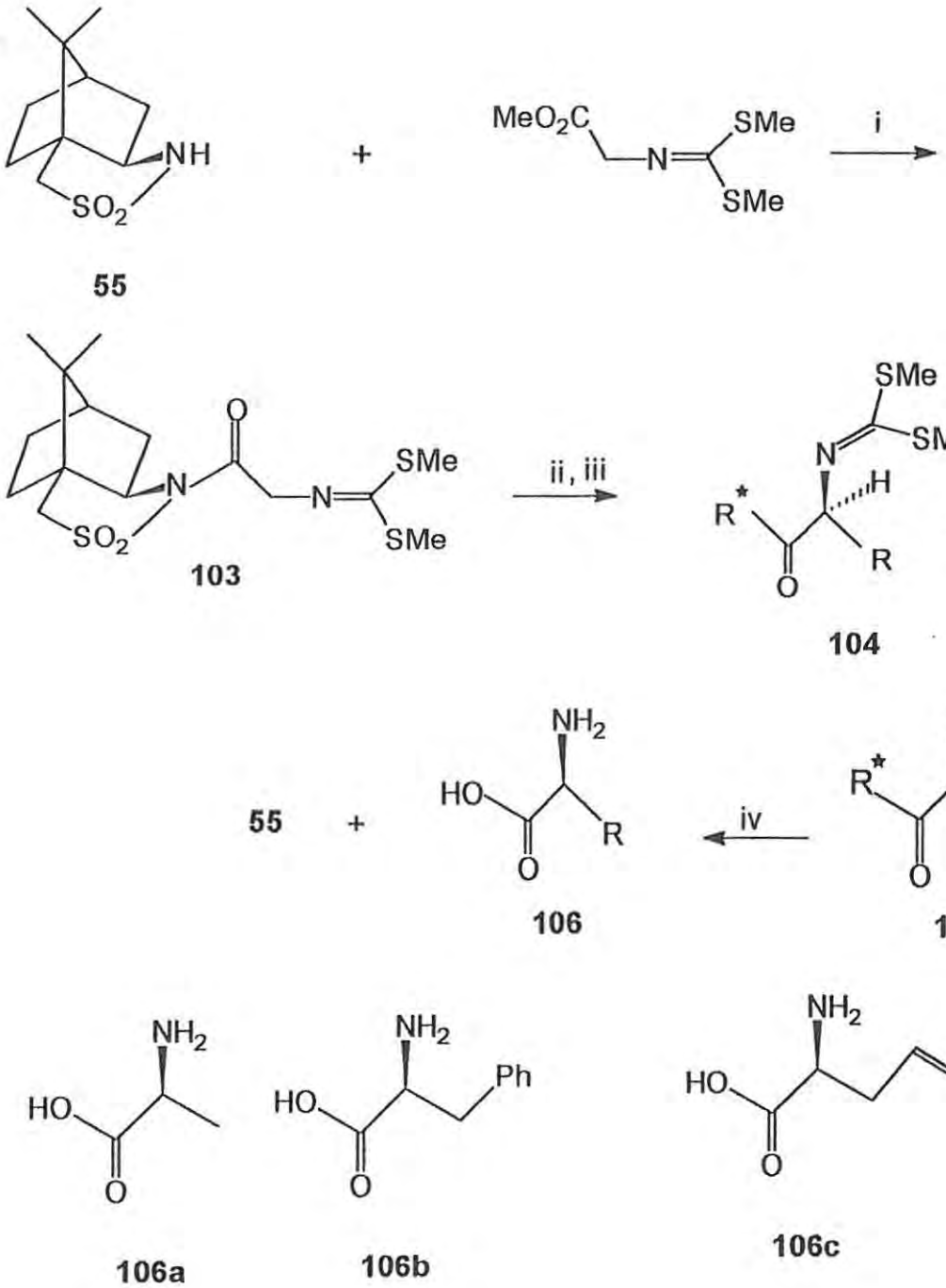


101



102

SCHEME 23



REAGENTS

i, Me_3Al ;ii , BuLi ;iii, RX; iv, aq.HCl ;v, aq. LiOH .

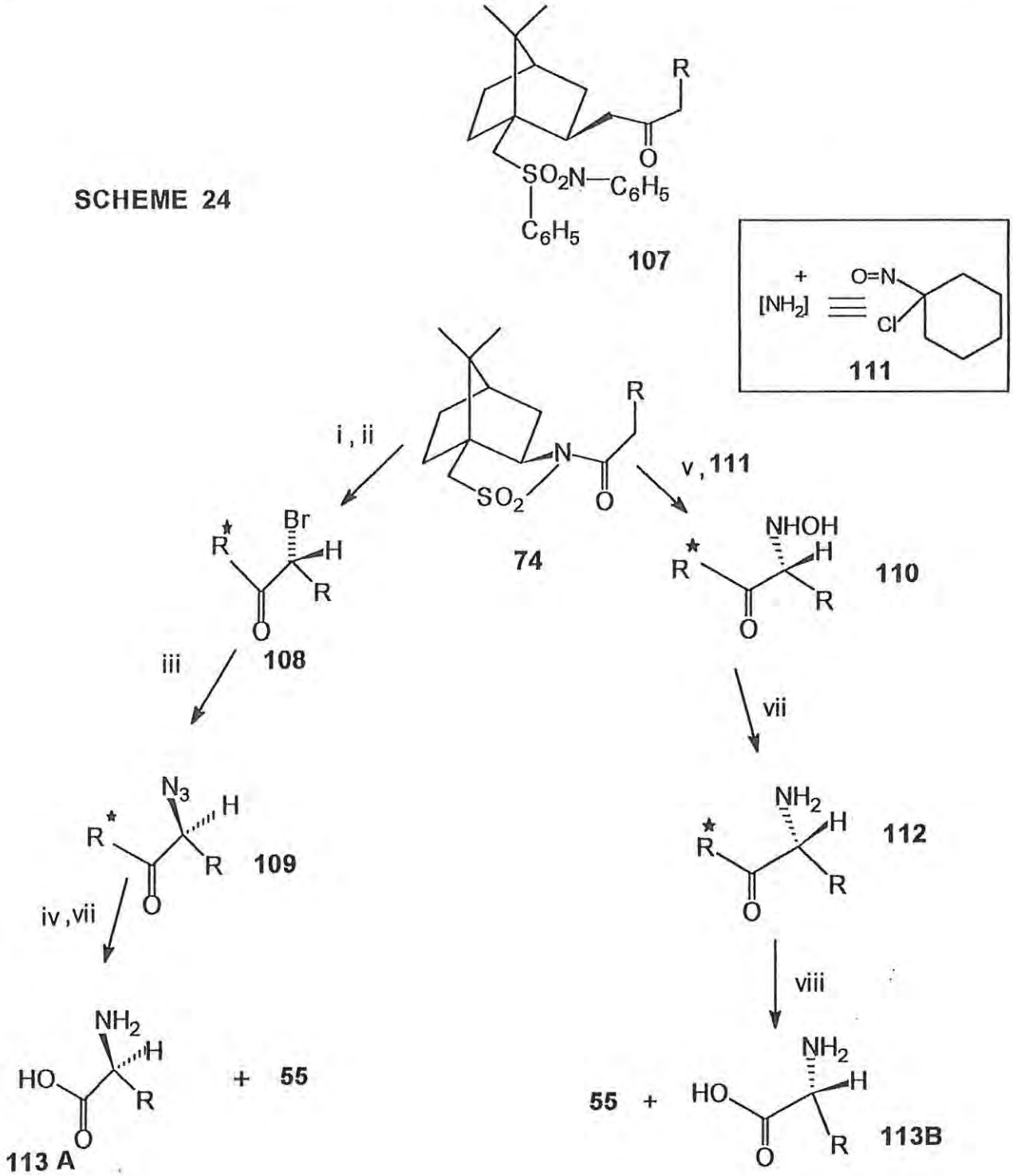
attached to the α-C of the N-acyl sultam in a highly π-face selective manner.[61] The bromo derivative **108**, prepared from the sulphonamide **74** as shown in Scheme 24, undergoes S_N2 displacement by azide. Hydrogenolysis of the azide group followed by saponification affords the (*S*)-amino acids **110**. *N*-acylation of the primary amino group prior to saponification affords the corresponding *N*-protected amino acids.

The choice of amination reagents for the asymmetric synthesis of amino acids has, until recently, been limited to di(*tert*-butyl)azodicarboxylate,[63] 2,4,6-tri-*iso*propylbenzene-sulphonyl azide[64] and ethyl azidoformate.[65] Oppolzer[66] has extended the available options by introducing 1-chloro-1-nitrosocyclohexane **111** as a convenient source of electrophilic nitrogen. The electrophile attacks the (*Z*)-enolate of the acyl derivative **74** exclusively from the C_α-*Re* face to give the hydroxylamine **112**. When subjected to hydrogenolysis using Zn/H^+, the hydroxylamine **112** yielded the corresponding amine **113**, hydrolysis of which gave the enantiomerically pure (*R*)-amino acids **114**. By following the same sequence of steps using the sultam derivative of the available antipodal auxiliary **56**, (*S*)-α amino acids can be prepared.

1.2.5 Camphor Derivatives as Chiral Auxiliaries in Natural Products Synthesis

Oppolzer's camphor sultam derivatives have been extensively used for the total synthesis of many naturally occurring compounds. (-)-Pulo'upone **116**, isolated from a *caphalaspidean mollusc*, was synthesised (Scheme 25)[67] *via* a crucial intramolecular Diels-Alder addition which, in one single step, establishes four stereogenic centres, *viz.*, C-6′, C-9′, C-13′ and C-14′, and highlights the π-face differentiating bias of the camphor skeleton.

SCHEME 24

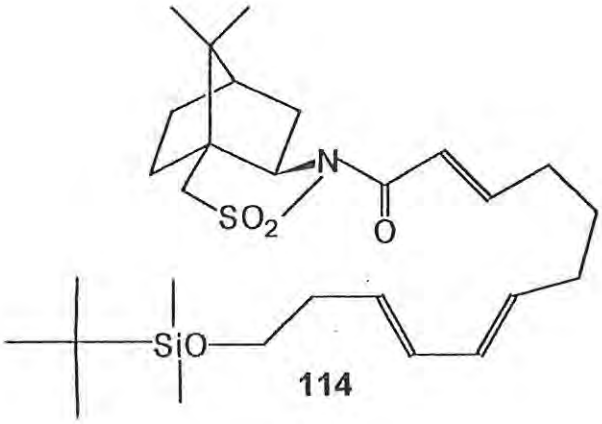


REAGENTS

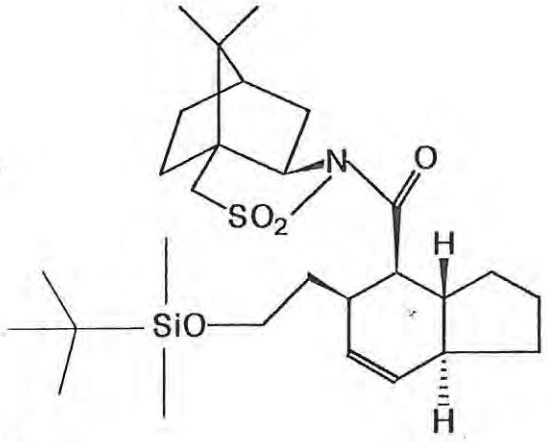
i. Bu_2BOTf , R_3N ; ii. NBS , THF; iii. $(Me_2N)_2C=NH^+N_3^-$;

v.LiOH, THFv , $NaN(SiMe_3)_2$, HCl ; vii , Zn,HCl; viii ,LiOH ; iv , H_2/Pd-C

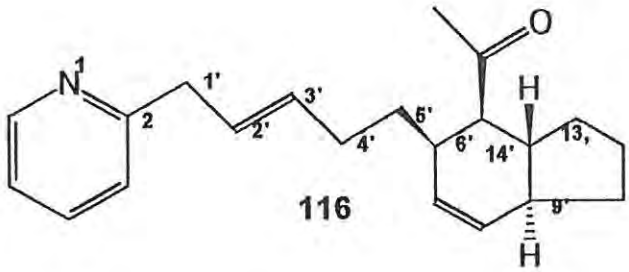
SCHEME 25



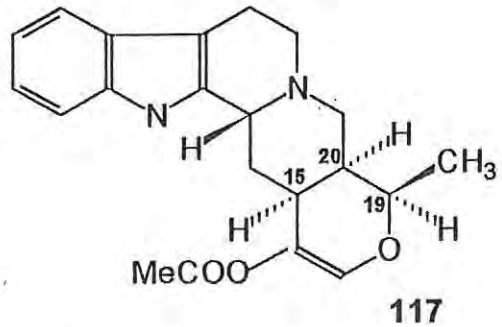
114



115



116



117

REAGENTS

i , $(CH_3)_2AlCl$, $NaHCO_3$.

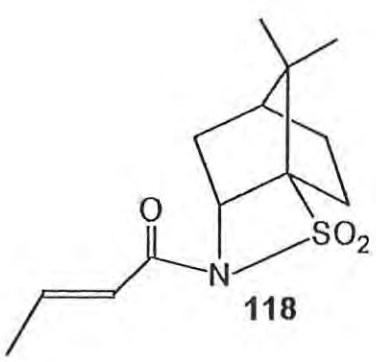
skeleton. The first total synthesis of the himbine alkaloid (+)-3-isoauniticine **117** was accomplished[68] *via* a sequence of 14 steps. The crucial step in the formation of this target molecule was to fix the configuration at C-15 and C-20, and this was achieved using the camphor precursor **103**.

The enantiomerically pure iridoid (-)-1-*O*-methyl-loganin aglucone **121** was obtained *via* the acrylate-derived adduct **119** obtained by the Diels-Alder addition of camphor sultam **118** with cyclopentadiene.[69] LAH reduction of the adduct **119** yielded the alcohol **120** which was readily transformed to the iridoid **121**. In another Diels-Alder approach (see section 1.2.1, Scheme 12) the adduct **45** derived from the camphor acrylate **44**, provides access, *via* LAH reduction, to the cyclohexenyl alcohol **121b**, oxidation of which with Jones' reagent affords the chiral acid **121c**. The cyclohexyl derivatives, **121b** and **121c** serve as precursors for the synthesis of sarcomycin,[70] and shikimic acid[71] respectively.

The synthesis of enantiomerically pure (-)-ß-santalene **125**, the major sandal wood constituent, was accomplished by Diels-Alder addition of cyclopentadiene to the camphor-derived allenic ester **122**.[72] Selective hydrogenation of the adduct **123** followed by α-alkylation of the resulting ester, furnished compound **124** which served as the precursor for the asymmetric synthesis of (-)-ß-santalene **125** (Scheme 27).[73]

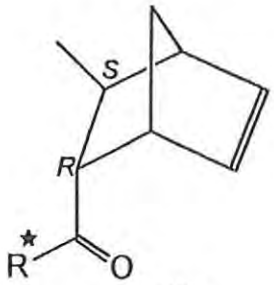
The phenyl substituted, camphor-derived allyl bornate **126** reported by Hoffman,[74] was successfully employed as a chiral auxiliary in the synthesis[75] of δ-multistriatin **127** and the Prelog-Djerassi lactone **128**. The readily available ß-keto ester **129a**, prepared by Taber,[76]

SCHEME 26



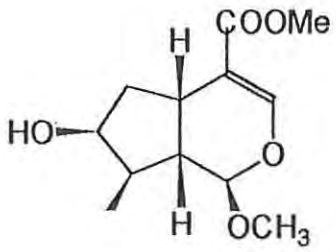
118

i , ii

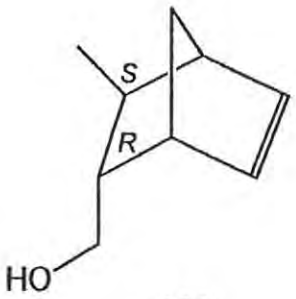


119

iii



121a



120

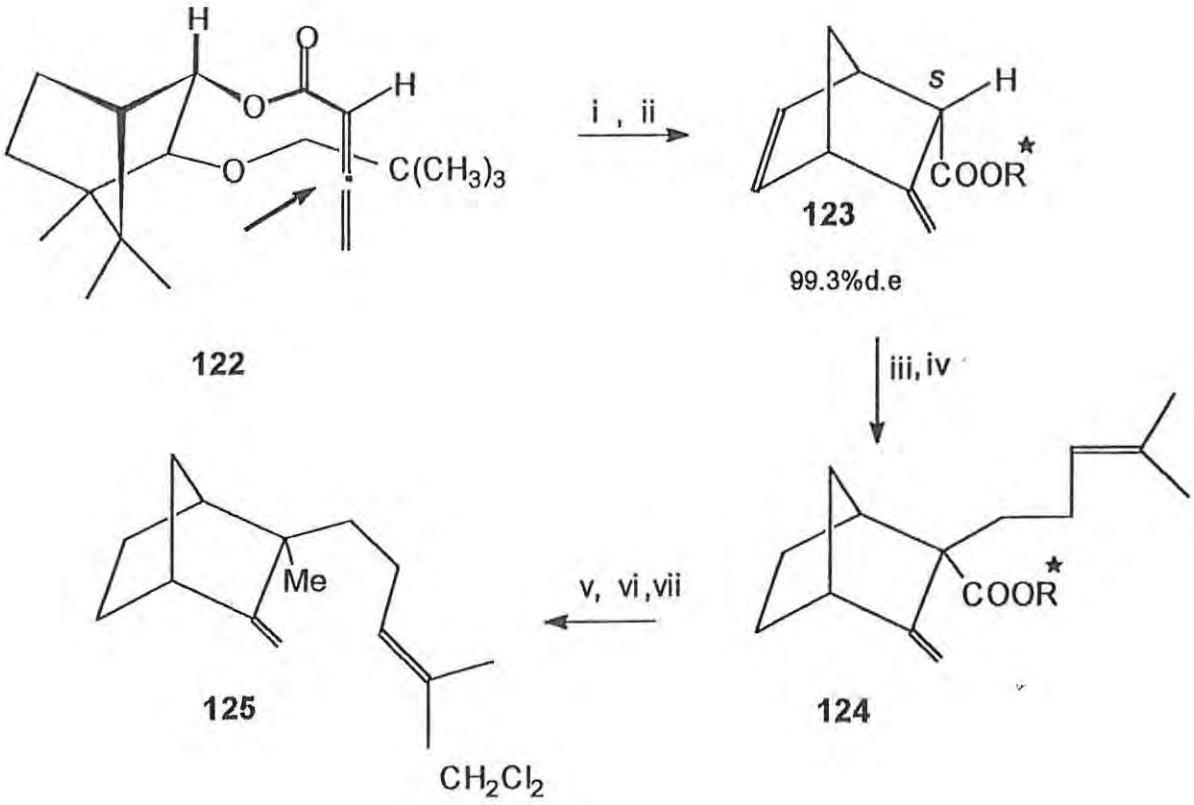
REAGENTS

i $TiCl_4$; ii , cyclopentadiene ; iii, LAH.

121b R = CH_2OH

121c R = COOH

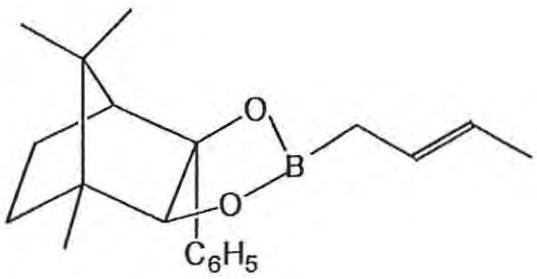
SCHEME 27



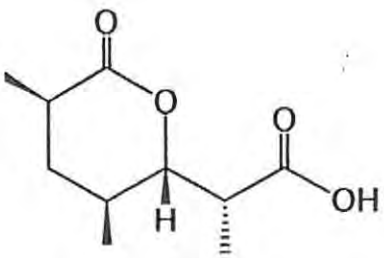
REAGENTS

i ,cyclopentadiene; ii, $TiCl_2(OiPr)_2$, iii, $NaBH_4$; iv, LDA ,2,4-methyl-3-pentenyl iodide;

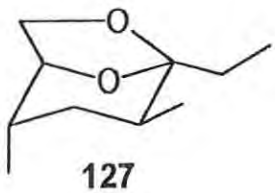
v, LAH; vi, NH_2NH_2; vii, PCC ·



126



128



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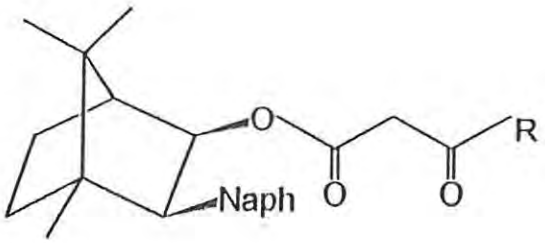

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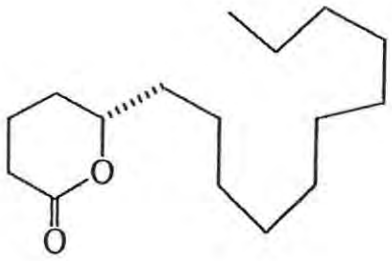

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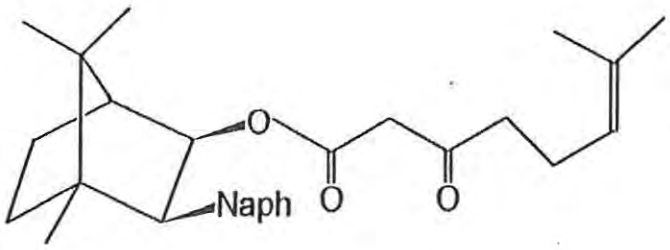

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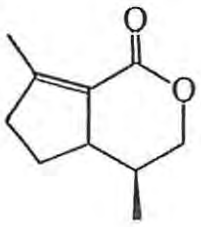

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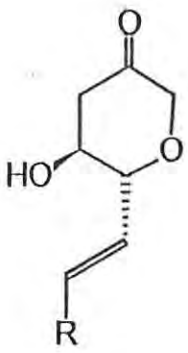
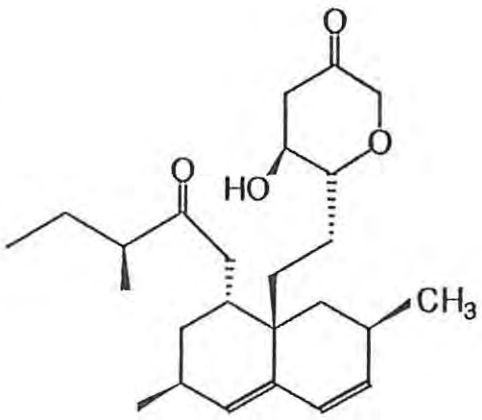


132

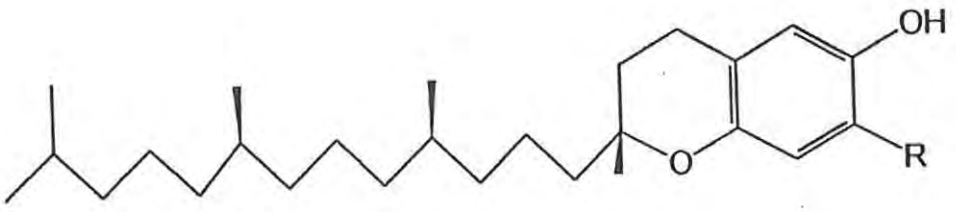


133

has been successfully employed in the enantioselective preparation of (-)-(*S*)-hexadecanolide **130**,[44] a pheromone of the wasp *vespa orientalis*,[77] and (+)-iso-neopentalactone **131**, a constituent of the essential oil of *actinidia poliama*.[78] The ß-keto ester **129b**, on the other hand, was used in the stereoselective construction[79] of the ß-hydroxy lactone unit **132** of a synthetic analogue of Prevastati **133**, a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase, the rate limiting enzyme in cholesterol biosynthesis.

Helmchen has reported the total synthesis of tocopherol **134** (Vitamin E) in nine steps and 58% overall yield.[80] The key step in this synthesis is the formation of the enantiomerically pure side chain **135**, which was accomplished using the chiral propionate derivative of the sulphonamide-shielded alcohol **84** (see section 1.2.3) and a novel assembling technique using propionate and acetate units.[81]

Dictyopterene **136**, one of the main constituents of essential oils from several *Dictyopteris* species, has been stereoselectively synthesised by the $S_{cN'}$ reaction of the sulphonamide camphor derivative.[82] Botrydial **137**, and dihydrobotrydiol **138** and related metabolites produced by the phytopathogenic fungus *Botrytis cincerea*, contain an unusual sesquiterpenoid skeleton. Synthesis of the optically active compound **139**,[83] a precursor for compounds **137** and **138** has been stereoselectively accomplished using camphor derivatives as chiral auxiliaries.[84]



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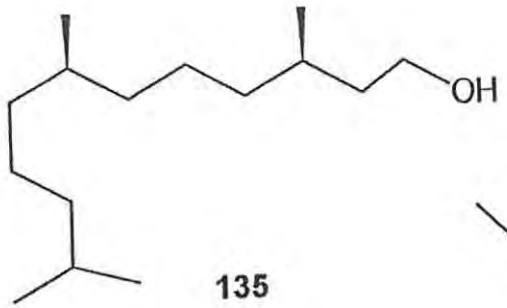
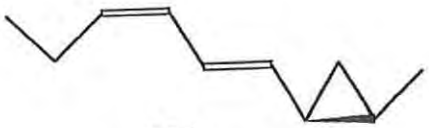
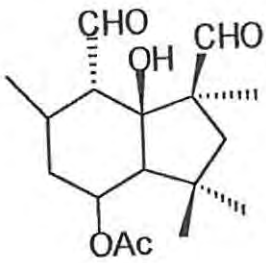


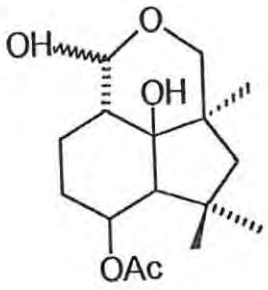
135



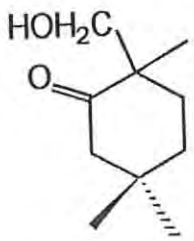
136



137



138



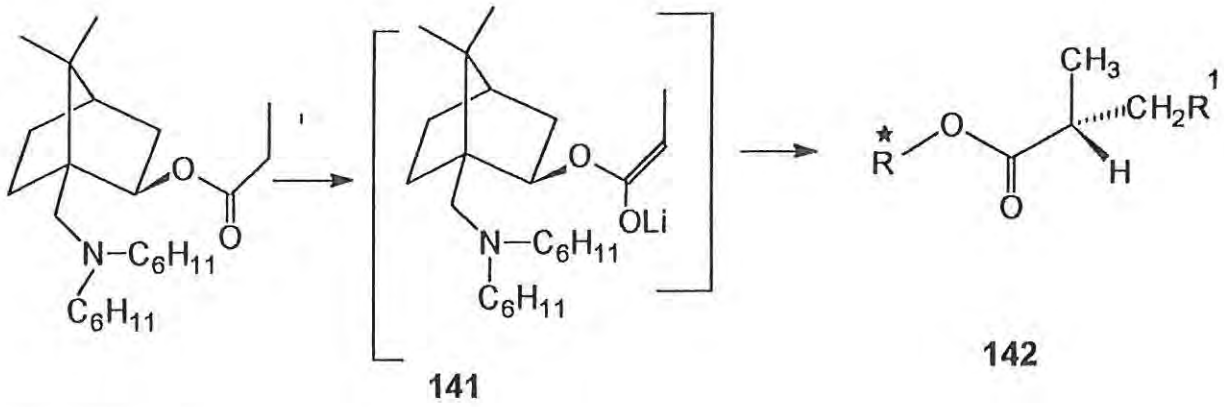
139

1.2.6 Asymmetric Alkylation of Camphor-derived Enolates

The significant asymmetric induction obtained during the alkylation of the camphor-derived propionate ester **140** once again highlights the asymmetric bias of the camphor skeleton. Kinetically controlled deprotonation of the propionate **140**,[85] followed by the addition of a primary alkyl bromide to the enolate **141** yielded the α-substituted esters **142** in 84% to 89% d.e. (Scheme 28). The selectively prepared (*E*)- or (*Z*)-enolates **144** and **145** respectively, undergo alkylation to afford the corresponding enantiomerically pure alkylated esters **147** and **148**.[54] LAH reduction of these alkylated esters afforded the corresponding enantiomerically pure alcohols in 79-90% d.e. (Scheme29)[86]

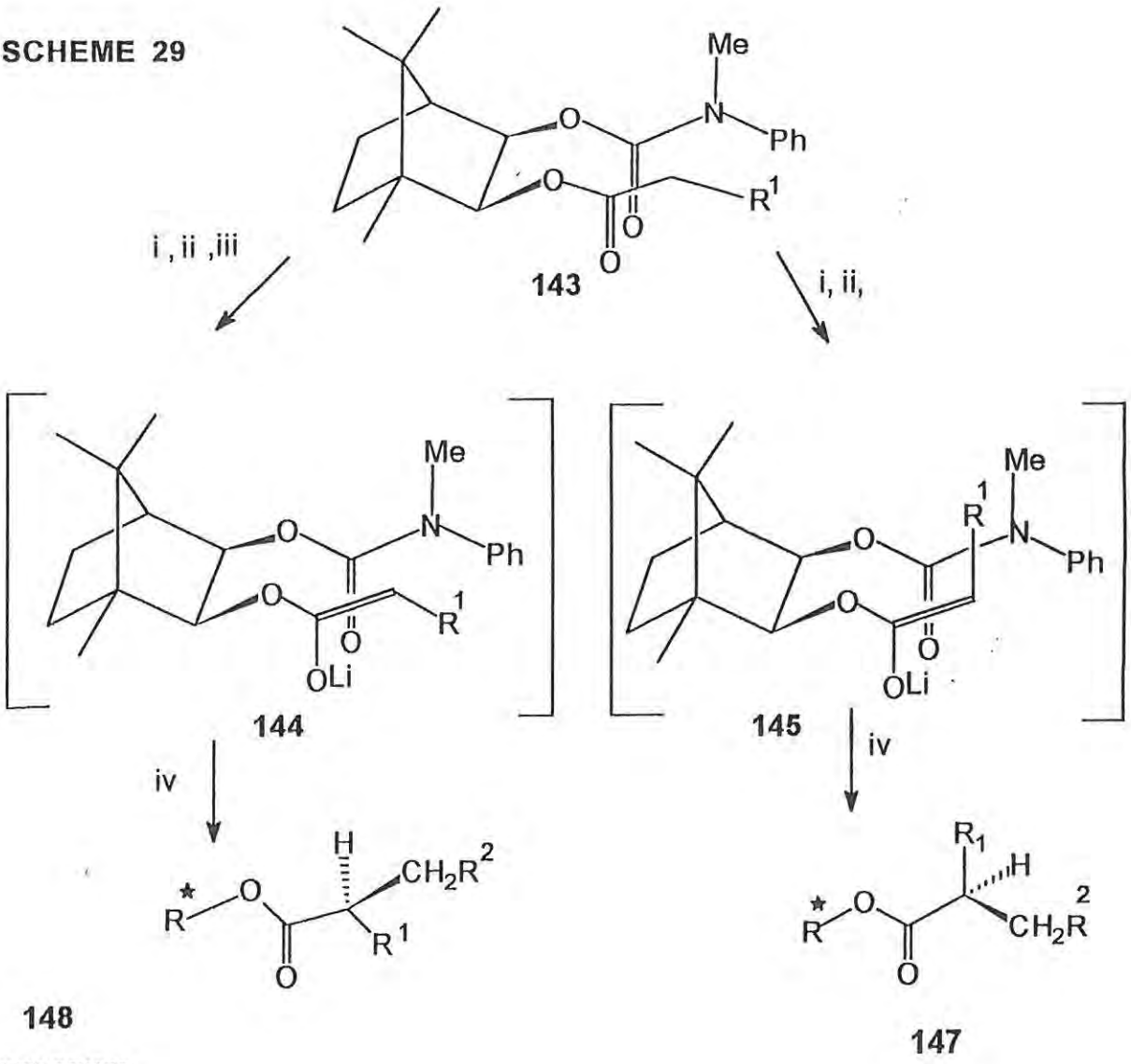
The aryl sulphonamido-bornyl esters **148** and **149** also exhibit remarkable π-face differentiation upon α-substitution.[87] The propionate **148** is selectively deprotonated to give either the (*E*)-enolate **150** (method A: LICA, THF) or the (*Z*)-enolate **152** (method B: LICA, THF, HMPA); alkylation of the enolates with primary halides or benzyl bromide furnished the corresponding alkylated products **151** and **153** (Scheme 30).[88] The asymmetric induction observed in the *endo* ester **149** (90 to 96%) was significantly higher than the induction observed for the *exo* ester **148** (52 to 88%) (Scheme 30). On the other hand, alkylation of *O*-benzyl glycolate esters took place only *via* the (*E*)-enolates whether or not method A or B was used, and subsequent alkylation yielded the α-benzyloxy esters in 87 to 94% d.e..

SCHEME 28



141 **142**

SCHEME 29

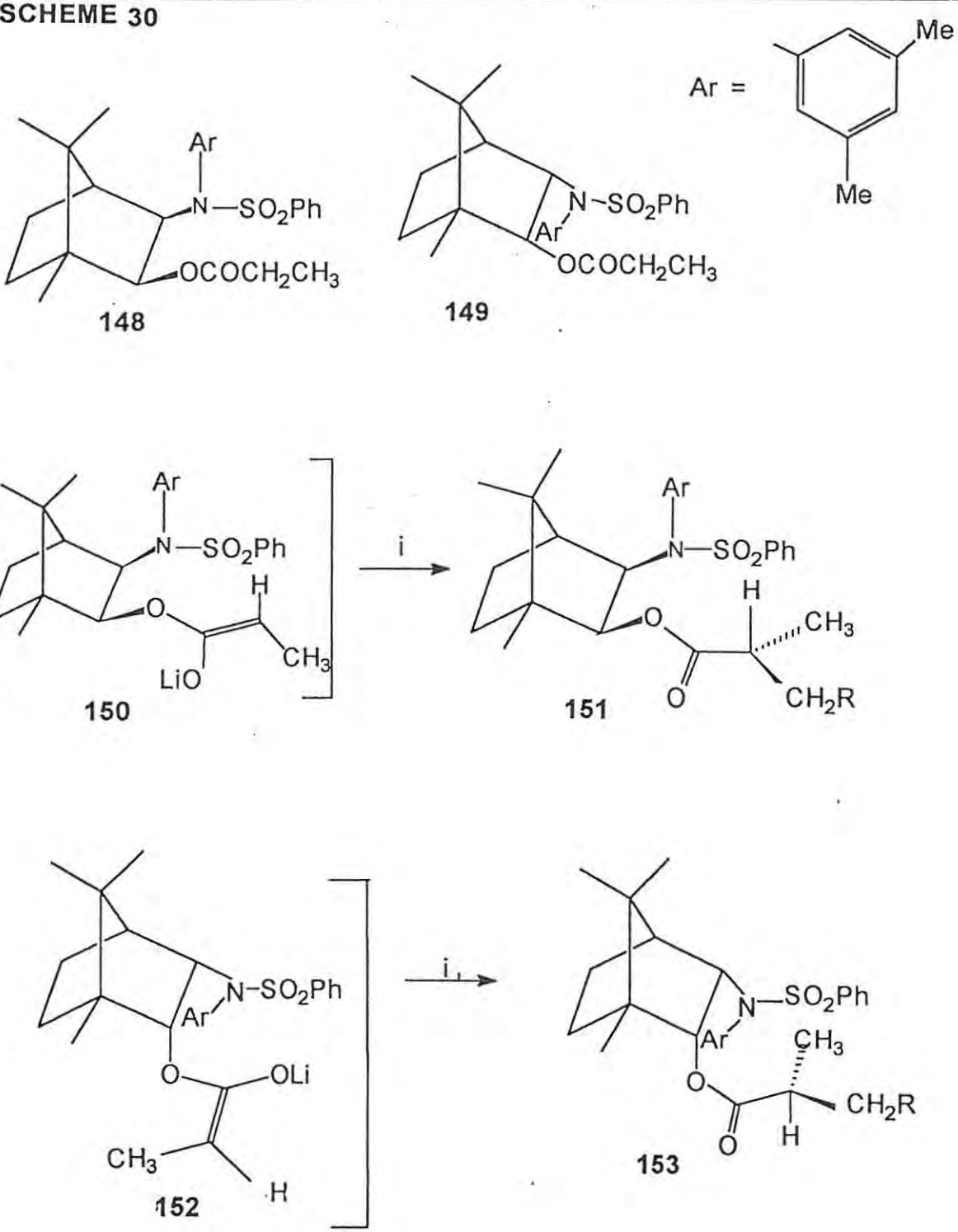


143 **144** **145** **147** **148**

REAGENTS

i LICA ; ii THF ; iii, HMPA; iv, R^2CH_2X

SCHEME 30



REAGENT

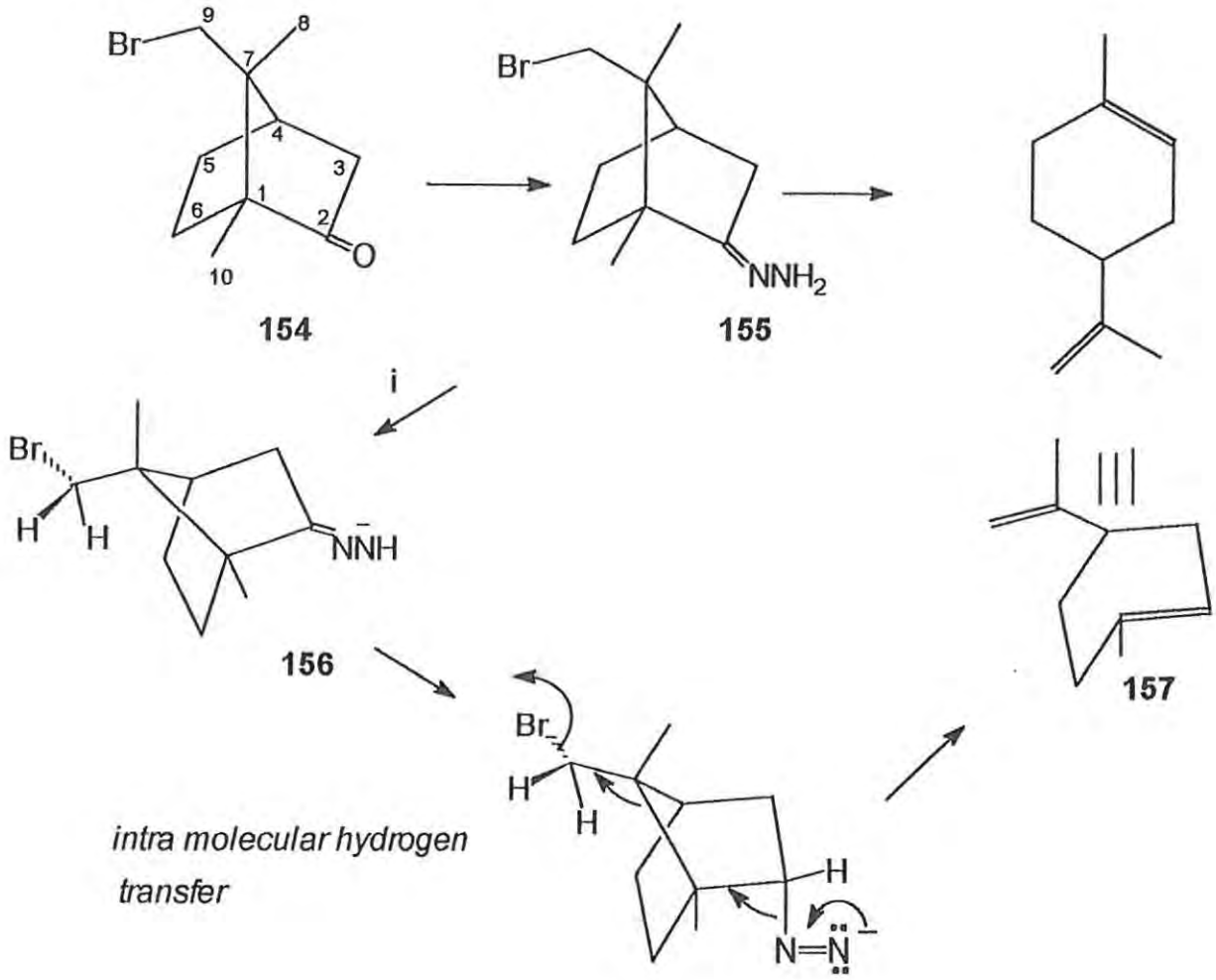
i, RCH_2Br

1.2.7 Camphor Derivatives and the Six-membered Chiral Pool

The fragmentation of 9-bromo camphor **154** during an attempted Wolff-Kishner reduction was first reported by Gustafson.[89] The only product obtained during this reaction was limonene **157**, a six membered ring compound arising from C1-C7 bond cleavage of 9-bromo camphor (Scheme 31). This new fragmentation pattern led to the synthesis of compounds containing useful quaternary carbon centres in six-membered carbocylic systems.[90] In a recent compilation of 374 chiral pool elements, there were no examples of compounds containing chiral quaternary carbons except simple bicyclic [2.2.1] derivatives of camphor, camphoric acid and fenchone.[91] 9-Chlorocamphor also undergoes fragmentation during reduction using Na-K alloy.[92] Fragmentation of the bridging C1-C7 bond is also facilitated when a negative charge is allowed to develop at C-9 in the presence of a leaving group at the *endo* C2 position. Thus in a few simple steps from camphor, one may produce functionalised, stereogenically pure six-membered chiral pool substances. Moreover, the quaternary carbon possesses useful branching appendages, in the form of a methyl and an isopropyl group, the latter providing a handle for further elaboration.[93]

This synthetic pathway can be used much more effectively when the camphor skeleton is derivatised prior to fragmentation. This approach affords an array of six-membered, substituted ring synthons. Vaillancourt[94] has successfully applied this strategy and, starting from an aldol derivative of bromocamphor and 2-furaldehyde, has accomplished the syntheses of (-)-furodysin **158** and (-)-furodysinin **159** in three steps. These syntheses have allowed assignment of the absolute configuration of a number of marine furano sesquiterpenes, produced by sponges of the genus *Dysielea*.

SCHEME 31



REAGENTS

i, t-BuOK; ii, DMSO

1.2.8 Bond Cleavage to give access to the Five-membered Chiral Pool

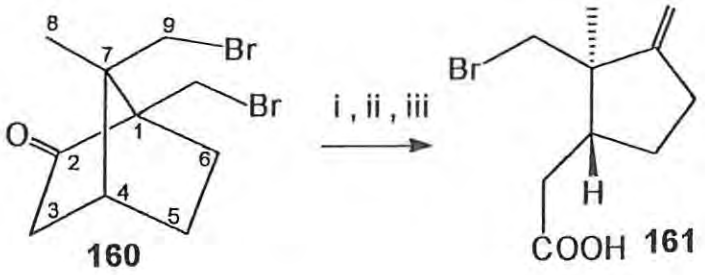
Cleavage of the C(1)-C(2) bond in camphor and its derivatives has been accomplished[95] by making use of reagents such as $MeCO_3H$-NaOAc, NaOH-EtOH, O_3-MeOH and KOH-dimethyl sulphoxide, and has led to the development of a functionalised five-membered chiral pool. The 9,10-dibromo compound **160** derived from (+)-camphor, undergoes ring cleavage to provide the functionlised five-membered compound **161** which has served as the key intermediate in the synthesis of (*Z*)-3-methyl-6-isoprenyl-3,9-decadien-1-yl acetate **162**, one of the sex pheromones of the female california red scale (Scheme 32).

(-)-Borneol **163** has been observed to undergo ring cleavage[96] in a similar way to give campholenaldehyde **164**, which may be elaborated to a synthetic precursor for the A-ring in a Vitamin B synthesis. Cleavage of the substituted borneol **165** yielded yet another functionalised five-membered structure **166** used for constructing the B-ring in a Vitamin B synthesis (Scheme 33).[97]

The oxamino ester derivative **167** of camphor undergoes Beckman fragmentation[98,99] to give the exocyclic cyanoester **168a**[100] which is a key intermediate in the synthesis of 17-ketosteroids, and the endocyclic ester **167b** which was successfully used in the enantioselective total synthesis of cortisone and related steroids (Scheme 34).[101]

Fusion of the ammonium salt of the camphor-10-sulphonic acid **169** with KOH also results in C1-C2 bond cleavage[102] leading to the formation of campholenic acid **170** which serves as a chiral synthon for the total synthesis of the zizane sesquiterpenes,

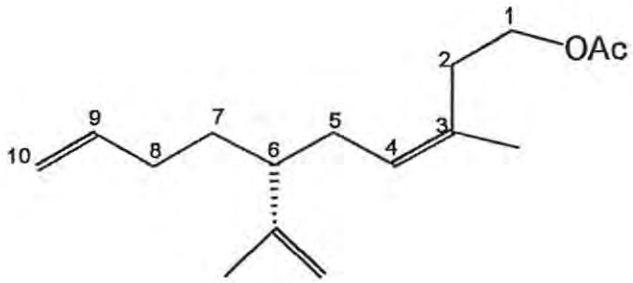
SCHEME 32



160 **161**

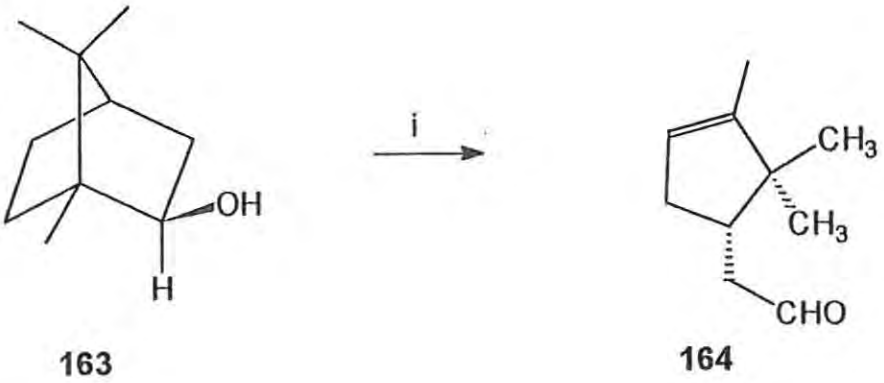
REAGENTS

i KOH; ii, DMSO; iii, H_2O.

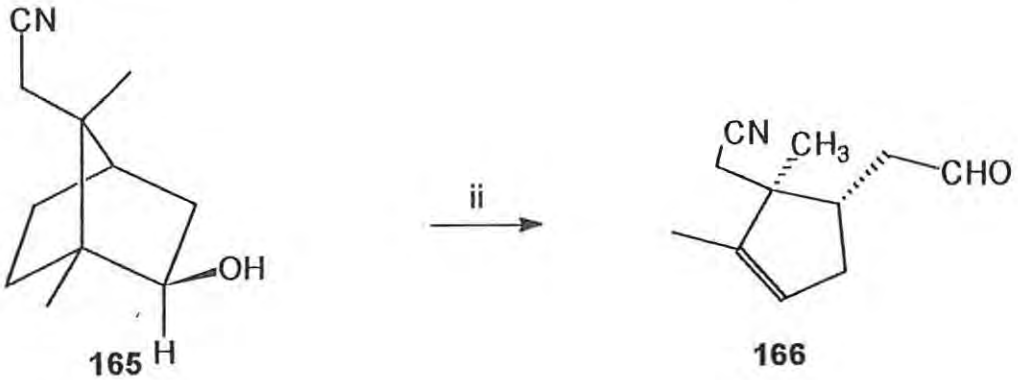


162

SCHEME 33



163 **164**

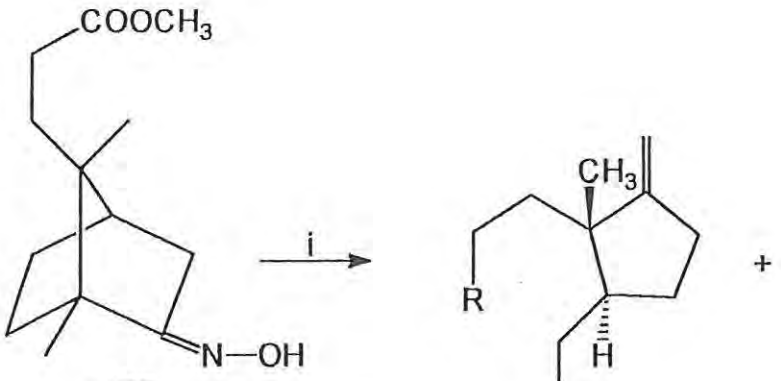


165 **166**

REAGENT

i CAN (cerium ammonium nitrate)

SCHEME 34

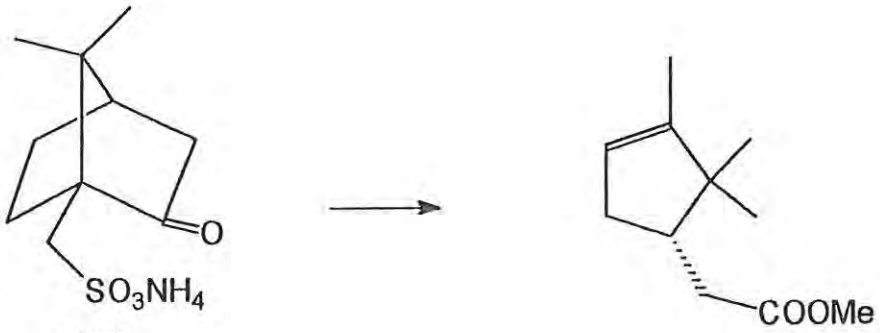


167 **168**

REAGENTS

i , *p*-TsCl ; ii , CF_3COOH

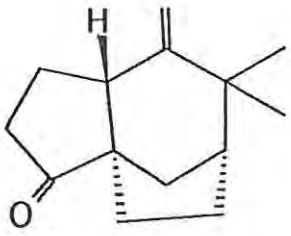
SCHEME 35



169 **170**

REAGENTS

i KOH, K_2CO_3



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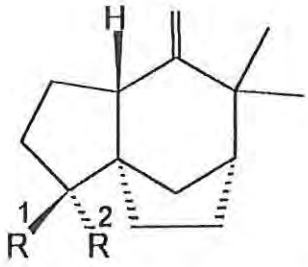


172

172 A R^1 = COOH, R^2 = H

172 B R^1 = H, R^2 = COOH

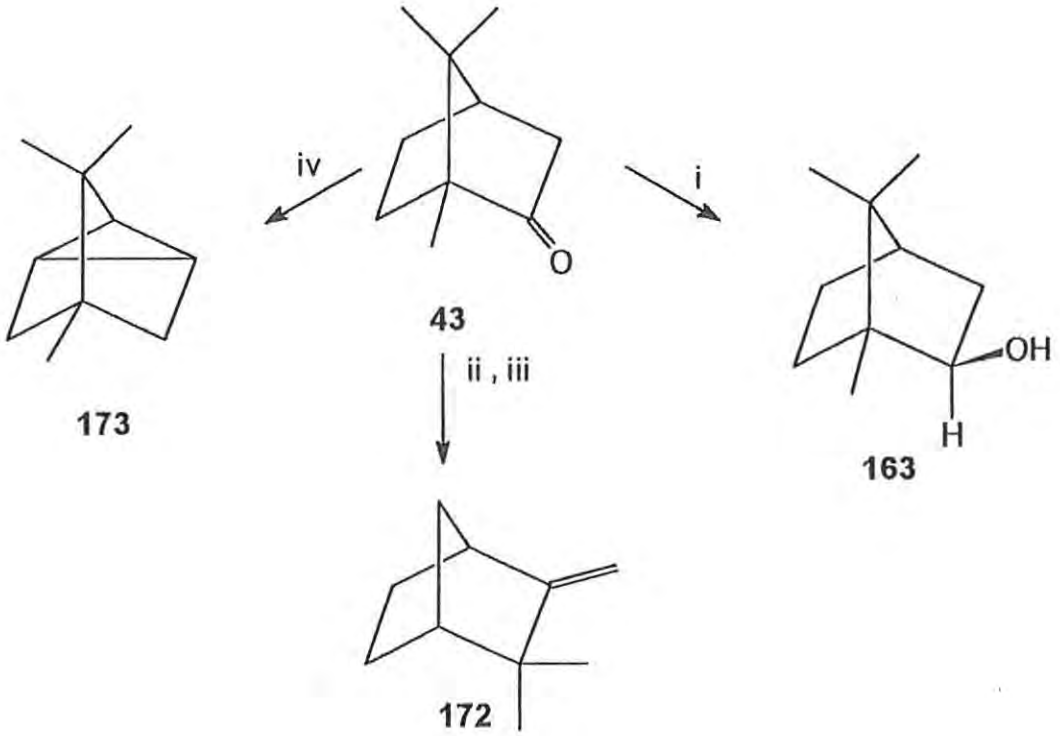
(-)-kushimone **171**, (+)-zizanoic acid **171a** and epizizanic acid **172b**, which are the odiferous components of the essential oil of vetiver varieties (Scheme 35).[103]

1.2.9 Camphor as a Precursor in Natural Product Synthesis

(+)-Camphor **45**, (+)- borneol **163**, (+)-camphene **172** and tricyclin **173** represent a quartet of monoterpenoid compounds that are synthetically related to each other.[104] From a synthetic point of view, (+)-camphor can be regarded as the parent compound, which may be readily converted to the other three members of the quartet by reduction, dehydration or rearrangement (Scheme 36). A structural survey of the sesquiterpenoids reveals the possibility of similar structural quartets in which each individual sesquiterpenoid can be regarded as a isoprenylog of camphor, borneol, camphene or tricyclin.

Thus, starting from 9-bromocamphor **154** Corey[105] has successfully prepared the camphene derivative (+)-α-santalene **174** while, starting from camphane, Wollinsky[106] has successfully prepared ß-santalol **175**.[107] Reduction of (-)campherenone **177** [obtained from (-)-8-iodocamphor **176** as shown in Scheme 37] provided (-)-campherenol **178** and isocampherenol **179**.[108] The latter compound, on heating with *p*-toluenesulphonyl chloride in pyridine, was converted to (-)-ß-santalene **180**. In a similar way, starting from the acetal iodide **181**, (+)-epicampherenone **182** was synthesised and subsequently transformed to (+)-epi-ß-santalene **184**. The campherenones **177** and **182** occupy key positions in this general synthetic strategy and their configurational integrity is maintained during subsequent transformations into the above sesquiterpenes.

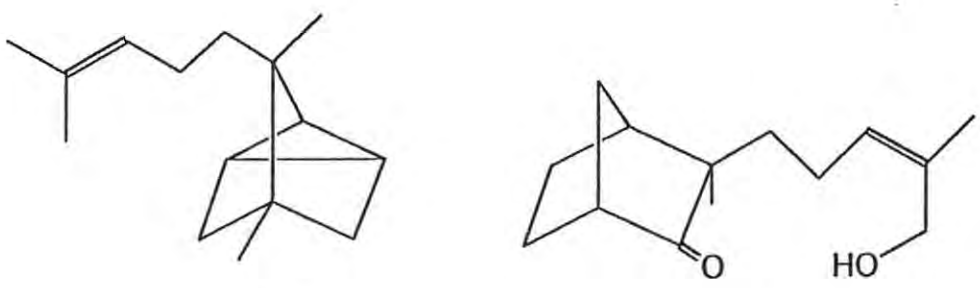
SCHEME 36



REAGENTS

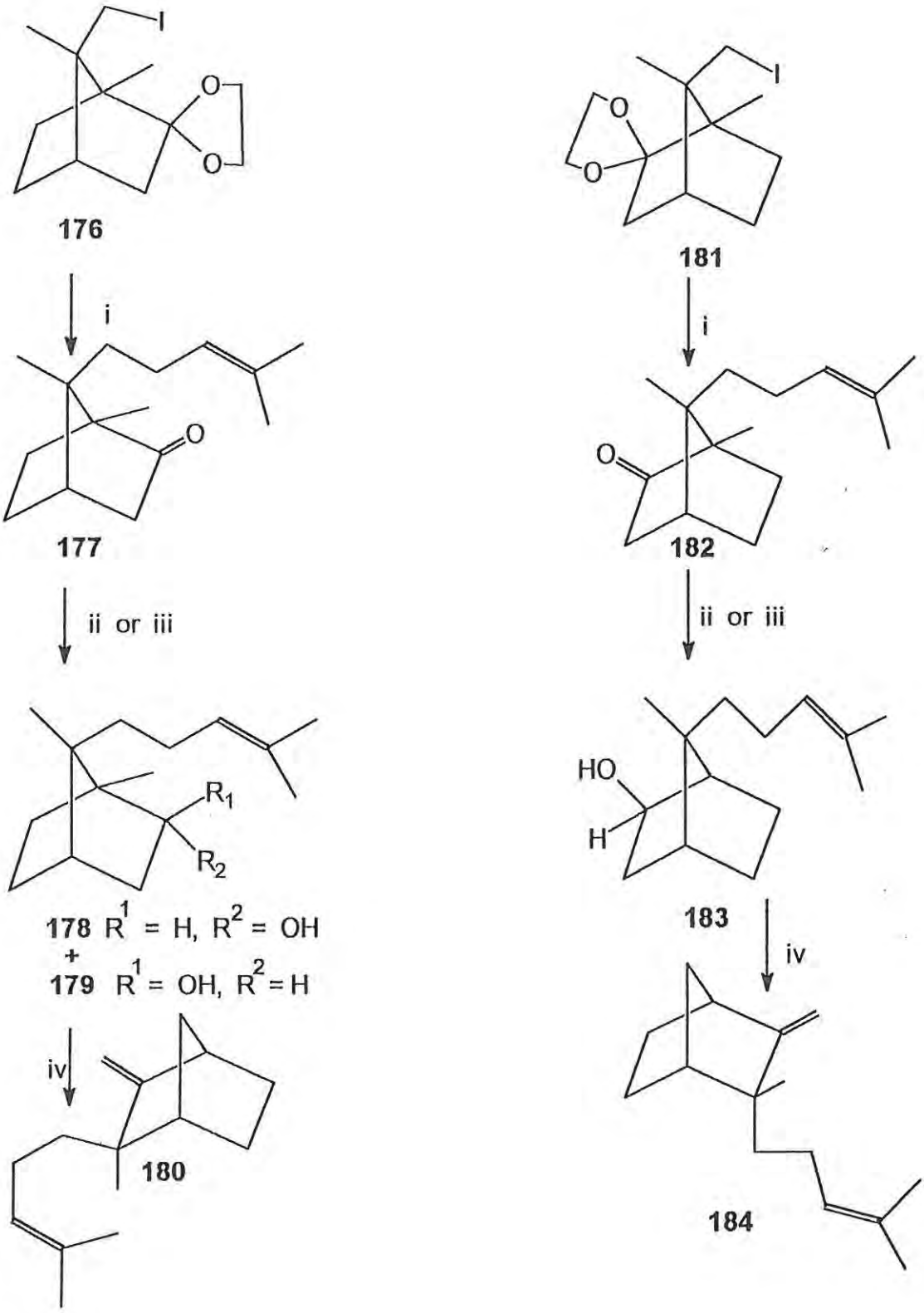
i Ca ,NH_3; ii, $LiAlH(O^tBu)_3$,THF; iii ,PTSCl , C_5H_5N; v, HgO

iv, NH_2NH_2, H^+; v, HgO.



174 **175**

SCHEME 37



REAGENTS

i, Nickel allyl complex; ii, $LiAl(OMe_3)H$; iii , Na-PrOH ; iv PTSCl

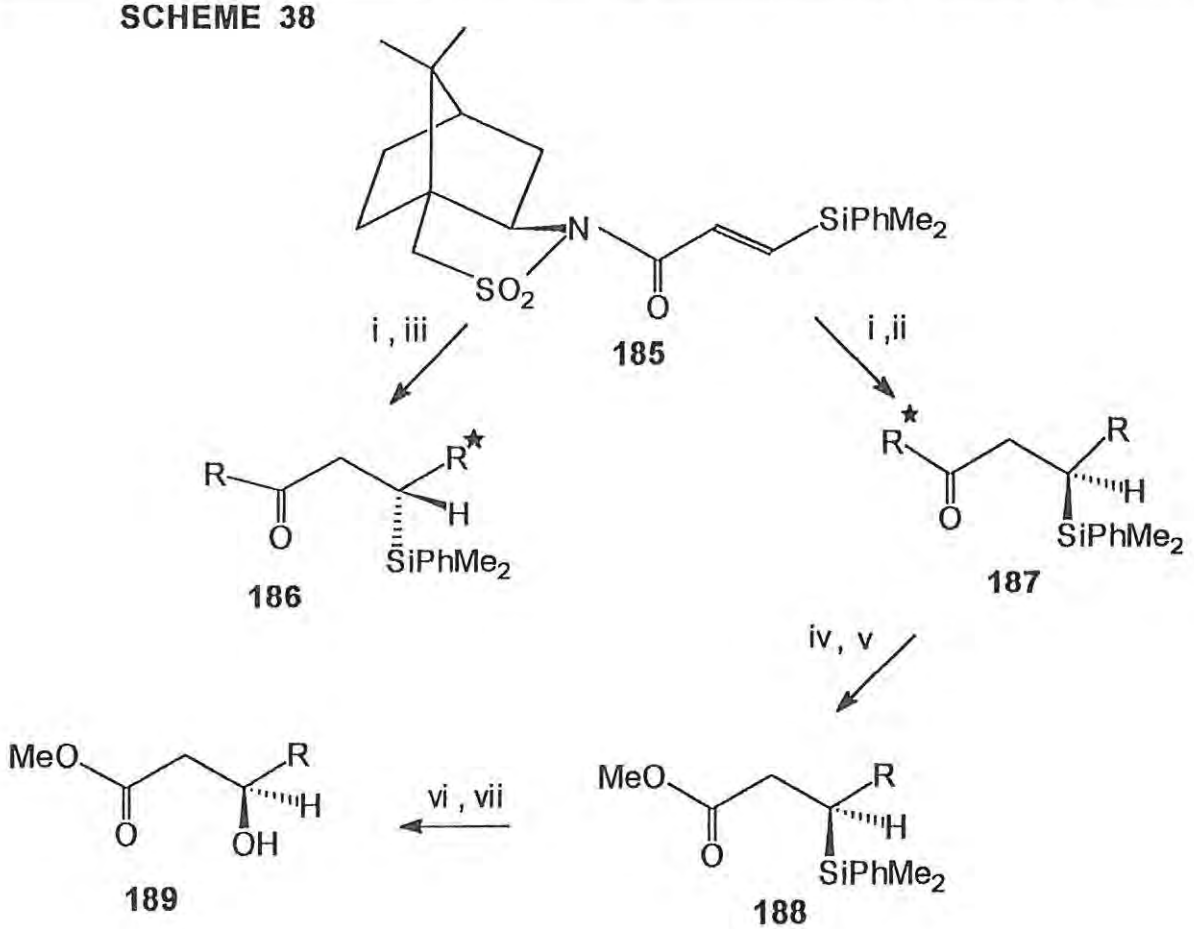
1.3 CAMPHOR-BASED SILICON COMPOUNDS IN ASYMMETRIC SYNTHESIS

A new approach, combining organosilicon chemistry and the use of chiral auxiliaries into one viable strategy for asymmetric synthesis, has advanced significantly in the last few years. The *O*-silyl ketene acetals of Helmchen,[109] the allyl silanes of Taddei[110] and the silylenoyl sultams of Oppolzer,[111,112] all of which contain the rigid bicyclic camphor skeleton as the chiral auxiliary, have been successfully employed in asymmetric synthesis.

The first asymmetric synthesis of ß-silyl carboxylates **188** and their transformation into enantiomerically pure alcohols **189** was reported by Oppolzer (Scheme 38). The *N*-[ß-(silyl)enoyl] sultam **185**, derived from camphor sultam **55**, underwent conjugate addition with a tributylphosphine-stabilised organocopper reagent to give, depending on the conditions, the (*R*)-isomer **186** or its (*S*)-epimer **187**. Mechanistically, this striking difference is attributed to a preference for a monocoordinated transition state (Fig. 1) when BF_3 is used as a Lewis acid, or a *bis*-coordinated transition state (Fig. 2) when $EtAlCl_2$ (used instead of BF_3) coordinates with the SO_2 and CO groups. The sultam auxiliary **55** is non-destructively removed by mild hydrolysis in both paths.

The *O*-silyl ketene acetals **191** prepared by Helmchen[109] from the sulphonamide shielded alcohols **83** and **84** undergo highly stereoselective $TiCl_4$ catalysed addition to aldehydes to give the adducts **192** and **193** with up to 95% d.e.. Hydrolysis of the esters **192** and **193** affords the corresponding carboxylic acids (Scheme 39). In a similar way, the propionate derivative **194** of the alcohol **84** furnished the (*E*)-*O*-*t*-butyldimethylsilyl ketene acetal **195**, which also underwent Mukaiyama reaction in a stereoselective manner to give the adduct **196** in 92% d.e..

SCHEME 38

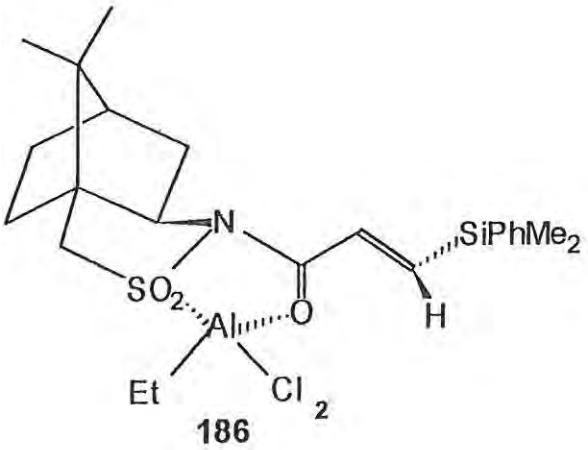


REAGENTS

i R_2Li, CuI, PBu_3 ; ii , BF_3 ; iii , Et $AlCl_2$; iv, LiOH,THF ; v, CH_2N_2

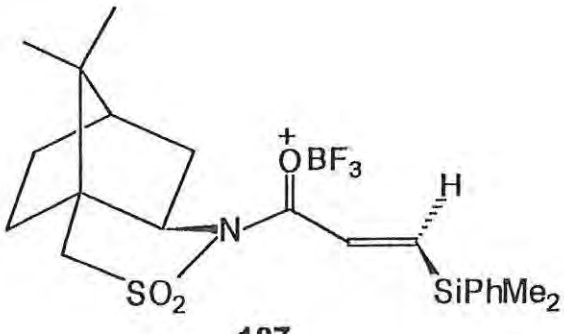
vi, HBF_4 ; vii, *m*-$ClC_6H_4CO_3H$

FIG



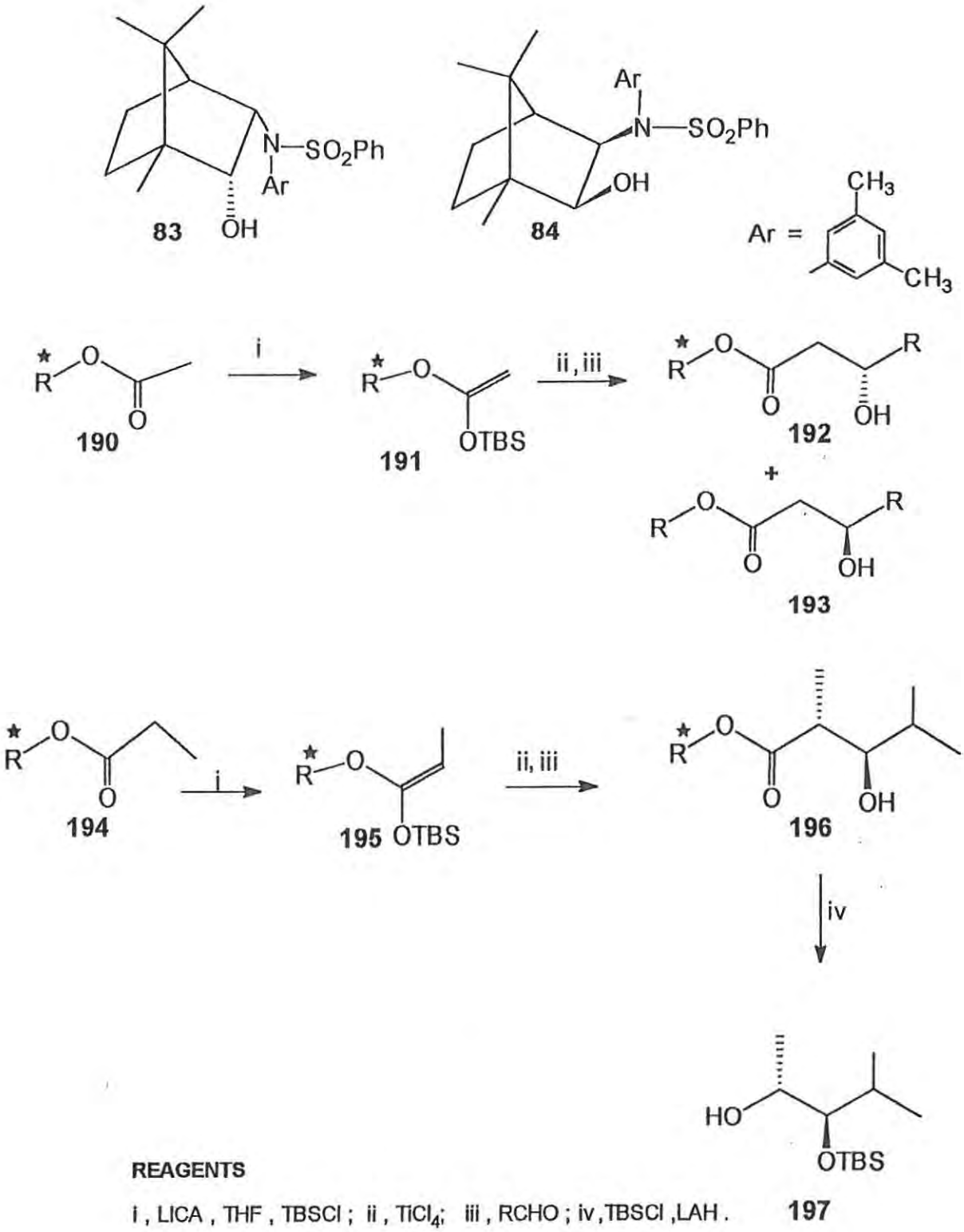
186

FIG



187

SCHEME 39



REAGENTS

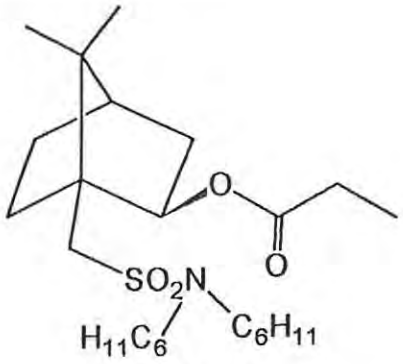
i , LICA , THF , TBSCl ; ii , $TiCl_4$; iii , RCHO ; iv ,TBSCl ,LAH .

The ester **196** was reduced to the alcohol **197**, which is used as a building block in the synthesis of avermectin.

Oppolzer's silyl ketene acetals **199** and **200** have also been successfully employed in asymmetric synthesis (Scheme 40).[111] Kinetic deprotonation of the propionate ester **198** followed by silylation with TBSTf (*tertiary* butyl silyl triflate) resulted in the (*E*)-ketene acetal **199**. Mukaiyama reaction of these acetals gave, preferentially, the *anti*-aldols **201** in 99% e.e. On the other hand, thermodynamically controlled deprotonation of the ester **198**, followed by silylation, resulted in the (*Z*)-ketene acetal **200**. Subsequent treatment of compound **200** with aldehydes in the presence of $BF_3.Et_2O$, gave, preferentially, the *anti*- aldols **202**. Non-destructive removal of the chiral auxiliary with KOH yielded the ß-hydroxy carboxylic acids **203** and **204**.

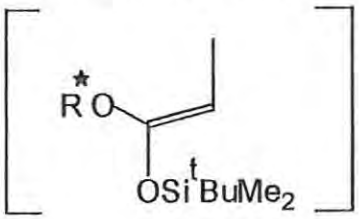
Taddei *et al.*[110] have also successfully combined the advantageous rigid topology of the camphor skeleton with the reactivity of the organo silicon compounds in the preparation of C-centered optically active allylsilanes. In these substrates, the bornane moiety effectively hides one of the sides of the double bond in the allyl group. The chlorosilane **205**, prepared in four simple steps from camphor, was readily converted to the allyl silane **206a**. When treated with MCPBA followed by tetrabutylammonium fluoride (TBAF), the allyl silane **206** yielded the allylic alcohols **208** in 32-87% e.e. (Scheme 41). Condensation of the allyl silane **206b** with butyraldehyde in the presence of $TiCl_4$, however, formed the alcohol **209** with only 18% d.e.. Further work performed by Taddei on chiral ally silanes will be discussed in section 1.4.3.2.

SCHEME 40



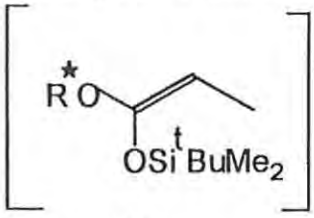
198

kinetic control



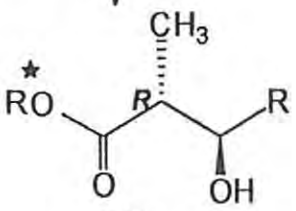
199

thermodynamic control



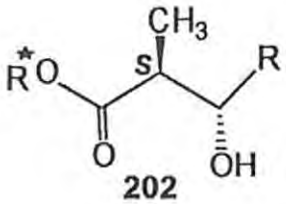
200

ii , iii



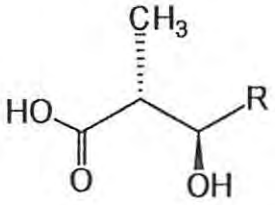
201

i , iii



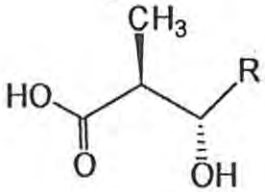
202

vi



203

iv

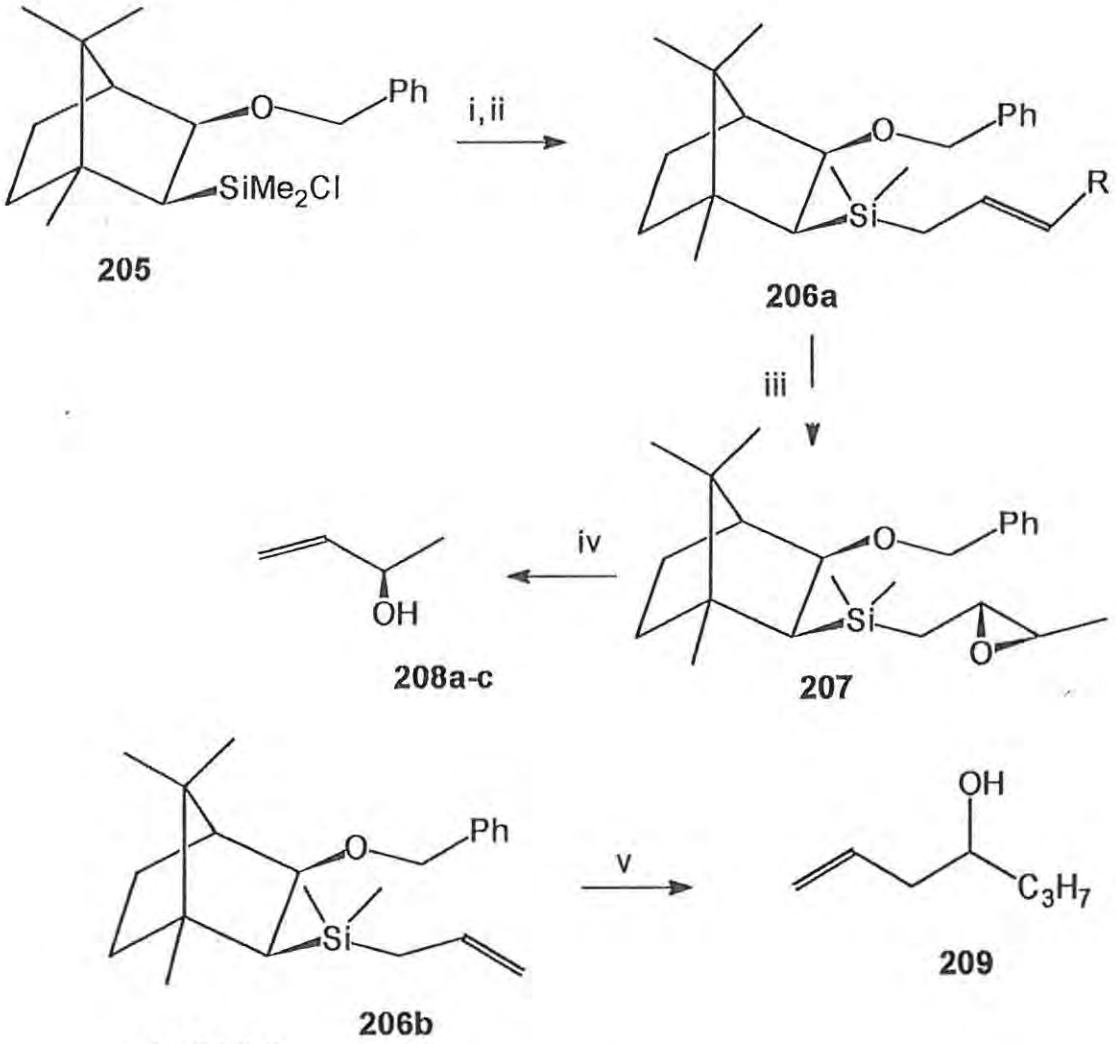


204

REAGENTS

i, $BF_3.Et_2O$; ii, $TiCl_4$; iii, RCHO ; iv, LiOH

SCHEME 41



205 **206a** **207** **208a-c** **209** **206b**

REAGENTS

i BuLi, $KOBu^t$; ii ,  ; iii ,MCPBA ; iv , Bu_4NF ;

v $TiCl_4$, C_3H_7CHO.

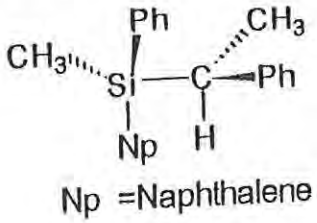
	R	% e.e
208a	C_4H_9	76
208b	C_6H_5	32
208c	$(CH_3)_2CH$	87

1.4 ORGANOSILICON COMPOUNDS IN ASYMMETRIC SYNTHESIS

In the last decade the use of organosilicon compounds as reagents and synthetic intermediates has become a powerful tool in organic synthesis. Reactions such as hydrogenation, oxidation, epoxidation, base catalysed alkylation, hydroboration, electrophilic substitution, intramolecular addition etc.,[113-117] have all been carried out successfully on organosilicon compounds. Much work has also been done to incorporate the synthetically useful reactions of organosilanes into the field of asymmetric synthesis.[118] Chiral organosilicon compounds may derive their chirality from a Si atom (" Si centred") as in compound **210** or from a C atom ("C centred") as in compound **211**.

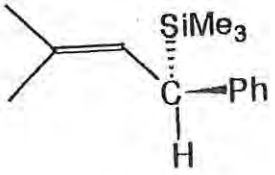
1.4.1 Si-centred Silyl Enol Ethers

Elucidation of the stereochemistry and mechanism of substitution reactions at Si-centred organosilanes was pioneered by Sommer[119] and Corriu.[120] Paquette[121] reported very low enantiomeric excess (3.9-5.5%) in the reaction of chiral allylsilanes with acetals, and Fry[122] also observed low levels of asymmetric induction (6.6-12.7% e.e.) in the fluoride ion catalysed reactions between (R)-(+)-methyl-α-naphthylphenylsilane **210** and several prochiral aromatic ketones. Brook *et al.*[123-125], Larson *et al.*[126,127] and Bonini *et al.*[128,129] also observed low asymmetric induction in the reactions of Si-centred silyl enol ethers.



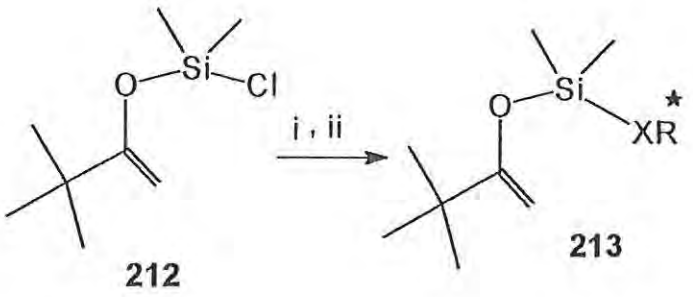
Np =Naphthalene

210

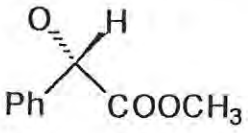
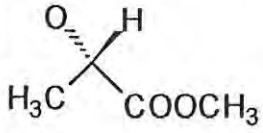
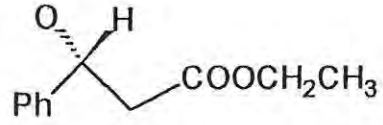


211

SCHEME 42



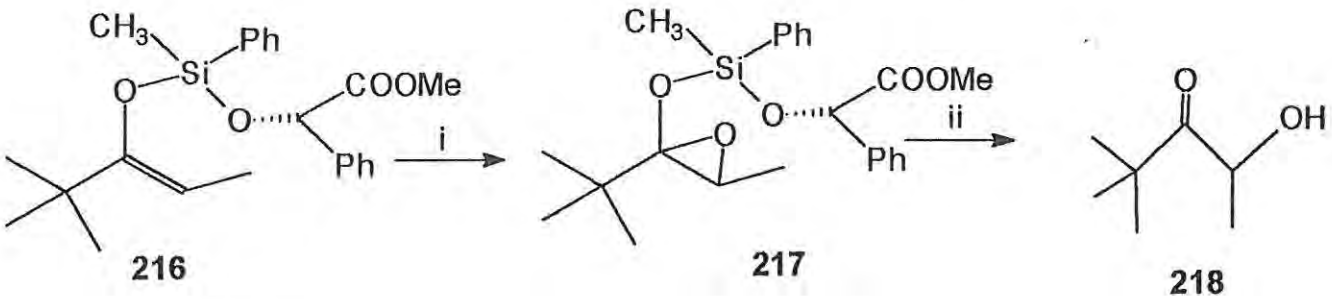
212 **213**

	X★R
213	
214	
215	

REAGENTS

i , RXH ; ii , Et_3N , CH_2Cl_2.

SCHEME 43

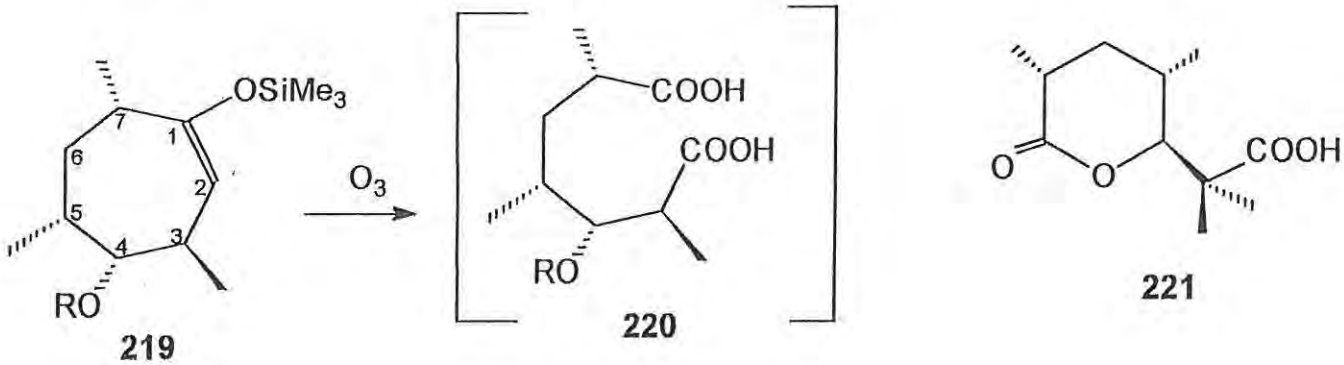


216 **217** **218**

REAGENTS

i , MCPBA ; ii , Bu_4NF

SCHEME 44



219 **220** **221**

REAGENTS

i ,LDA ; ii , Me_3SiCl ; iii ,$PhSCH_2Cl$; Raney Nickel

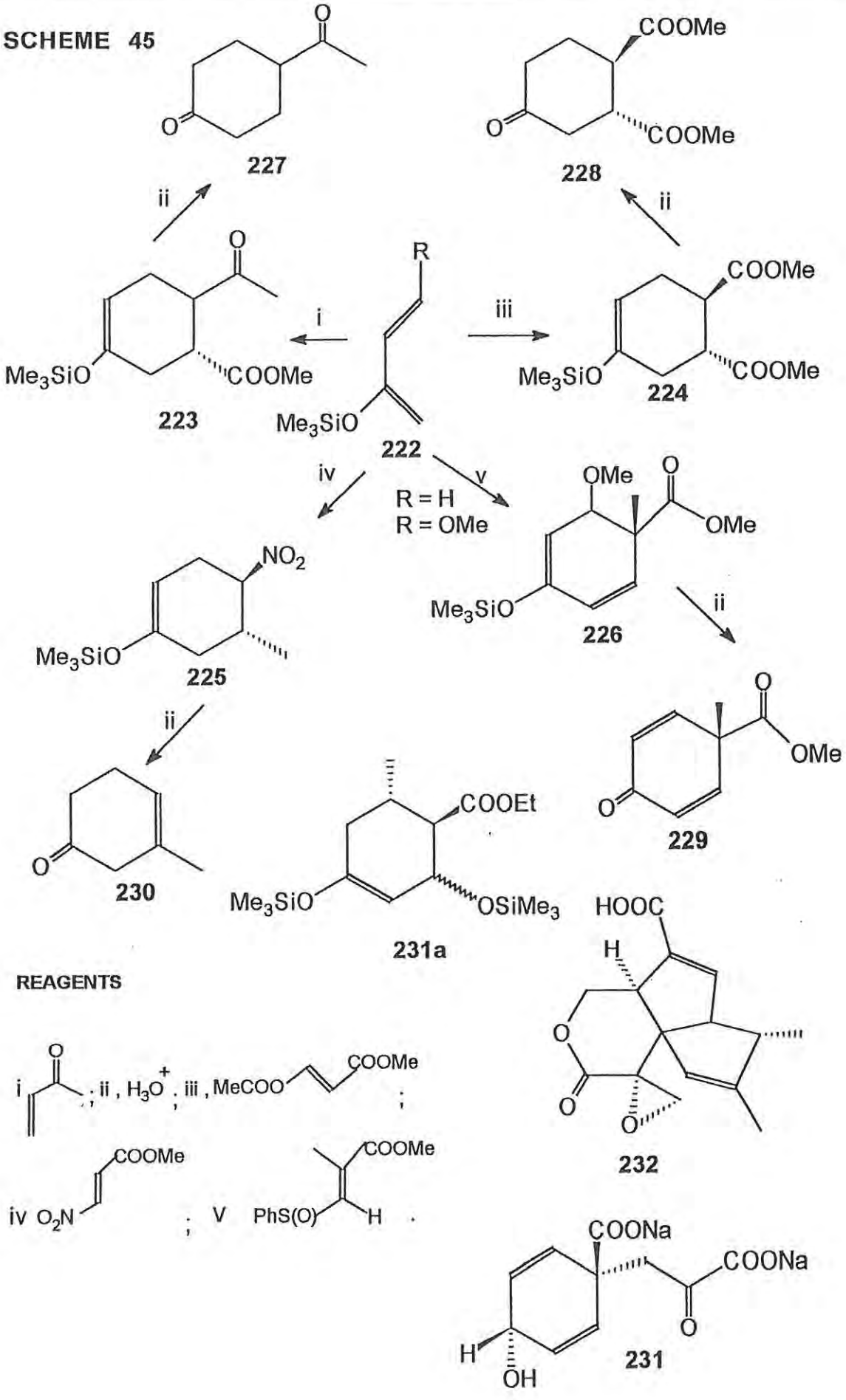
1.4.2 C-centred Silyl Enol Ethers

Fleming and co-workers[130] have studied the effect of changing the substituents (alkyl, phenyl) about the silicon atom and in a similar manner Walkup[131] envisioned that a judiciously chosen non-alkyl ligand placed on the Si atom in a chiral silyl enol ether might profoundly affect the reactivity of such an enol ether, by altering the electron distribution in the enol ligand. With this in mind, he prepared the very first chloro silyl enol ether **212** which paved the way for the general synthesis of a variety of chiral silyl enol ethers **213-215** (Scheme 42). The peracid oxidation[132] of silyl enol ethers such as **216** (prepared from the chloro silyl enol ether **212**) yielded the ß-hydroxy ketone **218** with moderate diastereo selectivity (10-14%).

A wide range of ketone-derived silyl enol ethers are cleaved[133] by ozone to yield substituted carboxlic acids of various types. The kinetically generated silyl enol ethers are cleaved regiospecifically away from the more substituted side, so complementing Baeyer-Villager oxidative cleavage. Selective ozonolysis based on the high nucleophilicity of the silyl enol ether double bond is also possible and has been employed recently by Stork[134] in a stereocontrolled synthesis of the Djerassi-Prelog lactone **221**.

2-Trimethylsilyloxy-1,3-butadiene **222** reacts in a regio- and stereospecific manner with a range of dienophiles to give the chiral silyl enol ethers **223**,[135] **224**[136] and **225**[137] respectively, desilylation of which led to functionalised cyclohexanones (Scheme 45).[138] The chiral silyl enol ether **226** formed in another Diels-Alder reaction led to functionalised enones **229**. Ibuka *et al.*[139] have successfully carried out the stereoselective synthesis of pumiliotoxin

SCHEME 45

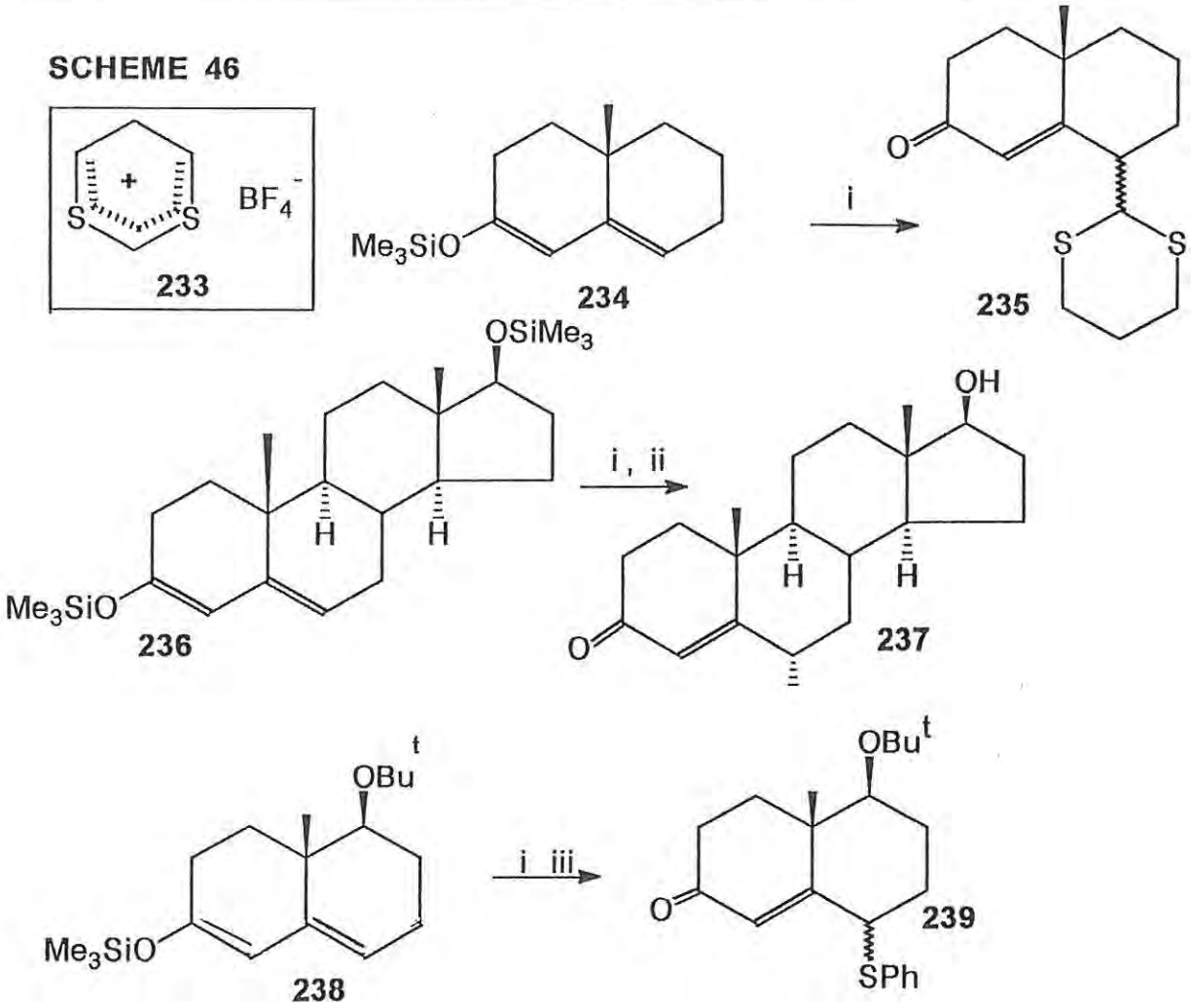

227
228
223
224
222
225
226
230
229
231a
231
232
R = H
R = OMe
i
ii
iii
iv
v
REAGENTS
i ; ii , H_3O^+ ; iii , MeCOO ;
iv ; V

(a toxin with neuromuscular activity) in which a key intermediate was the Diels-Alder adduct **230**. Danishefsky has also employed the silyl enol ether **222** as a dienophile and carried out similar Diels-Alder reactions in the synthesis of the natural products (±)-disodium prephenate **231**[140] and (-)-pentalenolactone **232**.[141]

Unlike the lithium dienolates of α,ß-unsaturated carbonyl compounds, which react with electrophiles selectively at the α-position,[142] (under kinetic conditions) the *O*-silylated dienol ethers react with electrophiles selectively at the γ position.[143] The γ products are selectively protected 1,5-dicarbonyl compounds, containing the versatile dithio acetal unit[144] for further manipulation. Thus the electrophile **233** (1,3-dithienium fluoroborate) reacted smoothly and rapidly with the *O*-silylated dienolate **234** to give, selectively, the γ-product **235**.[145] In a similar way, silyl enol ether **236**, derived from testosterone, also reacted selectively with the electrophile **233** to give the corresponding dithio acetals, which on subsequent treatment with W-2 Raney Ni and acetone gave 6α-methyltestosterone **237** (Scheme 46).

Still *et al.*[146] have described an elegant method for the protection of α,ß-unsaturated ketones by, *inter alia*, lithium dimethylcuprate. ß-Stannyl silyl enol ether **241**[147] obtained from α,ß-unsaturated ketones as shown in (Scheme 47) are relatively unreactive towards most nucleophiles but are smoothly reconverted into enones **242** by mild oxidation.

SCHEME 46

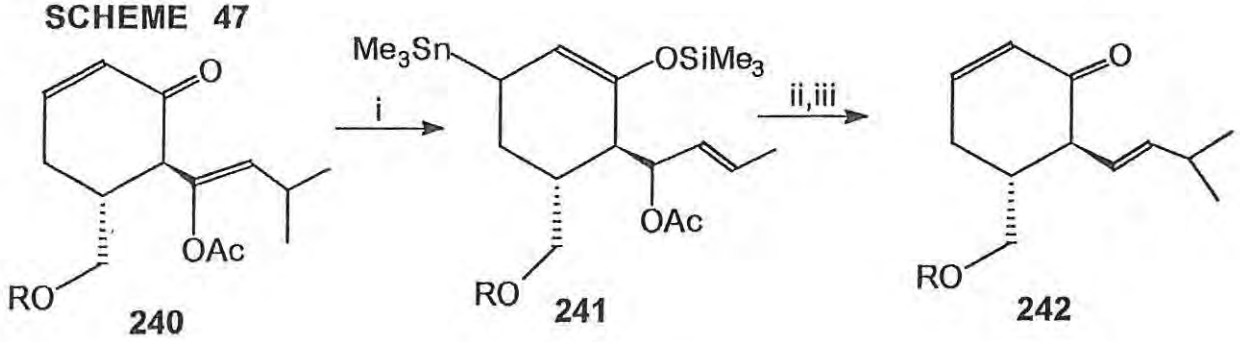


REAGENTS

i, compound **233** ; ii Raney Nickel, Me_2CO;

iii, PhSCl.

SCHEME 47



REAGENTS

i $LiSnMe_3$, Me_3SnCl ; ii $LiCuMe_2$; iii ,MCPBA·

1.4.3 Allylsilanes in Asymmetric Synthesis

Allylsilane analogues are useful synthetic intermediates with highly nucleophilic double bonds.[148,149] Chiral allylsilanes may owe their optical activity to a chiral silicon atom ("Si-centred"), as in compound **243**, or to a chiral carbon atom ("C-centred"), as in compound **246**.

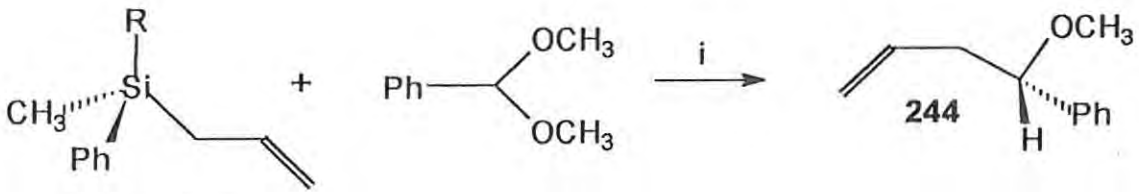
1.4.3.1 Si-centred Allylsilanes

The reaction of (-)-1-methylnaphthylphenylallylsilane **243** with aldehydes and with dimethylacetals was investigated by Hathaway and Paquette.[150] Although the allylsilane **243** failed to react with aldehydes in the presence of $BF_3.Et_2O$ as the Lewis acid, the reaction with dimethylacetals took place to give the homoallylic ether **244** (Scheme 48). However, the chemical yields obtained were less than 30% and the enantiomeric excess was only *ca.* 5%. The low yield was attributed to the steric hindrance by the pendant aryl groups attached to silicon.

1.4.3.2 C-centred Allylsilanes

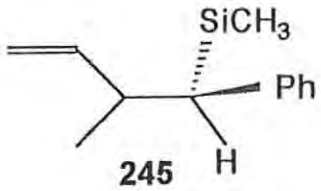
The very first general procedure for the preparation of "C-centred" allylsilanes (*via* catalytic asymmetric Grignard cross coupling[151]) as well as the unambiguous stereochemistry (involving anti-attack) of S_E' reactions[152] of allylsilanes were put forward by Kumado *et al.*[153] Reaction of the (*R*)-(*E*)-allylsilanes **246** with electrophiles (Scheme 49) led to products **247** having an (*S*)-configuration, whereas the (*R*)-(*Z*)-allylsilanes led to products **249** with an (*R*)-configuration.[153] Reaction of the (*R*)-(*E*) and (*Z*)-allylsilanes **250** and **252** with aldehydes in the presence of $TiCl_4$, yielded the optically active homoallylic alcohols **251** and **253** respectively;[154]

SCHEME 48



R = ...Naphthyl

243

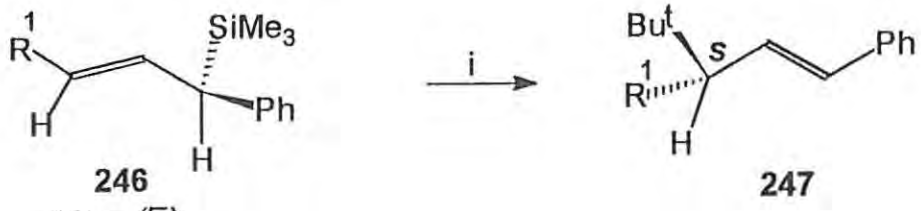


245

REAGENTS

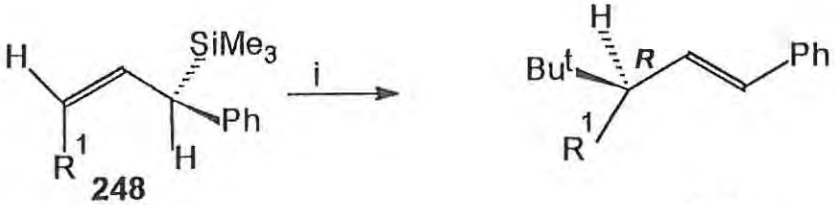
i $BF_3.Et_2O$

SCHEME 49



(R) – (E)

R^1= Me,Ph



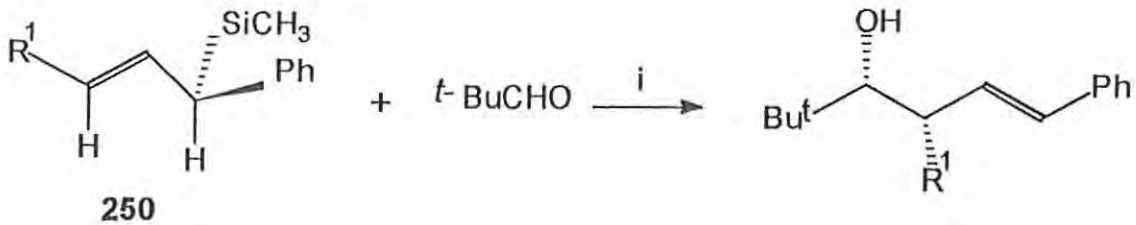
(R)-(Z)

R^1= Me , Ph

REAGENTS

i , Bu^tCl, $TiCl_4$, CH_2Cl_2

SCHEME 50

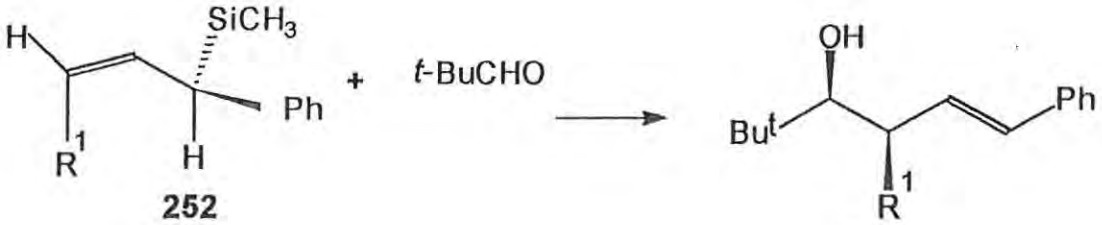


250

(R)– (E)

R^1 = Ph, Me

251



252

(R)–(Z)

R^1= Me , Ph

253

REAGENTS

i $TiCl_4$, CH_2Cl_2.

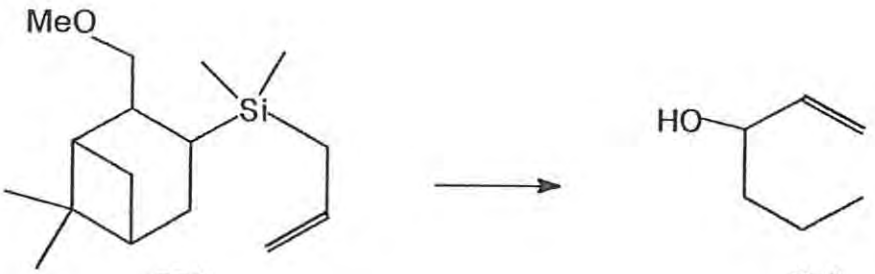
the carbon double bond having an (*E*)-configuration in all cases. The alcohols **251** were obtained in very high enantiomeric excess (> 85%), whereas the alcohols **253** were obtained in much lower enantiomeric excess (14-18%) (Scheme 50). The stereochemical results obtained were in accordance with the mechanism[155] and transition states[156] proposed for S_E reactions of allylsilanes.

Taddei[157] has investigated the reaction of allylsilane **254** with aldehydes such as butanal which, in the presence of $TiCl_4$, yielded the homoallylic alcohol **255** with enantiomeric excess varying from 21 to 56% (Scheme 51). Chan *et al.*[158] have also reported similar reactions of chiral allylsilanes, such as **256**, with aldehydes to give homoallylic alcohols in significantly improved material yield, but with reduced enantiomeric excess (*ca.*15%). The pyrollidinylmethylallylsilane **257**,[159] however, reacted to give homoallylic alcohols with much improved enantiomeric excess (up to 50%).[121]

Taddei[160] has further investigated the reaction of the allylsilanes **258** with electrophiles such as MCPBA, phenylsulphenyl chloride (PhSCl) and chlorosulphonyl isocyanate (CSI). The stereoselectivity of the reaction with MCPBA was quite poor (*ca.* 10% d.e.), but better stereoselectivity (up to 98% d.e.) was obtained using PhSCl and CSI (Scheme 52).

Allylsilanes have also been successively employed in the asymmetric synthesis of natural products.[161] The [2 + 2] cycloaddition between the allylsilane **262** and dichloroketene resulted in the formation of a C-centered chiral allylsilane **263**, which reacted with electrophiles to give the lactones **264** and **265** which are synthetic precursors for prostaglandins[162] and loganin[163] respectively (Scheme 53).

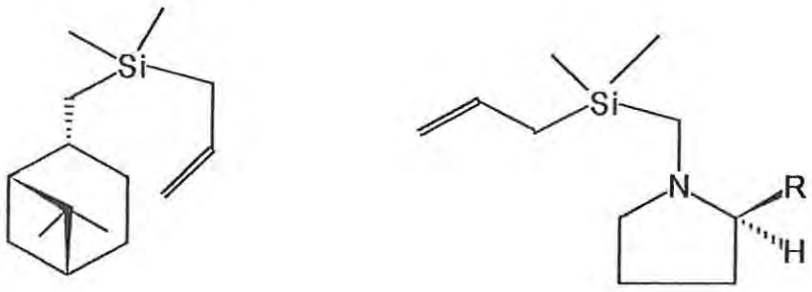
SCHEME 51



254 **255**

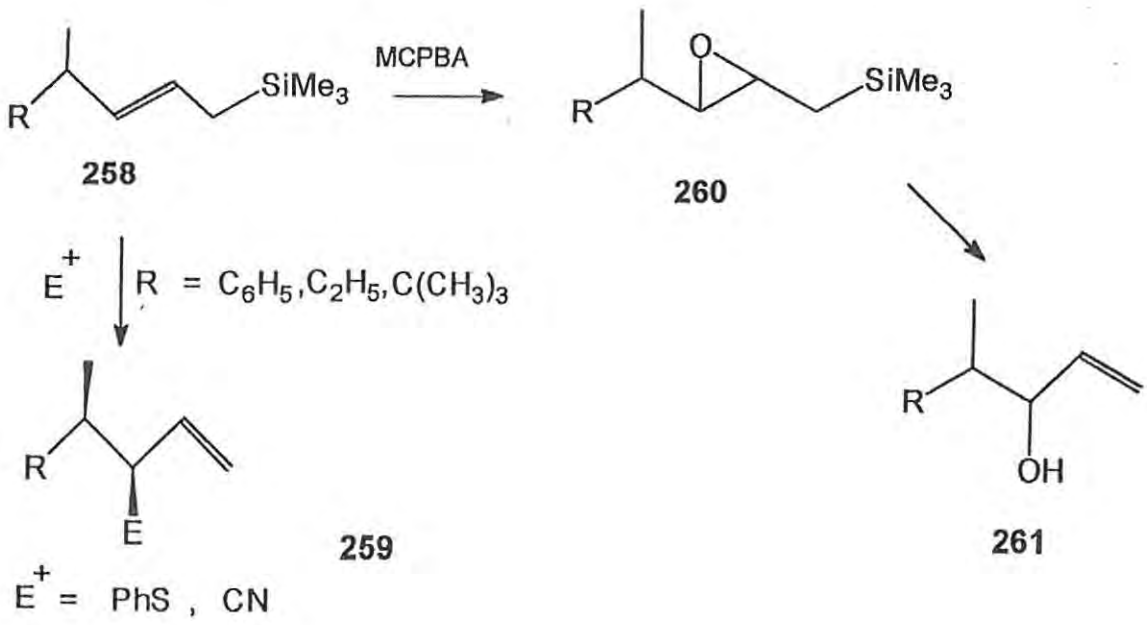
REAGENTS

i , Lewis acid, $CH_3CH_2CH_2CHO$.



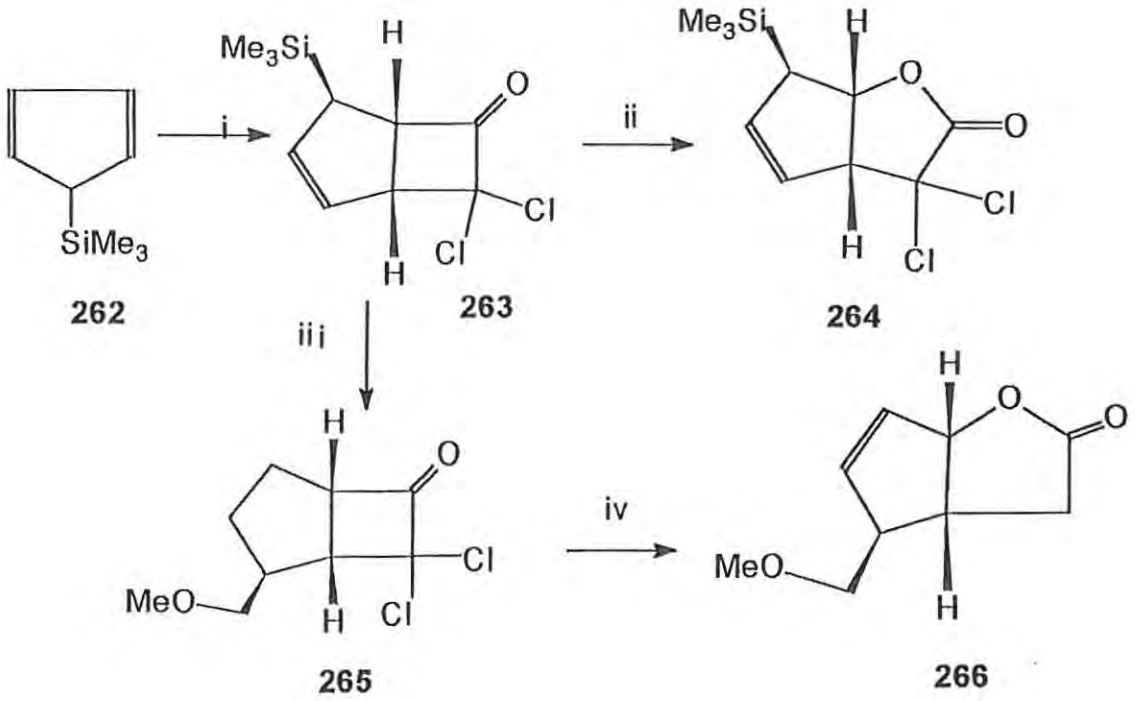
256 **257**

SCHEME 52



258 **260** **259** **261**

SCHEME 53

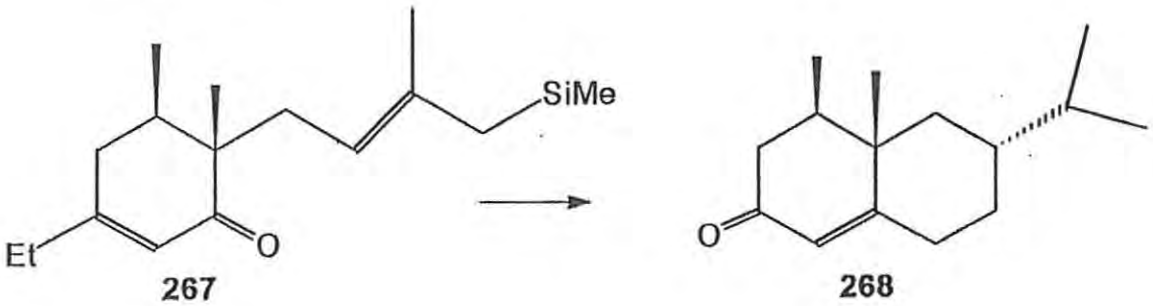


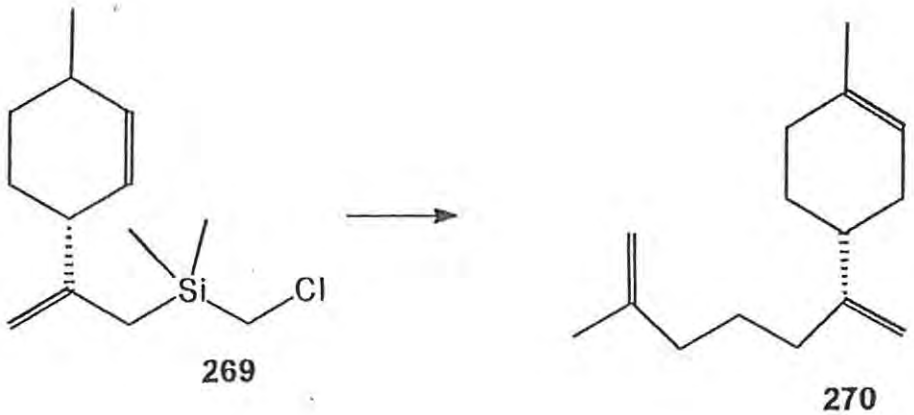
REAGENTS

i Cl_2CCO ii H_2O_2, CH_3COOH

iii $MeOCH_2Cl$, $SnCl_4$, iv H_2O_2, Zn, AcOH

SCHEME 54





From the chiral allylsilane **267**, Majetich *et al.*[164] have carried out the asymmetric synthesis of valencene **268** and its deoxy analogue nootkatoone, while Chan[165] has successfully achieved the asymmetric synthesis of α-(*E*)-bisabolene **270** using the allylsilane **269**.

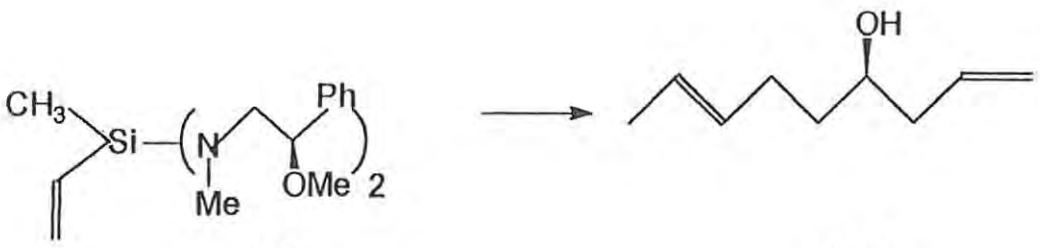
1.5 VINYLSILANES IN ASYMMETRIC SYNTHESIS

Vinylsilanes are versatile synthetic reagents since their carbon silicon bond can be readily cleaved by various electrophiles in a regio- and stereoselective manner.[166] Tamao and Kumado[167] were the first to prepare the chiral vinylsilane **271** (*in situ* from ephedrine methyl ether and vinylmethyldichlorosilane) which they employed to synthesise the alcohol **272** in 60% e.e..

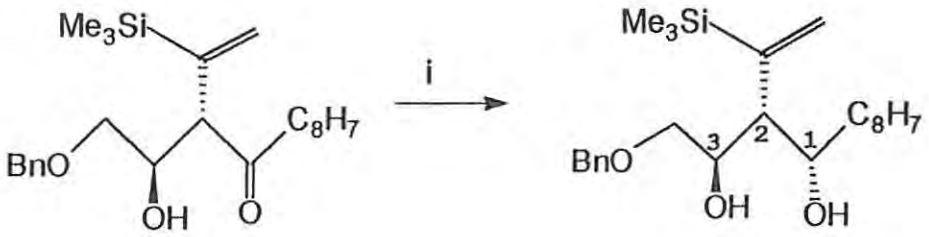
The vinylsilanes **273-275** underwent stereoselective reduction[168] with lithium triethylborohydride or diisobutyl aluminium hydride to give the 1,3-diols **274** and **276** with 2,3-*syn* stereochemistry having three consecutive stereogenic centers.[169] The presence of the trimethyl silyl substituent in the α-position of the vinyl group firmly establishes the *syn*-relationship[170] between the newly formed hydroxyl group and the vinyl group. In an extension of this approach, two isomeric lactones, avenaciolide **277**[171] and isoavenaciolide **278**[172] have been synthesised (Scheme 55).[173]

Panek *et al.*[174,175] reported the use of the Ireland ester Claisen methodology[173,176] to transform chiral C-3 oxygenated vinylsilanes **279** into the desired (ß)-silylhexenoic acids **280** and **281** (Scheme 56), which serve as precursors for the ansamycin class of antitumour antibiotics.

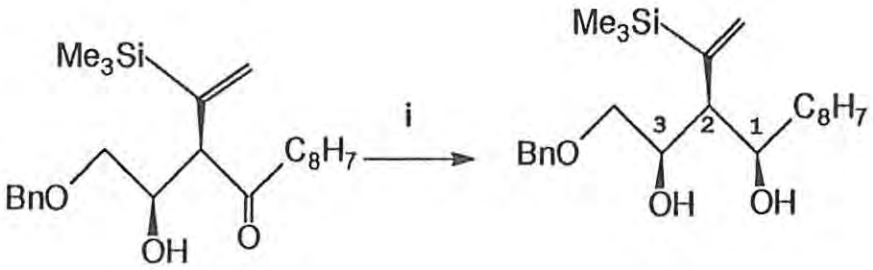
SCHEME 55



271 **272**



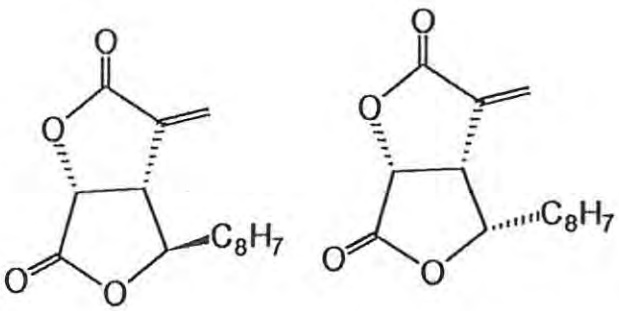
273 **274**



275 **276**

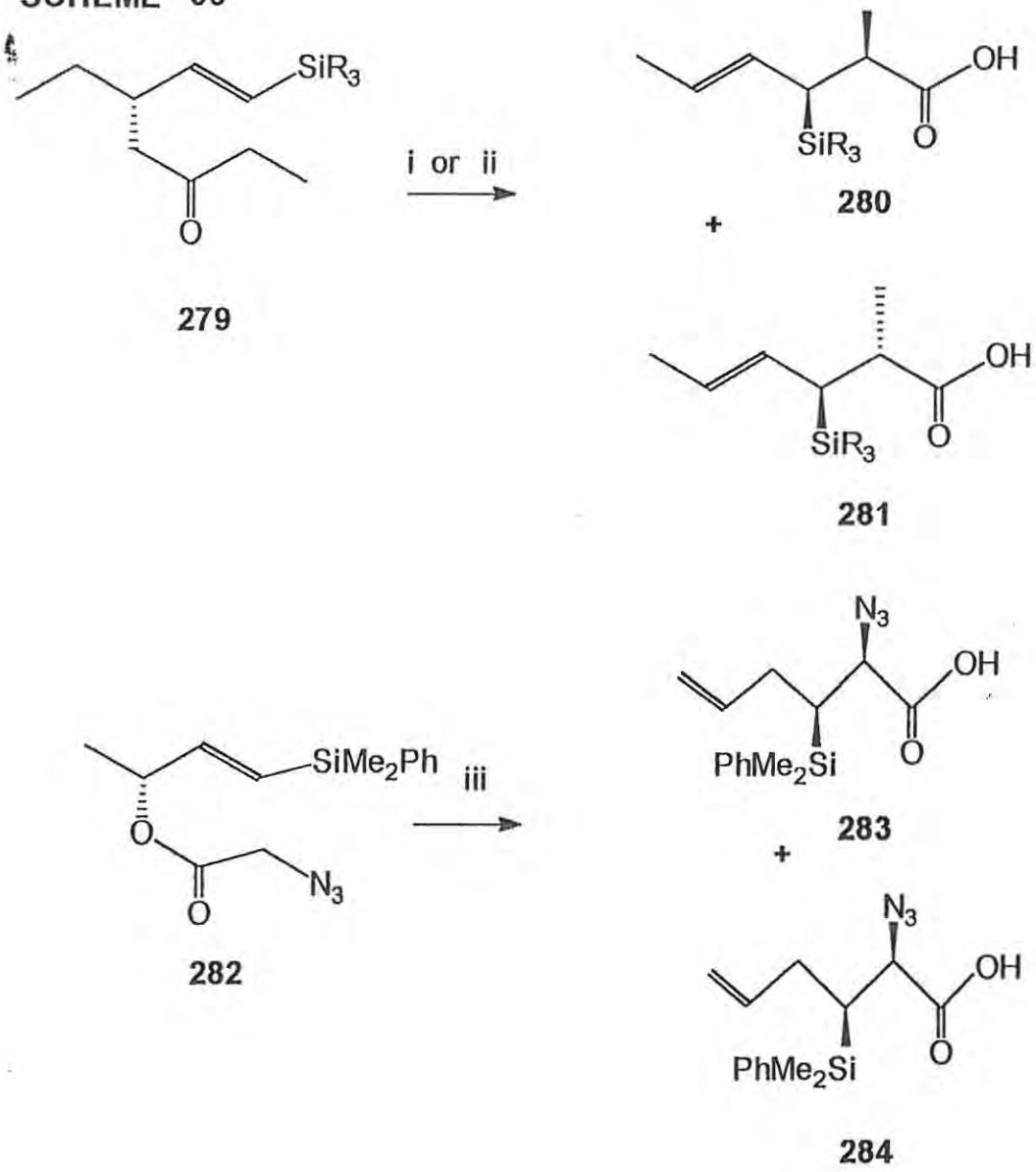
REAGENTS

i $LiEt_3BH_4$, THF



277 **278**

SCHEME 56



REAGENTS

	280	:	**281**
i LDA / TMSCl	1	:	12
ii LHMDS / HMPA	16	:	1

iii TBSOTf (1.5 equiv)., Et_3N (2 equiv.)

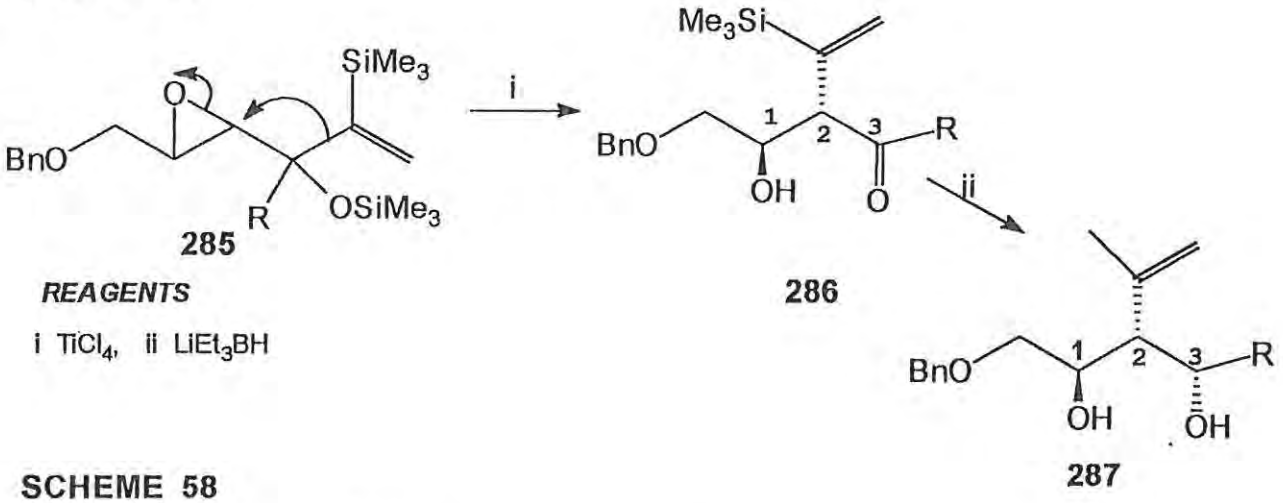
The reaction of the α-azido acetate **282** with *tert*-butylsilyl triflate (TBSOTf) provides the first example of a Claisen rearrangement involving an α-azido ester, and offers a new approach to the asymmetric synthesis of α-amino acids (Scheme 56).[177]

The epoxy vinylsilanes **285**[178] have been shown to undergo stereospecific 1,2-rearrangement in the presence of a Lewis acid, to give the chiral vinylsilanes **286** which, on reduction, gave the 1,3-diols **287** having 2,3-*syn* stereochemistry.[179] The trimethylsilylvinyl moiety not only serves as a good migrating group in the 1,2-rearrangement, but also as a controlling element for dictating the orientation of subsequent hydride attack. In a similar manner, the epoxy silyl ether **288**[180] gave the chiral vinylsilane **289** which underwent nucleophilic addition to yield the 1,3-diol **290** with 2,3-*anti* stereochemistry. When a silyl ketene acetal **290a** was used as the nucleophile, the isolated product was the lactone **291a**, with three consecutive chiral centres. Furthermore; when a prostereogenic silyl ketene acetal **290b** was used as the nucleophile, the product was the lactone **291b** with four consecutive chiral centres. Thus, 1,2-rearrangement-nucleophilic addition reactions of vinyl silanes provides a new approach for establishing three or four contiguous asymmetric centres in one single step, and highlights the synthetic potential of vinyl silanes.

1.6 PREVIOUS WORK DONE IN THE GROUP

Some work has already been done in our laboratories on the preparation and electrophilic reactions of the C-centred silyl enol ethers.[181] A convergent synthesis[182] for the preparation of silyl enol ethers was established, for certain compounds,which proved to be superior to the one

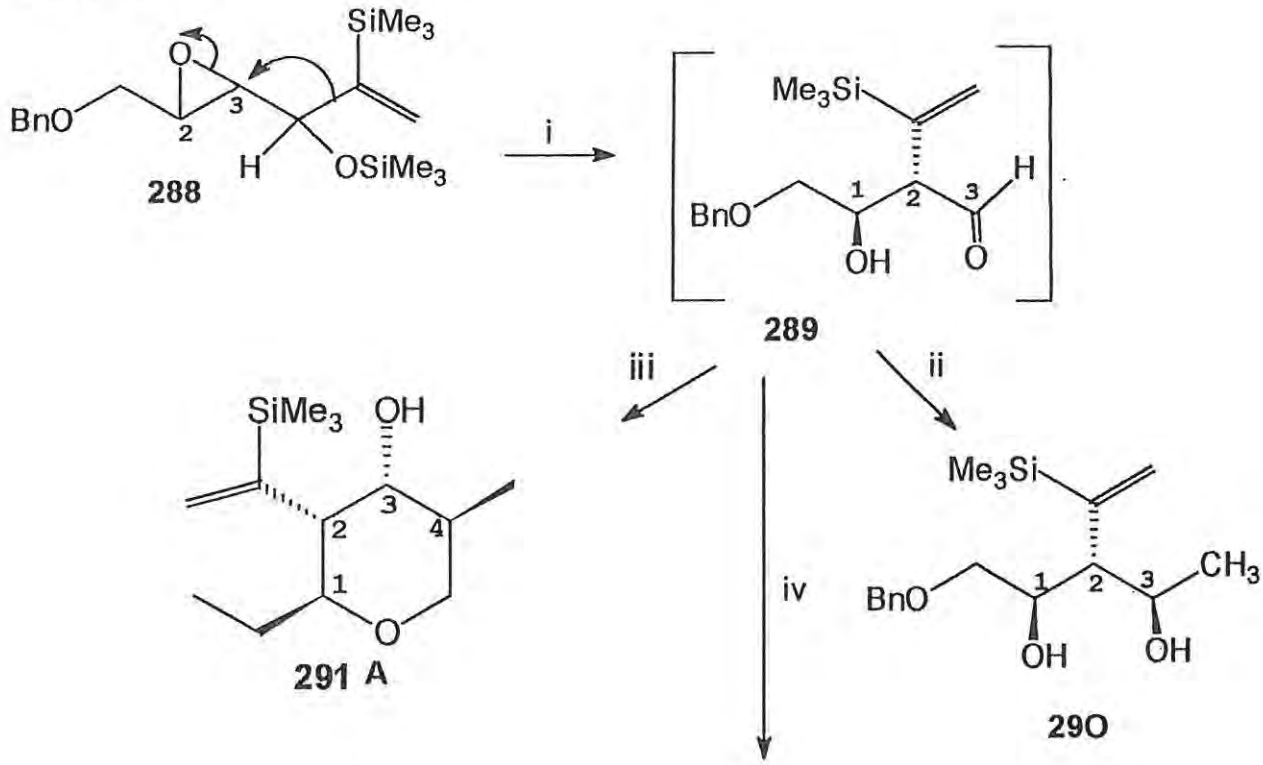
SCHEME 57



REAGENTS

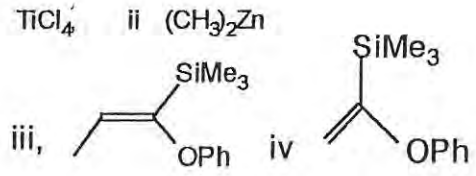
i $TiCl_4$, ii $LiEt_3BH$

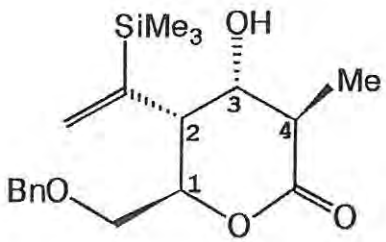
SCHEME 58



REAGENTS

i $TiCl_4$ ii $(CH_3)_2Zn$





superior to the one-pot synthesis of Walkup *et al.*[183] The convergent synthesis involves reaction between a chiral alkoxy chlorosilane [prepared by treating a chiral alcohol (menthol or borneol) with dichlorodimethylsilane] and the lithium enolate of the corresponding ketone. This approach was successfully used to prepare the silyl enol ethers **292-299** in good yield, and these chiral silyl enol ethers were used to explore stereocontrol in the following reactions:

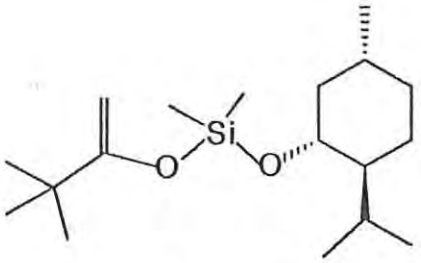
(i) MCPBA oxidation;[184]

(ii) alkylation using *tert*-butyl chloride;[185] and

(iii) the Mukaiyama reaction with benzaldehyde.[186]

MCPBA oxidation in the presence of excess of sodium bicarbonate, following a procedure similar to that employed by Walkup *et al.*,[187] proceeded with migration of the chiral auxiliary to afford diastereomeric α-substituted ketones (*e.g.* **300**). Similar products were obtained in the pioneering MCPBA oxidation work of Rubottom *et al.*[188,189] on achiral substrates, but the intermediate silyl epoxides reported by other workers[190,191] were not detected. The stereoselectivities although poor (0-14%) were comparable with those obtained in a concurrent oxidation study by Davis and Sheppard,[192] who used a chiral oxaziridine reagent. Chloro(menthyloxy)dimethylsilane was also utilised in the preparation of diastereomeric silyl acetals (*e.g.* **303 - 305**), GLC analytical resolution of which, represented a novel application of silyl ethers as chiral GLC probes.[193]

Various silyl enol ethers were also reacted with carbon electrophiles[5] (Scheme 59). For example, the $TiCl_4$ catalysed alkylation of the tetralone silyl enol ethers **296** and **299** with *tert*-butyl chloride, yielded the α-alkylated tetralone **306**.[194] The enantiomeric excess was determined



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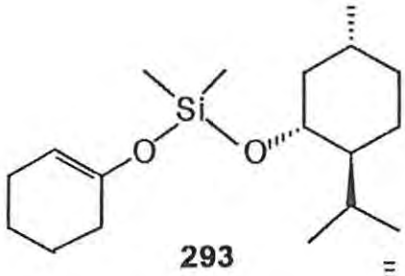

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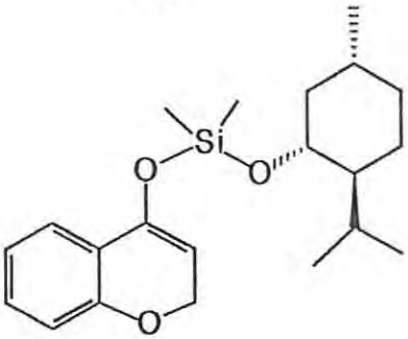

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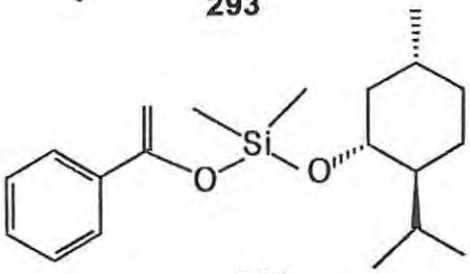

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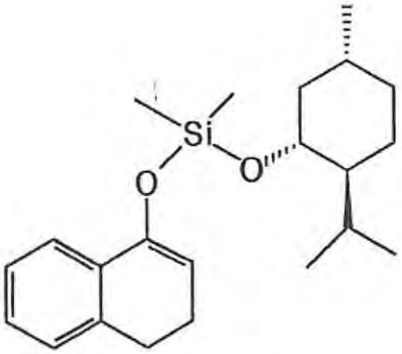

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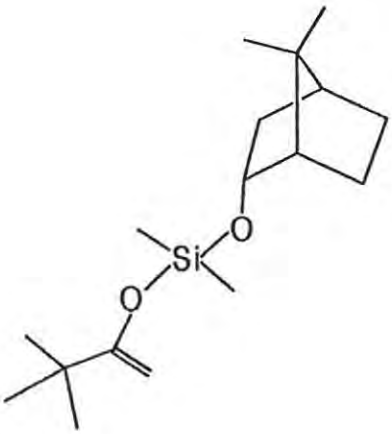

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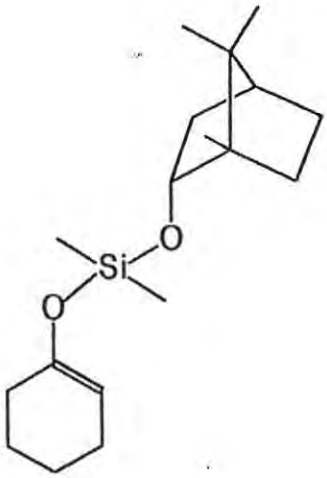

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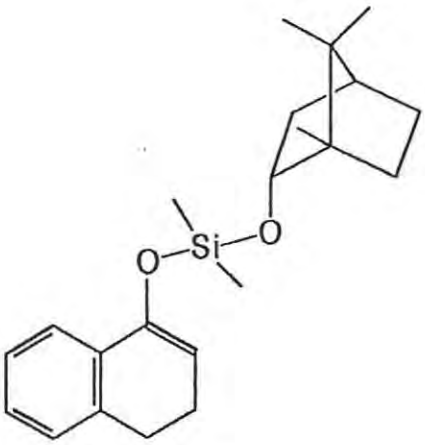

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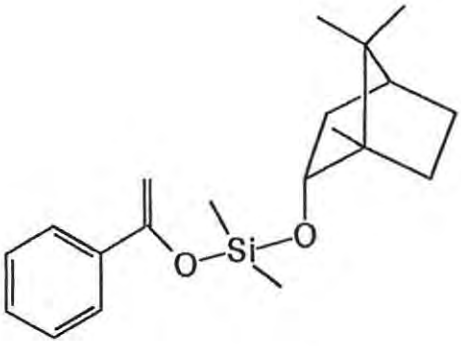
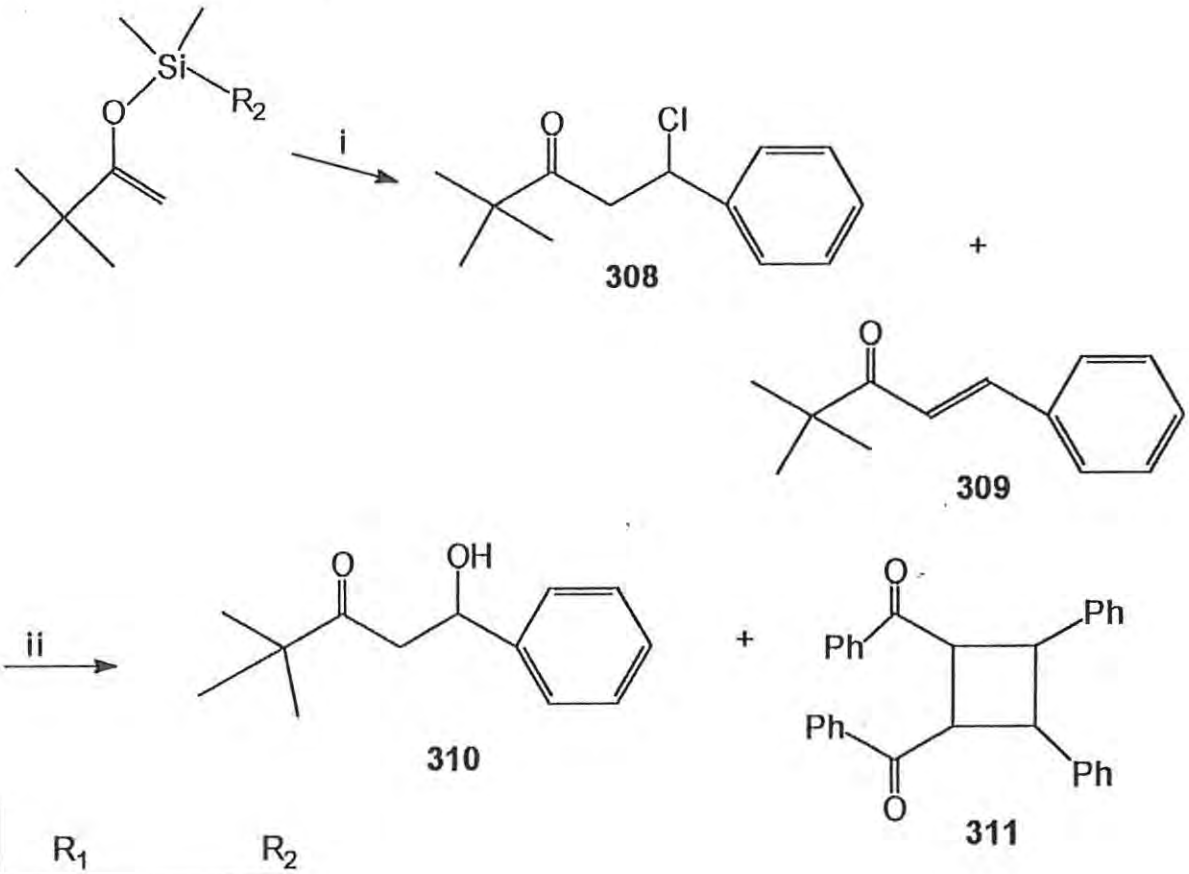
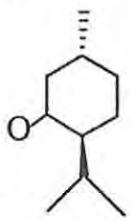
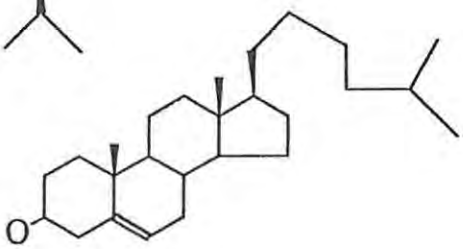


305

SCHEME 60



	R_1	R_2
292	Bu^t	
294	Ph	
307	Bu^t	

REAGENTS

i $TiCl_4$, PhCHO; ii, freshly distilled $TiCl_4$

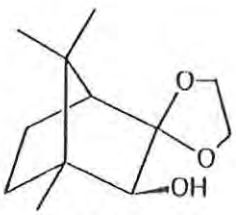
by integration of the *tert*-butyl singlets which were resolved by the addition of chiral shift reagents [$Eu(tfc)_3$ and $Pr(tfc)_3$]. The MCPBA oxidation of these chiral silyl enol ethers **295**, **296** and **299** yielded the corresponding α-silyloxy ketones **300-302**. The $TiCl_4$ catalysed reactions of the pinacolone silyl enol ether **292**, **294** and **307** with benzaldehyde were also investigated[194]. The silyl enol ether **292** and **307** yielded the β-chloroketone **308** and the α,β-unsaturated ketone **309**. When the same reaction was repeated using freshly distilled $TiCl_4$, the desired β-hydroxy ketone **310** and the α,β-unsaturated ketone **309** were obtained. The reaction of the silyl enol ether **294** with benzaldehyde in the presence of $TiCl_4$ yielded the β-chloroketone **308** and an unusual chalcone dimeride, 1,2-dibenzoyl-3,4-diphenyl-cyclobutane **311**, whereas when the reaction was repeated using freshly distilled $TiCl_4$, the only product obtained was the desired β hydroxy ketone **310** (6-14% e.e.) (Scheme 60).

Attention was focused on the use of camphor derived auxiliaries, many of which have been successfully used in asymmetric synthesis. The popularity of camphor stems from the fact that it is available in both enantiomeric forms and is conformationally rigid. Three chiral auxiliaries, **312**, **313** and **314**, having the following common features were targeted.

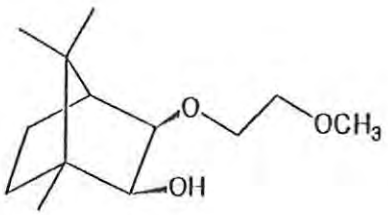
(i) A bicyclic rigid camphor skeleton which was expected to enhance the rigidity in the transition state.

(ii) An alcohol group which would permit easy linkage of the silyl moiety.

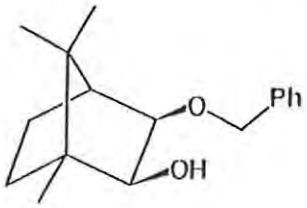
(iii) A close coordination site at position 3.



312

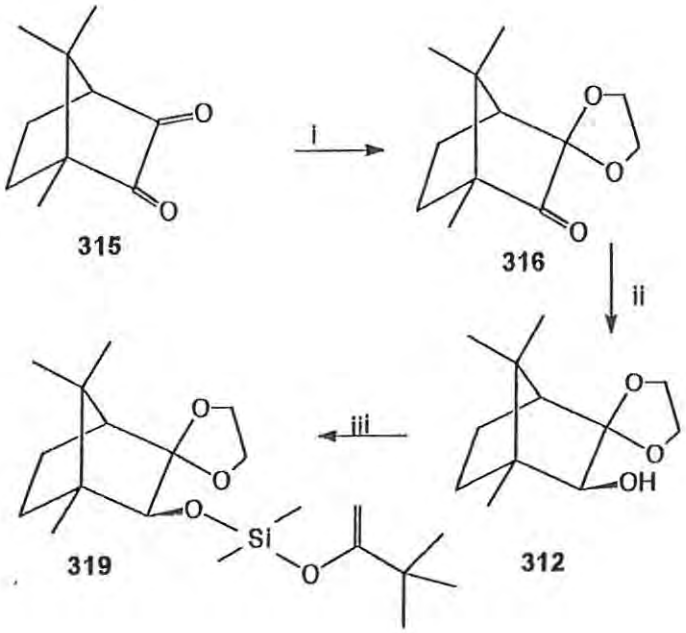


313



314

SCHEME 61



315 **316** **312** **319**

REAGENTS

i. Ethylene glycol, PTSA , ii. L-Selectride iii $Me_2Si Cl_2$, **318**

The auxiliaries **312** and **313** are known and were prepared following the procedure of Oppolzer *et al.*[183] A similar approach was also used for the preparation of the novel auxiliary **314**. Reaction of the novel silyl enol ether **318** with benzaldehyde (Scheme 61) in the presence of $TiCl_4$ afforded the β-hydroxy ketone **310** in good material yield and with somewhat improved stereocontrol (enantiomeric excess estimated to be 26% by ^1H NMR analysis).[185]

1.7 AIMS OF THE PRESENT STUDY

The encouraging results obtained in the previous studies by Learmonth[181] suggested that the 2,3-disubstituted bornane auxiliaries had the potential to improve asymmetric induction in the hydroxyalkylation of chiral silyl enol ethers. This improvement was attributed to the enhanced co-ordination capabilities of the auxiliary and to the rigid bicyclic structure of the camphor skeleton. The objectives of the present investigation have been concerned with an extension of this earlier work and further development of novel systems for achieving asymmetric induction. The project has involved the following:-

(i) To extend earlier work on the asymmetric Mukaiyama reactions of camphor-derived chiral silyl enol ether **312**;

(ii) To explore the asymmetric induction in α-benzylation of the carboxylate esters obtained using camphor-derived chiral alcohols;

(iii) To investigate conformational preferences in the enolates of these esters using computer modelling techniques; and

(iv) To explore novel approaches to the synthesis of amino acids using camphor-derived chiral auxiliaries.

2. DISCUSSION

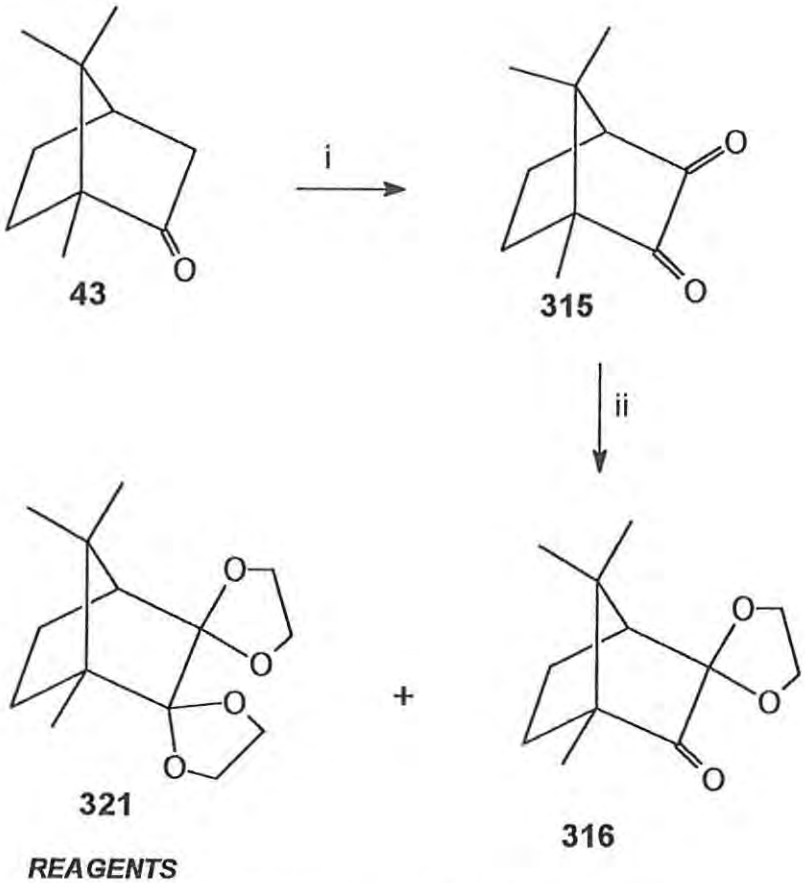
The initial objective in this project was to explore and extend earlier work[186] on the the asymmetric induction obtained during the $TiCl_4$ catalysed reaction of aldehydes with the chiral silyl enol ether **319**. The preparation and electrophilic substitution reactions of the silyl enol ether **319** are covered in the following Section. In subsequent sections the development of this research on other applications of camphor-derived chiral auxilliaries is described.

2.1. PREPARATION AND MUKAIYAMA REACTIONS OF THE CAMPHOR-DERIVED SILYL ENOL ETHER 319

2.1.1 Preparation of Silyl Enol Ether 319

The synthetic approach to the chiral auxiliary **319** required for the initial studies is outlined in Scheme 61. Camphorquinone was prepared by SeO_2 oxidation[196] of the commercially available D-(+)-camphor **43** and acetalisation of the resulting camphorquinone with ethylene glycol yielded the desired 3,3-ethylenedioxy camphor **316**[197] together with some of the diacetal **321** (Scheme 62). The pure monoacetal **316** crystallised out spontaneously from the mother liquor, while the diacetal **321** and residual monoacetal were separated by flash chromatography of the mother liquor. The stereoselective reduction of the monoacetal **316** to the alcohol **312** required *endo*-hydride attack and L-Selectride[198,199] (lithium tri-secondary-butylborohydride) was initially used to bring about this transformation. This highly hindered, reactive reducing agent was the first of its kind to be reported and exhibits

SCHEME 62

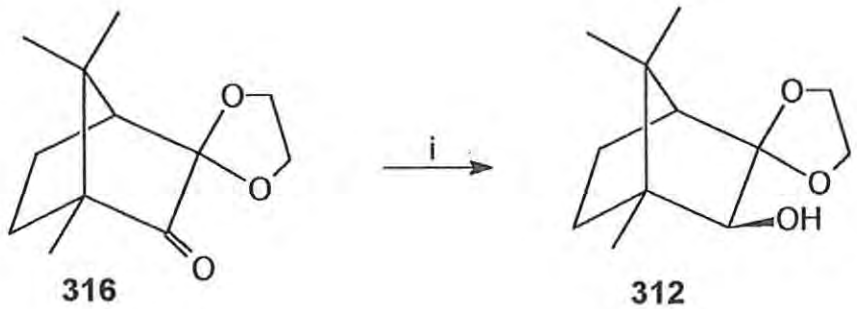


43 **315** **321** **316**

REAGENTS

i SeO_2, acetic anhydride; ii, PTSA; ethylene glycol.

SCHEME 63

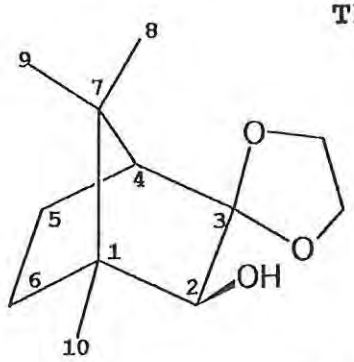


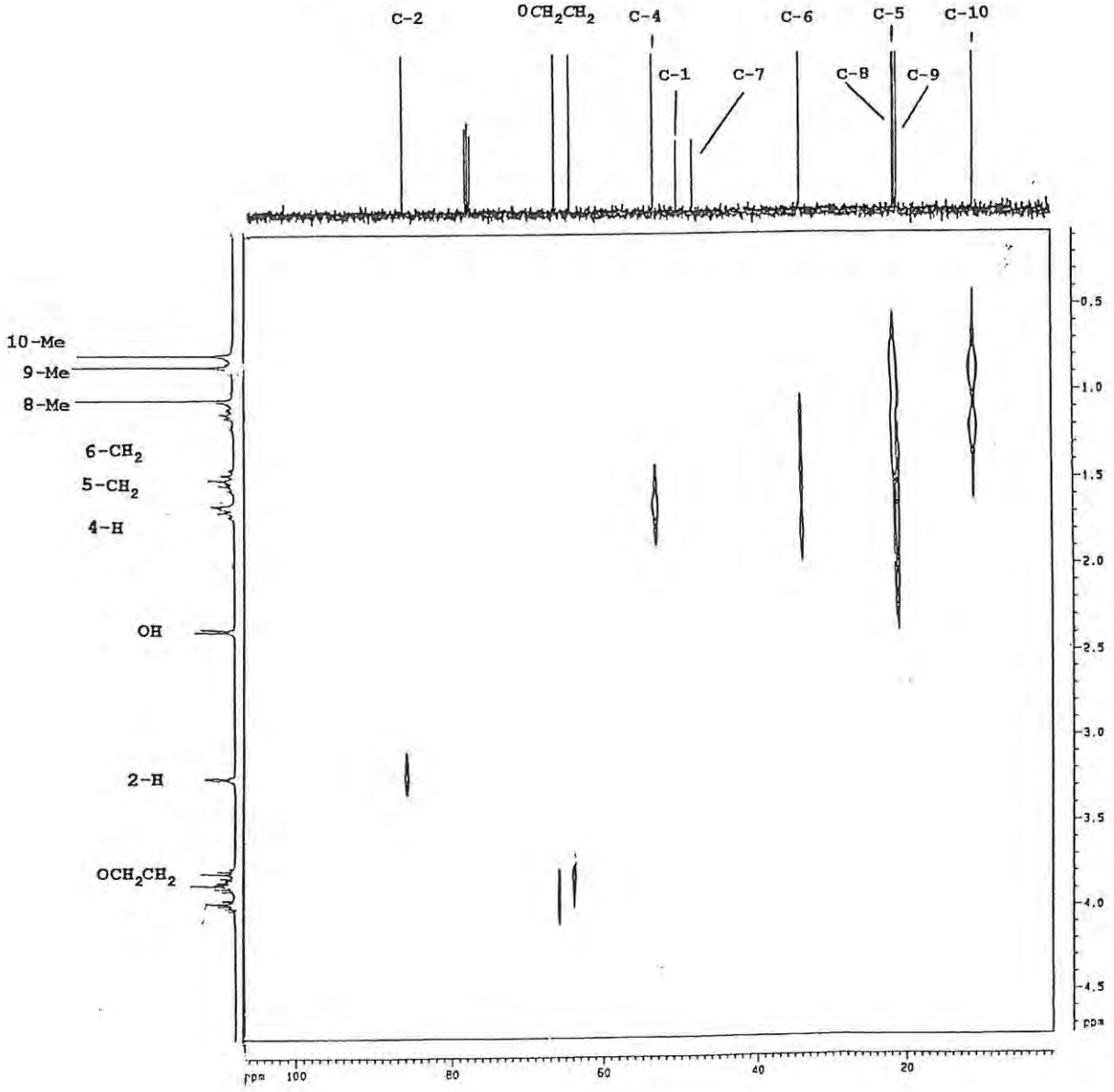
316 **312**

REAGENTS

L-Selectride or K-Selectride or Super Hydride or $NaBH_4$

FIGURE 3 400 MHz HETCOR NMR SPECTRUM OF THE CHIRAL ALCOHOL 312





essentially `enzyme-like' stereoselectivity in the reduction of cyclic and bicyclic ketones. Following Oppolzer's procedure,[199,200] the monoacetal **316** was reduced to the *exo* alcohol alcohol, and the structure was confirmed by 1-D (^{1}H and ^{13}C) and 2-D (HETCOR and COSY) NMR experiments. Since the availability of L-Selectride was limited, alternative reducing agents were examined and the reduction was also successfully achieved using K-Selectride[201] (potassium tri-secondary-butylborohydride), superhydride[202] (lithium tri-ethylborohydride) and the inexpensive $NaBH_4$.[203,204] In all cases, comparable yields of the required stereoisomer were obtained indicating that steric constraints in the substrate **316** are sufficient to ensure *endo* hydride delivery, even with less hindered reducing agents. The *exo* alcohol was fully characterised by 1-D (^{1}H, ^{13}C, DEPT) and 2-D (HETCOR and COSY) NMR experiments (Figure 3).

The preparation of the pinacolone chlorosilane **318** was achieved by adding one equivalent of dichlorodimethylsilane to the lithium enolate (generated *in situ* from lithium diisopropylamide and pinacolone). LiCl, which formed as a fine precipitate, had to be removed prior to distillation of the crude mixture. Walkup[205] has suggested filtration using celite; this method however, failed in our hands because of the extreme sensitivity of the chlorosilane **318** to the moisture. An alternative method was found to be more successful; *viz.*, decantation of the supernatant liquid under nitrogen to another reaction vessel by means of a cannula. The yield of chlorosilane **318** was further improved by adopting the following procedures.

(1) All apparatus was flame-dried under vacuum prior to use.

(2) Nitrogen gas of the highest available purity was used.

(3) Molecular sieves (used for dynamic drying of solvents and reagents) as well as drying agents (used in the drying train connected to nitrogen line) were vacuum dried in a furnace prior to use.

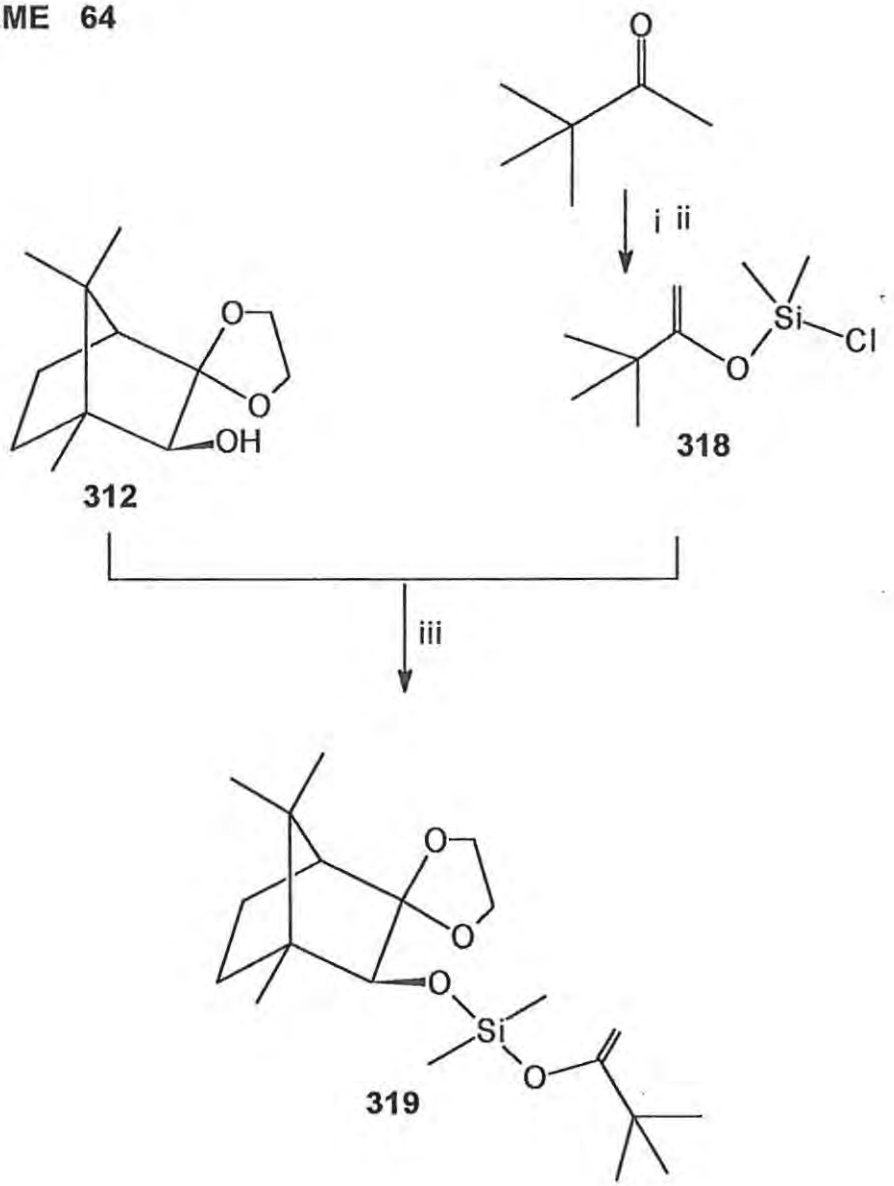
The chlorosilane **318**, in the absence of moisture, proved to be stable and could be stored in septum-sealed containers under refrigeration for several months.

The silyl enol ether **319** was prepared by reacting the chlorosilane **318** with the alkoxide generated by treating the chiral alcohol **312** with NaH. Evaporation of the solvent, after usual work-up yielded a crude mixture, NMR spectroscopy of which confirmed the presence of the silyl enol ether **319** (Scheme 64). Conventional flash chromatography techniques,[206] afforded the required product in disappointingly low yields (*ca.* 24%). This was attributed to the sensitivity of the silyl enol ether **319** to moisture; by using dried compressed air and dry solvents, however, the C-centred chiral silyl enol ether **319** was isolated in a much better yield (*ca.* 56%). The silyl enol ether **319** was fully characterised by 1-D (^{1}H, ^{13}C and DEPT) and 2-D (HETCOR and COSY) NMR experiments (Figures 4 and 5).

2.1.1.2 Mass Spectrometric Study

In a mass spectrometric study of menthyloxy and bornyloxy sily enol ethers, undertaken previously in our group,[208] various fragmentation patterns were proposed, including pathways A and B (Scheme 65).

SCHEME 64



REAGENTS

i Et_2O, LDA, ii, $(CH_3)_2SiCl_2$ iii, THF, NaH.

FIGURE 4 400 MHZ ^{1}H and ^{13}C NMR spectrum of the CHIRAL SILYL ENOL ETHER 319.

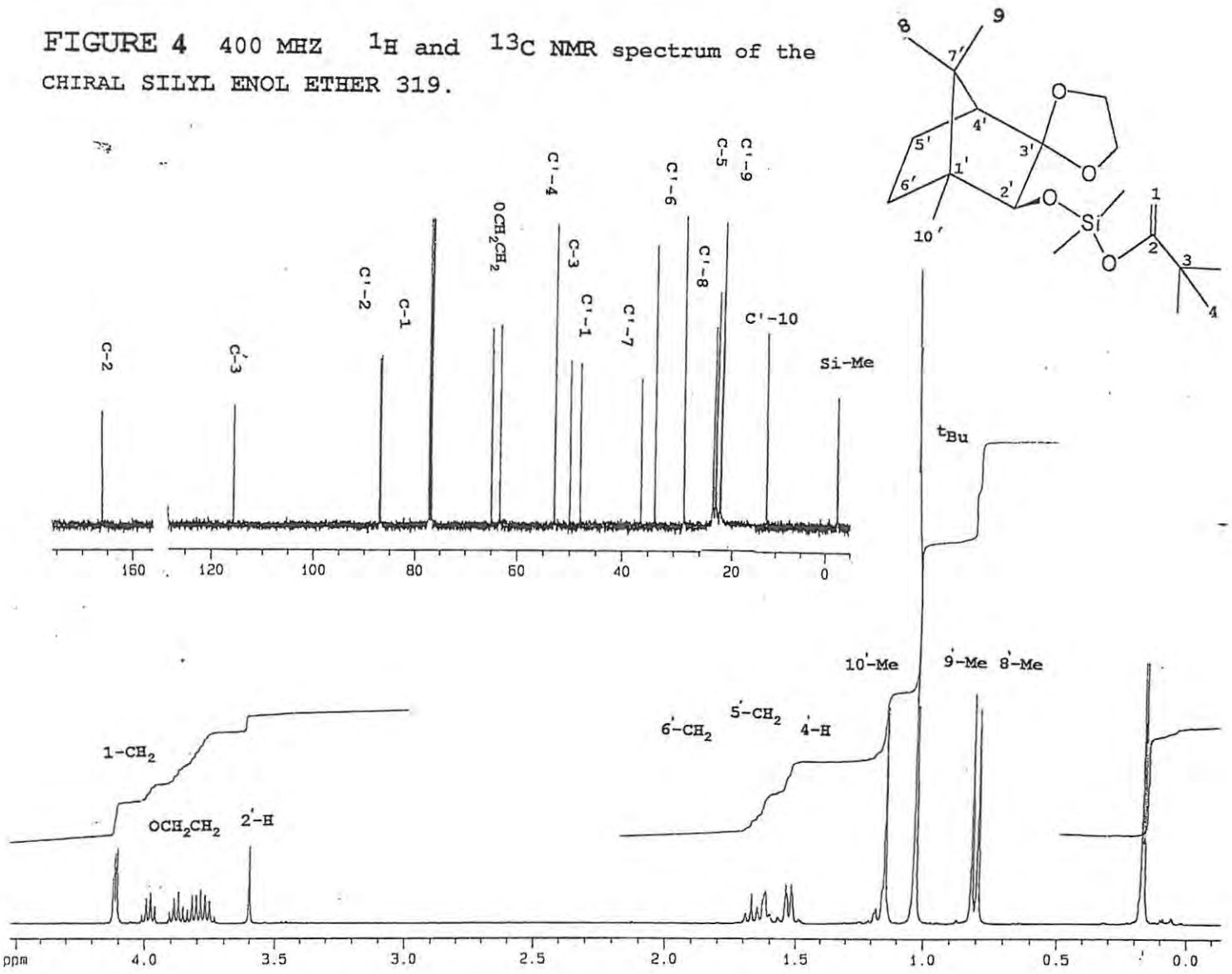


FIGURE 5 400 MHz COSY NMR spectrum of the chiral Silyl enol ether 319

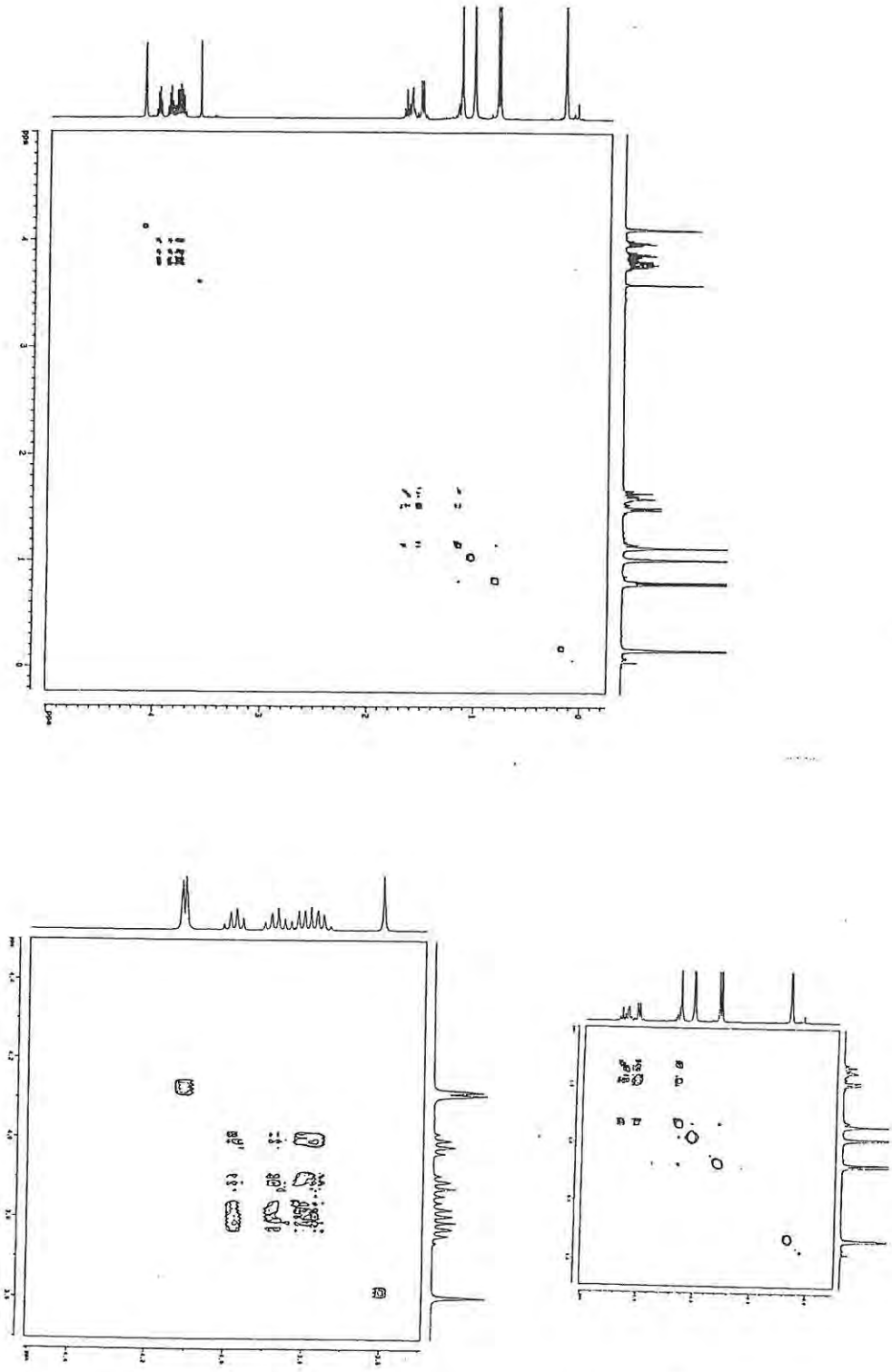
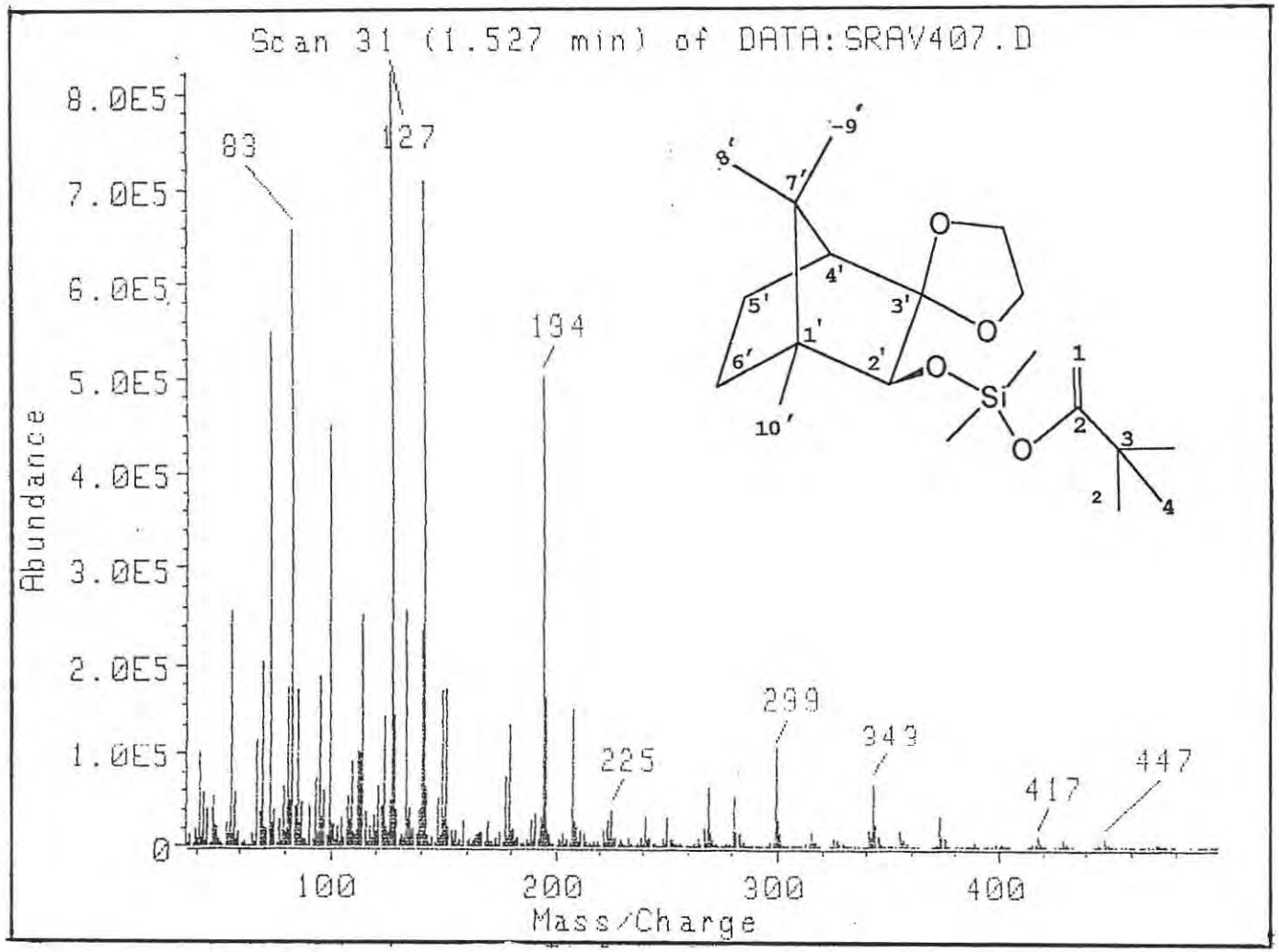
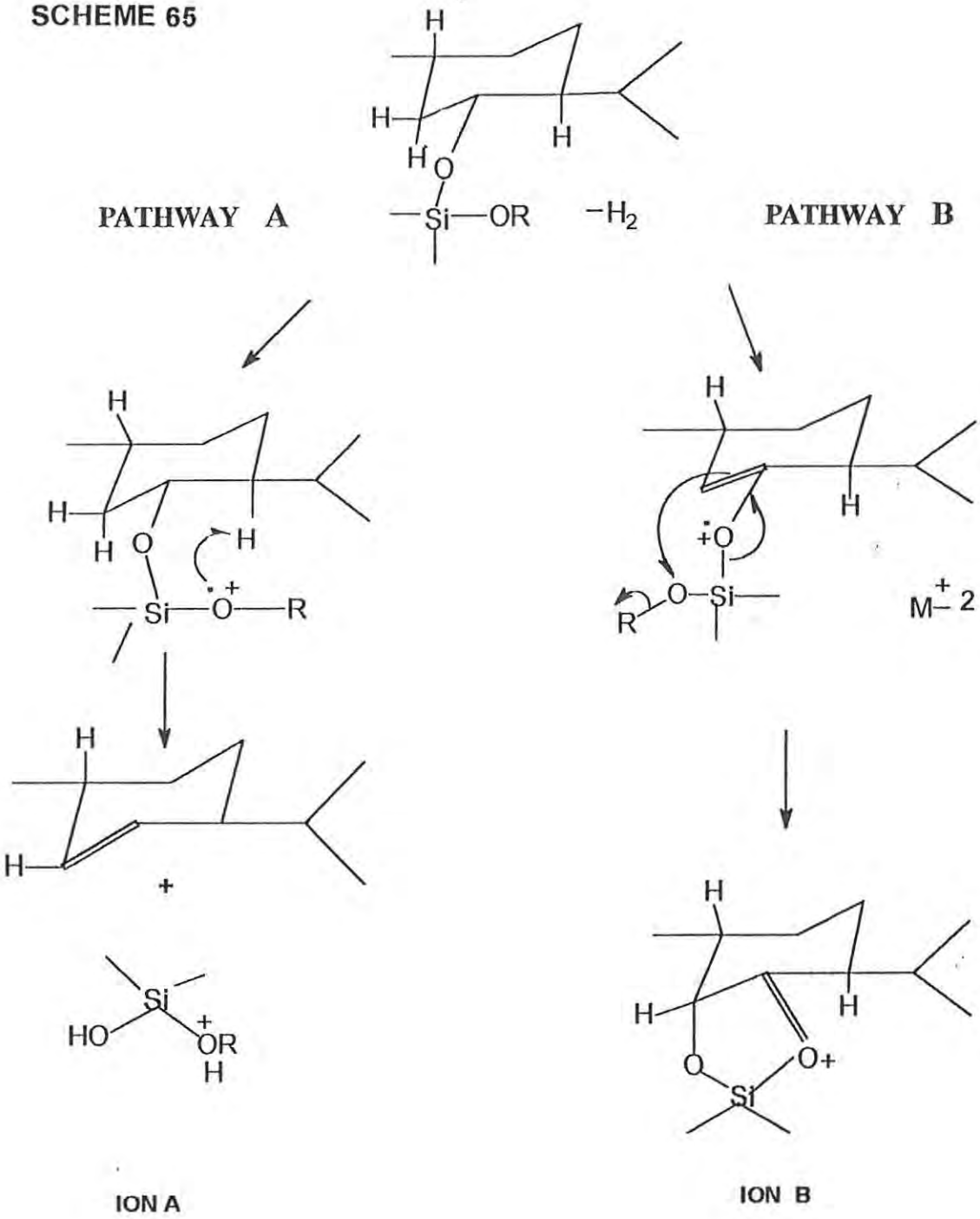


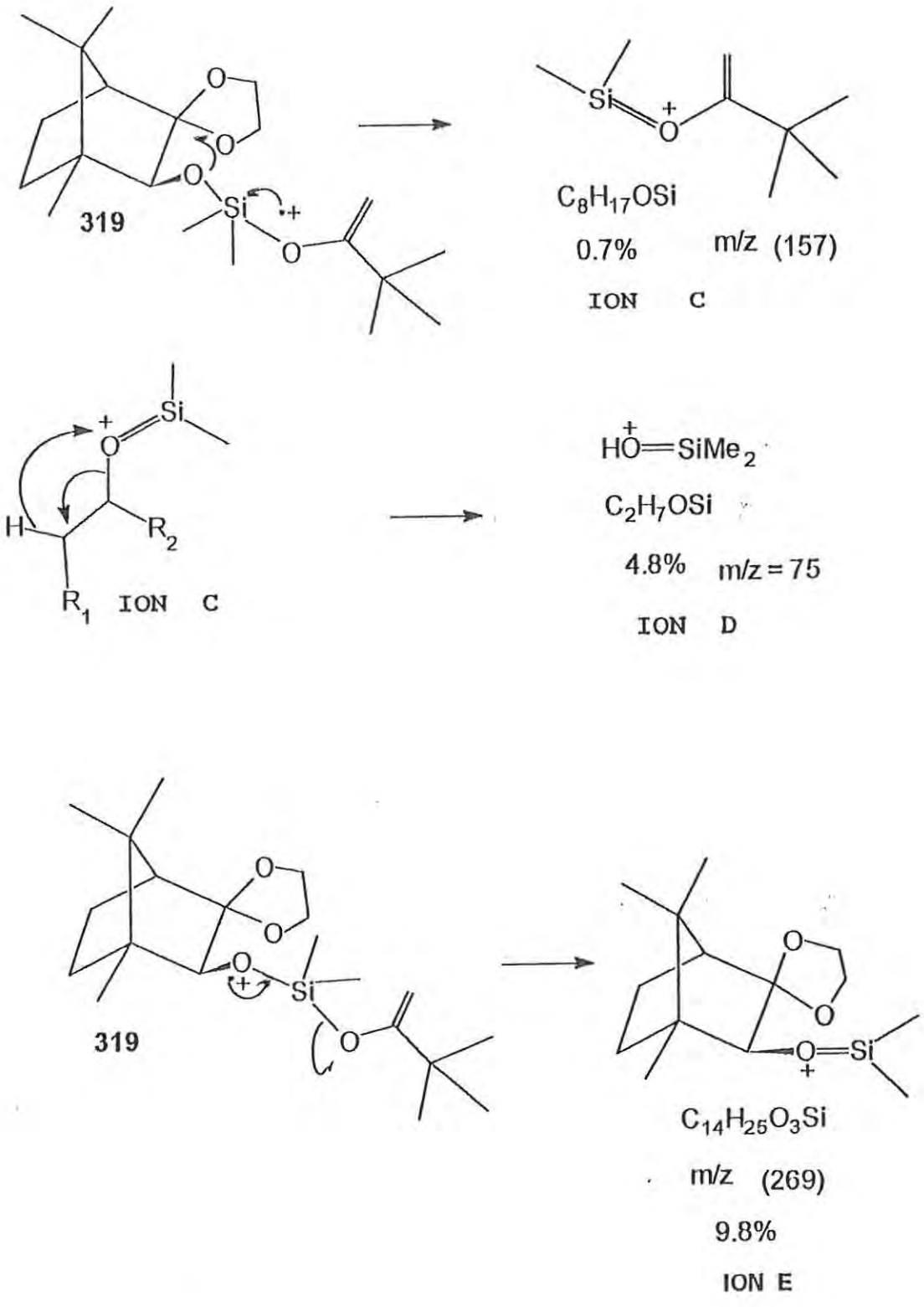
FIGURE 6 Mass spectrum of the chiral Silyl enol ether 319



SCHEME 65



SCHEME 66


319
$C_8H_{17}OSi$
0.7% m/z (157)
ION C
ION C
$HO{=}SiMe_2$
C_2H_7OSi
4.8% m/z = 75
ION D
319
$C_{14}H_{25}O_3Si$
m/z (269)
9.8%
ION E

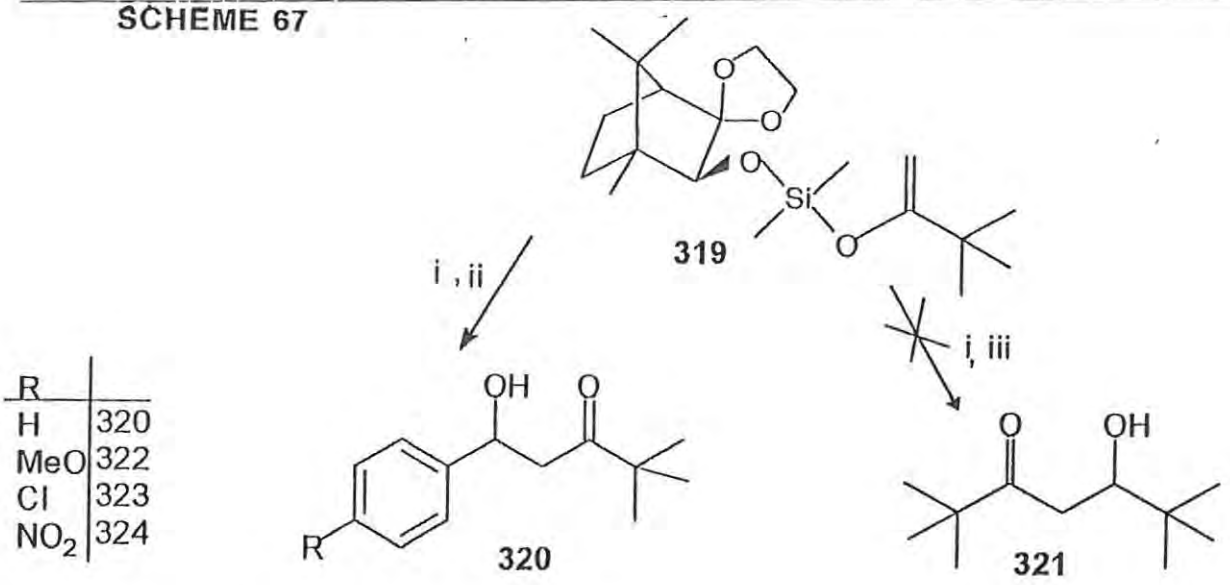
Pathways A and B both require the presence of H atoms α to the carbon bearing the silyl enol moiety. Although such α H atoms are absen in the camphor derived silyl enol ether **319** the analogous ion a is still observed in the mass spectrum of this compound. This observation may be rationalised by assuming involvement of the C-9 or C-10 methyl groups to give a corresponding siladioxalane species.

The camphor-derived silyl enol ether also exhibit the ions c, d and e analogous to those observed for the menthyloxy and bornyloxy silylenol ethers. A possible fragmentation pathway for the formation of ion d *via* ion c, analogous to that proposed by House *et al.*[207] is outlined in Scheme 66. An alternative fragmentation, *viz.* initial homolysis of the enolate Si—O bond, appears to be considerably more favoured as judged by the relative intensities of ions c, d and e.

2.1.3 Mukaiyama Reaction of Silyl Enol Ether 319

The stereo-directing potential of the silyl enol ether **319** in reactions with suitable aldehydes was then explored. The facile nucleophilic attack by silyl enol ethers on carbonyl compounds, activated by Lewis acids, was pioneered by Mukaiyama *et al.*[209] In place of the Lewis acid,[210] trimethylsilyl trifluoromethanesulphonate (TMSOTf)[211] trityl salt,[212] fluoride anion,[213,214] transition metal complexes,[215] lanthanide chloride,[216,217] or triflate catalysts[218] have also been used. In the present study, $TiCl_4$ (freshly distilled from CaH_2)[186] was used as the catalyst. A series of aromatic aldehydes, *viz.*, benzaldehyde, *p*-chlorobenzaldehyde, *p*-nitro-benzaldehyde and *p*-methoxybenzaldehyde were all reacted with the silyl enol ether **319** in the presence of $TiCl_4$ (Scheme 67). The corresponding β-hydroxyketones **320**, **323**, **324** and **325** (Table 1) obtained from the reactions were purified by repeated flash chromatography.

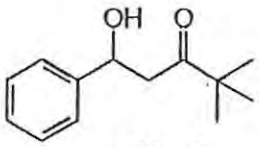
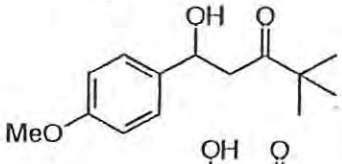
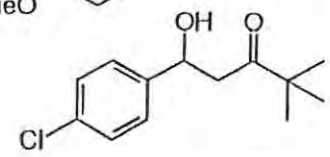
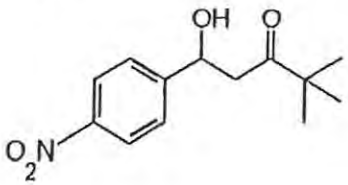
SCHEME 67



R	
H	320
MeO	322
Cl	323
NO_2	324

REAGENTS I , $TiCl_4$; ii $ArCHO$; iii,Bu^tCHO.

TABLE **Data for the Mukaiyama reaction of the silyl enol ether 319 with aldehydes**

PRODUCT	YIELD [a] / %	e.e [b] / %
	74	12
	56	12
	60	12
	58	9

[a] Based on chromatographed material

[b] Determined by ^1H NMR spectroscopy

Attempted purification of the β- hydroxy ketones by preparative layer chromatography appeared to lead to dehydration of the β- hydroxy ketone and, consequently, this technique was not used.

In order to obviate competition from aldol reactions, it was necessary to use aldehydes without in the electrophilicity of the aldehyde carbon due to the presence of the electron-releasing nature of the *tert*-butyl substituents,[219] whereas in the case of aromatic aldehydes, the electron-withdrawing inductive effect of the phenyl ring increases the electrophilicity of the aldehyde carbon. The yields and enantiomeric excesses for the successful Mukaiyama reactions are summarised in Table 1.

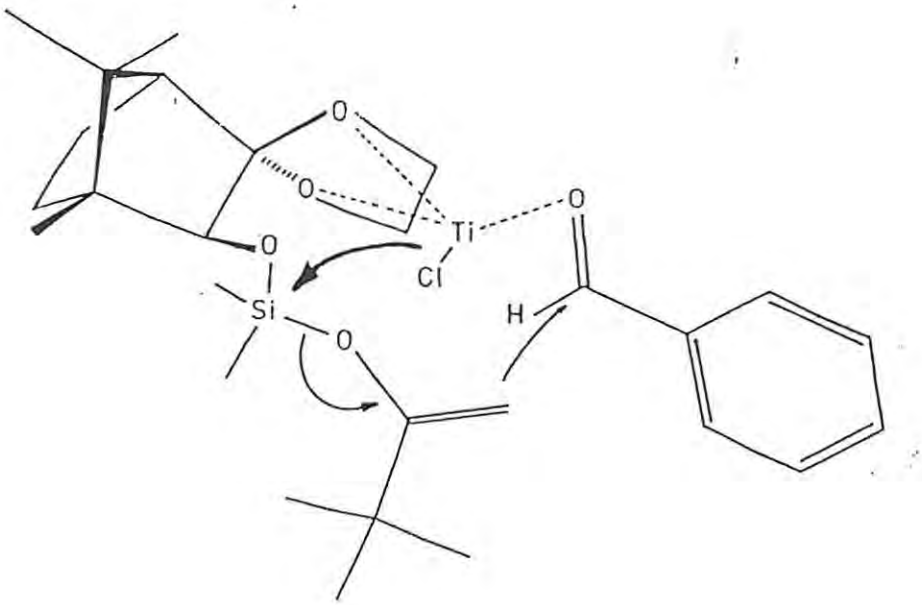
Two chiral shift reagents, *viz.*, the praseodymium reagent, $Pr(tfc)_3$ {tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate praseodymium (III)} and the europium reagent, $Eu(tfc)_3$ {Tris[3-(heptafluoropropylhydroxymethylene-(+)-camphorate europium} were used independently. The europium reagent did not fully resolve the signals of interest and, therefore, use was made of the praseodymium reagent. The *tert*-butyl singlets for compounds **320, 323** and **324** were well resolved and the relative integrals indicated an enantiomeric excess of 9 - 12%. In the case of the *p*-methoxy analogue **322**, the *tert*-butyl signals were not fully resolved and, consequently, the well-resolved methoxy singlets were used to determine the enantiomeric excess. In a previous study,[220] using the same reagents

the β-hydroxy ketone **320** was also obtained in 74% yield, but the enantiomeric excess was estimated to be 26% using 60 MHz ^{1}H NMR spectroscopic data and curve digitisation and resolution techniques. The enantiomeric excess observed in the present study, however, was lower than expected. Nevertheless, some stereocontrol is evident (Figure 7). In the proposed transition state complex (Figure 7), co-ordination of one or both acetal oxygen(s) with titanium was expected to locate the Lewis acid - aldehyde complex in a channel between parallel acetal and silyl enol moieties. The disappointing enantiomeric excesses actually obtained could be due to one or more of the following factors.

1. Steric hindrance may inhibit efficient simultaneous co-ordination of the bulky Lewis acid with the acetal oxygen(s), enolate oxygen and aldehyde oxygen.
2. The chiral auxiliary moiety may be too far removed from the enolate site, at which the reaction occurs, to exert the expected asymmetric influence. Due to the consequent lack of sufficient rigidity, internal rotation in the extended silyl enol system may also increase the conformational options in the transition state. As indicated in Section 1.4.2, Taddei's[157] camphor-derived allyl silane — underwent efficient stereoselective epoxidation (*i.e.* up to 87% d.e.); an important feature of the auxiliary in this case is that silicon is directly connected to the camphor skeleton, thus enabling the Si-methyl groups to overlap with the methyl groups of the camphor skeleton and restrict rotation about the C(2)-Si bond.
3. It is possible that nucleophilic attack at silicon, and hence loss of the chiral auxiliary, preceded the attack by the electrophile at the enol ether site. If this were the case, the chiral silyl group would not exert efficient stereocontrol during electrophilic attack.

The results of this work have now been published [221]

FIGURE 7 A representation of the proposed transition state complex responsible for improved stereocontrol in the hydroxyalkylations of pinacolone-derived silyl enol ether 319



2.2. ASYMMETRIC ∝-ALKYLATION OF CARBOXYLATE ESTERS

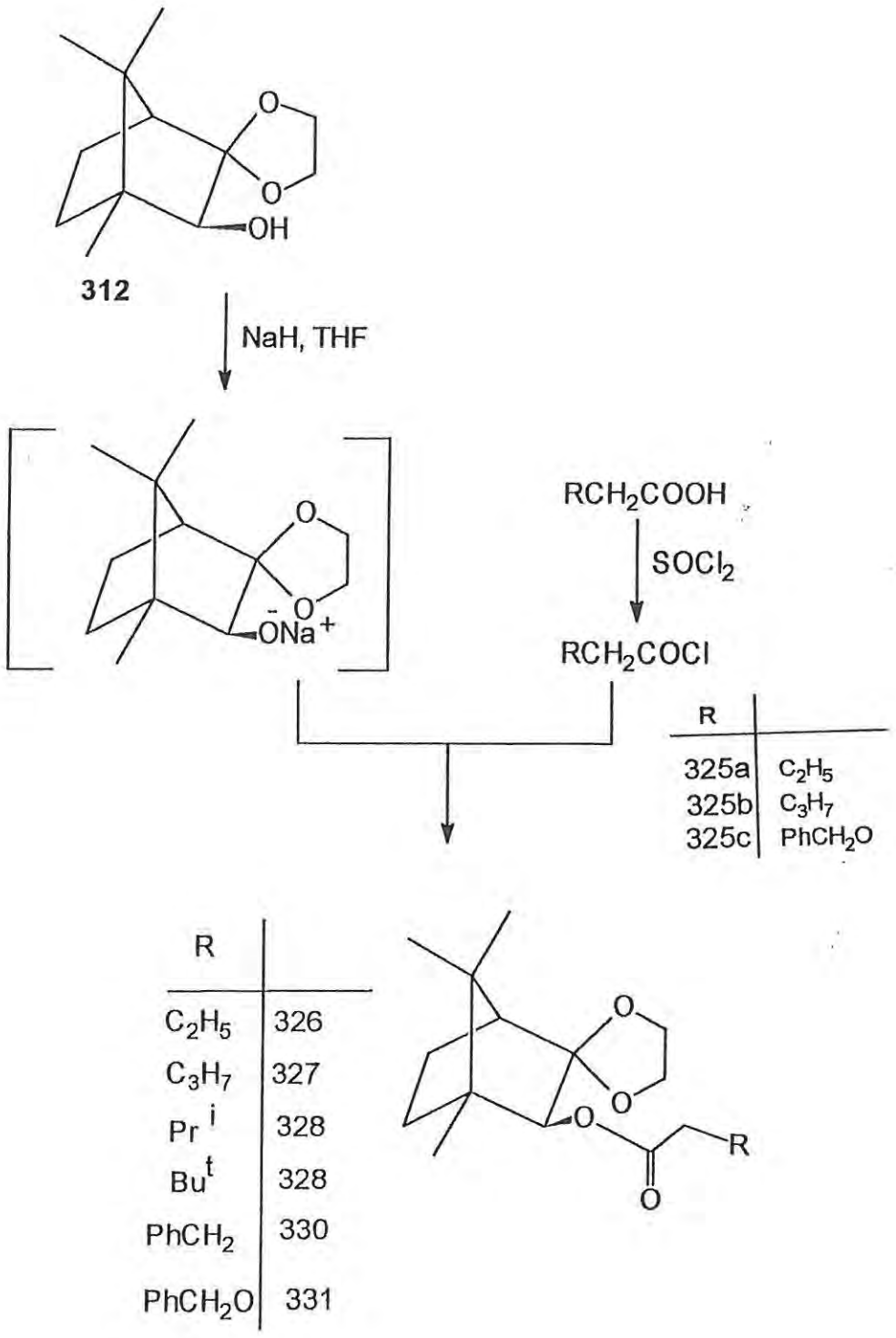
The excellent stereo-control observed using camphor-derived chiral auxiliaries by Oppolzer *et al.*,[37] Helmchen *et al.*,[80,82] Taber *et al.*,[79] and other workers (see Introduction), prompted us to explore the asymmetric induction in reactions of carboxylate esters prepared using our chiral auxiliaries **312**, **313** and **314**. In these chiral auxiliaries, the reactive site is one atom nearer to the camphor skeleton, compared to the silyl enol ether **319** prepared from the same chiral auxiliary **312**.

2.2.1 Preparation of Camphor-derived Chiral Esters

Several methods are available for the preparation of esters using the corresponding alcohol and acid. But most of these methods require the use of excess of alcohol[222] and so are not suitable when the availability of the alcohol is limited. In the present study, the preparation of the chiral alcohol **312** involves several steps, including, regioselective mono-acetalisation and stereoselective reduction (Schemes 62 and 63). Therefore, a method that does not require excess alcohol was chosen, *viz.*, use of NaH to deprotonate the alcohol and subsequent reaction of the alkoxide with an acid chloride.[223,224] The acid chlorides were chosen in such a way that the corresponding esters would show a graded increase in steric bulk. Some of the acid chlorides were commercially available, *viz.*, phenylacetyl chloride, *tert*-butylacetyl chloride (pivaloyl chloride) and isovaleryl chloride, while others (propanoyl chloride, butanoyl chloride and phenoxyacetyl chloride) were specially prepared.

Propanoyl and butanoyl chlorides were prepared using a standard procedure[225] which involves treating the corresponding acid with thionyl chloride, whereas phenoxyacetyl chloride was prepared by refluxing a solution of solid phenoxyacetic acid in anhydrous 1,2-dichloroethane, containing a few drops of dimethylformamide, with thionyl chloride.[226] The identity of the vacuum-distilled acid chlorides, obtained in 72-86% yield, was confirmed by 60 MHz ^{1}H NMR and IR spectroscopy. For example, the acid chlorides were readily distinguished from their carboxylic acid precursors by the absence of the IR hydroxyl stretching band and the presence of a carbonyl band at *ca.* 1800 cm^{-1}. The chiral *exo*-alcohol **312** was deprotonated by refluxing with sodium hydride in THF.

SCHEME 68


O
O
OH
312
NaH, THF
O
O
ONa+
RCH2COOH
SOCl2
RCH2COCl
R
325a C2H5
325b C3H7
325c PhCH2O
R
C2H5 326
C3H7 327
Pr i 328
Bu t 328
PhCH2 330
PhCH2O 331
O
O
O
R
O

The resulting sodium alkoxide solution was allowed to cool to *ca.* 32°C before adding the appropriate acid chloride (Scheme 68). After stirring overnight and refluxing for two hours, work-up and flash chromatography afforded the esters **326-331** in good yield (see Table 3). Each of these esters **326-331** was fully characterised by elemental analysis (high resolution MS) and IR and NMR (^{1}H, ^{13}C and DEPT) spectroscopy. In all these esters, the 2-H *endo* proton appeared as a singlet at 4.28-4.38 ppm in a region of the ^{1}H NMR spectrum where no other signal was seen. **Table 3** Data for preparation of carboxylic esters **326-331**

	R	Yield %[a]
326	CH_3	54
327	CH_3CH_2	70
328	^{i}Pr	69
329	Bu^t	55
330	Ph	48
331	$PhOCH_2$	65

[a]Based on chromatographed material

2.2.2. α-Benzylation of the Chiral Esters 326-331.

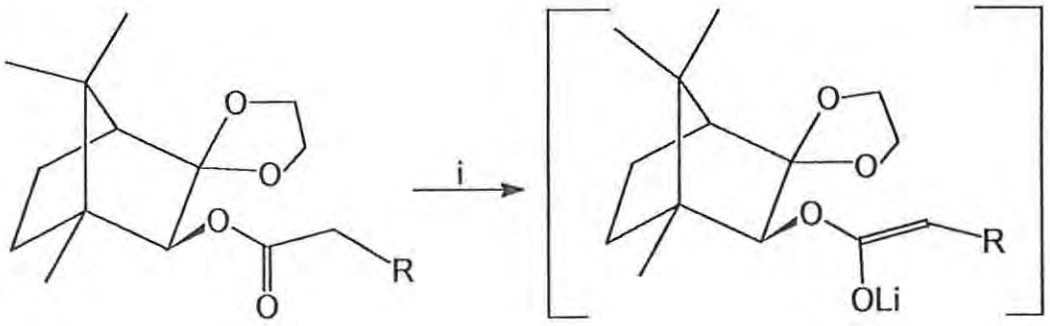
Having prepared the chiral esters **326-331**, their stereodirecting potential in α-benzylation reactions was then explored. Removal of the α-proton from an ester gives a resonance stabilised enolate anion,[227] but such anions may participate in a Claisen condensation[228] unless special conditions are used. When lithium ester enolates are generated[229] at low temperatures (*ca.* -78°C), using appropriate lithium bases, such as:- lithium isopropylcyclohexylamide (LICA),[230] lithium diisopropylamide (LDA),[231] lithium bis(triethylsilyl)amide, lithium bis(dimethylphenylsilylamide) and lithium 2,2,6,6-

tetramethylpiperidide (LTMP), self condensation is minimised.[232]

In the present study, it was decided to use LDA for the abstraction of the α-proton. A series of preliminary reactions using the ester 327 were carried out to optimise the conditions for enolate formation and α-benzylation of the esters. In all cases, LDA was prepared *in situ* under anhydrous conditions from diisopropylamine and butyllithium at *ca* -78°C. In the first case, the reaction was conducted in Et_2O and, after generation of the enolate, benzyl chloride was added at *ca.* -78°C. One half of the resulting mixture was quenched after warming gradually to 0°C, while the other half was allowed to stir overnight and then refluxed for two hours before quenching. Preparative layer chromatography of both crude products failed to yield any of the expected α-benzylated ester. The reaction was then repeated using two different solvents, *viz.*, THF and hexane. When hexane was used as the solvent, once again, none of the required product was obtained; use of THF as solvent, however, yielded the α-benzylated ester **333** in low yield (31%).

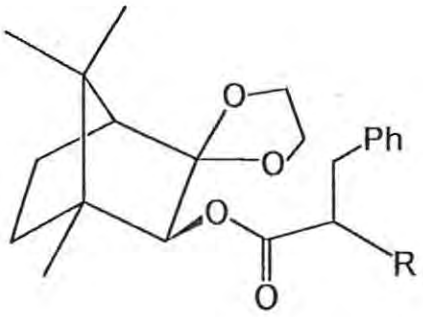
The nature of the solvent is known to determine the environment immediately around the carbanion.[233] In non-polar solvents, such as hexane, or slightly polar solvents (compared to THF), such as Et_2O, carbanions are closely associated with the metal ion thus inhibiting alkylation. In polar solvents, such as THF, this difficulty is overcome. In a further modification, the use of benzyl bromide instead of benzyl chloride greatly enhanced the yield of the α-benzylated ester **327** (70%), bromide being a better leaving group than chloride.

SCHEME 70



REAGENTS

i, LDA THF; ii, $PhCH_2Br$.



R	
C_2H_5	326
C_3H_7	327
Pr^i	328
Bu^t	329
$PhCH_2$	330
$PhCH_2O$	331

	R
332	Me
333	Et
334	Pr^i
335	Bu^t
336	Ph
–	$PhCH_2O$

Consequently, the esters **326-330** were successfully benzylated using THF as solvent and benzyl bromide instead of benzyl chloride (Scheme 70); the phenoxyacetyl ester **331**, however, failed to react with benzyl bromide. The protocol of quenching the reaction on the same day was followed, since extended stirring and refluxing prior to quenching made no appreciable difference either in the material yield or diastereoselectivity. Preparative layer chromatography was used to isolate the pure α-benzylated esters in good yield (see Table 4) and the diastereomeric excess (d.e.) in each case was determined from the ratio of the *endo* 2-H NMR integrals (*e.g.* Figure 17). The α-benzylated esters **332-336** were completely characterised by elemental (high resolution MS) and spectroscopic (IR and NMR) analysis. The 1D and 2D NMR spectra for the esters **329** and **327** are included in Figures **11-15**

Table 4 Data for the α-benzylation of carboxylate esters **326-331**

	R	Yield %[a]	d.e. %[b]
332	Me	77	16
333	Et	70	28
334	Pr^i	55	23
335	Bu^t	48	47
336	Ph	80	38

[a]Based on chromatographed material
[b]Determined by ^1H NMR spectroscopy

FIGURE 11 400 MHz H NMR spectrum of
3,3 - (Ethylenedioxy) - 2 exo - bornyl 2 - benzyl - 3,3 - dimethylbutanoate 335

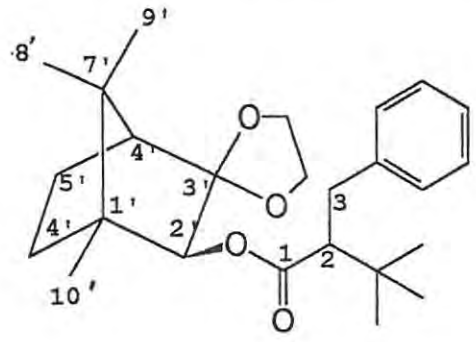


FIGURE 12 COSY NMR SPECTRUM OF

3,3-(ETHYLENEDIOXY)-2-EXO-BORNYL 2-BENZYL-3,3-DIMETHYLBUTANOATE 335

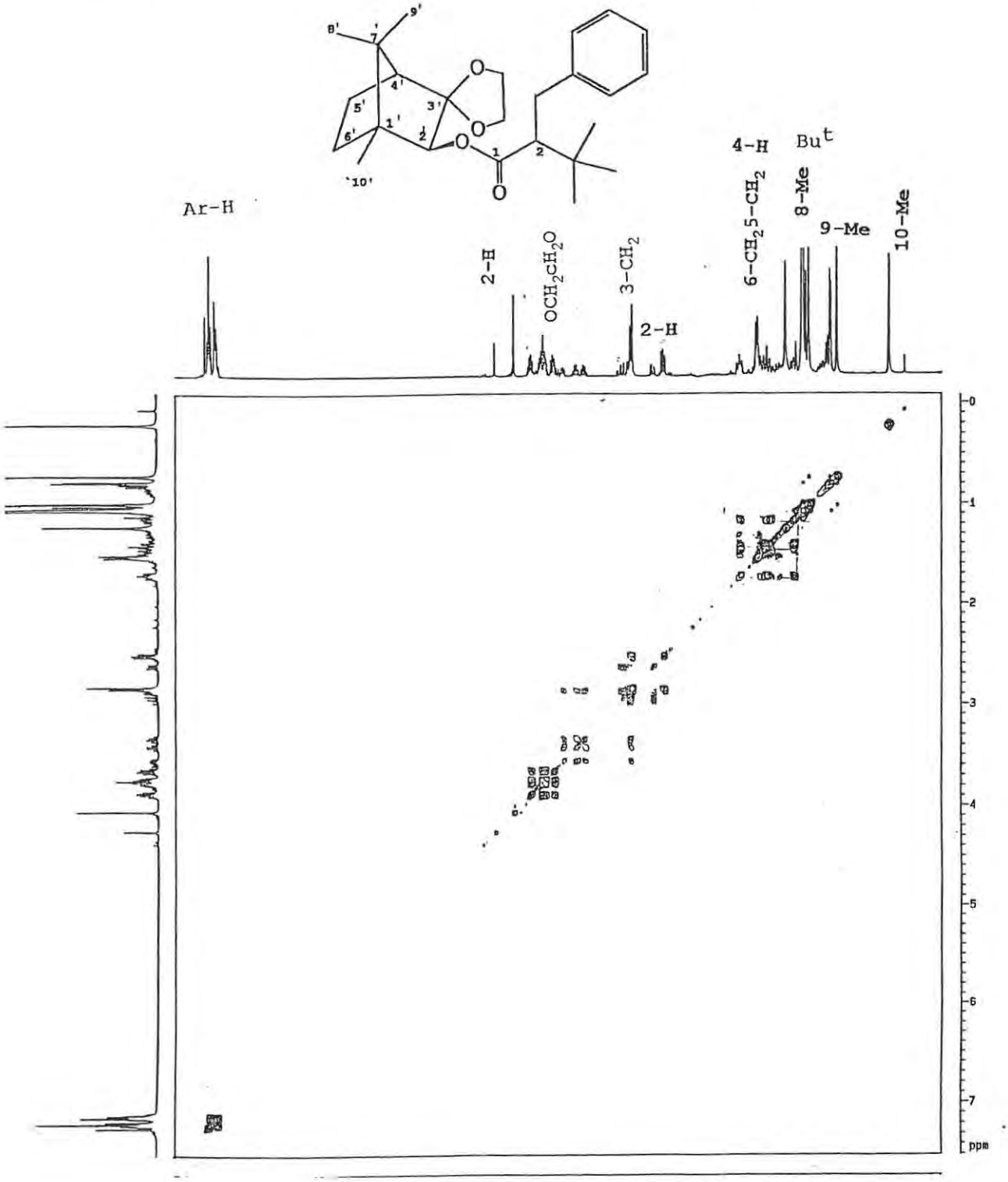


FIGURE 13 HETCOR NMR SPECTRUM OF

3,3-(ETHYLENEDIOXY)-2-EXO-BORNYL 2-BENZYL-3,3-DIMETHYLBUTANOATE 335

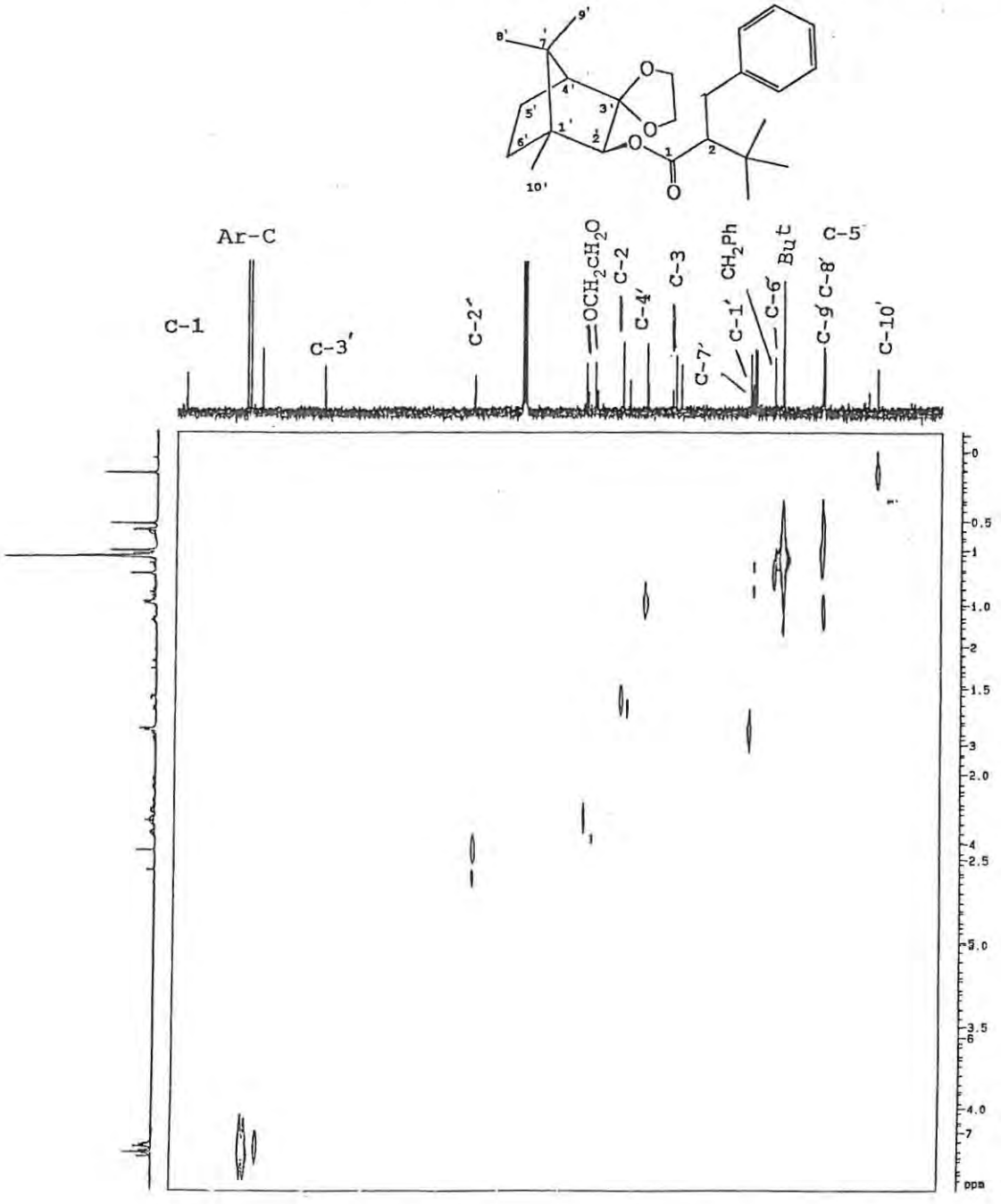


FIGURE 14 400 MHz ^{1}H NMR Spectrum of (3,3-ethylenedioxy)

2-*exo*-bornyl-2,3-diphenylpropanoate 336

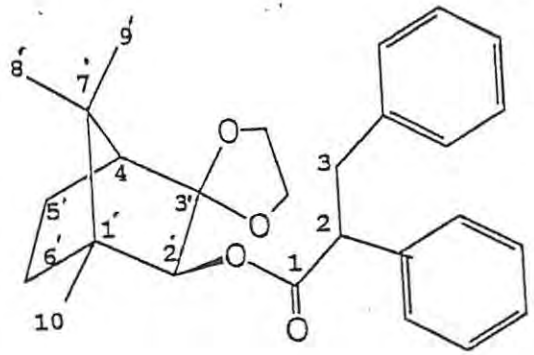


FIGURE 15 400 MHz ^{1}H NMR spectrum of
3,3 - (Ethylenedioxy) - 2-*exo*-bornyl-2,3-diphenylpropanoate 336

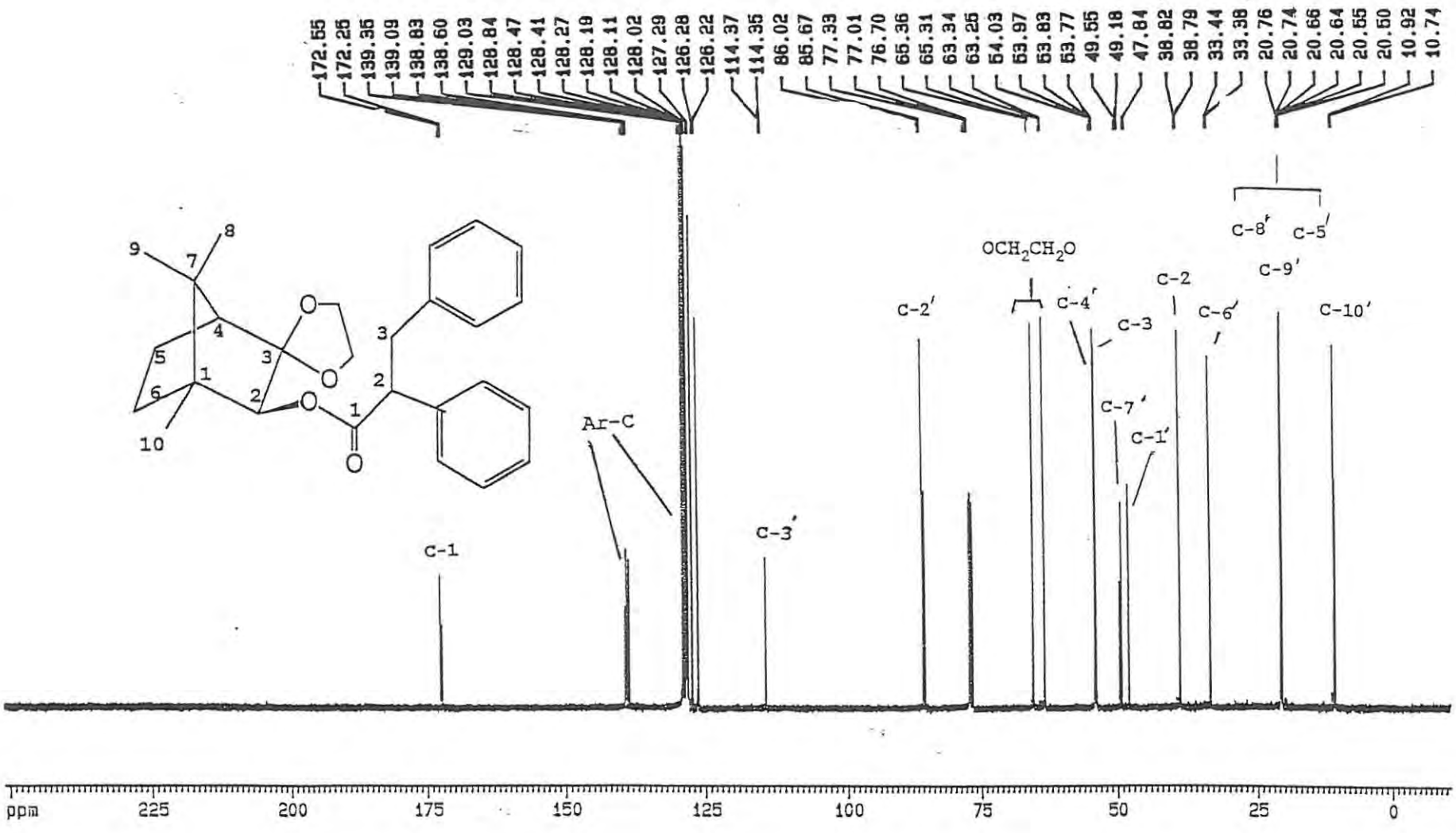


FIGURE 12 COSY NMR SPECTRUM OF

3,3-(ETHYLENEDIOXY)-2-EXO-BORNYL 2-BENZYL ETHANOATE 333

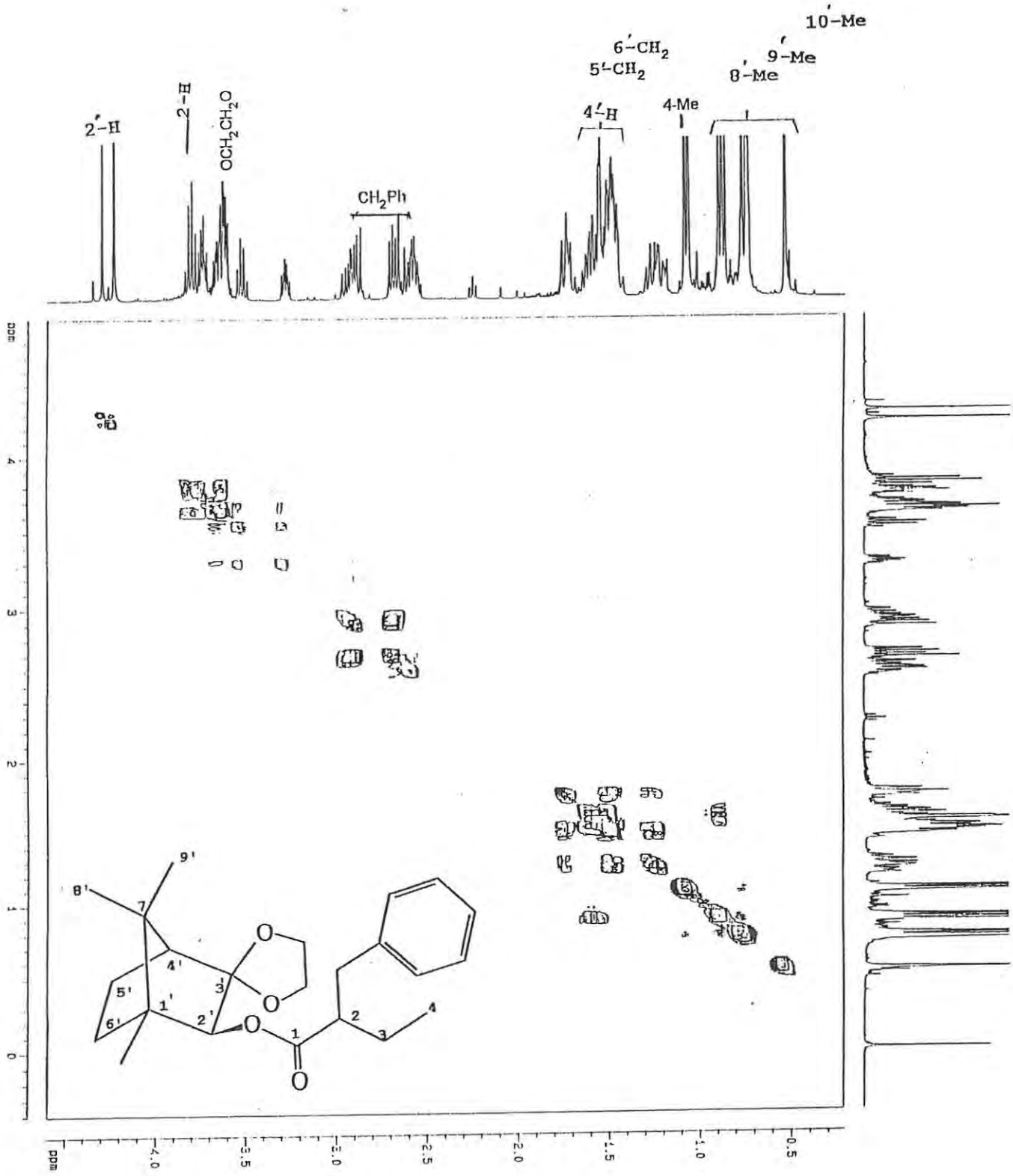
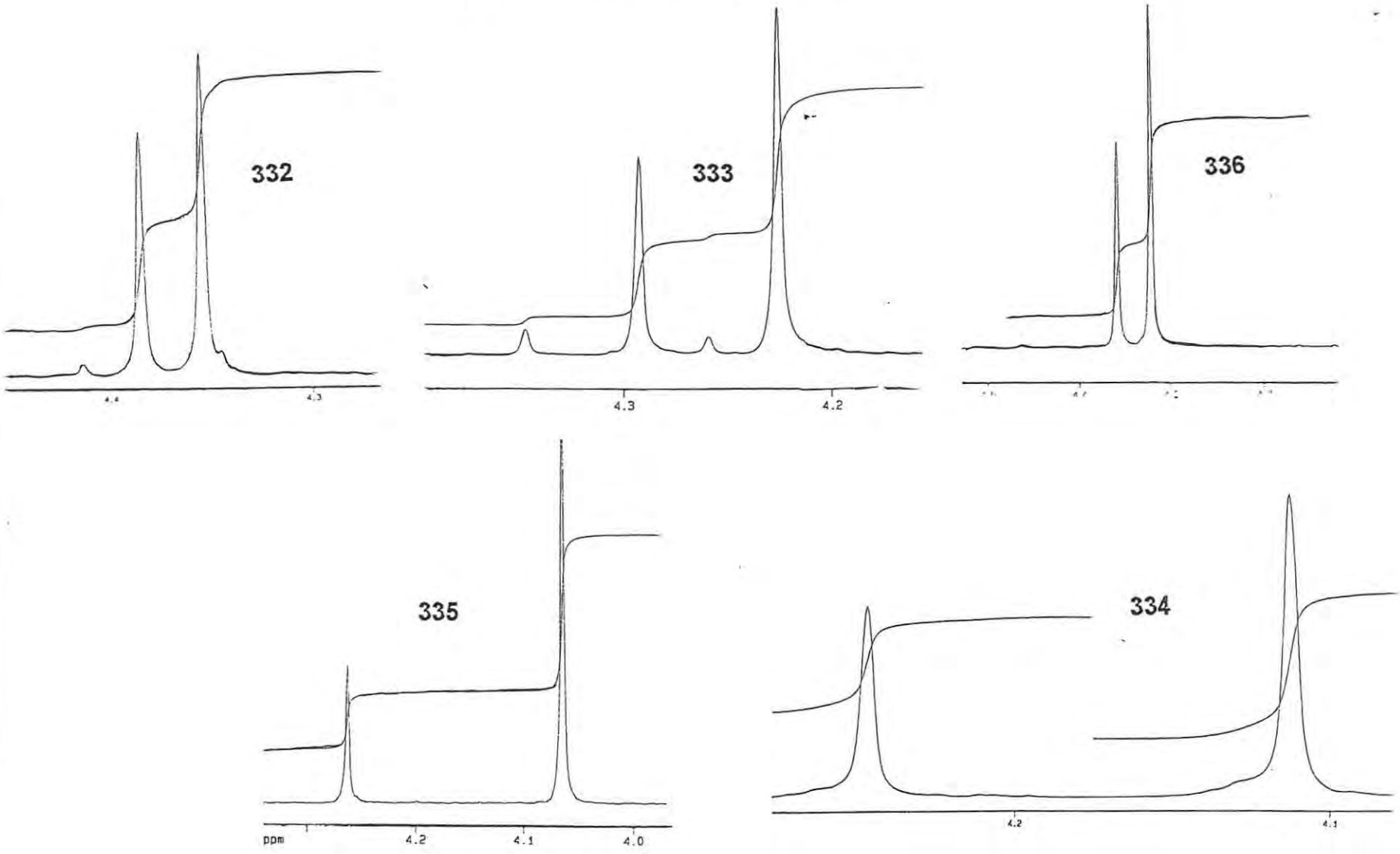


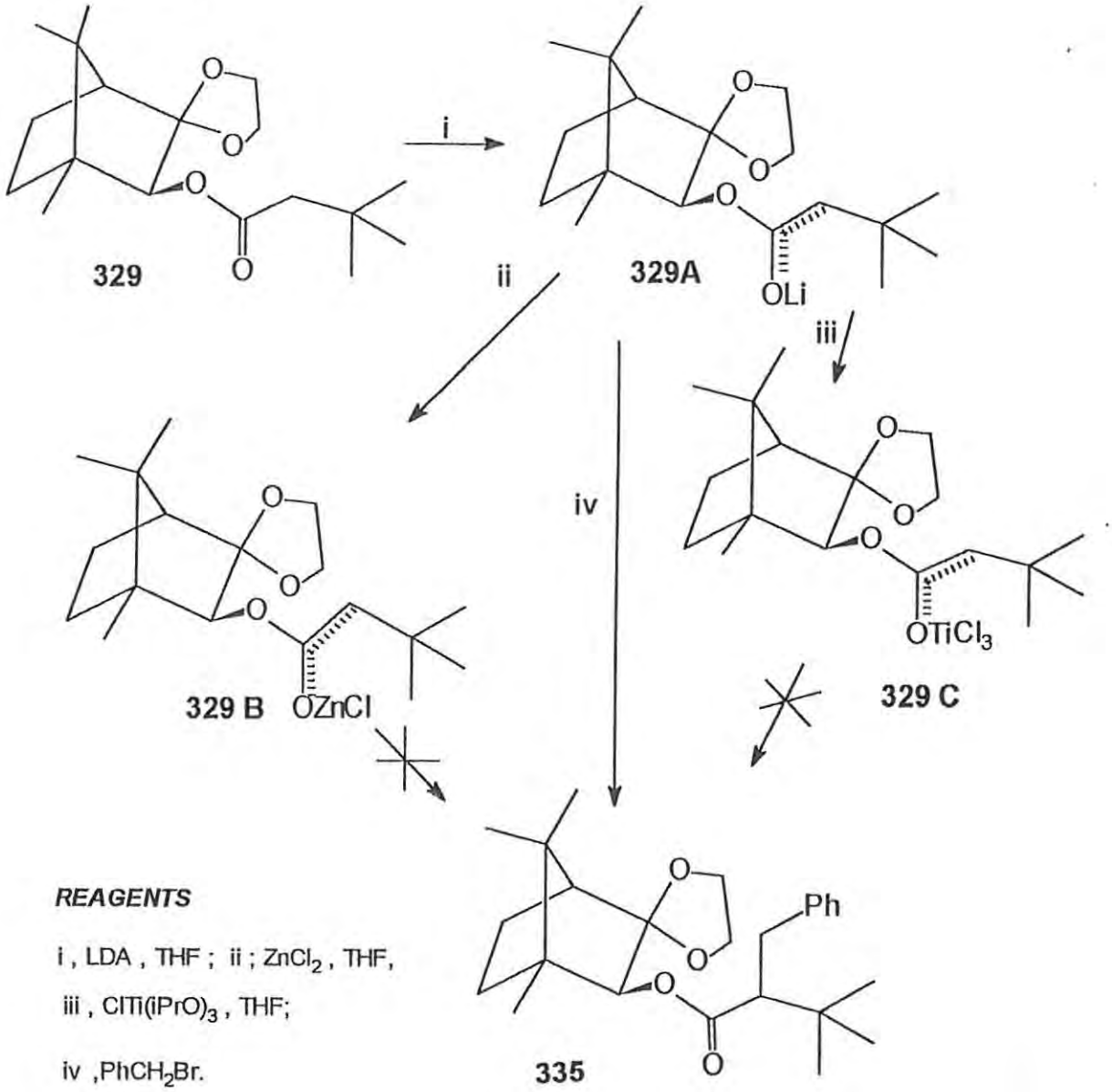
FIGURE 17 ^{1}H NMR Integral ratios of the endo-2-H nuclei showing diastereoselectivity in the synthesis of the esters 332 – 336



The measured diastereoselectivities range from 16 to 47% and show a remarkable improvement on the stereoselectivity obtained during the Mukaiyama reactions of the silyl enol ether **319**, containing the same chiral auxiliary. In the series of esters examined the increase in diastereomeric excess may be readily correlated with the corresponding increase in the steric bulk of the substituent R (Table 4), although the result for the isopropyl analogue **333** appears to be anomalous. A similar stereoselectivity trend has been observed by Heathcock *et al.*,[234] in aldol reactions of the lithium enolates. Attempts to achieve α-alkylation of the esters **330** and **331** using *t*-butyl chloride and α-benzylation of the ester **331**, however, failed to yield any of the desired products.

In order to explore the potential for increasing chelation in the transition state complex, (which would increase rigidity and possibly lead to higher diastereoselectivity), the use of different Lewis-acids, *viz.*, chlorotitaniumtriisopropoxide [$ClTi(iPrO)_3$] and zinc chloride was examined. House *et al.*[235] and other groups[236] have successfully employed zinc enolates in alkylation. Thus, following the protocol of Yang *et al.*,[237] the zinc enolate **329B** was generated from the corresponding lithium enolate of the pivaloyl ester **329**, using anhydrous $ZnCl_2$ (Scheme 69). Addition of an ethereal solution of zinc chloride to the lithium enolate **329A** was accompanied by a change in colour from yellow to orange, suggesting formation of the zinc enolate **329B**. However, addition of benzyl bromide, followed by the usual work-up and isolation using preparative layer chromatography, failed to yield any of the expected α-benzylated ester. Although the $ZnCl_2$ used was dried by repeated flame drying, fusion and evacuation, it is possible that the material was still not sufficiently dry.

SCHEME 69



REAGENTS

i , LDA , THF ; ii ; $ZnCl_2$, THF,

iii , $ClTi(iPrO)_3$, THF;

iv ,$PhCH_2Br$.

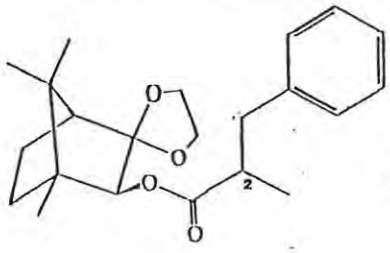
At this stage of our investigation, an important publication by Ahn *et al.*[238] appeared in the literature. These workers reported high stereoselection in aldol reactions using the triisopropoxytitanium enolate of a camphor derivative. Although lithium enolates are much more reactive, they are less stereoselective than the corresponding titanium enolates.[239,240] Seebach *et al.*[241] have also successfully used chlorotitaniumisopropoxide [$TiCl(iPrO)_3$] as a Lewis-acid in various reactions for generating chiral titanium enolates. The use of $TiCl(iPrO)_3$ as a Lewis-acid was therefore investigated and an excess of $ClTi(iPrO)_3$ was added to a solution of the lithium enolate **329A** in Et_2O. This solvent was used rather than THF since the greater solvating power of THF has been found[239] to reduce the ability of titanium to chelate, and hence to reduce the amount of chelation-controlled product; use of excess $ClTi(iPrO_3)_3$ drives the equilibrium in favour of the titanium enolate. The reaction mixture was stirred at -78°C for 3h, after which, benzyl bromide was added. Usual work-up, followed by preparative layer chromatography, failed to yield any of the expected α-benzylated ester. Due to the difficulties encountered[+] in handling $ClTi(iPrO_3)_3$, this method was not explored further.

Helmchen *et al.*[81] have investigated the α-benzylation of a series of analogous camphor-derived esters, including one of our chiral esters **326**, using and LICA—HMPT complex for deprotonating the ester. When LICA and HMPT were used in the ratio 2:1, they observed a diastereoselectivity of 30% d.e. for this ester **326**, which is higher than the

[+]Chlorotitaniumtriisopropoxide has a low melting point (35°C) and, prior to use, the bottle had to be warmed. Although a pre-warmed syringe was used for transferring this reagent to the lithium enolate at -78°C, repeated blocking of the needle occurred due to freezing of the reagent.

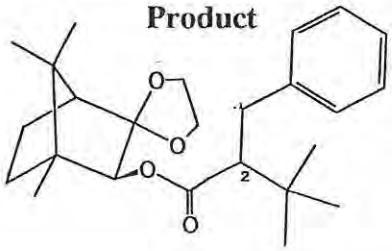
observed diastereoselectivity (17%) in the present study. Consequently, we decided to investigate a similar approach using LDA and DMPU, [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone], an equivalent for HMPA for the generation of the enolate of the ester - **329**.

TABLE: 5 Data for Helmchen's Work on α-Benzylation of the Chiral Propionate 326.

Compound	Entry	Deprotonation Conditions	Diastereo-selectivity %	Configuration at the new Chiral Centre‡
	1.	2 eq. LICA	30	*R*
	2.	1.2 eq. LICA	27	*R*
	3.	2 eq. LICA & 1 eq. HMPT	16	S

Subsequent benzylation, followed by the usual work-up and isolation using preparative layer chromatography, yielded the α-benzylated ester **332** in a higher material yield (86%) but much lower diastereoselectivity. The results for these additional reactions are summarised in Table 6.

TABLE 6 Data for α-Benzylation of Ester 329.

Product	335	LDA	LDA-HMPA
	yield/%[a]	48	86
	d.e./%[b]	47	6.1

[a] Based on chromatographed material yield.
[b] Determined by ^{1}H NMR spectroscopy.

2.2.3. Determination of the Configurational Bias at the New Chiral Centre.

While the degree of stereocontrol is readily determined from the NMR data, it is necessary to establish the favoured configuration at the new chiral centre, so as to elucidate the transition state preferences. Two approaches were used:

(i) deductions from molecular modelling and

(ii) isolation of product(s) whose optical rotation is known.

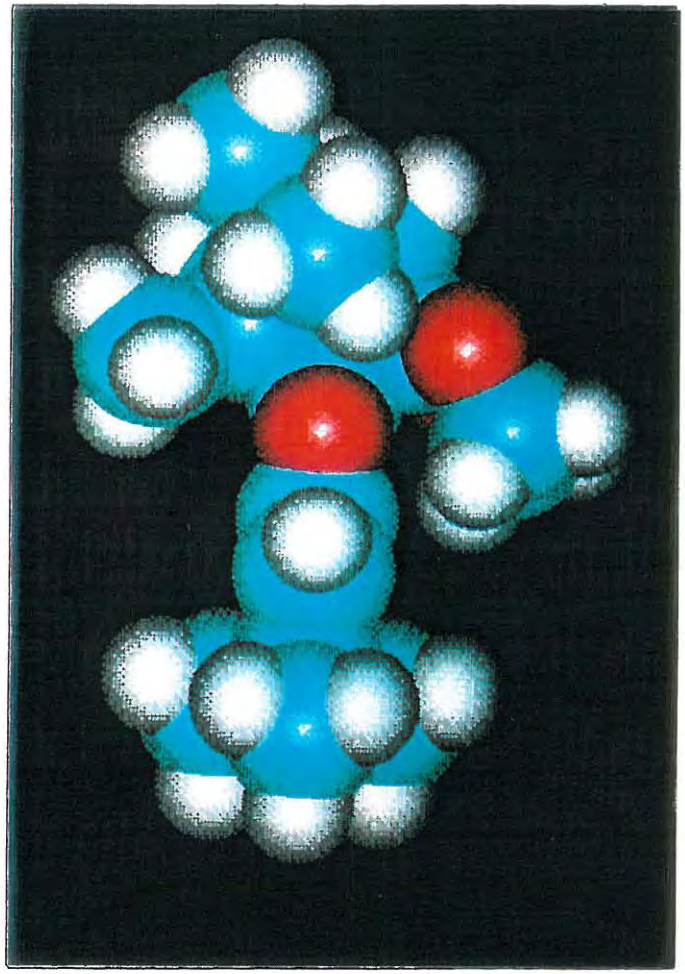
The configuration and optical rotation of the carboxylic acid **337** and alcohol **338**[27] (Scheme 71) corresponding to the α-benzylated carboxylate ester **336** have been previously established by unambiguous synthesis. Consequently, it was decided to either hydrolyse or reduce the ester **336**. Measurement of optical rotation of the derivative(s) was then expected to provide information about the configuration of the dominant enantiomer.

The α-benzylated ester **336** was readily hydrolysed using 1**M** NaOH.Thus, a solution of the ester **336** in THF was heated under reflux with aqueous NaOH for 3h. Neutralisation and work-up afforded a white powder, which was crystallised from EtOAc to give 2-3-diphenylpropanoic acid **337**, as white needle-shaped crystals [m.p. 81°C (lit.,[242] 83°C)]. The acid **337**, which was fully characterised by ^{1}H and ^{13}C NMR spectroscopy, showed an optical rotation of +2.1° (in benzene) {lit.[243] $[\alpha_D^{20}]$ + 94.04 (in benzene)}. This result indicates only a slight excess of the dextrorotatary (*S*)-enantiomer. However, the diastereomeric excess determined for the parent ester **336** was 38% In order to check the enantiomeric excess of the (*S*)-acid in the hydrolysed product, ^{1}H NMR spectra were run using the chiral shift reagents, $Eu(tcf)_3$ and $Pr(tfc)_3$ but no signal splitting was observed. These observations led to the conclusion that almost complete racemisation occured during the hydrolysis, thus accounting for the reduced optical activity.

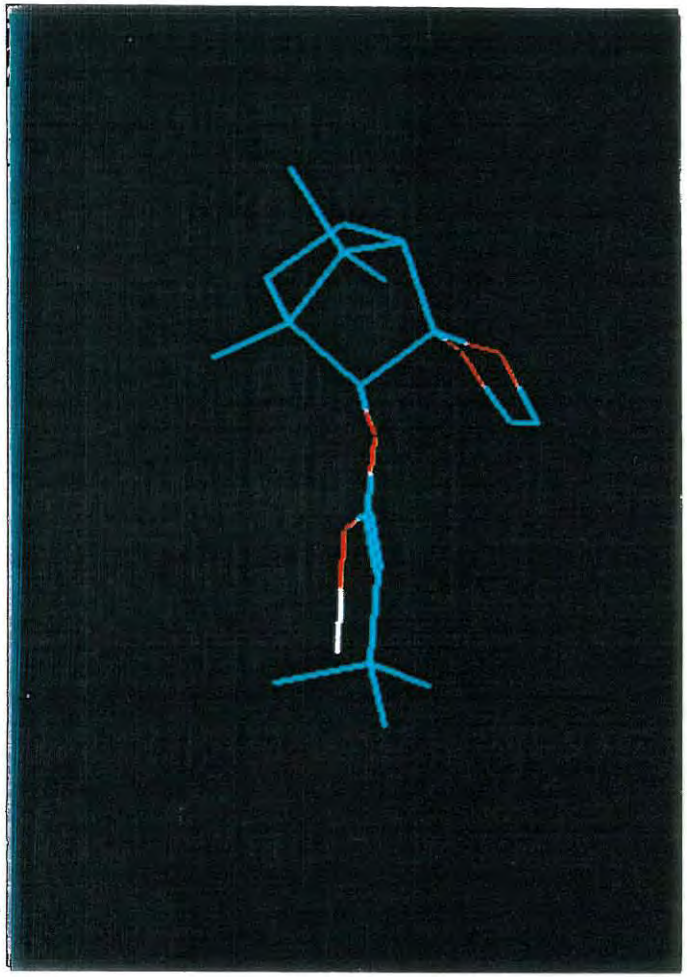
An alternative method of cleaving the ester **336** without compromising the configuration at the α-carbon was then explored, *viz.*, reduction using LAH.[244] The formation of a large amount of aluminium hydroxide during the work-up, made isolation of the product from the very small scale reactions difficult and the alchol**338** was obtained in only 27% yield. However, when the reduction was carried out using (lithium tri-ethylborohydride, the expected alcohol **338** was obtained in a better yield (57%) and the optical rotation was found to be + 23.33° {lit.[245] $[\alpha]_D^{25}$ + 76.3° (c=5.3, chloroform)} indicating a 31% excess of the dextrorotatory (*S*)-enantiomer, which is in reasonable agreement with the diastereomeric excess of the parent ester (38%; see Table 5). These results are consistent with molecular modelling studies of the transition state interactions which will be discussed in the next section.

FIGURE 18

Computer-modelled structure of the lithium enolate of 3,3-(ethylenedioxy)-2-*exo*-bornyl 3,3-dimethylbutonoate, preferential attack by the electrophile occurring at the less hindered *Si* face (LHS drawn): b) Stick rendering. a) Space filling sphere rendering.



a



b

2.2.4. Computer Modelling Studies

When considering π-facial selectivity during alkylation of ester enolates, both steric and stereoelectronic[2] factors in the diastereomeric transition states should be taken into account.[3] Optimal stabilisation of the transition state is achieved when orbital overlap is maintained between the enolate π-bond and the partially formed σ-bond. However, while stereoelectronic effects may play a significant role, steric effects are generally the dominant factors in determining enolate π-facial selectivity. Moreover, several researchers have pointed out that enolate-alkyl halide transition states are largely reactant-like. Consequently, our analysis of the transition state interactions is based on the preferred conformation of the ester enolate species. Selected enolate models were constructed (Figs. 17 A and B) using the molecular modelling package "HYPERCHEM"; energy-minimised conformations were modified by introducing the torsion angle constraints necessary to establish the required *endo-s-trans* arrangement of the enolate moiety. In the conformation illustrated in Fig. 17

(i) the planar (*E*)-enolate lies parallel to the ethylenedioxy group;

(ii) internal rotation (see arrows) about the C-O-C bonds is restricted by the 1 methyl and the ethylenedioxy groups;

(iii) the enolate carbonyl oxygen adopts the *endo-s-trans* arrangement shown in Fig. 17 in order to minimise unfavourable lone pair interaction between the ester oxygens and unfavourable steric interaction with the 8-methyl group; and

(iv) the ethylenedioxy group is expected to block approach of the electrophile to the *Re*-face.

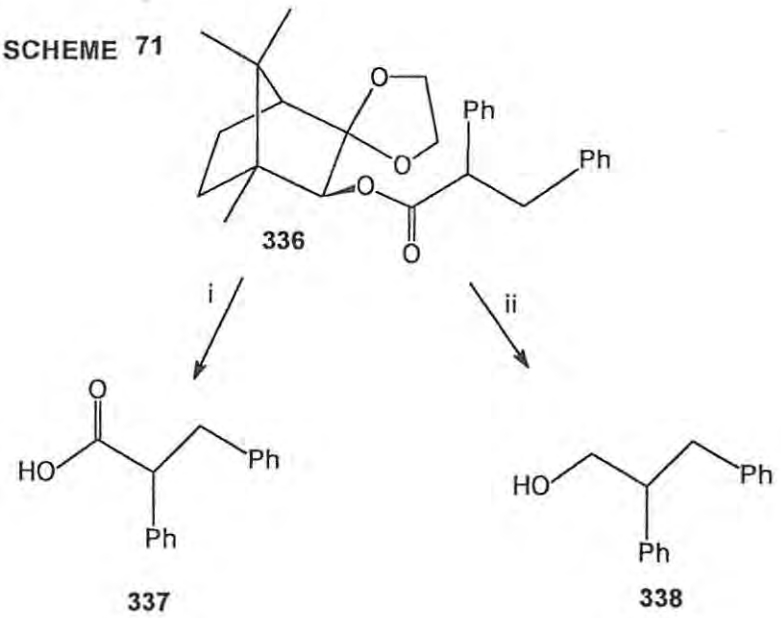
On the basis of this model, the electrophile should approach the enolate preferentially from the less hindered *Si*-face. This expectation is supported by the observed preference for an (*S*)-configuration at the α-carbon of the α-benzylated ester **336** (see page 116 for a discussion of the configuration of this product).

Helmchen *et al.*,[85] have carried out α-benzylation on a series of camphor-derived propionates **143** which have different bulky groups at C-3 (see Introduction, Section 1.2.6 page 43), using LICA and HMPT mixtures for deprotonating the propionates. They observed that use of LICA - THF led to the (*Z*)-enolate intermediate whereas use of LICA-HMPT led to the (*E*)-enolate intermediates. α-Benzylation of these enolates led to corresponding esters with (*R*) and (*S*) configurations at the α-carbon, respectively. In the present study, α-benzylation of the *tert*-butylacetyl ester **329** using LDA-DMPU afforded the benzylated ester **335** in increased material yield, but the diastereoselectivity decreased[+] remarkably (see page Table 6). It is well documented[247] that reversal in enolate selectivity may be obtained by employing different reaction media. Helmchen's work has been limited to propionate systems in which it is possible for the ester enolates to adopt both the (*Z*)- and (*E*)-enolate geometries in the transition state. When the R group is bulky (*tert*-butyl, isopropyl, butyl, or phenyl), however, severe steric interactions are expected to disfavour a (*Z*)-enolate arrangement. This expectation is supported by our computer modelling studies (see Figs. 17).

[+]A similar decrease in diastereoselectivity when deprotonation was carried out using HMPT-THF as solvent has been reported and the decrease in the diastereoselectivity was attributed to the disruption in the transition state.

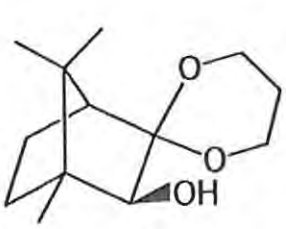
When the transition state model (*e.g.* Fig. 16) is viewed from above, it can be seen that the steric bulk of ethylenedioxy group is not significantly greater than that of the 10-methyl group. As a result, the preference for attack at the *Si*-face is not likely to be as great as anticipated. Thus, chiral auxiliaries with a bulkier group at C-3 were targeted. The two chiral alcohols **343** and **339** , which to the best of our knowledge are novel, were expected to block access to the *Re*-face more efficiently and identified, in the following section, the synthesis of these chiral alcohols will be discussed.

SCHEME 71

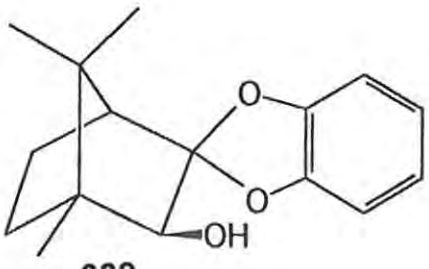


REAGENTS

i THF, 1M NaOH ii LAH or $Li(C_2H_5)_3BH$



343



339

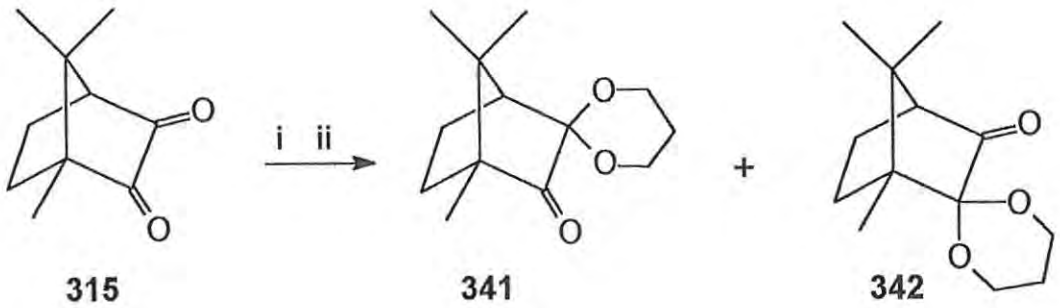
2.3 DEVELOPMENT OF STERICALLY HINDERED CAMPHOR ACETALS AS NOVEL CHIRAL AUXILLIARIES

In alcohol **339** the bulky aromatic ring was expected to act as a substantial steric shield, while in alcohol **343**, the steric bulk of the acetal is extended by one methylene group (compared to alcohol **312**). The increased steric bulk in both systems was expected to further inhibit approach of the electrophile at the *Re*-face of the corresponding enolates.

2.3.1 Preparation of propane-1,3-diol acetate

The synthetic approach to the chiral alcohol **343** is outlined in Schemes 72 and 73. The acetalisation was carried out by refluxing propane-1,3-diol with a solution of camphorquinone containing a catalytic amount of *p*-toluenesulphonic acid, in a Dean and Stark apparatus. Work-up followed by flash chromatography, afforded a major (liquid) and a minor crystalline product, both of which showed IR carbonyl bands at *ca.*, 1720 cm^{-1}. Using 1-D and 2-D NMR spectroscopy, the major and minor products were identified as 3,3-propylenedioxy-2-bornanone **341** and the regioisomeric 2,2-propylenedioxy-3-bornanone **342** respectively. The ^{13}C chemical shift data for the two regioisomers **341** and **342** are listed in Table 7. From the tabulated data it is apparent that the following ^{13}C nuclei show significant chemical shift differences:— C-1, C-2, C-3 and C-4. The addition of the propylenedioxy moiety to the C-3 and C-2 carbonyl groups leads to the major and minor regioisomers respectively. Since the carbonyl group is less hindered at C-3, acetalisation is favoured at this site, thus accounting for the predominance of the 3,3-propylenedioxy product **341**.

SCHEME 72

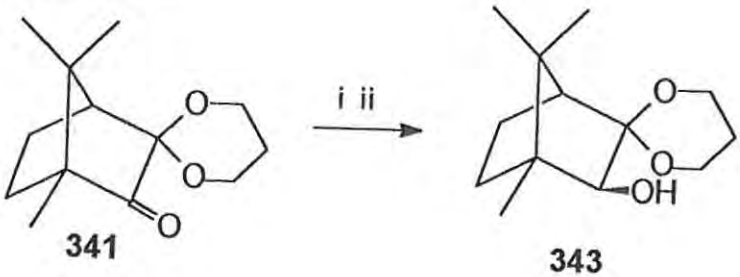


315 **341** **342**

REAGENTS

i , propane 1,3-diol; ii, PTSA

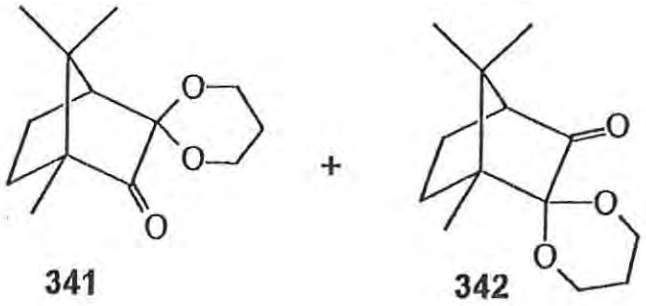
SCHEME 73



341 **343**

REAGENTS

i LAH ,Et_2O ; ii , Super Hydride, THF.



341 **342**

Table 7 Comparative ^{13}C Chemical Shift Data (ppm) for the Regioisomers **341** and **342**

C-10	9.33	3.88
C-9	19.80	18.89
C-5	21.86	22.85
C-8	20.07	21.74
$OCH_2CH_2CH_2$	25.31	25.28
C-6	31.16	28.02
C-7	43.60	43.60
C-4	52.73	60.45
C-1	58.89	53.75
OCH_2CH_2O	61.37 & 62.01	61.01 & 61.99
C-3	97.88	214.69
C-2	214.20	96.75

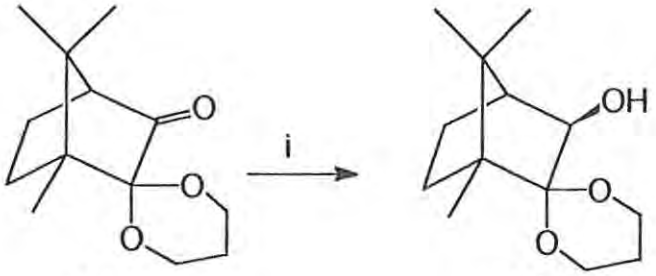
Reduction of the carbonyl group in acetal **341**, when carried out using LAH, yielded the desired chiral alcohol **343** in 57% yield, while reduction using "Superhydride" yielded the required alcohol (after flash chromatography) in a much higher yield (83%). The alcohol **343** was characterised by elemental analysis, IR and by 1- and 2-D NMR spectroscopy (see Figs. 18 and 19). The IR spectrum indicated the absence of a carbonyl band and the presence of the expected hydroxyl band at 3560 cm^{-1}. Hydride delivery to the less hindered *endo*-face of the carbonyl group is expected to afford the 2-*exo*-hydroxy compound **341**. In the ^1H NMR spectrum, the doublets at 2.72 and 3.22 ppm. are attributed to the coupled hydroxy and 2-*endo* protons; addition of D_2O resulted in the complete disappearance of the doublet at 3.32 ppm. and the collapse of the doublet at 2.72 ppm to a singlet, providing unambiguous support for the presence of the hydroxyl group and these signal assignments.

The isomeric ketone **342** was reduced in a similar manner, using "Superhydride", to give the alcohol **344** (Scheme 74). The IR spectrum of the product indicated the presence of hydroxyl band at *ca.* 3550 cm^{-1} and the absence of a carbonyl band. The orientation of the C-3 substituents can be assigned from ^1H NMR coupling constant analysis.[248] The dihedral angle between the 3-H and 4-H in the 3-*exo*-hydroxy isomer is close to 90° and so no appreciable coupling of these protons would be expected. Since the ^1H and COSY NMR spectra of the alcohol **344** showed no coupling between the 3-H and the bridgehead 4-H nuclei, the hydroxy group at C-3 was assigned the *exo* orientation and, on the basis of the

elemental (high resolution MS) and spectroscopic evidence, the reduction product was identified as 2,2-propylenedioxy-3-*exo*-hydroxybornane **344** (see Figs. **20** and **21**).

The *exo*-orientation of the 3-hydroxy group is, of course, consistent with the expected *endo* hydride attack at the 3-carbonyl position.

SCHEME 74



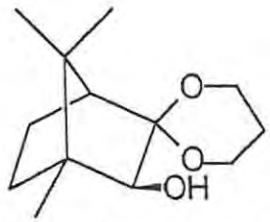
342 **344**

REAGENTS

i, $NaBH_4$, CH_3OH

FIGURE 19 100 MHz ^{13}C and DEPT NMR SPECTRA OF THE ALCOHOL

3,3-PROPYLENEDIOXY- 2-EXO-HYDROXY BORNANE 343



343

FIGURE 21 COSY NMR SPECTRUM OF THE ALCOHOL

2,2-PROPYLENEDIOXY- 3-EXO-HYDROXY BORNANE 344

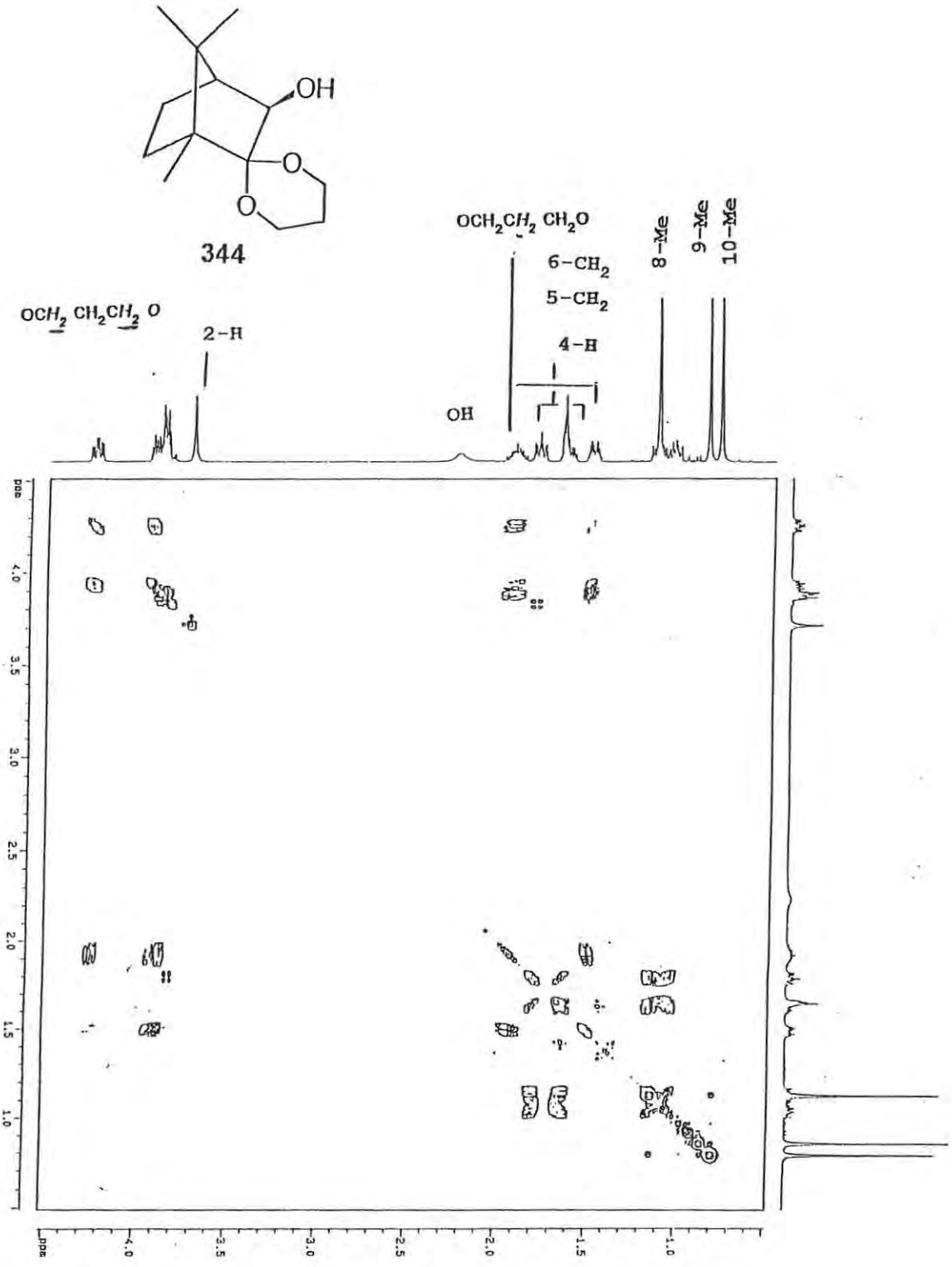
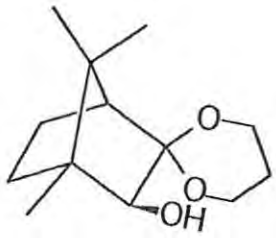


FIGURE 18 400 MHz COSY NMR SPECTRUM OF THE ALCOHOL

3,3-PROPYLENEDIOXY- 2-EXO-HYDROXY BORNANE 343



343

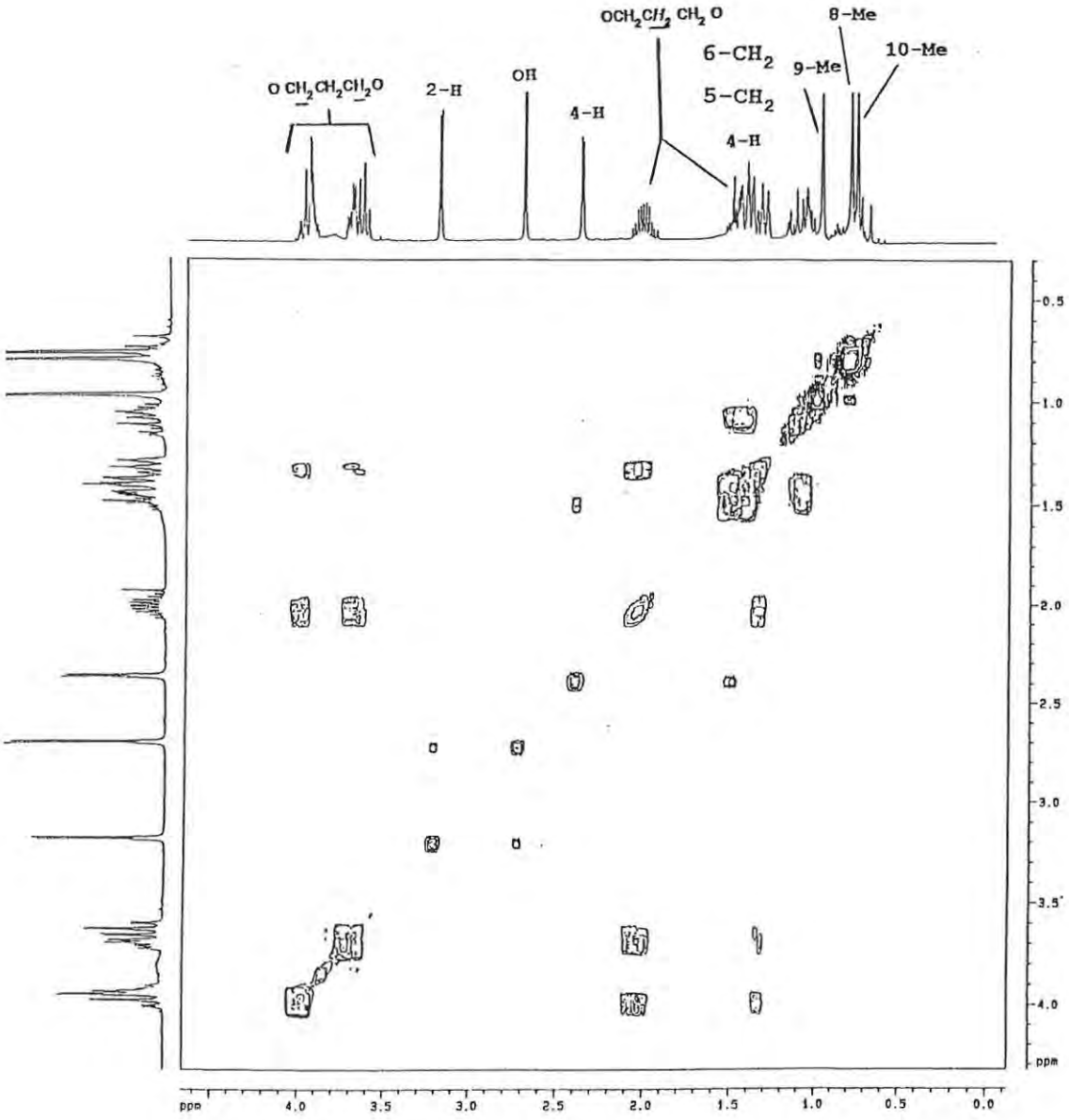
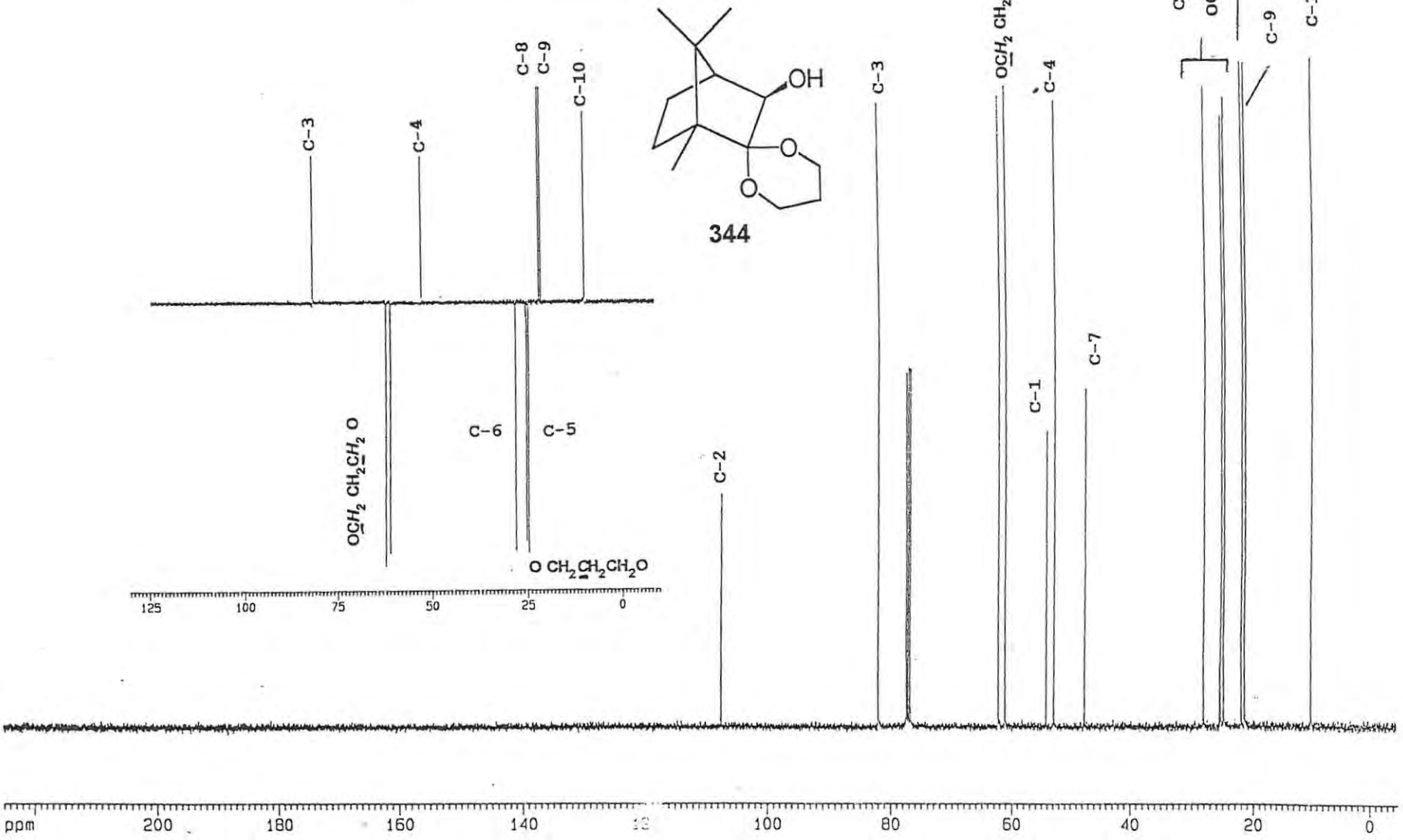


FIGURE 20 100 MHz ^{13}C and DEPT NMR SPECTRA OF THE ALCOHOL

2,2-PROPYLENEDIOXY- 3-EXO-HYDROXY BORNANE 344



2.3.2 Approaches to Catechol Acetal Derivatives

Following a procedure which was successfully used for the preparation of acetals **316** and **341**, camphorquinone was heated with catechol in the presence of p-toluenesulphonic acid. Work-up, followed by flash chromatography, afforded a white crystalline compound (m.pt 115°C), the IR spectrum of which failed to show any significant carbonyl stretch. From elemental analysis (high resolution MS) and 1-D (^{1}H, ^{13}C and DEPT) NMR spcetroscopy the product was identified as the camphorquinone bis-catechol acetal **345** (Scheme 75).

The C-2 carbonyl is more hindered than the carbonyl at C-3 and it was expected (as in the case of the acetal **341**) that catechol, being bulky, would add more readily to the C-3 carbonyl group. Therefore, attention was given to establishing conditions suitable for the selective formation of the catechol C-3 mono-acetal **346**. The various conditions under which the reaction was repeated and the compounds which were isolated in each case are found in Table 8

SCHEME 75

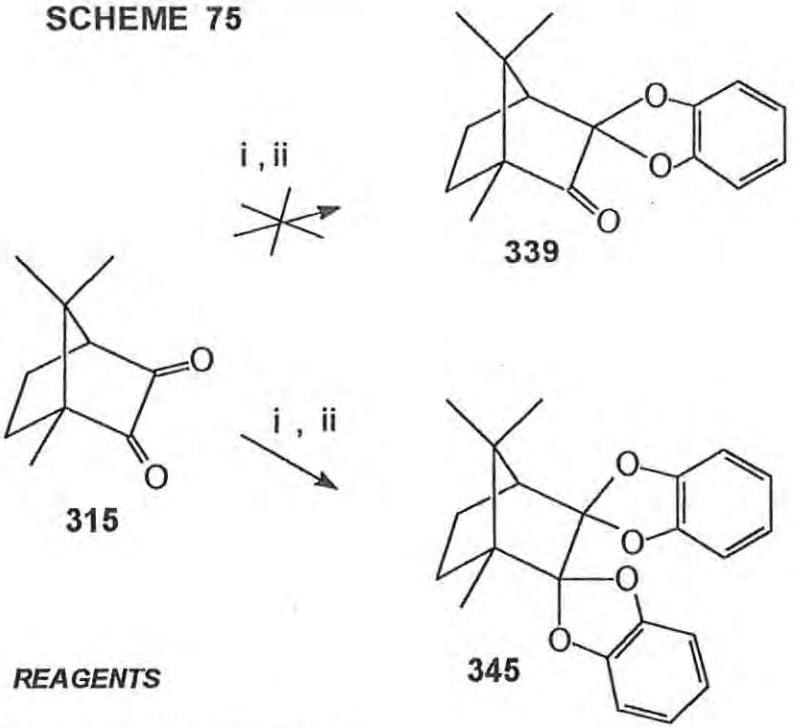


TABLE: 8 Conditions Employed for the Attempted Preparation of the Monocatechol Derivative 346 from Camphorquinone 315.

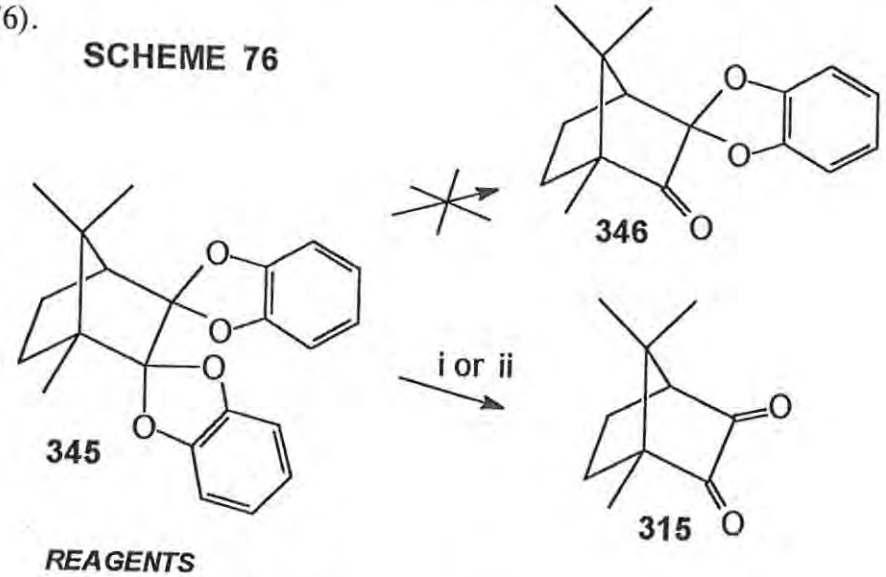
Catalyst	Solvent	Reflux Period/h	Equivalents of catechol	Isolated Compounds
PTSA	benzene	12	2	**345**
PTSA	hexane	3	1	**315, 345**
PTSA	THF	1	1	**315, 345**
PPTS[a]	benzene	6	2	**345**
PPTS	hexane	1	1	**315, 345**

[a]prepared by reacting pyridine with *p*-toluenesulphonic acid and recrystallising the crude product with hot acetone.

Although the reaction was attempted under various conditions the required mono-catechol was never isolated. Favourable π-stacking of the phenyl rings could account for the apparently facile addition of a second molecule of catechol, thus giving the bis-catechol (**345**) as the sole product.

The possibilities of selective cleavage of one of the catechol groups in the bis-catechol derivative (**345**) was then explored. The acetal at C-3 being less hindered, might be expected to be cleaved more readily than the one at C-2. Acetals, although stable in alkaline medium, are readily cleaved by acid hydrolysis[249,250]. Consequently, a solution of the bis-catechol derivative in THF was refluxed for 6h. with 1 equivalent of dil. HCl. Work-up however, afforded camphorquinone. When the bis-catechol derivative **345** was heated at 60° for 1h. in a benzene-dil. HCl mixture, the compounds isolated were the bis-catechol derivative **345** and camphorquinone **315**. Attempts to effect hydrolysis by stirring the reaction mixture at room temperature for 24h., using THF or benzene as solvent, failed to cleave the bis-catechol at all (Scheme 76).

SCHEME 76



REAGENTS

i THF, HCl ;ii benzene, HCl

Since selective mono-acetalisation of camphorquinone using catechol and selective de-acetalisation of the bis-catechol derivative **345** both failed to yield the desired mono-catechol derivative of camphorquinone, transacetalisation was then explored since acetals have been successfully prepared by the transacetalation route.[251] Thus, the chiral hydroxy acetal **312**, (prepared by regioselective acetalation of camphorquinone, followed by stereoselective reduction Schemes 62 and 63) was heated with catechol in the presence of a catalytic amount of PPTS or PTSA in a Dean and Stark apparatus.

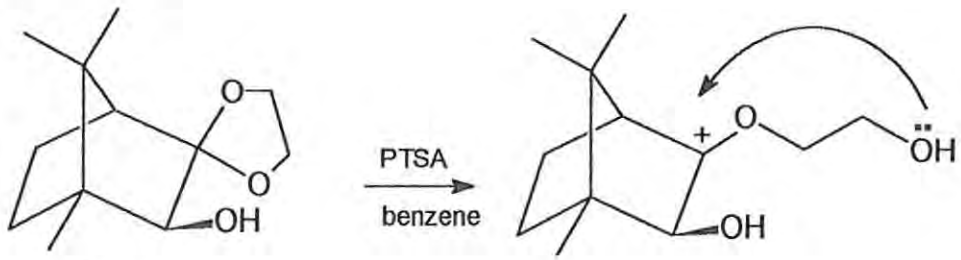
The reaction was repeated under various conditions which are summarised in Table 9.

TABLE 9: Conditions Employed for Transacetalisation of the Hydroxyacetal 372.

Catalyst	Solvent	Time/h
PTSA	benzene	12
PTSA	xylene	24
PTSA	toluene	24
PPTS	benzene	12
PPTS	toluene	24
PPTS	xylene	24

When acetals are treated with an alcohol of higher molecular mass, than the one already present, it is possible to drive the transacetalisation equilibrium in the required direction by removing the lower boiling alcohol from the reaction mixture. In the present study, although it is possible that initial cleavage of the ethylenedioxy group did, in fact, take place giving rise to a carboction intermediate, the ethylene glycol being still attached to the carbocation (see Scheme 78) could have recombined with it more readily than attack by catechol.

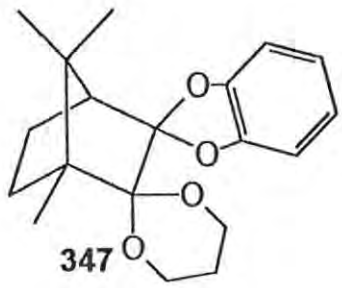
SCHEME 78



312

The possibility of preparing a mono-catechol acetal from camphor derivatives having a single free carbonyl group was then explored. Several substrates were examined, *viz.* compounds **341**, **342**, and **343**. Thus, using a procedure described for the preparation of acetal **316**, a solution of 3-bromocamphor in benzene was heated with catechol and a catalytic amount of PTSA. However, work-up followed by flash chromatography, yielded the

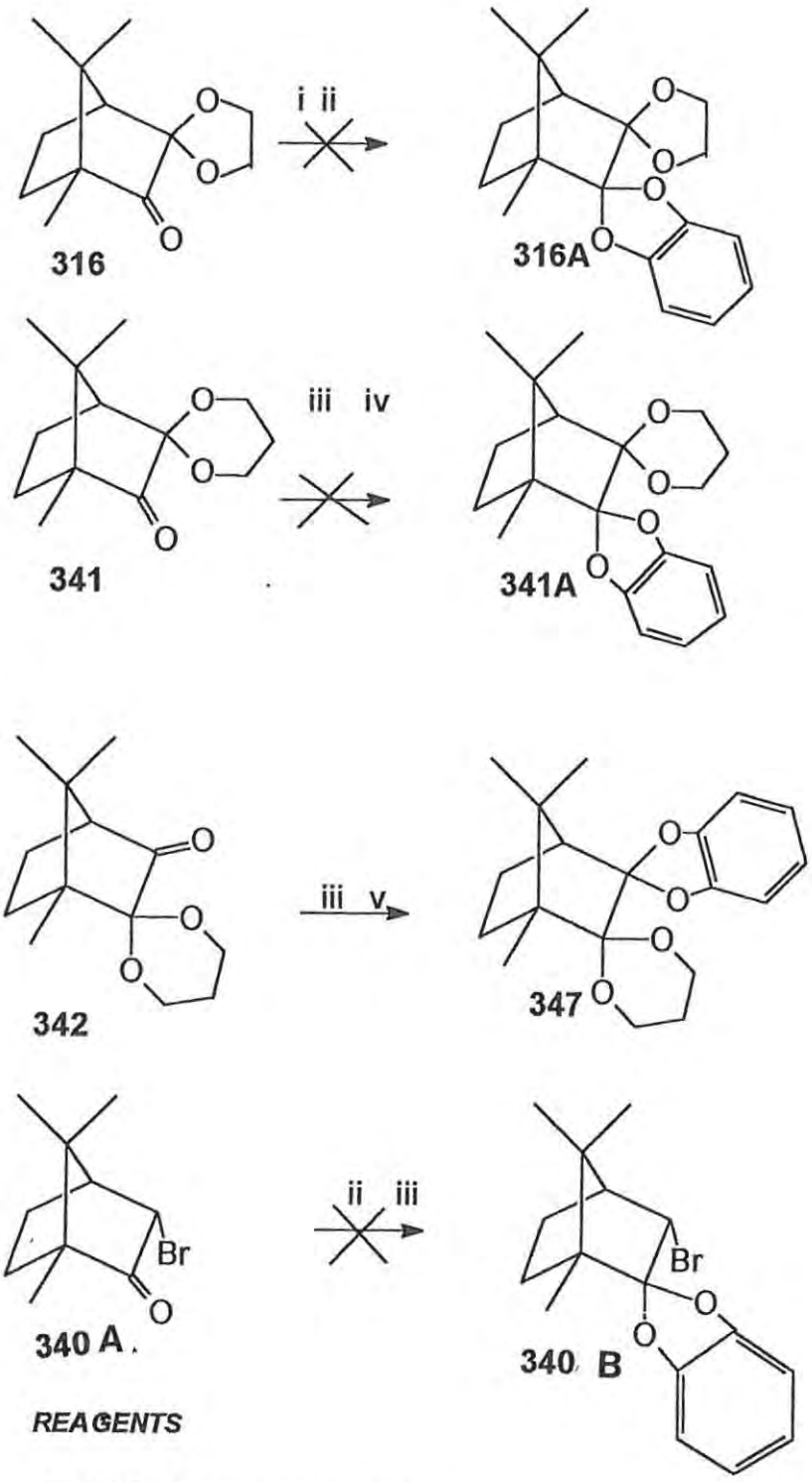
starting material . The reaction was repeated using higher boiling solvents, such as toluene and xylene, and PPTS as catalyst, but without success, and it is presumed that the bulky *endo*-3-bromo substituent effectively blocks approach of catechol to the C-2 carbonyl group. The C-3 mono-acetals **316** and **341** (Scheme 77) similarly failed to give the corresponding mono-catechol derivatives **316a** and **341a**, under a variety of conditions. The propane 1,3-diol acetal **342**,in which the carbonyl is at the less hindered C-3 position, however, finally with catechol when refluxed for 12h. in anhydrous toluene using PTSA as the catalyst. Work-up, followed by repeated preparative layer chromatography, afforded the mono-catechol derivative **347** as a yellow liquid in 20% yield. Due to the low yield and the difficulties encountered in isolation this particular approach was not developed further (Scheme 79).



347

The use of 3-*exo*-hydroxy camphor **348** was then explored. Following a procedure described by Pfrunder *et al.*,[196] camphorquinone was reduced using Raney nickel, at pressure of 1 atm. Work-up, followed by flash chromatography, afforded a white crystalline compound, [m.p. 205°C (lit.[196] 209° - 211°C)] shown by 400 MHz ^{1}H NMR spectroscopy

SCHEME 79



REAGENTS

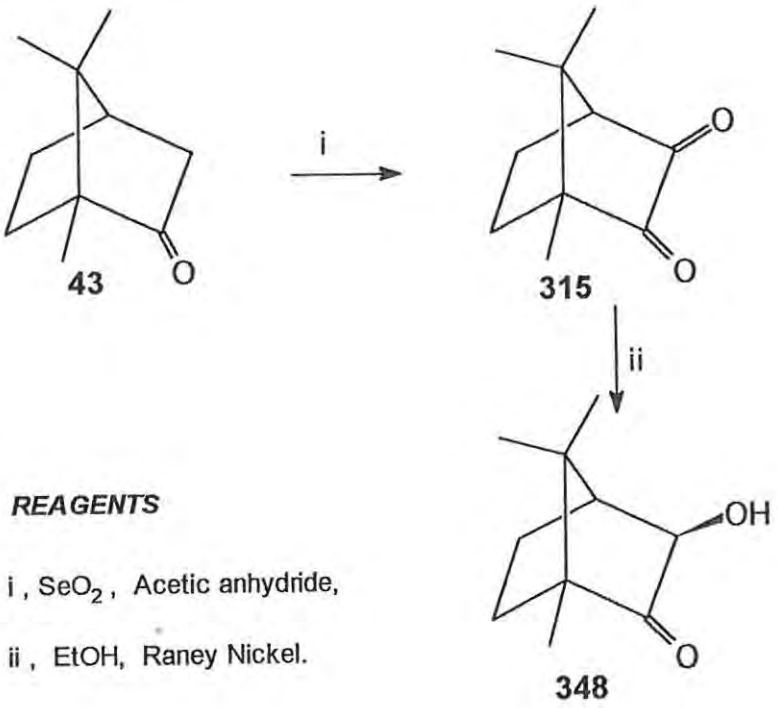
i ,PPTS ; ii benzene, iii , PTSA; iv, xylene.

to be the expected 3-*exo*-hydroxy camphor[+] as a white powder (Scheme 80). When 3-*exo*-hydroxy camphor **348** was heated with catechol in benzene using PTSA as catalyst, a white crystalline compound was obtained in 37% yield. The ^{1}H and ^{13}C NMR spectra of this crystalline compound indicated the presence of six methyl groups and 20 carbon atoms.

Elemental and spectroscopic analysis permitted the identification of this compound as the dibornyl ether **349**. McPhail *et al.*[252] have reported the *exo*:*endo* and *endo*:*endo* dimers of camphor and Rautenstrauch *et al.*[253] have reported the *endo*:*exo*, *exo*:*exo* and *endo*:*endo* dimers of borneol. To the best of our knowledge, however, a dibornyl ether has not been reported previously. McPhail *et al.* and Rautenstrauch *et al.* have clearly indicated that, due to the C-2 axis of symmetry, the *exo*:*exo* and *endo*:*endo* borneol dimers show only 3 methyl singlets whereas the *exo*:*endo* dimer shows 6 methyl singlets, in their ^{1}H NMR spectra. The ^{1}H NMR spectrum of the dibornyl ether **349** isolated in the present study, showed six clearly resolved methyl singlets in the ^{1}H NMR spectrum and and six methyl carbons in the ^{13}C and DEPT NMR spectra. Although the IR spectrum showed the presence of only one carbonyl group (at *ca.*, 1740 cm^{-1}), the ^{13}C spectrum clearly indicated the presence of two different carbonyl groups. Moreover, all the typical "camphor" ^{1}H and ^{13}C NMR signals were doubled, suggesting a dimeric product.

[+]The ^{1}H NMR data also indicated the presence of one or more minor contaminants which were not identified. Since no coupling was observed between the 3- and 4-H nuclei in the 400 MHz ^{1}H NMR spectrum, the major compound was identified as 3-*exo* hydroxy camphor

SCHEME 80

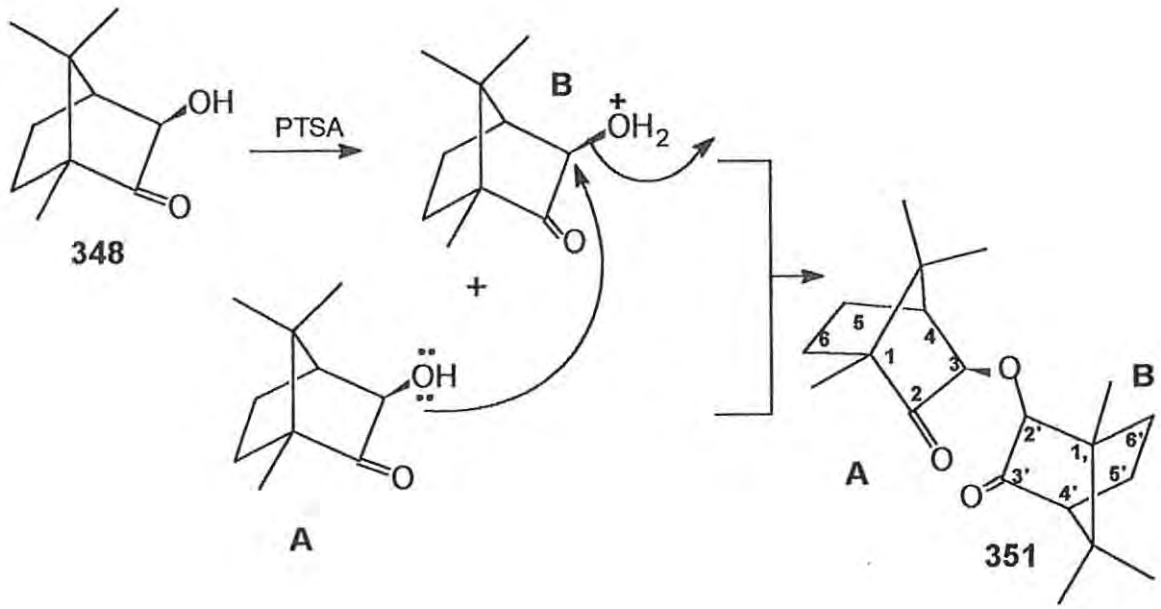


REAGENTS

i , SeO_2 , Acetic anhydride,

ii , EtOH, Raney Nickel.

SCHEME 81



The possibility of this dimer having a 3-*exo*-3'-*exo* linked ether structure **350** may be excluded by the fact that the *exo*:*exo* compound would have a C_2 axis of symmetry and, consequently, would give rise to only 10 signals in the ^{13}C NMR spectrum rather than the 20 signals observed. The dimer having the structure **351**, in which a 3-*exo*-3'-*endo* link would account for the absence of a C-2 symmetry was then considered; the required inversion of configuration at C-3 on one of the monomeric units can be explained in terms of the S_N2 displacement proposed in Scheme 81. However, this possibility was also ruled out by careful consideration of the 3-, 3′-, 4- and 4′-H signal multiplicities and the C-4 chemical shifts. The 3- and 3′-H nuclei resonate as singlets, while the 4- and 4′-H nuclei resonate as a pair of doublets in the ^1H NMR spectrum of the dimer (see Fig 22). In structure **351**, the 4-H nucleus would be expected to couple with both the *endo* 3-H (the dihedral angle being > 90°) and the 5-H nuclei and should thus appear as a more complex multiplet. While the ^1H NMR chemical shifts were comparable for the two "monomeric" units in the dimeric compound, ^{13}C and DEPT spectra showed the presence of two significantly different values for the C-4 nuclei, *viz.*, 49.1 and 59.9 ppm, indicating that in only one of the "monomeric" units is the C-4 nucleus desheilded by an adjacent carbonyl group. In the light of these observations, the dimer was finally assigned the structure **349**, which satisfactorily accounts for the observed multiplicities for the 3-H and 4-H signals . Table 10). Moreover, in this structure the C-4 nuclei are also different. Formation of this dimeric compound requires that one of the units should have undergone both isomerisation, presumably *via* an "enediol intermediate", and subsequent nucleophilic attack by the other molecule to form the corresponding dimer **349,** as indicated in Scheme 82.

SCHEME 82

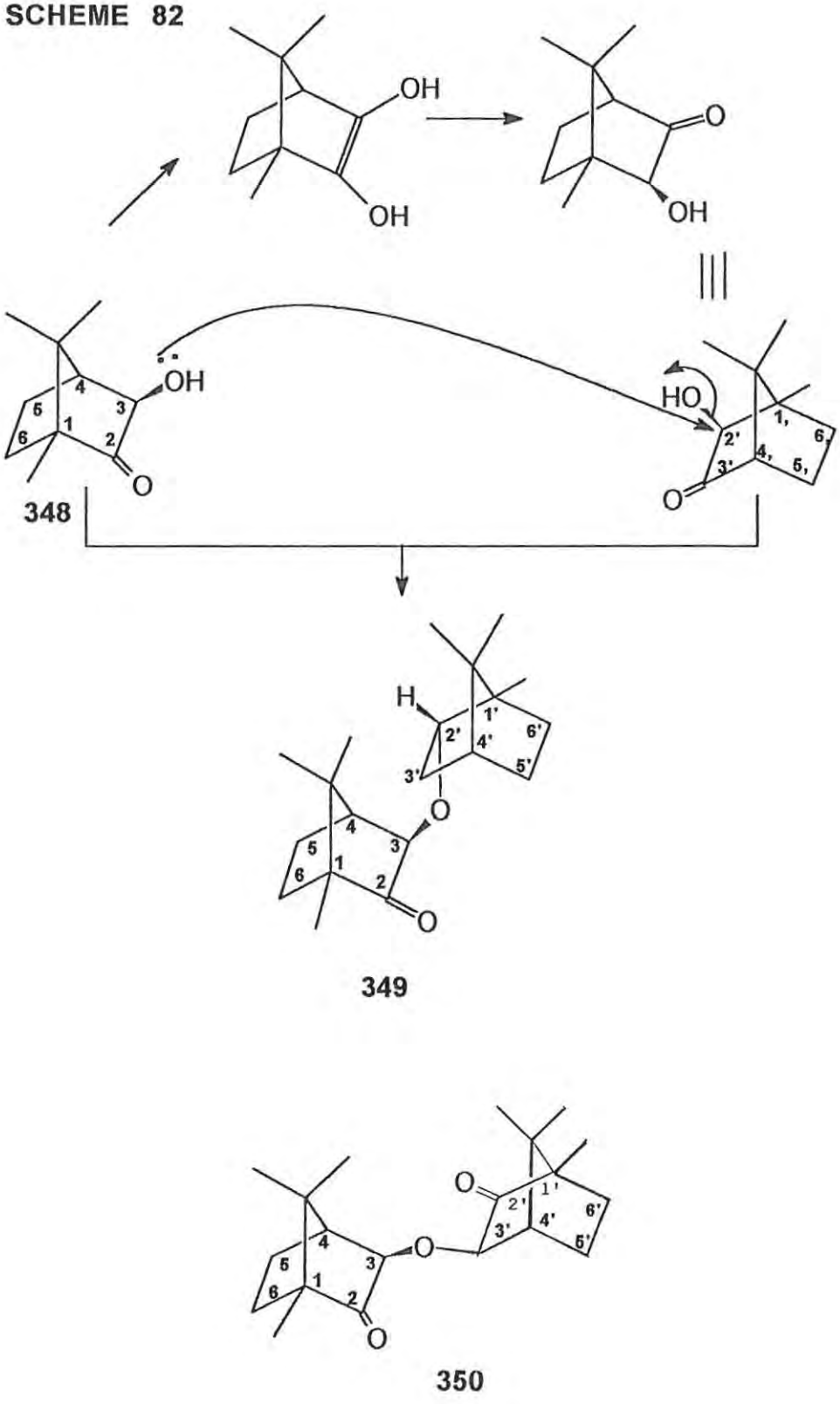
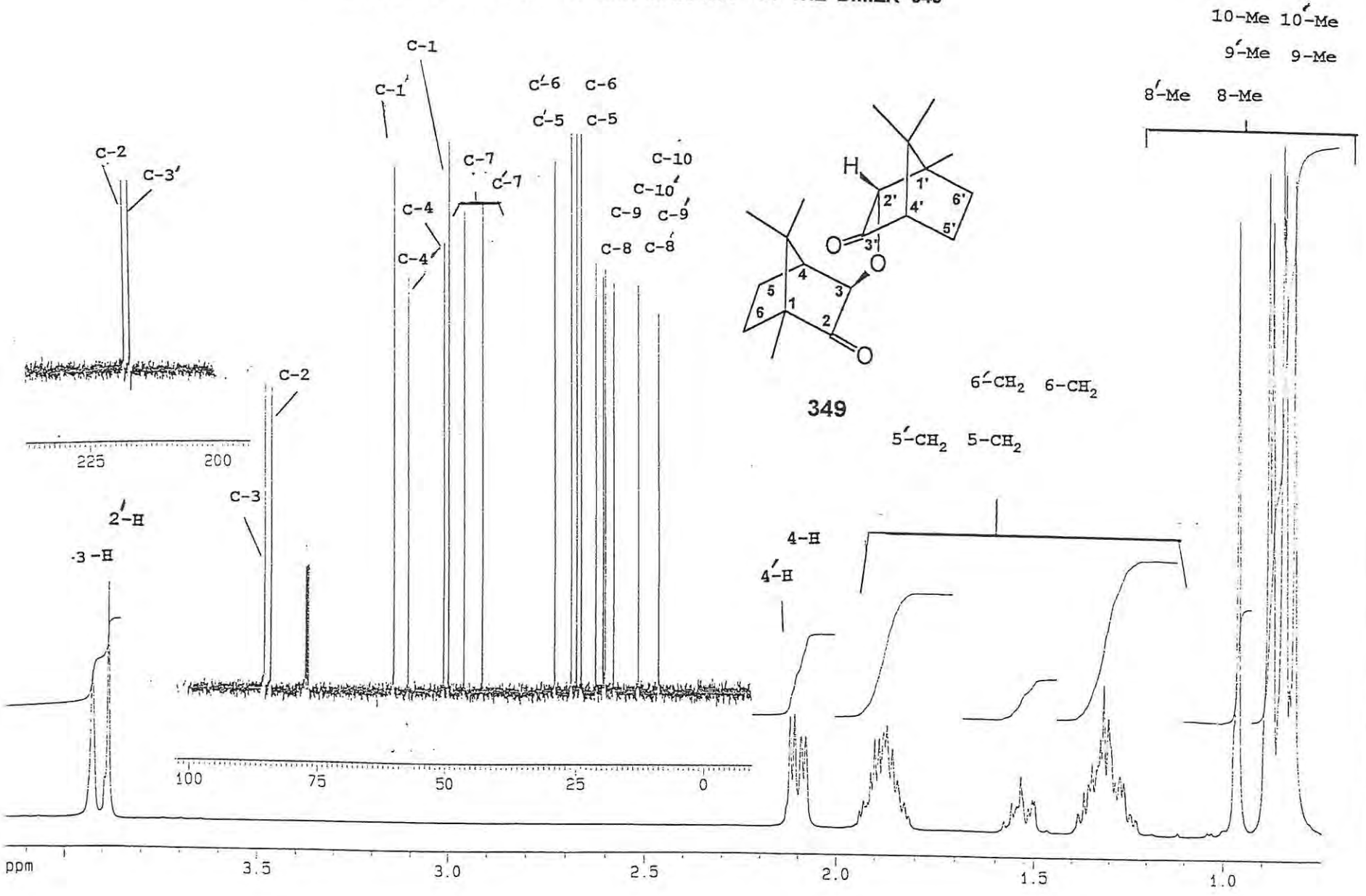
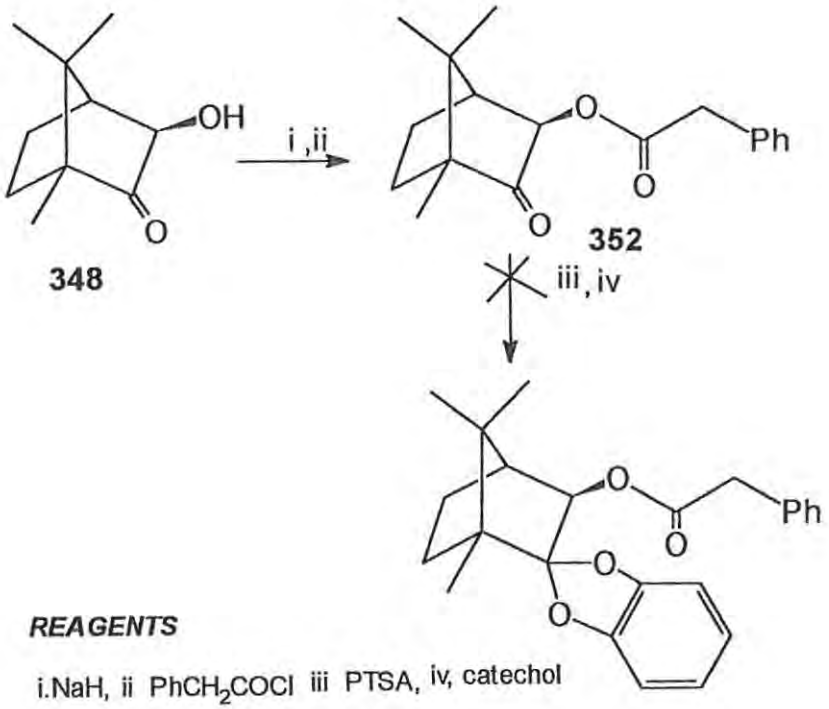


FIGURE 23 ^{1}H and ^{13}C NMR SPECTRA OF THE DIMER 349



Since esterification of the 3-hydroxyl group in 3-*exo*-hydroxycamphor **348** would prevent formation of a dibornyl ether, without blocking the carbonyl at C-2, it was decided to explore the alternative approach to the monocatechol acetal **340**. Thus, the ester **352** was prepared, following the method used for the preparation of ester **327** (Scheme 66). Work-up, followed by flash chromatography, yielded the ester **352**, which was characterised by elemental (high resolution MS) and spectroscopic analysis (Scheme 83). A solution of the ester **352**, catechol and a catalytic amount of PTSA in benzene was then heated under reflux using a Dean and Stark apparatus. As no water was produced, more catechol and PTSA were added from time to time and the solution was heated for a total of 48 hours. However, after work-up the starting material was recovered quantitatively.

SCHEME 83

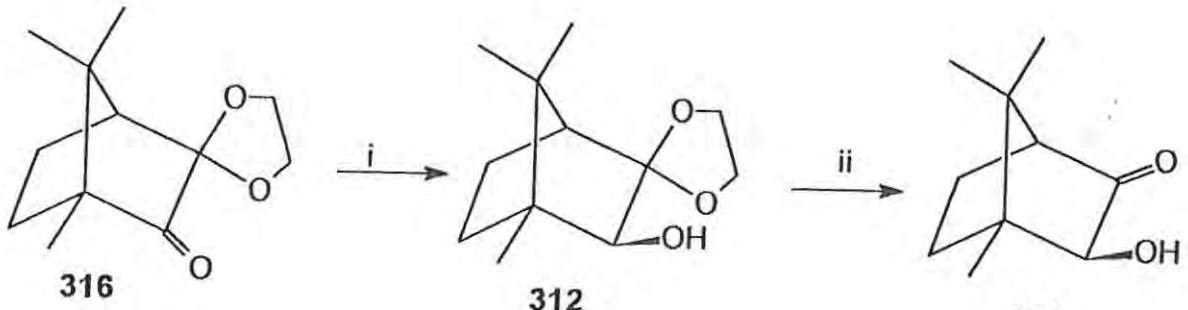


REAGENTS

i.NaH, ii $PhCH_2COCl$ iii PTSA, iv, catechol

An overview of the reactions carried out thus far revealed that a monocatechol acetal formed only at the less hindered C-3 carbonyl group of compound **342**. Attention was therefore given to the preparation of a camphor derivative, having a carbonyl group at C-3, and a hydroxyl group at C-2 (which would also permit the subsequent linking of an ester group) (Scheme 84). The *exo*-alcohol **312** prepared by the regioselective acetalisation of camphorquinone **315**, followed by stereoselective reduction of the acetal **316** (Scheme 63), was deacetalated by gentle reflux in a THF - dil. HCl mixture, to give the known 2-*exo*-hydroxy-3-bornanone **353** as a white solid, which was identified by IR and NMR spectroscopy.

SCHEME 84



316 **312** **353**

REAGENTS

i, $NaBH_4$; ii , dil. HCl.

Attention was then given to the preparation of the monocatechol acetal derivative **339**. A solution of the hydroxyketone **353**, catechol and catalytic amount of PTSA in benzene was then heated under reflux using a Dean and Stark apparatus. Work-up and flash chromatography afforded two major fractions; the ^{1}H and ^{13}C NMR spectra of one of these indicated a mixture of the starting material **353** and the desired monocatechol acetal **340**. Attempts to separate theses two compounds resulted in the degradation of the acetal. The second fraction, a white crystalline compound with m.p. 118°C, was obtained in 32% yield.

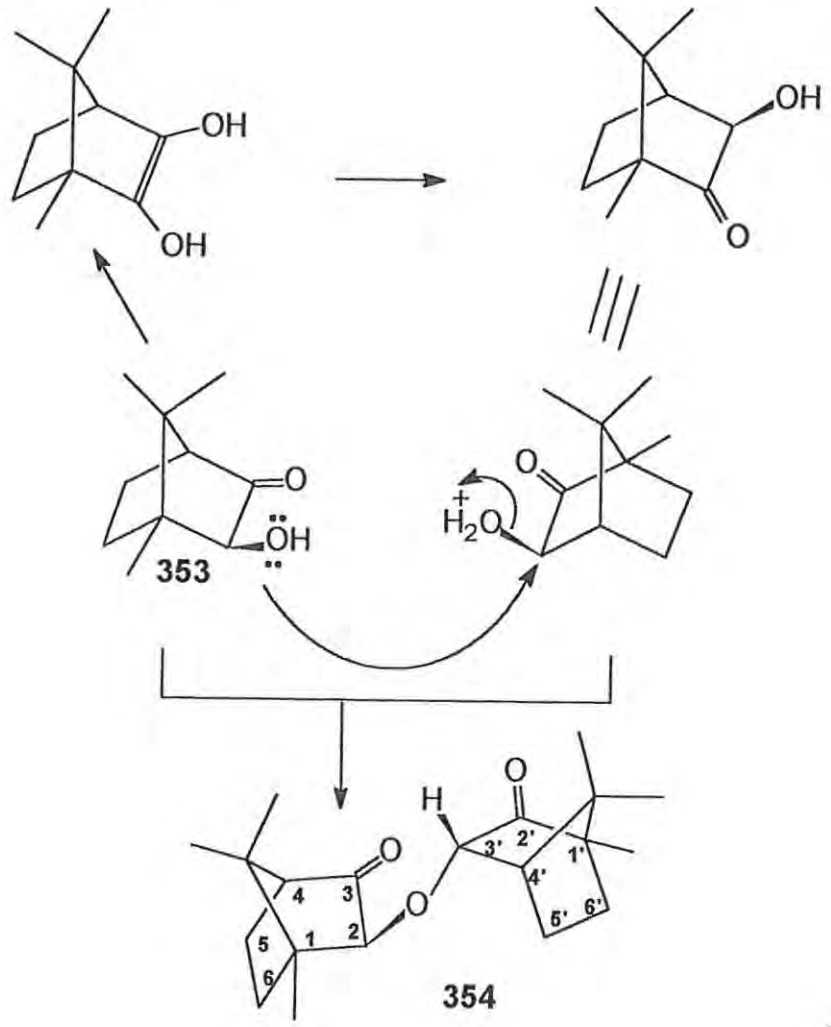
The IR spectrum showed the presence of a carbonyl group while the ^{13}C NMR spectrum indicated the presence of two carbonyl carbons. Here again, as observed for the dimer **349**, doubling of all the ^{1}H and ^{13}C NMR signals indicated both the presence of a dimer and the absence of a C-2 symmetry. DEPT NMR spectra also indicated the presence of two dissimilar C-4 nuclei indicating that in only one of the monomeric units, the C-4 nucleus is deshielded by an adjacent carbonyl group. Although the ^{13}C and DEPT NMR spectra for this compound and the 3-*exo*-2'-*endo* dimer **354** are very similar the ^{1}H NMR spectra clearly indicated several differences which are detailed in Table 10.

TABLE: 10 ^{1}H and ^{13}C NMR Data for the Dimers 349 and 354.

	349	354
8-Me, 8′-Me, 9-Me, 9′-Me, 10-Me and 10′-Me	0.82, 0.84, 0.85, 0.88, 0.96 (18H, 5xs)	0.82, 0.82, 0.86, 0.95, 0.96,0.97 (18H, 6xs)
5-CH_2, 5′-CH_2, 6-CH_2 and 6′-CH_2	1.22 - 2.01 (8H, m)	1.36 - 1.89 (8H, m)
4-H and 4′-H	2 x d, 2.08 and 2.11	2.048, (1H, d) and 2.31, (1H, t)
3-H and 2′-H	3.88 and 3.92, 2H (2xd) (3-H and 2′-H)	3.81 (1H, s, ′2-H) 4.25 (1H, d, 3′-H)
C-10 and C-10′	8.85 and 12.91	9.30 and 10.49
C-9 and C-9′	17.00 and 19.28	18.53 and 18.71
C-8 and C-8′	19.66 and 21.05	18.85 and 19.85
C-7 and C-7′	42.58 and 46.15	42.59 and 46.09
C-6 and C-6′	23.89 and 24.75	20.69 and 21.34
C-5 and C-5′	25.76 and 28.88	31.78 and 33.65
C-4 and C-4′	49.14 and 59.89	48.32 and 59.24
C-3 and C-2	84.31 and 85.31 (C-3 and C-2′)	85.62 and 81.66 (C-2 and C-3′)
C-2 and C-3	216.93 and 218.12 (C-2 and C-3′)	217.77 and 217.87 (C-3 and C-2′)
C-1 and C-1′	50.16 and 57.17	49.98 and 58.36

The dimer was finally assigned the structure **354**, which has a 2-*exo*-3-*endo* link which accounts for the multiplicities of the 3-H and 4-H signals (Table10) as well as the differences between the C-4 nuclei in the two monomeric units. Confirmation of signal assignments and coupling relationships is provided by the NMR spectra Figures 22, 23, and 24 of the 3-*exo*-2′-*endo* dimer **349**, the 2-*exo*-3′-*endo* dimer **354** could also have been formed from two monomeric units, one of which must have isomerised *via* an "enediol" intermediate (Scheme 85).

SCHEME 85



354

FIGURE 22 400MHz ^{1}H and ^{13}C NMR SPECTRA OF THE DIMER 354

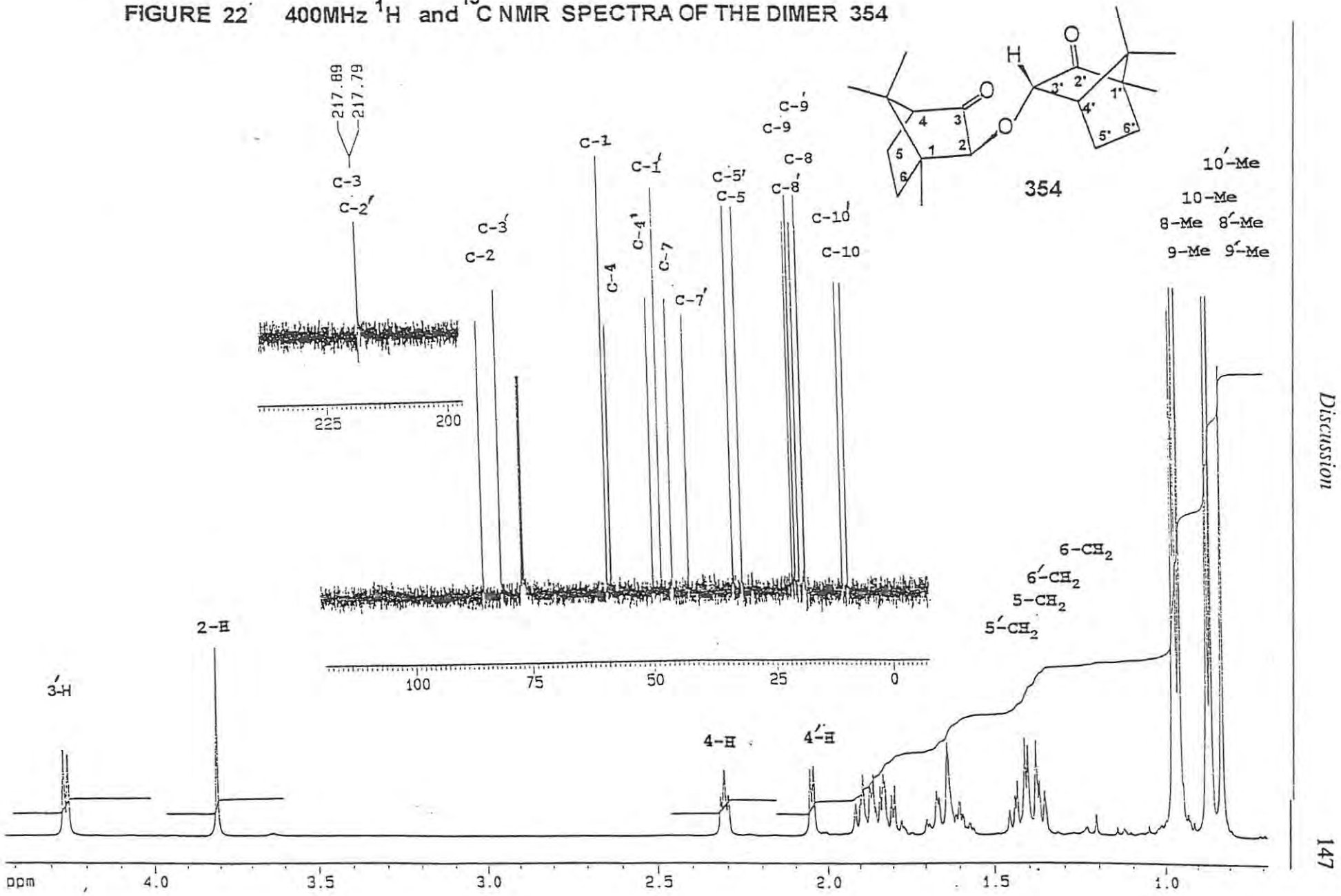
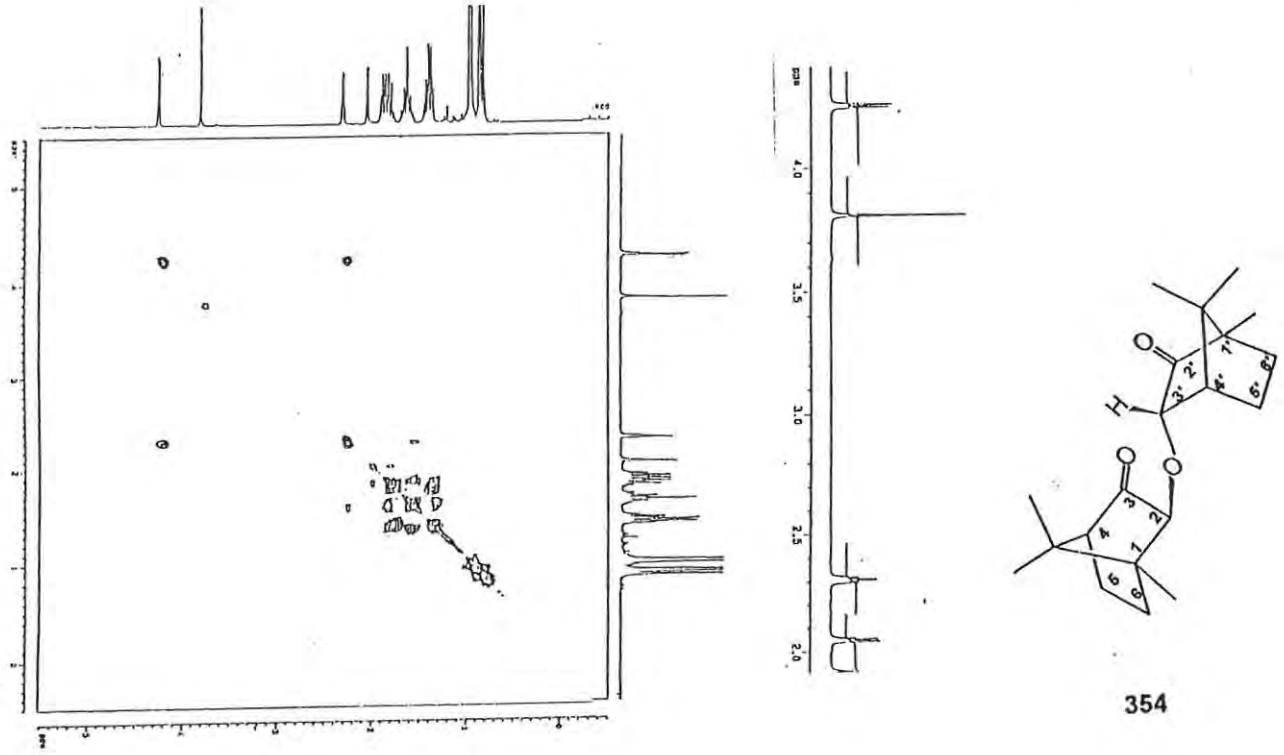
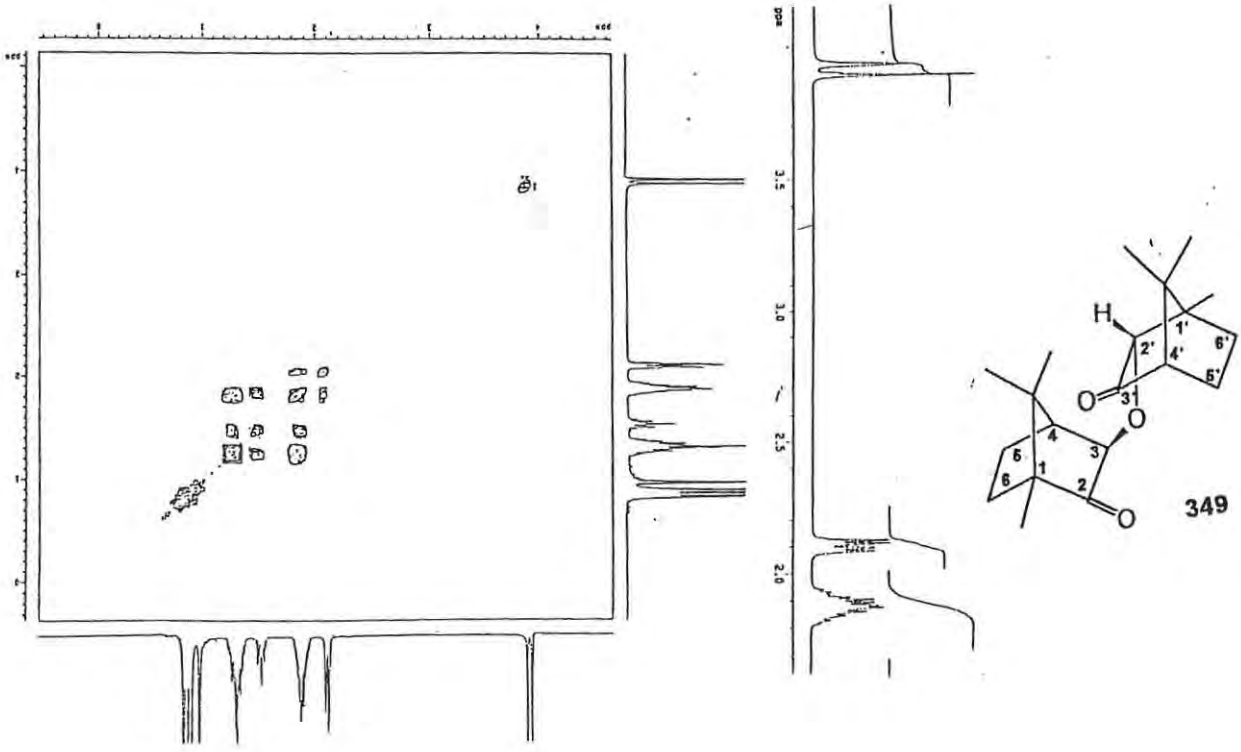


FIGURE 24 COSY NMR SPECTRUM OF THE DIMERS 349 and 354





2.3.3 Preparation and α-benzylation of the carboxylate esters 354A 355, 359 and 356 derived from the chiral alcohols 343 and 344

It can be seen from Table 4 that the chiral esters **335** and **336** with bulky substituents [(**335**) R = Bu^t and (**336**) R = Ph] showed better diastereoselectivity towards α-benzylation. Consequently, the corresponding esters **354A** and **355** were prepared in yields of 71% and 40% respectively from the chiral alcohol **343** using *tert*-butylacetyl chloride and phenylacetyl chloride (Scheme 87). The esters were fully characterised by elemental analysis and NMR (^{1}H, ^{13}C and DEPT) spectroscopy . The 2-*endo* proton singlet for the *tert*-butylacetyl ester **354A** appeared at 4.44 ppm. and at 4.57 ppm. for the phenylacetyl ester **355** in a region of the spectra where no other signals were seen.

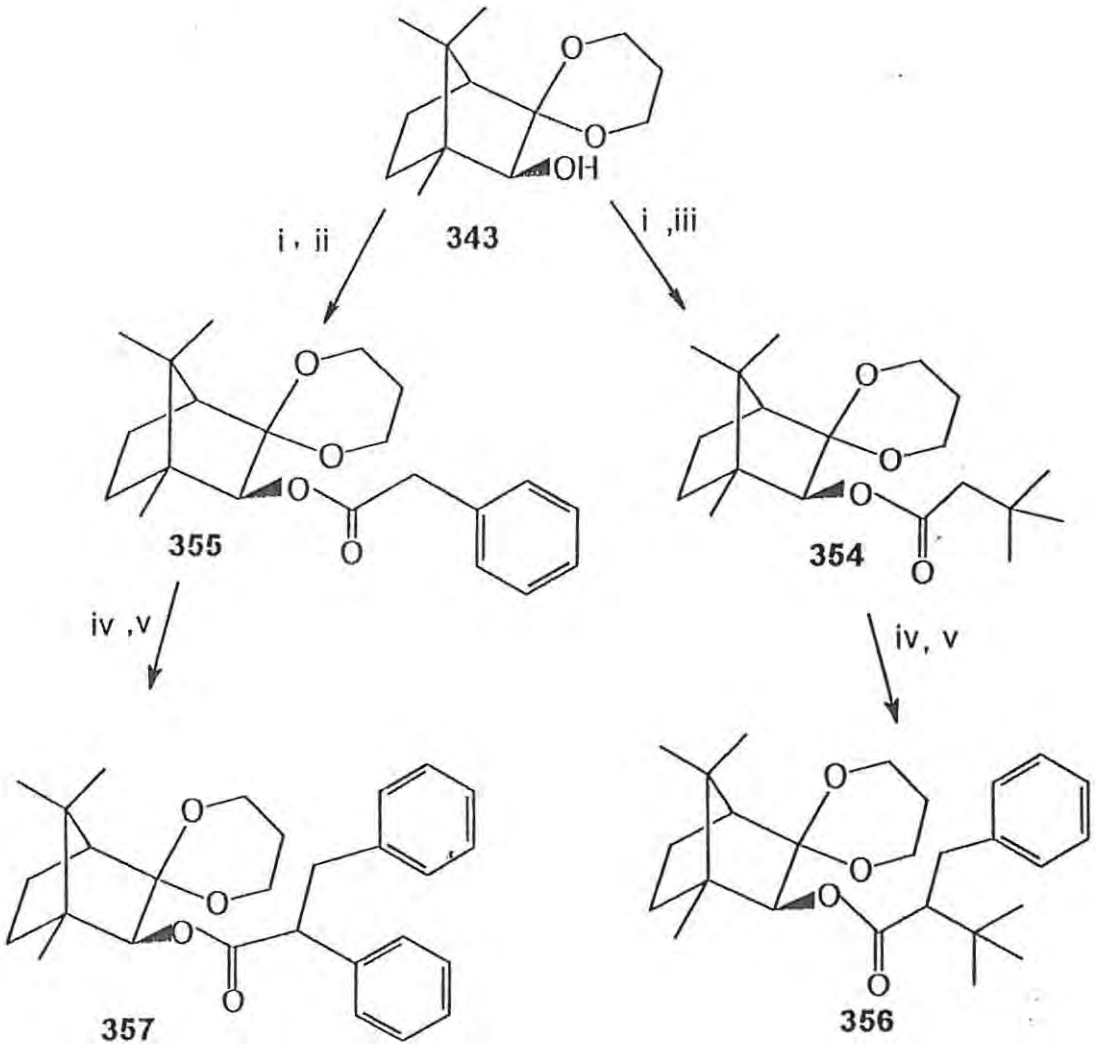
The stereodirecting potential of the esters **354A** and **355** towards α-benzylation (employing a method similar to that used in the ethylenedioxy system) was then investigated. The crude products obtained after α-benzylation were purified by preparative layer chromatography to give the α-benzylated esters **356** and **357** (Scheme 87). The observed yields and diastereoselectivities are summarised in Table 11.

TABLE:-11 Data for the α-Benzylation of Carboxylate Esters 354 A and 355.

Product	R	Yield/%	d.e./%
356	Bu^t	63	6
357	Ph	68	17

The diastereoselectivity observed was, initially, surprising, but can be explained by considering the conformation of the acetal moiety in the ester enolate. The six-membered propylenedioxy group lacks the relative rigidity of the analogous ethylenedioxy group and may adopt a chair conformation in which the steric constraint offered by the propylenedioxy group is not as great as the ethylenedioxy group.

SCHEME 87



REAGENTS

i NaH ; ii , $PhCH_2COCl$; iii , Bu CH_2COCl; iv ,LDA;

v ,$PhCH_2Br$

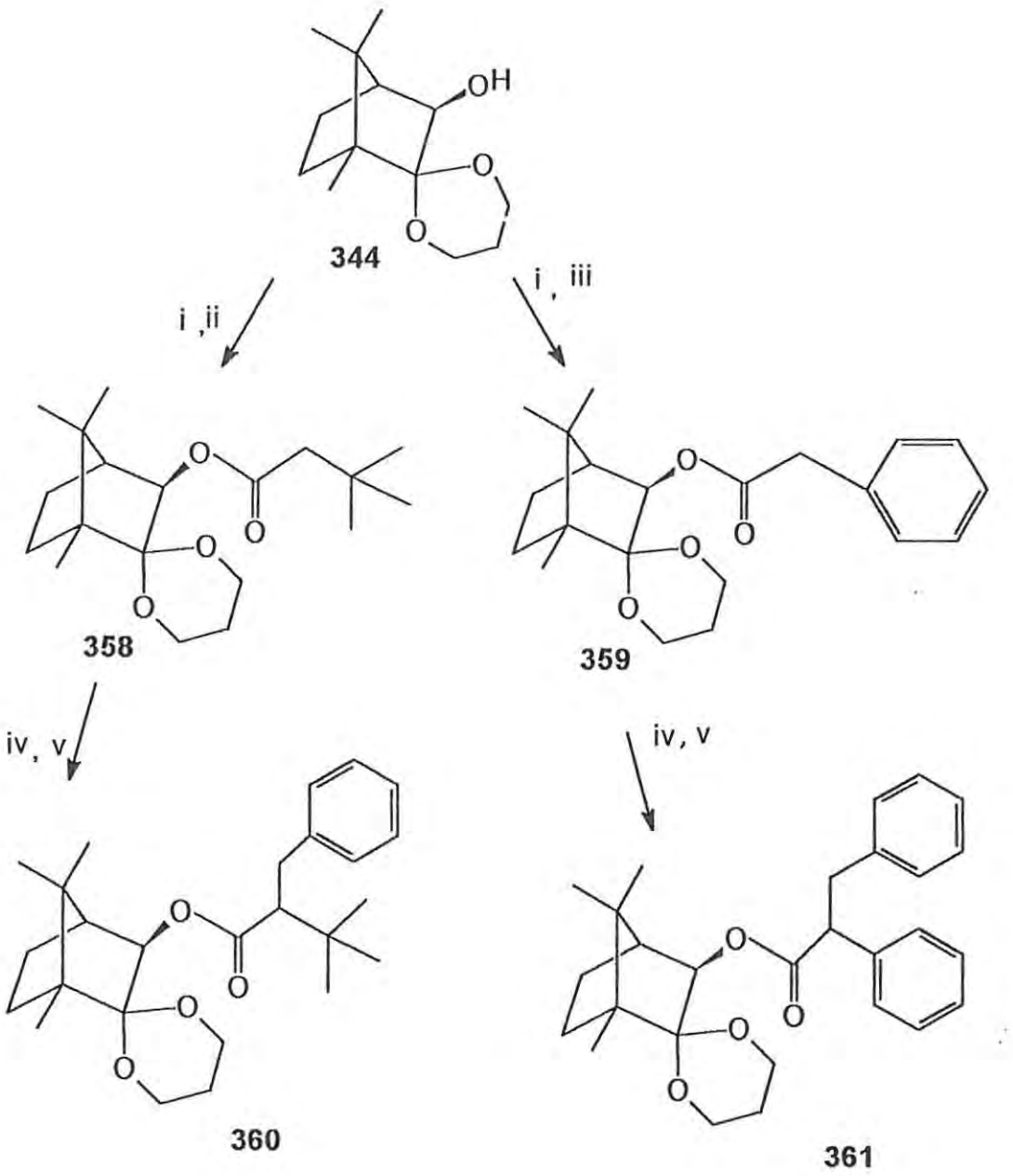
Computer modelling has been used to explore the enolate conformation (see pg.155).

Since the regioisomeric alcohol **344** was also available, it was decided to prepare the *tert*-butylacetyl ester **358** and phenylacetyl ester **360** and then to carry out α-benzylation to evaluate the stereodirecting potential of this auxiliary. The 2,2-propylenedioxy group is expected to effectively block the *Si*-face of the enolate double bond (rather than the *Re*-face as is the case with the 3,3-propylenedioxy system). A buttressing effect afforded by the 8-methyl group is also expected to enhance the steric blocking of the *Si*-face. Moreover, the *Re* face of the enolate is complete unhindered and it was realised that diastereofacial selectivity in the regioisomer **344** may be significant.

A slight modification was made to the procedure used for esterifying the chiral alcohol **344**; *viz.* the alkoxide was generated using NaH at room temperature (instead of heating under reflux for several hours) since the alcohol **344** is not as sterically hindered as its regioisomer **343**. The alkoxide was then treated with the appropriate acid chlorides and the crude esters were purified by flash chromatography. Although the *tert*-butylacetyl ester **358** was obtained in 82% yield, the phenylacetyl ester **359** was initially obtained in only 23% yield. The ^{1}H NMR spectrum of phenylacetyl chloride showed the presence of phenylacetic acid, as a minor contaminant, and the yield of the phenylacetyl ester **359** was increased to 58% when purified[+] phenylacetyl chloride was used. The esters **358** and **359** were fully characterised by elemental analysis (high resolution MS) and IR and 1-D (^{1}H, ^{13}C and DEPT) NMR spectroscopy. The *endo*-3-H signal appeared as a singlet, at 4.32 and 4.38 ppm for the

[+] By refluxing with anhydrous $MgSO_4$ under N_2 and subsequent distillation.

SCHEME 88



REAGENTS

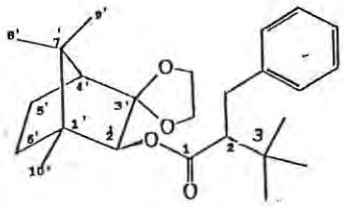
i , NaH , THF ;ii, Bu^tCH_2COCl , iii , $PhCH_2COCl$,

iv , LDA ; v, $PhCH_2Br$.

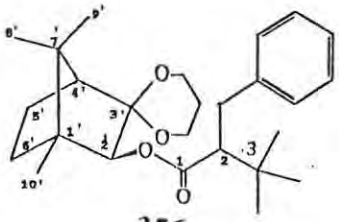
tert-butylacetyl ester **338** and phenylacetyl ester **359** respectively, as usual, in a region of the ^1H NMR spectra where no other signals were seen. The absence of coupling between the 4-H and *endo* 3-H nuclei has been noted already (see p.124).

TABLE 11 Comparative ^{13}C NMR Data (ppm) for the α-Benzylated Esters 335, 356 and 360.

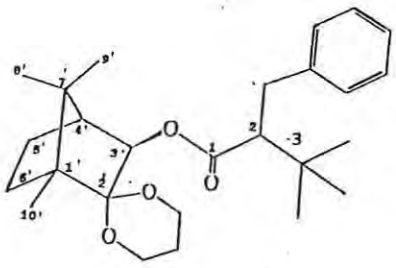
	335	356	360
C-1	173.8	173.55/173.63	174.32
C-2	57.6/58.8	57.9/58.9	58.59/59.65
C-3	49.5	29.65/30.89	33.81
CH_2Ph	34.0/34.3	34.12/34.37	34.44/34.73
Bu^t	28.0/28.2	28.13/28.01	27.87/28.08
C-1′	47.8/47.9	47.97	54.22/54.10
C-2′	86.3/86.4	86.71/86.74	106.52
C-3′	114.4	105.3/105.7	82.01/82.87
C-4′	54.1/54.3	46.7/48.7	50.67/58.83
		20.08/20.18	24.40/24.53
C-6′	33.5/33.9	33.85/34.08	27.85
C-7′	48.9	48.2/48.4	46.99
C-5′	20.5-20.8	20.51/20.68, 21.72	21.02/21.44 20.08
C-8′,C-9′, C-10′	10.62/12.22	10.62/12.22 25.2/25.4	9.85/9.97 25.30/25.39
ACETAL CARBONS	65.2/65.5 and 63.5/63.9	60.73, 60.92 and 61.22	61.77/68.2 and 62.0/62.25
Ar-C	125.6-140.9	126.0-140.2	126.09-139.77



335,



356



360

The α-benzylation of the chiral esters **358** and **359** was effected by treating the corresponding lithium enolates with benzyl bromide (Scheme 88) and the crude diastereomeric products, obtained in each case, were purified by preparative layer chromatography. The diastereomeric excess in the case of the *tert*-butylacetyl derivative **360**, as determined by the ratio of the integrals for the *endo*-3-H protons, was 58%. The diastereomeric excess for the phenylacetyl analogue **361** at first seemed to indicate a diastereomeric excess of 100% since the *endo*-3-H signal did not split.[+] But splitting was observed for the 8-, 9-, 10-methyl groups and the splitting of every signal in the ^{13}C NMR spectrum (including C-3) clearly indicated the presence of a mixture of diastereomers.

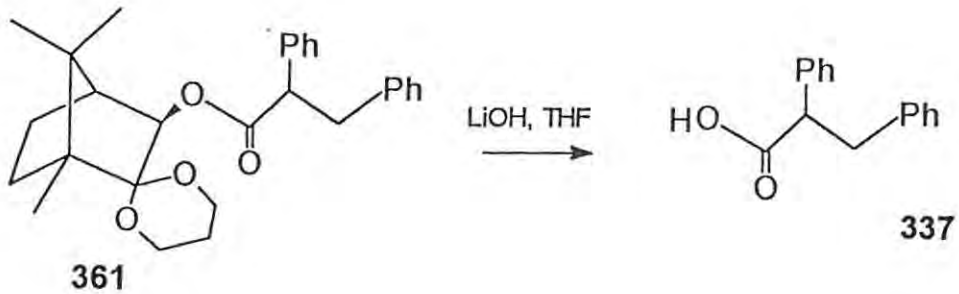
In order to use the ^{13}C signal intensities as a means of determining the diastereomeric excess, the acquisition delay was increased to ensure complete relaxation and reliable signal integration. From this experiment the diastereomeric excess in the case of ester **361** was determined to be 18%.

[+] In the determination of diastereomeric excess in all the diastereomers discussed in this study, the integral ratio of the *endo*-3H or *endo*-2H signals allowed evaluation of the %d.e.

2.3.4 Determination of the configurational bias at the new chiral centre.

Since the configuration and optical rotation of the carboxylic acid **337** has already been established,[243] it was decided to hydrolyse the diastereomers **361** and measure the optical rotation of the carboxylic acid thus obtained, to provide confirmation of the dominant enantiomer. Thus, the α-benzylated ester **361** was hydrolysed by stirring with LiOH in THF at room temperature for *ca.* 3 days (Scheme 89). Work-up afforded the white crystalline 2,3-diphenylpropanoic acid **337**, which was characterised by ^{1}H and ^{13}C NMR spectroscopy and which showed an optical rotation of -27° (in benzene) {lit.[243] $[\alpha]_D^{20}$ +94.04 (benzene)*}. This result indicates the laevorotatory (*R*)-enantiomer to be present in an enantiomeric excess of 29%. By implication, the favoured configuration at the α-carbon of the diastereomeric ester **361** must also be (*R*). These results are consistent with conclusions drawn from the computer modelling studies discussed below.

SCHEME 89



361 **337**

* For pure dextrorotatory enantiomer .

Computer Modelling Studies.

Various factors in our earlier analysis of the transition state preferences of the ester lithium enolates (see pg. 118) are expected to apply to both the 2,2- and 3,3-propylenedioxy acetals **343** and **344**.

In the case of the 3,3-propylenedioxy acetals **343**, the chair conformation of the acetal moiety (illustrated for the *tert*-butyl derivative **354** in Figure 25) explains why the expected increase in steric blocking of the *Re*-face was not realised.

In the case of the 2,2-propylendioxy acetals **344**, the ester enolates are expected to adopt the conformational arrangement illustrated in Figure 26. In this conformation:—

(i) the propylenedioxy group lies parallel to the enolate and effectively blocks the *Si*-face;

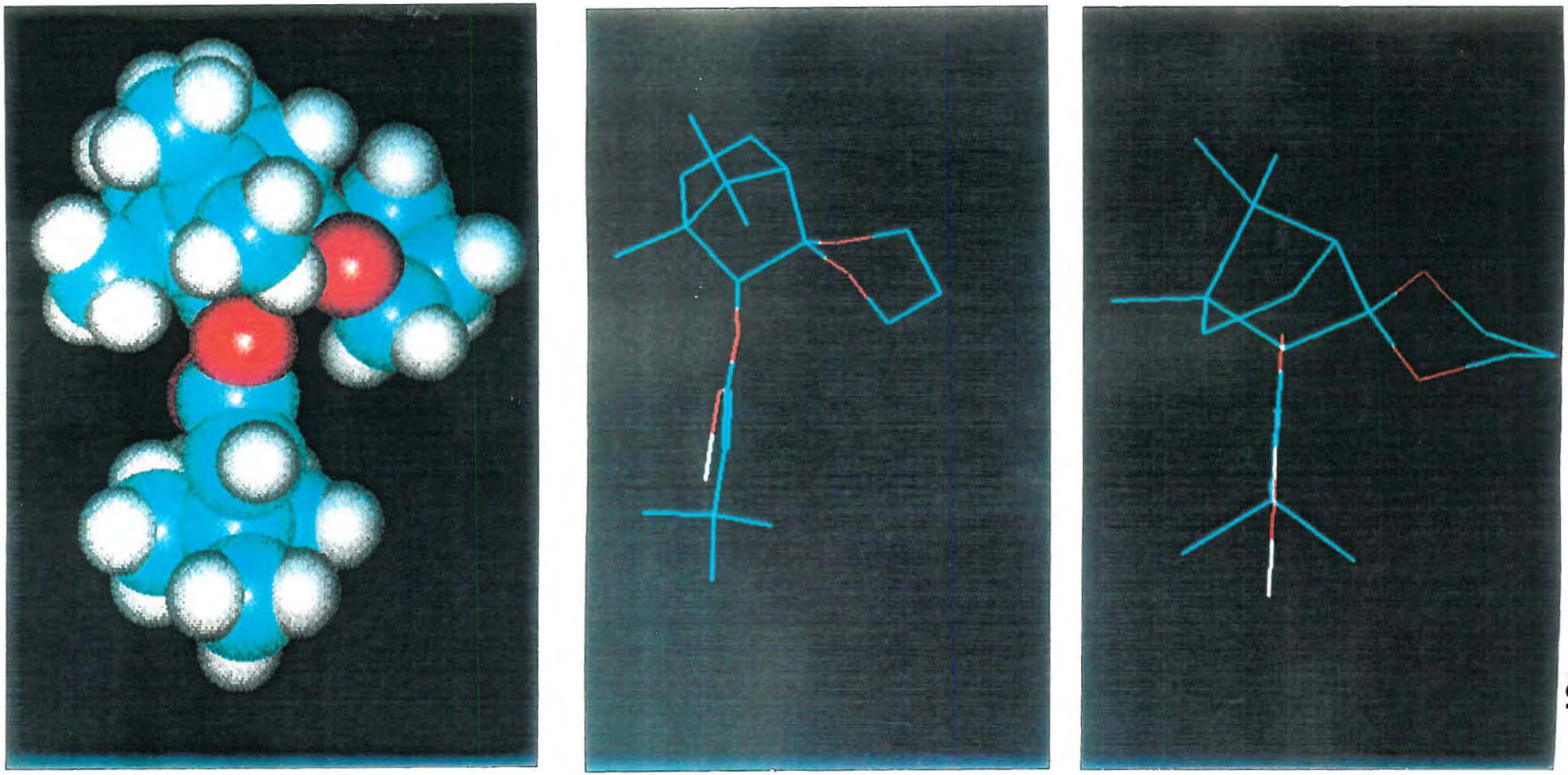
(ii) the 8-methyl group serves to enhance the steric blocking of the Si-face by buttressing the propylenedioxy group; and

(iii) the *endo-s-trans* arrangement of the enolate moiety is favoured as discussed earlier (section 2.2.4, page 117).

On the basis of this model, the electrophile should approach the enolate group preferentially from the less hindered *Re*-face leading to α-benzylated products in which the (*R*) configuration is predominant. Confirmation of these proposals is provided by the polarimetric analysis discussed above.

FIGURE 25

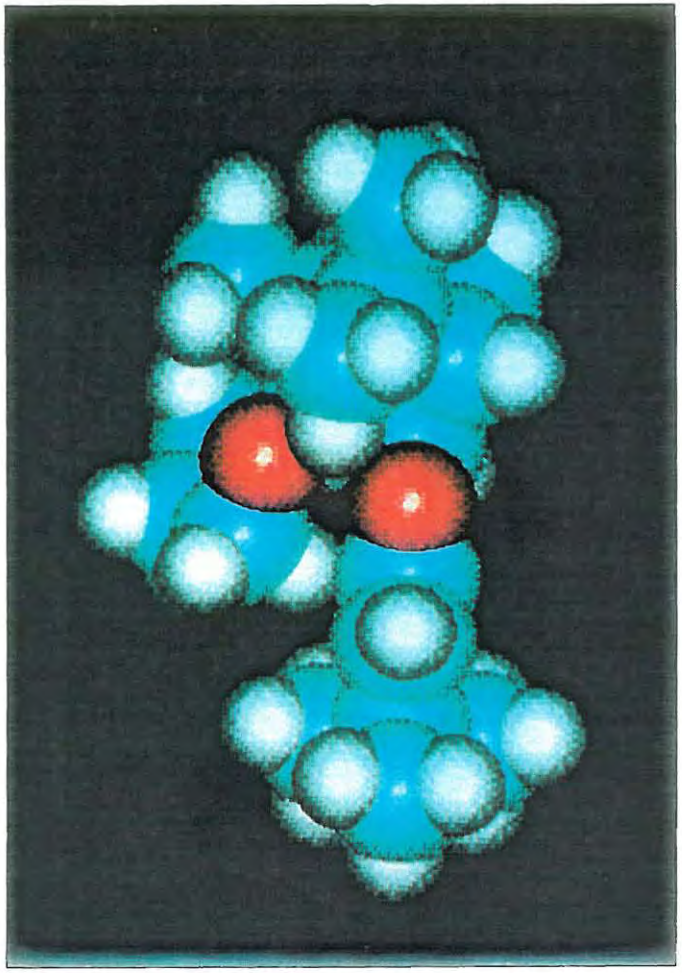
Computer-modelled structure of the lithium enolate of 3,3-(propylenedioxy-2-*exo*-bornyl 3,3-dimethylbutonoate, preferential attack by the electrophile occurring at the less hindered *Si* face (LHS drawn): a) Stick rendering. b) Space filling sphere rendering. c) Stick rendering emphasising the chair conformation of the 3,3-propylenedioxy group.



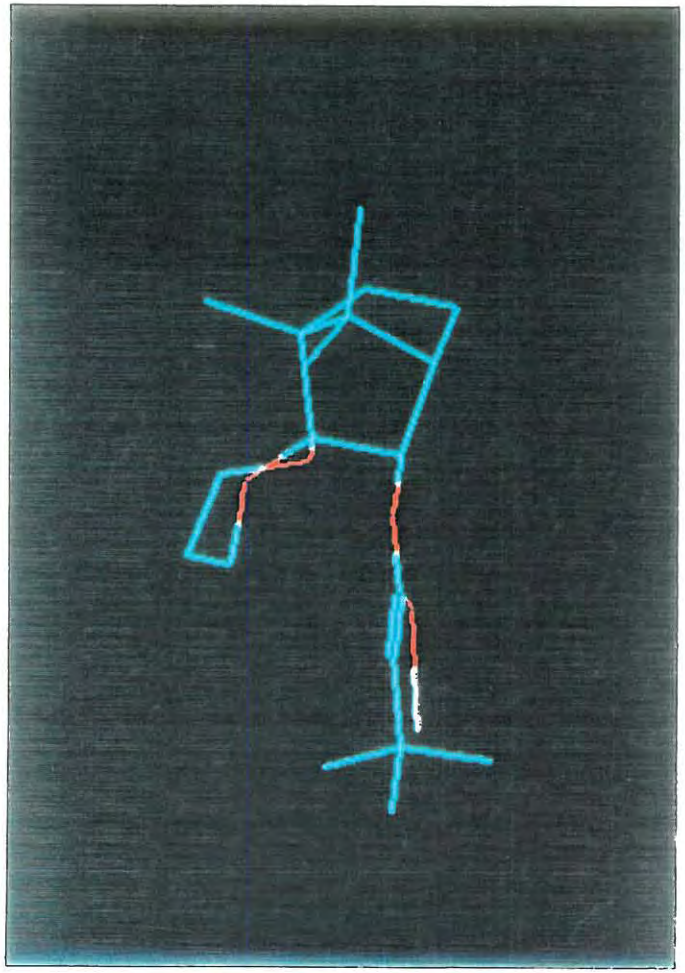
a b c

FIGURE 26

Computer-modelled structure of the lithium enolate of 2,2-(propylenedioxy-2-*exo*-bornyl 3,3-dimethylbutonoate, preferential attack by the electrophile occurring at the less hindered *Re* face (RHS drawn): a) Stick rendering. b) Space filling sphere rendering.



B



A

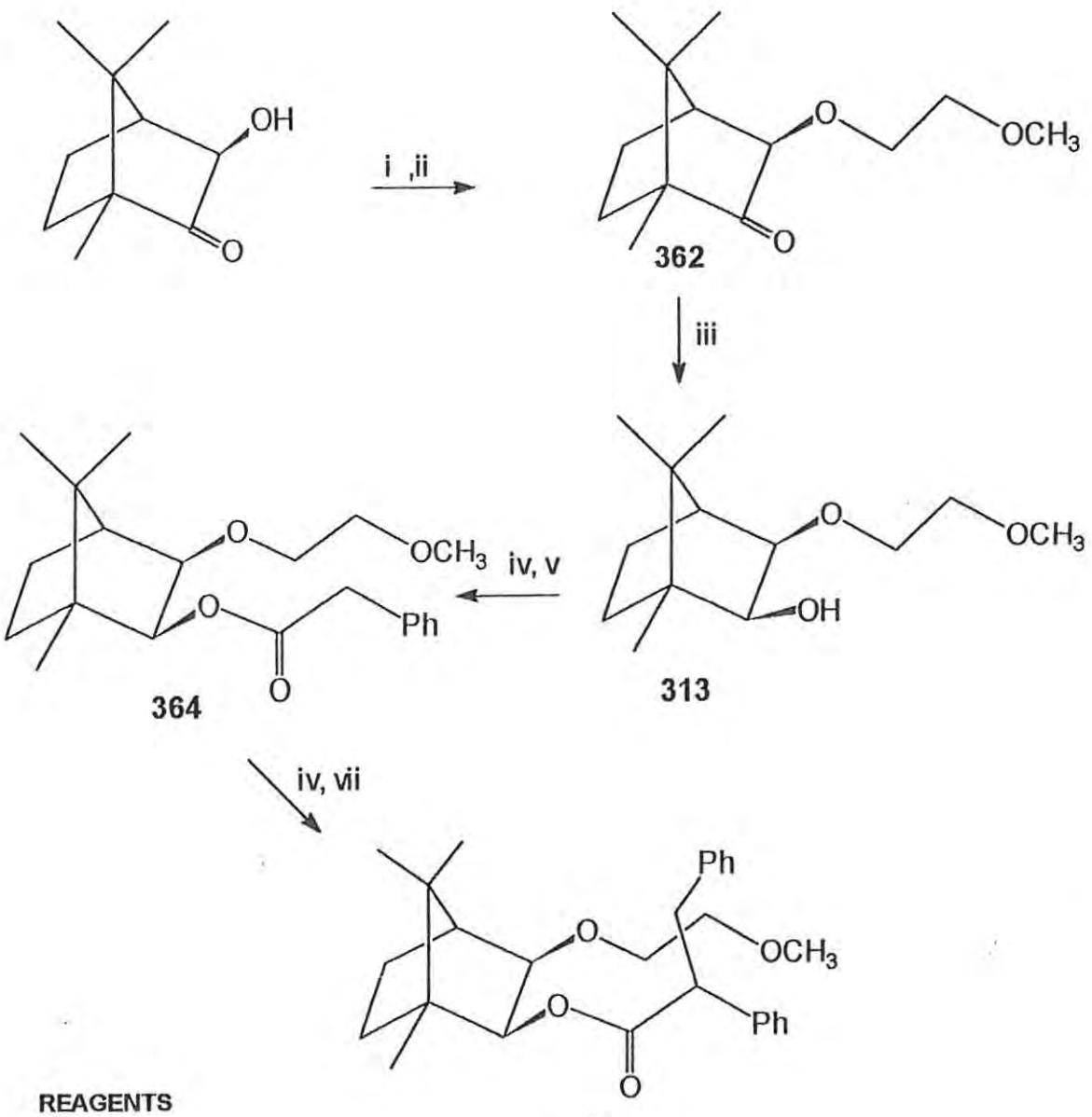
2.4 Application of the chiral alcohols 313 and 314.

The availability of the α-ketol **348** prompted us to explore the possibility of preparing the methoxyethyl derivative **313** and the benzyloxy derivative **314**. Following a route used by Learmonth[249] the alcohol **313** was prepared as summarised in Scheme 90. Thus, 1-chloro-2-methoxyethane **361** (prepared by treating 2-methoxyethanol with $SOCl_2$) was added to the sodium alkoxide of the α-ketol **348**. Work-up afforded the ketone **362** which was regioselectively reduced to the alcohol **313**.[249] The benzyloxy alcohol **314** was prepared by following Oppolzer's route,[250] outlined in Scheme 91.

The esters **364** and **366** were prepared by treating the respective alkoxide precursors with phenylacetyl chloride, purified by flash chromatography. In the ^{1}H NMR spectrum of the benzyl derivative **366**, the 2-H signal appeared as a doublet at *ca.*, 4.8 ppm, reflecting coupling to the adjacent *endo*-3-H nucleus. However, the ^{1}H NMR spectrum of the methoxyethyl analogue **364** revealed a double doublet at *ca.* 4.6 ppm, presumably indicating the presence of additional long range coupling.

Both the esters **364** and **366** which were fully characterised, were then subjected to α-benzylation, and the resulting diastereomeric esters **365** and **367** respectively were purified by preparative layer chromatography. The complexity of the 2-H multiplets in both diastereomeric mixtures made evaluation of the diastereomeric excesses somewhat difficult, but careful examination of the spectra permitted determination of the stereoselectivities (see Table 12).

SCHEME 90

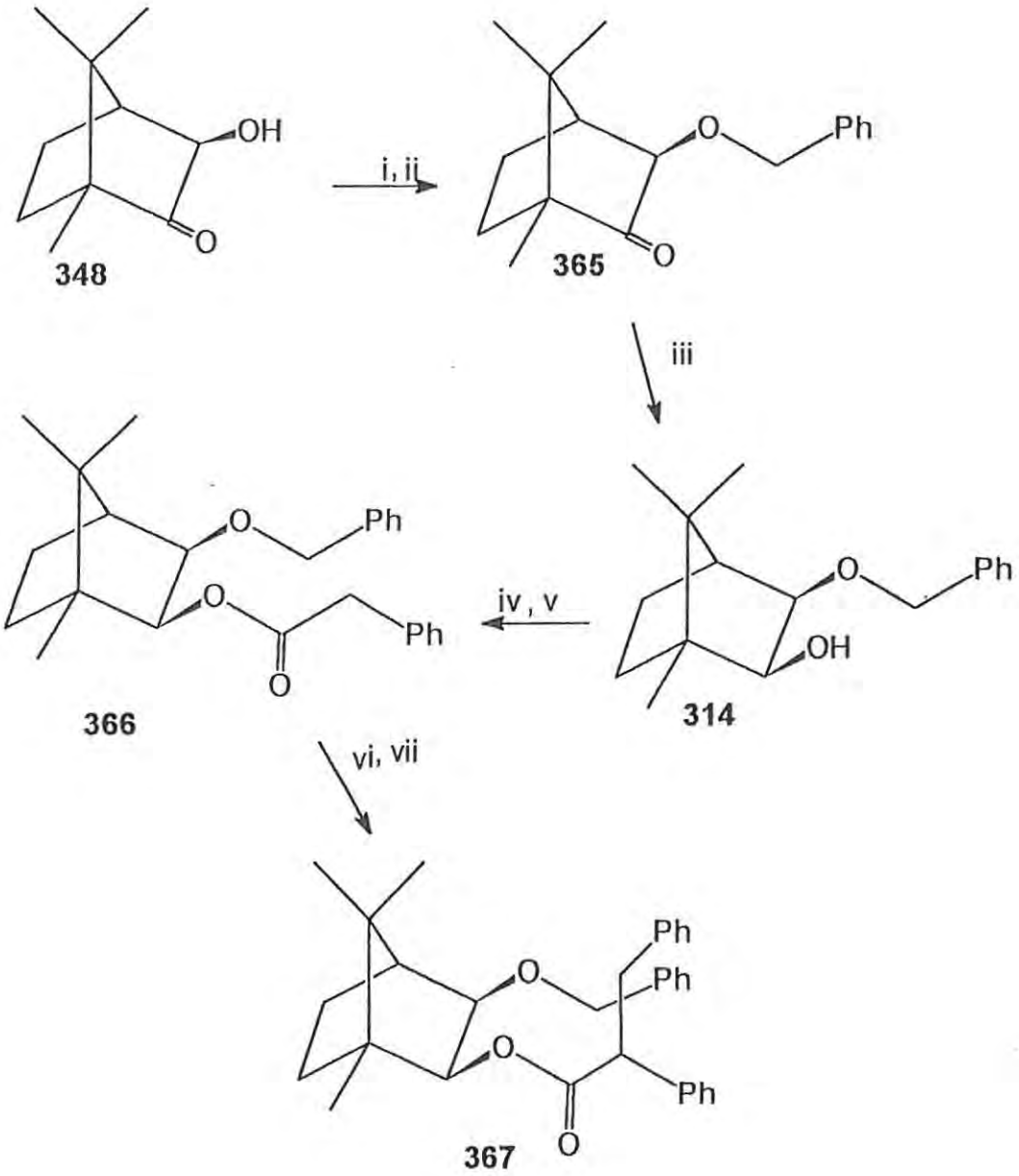


REAGENTS

i NaH,DMF, ii $CH_3OCH_2CH_2Cl$; iii, L-Selectride; iv, NaH , THF,$PhCH_2COCl$;

vi, LDA vii, $PhCH_2Br$.

SCHEME 91



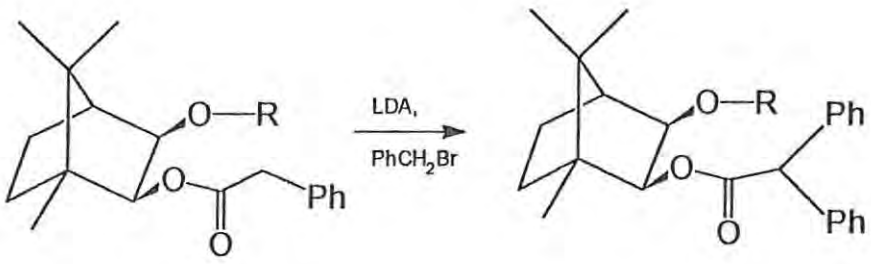
REAGENTS

I , NaH, DMF; ii, $PhCH_2Br$, iii , L Selectride;

iv, NaH, THF v, $PhCH_2COCl$, vi, LDA,THF vii $PhCH_2Br$

It is apparent from the diastereoselectivities observed that neither the methoxyethyl nor the benzyloxy groups are as effective as the acetal groups in aiding stereoselectivity.

TABLE 12 Data for the Preparation and α-Benzylation of the Carboxylate Esters 364 and 366



R	Compound	Yield %	Compound	Yield %[a]	d.e. %[b]
CH_2CH_2OMe	**365**	53	363	58	26%
CH_2Ph	**367**	59	366	62	15

[a]Based on chromatographed material yield
[b]Based on ^1H NMR integral ratio

2.5 EXPLORATORY STUDIES OF THE APPLICATION OF CAMPHOR - DERIVED CHIRAL AUXILIARIES IN THE SYNTHESIS OF CHIRAL α-AMINO ACID DERIVATIVES

The number of known α-amino acids has grown substantially beyond the 20 odd naturally occurring α-amino acids normally found in proteins; in fact, over 500 amino acids are now known[251]. There has been a tremendous surge of interest in the asymmetric synthesis of relatively inaccessible unnatural amino acids, whose potential biological properties and general synthetic utility are just beginning to be realised. Of all the members of the "Chiral Pool", the amino acids are the most versatile. All 19 of the common α-amino acids (glycine excluded) are available commercially in both enantiomeric forms. Moreover, the inherent chirality of these amino acids can be used to induce asymmetry in reactions that would not normally be asymmetrically biased.

Enantiomeric α-amino acids exhibit striking dissimilarities in their properties. For example the amino acid D-penicillamine, a chelating agent used to remove heavy metals from the body, is used as an efficacious antidote for lead or mercury poisoning. In contrast, the L-antipode of penicillamine causes optic atrophy, which can lead to blindness.[252]

The dipeptide ester aspartame is rapidly gaining importance as a low calorie sweetener and is used extensively in soft drinks. Its backbone is composed of two amino acids; L-aspartic acid, which has no taste; and L-phenylalanine, which is bitter. Together they form a molecule with intensely sweet taste characteristics (approximately 160 times sweeter than sucrose). Substitution of the L-phenylalanine portion of the molecule with its antipode D-

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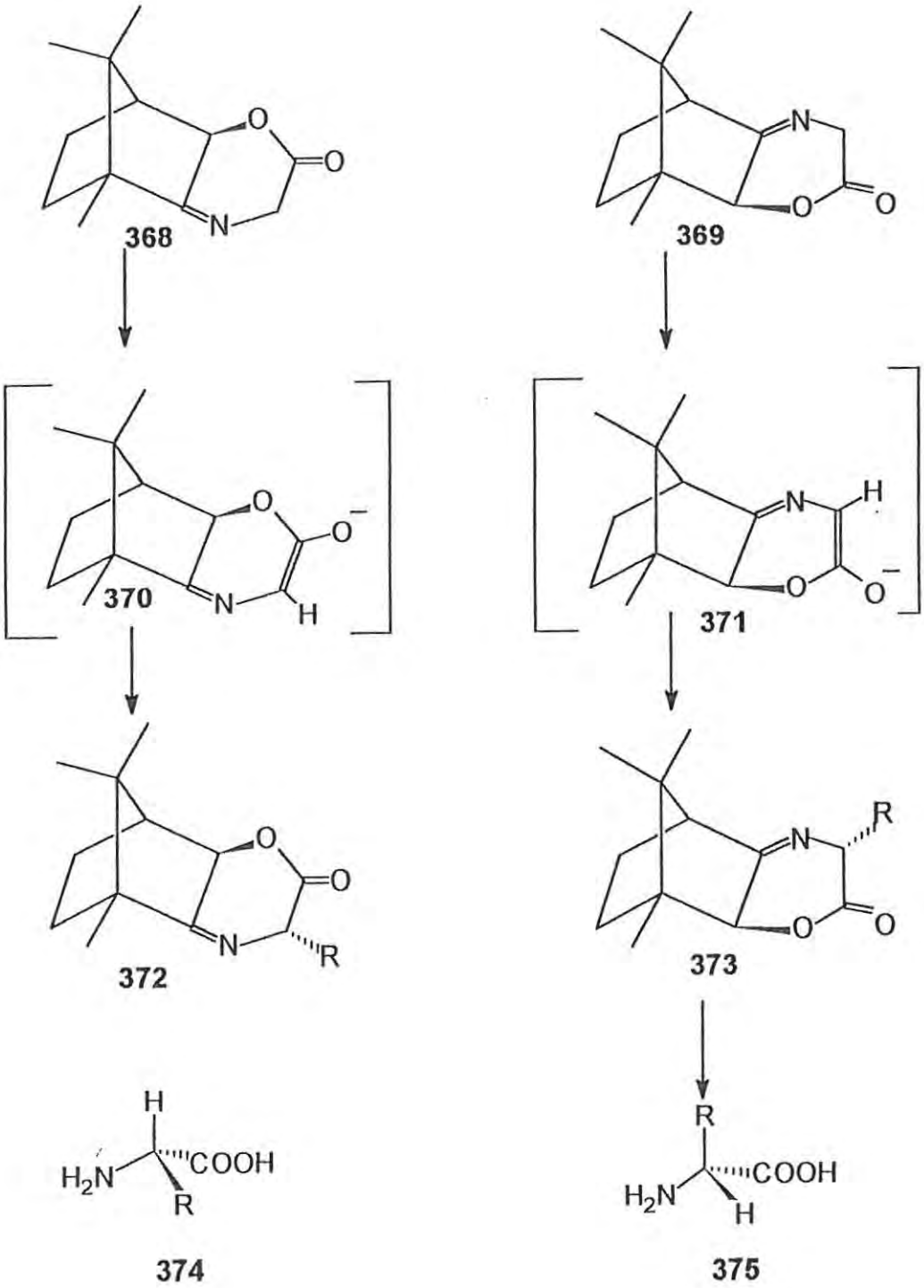
phenyl alanine, which in itself is sweet-tasting, causes the resulting dipeptide to taste bitter.[253] Despite the great variety of well-tried methods, the development of new general and efficient approaches to chiral α-amino acids remains a challenge in synthetic organic chemistry.

A wide range of methods are available for the synthesis of α-amino acids.[254] These include the Strecker synthesis, approaches through hydantoins, amination of α-halo acids and oxazolones, as well as syntheses in which the amino group is introduced by reduction or rearrangement. Many of these methods, which were developed in the early days of amino acid chemistry, still retain their importance but have undergone remarkable developments in the last few years. For example, the most widely used method, which makes use of malonic acid derivatives, has been extended[255] to include enzymatic resolution in the final stage.

Camphor-derived chiral auxiliaries have also found use in the asymmetric synthesis of α-amino acids, and these applications are of particular relevance to the present study. The bornane-10,2-sultam **55** and its antipode **56** rank among the most versatile chiral auxiliaries available and have been employed in the enantioselective synthesis of α-amino acids (see introduction 1.2.4 , page 27). McIntosh *et al.*[256] have carried out asymmetric alkylation, with benzyl halides, on anions derived from the D-camphor imine of *tert*-butyl glycinate and have observed remarkable diastereoselectivity in the alkylated products.

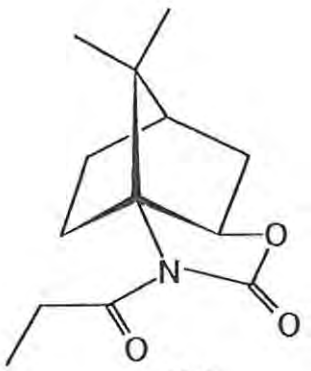
We considered that cyclic derivatives such as **368** and **369** (Scheme 92) would be particularly useful substrates for the asymmetric synthesis of α-amino acids. The corresponding enolates **370** and **371** are expected to be rigid due to the cyclic arrangement

SCHEME 92


O
O
N
368
N
O
O
369
O
O⁻
N
H
370
N
H
O
O⁻
371
O
O
N
R
372
N
R
O
O
373
H
H₂N
COOH
R
374
R
H₂N
COOH
H
375

and, during alkylation, the approach of the electrophile from the *endo* face of the camphor skeleton to the C_α-*Si* face of the enolate **370** would yield the alkylated cyclic derivative **372**, which after removal of the auxiliary would furnish the alkylated α-amino acid **374**. Similarly *endo* approach of the electrophile the the C_α-*Re* face of the enolate **371** would, after work-up, yield the amino acid **375**.

Precedents for our general strategy are provided by the camphor-based oxazolidones **376**,[37] oxazolines **377**,[257] oxazolidinones **378**[258] and oxazinones **379**,[259] all of which have a cyclic group built on to the camphor skeleton and show excellent diastereoselectivity in various asymmetric reactions.



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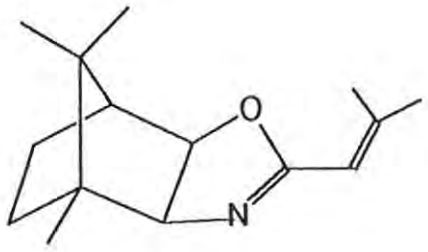
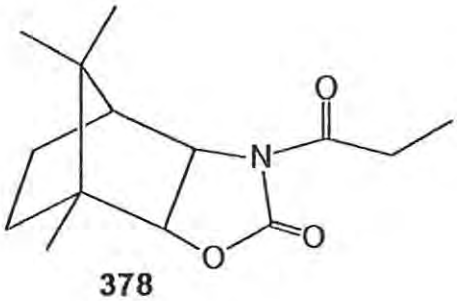
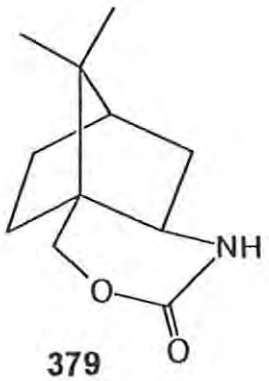


377



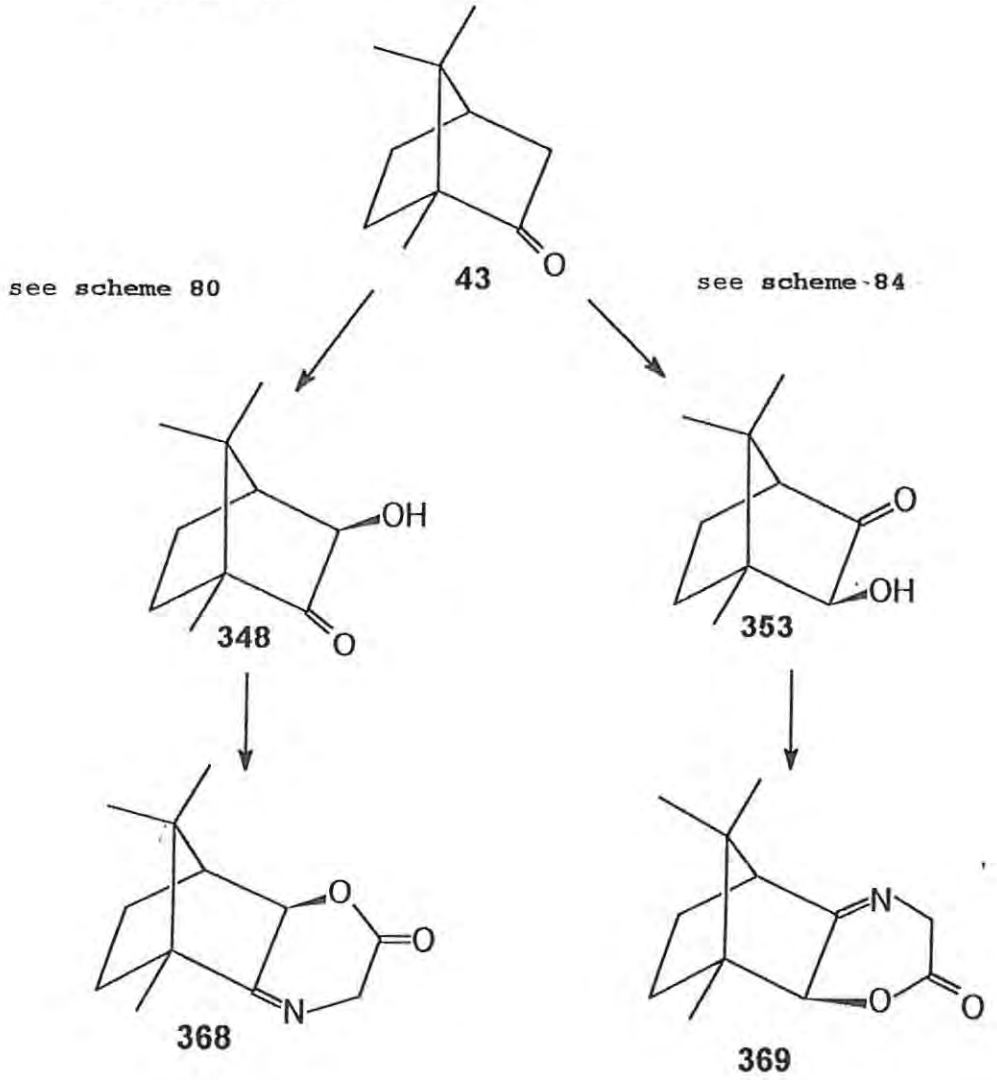
378



379

The camphor ketol **348** has the advantage of possessing two functional groups, the 3-*exo*-hydroxy group, which may be esterified, and the C-2 carbonyl which may be converted to an imine. Thus, an imine lactone could in principle be built on the 2,3- positions of the camphor skeleton. Both regioisomeric ketols **348** and **353** were available by reaction sequences already summarised in schemes 80 and 84 and could, in principle, provide access to the diastereomeric chiral glycine derivatives **368** and **369** (Scheme 93).

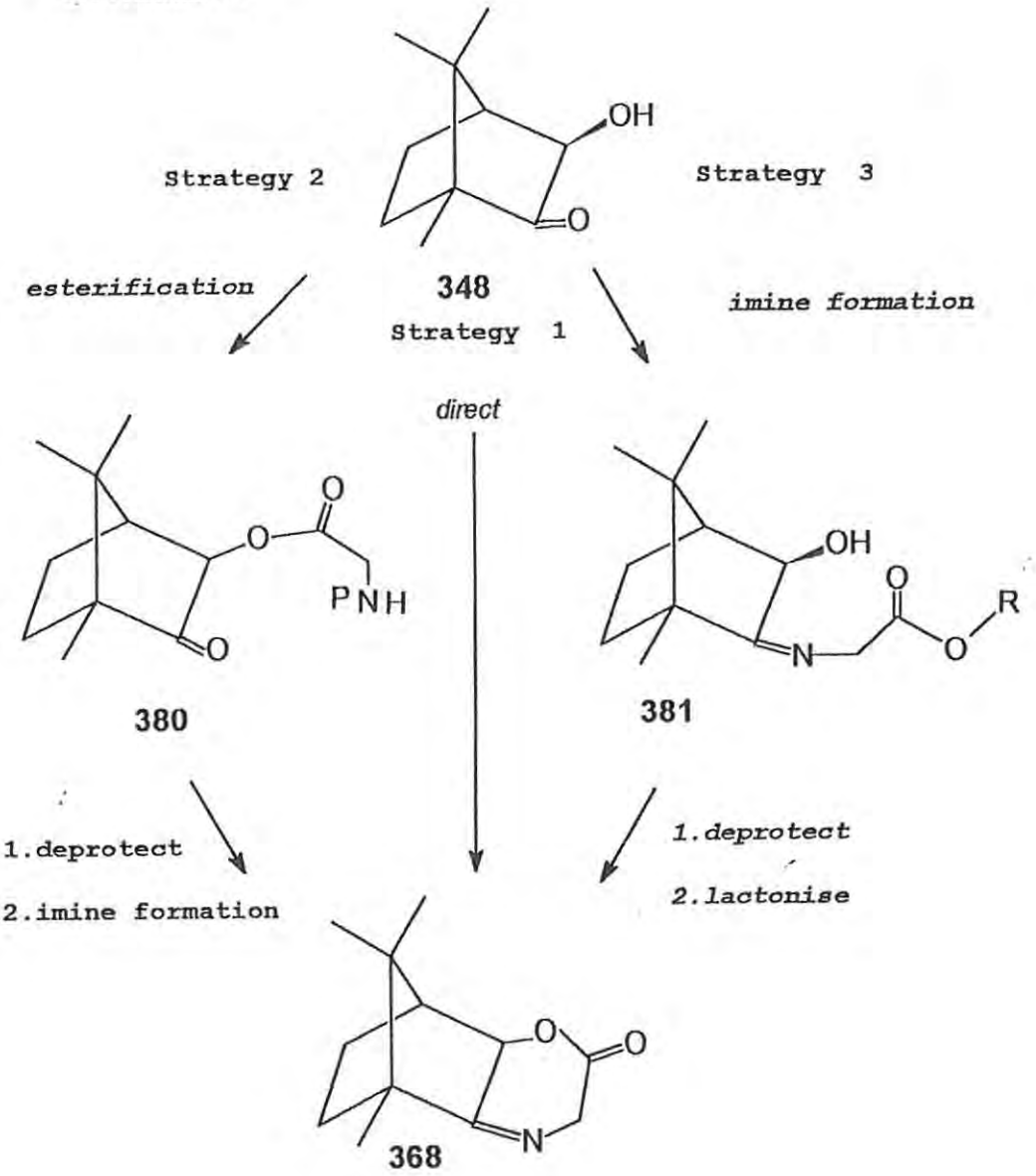
SCHEME 93



Several strategies for the preparation of the chiral substrate **368** were considered (Scheme 94):—

1. Direct cyclisation of the α-ketols **348** (or **353)** with unprotected glycine (Strategy I).
2. Reaction of *N*-protected, acyl-activated glycine to form the intermediate ester **380,** followed by deprotection and imine formation (Strategy II).
3. Initial formation of the acyl-protected imine **381** followed by deprotection and lactonisation (Strategy III).

SCHEME 94



The direct approach (Strategy I), which would involve a simultaneous or one-pot reaction of both the carbonyl and hydroxyl groups in the ketol **348** with the unprotected glycine was attempted first. Thus, a solution of the ketol **348** and glycine in benzene was heated under reflux using a Dean and Stark apparatus. During the course of the reaction, more glycine and PTSA were added. Work-up, followed by flash chromatography, afforded several fractions none of which proved to be the required product. One of the components, a white crystalline solid was shown by ^{1}H NMR spectroscopy to be the dibornyl ether **349** previously isolated from the reaction of PTSA with the α-hydroxyketol **348** (see scheme 81). The reaction was repeated under the various conditions summarised in Table 12.

TABLE 12 Data for attempted preparation of cyclic camphor derivative 368 using Strategy I

Catalyst	Solvent	Time/h	Compound Isolated
PTSA	benzene	12	349
$BF_3.Et_2O$	toluene	6	348
PTSA	xylene	12	349
BF_3Et_2O	xylene	6	348

In order to avoid the undesirable amino acid dimerisation (presumed to be consuming the glycine)[260],

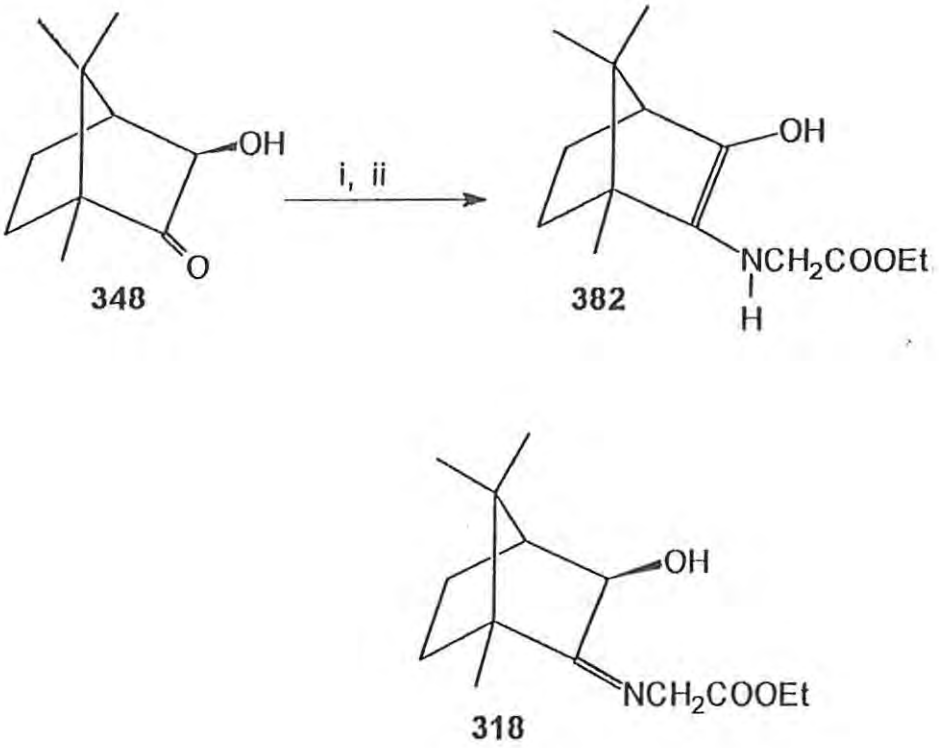
ethyl glycine hydrochloride was prepared by bubbling dry HCl gas into an ethanolic suspensionof glycine. A solution of the ketol **348** in benzene was heated with ethyl glycine hydrochloride and a catalytic amount of PTSA in a Dean and Stark apparatus. The presence of the hydroxycamphor dimer **349** was once again detected by TLC. The reaction was then carried out at an elevated temperature using toluene as the solvent in the absence of PTSA. Usual work-up followed by repeated preparative layer chromatography affording 12% yield the enamine derivative **382** which is tautomeric with the required imine **381** (Scheme 95). IR spectroscopy of this derivative indicated the presence of an OH stretch. In the ^{1}H NMR spectrum (Fig. 24)

i) the diastereotopic CH_2 nuclei resonate as two doublets at 4.5 and 5.0 ppm, indicating linkage to the chiral auxiliary; and

ii) the presence of the ethyl moiety, evidenced by the CH_3CH_2OCO signals, indicates that lactonisation has not taken place.

From the IR and NMR spectroscopic data, the compound was assigned the enamine structure **382**. Unfortunately the yield of this enamine derivative could not be improved even using $BF_3.Et_2O$ as catalyst, or toluene or xylene as solvents. The C-2 carbonyl group in the camphor skeleton is hindered, and although condensation of benzylamine with camphor has been reported,[261] several other groups have commented on the difficulty[262,263] and failure of this very same reaction. A camphor imine has been prepared previously *via* thiocamphor,[256] and it is possible that the use of the thiocarbonyl analogue of the ketol **348** may provide more efficient access to the required imine derivative.

SCHEME 95



REAGENTS

i, Toluene; ii, ethyl glycine hydrochloride

In variations of strategy II (Scheme 96) formation of an imine derivative was attempted by:-

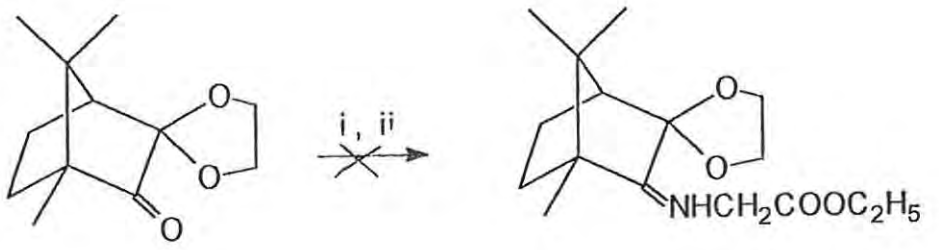
i) heating the readily available *endo*-3-bromocamphor with ethyl glycine hydrochloride in the presence of PTSA or $BF_3.Et_2O$ as catalysts (Scheme 96);

ii) heating *endo*-3-bromocamphor and silver glycinate (prepared by heating glycine with freshly prepared Ag_2O); and

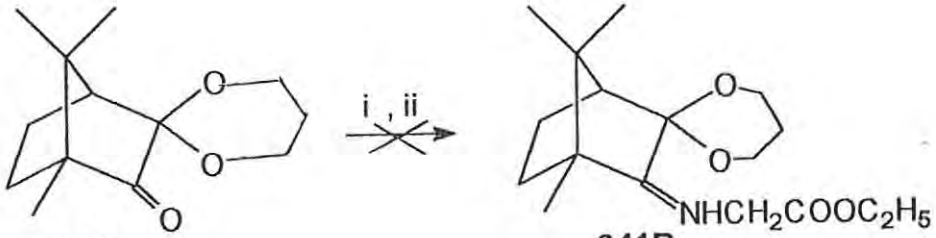
iii) heating the acetals **316** and **341** with ethyl glycine hydrochloride in benzene, with PTSA or $BF_3.Et_20$ as catalysts.

The imine derivatives of the acetals **316** and **341** would have provided additional options for use as acyclic but sterically hindered substrates for subsequent α-alkylation. However these reactions (Scheme 96) proved unsuccessful.

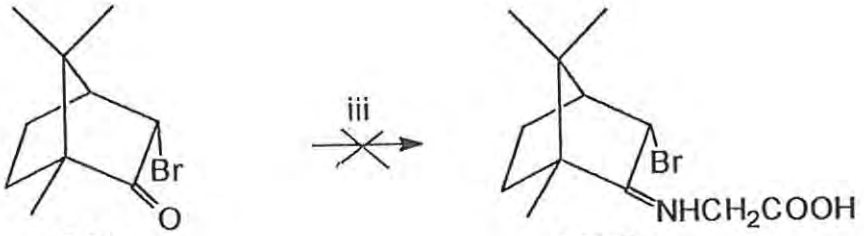
SCHEME 96



314 **314B**



341 **341B**



340 **340 B**

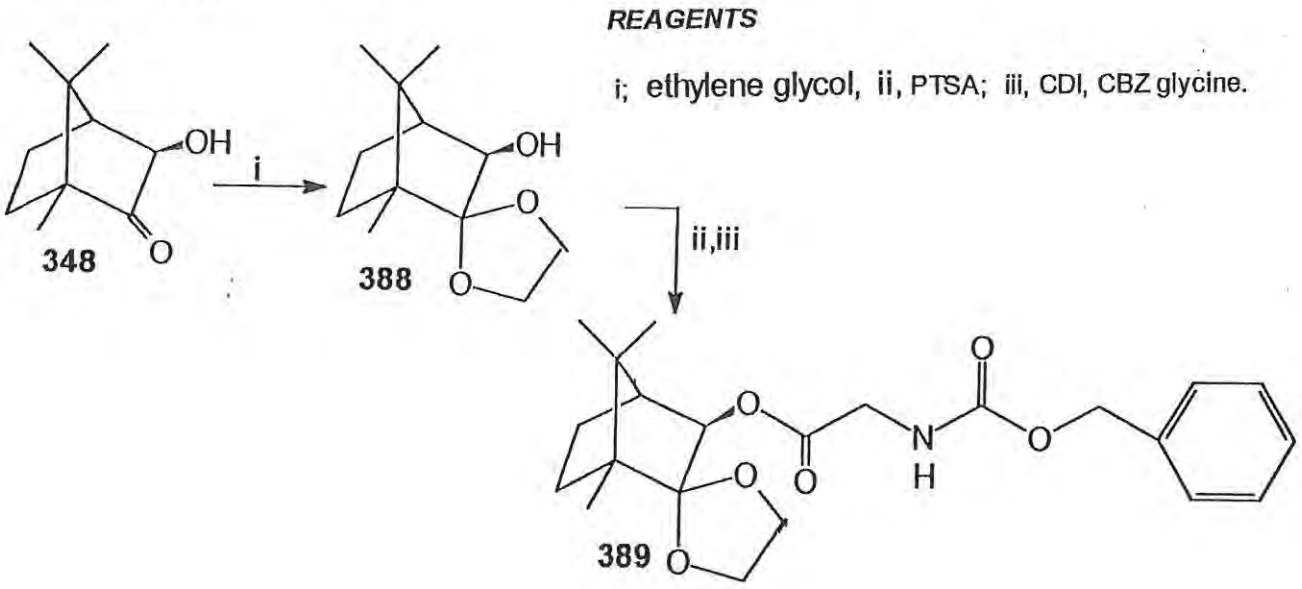
REAGENTS

i, ethyl glycine chydrochloride, ii, PTSA / $BF_3.Et_2O$ iii, silver glycinate.

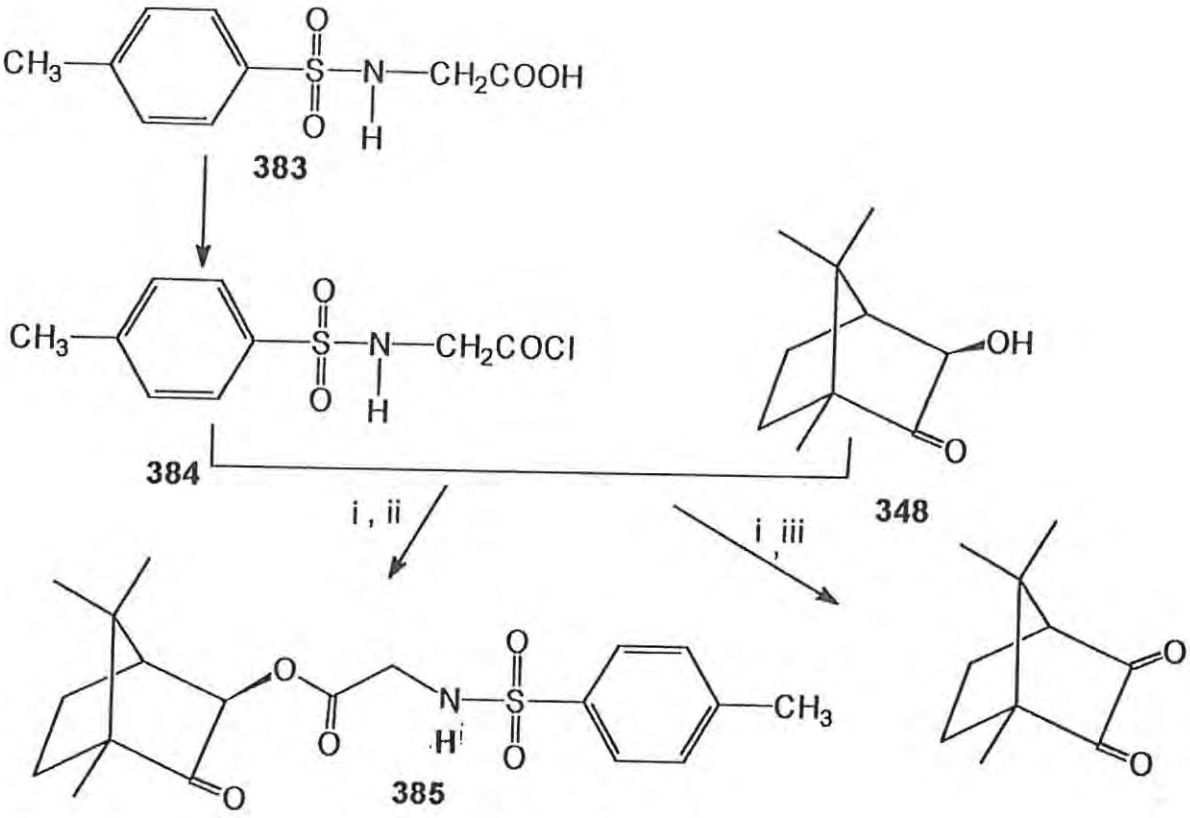
Strategy III, the third approach, *i.e.* initial linking of *N*-protected glycine to the chiral auxiliary *via* an ester bond was then explored. *p*-Toluenesulphonylglycine **383** (prepared from glycine and *p*-toluenesulphonyl chloride) was activated by formation of the acid chloride **384** which, on reaction with the sodium alkoxide of ketol **348** in DMF (Scheme 97), afforded the required *exo*-ester **385** in 20% yield. The presence of the *endo*-ester, as a minor contaminant, was indicated by ^{1}H NMR spectroscopy. When the reaction was conducted in THF, however, camphorquinone **315** was isolated in 32% yield.

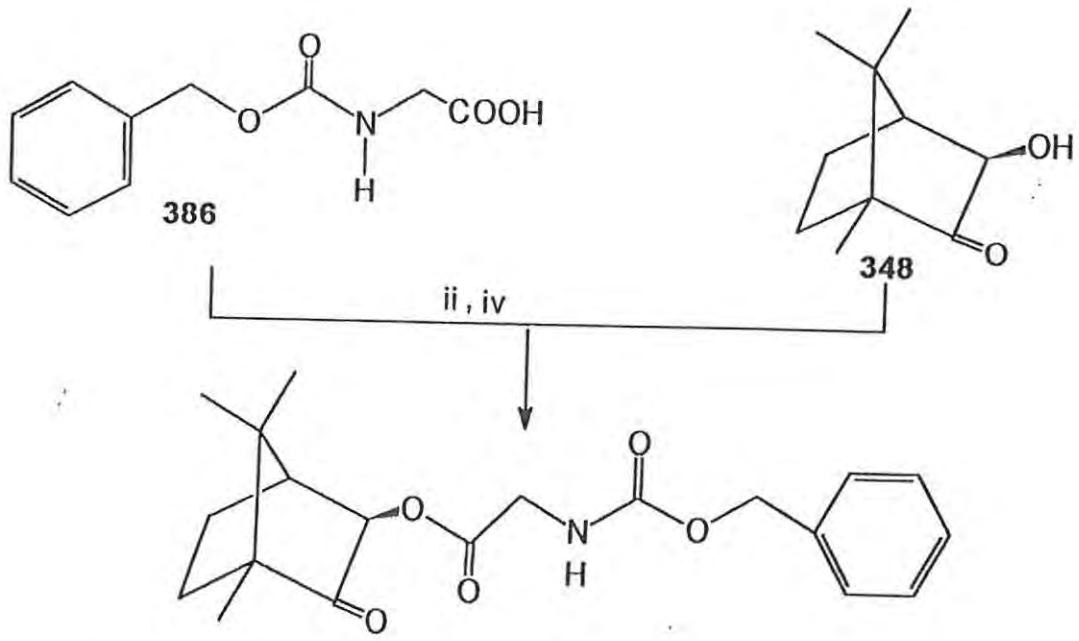
The use of carbonyl diimidazole (CDI) as a coupling agent was then examined. Reaction of *p*-toluenesulphonylglycine **380** and CBZ-glycine **379** with the ketol **348** afforded the corresponding *exo*-esters **385** and **387** in 72% and 78% yield respectively (Scheme 98). In both cases, the products contained the corresponding *endo*-esters as minor contaminants. In a slight variation of the general strategy, CDI was also used to effect coupling of the hydroxy acetal **388** with CBZ glycine (Scheme 98), the intention being to explore the stereo-directing potential of the acetal group in the resulting ester **389**.

SCHEME 98



SCHEME 97

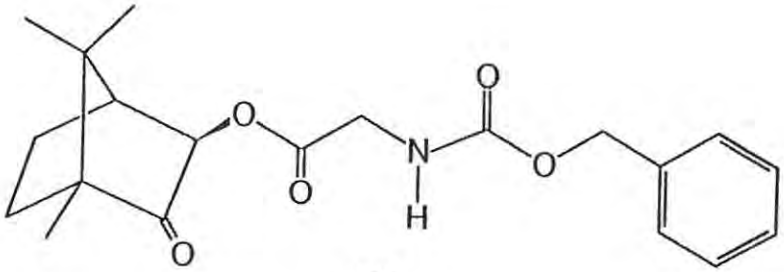




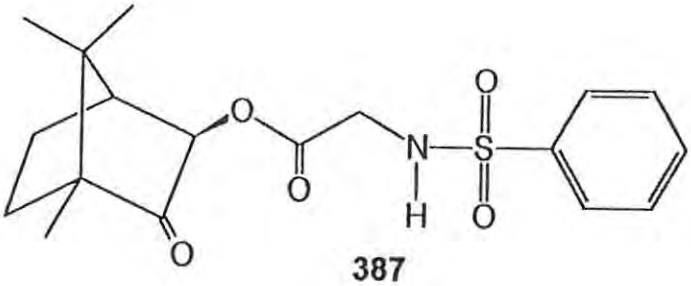
REAGENTS

i NaH, ii ,DMF; iii , THF ; iv ,CDI.

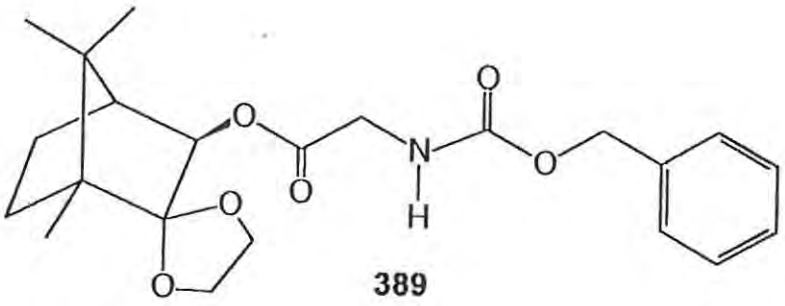
Efficient routes to the chiral glycine ester derivatives **385**, **387** and **389** have thus been established but, due to the lack of time, it was necessary to curtail the research at this stage. The development of efficient methods for the α-alkylation of these chiral glycine derivatives, as well as the selective *N*-deprotection and subsequent cyclisation of the 2-*exo* analogues **385** and **387** will be addressed in a future project.



385



387



389

2.7 CONCLUSION

The present investigation was initially concerned with the asymmetric induction obtained during the $TiCl_4$-catalysed Mukaiyama reactions of various aldehydes with a camphor acetal-derived chiral silyl enol ether. The ß-hydroxy ketone products, however, showed disappointing enantiomeric excess (up to 13%).

The availability of the camphor acetal as a chiral auxilliary prompted us to explore stereodirecting potential in the α-benzylation of a series of carboxylate esters. A range of such camphor-derived carboxylate esters was thus prepared and α-benzylation was observed to proceed with an encouraging increase in the diastereoselectivity, the *tert*-butylacetate derivative showing a diastereoselectivity of 47%. Hydrolytic and reductive cleavage of a benzylated ester furnished the known products, *viz.*, 2,3-diphenylpropanoic acid and 2,3-diphenylpropanol; the optical rotation data for these compounds permitted the configuration at the new chiral centre to be established. These findings were consistent with transition state proposals involving an *endo-s-trans* arrangement of the enolate system.

Computer modelling studies revealed that the steric bulk offered by the ethylenedioxy group is only marginally greater than that of the 10-methyl group, and so attention was given to the preparation of derivatives with bulkier shielding groups. Two such derivatives of the 2,2-propylenedioxy camphor acetal were successfully prepared. The failure of the 3,3-propylenedioxy derivative to exhibit enhanced diastereoselectivity during α-benzylation has been rationalised. α-Benzylation of the *tert*-butylacetal of the 2,2-propylenedioxy derivative, however, occured with 57% d.e. Hydrolysis of the α-phenylacetate analogue yielded the known 2,3-diphenylpropanoic

known 2,3-diphenylpropanoic acid whose optical rotation was consistent with the preferred attack at the *re*-face of the proposed transition state conformation of the enolate moiety.

Although attempts to introduce catechol as a substantial steric blocking group did not meet with success, they did lead to the isolation of two novel dibornyl ethers, the structures of which were established by NMR spectroscopy.

In an exploratory study of the asymmetric synthesis of α-amino acids using camphor-derived chiral auxilliaries, three novel chiral glycine derivatives have been prepared as potential substrates for the asymmetric synthesis of α-amino acids.

Future work is expected to involve:—

(i) the preparation of camphor-derived organosilicon compounds in which the reaction site is closer to the chiral auxilliary;

(ii) the development and α-alkylation of camphor derivatives having efficient blocking groups such as catechol in the 2,2-position; and

(iii) the use of cyclic camphor derivatives in the asymmetric synthesis of α-amino acids.

3. EXPERIMENTAL

3.1 General

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 180 spectrophotometer, as liquid films or KBr discs. NMR spectra were recorded on a Bruker AMX400 spectrometer. The ^1H NMR spectra of silyl enol ether was recorded in CCl_4 without TMS as an internal standard. All other spectra were recorded in $CDCl_3$ with TMS as internal standard, unless otherwise stated. Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer. High resolution mass spectra were obtained by the Cape Technickon Mass Spectrometry Unit, using a Kratos high resolution mass spectrometer. Optical rotations were conducted on a Perkin Elmer 141 polarimeter.

The atom numbering used in quoting the NMR data follows the systematic nomenclature. For all compounds incorporating the camphor group the "dashed" notation (eg. 4′-H_{exo} or 10′-Me) is used for the labelling of protons and carbons in the chiral auxilliary moeities to facilitate comparison of signals for the variety of compounds prepared.

Anhydrous solvents were obtained as follows:

(i) Et_2O, THF, benzene, toluene and hexane were dried by refluxing over sodium wire, in the presence of benzophenone.

(ii) CH_2Cl_2 was refluxed over polymer-supported P_2O_5, fractionally distilled,

and stored over 3Å molecular sieves.

(iii) DMF was refluxed over 4Å molecular sieves, distilled under reduced pressure, and stored over 4Å molecular sieves.

(iv) EtOH and MeOH were refluxed over $Mg(OEt)_2$and $Mg(OMe)_2$ respectively.

(v) Et_3N was dried in the same manner as DMF.

All transfers of the chiral shift reagents $Eu(tfc)_3$ and $Pr(tfc)_3$ were done under an inert atmosphere and all weighings of these reagents were carried out in sealed containers. Inert atmospheres were achieved with spectroscopic grade argon or nitrogen.

Flash chromatography was achieved using Merck silica gel 60 [particle size 0.040-0.063 nm (230-400 mesh)]. Preparative layer chromatography was performed on Merck silica gel PF_{254} plates and thin layer chromatography on Merck silica gel 60 F_{254} pre-coated plates. TLC plates were analysed by inspection under UV light or using iodine vapour.

The computer modelling was conducted on an CW16 microcomputer, using "HYPERCHEM Molecular Modelling Software" supplied by Autodesk Inc.

3.2 Synthetic Procedures

Camphorquinone (**315**). — SeO_2 (50g 0.45mol) was added to a stirred solution of (+)-camphor (40g 0.27mol) in acetic anhydride (40ml) and the resulting suspension was then boiled under reflux for 5h. and left stirring overnight at room temperature. The resultant black selenium powder was removed by filtration and the filtrate was neutralised by 10% aq. NaOH. The yellow precipitate was filtered, washed with water and suction-dried. The semi-dry material was dissolved in petroleum ether (80-100° boiling range) and the residual aqueous layer was separated off. The organic layer was concentrated *in vacuo* until crystallisation began. The solution was then stored overnight at 10°C to facilitate complete crystallisation. Filtration gave bright yellow needles of camphorquinone (**315**) (34g 74%), m.p. 195-196°C (lit.[196] 183-186°C); δ_H (400MHz; $CDCl_3$) 0.90, 1.03 and 1.07 (9H,3xs,8-,9- and 10-Me), 1.56-2.19 (4H,m,5- and 6-CH_2) and 2.59 (1H,d,4-H); υ_{max} (KBr) 1770 and 1750 cm^{-1} (C=O).

3,3-(Ethylenedioxy)-2-bornanone (**316**). — A solution of camphorquinone (**315**) (25.0g, 0.15mol), ethylene glycol (18.8g, 0.303mol) and *p*-toluene sulphonic acid (1.50g) in anhydrous benzene (120ml) was refluxed in a reaction vessel equipped with a Dean and Stark trap. (During this time *ca.* 3ml of H_2O was collected). The reaction mixture was washed with 1M NaOH (100ml) and H_2O (100ml). The organic layer was separated, dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. The residual oil was stored for two days at 10°C to facilitate crystallisation. The solid was filtered

off and recrystallised from hot EtOH to afford transparent needle shaped crystals of 3,3-(ethylenedioxy)-2-bornanone (**316**) (14.60g, 46%), m.p. 86-88°C (lit.[196] 88°C); δ_H (400MHz; $CDCl_3$) 0.86, 0.94 and 0.98 (9H,3xs,8-, 9- and 10-Me), 1.51-1.97 (5H,m,4-H, 5- and 6-CH_2) and 3.89-4.26 (4H,m,OCH_2CH_2O); υ_{max} (KBr) 1740 cm^{-1} (C=O); and *camphorquinone diacetal* **321** (7.4g, 20%), m.p. 120°; δ_H (400 MHz, $CDCl_3$) 1.17, 0.86 and 0.79 (9H,3xs,8-, 9- and 10-Me), 1.30-1.976 (5H,m,4-H, 5- and 6-CH_2) and 3.27-3.94 (4H,complex of multiplets,OCH_2CH_2O); δ_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); *m/z* 254 (M^+, 0.08%).

*3,3-Ethylenedioxy-2-*exo*-hydroxybornane* (**312**). —

Method 1: Reduction using L-Selectride {$LiB[CHCH_3)C_2H_5]_3H$ in hexane as supplied by Aldrich}:

1**M** L-Selectride (12ml, 12mmol) was added to a solution of 3,3-ethylenedioxy-2-bornanone (**316**) (2.00g, 10mmol) in anhydrous THF (50ml) at -78°C under an inert atmosphere. The resulting solution was stirred overnight at room temperature and the reaction was then quenched by the successive addition of H_2O (3ml), EtOH (12ml) and 3**M** NaOH (16ml) to the ice-cooled reaction mixture, followed by the slow addition of 30% H_2O_2 (12ml). Solid K_2CO_3 was added to the two phase mixture until saturation of the aqueous layer occured. The organic layer was separated and the aqueous layer was re-extracted with Et_2O (2x25ml). The combined organic layers

were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with benzene-Et_2O (8:2)] afforded 3,3-ethylenedioxy-2-*exo*-hydroxybornane (**312**) (1.19g, 70%); υ_{max} (liquid film) 3530 cm^{-1} (OH); m/z 212 (M^+, 7.4%), 197 (17), 141 (27) and 127 (100); δ_H (400 MHz, $CDCl_3$) 0.82, 0.89 and 1.08 (9H,3xs,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);[a] δ_C (100MHz; $CDCl_3$) 11.3 (C-10), 20.3 (C-9), 21.1 (C-8), 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).

Method 2: Reduction using superhydride 1**M** [($LiEt_3BH$)in hexane as supplied by Aldrich: 1**M** Superhydride ($LiEt_3BH$) (14ml, 14mmol) was added to a solution of 3,3-(ethylenedioxy)-2-bornanone (**316**) (2.10g, 10mmol) in anhydrous THF (50ml) at -78°C under an inert atmosphere. The resulting solution was stirred overnight at room temperature and quenched by the successive addition of H_2O (4ml), EtOH (12ml) and 3**M** NaOH (16ml) to the ice-cooled reaction mixture followed by the slow addition of 30% H_2O_2 (12ml). The reaction mixture was stirred at room temperature for 1h. Solid Na_2CO_3 was added until the saturation of the aqueous layer was achieved. The organic layer was separated and the aqueous layer was extracted with Et_2O (2x25ml). The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with benzene-

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[a] The doublets at 2.34 and 3.27 ppm are attributed to coupling of the hydroxyl proton bonded to the adjacent carbon. Addition of D_2O to the NMR solution resulted in the complete disappearance of the doublet at 2.37 ppm and collapse of the doublet at 3.27 ppm to a singlet.

Et_2O (7:3)] afforded 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane (**312**) (1.78g, 84%).

Method 3: Reduction using K-selectride 1M $KB[CH_3)C_2H_5]_3H$ in hexane as supplied by Aldrich}:

K-Selectride (7ml, 7mmol) and a solution of 3,3-(ethylenedioxy)-2-bornanone (**316**) (1.00g, 5mmol) in anhydrous THF (50ml) were reacted together as described for the L-selectride reduction of compound **316** [method (1) above]. Flash chromatography of the residue [elution with benzene-Et_2O (8:2)] afforded 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane (**312**) (1.25g, 78%).

Method 4: Reduction using $NaBH_4$:

$NaBH_4$ (0.35g, 10mmol) was added to an ice-cold solution of 3,3-(ethylenedioxy)-2-bornanone **316** (2.00g, 10mmol) in methanol (40ml) and stirred for 2h at 0°C and for 10h at room temperature. The resulting solution was quenched with H_2O (5ml) and evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-ethyl acetate (7:2)] afforded 3,3-(ethylenedioxy)-2-*exo*-hydroxybornanone **312** (1.00g, 61%).

Chlorodimethyl(3,3-dimethylbut-1-en-2-yloxy)-silane (**318**). —

1.5M BuLi (43ml, 65mmol) was added to a solution of diisopropylamine (6.46g, 64mmol) in anhydrous ether (150ml) at -78°C and the resulting solution was stirred at that temperature for 30 min. A solution of pinacolone (6.00g, 60mmol) in Et_2O (30ml) was added and the mixture stirred for a further 1 h at -78°C. Cl_2SiMe_2 (7.74g, 61mmol) was added to thereaction mixture which was then allowed to warm to room

temperature overnight. The inorganic salts were allowed to precipitate and the supernatant was then decanted under an inert atmosphere. The solvent was removed by distillation under an inert atmosphere and vacuum distillation of the residue afforded chlorodimethyl(3,3-dimethylbut-1-en-2-yloxy)silane **318** (5.5g, 48%) b.p. 52-53°C/10 mmHg (lit.[206] 27-30°C/2.1 mmHg); υ_{max} (liquid film) 1625 (C=C) and 1260 cm^{-1} (Si—Me); δ_H (60 MHz, $CDCl_3$) 0.50 (6H,s,2xSiMe) 1.05 (9H,s,Bu^t) and 4.30 (2H,s,vinyl CH_2).

*3,3-(Ethylenedioxy)-2-*exo*-[dimethyl(3,3-dimethylbut-1-en-2-yloxy)siloxy]bornane* (**319**). — A solution of the chiral alcohol (**312**) (2.0g, 9mmol) in anhydrous THF (10ml) was added to a suspension of pre-washed NaH (50% dispersion in oil; 0.54g, 11.3mmol) in anhydrous THF (75ml). The reaction mixture was stirred for 6h at room temperature, boiled under reflux for 1h, and then cooled to room temperature before adding the chlorosilane (**318**) (2.70g, 14mmol). The resulting mixture was stirred overnight at room temperature and then boiled under reflux for 1h. The solvent was evaporated *in vacuo* and cold, saturated aq. $NaHCO_3$ (50ml) was added to the residue. The resulting mixture was extracted with Et_2O (2x50ml) and the combined organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-Et_2O (95:5)] afforded, as an oil, 3,3-*ethylenedioxy-2-*exo*-[dimethyl(3,3-dimethylbut-1-en-2-yloxy)siloxy]bornane* (**319**) (1.89g, 56%); δ_H (400MHz; $CDCl_3$) 0.17 and 0.18 (6H,2xs,2xSiMe), 0.80, 0.82 and 1.14 (9H,3xs,8-,9-, and 10-Me), 1.04 (9H,s,Bu^t), 1.46-1.71 (5H,m,4-H,5-CH_2 and 6-CH_2), 3.60 (1H,s,2-H), 4.12 (2H,d,C=CH_2) and 3.74-4.01 (4H,complex of multiplets,-

OCH_2CH_2O-); δ_C (100MHz; $CDCl_3$) -2.4 and -2.5 (2xSiMe), 11.8, 21.0 and 21.1 (C-8, C-9 and C-10), 20.7 (C-5), 28.0 [$(CH_3)_3C$], 33.7 (C-6), 36.4 (C-7), 47.9 (C-1), 49.9 (C-3′), 52.9 (C-4), 63.4 and 65.0 ($OCHCH_2O$), 86.8 (C-2), 87.1 (C-1′), 115.6 (C-3) and 166.0 (C-2′); υ_{max} (liquid film) 1630 (C=C) and 1255 cm^{-1} [Si-O(C)]; m/z 368 (M^+, 0.6%) and 75 (100%).

1-Hydroxy-4,4-dimethyl-1-phenyl-3-pentanone (**320**). — A solution of the silyl enol ether (**319**) (1.00g, 3.0mmol) in CH_2Cl_2 (10ml) was added to a stirred solution of benzaldehyde (0.30g, 2.9mmol) and $TiCl_4$ (freshly distilled from CaH_2; 0.40ml) in CH_2Cl_2 at -78°C under N_2. The reaction mixture was then stirred for 5h at -65±5°C before being quenched by the addition of 5% aq. $NaHCO_3$ (25ml) at -78°C. After being allowed to warm to room temperature, the resulting mixture was extracted sequentially with CH_2Cl_2 (2x20ml) and Et_2O (2x20ml). The combined organic extracts were dried (anhyd. $MgSO_4$), concentrated *in vacuo* and chromatographed [flash chromatography on silica; elution with benzene-Et_2O (8:2)] to afford 1-hydroxy-4,4-dimethyl-1-phenyl-3-pentanone (**320**) (412mg, 74%); δ_H (400MHz, $CDCl_3$) 1.12 (9H,s,Bu^t), 2.88 (2H,d,CH_2), 3.57 (1H,br s,OH), 5.12 (1H,t,CH), 7.27-7.38 (5H,m,ArH); υ_{max} (liquid film) 3450 (OH) and 1702 cm^{-1} (CO); *m/z* 206 (M^+, 14%) and 107 (100%).

1-Hydroxy-1-(4-methoxyphenyl)-4,4-dimethyl-3-pentanone (**322**). — The silyl enol ether (**319**) (1.00g, 3.0mmol), *p*-methoxybenzaldehyde (0.69g, 5mmol) and HCl-free $TiCl_4$

(0.40ml) in CH_2Cl_2 (20ml) were reacted together following the procedure described for the preparation of compound (**320**). Preparative layer chromatography of the residue [elution with benzene-Et_2O (9:1)] afforded, as an oil, *1-hydroxy-1-(4-methoxyphenyl)-4,4-dimethyl-3-pentanone* (**323**) (56%); υ_{max} (liquid film) 3465 (OH) and 1695 cm^{-1} (CO); δ_H (400MHz; $CDCl_3$) 1.00 (9H,s,Bu^t), 2.73 (2H,m,CH_2), 3.35 (1H,br s,OH), 3.67 (3H,s,OCH_3), 4.95 (1H,t,CH), 6.75 (2H,d,ArH) and 7.26 (2H,d,ArH); δ_C (100MHz; $CDCl_3$) 26.07 [C(CH_3)$_3$], 44.35 [C(CH_3)$_3$], 45.10 (C-2), 50.75 (OMe), 69.45 (C-1) and 127.59, 119.01, 110.72 and 128.59 (Ar-C); *m/z* 236 (M^+, 10%) and 137 (100%) (Found: M^+ 236.1420. $C_{14}H_{20}O_3$ requires: *M*, 236.1412).

1-(4-Chlorophenyl)-1-hydroxy-4,4-dimethyl-3-pentanone (**323**). — The silyl enol ether (**319**) (1.00g, 3.0mmol), *p*-chlorobenzaldehyde (0.57g, 4mmol) and $TiCl_4$ in CH_2Cl_2 (20ml) were reacted together following the procedure described for the preparation of compound (**320**). Flash chromatography of the residue [elution with benzene-EtOAc (9:1)] afforded, as white needles, *1-(4-chlorophenyl)-1-hydroxy-4,4-dimethyl-3-pentanone* (**324**) (420mg, 60%), m.p. 68°C; υ_{max} (KBr) 3460 (OH) and 1695 cm^{-1} (CO); δ_H (400MHz; $CDCl_3$) 1.11 (9H,s,Bu^t), 2.84 (2H,m,CH_2), 3.58 (1H,br s,OH), 5.10 (1H,m,CH) and 7.30 (4H, AB quartet,ArH); δ_C (100MHz; $CDCl_3$) 26.1 [(CH_3)$_3$C], 44.4 (C-4), 45.3 (C-2), 69.5 (C-1), 127.1, 128.6, 133.3 and 141.6 (ArC) and 216.7 (C-3); *m/z* 240 (M^+, 17%) and 141 (100%) (Found: M^+ 240.019; $C_{13}H_{17}O_2{}^{35}Cl$ requires:*M*, 240.0917).

1-Hydroxy-4,4-dimethyl-1-(4-nitrophenyl)-3-pentanone (**324**). — The silyl enol ether (**319**) (1.00g, 3.0mmol), nitrobenzaldehyde (0.60g, 4mmol) and $TiCl_4$ (0.4ml) in CH_2Cl_2

(20ml) were reacted as described for the preparation of compound (**320**). Flash chromatography [elution with benzene-EtOAc (8:2)] followed by preparative layer chromatography [elution with benzene-EtOAc (85:15)] afforded, as white needle-shaped crystals, *1-hydroxy-4,4-dimethyl-1-(4-nitrophenyl)-3-pentanone* (**325**) (58%), m.p. 104°C; δ_H (400MHz; $CDCl_3$) 1.13 (9H,s,Bu^t), 2.85 (2H,m,CH_2), 3.72 (1H,br s,OH), 5.22 (1H,m,CH), 7.55 (2H,d,ArH) and 8.21 (2H,d,ArH); δ_C (100MHz; $CDCl_3$) 26.1 [$(CH_3)_3C$], 44.5 (C-4), 45.1 (C-2), 69.3 (C-1), 123.7, 126.5, 146.0 amd 150.3 (ArC) and 216.3 (C-3); *m/z* 251 (M^+, 7%) and 57 (100%).

Propanoyl chloride (**325a**). — Propanoic acid (11.1g, 0.15mol) was slowly dropped into $SOCl_2$ (18g, 0.15mol) at 60°C. The reaction mixture was refluxed for 1h. and distilled under vacuum to give propanoyl chloride (**325a**) (9.93g, 72%), b.p. 80°C (lit.,[274] 80°C).

Butanoyl chloride (**325b**). — Butyric acid (11.0g, 0.13mol) was slowly added to $SOCl_2$ (14.87g, 0.125mol) at 60°C over a period of 30 min. The reaction mixture was boiled under reflux for 1.5 h. and then distilled. Redistillation of the crude distillate, collected between 70°-110°C, afforded a colourless liquid, butanoyl chloride (**325b**) (11.5g, 86%), b.p. 100-102°C (lit.,[275] 100-101°C/760mmHg).

Phenoxyacetyl chloride (**325c**). — A solution of phenoxyacetic acid (7.8g, 0.051mol) in CH_2Cl_2 (20ml) was heated to 60°C. $SOCl_2$ (7.93g, 0.067mol) was added in a dropwise manner and the resulting solution was boiled under reflux for 2h. Vacuum distillation of the mixture yielded a colourless oil, phenoxyacetyl chloride (**325c**), b.p. 88°C/3mmHg

(lit.,[276] 109°C/9mmHg) (Yield 83%).

3,3-(Ethylenedioxy)-2-exo-*bornyl propanoate* (**326**). — The method described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) was followed, using a solution of the hydroxy acetal (**312**) (1.95g, 8.96mmol) in THF (40ml), NaH (0.56g, 11.65mmol) and propanoyl chloride (1.15g, 12.5mmol). Work up and flash chromatography of the residue [elution with hexane-ethyl acetate (8:2)] yielded, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl propanoate* (**326**) (1.73g, 70%); υ_{max} (liquid film) 1750 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.70, 0.73 and 1.03 (9H,3xs,8′-,9′- and 10′-Me), 1.04 (3H,t,3-Me), 1.2-1.7 (5H,several m,4′-H,5′-CH_2 and 6′-CH_2), 2.24 (2H,q,2-CH_2), 3.7-3.9 (4H,m,OCH_2CH_2O) and 4.28 (1H,s,2′-H); δ_C (100MHz; $CDCl_3$) 9.2 (C-3), 11.2 (C-10′), 20.62 and 20.74 (C-8′ and C-9′), 20.64 (C-5′), 27.8 (C-2), 33.5 (C-6′), 47.8 (C-1′), 49.1 (C-7′), 54.0 (C-4′), 63.5 and 65.7 (OCH_2CH_2O), 85.6 (C-2′), 114.5 (C-3′) and 173.4 (C-1); *m/z* 268 (M^+, 6.7%) and 127 (100) (Found M^+ : 268.1672. $C_{15}H_{24}O_4$ requires: *M*, 268.1674).

3,3-(Ethylenedioxy)-2-exo-*bornyl butanoate* (**327**). — A solution of the hydroxy acetal (**312**) (1.75g, 8.25mmol) in dry THF (10ml) was added to a pre-washed suspension of NaH (0.48g, 9.90mmol) in dry THF (50ml), under dry N_2, and the resulting mixture was stirred for 1h. at room temperature, boiled for 1h. under reflux and then allowed to cool. Butanoyl chloride (**325b**) (1.05g, 9.90mmol) was added in a dropwise manner, the resulting mixture stirred overnight at room temperature and then boiled under reflux for 1.5h. The solvent was evaporated *in vacuo* and the residue was treated with cold, satd.

aq. $NaHCO_3$ (40ml) and then extracted with Et_2O (3x20ml). The combined organic extracts were dried (anhyd. $MgSO_4$), concentrated *in vacuo* and chromatographed [flash chromatography on silica; elution with hexane-EtOAc (9:0.5)] to give, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl butanoate* (327) (1.61g, 70%), υ_{max} (liquid film) 1740 (CO) cm^{-1}; δ_H (400MHz, $CDCl_3$) 0.72, 0.75 and 1.05 (9H,3xs,8′-,9′- and 10′-Me), 0.86 (3H,t,4-Me), 1.2-1.8 (7H,m,4′-H,5′-CH_2,6′-CH_2, and 3′-CH_2), 2.21 (2H,t,2-CH_2), 3.7-3.8 (4H,m,OCH_2CH_2O) and 4.29 (1H,s,2-H); δ_C (100MHz, $CDCl_3$) 11.2 (C-10′), 13.6 (C-4), 18.4 (C-3), 20.6 (C-5′ and C-9′), 20.7 (C-8′), 33.4 (C-6′), 36.4 (C-2), 47.8 (C-1′), 49.0 (C-7′), 54.0 (C-4′), 63.4 amd 65.7 (OCH_2CH_2O), 85.5 (C-2′), 114.4 (C-3′) and 172.5 (C-1); *m/z* 282 (M^+, 8.2%) and 127 (100%) (Found M^+: 282.1813. $C_{16}H_{26}O_4$ requires: *M*, 282.1813).

3,3-(Ethylenedioxy)-2-exo-*bornyl 3-methylbutanoate* (**328**). — The method described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) was followed using a solution of the hydroxy acetal (**312**) (1.6g 7.98mmol) in THF (40ml), NaH (0.46g, 9.57mmol) and 3-methylbutanoyl chloride (1.35g, 11.16mmol). Work up and flash chromatography of the residue [elution with hexane-EtOAc (9:1)] yielded, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl 3-methylbutanoate* (**328**) (1.58g, 69%); υ_{max} (liquid film) 1742 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.75, 0.78 and 1.08 (9H,3xs,8′-, 9′- and 10′-Me), 0.90 and 0.91 (6H,2xs,Me_2CH), 1.3-1.8 (5H,m,4′-H,5′-CH_2 and 6′-CH_2), 2.0-2.1 (1H,m,3-H), 2.1 (2H,d,2-CH_2), 3.7-3.9 (4H,m,OCH_2CH_2O) and 4.33 (1H,s,2-H); δ_C (100MHz; $CDCl_3$) 11.4 (C-10′), 20.6 (C-5′), 20.7 and 20.8 (C-8′ and C-9′), 22.35 and 22.41 [(CH_3)$_2$CH], 25.6 (C-3), 33.5 (C-6′), 43.7 (C-2), 47.9 (C-1′), 49.1 (C-7′)

54.1 (C-4′), 63.6 and 65.7 (OCH_2CH_2O), 85.6 (C-2′), 114.5 (C-3′) and 172.1 (C-1); *m/z* 296 (M^+ 5.3%) and 127 (100%) (Found M^+ : 296.1993. $C_{17}H_{28}O_4$ requires: *M*, 296.1987).

3,3-(Ethylenedioxy)-2-exo-*bornyl 3,3-dimethylbutanoate* (**329**). — The method as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) was followed using a solution of the hydroxy acetal (**312**) (2.0g, 9.4mmol) in THF (50ml), NaH (0.54g, 11.3mmol) and 3,3-dimethyl butanoyl chloride (2.30g, 15.09mmol). Work up and flash chromatography of the residue [elution with hexane-EtOAc (82:18)] afforded, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl 3,3-dimethylbutanoate* (**329**) (2.01g, 69%); υ_{max} (liquid film) 1740 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.81, 0.83 and 1.13 (9H,3xs,8′-,9′- and 10′-Me), 1.03 (9H,s,*t*-Bu), 1.3-2.0 (5H,m,4′-H, 5′-CH_2 and 6′-CH_2), 2.22 (2H,s,2-CH_2), 3.7-3.9 (4H,m,OCH_2CH_2O) and 4.37 (1H,s,2-H); δ_C (100MHz; $CDCl_3$) 11.6 (C-10′), 20.65 (C-9′), 20.69 (C-5′), 20.8 (C-8′), 29.6 [C(CH_3)$_3$], 30.7 (C-2), 33.6 (C-6′), 47.9 (C-1′), 48.2 (C-3), 49.0 (C-7′), 54.2 (C-4′), 63.6 and 65.7 (OCH_2CH_2O), 85.8 (C-2′), 114.5 (C-3′) and 171.5 (C-1); *m/z* 310 (M^+, 8.2%) and 127 (100%) (Found M^+: 310.2163. $C_{18}H_{30}O_4$ requires : *M*, 310.2144).

3,3-(Ethylenedioxy)-2-exo-*bornyl phenylethanoate* (**330**). — The method described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) was followed using a solution of the hydroxy acetal (**312**) (1.75g, 8.25mmol) in THF (50ml), NaH (0.48g, 9.90mmol) and phenyl acetyl chloride (1.78g, 11.56mmol). Work up and flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded, as an oil, *3,3-*

(ethylenedioxy)-2-exo-*bornyl phenylethanoate* (**330**) (1.9g, 70%); υ_{max} (liquid film) 1720 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.64, 0.75 and 1.00 (9H,3xs,8′-,9′- and 10′-Me), 1.2-1.8 (5H,m,4′-H, 5′-CH_2 and 6′-CH_2), 3.55 (2H,s,2-CH_2), 3.4-3.8 (4H,m,OCH_2CH_2O), 4.30 (1H,s,2′-H) and 7.2 (5H,s,ArH); δ_C (100MHz; $CDCl_3$) 11.1 (C-10′), 20.58 (C-9′), 20.62 (C-5′), 20.69 (C-8′), 33.4 (C-6′), 41.8 (C-2), 47.8 (C-1′), 49.2 (C-7′), 54.0 (C-4′), 63.4 and 65.7 (OCH_2CH_2O), 86.2 (C-2′), 114.4 (C-3′), 126.9, 128.3, 129.4 and 134.2 (ArC) and 170.6 (C-1); *m/z* 330 (M^+, 15%) and 127 (100%) (Found M^+: 330.1831. $C_{20}H_{26}O_4$ requires: *M*, 330.1839).

3,3-(Ethylenedioxy)-2-exo-*bornyl phenoxyethanoate* (**331**). — The method as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) was followed using a solution of the hydroxy acetal (**316**) (1.5g, 7.07mmol) in THF (50ml), NaH (0.44g, 9.20mmol) and phenoxyacetyl chloride (1.69g, 9.90mmol). Work up and flash chromatography of the residue [elution with hexane-EtOAc (85:15)] afforded, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl phenoxyethanoate* (**331**) (1.28g, 52%); υ_{max} (liquid film) 1720 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.72, 0.77 and 1.04 (9H,3xs,8′-,9′- and 10′-Me), 1.2-1.8 (5H,m,4′-H, 5′-CH_2 and 6′-CH_2), 3.6-3.9 (4H,m, CH_2CH_2O), 4.38 (1H,s,2′-H) 4.59 (2H,s,2-CH_2) and 6.8-7.2 (5H,2xm,ArH); δ_C (100MHz; $CDCl_3$) 11.3 (C-10′), 20.60, 20.69 and 20.70 (C-5′,C-8′ and C-9′), 33.4 (C-6′), 47.9 (C-1′), 49.1 (C-7′), 54.1 (C-4′), 63.7 (C-2), 65.0 and 65.8 (OCH_2CH_2O), 86.9 (C-2′), 114.7, 121.6, 129.4, 129.6 and 157.8 (ArC) and 168.2 (C-1); *m/z* 346 (M^+, 15%) and 127 (100%) (Found M^+: 346.1770. $C_{20}H_{26}O_5$ requires: *M*, 346.1780).

*Attempted preparation of 3,3-(ethylenedioxy)-2-*exo*-bornyl 3,3-dimethyl-2-phenylbutanoate* (**331a**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**120**) was followed, using 3,3-(ethylenedioxy)-2-*exo*-bornyl phenylethanoate (**117**) (0.50g, 1.51mmol) in THF (20ml), LDA (2.19mmol) and *tert*-butylchloride (0.19g, 1.97mmol). Workup and preparative layer chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded the starting material (**117**) (0.38g).

*Attempted preparation of 3,3-(ethylenedioxy)-2-*exo*-bornyl 3,3-dimethyl-2-benzyloxybutanoate.* — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate was followed, using 3,3-(ethylenedioxy)-2-*exo*-bornyl phenoxyethanoate (1.00g, 2.80mmol), LDA (3.8mmol) and *tert*-butylchloride (0.34g, 3.64mmol). Workup and preparative layer chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded the starting material (**331**).

*3,3-(Ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate* (**332**). —

Method 1:

A solution of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) (0.90g, 3.19mmol) in dry THF (10ml) was added dropwise to a stirred solution of LDA [3.8mmol; generated *in situ* from diisopropylamine and butyllithium in THF (15ml)], under N_2 at *ca.* -78°C. After 1h., benzyl bromide (0.65g, 3.8mmol) was added to the cold solution and stirring continued at *ca.* -78°C for 1.5h. before allowing the mixture to warm to room temperature overnight. After quenching with satd. aq. $NaHCO_3$ (30ml), the resulting mixture was extracted with EtOAc (4x10ml). The combined organic extracts were dried

(anhydr. $MgSO_4$), concentrated *in vacuo* and chromatographed {flash chromatography on silica [elution with hexane-EtOAc (9.5:0.5)] followed by preparative layer chromatography on silica [elution with hexane-EtOAc (9.7:0.3)]} to give, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl 2-benzylbutanoate* (**332**)[b] (75%); υ_{max} (liquid film) 1730 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.54/0.74[c] and 0.75/0.77 and 1.06/1.08 (9H,6xs,8′-, 9′- and 10′-Me), 0.88 (3H,t,4-Me), 1.2-1.8 (7H,m,4′-H, 5′-, 6′- and 3-CH_2), 2.5-3.0 (3H,3xm,2-H and C*H*$_2$Ph), 3.5-3.9 (4H,m,OCH_2CH_2O), 4.23/4.29 (1H,2xs,2′-H), and 7.0-7.2 (5H,m,ArH); δ_C (100MHz; $CDCl_3$) 11.1 (C-10′), 11.6/11.7 (C-4), 20.6, 20.7 and 20.8 (C-5′,C-8′ and C-9′), 25.0/25.1 (C-3), 33.5/33.6 (C-6′), 37.7/38.1 (C-5), 47.90/47.92 (C-1′), 49.1/49.4 (C-2), 54.1/54.2 (C-4), 63.5/63.7 and 65.5/65.7 (OCH_2CH_2O), 85.7/85.9 (C-2′), 114.4/114.4 (C-3′), 126.15/126.16, 128.26/128.29, 128.87/128.97 and 139.5/139.7 (ArC) and 174.5/174.6 (C-1); *m/z* 372 (M^+, 3.4%) and 91 (100%) (Found M^+: 372.2300. $C_{23}H_{32}O_4$ requires: M, 372.2281). The diastereomeric excess (d.e.) (based on the ratio of the 2′-H proton integrals) was determined to be 28%.

Method 2:

A solution of the 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) (0.9g, 3.2mmol) in dry Et_2O (10ml) was added dropwise to a stirred solution of LDA [3.8mmol; generated *in situ* from diisopropylamine and butyl lithium in Et_2O (15ml)] under N_2 at *ca* -78°C. After 30 min., benzyl chloride (0.48g, 3.8mmol) was added neat to the cold solution and

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[b] As a diastereomeric pair.

[c] The two chemical shift values quoted in this format, here and below, refer to corresponding signals for the diastereomeric products (**332**), the combinations, in some cases being necessarily tentative.

stirring continued at *ca* -78°C for 1h., before allowing the mixture to warm to room temperature overnight. To the ice-cold solution, satd. aq. $NaHCO_3$ (10ml) was added and the resulting mixture was extracted with EtOAc (4x10ml). The combined organic extracts were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with benzene-Et_2O (8:2)] afforded the starting material (**327**) (0.320g).

Method 3: Reaction in the presence of (chlorotitanium triisopropoxide)

To a stirred solution of LDA [3.87 mmol; generated *in situ* in Et_2O (20ml)] under N_2 at *ca* -78°C was added a solution of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) (0.8g, 3.22mmol) in Et_2O (20ml). The resulting solution was stirred for 1h. at *ca* -78°C, and $\{[(CH_3)_2CHO]_3TiCl\}$ 1.8ml, 7.74mmol) was then added using a warm syringe to prevent crystallisation of the reactant. The reaction mixture was then allowed to warm to -30°C and stirred for 2h. at that temperature. After re-cooling to -78°C, benzyl bromide (0.66g, 3.87mmol) was added, and the resulting mixture was stirred at -78°C for 3h., before it was allowed to warm to room temperature overnight. The resulting solution was quenched with 10% aq. NaF (5ml) and the aqueous layer was then extracted into EtOAc (4x10ml). The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with hexane-EtOAc (9:1)] afforded the starting material (**327**) (0.35g).

Method 4: Reaction in presence of 4-dimethylaminopyridine

A solution of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) (0.35g, 1.11mmol) in THF (2ml) was added to a solution of LDA [1.48mmol; generated *in situ* in THF (30ml)]

under N_2 at *ca* -78°C, and the resulting solution was stirred for 1h. To this solution 1,3-dimethyltetrahydro-2(1*H*)-pyrimidinone (DMPU) (1ml) was added and the resulting solution was stirred for 2h. at *ca* -78°C. Benzyl bromide (0.32g, 1.88mmol) was then added and the temperature was maintained at *ca* -78°C for a further 3h. before allowing the reaction mixture to warm to room temperature overnight. After quenching with saturated aq. $NaHCO_3$ (10ml), the resulting mixture was extracted with EtOAc (4x10ml). The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Preparative layer chromatography of the residue [elution with hexane-EtOAc (95:5)] yielded, as a colourless oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl 2-benzylbutanoate* (**333**) (86%). The diastereomeric excess was determined to be 6.7%.

Method 5. Reaction in the presence of zinc chloride

The ester (**327**) (1.5g, 5.4mmol) in THF (30ml) was added to dry $ZnCl_2$[d] (2.29g, 16.8mmol) and the resulting mixture was stirred at *ca.* -78°C under N_2 for 2h. LDA [(8.4mmol) generated *in situ* in a separate flask in THF (5ml) at -78°C] was added dropwise using a cannula and stirring was continued for 2h. at -78°C. Benzyl bromide (1.43g, 8.4mmol) was then added and the reaction mixture was stirred at -78°C for a further 4h. before allowing it to warm to room temperature overnight. One half of the solution was quenched with saturated aq. $NaHCO_3$; and the other half of the solution was quenched in the same way after refluxing for a further 2h. The aqueous layers were extracted separately into EtOAc (4x10ml). The organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Preparative layer chromatography of the crude residues

[d] $ZnCl_2$ was introduced into the flask and heated under reduced pressure until it fused. It was then allowed to cool under N_2. This process was repeated three times.

[elution with hexane-EtOAc (9:1)] yielded the starting ester (**327**) in both cases.

3,3-(Ethylenedioxy)-2-exo-*bornyl 2-methyl-3-phenylpropanoate* (**332**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed using a solution of 3,3-(ethylenedioxy)-2-*exo*-bornyl 3-phenylpropanoate **326** (0.70g, 2.40mmol) in THF (25ml), LDA (3.08mmol) and benzyl bromide (0.53g, 3.08mmol). Work-up and preparative layer chromatography of the residue [elution with hexane-EtOAc (95:5)] afforded, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl 2-methyl-3-phenylpropanoate* (**332**) (77%); υ_{max} (liquid film) 1730 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.68/0.79, 0.83/0.84 and 1.15/1.19 (12H,3-, 8′-, 9′- and 10′-Me), 1.25-1.86 (5H,m,4′-H, 5′-CH_2 and 6′-CH_2), 2.6-2.7 (1H,m,2-H), 2.76-2.81 and 3.04-3.13 (2H,2xm,CH_2Ph), 3.6-3.9 (4H,m,OCH_2CH_2O), 4.35/4.38 (1H,2xs,2-H) and 7.1-7.3 (5H,m,Ar-H); δ_C (100MHz; $CDCl_3$) 11.2/11.3 (C-10′), 16.8/17.0 (2-Me), 20.67, 20.69 and 20.8 (C-5′, C-8′ and C-9′), 33.48/33.53 (C-6′), 39.4/39.6 (C-3), 41.6/41.8 (C-2), 47.9 (C-1′), 49.2/49.3 (C-7′), 54.1/54.2 (C-4′), 63.5/63.6 and 65.6/65.8 (OCH_2CH_2O), 85.6/85.7 (C-2′), 114.46/114.51 (C-3′), 126.19/126.21, 128.27/128.30, 128.94/129.02 and 139.4/139.6 (ArC) and 175.0/175.2 (C-1); *m/z* 358 (M^+, 14%) and 127 (100%) (Found M^+: 358.2144. $C_{22}H_{30}O_4$ requires: *M*, 358.2156). The diastereomeric excess was determined to be 16%.

3,3-(Ethylenedioxy)-2-exo-*bornyl 2-benzyl-3-methylbutanoate* (**334**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed, using 3,3-(ethylenedioxy)-2-*exo*-bornyl 3-methylbutanoate (**328**) (0.70g,

in THF (25ml), LDA (3.08mmol) and benzyl bromide (0.53g, 3.08mmol). Work-up and preparative layer chromatography of the residue [elution with hexane-EtOAc (95:5)] afforded, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl 2-benzyl-3-methylbutanoate* (**334**) (55%); υ_{max} (liquid film) 1728 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.36/0.73, 0.71/0.75 and 0.9-1.0 (15H, 8′-, 9′- and 10′-Me and Me_2CH), 1.1-1.8 (5H,m,4′-H, 5′-CH_2 and 6′-CH_2), 1.8-2.0 (1H,m,3-H), 2.4-2.6 (1H,2xm,2-H), 2.7-3.0 (2H,m,CH_2Ph), 3.3-3.9 (4H,m,OCH_2CH_2O), 4.11/4.24 (1H,2xs,2-H) and 7.0-7.2 (5H,m,ArH); δ_C (100MHz; $CDCl_3$) 11.0/11.8 (C-10′), 20.53 (C-5′), 20.02/20.17 and 20.27/20.31 (C-8′ and C-9′), 20.62/20.65 and 20.75/20.78 (Me_2CH), 30.6/30.7 (C-3), 33.5/33.7 and 34.7/35.7 (C-6′ and CH_2Ph), 47.8/47.9 (C-1′), 49.0/49.3 (C-7′), 53.9/54.1 (C-2), 54.2/54.7 (C-4′), 63.4/63.8 and 65.2/65.6 (OCH_2CH_2O), 85.8/86.1 (C-2′), 114.3 (C-3′), 125.96/126.01. 128.16/128.22, 128.8/128.9 and 139.95/140.21 (ArC) and 173.6/174.1 (C-1); *m/z* 386 (M^+, 3%) and 127 (100%) (Found M^+: 386.2457. $C_{23}H_{32}O_4$ requires: *M*, 386.2452). The diastereomeric excess was determined to be 23%.

3,3-(Ethylenedioxy)-2-exo-*bornyl 2-benzyl-3,3-dimethylbutanoate* (**335**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed, using a solution of 3,3-(ethylenedioxy)-2-*exo*-bornyl 3,3-dimethylbutanoate (**329**) (0.70g, 2.25mmol) in THF (30ml), LDA (2.9mmol) and benzyl bromide (0.56g, 3.25mmol). Work-up and preparative layer chromatography of the residue [elution with hexane-EtOAc (97:3)] afforded, as an oil, *3,3-(ethylenedioxy)-2*-exo-*bornyl 2-benzyl-3,3-dimethylbutanoate* (335) (48%); υ_{max} (liquid film) 1733 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.26 and 0.74-1.07 (9H,3xs,8′-, 9′- and 10′-Me), 1.08 (9H,s,Bu^t), 1.1-1.8 (5H,m,4′-H,

5′-CH_2 and 6′-CH_2), 2.52/2.64 (1H,2xdd,2-H), 2.8-3.9 (6H,series of multiplets,3-CH_2 and OCH_2CH_2O), 4.06/4.26 (1H,2xs,2-H) and 7.1-7.3 (5H,m,ArH); δ_C (100MHz; $CDCl_3$) 10.9/12.4 (C-10′), 20.5-20.8 (cluster of 5 peaks, C-5′, C-8′ and C-9′), 28.0/28.2 [$(CH_3)_3C$], 33.5/33.9 (C-6′), 34.0/34.3 (CH_2Ph), 47.8/47.9 (C-1′), 48.9 (C-7′), 49.5 (C-3), 54.1/54.3 (C-4′), 57.6/58.8 (C-2), 63.5/63.9 and 65.2/65.5 (OCH_2CH_2O), 86.3/86.4 (C-2′), 114.4 (C-3′), 126.0, 128.2, 128.9 and 140.3 (ArC) and 173.8 (C-1); *m/z* 400 (M^+, 11%) and 127 (100%) (Found M^+: 400.2621. $C_{25}H_{36}O_4$ requires: *M*, 400.2613). The diastereomeric excess was determined to be 47%.

*3,3-(Ethylenedioxy)-2-*exo*-bornyl 2,3-diphenylpropanoate* (**336**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed, using 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-phenylethanoate (**330**) (0.70g, 2.12mmol) in THF (25ml), LDA (2.91mmol) and benzyl bromide (0.15g, 2.97mmol). Workup and preparative layer chromatography of the residue [elution with hexane-EtOAc (95:5)] afforded, as an oil, *3,3-(ethylenedioxy)-2-*exo*-bornyl 2,3-diphenylpropanoate* (**336**) (80%); υ_{max} (liquid film) 1732 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.39/0.46, 0.72/0.73 and 1.02/1.05 (9H,6xs,8′-, 9′- and 10′-Me), 1.02/1.05 (3H,2xs,10′-Me), 1.18-1.73 (5H,m,4′-H, 5′-CH_2 and 6′-CH_2), 2.9-3.1 (2H,m,3-CH_2), 3.3-3.7 (4H,m,OCH_2CH_2O), 3.8-3.9 (1H,m,2-H), 4.26/4.30 (1H,2xs,2′-H) and 7.0-7.4 (10H,m,ArH); δ_C (100MHz; $CDCl_3$) 10.7/10.9 (C-10′), 20.50/20.55, 20.64/20.66 and 20.74/20.76 (C-5′, C-8′ and C-9′), 33.38/33.44 (C-6′), 38.79/38.82 (C-2), 47.8 (C-1′), 49.2/49.6 (C-7′), 53.77/53.83 and 53.97/54.03 (C-3 and C-4′), 63.25/63.34 and 65.31/65.36 (OCH_2CH_2O), 85.7/86.0 (C-2′), 114.35/114.37 (C-3′), 126.22/126.28, 127.29,

128.0/128.1, 128.2/128.3, 128.4/128.5, 128.8/129.0, 138.6/138.8 and 139.2/139.4 (ArC) and 172.3/172.6 (C-1); *m/z* 420 (Found: M^+: 420.2300. $C_{27}H_{33}O_4$ requires: *M*, 420.2265). The diastereomeric excess was determined to be 38%.

Reductive cleavage of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2,3-diphenylpropanoate 337; preparation of 2,3-diphenyl-1-propanol

2,3-Diphenyl 1-propanol (**338**). —

Method 1: Using lithium aluminium hydride

A solution of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2,3-diphenylpropanoate (**337**) (0.97g, 2.3mmol) was added to a suspension of LAH (0.27g, 7.14mmol) in THF (50ml), and the resulting solution was refluxed for 8h. and then stirred at room temperature overnight. To quench the reaction, H_2O (5ml) and 10% NaOH (5ml) were successively added and the THF was evaporated *in vacuo*. The residue was gently refluxed for 1h. in EtOAc (40ml), filtered and the filtrate was dried (anhydr. $MgSO_4$) and evaporated *in vacuo*. Preparative layer chromatography of the residue [elution with hexane-EtOAc (7:3)] afforded, as an oil, 2,3-diphenyl propanol (**338**) (27%), υ_{max} (dilute solution of $CDCl_3$) 3540 cm^{-1} (O-H); δ_H (400MHz; $CDCl_3$) 1.45 (1H,br s,OH), 2.81-2.89 (1H,m,2-H), 2.93-3.66 (2H,m,3-CH_2), 3.72 (2H,d,1-CH_2) and 7.00-7.25 (10H,m,ArH); δ_C (100MHz; $CDCl_3$) 38.7 (C-1), 50.2 (C-2), 66.4 (C-3), 126.0, 126.9, 128.1, 128.3, 128.6, 129.1, 139.9 and 141.9 (ArC).

Method 2: Using lithium triethylborohydride

Lithium triethylborohydride (2.5ml; 2.5mmol) was added to a solution of

3,3-(ethylenedioxy)-2-*exo*-bornyl 2,3-diphenylpropanoate **337** (0.97g, 2.3mmol) in anhydrous THF (50 ml) at -78°C under an inert atmosphere. The reaction mixture was stirred at -78°C for 3h. and allowed to warm to room temperature overnight. The reaction was quenched by successive addition of H_2O (2ml), 3M NaOH (10ml) and, dropwise to the ice-cooled solution, 30% H_2O_2 (10ml). Solid, anhydrous K_2CO_3 was added to the two-phase mixture until saturation was achieved. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x10ml) and EtOAc (2x25ml). The combined organic extracts were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Preparative layer chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded, as an oil, 2,3-diphenyl propanol (**338**) (57%).

Hydrolysis of 3,3-(ethylenedioxy)-2-*exo*-bornyl-2,3-diphenyl propanoate 337; preparation of 2,3-diphenyl propanoic acid

2,3-diphenylpropanoic acid (**337**). — To a solution of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2,3-diphenylpropanoate (0.23g, 0.056mmol) in EtOH (10ml) was added a solution of 1M NaOH (5ml) and the reaction mixture was gently refluxed for 2 days. The solvent was evaporated *in vacuo* and water (10ml) was added to the residue, followed by dropwise addition of dil. HCl, just enough to neutralise the resulting solution, which was then extracted with EtOAc (5x10ml). The combined organic extracts were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Preparative layer chromatography on silica [elution with hexane-EtOAc (8:2)] gave, as a white solid, 2,3-diphenylpropanoic acid **337** (70%), m.p. 81°C (Lit.,[243] 83-89°C); υ_{max} 3400-2600 (br band O-H), 1705 (C=O), 1220 (C-O); δ_H (400MHz; $CDCl_3$) 2.93-2.98 and 3.30-3.35 (2H,2xm,3-CH_2), 3.78 (1H,t,2-H), 7.012-

7.22 (10H,m,ArH) and 9.22 (1H,br s,OH); δ_C (100MHz; $CDCl_3$) 39.3 (C-3), 53.4 (C-2), 126.4, 127.6, 128.1, 128.3, 128.7, 128.9, 137.9, 138.7 (ArC) and 179.2 (C-1).

3-exo-*(1-methoxyethoxy)-2-bornanone* (**363**). — A solution of 3-*exo*-hydroxy-2-bornanone (**348**) (4.0g, 29mmol) in dry DMF (10ml) was added to a suspension of pre-washed NaH (0.69g, 29mmol) in dry DMF (55ml) and the resulting mixture was stirred for 1h. at room temperature. A solution of 1-chloro-2-methoxyethane (**362**) (2.69g, 29mmol) in dry DMF (10ml) was added to the resulting slurry. The reaction mixture was then stirred at room temperature for 3h. and subsequently refluxed for 2h. The DMF was evaporated *in vacuo*, H_2O (30ml) was added to the residue and the mixture was extracted into EtOAc (4x20ml). The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Repeated flash chromatography of the multi-component system [elution with hexane-EtOAc (95:5)] afforded, as an oil, 3-*exo*-(1-methoxyethoxy)-2-bornanone (**363**) (2.10g, 40%), υ_{max} (liquid film) 1745 cm^{-1} (CO); δ_H (400MHz; $CDCl_3$) 0.75, 0.80 and 0.89 (9H,3xs,8-, 9- and 10-Me), 1.28-1.82 (4H,m,5- and 6-CH_2), 2.20 (1H,t,4-H), 3.27 (3H,s,OMe) and 3.29-3.82 (5H,m,3-H and 2 x OCH_2); δ_C (100MHz; $CDCl_3$) 9.31, 18.91 and 19.75 (C-8,C-9, and C-10), 18.38 (C-5), 31.77 (C-6), 42.78 (C-7), 47.06 (C-4), 58.36 (C-1), 59.05 (OMe), 69.89 and 71.93 (2 x OCH_2), 81.50 (C-3) and 217.70 (C-2); *m/z* 226 (M^+, 14%) (Found M^+: 226.1569. $C_{13}H_{22}O_3$ requires *M*, ***).

2-Exo-*hydroxy-3*-exo-*(1-methoxyethoxy)bornane* (**313**). — *L*-Selectride (1M solution, 10ml, 10mmol) was added to a solution of 3-*exo*-(1-methoxyethoxy)-2-bornanone (**128**) (3.00g, 13.3mmol) in anhydrous THF (50ml) at -78°C under an inert atmosphere. The

resultant solution was stirred overnight at room temperature and the reaction was then quenched by the successive addition of H_2O (3ml), EtOH (15ml) and 3**M** NaOH (20ml) to the ice-cooled reaction mixture, followed by the slow addition of 30% H_2O_2 (20ml). Solid K_2CO_3 was added to the two-phase mixture until saturation of the aqueous layer occured. The organic layer was separated and the aqueous layer was re-extracted with EtOAc (4x15ml). The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with benzene-Et_2O (95:5)] afforded 2-*exo*-hydroxy-3-*exo*-(1-methoxyethoxy)-bornane (**313**) (1.83g, 61%); υ_{max} (liquid film) 3490 cm^{-1} (OH); δ_H (400MHz; $CDCl_3$) 0.86 and 0.90 (9H,2xs,8-,9- and 10-Me), 1.05-1.81 (4H,m,5- and 6-CH_2), 1.89 (1H,t,4-H), 2.97 (1H,br s,OH), 3.38 (3H,s,OMe), 3.54-3.66 (4H,m,OCH_2CH_2O), 3.80 (1H,dd,2-H) and 3.86 (1H,dq,3-H); δ_C (100MHz; $CDCl_3$) 14.92, 18.08 and 19.82 (C-8, C-9 and C-10), 18.29 (C-5), 25.39 (C-6), 44.42 (C-7), 48.48 (C-4), 49.57 (C-1), 58.79 (OMe), 69.31 and 71.68 (OCH_2CH_2O), 73.47 (C-2) and 76.37 (C-3); *m/z* 228 (M^+ 0.28%) (Found M^+: 228.1712. $C_{13}H_{24}O_3$ requires: *M*, 228.1725).

3-Exo-*(2-methoxyethoxy)-2*-exo-*bornyl phenylethanoate* (**364**). — The method described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) was followed, using a solution of 2-*exo*-hydroxy-3-*exo*-(1-methoxyethoxy)-bornane (**313**) (1.5g, 6.5mmol) in THF (40ml), NaH (0.38g, 7.89mmol) and phenylacetyl chloride (1.32g, 8.5mmol). Work-up and repeated flash chromatography [elution with hexane-EtOAc (9:1)] afforded, as an oil, *3*-exo-*(2-methoxyethoxy)-2*-exo-*bornyl phenylethanoate* (**364**) (1.05g, 53%); υ_{max} (liquid film) 1735 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.68 and 0.82 (9H,2xs,8-, 9- and 10-

Me), 1.10-1.80 (4H,m,5- and 6-CH_2), 1.84 (1H,t,4-H), 3.25 (3H,s,OMe), 3.33-3.38 (4H,m,OCH_2CH_2O), 3.61 (2H,d,CH_2Ph), 3.82 (1H,dq,4-H) and 4.71 (1H,dq,2-H); δ_C (100MHz; $CDCl_3$) 13.9 (C-10), 18.2 (C-5), 18.5 (C-9), 19.6 (C-8), 26.8 (C-6), 41.4 (CH_2Ph), 44.6 (C-7), 48.3 (C-4), 48.5 (C-1), 59.9 (OMe), 69.5 and 71.9 (OCH_2CH_2O), 75.5 (C-2), 76.7 (C-3), 126.8, 128.3, 129.5 and 134.5 (Ar-C) and 171.8 (C=O); *m/z* 346 (M^+, 0.6%) (Found M^+: 346.2158. $C_{21}H_{30}O_4$ requires *M*, 346.2144).

3-Exo-*(2-methoxyethoxy)-2*-exo-*bornyl 1,3-diphenylpropanoate* (**365**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed using 3-*exo*-(2-methoxyethoxy)-2-*exo*-bornyl phenylethanoate (**364**) (0.40g, 1.3mmol) in THF (25ml), LDA (1.6mmol) and benzyl bromide (0.28g, 1.6mmol). Work-up and preparative layer chromatography of the residue [elution with hexane-EtOAc (95:5)] afforded, as an oil, *3*-exo-*(2-methoxyethoxy)-2*-exo-*bornyl-1,3-diphenylpropanoate* (**365**) (59%); υ_{max} (liquid film) 1728 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.54, 0.56, 0.85 and 0.86 (9H,3xs,8′-, 9′- and 10′-Me), 1.10-1.81 (4H,m,5′- and 6′-CH_2), 1.85-1.89 (1H,m,4′-H), 3.05-3.51 (9H,complex set of multiplets,3-CH_2, OCH_3, and OCH_2CH_2O), 3.81-3.89 (1H,2xdq,3′-H), 3.90-3.92 (1H,m,2-H), and 4.71-4.69 (1H,dq,2′-H); δ_C (100MHz; $CDCl_3$) 13.60 (C-10′), 18.15/18.20 (C-5′), 18.54 (C-9′), 19.55/19.60 (C-8′), 39.28/40.02 (C-3), 44.44 (C-7′), 48.53/48.56 (C-1′), 48.70/48.65 (C-4′), 53.86/53.56 (C-2), 58.78/58.90 (OMe), 69.20/69.35 and 71.62/71.83 (OCH_2CH_2O), 75.40/75.99 (C-2′), 76.44/76.55 (C-3′), 126.13, 126.22, 127.05, 127.07, 128.16, 128.22, 128.25, 128.28, 128.32, 128.36, 128.93, 129.05, 138.83, 139.10, 139.20 and 139.39 (Ar-C) and 173.44/173.52 (C-1); *m/z* 436 (M^+, 0.17%) (Found M^+: 436.2620.

$C_{28}H_{36}O_4$ requires *M*, 436.2613). The diastereomeric excess was determined to be 28%.

3-Exo-*(benzyloxy)-2-bornanone* (**365**). — A solution of 3-*exo*-hydroxy-2-bornanone (**348**) (3.07g, 18.5mmol) in dry DMF (10ml) was added to a suspension of pre-washed NaH (0.74g, 24mmol) in dry DMF (30ml) and the resulting mixture was stirred at room temperature for 2h. A solution of benzyl bromide (3.42g, 20mmol) in dry DMF (10ml) was added to the resultant slurry. The reaction mixture was then stirred overnight at room temperature. DMF was evaporated *in vacuo*, H_2O (30ml) was added to the residue and the mixture was extracted with EtOAc (4x10ml). The combined organic extracts were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Repeated flash chromatography of the residue [elution with benzene-Et_2O (90:10)] afforded, as an oil, 3-*exo*-(benzyloxy)-2-bornanone (**365**) (2.13g, 45%) υ_{max} (liquid film) 1750 cm^{-1} (C=O); δ_H (400MHz; $CDCl_3$) 0.80, 0.90 and 0.96 (9H,3xs,8-, 9- and 10-Me), 1.43-1.95 (4H,m,5-CH_2 and 6-CH_2), 2.22 (1H,t,4-H), 3.92 (1H,d,3-H), 4.69 (2H,dd,CH_2Ph) and 7.23-7.36 (5H,m,ArH); δ_C (100MHz; $CDCl_3$) 9.14, 18.67 and 19.49 (C-8, C-9 and C-10), 18.31 (C-5), 31.52 (C-6), 42.55 (C-7), 46.87 (C-4), 57.99 (C-1), 71.90 (*C*H_2Ph), 79.96 (C-3), 127.30, 127.34, 127.42, 127.95, 127.99, 128.02 and 137.64 (ArC) and 217.5 (C=O); *m/z* 258 (M^+, 0.3%) (Found: M^+ 258.1607. $C_{17}H_{22}O_2$ requires *M*, 258.1620).

3-Exo-*benzyloxy-2*-exo-*hydroxybornane* (**314**). — 1M *L*-Selectride (8.25g, 8.5mmol) was added to a solution of 3-*exo*-(benzyloxy)-2-bornanone (**365**) (1.70g, 6.5mmol) in THF (40ml) at -78°C under an inert atmosphere. The resulting solution was stirred overnight at room temperature and the reaction was then quenched by the successive addition of H_2O

(5ml), EtOH (20ml) and 3M NaOH (25ml) to the ice-cooled mixture, followed by the slow addition of 30% H_2O_2 (20ml). Solid K_2CO_3 was added to the two phase mixture until saturation of the aqueous layer occured. The organic layer was separated and the aqueous layer was re-extracted with EtOAc (4x10ml). The combined organic layers were dried (anhyd. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (95:5)] afforded, as an oil, 3-*exo*-benzyloxy-2-*exo*-hydroxybornane (**314**) (1.34g, 40%), υ_{max} (liquid film) 3550 cm^{-1} (OH); δ_H (400MHz; $CDCl_3$) 0.82, 0.86 and 0.88 (8-, 9- and 10-Me), 1.11-1.82 (4H,m,5- and 6-CH_2), 1.89 (1H,t,4-H), 2.79 (1H,br s,OH), 3.80 (1H,dd,2-H), 3.92 (1H,qd,3-H), 4.46 (2H,dd,CH_2Ph) and 7.24-7.32 (5H,m,ArH); δ_C (100MHz; $CDCl_3$) 13.85, 18.02 and 19.88 (C-8,C-9 and C-10), 18.24 (C-5), 25.37 (C-6), 44.14 (C-7), 48.08 (C-4), 49.21 (C-1), 71.58 (*C*H_2Ph), 73.48 (C-2), 75.01 (C-3) and 127.34, 127.42, 127.46 and 128.15 (ArH); *m/z* 260 (M^+, 1.93%).

3-Exo-*(benzyloxy)-2*-exo-*bornyl phenylethanoate* (**366**). — The method as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl butanoate (**327**) was followed, using a solution of 3-*exo*-(benzyloxy)-2-*exo*-hydroxybornane (**314**) (1.5g, 5.8mmol) in THF (40ml), NaH (0.35g, 7.5mmol) and phenylacetyl chloride (1.5g, 9.7mmol). Work-up and repeated flash chromatography of the multi-component system [elution with hexane-EtOAc (8:2)] afforded, as an oil, *3*-exo-*(benzyloxy)-2*-exo-*bornyl phenylethanoate* (**366**) (32%); υ_{max} (liquid film) 1735 cm^{-1} (CO); δ_H (400MHz; $CDCl_3$) 0.69, 0.82 and 0.83 (9H,3xs,8′-, 9′- and 10′-Me), 1.19-1.81 (4H,m,5′-, 6′-CH_2), 1.84 (1H,t,4′-H), 3.54 (2H,d,CH_2Ph), 3.93-3.97 (1H,m,3′-H), 4.25 (2H,q,2-CH_2) and 4.75 (1H,dd,2-H); δ_C (100MHz; $CDCl_3$) 13.90 (C-10′), 18.33 (C-5′), 18.56 (C-9′), 19.67 (C-8′), 26.77 (C-

6′), 41.36 (C-2), 45.68 (C-7′), 48.34 (C-1′), 48.44 (C-4′), 71.87 (*C*H$_2$Ph), 74.91 (C-3′), 77.01 (C-2′), 126.75, 127.27, 127.38, 128.17, 128.27, 129.45, 134.37 and 138.88 (ArC) and 171.91 (C-1); *m/z* 378 (M$^+$, 0.4%(and 91 (100%) (Found M$^+$: 378.2180. $C_{25}H_{36}O_4$ requires *M*, 378.2195).

3-Exo-*(benzyloxy)-2*-exo-*bornyl 2,3-diphenylethanoate* (**366**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate **33** was followed, using 3-*exo*-(benzyloxy)-2-*exo*-bornyl phenylethanoate **366** (0.378g, 9mmol) in THF (20ml), LDA (9mmol) and benzyl bromide (1.5g, 9mmol). Work-up and preparative layer chromatography of the residue [elution with hexane-EtOAc (85:15)] afforded as an oil 3-*exo*-(benzyloxy)-2-*exo*-bornyl 2,3-diphenylethanoate **366** (85%); υ_{max} (liquid film) 1730 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.68, 0.85, 0.87 (9H,3xs,8′-, 9′- and 10′-Me) 1.18-1.83 (5H,m,5′-, 6′- and 4′-H), and 3.15-3.56 (4H,complex set of multiplets, 3-CH_2, C*H*$_2$Ph) and 3.71-3.82 (1H,m,3′-H), 3.90-3.93 (1H,m,2-H) and 4.81-4.85 (1H,m,2′-H); δ_C (100MHz; $CDCl_3$) 9.86/9.9 (C-10′), 19.8/19.9 (C-9′), 20.0/21.3 (C-8′), 25.1/25.2 (C-5′), 25.6/25.8 (C-6′), 38.3/40.1 (C-3), 45.3 (C-7′), 48.6/49.1 (C-1′), 49.4/49.5 (C-4′), 52.8/52.9 (C-2), 76.5/76.8 (C-2′), 78.4/78.7 (C-3 and *C*H$_2$Ph), 124.9, 125.1, 127.3, 127.5, 127.8, 129.3, 129.5, 129.8, 129.9, 130.1, 131.3, 131.5, 138.6, 138.7, 138.8, 139.1, 139.3 (ArC) and 172.4/172.5 (C-1); *m/z* 503 (M$^+$, 4.18%).

3-exo-*(Benzylcarbonyloxy)camphor* (**352**). — A solution of the hydroxy ketone (**348**) (1.5g, 8.93mmol), NaH (0.51g, 10.1mol) and phenylacetyl chloride (1.79g, 11.6mmol) were reacted together according to Method A as described for the preparation of

compound (**327**). Flash chromatography [elution with benzene-Et_2O (8:1)] yielded, as an oil, 3-*exo*-(benzylcarbonyloxy)camphor (**352**) (1.86g, 73%); υ_{max} (liquid film) 1750 (C=O) and 1728 (CO.O) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.84, 0.86 and 0.90 (9H,3xs,8′-, 9′- and 10′-Me), 1.31-1.67 (4H,m,4′- and 5′-CH_2), 2.27 (1H,t,4′-H), 3.63 (2H,s,2-CH_2), 5.14 (1H,d,3′-H) and 7.15 and 7.25 (5H,ArH); δ_C (100MHz; $CDCl_3$) 8.9 (C-10′), 18.33 (C-9′), 19.45 (C-8′), 31.39 (C-5′), 40.62 (C-6′), 43.62 (C-2), 46.98 (C-7′), 57.89 (C-1′), 126.72, 126.74, 128.14, 128.84 and 128.87 (ArC), 170.33 (C-1) and 213.25 (C-2′); *m/z* 286 (M^+, 5.3%) and 91 (100%) (Found M^+: 128.1549. $C_{18}H_{22}O_3$ requires *M*, 286.1569).

Attempted preparation of the catechol acetal of 3-*exo*-(benzylcarbonyloxy)camphor

Catechol acetal of 3-exo-*(benzylcarbonyloxy)camphor* (**352A**). — A solution of catechol (0.37g, 3.36mmol) and of 3-*exo*-(benzylcarbonyloxy)camphor (**352**) (0.80g, 2.80mmol) in anhydrous toluene (10ml) containing a catalytic amount of *p*-toluene sulphonic acid (0.032g) was refluxed for 10h. in a reaction vessel equipped with a Dean and Stark apparatus, under nitrogen. The reaction mixture was washed sequentially with 1M NaOH (10ml) and water (10ml) and then extracted into EtOAc (5x10ml). The combined organic layers were dried (anhydr. $MgSO_4$) and evaporated *in vacuo*. Flash chromatography of the residue yielded the starting material, 3-*exo*-(benzylcarbonyloxy)camphor (**352**) (0.60g).

3-exo-*3′*-endo-*dibornyl ether* (**349**). — A solution of the alcohol (**348**) (1.28g, 7.5mmol) in dry benzene (20ml), catechol (1.00g, 9.1mmol) and a catalytic amount of *p*-toluenesulphonic acid (0.12g) were refluxed for 2 days in a reaction vessel equipped with

a Dean and Stark trap. The reaction mixture was washed with 1M NaOH (3ml) and water (3ml). The organic layer was separated, dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded *3*-exo-*3′*-endo-*dibornyl ether* (**349**) as a white solid (0.89g, 37%), m.p. 115°C (from EtOAc); υ_{max} (dilute solution in $CDCl_3$) 1742 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.82, 0.84, 0.85, 0.88 and 0.96 (18H,6xs,8-, 9-, 10-, 8′-, 9′-, and 10′-Me), 1.26-1.91 (8H,m,5-5′, 6- and 6′-CH_2), 2.08 and 2.11 (2H,2xd,4-H and 4′-H) and 3.88 and 3.89 (2H,2xs,3- and 3′-H); δ_C (100MHz; $CDCl_3$) 8.45 and 12.91 (C-10 and C-10′), 17.609 and 19.39 (C-9 and C-9′), 19.75 and 21.15 (C-8 and C-8′), 23.99 and 24.83 (C-5 and C-5′), 25.85 and 28.97 (C-6 and C-6′), 42.58 and 46.15 (C-7 and C-7′), 50.16 and 57.14 (C-1 and C-1′), 49.22 and 60.00 (C-4 and C-4′), 84.19 and 85.42 (C-3 and C-3′) and 218.95 and 218.12 (C-2 and C-2′); *m/z* 318 (M^+, 8.8%) and 123 (100%) (Found M^+: 318.218. $C_{20}H_{30}O_3$ requires: *M*, 318.2195).

Camphorquinone bis-*catechol acetal* (**345**). — A solution of camphorquinone (**315**) (5g, 0.03mol), catechol (6.6g, 0.06mol) and *p*-toluenesulphonic acid (0.30g) in anhydrous benzene (50ml) was refluxed overnight in a reaction vessel equipped with a Dean and Stark trap. The reaction mixture was washed with 1M NaOH (15ml) and H_2O (10ml). The organic layer was separated, dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. The residual solid was recrystallised from hot hexane to afford, as bright white crystals, the camphorquinone *bis*-catechol acetal (**345**) (5.06g, 48%), m.p. 201°C; δ_H (400MHz; $CDCl_3$) 1.09, 1.16 and 1.21 (8-, 9- and 10-Me), 1.50-2.24 (4H,m,5-CH_2, C-CH_2), 2.42 (1H,d,4-H) and 6.64-6.69 (8H,m,Ar-H); δ_C (100MHz; $CDCl_3$) 9.70 (C-10), 20.77 (C-9),

20.99 (C-5), 22.12 (C-8), 29.57 (C-6), 46.16 (C-7), 55.30 (C-1), 55.44 (C-4), 107.33 and 107.78 (C-2 and C-3), 107.33, 107.78, 117.22, 117.25, 117.48, 117.66, 122.72, 122.78, 123.01, 123.07, 143.88, 144.06, 145.08 and 145.16 (ArC); *m/z* 350 (M^+, 77.37%) (Found M^+: 350.1516. $C_{12}H_{22}O_4$ requires *M*, 350.1518).

Attempted preparation of the monocatechol acetal of camphor quinone by hydrolysis of the bis*catechol acetal* ***345****.* —

Method 1:

A solution of the *bis*-catechol acetal (**345**) (0.2g, 0.56mmol) in THF (20ml) and HCl (1**M**, 5ml) was refluxed for 5h. The resulting solution was concentrated *in vacuo*, and the residue was washed with water (10ml) and extracted into EtOAc (4x10ml). The combined organic layers were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*, to give yellow needles (0.075g), which were identified by ^{1}H NMR spectroscopy as camphorquinone (**100**).

Method 2:

A solution of the *bis*-catechol acetal (**345**) (0.165g, 0.047mmol) in THF (15ml) and HCl (1**M**, 0.5ml) was gently stirred at room temperature for 10h. TLC analysis indicated that no reaction had taken place. The reaction mixture was then gently heated to 40°C for 15 min. and TLC analysis indicated the presence of another compound. The reaction mixture was concentrated *in vacuo*, the residue was washed with water (10ml) and extracted into EtOAc (4x10ml). The organic layers were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography [elution with hexane-EtOAc (98:2)] afforded the starting

material (**345**) and camphorquinone (**315**).

*Attempted preparation of the monocatechol derivatives **316A** and **341A**.* — A solution of 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane (**312**) (1.0g, 4.72g) catechol (0.57g, 5.1mmol) and pyridinium *p*-toluenesulphonate (0.05g) in anhydrous benzene (40ml), was refluxed for 3h. in a reaction vessel fitted with a Dean and Stark apparatus. The reaction mixture was washed with H_2O (10ml) and 1**M** NaOH (10ml) and extracted into EtOAc (4x20ml). The combined organic layers were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded the starting material (0.650g).

2-Exo-*hydroxy-3-bornanone* (**353**). — To a solution of 3,3-(ethylenedioxy)-2-*exo*-hydroxy bornane (2.0g, 9.9mmol) in THF (40ml) dil. HCL (1**M**, 10ml) was added and the reaction mixture was gently refluxed for 2h. The resulting solution was concentrated *in vacuo* and the residue was washed with water (10ml) and extracted into EtOAc (4x20ml). The combined organic layers were dried and flash chromatography of the residue [elution with benzene-Et_2O (9:1)] afforded, as white crystals, 2-*exo*-hydroxy-3-bornanone (**353**) (1.51g, 90%), m.p. 225°C (lit.,[**] 228-230°C), υ_{max} (KBr) 3550 (OH) and 1750 cm^{-1} (C=O); δ_H (400MHz; $CDCl_3$) 0.92, 1.01 and 1.03 (9H,3xs,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); δ_C (100MHz; $CDCl_3$) 10.23 (C-10), 18.85 (C-9), 20.30 (C-5), 21.13 (C-8), 33.90 (C-6), 46.55 (C-1), 49.20 (C-7), 58.65 (C-4), 79.54 (C-2) and 218.46 (C-3).

*Attempted preparation of the catechol acetal of bromocamphor **340A***. — To a solution of 3-*endo*-bromocamphor (**340**) (2.0g, 8.65mmol) in anhydrous benzene[e] (20ml), catechol (1.14g, 10.38mmol) and *p*-toluenesulphonic acid were added, and the reaction mixture was stirred for 10h. under nitrogen in a reaction vessel equipped with a Dean and Stark apparatus. The resulting solution was washed with water (20ml) and 1**M** NaOH (20ml) and extracted into EtOAc (4x20ml). The combined organic layers were dried (anhydr. $MgSO_4$) and evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (8:2)] yielded needle shaped crystals (0.920g) which were identified by ^1H NMR spectroscopy to be the starting material (**340**).

3,3-(o-*Phenylenedioxy)-2,2-(propylenedioxy)bornane* (**347**). — A solution of 2,2-(propylenedioxy)-3-bornone (**342**) (0.3g, 1.3mmol), catechol (0.15g, 1.33mmol) and a catalytic amount of *p*-toluenesulphonic acid in anhydrous toluene (20ml) was refluxed under nitrogen for *ca.* 12h. in a reaction vessel equipped with a Dean and Stark apparatus. The reaction mixture was washed with water (5ml) and 1**M** NaOH (5ml). The organic layer was separated, dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (95:5)] followed by preparative TLC [elution with hexane-EtOAc (98:2)] afforded as a yellow oil *3,3-*(o-*phenylenedioxy)-2,2-(propylenedioxy)bornane* (**347**) (20%), δ_H (400MHz; $CDCl_3$) 0.89, 0.93 and 1.32 (9H,3xs,10-, 9- and 8-Me), 1.40-2.22 (7H,complex of multiplets,4-H, 5-CH_2 and $OCH_2CH_2CH_2O$), 3.63-3.96 (4H,m,$OCH_2CH_2CH_2O$) and 6.84-7.00 (4H,m,ArH); δ_C (100MHz; $CDCl_3$) 10.03 (C-10), 20.67 (C-5), 21.76 (C-9), 21.97 (C-8), 29.16

[e] The same reaction was carried out usinig identical quantities and in xylene (20ml) and here again the starting material was isolated.

($OCH_2CH_2CH_2O$), 31.78 (C-6), 45.54 (C-1), 56.54 (C-4), 57.65 (C-7), 65.54 and 65.44 ($OCH_2CH_2CH_2O$), 107.73 and 107.80 (C-2 and C-3), 115.73, 121.81, 121.89, 143.64 and 143.68 (ArC); *m/z* 316 (36.2%) (Found M^+: 316.1666. $C_{19}H_{24}O_4$ requires *M*, 316.1674).

2,2-(propylenedioxy)-3-exo-*hydroxy bornane* (**344**). — To an ice-cold solution of 2,2-(propylenedioxy)-3-bornanone (**342**) (2.0g, 8.9mmol) in MeOH (40ml), $NaBH_4$ (0.35g, 9.3mmol) was added in small portions, and the resulting solution was stirred at 0°C for 3h. and allowed to stir at room temperature overnight. The reaction was quenched by successive addition of H_2O (5ml) and 3M NaOH (5ml), and the resulting mixture filtered to remove the white precipitate, which was refluxed with EtOAc (40ml) for 1h. and filtered off. The combined filtrates were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded, as an oil, *2,2-(ethylenedioxy)-3*-exo-*hydroxybornane* (**344**) (0.80g, 40%); υ_{max} (liquid film) 3510 (OH) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.79, 0.85 and 1.10 (9H,3xs,8-, 9- and 10-Me), 1.32-1.06 and 1.48-2.14 (7H,m,4-H, 5-CH_2, 6-CH_2 and $OCH_2CH_2CH_2O$), 2.23 (1H,br s,OH), 3.71 (1H,s,3-H) and 3.71-4.26 (4H,m,$OCH_2CH_2CH_2O$); δ_C (100MHz; $CDCl_3$) 10.0 (C-10), 21.4 (C-9), 21.9 (C-8), 25.8 (C-5), 28.1 (C-6), 25.1 ($OCH_2CH_2CH_2O$), 47.5 (C-7), 52.8 (C-4), 54.1 (C-1), 61.0 and 62.1 ($OCH_2CH_2CH_2O$), 81.9 (C-3) and 107.4 (C-2); *m/z* 226 (M^+, 0.8%) (Found M^+: 226.1582. $C_{13}H_{22}O_3$ requires *M*, 226.1569).

2,2-(Propylenedioxy)-3-exo-*bornyl 2,3-dimethylbutanoate* (**358**). — To a solution of 2,2-(propylenedioxy)-3-*exo*-hydroxyboranone **344** (10.g, 4.4mmol) in THF (25ml), NaH (0.29g, 6.2mmol) was added and the resulting solution was stirred for 6h. To the above

solution 3,3-dimethylbutanoyl chloride (0.83g, 6.2mmol) was added. Work-up flash chromatography [elution with hexane-EtOAc (85:15)] yielded as an oil *2,2-(propylenedioxy)-3*-exo-*bornyl 2,3-dimethylbutanoate* (**358**) (0.990g, 77%); υ_{max} (liquid film) 1730 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.80, 0.83 and 1.04 (9H,3xs,8′-, 9′- and 10′-Me), 1.14-1.98 (7H,m,4′-H, 5′-CH_2, 6′-CH_2 and $OCH_2CH_2CH_2O$), 2.23 (2H,q,2-CH_2) and 4.83 (1H,s,3-H); δ_C (100MHz; $CDCl_3$) 9.9 (C-10′), 21.3 (C-9′), 21.5 (C-8′), 24.6 (C-5′), 25.4 ($OCH_2CH_2CH_2O$), 27.9 (C-6′), 29.7 [$C(CH_3)_3$], 31.0 (C-3), 47.7 (C-7′), 48.4 (4-CH_2), 51.2 (C-4′), 54.4 (C-1′), 61.9 and 62.5 ($OCH_2CH_2CH_2O$), 81.7 (C-3′), 106.6 (C-2′) and 171.5 (C-1); *m/z* 324 (M^+, 8.43%) (Found M^+: 324.2280. $C_{19}H_{22}O_4$ requires: *M*, 324.2300).

2,2-(Propylenedioxy)-3-exo-*bornyl phenylethanoate* (**359**). — The method described for the synthesis of 2,2-(propylenedioxy)-3-*exo*-bornyl 3,3-dimethylbutanoate **358** was followed using 2,2-(propylenedioxy)-3-*exo*-hydroxylbornane **344** (1.0g, 3mmol) in THF (25ml), NaH (0.83g, 6.2mmol). Work-up and flash chromatography [elution with hexane-EtOAc (9:1)] yielded, as an oil, *2,2-(propylenedioxy)-3*-exo-*bornyl phenylethanoate* **359**; (1.06g;70%); υ_{max} (liquid film) 3525 (OH) cm^{-1}; δ_H (400MHz, $CDCl_3$) 0.80, 0.85 and 1.15 (9H,3xH,8- 9- and 10-Me), 1.32, 1.16 and 1.52-2.20 (7H,m,4-H, 5-CH_2, 6-CH_2 and $OCH_2CH_2CH_2O$), 3.62-3.85 (4H,m,$OCH_2CH_2CH_2O$) and 4.6 (1H,s,3-H); δ_C (100MHz; $CDCl_3$) 10.9 (C-10), 19.9 (C-5), 21.5 (C-7), 24.3 ($OCH_2CH_2CH_2O$), 22.3 (C-8), 26.3 (C-6), 42.3 (CH_2Ph), 48.1 (C-1), 49.3 (c-7), 50.4 (C-4), 62.4 and 63.4 ($OCH_2CH_2CH_2O$), 86.1 (C-3′), 106.4 (C-2), 127.6, 127.8, 127.9 and 134.1 (ArC); *m/z* 344 (M^+, 44%) (Found: M^+: 344.2011. $C_{21}H_{28}O_4$ requires *M*,

344.1987).

2,2-(Propylenedioxy)-3-exo-*bornyl 2,3-diphenylpropanoate* (**361**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed, using *2,2-(propylenedioxy)-3*-exo-*bornyl phenylethanoate* (**359**) (0.50g, 1.5mmol) in THF (15ml), LDA (2.0mmol) and benzyl bromide (0.35g, 2.0mmol). Work-up and preparative layer chromatography [elution with hexane-EtOAc (97:3)] afforded, as an oil, 2,2-(propylenedioxy)-3-*exo*-bornyl 2,3-diphenylpropanoate (**360**) (58%); υ_{max} (liquid film) 1725 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.62/0.66, 0.69/0.70 and 0.86/0.88 (9H,3xs,8′-, 9′- and 10′-Me), 0.92-1.74 (7H,m,4′-H, 5′-CH_2, 6′-CH_2 and $OCH_2CH_2CH_2O$), 2.94-4.02 (7H,m,3-CH_2, 2-H and $OCH_2CH_2CH_2O$), 4.64 (1H,s,3-H) and 7.07-7.29 (10H,m,ArH); δ_C (100MHz; $CDCl_3$) 9.88/9.95 (C-10′), 20.95 (C-9′), 21.32/21.36 (C-8′), 24.35/24.26 (C-5′), 25.25/25.37 (C-′6), 27.91 ($OCH_2CH_2CH_2O$), 39.17/39.49 (C-3), CH_2Ph, 47.49/47.51 (C-7′), 50.74/51.05 (C-4′), 53.96/54.67 (C-2), 54.37/54.45 (C-1), 61.89/61.93 and 62.22/62.24 ($OCH_2CH_2CH_2O$), 81.92/82.68 (C-3′), 106.29/106.41 (C-2′) and 126.36, 126.42, 127.38, 127.43, 127.86, 128.11, 128.32, 128.34, 128.62, 128.65, 128.96 and 129.17 (ArC); *m/z* 434 (M^+ 18%)(Found M^+: 414.2782. $C_{26}H_{38}O_4$ requires: *M*, 434.2457).

Hydrolysis of 2,2-(propylenedioxy)-3-*exo*-bornyl 2,3-diphenylpropanoate 360 — preparation of 2,3-diphenylpropanoic acid

2,3-Diphenylpropanoic acid (**337**). — A solution of 2,2-(propylenedioxy)-3-*exo*-bornyl 2,3-diphenylethanoate (1.0g, 2.4mmol) in THF (20ml) and LiOH (0.86g, 3.6mmol) and

water (0.5ml) was stirred at room temperature for 48h. The resulting solution was evaporated *in vacuo*. Preparative thin layer chromatography of the residue [elution with hexane-ethyl acetate (9:1)] afforded, as a white solid, 2,3-diphenyl propanoic acid **337** (65%); m.p. 81°C (lit.,[242] 83-89°C); $[\alpha_D]^{20}$ -27° (in benzene) {lit.,[243] $[\alpha_D]^2{}_D$ 94.04 (benzene)}.

2,2-(Propylenedioxy)-3-exo-*bornyl 2-benzyl 3,3-dimethylbutanoate* (**360**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed using, 2,2-(propylenedioxy)-3-*exo*-bornyl 2,3-dimethylbutanoate (**358**) (0.68g, 2.11mmol) in THF (20ml), LDA (2.95mmol) and benzyl bromide (0.51g, 2.95mmol). Workup and preparative layer chromatography afforded as an oil 2,2-(propylenedioxy)-3-*exo*-bornyl 2-benzyl 3,3-dimethylbutanoate (**360**) (68%); υ_{max} (liquid film) 1735 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.39, 0.50 and 0.67/0.68 (9H,3xs,8′-, 9′- and 10′-Me), 1.01/1.03 (9H,2xs,Bu^t), 1.11-1.86 (7H,m,4′-H, 5′-CH_2, 6′-CH_2 and $OCH_2CH_2CH_2O$), 2.39-2.48 (1H,m,2-H), 2.73-2.83 (2H,m,CH_2-Ph), 3.59-4.02 (4H,m,OCH_2CH_2O) and 4.47-4.50 (1H,m,2-H); δ_C (100MHz; $CDCl_3$) 9.85/9.97 (C-10′), 20.08 (C-9′), 21.02/21.44 (C-8′), 24.40/24.53 (C-5′), 25.30/25.39 ($OCH_2CH_2CH_2O$), 27.85 (C-6′), 27.87/28.07 [$C(CH_3)_3$], 33.81 (C-3), 50.67 , 34.44/34.73 (CH_2-Ph), 46.99 (C-7′), 54.22/54.10 (C-1′), 50.67/58.83 (C-4′), 58.59/59.65 (C-2), 61.77/61.82 and 62.06/62.25 (OCH_2CH_2O), 82.01/82.87 (C-3′), 106.52 (C-2′), 126.09, 126.27, 128.29, 128.40, 129.28, 129.32 and 139.77 (ArC) and 174.32 (C-1); *m/z* 414 (M^+ 13.21%)(Found M^+: 414.148. $C_{26}H_{38}O_4$ requires: M, 414.146). The diastereomeric excess was determined to be 57.8%.

3,3-(Propylenedioxy)-2-bornanone (**341**) and *2,2-(propylenedioxy)-3-bornanone* (**342**). — A solution of camphorquinone (**315**) (20.00g, 0.12mmol), 1,3-propanediol (13.73g, 0.18mmol) and DBA in anhydrous benzene (120ml) was refluxed for 20h. in a reaction vessel equipped with a Dean and Stark trap. During this time 3.2ml of H_2O was collected. The reaction mixture was washed with 1**M** NaOH (100ml) and H_2O (100ml). The organic layer was separated, dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. All attempts to crystallise the residue with different solvents failed. Flash chromatography of the residue [elution with hexane-EtOAc (95:5)] afforded two fractions.

Fraction (1), as an oil, *3,3-(propylenedioxy)-2-bornanone* (**342**) (12.5g, 46%); υ_{max} (liquid film) (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.78, 0.86 (9H,3xs,8-, 9- and 10-Me), 1.37-1.88 (5-CH_2, 6-CH_2 and $OCH_2CH_2CH_2O$), 1.98 (1H,d,4-H), 3.35-3.75 and 4.27-4.34 (4H,2xm, $OCH_2CH_2CH_2$); δ_C (100MHz; $CDCl_3$) 9.3 (C-10), 19.8 (C-9), 21.9 (C-5), 20.1 (C-8), 25.3 ($OCH_2CH_2CH_2O$), 31.2 (C-6), 43.6 (C-7), 52.7 (C-4), 58.9 (C-1), 61.4 and 62.0 ($OCH_2CH_2CH_2O$), 97.9 (C-3) and 214.2 (C-2); *m/z* 224 (M^+, 0.02%) (Found M^+: 224.1431. $C_{13}H_{20}O_3$ requires: *M*, 224.1412).

Fraction (2) as white needle shaped crystals, *2,2-(propylenedioxy)-2-bornanone* (**342**) (8.5g, 30%), m.p. 88-89°C (from hexane) ; δ_H (400MHz; $CDCl_3$) 0.81 (6H,s,) and 0.90 (9H,s,8-, 9- and 10-Me), 1.27-1.42, 1.71-1.79 and 1.89-2.02 (7H,m,5-CH_2, 6-CH_2, 4-H and $OCH_2CH_2CH_2O$) and 3.65-3.73 and 4.39-4.51 (4H,m, $OCH_2CH_2CH_2O$); δ_C (100MHz; $CDCl_3$) 8.9 (C-10), 18.9 (C-9), 21.8 (C-8), 22.9 (C-5), 25.3 ($OCH_2CH_2CH_2O$), 28.0 (C-6), 43.6 (C-7), 53.8 (C-1), 60.5 (C-4), 61.0 and 62.0 ($OCH_2CH_2CH_2O$), 96.8 (C-2) and 214.7 (C-3); *m/z* 224 (M^+, 0.97%) (Found M^+: 224.1433. $C_{13}H_{20}O_3$ requires: *M*, 224.1412).

3,3-(Propylenedioxy)-2-exo-*hydroxy bornane* (**343**). —

Method 1: Reduction using LAH.

LAH (0.143g, 3.77mmol) was refluxed for 1h. in anhydrous Et_2O, and the resulting slurry was cooled to 0°C. 3,3-Propylenedioxy-2-bornanone (2.6g, 11.6mmol) in Et_2O (5ml) was added dropwise and the mixture was refluxed for 3h. To the ice cooled reaction mixture, H_2O (5ml) and 3M NaOH (2ml) were added successively. The white precipitate was removed by filtration and the residue was refluxed in EtOAc for 1h. and then filtered. The combined filtrates were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (8:2)] yielded, as an oil, *3,3-propylenedioxy-2*-exo-*hydroxybornane* (**343**) (1.51g, 57%); υ_{max} (liquid film) 3560 (OH) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.78, 0.82 and 0.99 (9H,3xs,8-, 9- and 10-Me), 1.05-1.11 (1H,m,6-H), 1.31-1.55 and 1.98-2.1 (5H, complex of multiplets, 5-H, 6-H and $OCH_2CH_2CH_2O$), 2.40 (1H,d,4-H), 2.72 (1H,d,OH; signal disappeared on D_2O exchange), 3.64-3.77 and 3.96-4.02 (4H,m,$OCH_2CH_2CH_2O$); δ_C (100MHz; $CDCl_3$) 10.8 (C-10), 20.7 and 22.2 (C-8 and C-9), 20.2 (C-5), 33.5 (C-6), 25.3 ($OCH_2CH_2CH_2O$), 46.2 (C-4), 48.0 (C-1), 49.8 (C-7), 61.2 and 61.6 ($OCH_2CH_2CH_2O$), 86.8 and 105.3 (C-3); *m/z* 228 (M^+, 4.1%) (Found M^+: 226.1552. $C_{13}H_{20}O_3$ requires: *M*, 226.1569).

Method 2: Reduction using Lithium tri(*sec*-butyl)borohydride.

Lithium tri(*sec*-butyl)borohydride (19ml, 13mmol) was added to a solution of 3,3-propylenedioxy-2-bornanone (2.89g, 12.9mmol) in anhydrous THF (50ml) at -78°C under an inert atmosphere. The reaction mixture was stirred at -78°C for 3h. and allowed to warm to room temperature overnight. The reaction was quenched by successive addition

of H_2O (2ml), 3M NaOH (10ml) and, dropwise to the ice-cooled solution, 30% H_2O_2 (10ml). Solid, anhydrous K_2CO_3 was added to the two phase mixture until saturation was achieved. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x10ml) and EtOAc (2x25ml). The combined organic extracts were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded, as an oil, *3,3-propylenedioxy-2*-exo-*hydroxybornane* (**343**) (2.15g, 83%).

3,3-(Propylenedioxy)-3-exo-*bornyl 3,3-dimethylbutanoate* (**354A**). — The method described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornylbutanoate (**327**) was followed, using a solution of 3,3-(propylenedioxy)-2-*exo*-hydroxybornane (**343**) (1.59g, 7.03mmol) in THF (50ml), NaH (0.39g, 8.4mmol) and 3,3-dimethylbutanoyl chloride. Work-up and flash chromatography [elution with hexane-EtOAc (9:1)] afforded, as a yellow oil, *3,3-(propylenedioxy)-3*-exo-*bornyl 3,3-dimethylbutanoate* (**354A**)(1.78g, 71%); υ_{max} (liquid film) 1743 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.71, 0.77 and 1.03 (9H,3xs,8′-, 9′- and 10′-Me), 0.97 (9H,s,*t*-Bu), 1.12-1.53 and 1.78-1.86 (6H,complex of multiplets,5′-CH_2, 6′-CH_2 and $OCH_2CH_2CH_2O$), 2.15 (2H,d,2-CH_2), 2.25 (1H,d,4-H), 3.58-3.86 (4H,m,$OCH_2CH_2CH_2O$) and 4.44 (1H,s,2′-CH); δ_C (100MHz; $CDCl_3$) 11.4 (C-10′), 19.9 (C-5′), 20.5 (C-9′), 21.6 (C-8′), 25.2 ($OCH_2CH_2CH_2O$), 29.5 [$C(CH_3)_3$], 30.4 (C-3), 33.7 (C-6′), 48.0 (C-4′), 48.1 (C-1′), 48.3 (C-7′), 49.6 (C-2), 61.1 and 61.1 ($OCH_2CH_2CH_2O$), 85.8 (C-2′), 105.5 (C-3′) and 171.2 (C-1); *m/z* 324 (M^+, 3.6%) (Found M^+: 324.2218. $C_{19}H_{32}O_4$ requires: *M*, 324.2300).

of H_2O (2ml), 3M NaOH (10ml) and, dropwise to the ice-cooled solution, 30% H_2O_2 (10ml). Solid, anhydrous K_2CO_3 was added to the two phase mixture until saturation was achieved. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x10ml) and EtOAc (2x25ml). The combined organic extracts were dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded, as an oil, *3,3-propylenedioxy-2*-exo-*hydroxybornane* (**343**) (2.15g, 83%).

3,3-(Propylenedioxy)-3-exo-*bornyl 3,3-dimethylbutanoate* (**354**). — The method described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornylbutanoate (**327**) was followed, using a solution of 3,3-(propylenedioxy)-2-*exo*-hydroxybornane (**343**) (1.59g, 7.03mmol) in THF (50ml), NaH (0.39g, 8.4mmol) and 3,3-dimethylbutanoyl chloride. Work-up and flash chromatography [elution with hexane-EtOAc (9:1)] afforded, as a yellow oil, *3,3-(propylenedioxy)-3*-exo-*bornyl 3,3-dimethylbutanoate* (**354**) (1.78g, 71%); υ_{max} (liquid film) 1743 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.71, 0.77 and 1.03 (9H,3xs,8′-, 9′- and 10′-Me), 0.97 (9H,s,*t*-Bu), 1.12-1.53 and 1.78-1.86 (6H,complex of multiplets,5′-CH_2, 6′-CH_2 and $OCH_2CH_2CH_2O$), 2.15 (2H,d,2-CH_2), 2.25 (1H,d,4-H), 3.58-3.86 (4H,m,$OCH_2CH_2CH_2O$) and 4.44 (1H,s,2′-CH); δ_C (100MHz; $CDCl_3$) 11.4 (C-10′), 19.9 (C-5′), 20.5 (C-9′), 21.6 (C-8′), 25.2 ($OCH_2CH_2CH_2O$), 29.5 [$C(CH_3)_3$], 30.4 (C-3), 33.7 (C-6′), 48.0 (C-4′), 48.1 (C-1′), 48.3 (C-7′), 49.6 (C-2), 61.1 and 61.1 ($OCH_2CH_2CH_2O$), 85.8 (C-2′), 105.5 (C-3′) and 171.2 (C-1); *m/z* 324 (M^+, 3.6%) (Found M^+: 324.2218. $C_{19}H_{32}O_4$ requires: *M*, 324.2300).

3,3-(Propylenedioxy)-2-exo-*bornyl phenylethanoate* (**355**). — The method described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornylbutanoate (**327**) was followed, using a solution of 3,3-(propylenedioxy)-2-*exo*-hydroxybornane (**343**) (2.37g, 10.48mmol) in THF (50ml), NaH (0.58g, 12.5mmol) and phenylacetyl chloride (2.1g, 13.63mmol). Work-up and flash chromatography [elution with hexane-EtOAc (83:17)] afforded, as a yellow oil, *3,3-(propylenedioxy)-2*-exo-*bornyl phenylethanoate* (**356**) (1.51g, 42%); υ_{max} (liquid film) 1730 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.62, 0.78 and 0.99 (9H,3xs,8′-, 9′- and 10′-Me), 1.26-1.54 and 1.55-1.76 (6H,complex of multiplets,5′-CH_2, 6′-CH_2 and $OCH_2CH_2CH_2O$), 2.20 (1H,d,4′-H), 3.59 (2H,d,2-CH_2), 3.62-3.86 (4H,m,$OCH_2CH_2CH_2O$) and 4.57 (1H,s,2′-CH); δ_C (100MHz; $CDCl_3$) 10.9 (C-10′), 19.9 (C-5′), 20.5 (C-9′), 21.5 (C-8′), 25.2 ($OCH_2CH_2CH_2O$), 33.5 (C-6′), 41.5 (C-2), 48.0 (C-1′), 48.8 (C-7′), 49.6 (C-4′), 61.3 ($OCH_2CH_2CH_2O$), 85.9 (C-2′), 105.5 (C-3′), 126.7, 128.1, 129.4 and 134.1 (ArC); *m/z* 344 (M^+, 17.8%) (Found M^+: 344.2018. $C_{21}H_{28}O_4$ requires: *M*, 344.1987).

3,3-(Propylenedioxy)-2-exo-*bornyl 2-benzyl 3,3-dimethyl-butanoate* (**356**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**) was followed using 3,3-(propylenedioxy)-2-*exo*-bornyl 3,3-dimethylbutanoate (**354**) (0.80g, 2.48mmol) in THF (40ml), LDA (2.98mmol) and benzyl bromide (5.1g, 2.9mmol). Work-up and preparative layer chromatography of the residue yielded, as an oil, *3,3-(propylenedioxy)-2*-exo-*bornyl 2-benzyl 3,3-dimethylbutanoate* (**356**) (63%); υ_{max} (liquid film) 1730 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.17 and 0.74-1.01 (9H,3xs,8′-, 9′- and 10′-Me), 1.08/1.11 (9H,2xs,Bu^t), 1.27-1.52 and 1.94-2.00 (7H,m,4′-H, 5′-CH_2

6′-CH_2 and $OCH_2CH_2CH_2O$), 2.46/2.60 (1H,2xdd,2-H), 2.80-3.05 (2H,m,3-CH_2), 3.33-3.93 (4H,m,$OCH_2CH_2CH_2O$), 4.21/4.39 (1H,2xs,2′-H) and 7.07-7.69 (5H,m,ArH); δ_C (100MHz; $CDCl_3$) 10.6/12.2 (C-10′), 20.1/20.2 (C-5′), 20.5-21.7 (cluster of 3 peaks C-8′ and C-9′), 25.2/25.4 ($OCH_2CH_2CH_2O$), 28.0/28.1 [$C(CH_3)_3$], 29.7/30.9 (C-3), 33.9/34.1 (C-6′), 34.1/34.4 (CH_2Ph), 46.7/48.7 C-4′), 47.97 (C-1′), 48.2/48.4 (C-7′), 57.9/58.9 (C-2), 60.7, 60.9 and 61.2 ($OCH_2CH_2CH_2O$), 86.7/86.7 (C-2′), 105.3/105.7 (C-3′), 125.8, 125.9, 128.1, 128.2, 128.9, 129.1, 140.6 and 140.9 (ArC) and 173.6 (C-1); *m/z* 414 (M^+, 14.7%)(Found M^+: 414.2791. $C_{26}H_{38}O_4$ requires: *M*, 414.2770). The diastereomeric excess was determined to be 6%.

3,3-(Propylenedioxy)-3-exo-*bornyl 2,3-diphenyl propanoate* (**357**). — Method 1 as described for the synthesis of 3,3-(ethylenedioxy)-2-*exo*-bornyl 2-benzylbutanoate (**333**)was followed using 3,3-(propylenedioxy)-3-*exo*-bornylphenylethanoate (355) (0.80g, 2.32mmol) in THF (20ml), LDA (0.28mmol) and benzyl bromide (0.52g, 0.03mmol). Work-up and preparative layer chromatography of the residue afforded as an oil *3,3-(propylenedioxy)-3*-exo-*bornyl 2,3-diphenyl propanoate* (**357**) (68%), υ_{max} (liquid film) 1735 (CO) cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.28/0.41 (3H,2xs,10′-Me), 0.67/0.70 and 0.93/0.96 (6H,4xs,8′-Me and 9′-Me), 1.15-1.52 (6H,m,5′-CH_2, 6′-CH_2 and $OCH_2CH_2CH_2O$), 1.98/2.04 (1H,2xd,4′-H), 2.96-3.61 (6H,m,$OCH_2CH_2CH_2O$ and 3-CH_2), 3.61-3.83 (1H,m,2-H) and 4.50/4.52 (1H,2xs,2′-H); δ_C (100MHz; $CDCl_3$) 10.7/10.9 (C-10′), 19.8/19.9 (C-5′), 20.7/20.7 (C-8′), 21.5/21.6 (C-9′), 25.2/25.3 ($OCH_2CH_2CH_2O$), 33.6 (C-6′), 48.0/48.1 (C-1′), 48.9/49.5 (C-7′), 50.3/51.4 (C-4′), 54.1/54.2 (C-2), 61.1, 61.4 and 61.5 ($OCH_2CH_2CH_2O$), 85.3/86.0 (C-2′), 105.6/105.7

(C-3′), 126.2, 126.2, 127.1, 127.2, 128.1, 128.2, 128.2, 128.3, 128.4, 129.0, 129.1, 138.7/138.9 and 139.3/139.6 (Ar-C) and 172.3/172.4 (C-1); *m/z* (M^+, 16.38%) (Found M^+: 434.2477. $C_{28}H_{34}O_4$ requires: *M*, 434.2457). The diastereomeric excess was determined to be 17%.

Glycine ethyl ester hydrochloride. — Dry HCl was passed into a solution of glycine (7.5g, 0.1mol) in absolute ethanol (50ml) until a clear solution was formed. More absolute ethanol (5ml) was added, and the reaction mixture was boiled under reflux for 10 min. The solution was cooled in an ice bath. The white crystals were filtered and washed with cold ethanol. The product was recrystallised from hot ethanol. m.p. 182°C (30g, 61%); δ_H (400MHz; D_2O) 1.402 (3H,t,CH_3), 4.03 (2H,s,CH_2NH_2) and 4.41 (2H,q,CH_2CH_3).

3-exo-*2′*-endo-*dimer* (dibornyl ether) (**349**). — A solution of the alcohol (**348**) (1.5g, 8.9mmol) in benzene (20ml), glycine (0.67g, 8.9mmol) and *p*-toluene sulphonic acid (0.1g) was refluxed for 12 h. in a vessel equipped with Dean and Stark apparatus. During the course of the reaction, more glycine (2x0.2g) and *p*-toluene sulphonic acid (0.1g) were added. The reaction mixture was washed with H_2O (10ml) and extracted into EtOAc (4x10ml). The combined organic layers were dried (anhydr. $MgSO_4$) and evaporated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] affored white crystals of 3-*exo*-2-*endo* dimer (**349**) (1.3g, 46%), m.p. 115°C; υ_{max} (KBr) 1720 cm^{-1}; δ_H (400MHz; $CDCl_3$) 0.82, 0.84, 0.85, 0.87, 0.88 and 0.96 (18H,6xs,8-, 8′-, 9-, 9′-, 10- and 10′-Me), 1.22-2.01 (8H,m,5-5′, 6 and 6′-CH_2), 2.08 and 2.11

(2H,2xd,4- and 4′-H) and, 3.88 and 3.92 (2H,2xd, 3- and 2-H); δ_C (100MHz; $CDCl_3$) 8.85 and 12.91 (C-10 and C-10′), 17.60 and 19.28 (C-9 and C-9′), 19.66 and 21.05 (C-8 and C-8′), 23.89 and 24.75 (C-5 and C-5′), 25.76 and 28.88 (C-6 and C-6′), 42.58 and 46.15 (C-7 and C-7′), 50.16 and 57.17 (C-1 and C-1′), 84.31 and 85.31 (C-3 and C-2′) and, 216.95 and 218.12 (C-2 and C-3′); *m/z* 318 (M^+, 5.9%) (Found M^+: 318.2180. $C_{20}H_{30}O_3$ requires M: 318.2195).

2-*exo*-3′-*endo*-dimer. — A solution of alcohol (**354**) (1.5g, 8.9mmol) in benzene (20ml), glycine (0.67g, 8.9mmol) and *p*-toluene sulphonic acid (0.1g) was refluxed for 12 h. in a vessel equipped with Dean and Stark apparatus. During the couse of the reaction, more glycine (2x2.0g) and *p*-toluene sulphonic acid (0.1g) were added. The reaction mixture was washed with H_2O (10ml) and extracted into EtOAc (4x10ml). The combined organic extracts were dried (anhydr. $MgSO_4$) and evaporated *in vacuò*. Flash chromatography of the residue [elution with hexane-EtOAc (9:1)] afforded, as a white solid, the dimer (**354**) (1.27g, 45%), m.p. 115°C; δ_H (400MHz; $CDCl_3$) 0.82, 0.82, 0.86, 0.95, 0.96 and 0.97 (18H,6xs,10-, 10′-, 9-, 9′-H and 8, 8′-Me), 1.36-1.89 (8H,m,5-CH_2, 5′-CH_2, 6-CH_2 and 6′-CH_2), 2.048 (1H,d,4-H), 2.31 (1H,t,2′-H), 3.84 (1H,s,2-H) and 4.25 (1H,d,3′-H); δ_C (100MHz; $CDCl_3$) 9.30 and 10.49 (C-10 and C-10′), 18.53 and 18.71 (C-9 and C-9′), 18.85 and 19.85 (C-8 and C-8′), 20.69 and 21.34 (C-6 and C-6′), 31.78 and 33.65 (C-5 and C-5′), 42.59 and 46.09 (C-7 and C-7′), 50.16 and 57.17 (C-1 and C-1′), 85.62 and 81.66 (C-3 and C-2′) and, 217.77 and 217.87 (C-2 and C-3′); υ_{max} (KBr disk) 1730 (C=O) and 1350 (OH); *m/z* 318 (M^+, 33.5%) (Found M^+ 318.2191. $C_{20}H_{30}O_3$ requires 318.2195).

1-Chloro-2-methoxyethane (**362**). — Thionyl chloride (98.0g, 0.82mmol) was added to an ice-cooled solution of 2-methoxyethanol in dimethylaniline (115ml) and the resulting solution was stirred overnight at room temperature. Dilute HCl was then added and the mixture was extracted with Et_2O. The organic layer was dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Fractional distillation of the residue afforded 1-chloro-2-methoxyethane (**362**) (49g, 69%), b.p. 89-90°C.

3-oxo-*3*-exo-*bornyl*-N-p-*toluene sulphonyl glycinate* (**385**). — To a solution of *p*-toluene sulphonyl glycine (0.89g, 4.16mmol) in anhydrous DMF (1ml), cyclohexadiamine (0.81g, 5.00mmol) was added and the mixture was stirred at room temperature for 30 mins. A solution of 3-*exo*-hydroxy camphor (**348**) (1.0g, 6mmol) in DMF (10ml) was added to the above solution and the resulting solution was stirred for 2 days and then refluxed for 4 h. The DMF was evaporated *in vacuo*, and flash chromatography of the residue [elution with hexane-EtOAc (1:1)] yielded the ester, *3*-oxo-*3*-exo-*bornyl*-N-p-*toluene sulphonyl glycinate* (**385**) (0.21g, 43%); δ_H (400MHz; $CDCl_3$) 0.79, 0.83 and 0.84 (9H,3xs,8-, 9- and 10-Me), 1.09-2.21 (5H,complex of multiplets,4-H, 5-CH_2 and 6-CH_2), 2.33 (3H,s,Ar-CH_3), 3.76 (2H,d,CH_2N), 4.62 (1H,s,3-H), 5.41 (1H,br s,N-H) and, 7.21 and 7.66 (2xd,Ar-H); δ_C (100MHz; $CDCl_3$) 8.73/8.76 (C-10), 19.31/19.56 (C-9), 20.43/21.19 (C-8), 24.68/28.32/31.68 (C-5 and C-6), 43.95/43.91 (CH_2NH_2), 46.17 (C-1), 47.84/46.96 (C-4), 58.04/56.91 (C-7), 76.28/76.26 (Ar-CH_3), 77.43/77.39 (C-3), 143.35/143.33, 136.25, 129.47 and 126.94 (Ar-C), 168.19/168.29 (C=O) and 212.96/213.19 (C-2); *m/z* 379 (M^+, 1.3%) (found M^+ 379.1448. $C_{19}H_{25}O_5NS$ requires 379.1454).

2,2-Ethylenedioxy-3-exo-*hydroxy bornane* (**388**). — A solution of 3-*exo*-hydroxy camphor (**348**) (0.5g, 3mmol) in benzene (20ml), ethylene glycol (ml, mmol) and a catalytic amount of *p*-toluene suphonic acid was heated under reflux for 10 h. in a reaction vessel equipped with a Dean and Stark apparatus. The reaction mixture was washed with H_2O, dried (anhydr. $MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded, as an oil, *2,2-ethylenedioxy-3*-exo-*hydroxybornane* (**388**) (g, %), δ_H (400MHz; $CDCl_3$) 0.77, 0.78 and 1.49 (9H,3xs,10-, 9- and 8-Me), 1.07-1.81 (5H,m,4-H, 5-CH_2 and 6-CH_2), 2.51 (1H,br s,OH), and 3.63-3.94 (4H,m,OCH_2CH_2O); δ_C (100MHz; $CDCl_3$) 9.26 (C-10), 20.60 (C-9), 21.12 (C-8), 24.54 (C-5), 29.06 (C-6), 47.70 (C-4), 51.58 (C-1), 51.78 (C-7), 63.89 and 66.53 (OCH_2CH_2O), 83.02 (C-3) and 116.92 (C-2); *m/z* 212 (M^+: 0.9%). (Found M^+ 212.1418. $C_{12}H_{20}O_3$ requires M: 212.1412)

2,2-(Ethylenedioxy)-3-exo-*bornyl carbobenzyloxy glycinate* (**389**). — To a solution of carbobenzyloxy glycine (0.49g, 2.35mmol), in DMF (2ml), cyclohexadiamine (0.49g, 3.1mmol) was added and stirred for 10 mins. The resulting solution was added to a solution of 2,2-ethylenedioxy-3-*exo*-hydroxy bornanone (0.5g, 2.35mmol) in DMF (5ml) at 32°C, and stirred over night. The reaction mixture was concentrated *in vacuo* and flash chromatography of the residue [elution with hexane-EtOAc (8:2)] afforded, as an oil, *2,2-ethylenedioxy-3*-exo-*bornyl carbobenzyloxy glycinate* (0.70g, 73%) δ_H (400MHz; $CDCl_3$) 0.77, 0.82 and 1.07 (9H,3xs,8-, 9- and 10-Me), 1.11-1.82 (5H,m,4-H, 5-CH_2 and 6-CH_2), 3.70-3.73 (2H,m,CH_2NH), 3.80-3.95 (4H,m,OCH_2CH_2O), 4.30 (1H,s,3-H), 5.10-5.16 (2H,m,CH_2Ph) and 7.30-7.36 (4H,m,ArH); δ_C (100MHz; $CDCl_3$) 9.19/9.25 (C-

10), 20.77/20.99 (C-8 and C-9), 24.32 (C-5), 28.84 (C-6), 63.84 (CH_2-NH_2), 66.63 (CH_2-Ph), 69.17 and 69.67 (OCH_2CH_2O), 86.66/87.06 (C-3), 116.01/116.06 (C-2), 128.12, 128.27, 128.30, 128.46, 128.55, 135.21 and 135.70 (ArC), 154.61 [C=O(amide)] and 155.07 [C=O (ester)]; *m/z* M^+ (12.8%).

2-oxo-*3*-exo-*bornyl* N-*carbobenzyloxy glycinate* (**387**). — To a solution of carbobenzyloxy glycine (1.24g, 5.95mmol) in anhydrous DMF (2ml), cyclohexadiamine (1.44g, 8.92mmol) was added and stirred for 10 min. The resulting solution was added in drops (*via* a syringe) to the alkoxide generated *in situ* by the reaction of NaH (0.34g, 7.1mmol) with 3-*exo*-hydroxy camphor (**348**) (1.0g, 5.95mmol) in THF (20ml). The resulting solution was stirred at *ca.* 34°C for 2 h and at room temperature over night. The reaction mixture was evaporated *in vacuo* and flash chromatography of the residue [elution with hexane-EtOAc (7:3)] afforded, as an oil, *2*-oxo-*3*-exo-*bornyl* N-*carbobenzyloxy glycinate* (**387**) (1.8g, 71%) δ_H (400MHz; $CDCl_3$) 0.90/0.91, 0.92 and 0.97 (9H,3xs,8-, 9- and 10-Me), 1.24-2.10 (5H,m,4-H, 5-CH_2 and 6-CH_2), 2.78 (1H,NH), 3.95-3.99 (2H,m,CH_2NH_2), 4.68 (1H,s,3-H), 4.82-5.34 (2H,m,CH_2Ph) and 7.25-7.32 (5H,m,ArH); δ_C (100MHz; $CDCl_3$) 8.98/9.01 (C-10), 20.91/20.07 (C-9), 20.68/20.97 (C-8), 24.80/25.18 (C-5), 28.44/28.56 (C-6), 42.82 (CH_2NH_2), 46.74/48.34 (C-1), 57.01/57.24 (C-7), 67.10 (CH_2Ph), 77.47/77.50 (C-3), 128.07, 128.17, 128.50 and 136.16 (ArC), 169.31 and 210.03 and 211.41 (ester C=O and benzyloxy C=O) and 219.81/213.66 (C-2); υ_{max} (liquid film) 1750 cm^{-1}; *m/z* 359 (M^+ 2.5%) (Found M^+ 359.1743; $C_{20}H_{25}O_5N$. requires M: 359.1733)

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